FALL 2016

biosupply trends

QUARTERLY

SPECIAL FOCUS:
INNOVATION

Healthcare Innovation

Breakthroughs in Therapies and Treatment

Targeted Therapies
DECLARING WAR ON CANCER

HEALTHCARE MONITORING
in 'Real-Time'

OPTIMIZING PATIENT CARE WITH
Medical Scribes

REVOLUTIONIZING TREATMENT WITH
Future Stem Cell Therapies

Extended Half-Life Factor Transforms Hemophilia Care p.46

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Protein Sciences CORPORATION

CPT Code: 90673

NDC Code: 42874-016-10

ICD.10 Code: z23

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.

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 years of age and older.

DOSAGE AND ADMINISTRATION

For intramuscular (IM) injection only (0.5 mL)

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%). In adults 50 through 64 years of age, the most common (≥10%) injection site reactions were pain (32%) and tenderness (37%); the most common (≥10%) solicited systemic adverse reactions were headache (17%), fatigue (13%), and muscle pain (11%). In adults 65 years of age and older, the most common (≥10%) injection site reaction was pain (19%); the most common (≥10%) solicited systemic adverse reactions were fatigue (13%) and headache.

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, or children. A pregnancy registry is available for Flublok. Contact: Protein Sciences Corporation by calling 1-888-855-7871. Revised: July 2016

*Flublok demonstrated a higher antibody response to the A strains during 2 clinical trials in adults ≥50 years old. The B strain antibody response was comparable to traditional trivalent vaccines.

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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.

BioSupply Trends Quarterly (ISSN 1948-2620) is a national publication, with quarterly themed issues.

Publisher: FFF Enterprises, Inc., 41093 County Center Drive, Temecula, CA 92591

Subscriptions to *BioSupply Trends Quarterly* are complimentary. Readers may subscribe by calling (800) 843-7477 x1351.

The Exciting Future of Medicine

In his book *The Future of Medicine: Megatrends in Health Care That Will Improve Your Quality of Life*, Stephen C. Schimpff, MD, FACP, writes about the changing paradigm that evolved from "diagnose and predict outcome," to "diagnose and treat" and, now, "predict and prevent." Soon, physicians will have an entire range of medicines that will treat deadly diseases. And, says Dr. Schimpff, "the possibility exists to know what a person is predisposed to develop with time — heart disease, cancer, diabetes, and so on." Indeed, at every bend in the medical road, advances are leading to promising treatments and cures for diseases that have plagued society for decades, as well as new methods that promise to substantially improve quality of care. We explore just such exciting innovations in this issue.

Cancer, the dreaded diagnosis! Cancer is elusive, adapting and evolving even with treatment. Still, fewer people are dying from a cancer diagnosis today due to cutting-edge research in the areas of targeted therapies, immunotherapy, combination therapies, vaccines and genomics. Our article "Breakthroughs in the War on Cancer" relates how Big Pharma, researchers, philanthropists and insurers are pooling their public and private resources to fight it.

A fledgling industry that is being hailed as science fiction turned reality is stem cell therapy. While the U.S. Food and Drug Administration hasn't yet approved any stem cell-based products beyond one to date, the technology is being used to treat and, in some cases, cure people with multiple sclerosis, severe combined immunodeficiency, stroke and traumatic brain injury. We delve into these current trends in our article "Stem Cell Therapies: The Era of Regenerative Medicine?" as well as the controversies. As this field advances, still to be answered are who has access to it (researchers and/or clinicians) and how ethical concerns grounded in moral and religious beliefs can be resolved.

There's no question that the displacement of "on-demand" treatment with routine prophylactic infusions was a life-changer for hemophilia patients. Even so, the process is cumbersome, requiring frequent infusions, and problematic, especially for children. Fortunately, as detailed in our article "Transforming Hemophilia Care: A New Generation of Extended Half-Life Factor Concentrates," introduction of extended half-life factor VIII and IX concentrates allows patients to infuse every seven to 14 days instead of multiple times each week, thus reducing treatment burden and potentially improving treatment adherence. Today, there are five licensed products and three pending approval.

Of course, treatment involves far more than medications. With the new electronic healthcare requirements, providers are caught in a quandary of compliance and optimal patient care. As explained in our article "The Growing Profession of Medical Scribes," these new team members are helping providers spend more face-to-face time during visits with patients, as scribes take on the burden of data entry.

Also trending as described in our article "Real-Time Healthcare Monitoring" is improving quality of care with remote digital technologies. From apps to watches, these devices allow providers to track patients' health status, reduce care costs and even predict patient outcomes.

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

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

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

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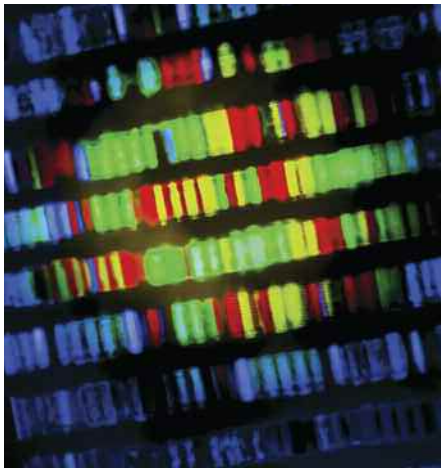
NIH Commits $260M to Centers for Common Disease Genomics



The National Institutes of Health (NIH) will spend $260 million over four years to fund four genome sequencing and analysis centers whose research is expected to focus on understanding the genomic bases of common and rare human diseases. The goal of the new Centers for Common Disease Genomics (CCDG), which will be funded through NIH's National Human Genome Research Institute (NHGRI), is to improve understanding of how genomic differences among people influence disease risk and to develop models for future studies of common disease.

CCDG investigators will focus initially on cardiovascular, metabolic and and neuropsychiatric diseases, but other disorders are also being considered, including inflammatory and autoimmune disorders, bone and skeletal diseases and Alzheimer's disease. NIH expects as many as 150,000 to 200,000 genomes to be sequenced. "These studies will reveal genomic variants that may increase the risk for — or, in some cases, protect against — diseases, which eventually might be helpful for their clinical management," said Adam Felsenfeld, PhD, director of the NHGRI Genome Sequencing Program. ❖

CMS Selects Markets for Primary Care Payment Initiative

In August, the Centers for Medicare and Medicaid Services announced 10 states in four regions in which it will launch its primary care quality improvement initiative: Arkansas, Colorado, Hawaii, Michigan, Montana, New Jersey, Oklahoma, Oregon, Rhode Island and Tennessee. The selections for the Comprehensive Primary Care Plus (CPC+) initiative were based on density and interest shown by practices and payers. In addition, 57 not-yet-named payers will participate in Kansas City, the North Hudson Valley in New York, Philadelphia and Northern Kentucky.

Under CPC+, CMS and other insurers will pay physicians a monthly fee for patient primary care visits under two tracks. In track one, providers will receive a monthly fee for specific services in addition to the fee-for-service Medicare payments. In track two, practices will receive an upfront monthly care-management fee and reduced fee-for-service payments. The latter is designed to let practices provide care outside of the traditional face-to-face encounter. The goal of CPC+ is to improve health outcomes and lower costs not only for Medicare beneficiaries, but also consumers enrolled in commercial plans and other coverage options such as insurer-managed Medicaid plans.

While CPC+ was originally expected to launch in up to 20 regions, CMS received interest from fewer markets than expected. However, CMS does expect that up to 5,000 primary care practices serving an estimated 3.5 million beneficiaries will participate. ❖

CMS Delays Rule on Pharmacy Reimbursement for Prescription Drugs

The Centers for Medicare and Medicaid Services (CMS) has delayed enforcement of a rule that changes the way state Medicaid agencies reimburse pharmacies for prescription drugs. While pharmacies requested a delay until October, CMS has instead delayed the enforcement date for inhalation, infusion, instilled, implanted or injectable drugs until July 2017. At that time, state Medicaid agencies will begin reimbursing pharmacies for prescription drugs based on acquisition costs. Previously, pharmacies were reimbursed based on the cost of the ingredients to make the drug plus a dispensing fee for filling the prescription.

Drugmakers requested delay of the rule so that they could determine the average manufacturer price (AMP) for that subset of drugs that are not generally dispensed through retail community pharmacies. CMS responded by giving manufacturers a "transition period" to make modifications and test their systems to calculate and report the AMP for drugs. According to CMS, the rule will save $2.7 billion over five years in state and federal costs, primarily because of alterations it made to the federal upper limit of drug reimbursements. ❖

HHS Awards $94M to Treat Opioid and Heroin Abuse Epidemic

The U.S. Department of Health and Human Services (HHS) has awarded $94 million in Affordable Care Act funding to 271 health centers in 45 states, the District of Columbia and Puerto Rico to improve and expand the delivery of substance abuse services with a specific focus on treatment of opioid and heroin use in underserved populations. Approximately 4.5 million people in the U.S. were nonmedical prescription pain reliever users in 2013, and an estimated 289,000 were current heroin users. HHS estimates the number of unintentional overdose deaths from prescription pain medications has nearly quadrupled from 1999 to 2013, and deaths related to heroin increased 39 percent between 2012 and 2013.

The awards will increase the number of patients screened for substance use disorders and connected to treatment, increase the number of patients with access to medication-assisted treatment for opioid use and other substance use disorder treatment, and provide training and educational resources to help health professionals make informed prescribing decisions. The investment is expected to help awardees hire approximately 800 providers to treat nearly 124,000 new patients. "The opioid epidemic is one of the most pressing public health issues in the United States today," said HHS Secretary Sylvia M. Burwell. "Expanding access to medication-assisted treatment and integrating these services in health centers bolsters nationwide efforts to curb opioid misuse and abuse, supports approximately 124,000 new patients accessing substance abuse treatment for recovery and helps save lives." ❖

HHS Awards $742,000 to Fight Zika Virus

Three health centers in America Samoa and the U.S. Virgin Islands and their 12 delivery sites that served nearly 26,000 patients in 2014, including more than 6,000 women ages 15 years to 45 years, have been awarded $742,000 in funding to fight the Zika virus by expanding preventive and primary care services, outreach, and patient education and screening. More than 50 cases of Zika have been reported to the Centers for Disease Control and Prevention in those regions, and that number is expected to rise.

"We are working to learn as much about the Zika virus as we can, as quickly as we can, and make sure the public is informed about the steps they can take to minimize their risk, as well as the risk to their families and communities, of getting Zika," said Health and Human Services Secretary Sylvia M. Burwell. "Our goal is to reduce the risk of Zika virus, especially among pregnant women and women of childbearing age." ❖

Senate Approves Medicare "Lock-In" Provision

In March, the U.S. Senate approved the Medicare "lock-in" provision that gives Medicare Part D plans the authority to require at-risk beneficiaries to use a single prescriber and pharmacy for frequently abused drugs. The provision, sponsored by Senators Pat Toomey (R-Pa.), Sherrod Brown (D-Ohio), Rob Portman (R-Ohio) and Tim Kaine (D-Va.), is an amendment to a larger prescription drug abuse bill called the Comprehensive Addiction and Recovery Act that, among other efforts, aims to curb the opioid abuse epidemic through enhanced grant programs. "As the pharmacy community is well aware, prescription drug abuse and dependency have been on the rise in America for several years," said American Pharmacist Association (APhA) Executive Vice President and CEO Thomas E. Menigham, BSPharm, MBA, ScD (Hon), FAPhA. "This epidemic is a major issue for our nation due to the devastating impact it has had on individuals, families and communities. We have made this a central theme for APhA 2016. As we inform and educate pharmacy professionals, they will be able to help their communities." While the amendment has passed, the Senate still has to vote on the broader comprehensive bill. ❖

OPPS 2017 Changes and Opportunities

BOTH PRIVATE PAYERS AND the Centers for Medicare and Medicaid Services (CMS) recognize that outpatient services present a myriad of opportunities for moving healthcare forward. As such, they have made these services the focal point of innovative and important changes they are striving to implement as quickly as possible. New models are being proposed and tested, and new or changed rules promulgated and implemented for the 2017 outpatient calendar year, beginning Jan. 1, 2017. The year covered by the inpatient prospective payment system began Oct. 1, 2016. Following are selected highlights affecting drugs and biologicals from the recently published proposed outpatient prospective payment system (OPPS), as well as suggestions for how to implement best practices.

What Remains Unchanged

The proposed 2017 OPPS rule is unique as there are no reimbursement changes for items that include payments for:

- drugs, biologicals and radiopharmaceuticals that do not have pass-through status (average sales price [ASP] plus 6% minus 2% sequestration)
- drugs, biologicals and radiopharmaceuticals with pass-through status (ASP plus 6% minus 2% sequestration)
- separately payable and specific covered outpatient drugs (ASP plus 6% minus 2% sequestration)
- biosimilar products (100% of biosimilar ASP plus 6% of reference product ASP while in a pass-through status minus 2% sequestration)
- blood clotting factors (ASP plus 6% minus 2% sequestration plus a furnishing fee)
- blood and blood products (established using CMS blood-specific cost-to-charge ratio methodology)

Note that there are no separate payments for blood and blood products when they appear on the same claim as services assigned to comprehensive Ambulatory Payment Classifications (C-APCs). This is because costs of blood and blood products are reflected in the overall costs of C-APCs.

Some Changes in 2017

Drugs that are not separately payable but are packaged/bundled due to cost. The threshold for these drugs, biologicals and radiopharmaceuticals is rising from $100 per day (as determined by ASP) to $110 per day. This applies when administered to Medicare outpatients. Payment is bundled into the code for the visit.

Determine which drugs in your outpatient settings will be affected, and budget for that revenue loss in the separately payable category. Consider whether there is a viable mechanism for transfer of the drug component of bundled/packaged payment to the pharmacy budget (intrafacility unbundling and distributing the payment segments). These products must continue to be dropped into the bill even though they will not be separately payable. This vital step helps guarantee an accurate and complete picture of all therapy a patient receives and assists in the future pricing of the bundle/package. Additionally, drug administration fees will continue to be paid for these products, but only if the product itself also appears on the bill. The revenue cycle team must cooperate in this and not discard charges that will not be separately reimbursable.

Drug administration fees. Several changes to the 42 healthcare common procedure coding system (HCPCS) codes that describe drug administration services are proposed, ranging from negligible changes of less than 1 percent to a 95 percent increase for three codes (96360, 96373, 96374) and a 43 percent decrease for two codes (96401, 96411). These fees are paid in addition to the drug or biological, but they come with documentation requirements.

Loss of revenue from the misuse and inconsistent use of drug administration services across all patient areas of the hospital continues to plague many facilities. Developing a strategy for correcting this, such as restructuring your electronic health record to accommodate this with ease, is essential.

Choosing correct HCPCS codes. CMS is highlighting HCPCS codes and assigned billing units that describe the same drug/biological but in different doses. In some cases, drug-specific packaging will be used to determine which payment methodology applies. These products will be separately payable as indicated by status indicator (SI) K. The cost of these are above the $110 daily threshold:

- C9257 Injection, bevacizumab, 0.25 mg (SI K)
- J9035 Injection, bevacizumab, 10 mg (SI K)
- J1460 Injection, gamma globulin, intramuscular, 1 cc (SI K)
- J1560 Injection, gamma globulin, intramuscular, over 10 cc (SI K)

Billing for waste. On June 10, CMS announced that MACs must delay until Jan. 1, 2017, implementation of a policy requiring the use of the JW modifier on Part B claims for appropriately discarded

leftovers from single-use vials or packages.

The billing for waste rule, which provides payment for some injectable drugs that have been wasted, went into effect in 2007 in part to compensate for Medicare's OPPS 2004 rule to reimburse only for actual dose administered indicated by billing unit conversion. Outpatient providers were losing money after Medicare stopped paying for an entire vial and began reimbursing only for the actual dose administered.

The original rule also required:

1) the amount wasted and the reason needed to be documented in the medical record (this requirement has not changed).

2) billing for both the drug itself and the amount wasted on the same claim, with both amounts converted into billing units. Differentiating which was waste and which was drug administered was accomplished by using two lines, with one line used for the actual drug used and the second line used for the wasted drug, notated by the JW modifier code. Subsequently, CMS gave MACs the leeway to determine whether they required the JW modifier and two-line billing. Some chose to stick with it, and some moved to one-line billing (a big problem with lack of transparency, poor documentation, potential abuse of the system, etc.). CMS has now rescinded that leeway and moved back to two-line billing.

Billing for waste is not mandatory, but if a facility wants to capture some of the cost of wasted drug, this is the process for doing that. It applies only:

- to Medicare outpatients
- when single-dose vials, amps, syringes, etc., are used
- when the drug itself is separately paid for (not for drugs costing less than $110/day, drugs paid in bundles or packages and drugs that Medicare doesn't pay for at all) (See Billing for Waste Example.)

Billing for Waste Example

- Drug A 100mg in a single-dose vial.
- CMS assigned billing unit is 10mg (found in the Long HCPCS Descriptor).
- There are 100/10 = 10 billing units in the vial. Overfill cannot be considered or counted or used.
- Patient's dose is 80 mg.
- Convert this to billing units 80/10 = 8, and bill for 8 billing units.
- Waste is 100mg-80mg = 20 mg.
- Convert this to billing units 20/10 = 2, and bill for 2 billing units of waste. Identify this on the claim with the JW modifier and chart it in the medical record.
- Both the drug used and drug wasted need to be billed on the same claim.
- If the dose is a fraction of a billing unit, then round up for dose and round down for waste. (For instance, if the patient dose is 75 mg or 7.5 billing units, round up to 8 billing units; if waste is 25mg or 2.5 billing units, round down to 2 billing units.)
- The total of dose plus waste cannot be more than was in the vial (10 billing units). Medicare payment is for 80% of the number of billing units submitted, paid at ASP plus 6% minus 2% sequestration, the same methodology used for the actual dose. There is no co-pay collection for waste.

Payment for off-campus physician-based departments (PBDs). This change is perhaps the most surprising and controversial and the most likely to at least initially cause billing errors. It reflects the implementation of section 63 of the Bispartisan Budget Act, and it is the next step in reining in the rising costs to Medicare and personally to patients (who sounded the alarm) when these practice sites are used. This complicated rule, which grandfathers in specific sites based on date of acquisition or affiliation, reduces payments to nonqualifying sites to physician rates (PFS) from OPPS rates. PFS rates are generally lower, while OPPS rates are generally higher and often accompanied by added-on facility fee charges. Additionally, the proposed rule limits the items and services payable under the OPPS for excepted off-campus PBDs and creates 19 clinical families to define this. The excepted items or services would be determined on a PBD-by-PBD basis according to whether an item or service is in the same clinical family as items or services billed for by off-campus PBD prior to the enactment date.

The impact of this rule on 340B eligibility (managed and determined by the Health Resources and Services Administration) is unclear. Eligibility will be based on a hospital's Medicare cost report, and left to be determined is whether off-campus PBDs that are no longer reimbursed under the OPPS would be included in the report.

It's imperative that facilities work with their legal teams to vet each and every possible site affected and adjust budgets accordingly.

Preparing for 2017

Plan for a revenue cycle tune-up! Telling the patient's story completely and accurately and in a manner that can be coded is critical from both data and reimbursement standpoints. It's every-

one's responsibility: The revenue cycle team can't code and ask for reimbursement or share data if the clinical support documentation is missing. Take the changes as an opportunity to review and then improve upon current practice to yield a healthier 2017.

Reach out to Medicare administrative contractors (MACs). Your MAC can provide guidance about the exact steps needed to document and bill for an unusual circumstance. Know which MAC covers your area and how to access the valuable information they provide. For example, Novitas provides billing and coding information regarding uses, including off-label uses, of anti-vascular endothelial growth factor for treating ophthalmological diseases (A53121). See the following link that shows which jurisdictions are covered by MACs for that drug: www.cms.gov/medicare-coverage-database/details/article-details. aspx?articleId=53121.

In my next column, I will discuss the final rule and include tables of drugs that have been affected. ❖

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.

Sources

1. JW Modifier: Drug Amount Discarded/Not Administered to any Patient. *MLN Matters* Number MM9603; Revised Related Change Request 9603. Accessed at www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/Downloads/MM9603.pdf.
2. Medicare Program: Hospital Outpatient Prospective Payment and Ambulatory Surgical Center Payment Systems and Quality Reporting Programs; Organ Procurement Organization Reporting and Communication; Transplant Outcome Measures and Documentation Requirements; Electronic Health Record (EHR) Incentive Programs; Payment to Certain Off-Campus Outpatient Departments of a Provider; Hospital Value-Based Purchasing (VBP) Program. *Federal Register*, July 14, 2016. Accessed at www.federalregister.gov/articles/2016/07/14/2016-16098/medicare-program-hospital-outpatient-prospective-payment-and-ambulatory-surgical-center-payment.
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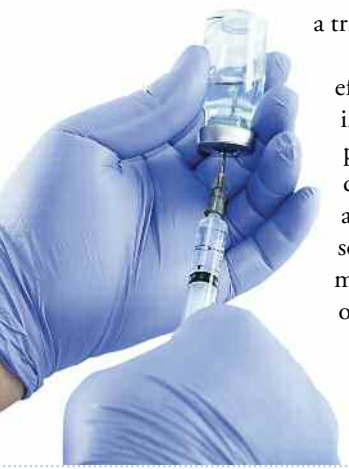
Policy

CDC Updates Annual Influenza Vaccine Recommendations

The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) has issued an update to its recommendations regarding the use of seasonal influenza vaccines for the 2016-17 season, including:

• Inactivated influenza vaccines will be available in both trivalent and quadrivalent formulations. Recombinant influenza vaccines will be available in a trivalent formulation.



• Because of low effectiveness against influenza A(H1N1) pdm09 in the U.S. during the 2013-14 and 2015-16 seasons, ACIP recommends against the use of live attenuated influenza vaccine (LAIV4). Because LAIV4 is still a licensed vaccine that might be available and that some providers might elect to use, previous recommendations for its use should be followed.

• The virus strains included in the U.S. trivalent influenza vaccines will be an A/California/7/2009 (H1N1)-like virus, an A/Hong Kong/4801/2016 (H3N2)-like virus and a b/Brisbane/60/2008-like virus (Victorian lineage). Quadrivalent vaccines will include an additional influenza B virus strain, a B/Phuket/3073/2013-like virus (Yamagata lineage).

• New vaccines for this season include an MF59-adjuvanted trivalent inactivated influenza vaccine, Fluad (Seqirus), which was licensed by the U.S. Food and Drug Administration (FDA) in November 2015 for persons aged 65 years and older, and a quadrivalent formulation of Flucelvax (cell culture-based inactivated influenza vaccine [Seqirus]), which was licensed by FDA in May for persons aged 4 years and older.

• It is no longer recommended that persons with an egg allergy be observed for 30 minutes post-vaccination for signs and symptoms of an allergic reaction. Instead, providers should consider observing for 15 minutes post-vaccination to decrease the risk for injury should they experience syncope.

• It is recommended that persons with a history of severe egg allergy (any symptoms other than hives) be vaccinated in an inpatient or outpatient medical setting (including but not limited to hospitals, clinics, health departments and physician offices) under the supervision of a healthcare provider who is able to recognize and manage severe allergic conditions. ❖

CDC: Updated Influenza Vaccine Recommendations Released. MPR News, Aug. 25, 2016. Accessed at www.empr.com/news/cdc-updated-influenza-vaccine-recommendations-released/article/518545.

Influenza

New Model Developed to Predict Flu Outbreaks

Researchers at Boston Children's Hospital conducted a study that resulted in the development of a new model to accurately predict national and local influenza (flu) activity. In the study, researchers combined records from athenahealth, a database containing insurance claims for 64 million people and medical records for 23 million patients seen by 72,000 healthcare providers, with historical patterns of the flu collected between 2009 and 2012. They then used total weekly counts of doctor visits, flu vaccine visits, flu visits, flu-like illness visits and other unspecified doctor visits for other viral infections to make their predictions, and found their model was generally more than 90 percent accurate at matching actual records from 2013 to 2015 as monitored by the Centers for Disease Control and Prevention.

The researchers hope that by better tracking the virus, there will be a reduction in the number of people affected by influenza each year. Other real-time tracking systems such as Google's Flu Trends tool that was shut down in August 2015 have not worked well. But, the new system may be to predict the timing and magnitude of the flu's peak in a country. "Our study shows the true value of considering multiple data streams in disease surveillance," said Dr. John Brownstein, chief innovation officer at Boston Children's Hospital. "While Google data provide incredible real-time population-wide information, clinical data add a more accurate and precise assessment of disease state. As EHR data become more ubiquitously available, we will see major leaps in our ability to monitor and track disease outbreaks." ❖

Feller S. Researchers Devise Model to Predict Flu Outbreaks. UPI, May 11, 2016 . Accessed at www.upi.com/Health_News/2016/05/11/Researchers-devise-model-to-predict-flu-outbreaks/5551462969176.

Research

New Findings Contradict Study That Showed FluMist Vaccine Is Ineffective

In June, the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommended against using FluMist, a live-attenuated nasal flu vaccine, for the 2016-2017 influenza (flu) season. Its decision was based primarily on data from the U.S. Flu Vaccine Effectiveness Network, which assesses the health of people who have an acute respiratory illness with cough for at least one week during flu season and are at least 6 months old. But a new Canadian study appears to contradict the research that led the ACIP to recommend against that vaccine.

In the Canadian study, researchers randomly assigned 1,186 children in 52 Hutterite communities in rural Canada, ages 3 years to 15 years, to receive either FluMist or the inactivated flu vaccine by injection. During the three flu seasons from 2012 to 2015, 5.3 percent of the children in the FluMist group and 5.2 percent of the children in the inactivated vaccine group had lab-confirmed influenza, meaning the two vaccines were equally effective. While the study lacked a control group of children who did not receive a vaccine, previous studies have shown a flu infection rate of about 10 percent among unvaccinated children and of 4 percent to 5 percent in vaccinated children in these communities.

The contradiction between the data is not simple, but rather very complex, according to Mark Loeb, the new study's lead author and director of the division of infectious diseases at McMaster University in Ontario, Canada: "Sometimes the public wants a very simple message, and unfortunately life's not like that. Things change as the evidence grows and we understand more. Unfortunately, that's how science and clinical medicine work. The challenge is to be able to help the public understand the shades of gray here."

The Canadian study's findings are parallel with early evidence for FluMist in the U.S., which ACIP preferentially recommended for children during the 2014-2015 flu season. In fact, CDC data consistently showed FluMist to be very effective in children until 2013, when the vaccine went from including three strains (trivalent) to including four strains (quadrivalent). The Canadian study utilized the trivalent vaccine, whereas ACIP analyzed data using the quadrivalent vaccine. It's possible, researchers say, that going from the trivalent to the quadrivalent vaccines could have introduced more vaccine interference. Each vaccine strain competes to infect enough cells so that the virus can replicate and induce an immune response, and with more strains, there is more competition among them to infect cells. But, other studies in countries outside of the U.S. show higher effectiveness with the quadrivalent vaccine. As such, another explanation could be that U.S. children have been vaccinated regularly enough since the first universal flu vaccine recommendation in 2007 that they've built up an underlying immunity

that could interfere with responses to new doses, lessening the vaccine's effectiveness each year.

According to Kawsar R. Talaat, MD, an assistant scientist at the Center for Immunization Research at Johns Hopkins Bloomberg School of Public Health and whose supervisor, Ruth Karron, MD, is head of the ACIP flu vaccine working group, "ACIP did what was in the public's interest given the U.S. epidemiological data. The flu vaccine is different every single year, so they do their best to make the recommendation for that particular season based on the data that's available. Given three years' worth of data showing this vaccine didn't work, do they wait to get more data?" In September, ACIP recommended against the use of FluMist for the 2016-2017 season. ❖

Haelle T. Study Says FluMist Vaccine Does Indeed Work, Contradicting CDC. NPR News, Aug. 15, 2016. Accessed at www.npr.org/sections/health-shots/2016/08/15/490092448/study-says-flumist-vaccine-does- indeed-work-contradicting-cdc.

Medicines

FDA Expands Berinert Approval for Pediatric and Geriatric Use

The U.S. Food and Drug Administration (FDA) has approved CSL Behring's Berinert (C1 esterase inhibitor [human]) to treat hereditary angioedema (HAE) attacks in pediatric patients, which expands the use of Berinert into all age groups, making it the first and only approved HAE treatment available to patients under 12 years of age. In addition to the pediatric indication, FDA approved an update to the Geriatric Use section of the package insert. Clinical studies have shown that intervention with Berinert at the onset of an HAE attack brings significantly faster relief to a patient and reduces the severity of the attack in both children and adults.

"This is an important milestone for children living with HAE and their caregivers, to know that there is an FDA-approved, safe and effective treatment option for children," said Bob Repella, executive vice president of commercial operations at CSL Behring. "This expanded indication is an example of CSL Behring's commitment to HAE and our continuing efforts to deliver on our promise to improve the care of patients living with serious medical conditions." ❖

Medicines

FDA Approves AFSTYLA Recombinant Factor VIII to Treat Hemophilia A

The U.S. Food and Drug Administration (FDA) has approved AFSTYLA (antihemophilic factor [recombinant]), CSL Behring's novel long-lasting recombinant factor VIII (FVIII) single-chain therapy for adults and children with hemophilia A for routine prophylaxis to reduce the frequency of bleeding episodes, on-demand treatment and control of bleeding episodes, and the perioperative management of bleeding. It is the first and only single-chain product for hemophilia A that is specifically designed for long-lasting protection from bleeds with two to three times weekly dosing.

FDA approval of AFSTYLA was based on results from the AFFINITY clinical development program, which includes two pivotal and one extension open-label multicenter studies evaluating the safety and efficacy of it in children, adolescents and adults with hemophilia A. In the trials, patients undergoing AFSTYLA experienced a median annualized spontaneous bleeding rate of 0.00. Once activated, AFSTYLA is identical to natural FVIII. Trials also demonstrated a strong safety profile with no inhibitors observed. ❖

U.S. FDA Approves CSL Behring's AFSTYLA — The First and Only Recombinant Factor VIII Single Chain Therapy for Hemophilia A. CSL Behring press release, May 26, 2016. Accessed at www.cslbehring.com/s1/cs/enco/11515172628O4/news/1252902724602/prdetail.htm.

Medicines

FDA Approves Tests for Autoimmune Thyroid Disease

The U.S. Food and Drug Administration has given 510(k) clearance for Thermo Fisher Scientific's new EliA IgG tests for detecting anti-Thyroglobulin (anti-TG) and anti-Thyroid Peroxidase (anti-TPO) autoantibodies in serum or plasma. EliA anti-TG and anti-TPO quantitatively measure a patient's autoantibodies to thyroglobulin or thyroid peroxidase, which provides information to help clinicians develop comprehensive disease management plans for patients with autoimmune thyroid disease such as Graves' disease and Hashimoto's thyroiditis. The new CLIA-moderate lab tests, performed on the fully automated Phadia 250/2500/5000 Laboratory Systems, are designed to provide higher sensitivity and wider measuring ranges to labs and clinicians. Formerly, they were offered on the ImmunoCAP technology platform. ❖

Thermo Fisher Scientific Receives FDA Clearance for EliA Anti-Thyroglobulin and Anti-Thyroid Peroxidase Tests for Autoimmune Thyroid Disease. BusinessWire, May 16, 2016. Accessed at www.businesswire.com/news/home/20160516005122/en/Thermo-Fisher-Scientific-Receives-FDA-Clearance-EliA.

Vaccines

Flu Vaccine Reduces Heart and Breathing Problems in Diabetics

A study has found that individuals with type 2 diabetes who receive the influenza (flu) vaccine may be less likely to be hospitalized for cardiovascular or respiratory problems. In the study, researchers examined data from nearly 125,000 individuals in Britain with type 2 diabetes, accounting for patients' age, weight, smoking status, gender and whether they had a diagnosis or prescription for conditions for a variety of other medical conditions, during both the flu season and summer months. They found that flu vaccination was associated with a 30 percent lower hospital admission rate for stroke, 22 percent lower rate for heart failure and 15 percent lower rate for pneumonia or influenza. They also found that patients who received the flu vaccine had a 24 percent lower death rate from all causes, as well as lower rates of hospitalization for heart attack (however, the difference in the latter wasn't big enough to rule out the possibility of chance). "Most severe influenza complications occur in the elderly and people who suffer from long-term conditions such as diabetes, heart disease and asthma," said lead study author Dr. Eszter Vamos, public health researcher at Imperial College London. "The potential impact of influenza vaccine to reduce serious illness and death highlights the importance to renew efforts to ensure that people with diabetes receive the flu vaccine every year."

The possibility that individuals included in the study had undiagnosed diabetes is one limitation of the study. Another is the possibility that people who get vaccinated are healthier in other ways than those who skip their annual flu vaccine. The study was published in the *Canadian Medical Association Journal*. ❖

Vamos EP, Pape UJ, Curcin V, et al. Effectiveness of the Influenza Vaccine in Preventing Admission to Hospital and Death in People with Type 2 Diabetes. *Canadian Medical Association Journal*, 151059; published ahead of print July 25, 2016, doi:10.1503/cmaj.151059. Accessed at www.cmaj.ca/content/early/2016/07/25/cmaj.151059.abstract?sid=d5db9f26-5e3d-43ad-8c40-5eb26a05ec3d.

Research

Plasma-Derived Factor VIII Results in Lower Incidence of Inhibitor Development

A recent study showed that early replacement therapy with plasma-derived factor VIII (FVIII) therapy was associated with a lower incidence of the development of neutralizing anti-FVIII alloantibodies (inhibitors) than was therapy with recombinant FVIII in patients with severe hemophilia A. The randomized trial was conducted to assess the incidence of FVIII inhibitors among patients treated with plasma-derived FVIII containing von Willebrand factor or recombinant FVIII. Of 303 patients screened, 264 underwent randomization and 251 were analyzed. In total, inhibitors developed in 76 patients, 50 of whom had high-titer inhibitors. Of those, inhibitors developed in 29 of the 125 patients (26.8 percent) treated with plasma-derived FVIII (20 of whom had high-titer inhibitors), and they developed in 47 of the 126 patients (44.5 percent) treated with recombinant FVIII (30 of whom had high-titer inhibitors). The cumulative incidence of high-titer inhibitors was 18.6 percent and 28.4 percent, respectively. For the primary end point of all inhibitors, recombinant FVIII was associated with an 87 percent higher incidence than plasma-derived FVIII, an association that did not change in multivariable analysis. ❖

Peyvandi F, Mannucci PM, Garagiola I, et al. A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A. *New England Journal of Medicine*, Vol. 374, No. 21, P. 2054. Accessed at www.nejm.org/doi/full/10.1056/NEJMoa1516437.

Research

Influenza Shot During Pregnancy Protects Newborns

A new study has shown that an influenza (flu) shot during pregnancy protects newborns against the flu primarily during the first eight weeks of life. While previous studies have also shown that the flu shot protects newborns, this study sheds light on the length of protection.

After assessing more than 1,000 infants born to women given a flu shot during pregnancy, the researchers found that compared with infants of placebo recipients, they were significantly more likely to have protective concentrations (more than 1:40 or more) of HAI antibodies to all vaccine strains (except for A/H1N1pdm09 at 24 weeks) at birth and throughout the first 24 weeks of life. However, the proportion of infants with titers that high at birth was less than 80 percent for the A/H1N1pdm09 and B/Victoria strains, and less than 60 percent for the A/H3N2 strain, and that proportion decreased substantially over time, particularly after the first eight weeks of life.

Because current vaccines don't work well in and aren't approved for infants younger than 6 months, the observation raises the question of whether a higher threshold level of protection should be considered in infants. The study was published online July 5 in the journal *JAMA Pediatrics*. ❖

Munoz FM. Infant Protection Against Influenza Through Maternal Immunization: A Call for More Immunogenic Vaccines. *JAMA Pediatrics*, July 5, 2016. Accessed at archpedi.jamanetwork.com/article.aspx?articleid=2531456.

Policy

AMA Adopts New Policies at Annual Meeting

At its national annual meeting, the American Medical Association adopted several new policies that touch on a number of public policy issues, including:

- Calling on the pharmaceutical industry to fund a program to dispose of unwanted medications as hazardous waste;
- Calling for parity laws to require private insurers to cover telemedicine-provided services comparable to that of in-person services;
- Recommending that television pharmaceutical advertisements come with a warning that patients should first consult with a physician before discontinuing medications;
- Supporting the American Board of Preventive Medicine's establishment of addiction medicine as a multispecialty-sponsored subspecialty (approved by the American Board of Medical Specialties [ABMS] and available to qualified physicians who are diplomats of any of the 24 ABMS member boards);
- Supporting legislation to remove all sales tax on feminine hygiene products (already effective in five states, with more considering similar legislation);
- Adopting a policy that physical therapists and other nonphysicians practicing dry needling should, at a minimum, have standards that are similar to the ones for training, certification and continuing education that exist for acupuncture; and
- Encouraging education of consumers on the safety benefits of protective eyewear when using air guns (e.g., paint ball and air guns). ❖

AMA Adopts New Policies on Final Day of Annual Meeting. American Medical Association press release, June 15, 2016. Accessed at www.ama-assn.org/ama/pub/news/news/2016/2016-06-15-new-policies-annual-meeting.page.

Research

Experimental Antibiotic Protects Against MRSA

A study that tested an experimental antibiotic developed by researchers at Rutgers University showed that it successfully treats methicillin-resistant Staphylococcus aureus (MRSA) infections, as well as restores the efficacy of a commonly prescribed antibiotic that has become ineffective against MRSA. TXA709 was used in combination with cefdinir, an antibiotic that has been on the market for almost two decades, to successfully treat MRSA infection in animals.

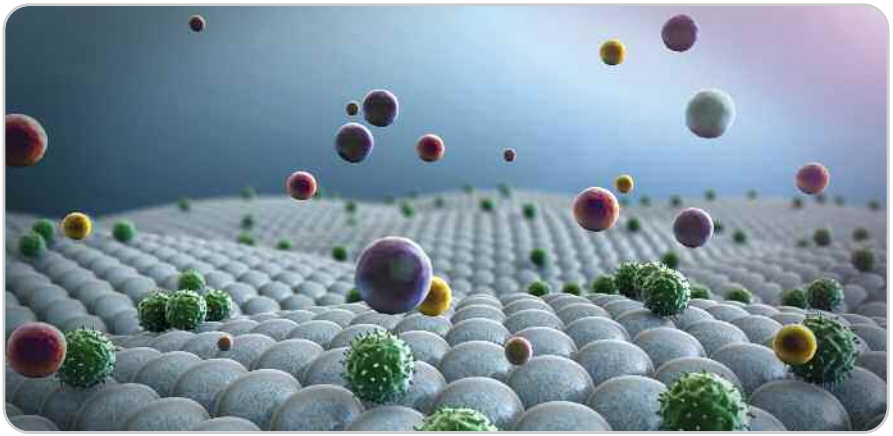
According to Daniel Pilch, associate professor in the department of pharmacology at Robert Wood Johnson Medical School, TXA709 kills MRSA bacteria in a unique manner unlike any other antibiotic in current clinical use, including the function of a protein, FtsZ, essential for the bacteria to divide and survive. By combining TXA709 with cefdinir, a cephalosporin antibiotic that acts similar to penicillin, the scientists were able to lower the dosage of the new antibiotic required to eradicate the MRSA infection. "This is important because even though TXA709 is effective on its own in treating MRSA, combining it with cefdinir — used to treat a wide range of bacterial infections like strep throat, pneumonia, bronchitis and middle ear and sinus infections — makes it even more efficacious, while also significantly reducing the potential for the MRSA bacteria to become resistant in the future," said Pilch. "Current standard-of-care drugs for the treatment of MRSA infections are limited. Furthermore, resistance to these drugs is on the rise, and their clinical effectiveness is likely to diminish in the future."

Phase I clinical trials to assess the safety and effectiveness of TXA709 in humans are expected to begin in spring 2017. ❖

Lally R. Experimental Antibiotic Treats Deadly MRSA Infection. *Rutgers Today*, June 13, 2016. Accessed at news.rutgers.edu/research-news/experimental-antibiotic-treats-deadly-mrsa-infection/20160606#.V3w_dat5WiY.

Research

Individuals' Immune Responses Are Linked to Flu Vaccine Effectiveness



New research shows that differences in individuals' immune responses might be linked to the effectiveness of the seasonal influenza (flu) vaccine. It's known that the effectiveness of the flu vaccine differs for individuals due to many factors, including age because people's immune systems become less effective as they get older. With an improved understanding of who will produce an appropriate response to the vaccine, scientists could design and create more effective ones.

In the study conducted at the Mayo Clinic, researchers gave the seasonal flu vaccine to 159 people aged 50 years to 74 years from whom blood samples were taken prior to vaccination and post-vaccination at days three and 28. They then analyzed the samples using flow cytometry to work out the relative levels of different types of immune cells at each time point. They also investigated how much immunity to the flu virus each person showed at day 28 by assessing the number of antibodies and B cells present against the flu strains they had been vaccinated against. Those who had higher levels had an increased immune response and better immunity against the flu virus. The researchers found that individuals differed significantly in their response to the flu vaccine and in how effective it proved, which correlated with a number of immune cell parameters. Those who had a better antibody response to the vaccine after 28 days had higher levels of HLA-DR (a cell surface protein that is a marker for immune stimulation) on a specialized type of dendritic cells. Prior to vaccination, those people also had more B cells in their blood, with more CD86 (a cell surface protein that allows the immune system to be activated quickly in response to a threat).

"Our research identifies key parameters within the immune system that people who show a good response to the flu vaccine exhibit," says Dr. Gregory Poland from the Mayo Clinic. "This information is important as it allows us to understand why some people might gain better immunity against flu from having the vaccine compared to others. However, we now need to examine the relationship between these factors in more detail to ensure we fully understand how these factors are linked. Ultimately, we hope that increasing our understanding of how the immune system functions at a cellular level will allow us to develop more effective vaccines, protecting the public from preventable diseases." ❖

Kennedy RB, Simon WL, Gibson MJ, Goergen KM, Grill DE, Oberg AL and Poland GA. The Composition of Immune Cells Serves as a Predictor of Adaptive Immunity in a Cohort of 50- to 74-Year-Old Adults. *Immunology*, May 17, 2016. Accessed at onlinelibrary.wiley.com/doi/10.1111/imm.12599/abstract.

Medicines

FDA Approves Keytruda for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

The U.S. Food and Drug Administration (FDA) has approved Keytruda (pembrolizumab), Merck's anti-PD-1 therapy, at a fixed dose of 200 mg every three weeks for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. The indication is based on data from the KEYNOTE-012 study that included patients with recurrent or metastatic HNSCC who had disease progression on or after platinum-containing chemotherapy or following platinum-containing chemotherapy administered as part of induction, concurrent or adjuvant therapy and ECOG performance status of zero or one. Data showed an objective response rate of 16 percent and complete response rate of 5 percent, with responses of six months or longer observed in 82 percent of responding patients. ❖

FDA Approves Merck's KEYTRUDA (pembrolizumab) for Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma with Disease Progression on or After Platinum-Containing Chemotherapy. BusinessWire, Aug. 5, 2016. Accessed at www.businesswire.com/news/home/20160805005807/en/FDA-Approves-Merck's-KEYTRUDA®-pembrolizumab-Patients-Recurrent.

Medicines

New Vaccine Developed to Treat Multiple Sclerosis

Scientists at the Institute of Bioorganic Chemistry of the Russian Academy of Sciences have developed a new form of a vaccine to treat multiple sclerosis (MS) that has successfully passed preclinical trials and two clinical stages. It was developed after the scientists proposed a vaccine whose main component are liposomes (lipid vesicle conveyers), which contain fragments of myelin protein that insulates nerve fibers in the body. In their experiment, three protein fragments were selected, one of which has a therapeutic effect in the early stages of MS, and two that are used to prevent the development of pathologies during the remission stage. They found that the most effective option is the co-administration of all three fragments inside mannosylated liposomes.

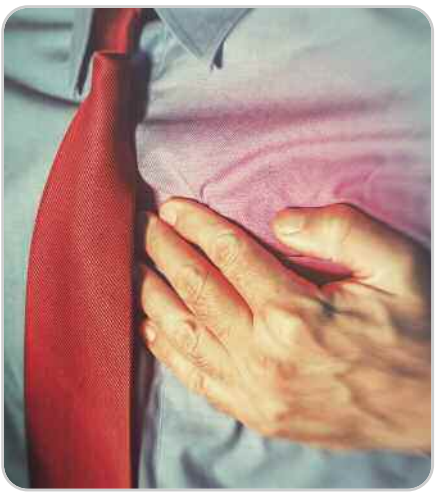
During preclinical tests on dark agouti rats suffering from experimental autoimmune encephalomyelitis (similar to MS in humans), results showed a positive effect of the myelin protein fragments, which led the scientists to work toward a vaccine. "The vaccines developed were tested in a series of clinical trials on healthy volunteers and patients suffering from MS," said Alexey Belogurov, PhD, one of the study's authors. From 2006 to 2008, researchers investigated autoantibodies from blood serum collected from patients suffering from MS and from lab animals that were developing experimental autoimmune encephalitis, which was the starting point in the development of the vaccine. "These trials were conducted at five national centers in Russia. We discovered that the drug is well-tolerated and has a very low probability of developing adverse events," added Belogurov.

The scientists are now awaiting the results of the final phase of the clinical trials, which will allow the vaccine to enter into clinical practice for the treatment of MS. ❖

Scientists Develop a Drug for the Treatment of Multiple Sclerosis. Medical Xpress, June 27, 2016. Accessed at medicalxpress.com/news/2016-06-scientists-drug-treatment-multiple-sclerosis.html.

Research

Blood Test Could Predict Heart Attack Risk



New findings suggest that a blood test could predict whether an individual is at risk of suffering a heart attack in the next five years. During a five-year trial of more than 1,700 people at risk of heart attacks, researchers at Imperial College London and University College London found that those with the highest levels of IgG antibodies were at lowest risk of heart attack. Specifically, they found there was a 58 percent lower risk of coronary heart disease and a 38 percent lower risk of a stroke or other heart event even if cholesterol and blood pressure levels were high. According to Dr. Ramzi Khamis, consultant cardiologist at the National Heart and Lung Institute, "Linking a stronger, more robust immune system to protection from heart attacks is a really exciting finding.... We hope that we can use this new finding to study the factors that lead some people to have an immune system that helps protect from heart attacks, while others don't. We also hope to explore ways of strengthening the immune system to aid in protecting from heart disease." ❖

Simple Test May Predict Your Chance of a Heart Attack. AOL News, June 20, 2016. Accessed at www.aol.com/article/2016/06/20/simple-test-may-predict-your-chance-of-a-heart-attack/21398654.

Breakthroughs in the War on Cancer

As the number of cancer cases continues to rise, scientists are bringing to light exciting discoveries that are being used to create targeted therapies to treat and, it is hoped, to eventually cure cancer.

By Ronale Tucker Rhodes, MS

NEARLY 40 PERCENT of men and women will be diagnosed with cancer at some point during their lifetime, according to the National Cancer Institute's Surveillance, Epidemiology and End Results Program. In 2013, an estimated 14,140,254 people were living with cancer in the U.S. In 2016, the estimated number of new cases is predicted to be 1,685,210, resulting in approximately 595,690 deaths.[1]

No doubt, cancer is big business. IMS Health, a global information and technology services company, reports global oncology sales exceeded $107 billion in 2015, and forecasts growth between 7.5 percent and 10.5 percent through 2020, reaching $150 billion. In just the past five years, more than 70 new cancer treatments have been launched.[2] Understandably, it's not just dollars at stake; it's the lives of the millions of patients who are counting on those billions of dollars spent in cancer care research to produce new and innovative drugs to combat the terrifying statistics. "The new science redefining cancer as a large number of narrowly defined diseases and yielding therapeutic options for an expanding number of patients is rapidly transforming the oncology treatment landscape," said Murray Aitken, IMS Health senior vice president and executive director of the IMS Institute for Healthcare Informatics. "Most health systems are struggling to adapt and embrace this evolution — including the regulatory systems, skilled professionals, diagnostic and treatment infrastructures, and financing mechanisms that are required to serve the needs of cancer patients around the world. These challenges deserve urgent attention in light of the strong near-term pipeline of clinically distinctive therapies and new programs such as the U.S. government's 'cancer moonshot' that are galvanizing research efforts to change the trajectory of cancer."[2]

These clinically distinctive therapies are a result of several cutting-edge areas of research and care: targeted therapies that include immunotherapy, combination therapies, vaccines and genomics — all of which are designed to block the growth and spread of cancer.

The Houdini of Cancer

There is, of course, a reason why cancer is so difficult to treat and why researchers have yet to find a cure after all this time (the first case of cancer dates back to 1500 B.C.[3]): Every patient's cancer is unique. According to professor Gerard Evan, head of the department of biochemistry at the University of Cambridge conducting a study of the genes that drive the development and growth of cancer, called oncogenes, "Cancers develop through the buildup of mutations (errors) in the genes that regulate and restrain the growth, division and movement of the cells that make up our bodies … and the cells then either die out or survive and multiply as a result of the complex, changing and still largely mysterious selective pressures in the body."[4]

Even with treatment, cancer cells adapt and evolve in response. "Even drugs that are initially very effective often have a progressively dwindling effect over time as the biological systems that are blocked by the treatment spontaneously compensate by rerouting the cancer cells' internal wiring, thereby restoring the cancer's ability to grow and spread," explains Evan. "To use an analogy, traffic hot spots in towns can cause major traffic jams, but cunning drivers will quickly find shortcuts to get around the congestion."[4] In essence, cancer cells are like Houdini: They almost always seem to find a way out.

> Drugs or other substances that block the growth and spread of cancer are one of the most promising new therapeutic strategies.

But, now, research is beginning to shed light on how cells escape past the immune system.

Researchers at Texas A&M College of Medicine found that when cancer cells are able to block the function of a gene called NLRC5, they are able to evade the immune system and proliferate. Biopsy samples from almost 8,000 cancer patients showed that the expression of the NLRC5 gene is highly correlated with cancer patient survival; patients who survive longer have greater expression of the gene. The discovery is significant, they say, because in the short term, it can more accurately predict how likely the tumor can be recognized and destroyed. And, in the long term, therapies could be developed that increase expression of the gene and use it to help fight cancer.[5]

In another study, a Kyoto University-led team found that structural changes affecting the regulation of the PD-L1 gene appear to help some cancers dodge the immune system. The team used genome and/or RNA sequence data for more than four dozen adult T-cell leukemia/lymphoma cases to search for noncoding structural variant clusters. What they found were structural variants in the 3'-untranslated region (UTR) of the PD-L1 that appeared to amplify the gene's expression, apparently contributing to tumors' ability to evade the immune system. Similar structural variant patterns were found in samples from individuals with diffuse large B-cell lymphoma and stomach adenocarcinoma. Follow-up experiments in a mouse model indicated that such 3'-UTR alterations can boost PD-L1 expression, prompting tumor protection from the immune

system. The researchers then demonstrated that they could dial up PD-L1 expression by using CRISPR-Cas9 to interfere with the PD-L1 3'-UTR in mouse or human cell lines. Experiments on mouse models showed diminished immune responses to cancer-causing cells containing the truncations. Based on their findings, the team speculated that "disrupted PD-L1 3'-UTR might serve as a genetic marker for identifying cancers that actively evade immune surveillance and, therefore, potentially respond to immune checkpoint blockade using antibodies against PD-1/PD-L1."[6]

In June, researchers from the United Kingdom discovered how two molecules join forces to help cancer cells survive as they metastasize. The finding occurred when they observed what happens when cancer cells break away from tumors in cell cultures, zebra fish and mice. They found that "integrins" (proteins on the surface of a cell that bind and communicate with its surroundings) play a role in cancer cells surviving after they detach from the primary tumor. Integrins are known to engage in "outside-in" and "inside-out" signaling, which helps cancer cells bind to their surrounding environment. But when cancer cells travel during metastasis, the integrins adopt "inside-in" signaling, causing a defense signaling to occur within the cell.

A growing number of studies are showing great success with targeted immunotherapies, both approved and experimental, for treating a host of diseases.

According to the study's authors, the integrin beta-1 (B1) teams up with a protein called c-Met, and both proteins travel together inside the cancer cell. The proteins then move to a location within the cell that is normally used for degradation and recycling of cell material. However, the proteins use this location to send a signal to other areas of the cancer cell, triggering a defense against cell death. The researchers then looked at what would happen if both B1 and c-Met were prevented from entering cells or from traveling to the location needed for defense signaling and then found that the cells were much less likely to metastasize. The findings suggest that stopping B1 from initially entering cancer cells could be an effective way to combat cancer metastasis.[7]

Most recently, researchers at the University of California, Los Angeles discovered key mechanisms in how melanoma becomes resistant to immunotherapy. In their study of 78 patients who were treated with pembrolizumab (Keytruda), 42 patients responded, but 15 patients relapsed. Of those 15, four met the study criteria. When analyzing pairs of tissue samples taken from the four individuals before starting treatment and after they relapsed, the researchers found that the post-relapse tumors were very similar to those of their initial tumors; however, some significant changes occurred that allowed the cancer to fight back. In one case, a tumor had lost the B2M gene, making it harder for T cells to recognize the cancer. In two other cases, genetic mutations in the tumors interfered with JAK1 and JAK2 genes, which limited the immune system's effectiveness in killing cancer cells. The fourth patient's tissue didn't have those genetic alterations, suggesting that other mechanisms of resistance may be discovered in the future.[8]

Beyond Cytotoxic Therapies

Many different types of cancer therapies are available that differ from cytotoxic radiation and chemotherapy. Most promising are targeted therapy, immunotherapy, vaccines and gene therapy.

The U.S. Food and Drug Administration (FDA) has approved a great number of targeted therapies for more than a dozen types of cancer. In addition, there are ongoing clinical trials being studied for both FDA-approved and experimental targeted therapies for specific types of cancer. These trials can be located under the types of therapies at the National Cancer Institute (www.cancer.gov/about-cancer/treatment/clinical-trials/search) or by doing a search of a type of cancer at clinicaltrials.gov.[9]

Targeted Therapies: The Cornerstone of Precision Medicine

Drugs or other substances that block the growth and spread of cancer are one of the most promising new therapeutic strategies. Known as targeted therapies (a cornerstone of precision medicine that uses information about a person's genes and proteins to prevent, diagnose and treat disease), they work by interfering with specific molecules that are involved in the growth, progression and spread of cancer. They differ from traditional chemotherapy because they 1) act on specific molecular targets that are associated with cancer, rather than acting on all rapidly dividing normal and cancerous cells; 2) are deliberately chosen or designed to interact with their target, rather than just killing cells; and 3) are often cytostatic, meaning they block tumor cell proliferation, rather than cytotoxic, meaning they kill tumor cells.

Several approaches are used to identify good targets. One is to compare the amounts of individual proteins in cancer cells with

those in normal cells. An example of this is the human epidermal growth factor receptor 2 protein (HER-2), which is expressed at high levels on the surface of some cancer cells. A second approach is to identify potential targets to determine whether cancer cells produce mutant (altered) proteins that drive cancer progression. And, a third approach is to look for abnormalities in chromosomes that are present in cancer cells but not in normal cells, which can sometimes result in the creation of a fusion gene (one that incorporates parts of two different genes) whose product, called a fusion protein, may drive cancer development. All of these proteins are potential targets for targeted cancer therapies.[9]

Targeted therapies are typically either small molecules or monoclonal antibodies. Small molecules can penetrate the cell membrane to interact with targets inside a cell, usually by interfering with the enzymatic activity of the target protein. Monoclonal antibodies target specific antigens found on the cell surface and, sometimes, they are conjugated to radioisotopes or toxins to allow specific delivery of the cytotoxic agents to the intended cancer cell target.

Unfortunately, as mentioned earlier, cancer cells adapt and evolve in response to treatment, causing them to become resistant to targeted therapies in two ways: mutating so that the targeted therapy no longer interacts well with it, and/or finding a new pathway to achieve tumor growth that doesn't depend on the target. Therefore, many targeted therapies work best in combination with one or more traditional chemotherapy drugs.[10]

Immunotherapy: Using the Body's Natural Defense System

While immunotherapy falls under the umbrella of targeted therapy, it differs because rather than aiming to inhibit molecular pathways that are crucial for tumor growth and maintenance, immunotherapy uses the body's own natural defense system by stimulating a host immune response to achieve long-lived tumor destruction. Targeted therapies and cytotoxic agents such as chemotherapy and radiation also achieve immune responses, so treatment strategies often combine them.[11]

A growing number of studies are showing great success with targeted immunotherapies, both approved and experimental, for treating a host of diseases.

Melanoma. In 2015, former president Jimmy Carter announced he was cancer-free after being treated with the immune-boosting drug Keytruda (pembrolizumab, Merck). Now, a new study shows that an estimated 40 percent of 655 people treated with Keytruda in a clinical trial to treat advanced melanoma were still alive three years after starting treatment. The three-year survival rate with older melanoma treatments was only 10 percent to 20 percent.[12]

Another study showed that 34 percent of melanoma patients treated with Opdivo (nivolumab, Bristol-Meyers Squibb) were alive five years after starting treatment. In comparison, the overall survival rate for patients with advanced melanoma has been about 15 percent to 20 percent, according to the American Cancer Society.[12]

Two cancer treatment vaccines are FDA-approved in the U.S.

And, in a third Phase II study known as CheckMate-069 that examined the combination of Yervoy (ipilimumab, Bristol-Meyers Squibb) and Opdivo, there was a 42 percent improvement in overall survival when compared with Yervoy as a monotherapy.[13]

Bladder cancer. Opdivo has also been shown to be effective for treating metastatic bladder cancer. A Phase I/II clinical trial treated 78 patients, five of whom (6.4 percent) had complete responses, 14 (18 percent) of whom had partial responses in which tumor burden shrank by at least 30 percent, and 22 (28.2 percent) had stable disease. Thirty (38 percent) patients had disease progression.[14]

In May, FDA approved the first immunotherapy to treat bladder cancer. Tecentriq (atezolizumab, Genentech), which works in a similar way as Keytruda by targeting the PD-L1 protein, won accelerated approval for treating patients with advanced urothelial cancer after chemotherapy stops helping them — a point when most usually die within six months. Approval was based on a study of 310 people with advanced urothelial cancer, which found that treatment stopped tumors from growing in 24 percent of patients and shrank tumors by 30 percent.[15]

Stomach cancer. Recently, new research suggests that advanced stomach cancer patients may live longer with an IMAB362 antibody therapy. IMAB362 is an antibody that focuses on a protein on cancer cells known as claudin 18.2. In a Phase II clinical trial of 161 stomach cancer patients, those who received the treatment and standard chemotherapy survived about 13 months versus those who received only chemotherapy whose median survival was just 8.4 months. Participants with the highest levels of claudin 18.2 had even longer survival rates, with a median survival of 17 months.[16]

Brain cancer. In May, the National Brain Tumor Society and Oligo Nation granted $250,000 to fund a preliminary study of an immunotherapy to treat oligodendroglioma, a type of brain cancer. Researchers at Stanford University have developed an antibody that will target the CD47 protein that sends a "don't

Generic Naming Formula for Targeted Therapies

Like other drugs, targeted cancer therapies typically have several different names. The name of a drug provides clues to the type of agent and its cellular target.

Monoclonal antibodies end with the stem "-mab" (monoclonal antibody). Small molecules end with the stem "-ib" (indicating that the agent has protein inhibitory properties). Monoclonal antibodies have an additional substem designating the source of the compound (e.g., "-ximab" for chimeric human-mouse antibodies, "-zumab" for humanized mouse antibodies and "-mumab" for fully human antibodies). Both monoclonal antibodies and small molecules contain an additional stem in the middle of the name describing the molecule's target. Examples for monoclonal antibodies include "-ci-" for a circulatory system target and "-tu-" for a tumor target; examples for small molecules include "-tin-" for tyrosine kinase inhibitors and "zom-" for proteasome inhibitors. At the beginning of the generic name is a prefix that is unique for each agent.

Generic Naming Forumula	Name = Prefix + Substem(s) = Stem
-mab	monoclonal antibody
-ib	small molecule with inhibitory properties
-ci(r)-	monoclonal antibody target circulatory system
-li(m)-	monoclonal antibody target immune system
-t(u)-	monoclonal antibody target substem for tumor
-ximab	monoclonal antibody soure chemieric human-mouse
-zumab	monoclonal antibody source humanized mouse
-mumab	monoclonal antibody source fully human
-tinib	small molecule tyrosine kinase inhibitor
-zomib	small molecule proteasome inhibitor
-ciclib	small molecule cyclin-dependent kinase inhibitor
-parib	small molecule poly ADP-ribose polymerase inhibitor

Source: Study Blue. Targeted Therapies — Classification and Naming

eat me" signal to immune cells, thus hiding tumors from the innate immune system. Currently in Phase I studies for a number of solid tumors and blood cancers, the new study aims to determine if patients with oligodendroglioma can clinically benefit from anti-CD47 treatment. To date, results from lab tests have shown the method is effective. Researchers are now conducting studies based on three approaches: 1) testing anti-CD47 using multiple animal models; 2) conducting in vivo animal testing of the anti-CD47 antibody in combination with various immunotherapies, including EGFR inhibitors and anti-CD-40 agents; and 3) performing in vivo testing of the efficacy of combined immunotherapies that encourage an adaptive response from the immune system, including inhibitors (PD-1, PD-L1 and CTLA-4).[17]

Another new potential treatment for brain cancer is the poliovirus, and FDA has given it breakthrough status. The treatment, developed at Duke University, involves injecting a genetically engineered poliovirus, known as PVS-RIPO, into deadly brain tumors known as glioblastoma, a virulent cancer that kills approximately 12,000 Americans every year — 60 percent of whom die within two years of diagnosis. Early testing involving primates and human patients has found PVS-RIPO locates cancer cells and destroys them, without harming healthy tissues. Once brain tumors are infected with PVS-RIPO, a patient's immune system recognizes and targets the virus infections and kills the cancer cells. The research is still in Phase I clinical trials, but since 2012, at least five patients have been treated. One 20-year-old woman who was treated is now cancer-free three years after the initial diagnosis.[18,19]

In July, researchers at the University of California, Los Angeles developed a new combination immunotherapy to treat glioblastoma, which works by preventing brain cancer cells from shielding themselves from a patient's own immune responses. In a three-year study, they found that blocking the immune cell's PD-1 surface receptors with antibodies in combination with a dendritic cell vaccine is more effective than either method used alone. PD-1 antibody blockade removes the shield that glioblastomas activate to hide from a patient's immune system; however, the shield doesn't activate a robust enough killer T cell response as the dendritic cell vaccine does. So, combining both the vaccine and antibody blockade provides a more effective immunotherapy.[20]

Lymphoma. In addition to its approval to treat melanoma and lung and kidney cancer, Opdivo also is now approved to

treat Hodgkin's lymphoma. FDA granted accelerated approval to Opdivo in May for classic Hodgkin's lymphoma that has returned or progressed after a specific type of stem cell transplant and post-transplant medicine. In clinical trials of 95 patients with relapsed or refractory disease treated with Opdivo, tumors shrank in 65 percent of patients: 58 percent achieved partial remission, and 7 percent achieved complete remission. The median duration of response was 8.7 months.[21]

Researchers at Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine are testing a cellular immunotherapy for treating patients with diffuse large B-cell lymphoma who have failed standard therapy. The investigational anti-CD19 chimeric antigen receptor T cell therapy, known as KTE-CD19, is being studied in a Phase II clinical trial for patients with aggressive non-Hodgkin's lymphoma. In the trial, the patient's own T cells are collected from peripheral blood and shipped to a special manufacturing facility where they are genetically engineered to display a novel receptor on their surface called a chimeric antigen receptor that enables the T cells to recognize a specific protein present on lymphoma cells called CD19. The modified cells are then returned and transfused back into the patient to target the lymphoma.[22]

Other cancers. An experimental drug is being tested in a small Phase Ib clinical trial to fight a variety of cancers. Pfizer's utomilumab (the proposed nonproprietary name for PF-05082566) targets the 4-1BB (also called CD137) agonist in combination with Keytruda, a PD-1 inhibitor, in patients with advanced solid tumors. Researchers are hopeful that combining the drugs, one that takes the brakes off the immune system with one that hits the accelerator, will offer long-lasting protection against cancer without adding serious side effects. In the trial of 23 patients with advanced pancreatic, colorectal, kidney, thyroid and two major forms of lung cancer, six experienced complete or partial responses, and one patient with small cell lung cancer and one with kidney cancer experienced complete remission. Utomilumab has already shown encouraging early results against a form of blood cancer when used with Roche's Rituxan.[23]

Also being studied is an immune-strengthening compound combined with radiation therapy to extend the immune response that the radiation therapy induces so that both irradiated tumor sites and tumors outside the radiation field are affected. Researchers treated mice with radiation in combination with L19-IL2, a combination of an antibody that targets tumor blood vessels and a cytosine, a small protein involved in cell signaling in the immune system. After treatment, mice were tumor-free. In addition, when the treated mice were re-injected with cancer cells 150 days after treatment, they did not form new tumors. In contrast, 100 percent of untreated mice formed new tumors. There was also an increase in the number of cells with an immunological memory. A Phase I/II clinical study in humans has been started to look at the combination treatment in patients with oligometastic solid tumors.[24]

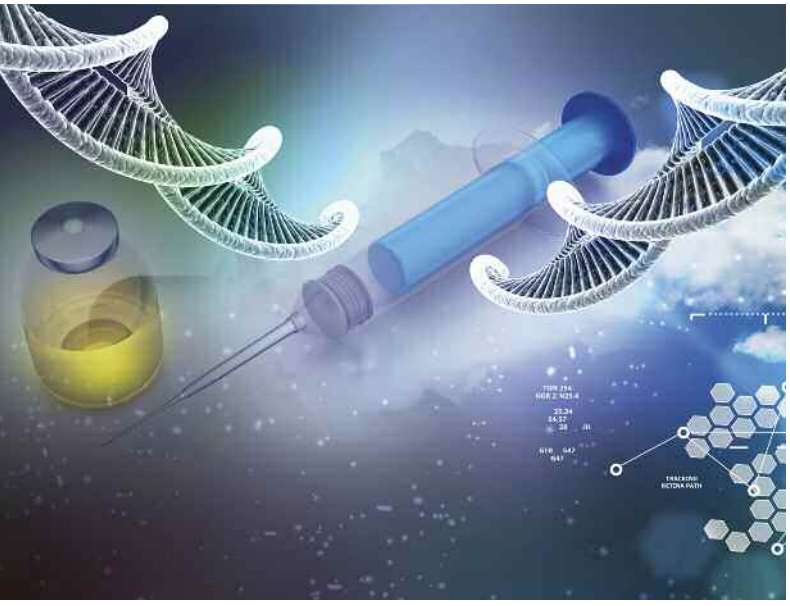
Using the Body to Fight Cancer: The Power of Cells and Proteins

Researchers are also making new discoveries that explain why some therapies don't work as well as they should, and that could provide potential for targeted immunotherapies.

Scientists at Dana-Farber Cancer Institute have developed a new approach that incites an immune system attack on tumors by changing the identity of key immune system cells dispersed throughout the tumor. Known as T regulatory (Treg) cells, they ordinarily prevent the more combative T effector (Teff) cells from attacking the tumor. But, researchers showed that eliminating a key protein in Tregs makes them so unstable that they become Teffs and join in destroying the tumor. While conversion from Tregs to Teffs occurs only in the inflammatory conditions that prevail in many tumors, when embedded in normal tissue through the body, Tregs continue to have a restraining effect on their local Teffs, which protects healthy organs from attack. A previous study showed that Tregs maintain their immune-suppressive properties under inflammatory conditions as long as they have high enough levels of a protein called Helios. When deprived of sufficient Helios, Tregs lose stability and turn into Teffs.

In the study, researchers explored whether converting Tregs to Teffs could be harnessed for therapeutic purposes in cancer. In the first experiment, they injected melanoma or colon cancer cells in mice engineered to lack Helios in their Treg cells and found that they developed tumors far more slowly than did animals with normal Treg cells. "Inspection of the animals' tumor tissue showed an unstable set of T regulatory cells, many of which had converted into Teffs," said senior author Hye-Jung Kim, PhD. They then explored whether stopping Helios production in tumor-dwelling Tregs could have the same effect by testing several antibodies that bind to key receptors on Tregs and cause a downturn in Helios production. Choosing an antibody that worked well, they tested it in mice and found the antibody had triggered conversion of Tregs to Teffs. The next step is to conduct a clinical trial using the approach in patients.[25]

T cells can also play a role in chemotherapy resistance in ovarian cancer patients. The tumor microenvironment is made up of many cell types, but the bulk tissue comprises effector T cells and fibroblasts. In a study at the University of Michigan, researchers looked at tissue samples from ovarian cancer patients and separated the cells by type to study the tumor microenvironment



in vitro and in mice. They then linked their findings back to actual patient outcomes. Ovarian cancer is typically treated with cisplatin, a platinum-based chemotherapy. They found that fibroblasts block platinum, preventing it from accumulating in the tumor and destroying it. T cells, on the other hand, overruled the protection of fibroblasts. By adding the T cells to the fibroblasts, they found that tumor cells began to die off. And, by boosting the effector T cell numbers, the researchers were able to overcome the chemotherapy resistance in the mouse model. They also used interferon, an immune cell secreted cytokine, to manipulate the pathways involved in cisplatin. In essence, by re-educating the fibroblasts and tumor cells with immune T cells after chemoresistance develops, the same chemotherapy can be used because it's effective again.[26]

Another way of making cancer cells more sensitive to chemotherapy is with a fasting-like diet. Researchers at the University of Southern California found that a fast-mimicking diet, when used with chemotherapy drugs, raises the levels of bone marrow cells that generate immune system cells such as T cells, B cells and natural killer (NK) cells that infiltrate tumors. In their mouse study, the researchers also found that the T regulatory cells that protect cancer cells were expelled. They traced this effect to a weakened enzyme, heme oxygenase-1 or HO-1, inside the T regulatory cells' mitochondria. HO-1 levels have been found to be elevated in tumors and are linked to several types of cancer.

The researchers examined the effects of a fast-mimicking diet on breast cancer and found that putting the mice on four days of the diet with chemo drugs doxorubicin and cyclophosphamide was as effective as two days of a water-only, short-term starvation diet. Both diets with the drugs slowed the growth of tumors while protecting healthy, normal cells. Similar effects were found with melanoma. They also found three cycles of the fasting diet combined with doxorubicin prompted a 33 percent increase in the levels of cancer-fighting white blood cells and doubled the number of progenitor cells in the bone marrow. The cancer-killing cells were also more effective at attacking and shrinking the tumors. In addition, the researchers found that short-term starvation and the low-calorie fasting-like diet in mice reduced the expression of the HO-1 gene in the T regulatory cells, making it easier for the chemotherapy drugs to attack the cancer.[27]

A new method of developing drugs that manipulates the immune system to fight cancer has also been developed by scientists at Rockefeller University's Laboratory of Molecular Genetics and Immunology. Specifically, they developed a new mouse model to create drugs that target CD40, a protein present on certain immune cells that functions to activate them. To date, attempts to develop antibodies targeting CD40 have been disappointing.

The scientists started by creating mice whose immune systems more closely mimic those of people. The new mouse model expresses the human versions of both the CD40 protein and Fc receptors, a group of proteins expressed in immune cells that bind to the back side of antibody molecules in a region known as the Fc domain. They then looked for antibodies that bind them more tightly. They found that engagement of a certain human Fc receptor called FcRIIB is essential for the therapeutic activity of human CD40 antibodies, whereas engagement of a different receptor called FcRIIA compromises their activity. "We found from our study that current antibodies under development don't fully utilize the potential of the CD40 approach," said Rony Dahan, a postdoctoral fellow at the lab. "We have used our new model to identify and select new Fc-engineered CD40 antibodies that have significantly enhanced antitumor activity. We then advanced the most promising candidate into clinical trials of various solid tumor types."[28]

Another method of using the body's immune system to develop new immunotherapies that better fight cancer has been found by researchers at the Walter and Eliza Hall Institute of Medical Research in Parkville, Victoria, Australia. By switching off the protective measure that stops the body's NK immune cells from attacking human tissue, they were able to drastically reduce tumor growth in mice. NK cells are specialized white blood cells that locate and kill deviant cells by releasing a chemical called perforin that blasts holes in its outer membrane and causes the cells to fall apart or self-destruct. But, the body's immune system also possesses checkpoints to protect healthy tissue. The researchers discovered a particular checkpoint with an inhibitor

protein made inside the cells that limited their ability to respond to the NK cells' command to kill cancer.

In their study, they found that by silencing the inhibitor protein's gene, the ability of NK cells to protect mice against melanoma, prostate cancer and breast cancer was increased. After 14 days, melanoma mice without the genetic modification had extensive tumor growth in their lungs. In contrast, metastatic growth was largely absent from mice with boosted NK cells. Mice with prostate cancer responded in a similar way. And, those with breast cancer showed that despite some microscopic spread to the lungs, there was no sign of the large metastases that would normally be observed. "This is about learning how to activate the NK cells of the individual patient and boost their immune system to tackle the disease," said lead scientist Dr. Nicholas Huntington. "We are hopeful our research will lead to new immunotherapies that supercharge the body's natural killer cells and maintain it in a highly active state to more efficiently and specifically fight cancer."[29]

Another discovery by a team of researchers at the Duke Human Vaccine Institute and Duke medical faculty has resulted in the creation of a recombinant antibody, mAb7968, that can target the human protein complement factor H (CFH), which is abundant in tumor tissues and is believed to play a role in stifling an immunological response to malignant cancer cells. To develop the antibody, scientists examined early-stage tumors in lung cancer patients that never progress and noticed that, when compared with more lethal tumors, the patients possessed antibodies against CFH. After identifying the antibody for CFH, they extracted it from human tissue and modified it to enhance its function. The newly engineered antibody could induce toxic conditions in more than nine cancerous cell lines and, consequently, kill many of those cells without any noticeable side effects. "This could represent a whole new approach to treating cancer, and it's exciting because the antibody selectively kills tumor cells, so we don't have significant side effects to achieve tumor control," said Edward Patz, Jr., professor at Duke University and senior author of the study. "We believe we can modulate the immune response and let the body's own immune system take over to either kill the tumor or keep it from growing."[30,31]

Lastly, researchers at the University of Eastern Finland and Eberhard Karls Universitat Tubingen in Germany have discovered a new molecular mechanism that can inhibit the growth of hepatocellular carcinoma, the most common liver cancer. Their study found that mouse and human liver cancer in which the function of the protein p53 is disturbed or inhibited is dependent on the interaction between the Aurora kinase A (AURKA) and MYC proteins. Using a specific drug molecule to interfere with the AURKA protein causes cancer cells to die. These findings, they say, can be used to develop treatments.[32]

Vaccines and Gene Therapy

Because cancer vaccines and gene therapy can sometimes interfere with the growth of specific cancer cells, they are often considered targeted therapies.

Preventive cancer vaccines have been available for some time, the first of which was approved in 1981. There are two types of cancer for which vaccines are approved: human papillomavirus and hepatitis B virus.[33]

Two cancer treatment vaccines are FDA-approved in the U.S. In April 2010, Provenge (sipuleucel-T, Dendreon) was approved for metastatic prostate cancer. Provenge stimulates an immune response to prostatic acid phosphatase, an antigen that is found on most prostate cancer cells. In clinical trials, it increased the survival of men with a certain type of metastatic prostate cancer by about four months. Unlike other cancer vaccines, which are only available in clinical trials, Provenge is customized to each patient. Then, in October 2015, FDA approved Imlygic (talimogene laherparepvec, Amgen) for the treatment of some patients with metastatic melanoma that cannot be surgically removed. Imlygic works by infecting or lysing cancer cells when injected directly into tumors, but it also induces responses in noninjected tumors.[34]

Cancer treatment vaccines work by boosting the body's natural defenses to fight cancer. They're designed to prevent cancer from coming back, destroy any cancer cells still in the body after treatment and stop a tumor from growing or spreading. But developing them is difficult for several reasons: 1) cancer cells suppress the immune system, which is how cancer is able to develop and grow (researchers are using adjuvants to try to fix this issue); 2) cancer cells develop from a person's own healthy cells, which means cancer cells may not look harmful to the immune system, causing the immune system to ignore them; 3) larger or more advanced tumors are hard to get rid of using only a vaccine, which is why other treatments are used in conjunction; and 4) people who are sick or older can have weak immune systems, so their bodies may not be able to produce a strong immune response after vaccination.[34]

Despite these drawbacks, there are many vaccines currently being tested in clinical trials. One in particular has recently been shown to kill tumors and keep them from coming back. In development by Intensity Therapeutics, the INT230-6 vaccine is composed of two chemotherapy drugs that are injected into tumors to kick-start the immune system to fight back. In preclinical studies, "injection of INT230-6 into large colon cancer tumors in mice caused tumor shrinkage in 100 percent of the subjects, with up to 80 percent experiencing a complete response. Complete responders further experienced an immunologically based, durable vaccine-like effect that protected the ani-

mals from multiple re-inoculation challenges using the same colon cancer cell type." According to Ian Walters, MD, of Intensity Therapeutics, "Even though we are using chemo, this works on the immune system. The tumors die from the inside out. When that happens, the immune cells can 'see' that it's cancer and form an extremely powerful immune response. It's almost a personalized vaccine."[35,36]

Another cancer treatment vaccine that has been in development for more than 20 years is Morphogenesis' ImmuneFx. It is an autologous cancer vaccine made from each patient's own cancer cells that are typically collected at the time of surgery when the tumor is removed. While the vaccine is not approved for use in humans, a version of it called IFx-VET is approved by FDA for use in animals, mostly in dogs and horses.[37] In fact, at the Cancer Moonshot summit held at Howard University in Washington, D.C., in June, a golden retriever diagnosed with melanoma in her mouth attended as an example of the vaccine's success in conjunction with radiation.[38]

> "The war on cancer will not be won in one dramatic battle. It will be a series of skirmishes."

Ultimately, what could be most promising is a "universal" cancer vaccine, which is also a type of personalized gene therapy that is being actively pursued. Researchers from Johannes Gutenberg University have developed a potential universal cancer vaccine based on the immune system's natural responses to viral infection. In early experiments in mice and three human patients with advanced melanoma, the vaccine, which consists of nanoscale poison darts with RNA payloads, was able to induce specific anti-tumor immune responses. RNA darts introduce genetic material that mimics a virus. In response, dendritic cells produce cancer-specific antigens that prompt a T-cell response directed against progressive tumors — those that otherwise would be treated as normal by the immune system. According to professor Ugur Sahin, who is lead scientist in the study, "Virtually any tumor antigen (protein) can be encoded by RNA. Thus, the nanoparticulate RNA immunotherapy approach introduced here may be regarded as a universally applicable novel vaccine class for cancer immunotherapy."[39,40]

Another promising gene therapy tool may be tested in humans in the very near future. Known as CRISPR, the gene-editing tool that rewrites immune system DNA, has won approval to proceed with its first human tests from the Recombinant DNA Advisory Committee, a federal ethics panel at the National Institutes of Health that reviews controversial experiments that change the human genome (the trial still needs final approval from FDA). Scientists from the University of Pennsylvania want to use CRISPR to edit the immune systems of 18 patients to target difficult-to-treat cases of multiple myeloma, sarcoma and melanoma. If the trial proceeds, the scientists will remove blood samples from patients, alter their T cells and then infuse them back into patients to evaluate the safety and effectiveness of the technique.[41]

Several Phase III gene therapy clinical trials that hold promise are also currently underway, including:

- Advantagene is using Gene Mediated Cytotoxic Immunotherapy (GMCI) ProstAtak therapy, which uses an adenovirus vector to deliver a herpes simplex virus thymidine kinase (tk) gene to tumor cells at the site of the injection. The tk gene works as a "suicide gene" that enzymatically converts a nontoxic, antiviral drug Valacyclovir into a cytotoxic drug that causes tumor cell death during radiotherapy.
- VBL Therapeutics is using its Vascular Targeting System known as VB-111 to treat recurrent glioblastoma multiforme. The gene therapy targets a highly malignant type of angiogenic brain tumor that generates vasculature tissue in a process known as angiogenesis. It is intended to be used in combination with chemotherapy and radiotherapy.
- Cold Genesys' adenovirus-mediated oncolytic gene therapy is targeting invasive bladder cancer. Similar to T-Vec, the CG0070-modified virus contains a cancer-specific promotor sequence and GM-CSF-encoding sequence that selectively lyses cancer cells and releases GM-CSF antigen to train the immune system.[42]

Targeting Drugs to Patients

With so many cancer treatments on the horizon, an additional problem still exists: No two cancers are the same, which means no two cancer patients respond the same to medication. Therefore, to prescribe the correct combination and dosage of drugs, physicians need a better understanding of the specific characteristics of each patient's cancer.

Enter CANScript, Mitra Biotech's promising technology that can rapidly test the impact of drugs on a cancer patient by examining a tiny tumor sample in a lab. Removed during a biopsy, the tumor tissue is tested with multiple drugs to replicate a patient's reaction to the medications. CANScript measures a

number of parameters, including tumor cell death, cell shape and structure and rate of tumor growth, to assign a single numeric score to a particular drug or combination of drugs. The higher the score, the greater the chance of tumor burden reduction.

In a study of CANScript conducted in 2015, the microenvironment of 109 patients suffering from head and neck squamous cell carcinoma and colorectal cancer was recreated. Researchers then tested the response of a set of drugs on the tumors, from which data were used to shape a predictive model. The model was then tested on a group of 55 patients with one of the cancers and treated with the same drugs. In the test, CANScript correctly predicted each cancer patient's response to the treatment.

CANScript delivers results with seven days at a cost of approximately $600.[43]

Declaring War on Cancer

Clearly, revolutionary advances are being made in the war on cancer. According to Vice President Joe Biden, who is spearheading the Obama administration's "moonshot" to cure cancer, the science is ready. "But the science, data and research results are trapped in silos, preventing faster progress and greater reach to patients. It's not just about developing game-changing treatments; it's about delivering them to those who need them," explains Biden. "Right now, only 5 percent of cancer patients in the U.S. end up in a clinical trial. Most aren't given access to their own data. At the same time, community oncologists — who treat more than 75 percent of cancer patients — have more limited access to cutting-edge research and advances." Biden's task, then, is to increase public and private resources to fight cancer and bring together researchers, philanthropists, Big Pharma and insurers. The federal effort will also fund research into how different immunotherapy treatments work in combination with one another, as well as efforts to improve prevention and early detection. However, says Massachusetts Institute of Technology cancer researcher Robert Weinberg: "The war on cancer will not be won in one dramatic battle. It will be a series of skirmishes."[44] ❖

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USING GENOMIC DATA TO PERSONALIZE CANCER TREATMENTS

By Enakshi Singh

LEADING RESEARCHERS in biomedicine have made tremendous progress in developing new ways to collect and analyze mass volumes of biomedical data, including DNA sequence data. Today, researchers are using genomics research to better understand how genetic variation contributes to human health and disease.

While a number of large-scale genomic projects are underway, collecting genomic data is only one step of the process. Ultimately, in-memory computing technology is needed to analyze and interpret mass amounts of genomic data. In order to derive meaning out of the chemical base pairs that make us who we are, genomic data must be combined with clinical data and include diagnoses and symptoms of individuals. By integrating genomic data with clinical data, scientists can determine associations between regions of the genome and the predisposition to certain diseases like cancer.

Why Cancer?

Cancer is among the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer-related deaths in 2012, according to the World Health Organization.

According to Bill McDermott, CEO of SAP, a company developing technologies to help defeat cancer: "Fighting cancer is fundamentally a data challenge." By developing common data standards in medicine and using big data analytics, research centers and physicians will be able to identify better treatment plans and individualized care for cancer patients.

Applying Genomic Data to Individualize Treatment

Through the use of in-memory technology, large-scale genomic variant data has been analyzed in near real-time, revolutionizing the work mode of researchers. Instead of waiting hours or days for their analyses to return, researchers can now interactively ask more and more questions of the data. Once collected, that sequencing data can be shared with physicians to help them make informed decisions and devise more individualized cancer treatment plans.

Personalized Pharmacogenomics

Pharmacogenomics, the study of how genetic variation contributes to an individual's response to drugs, is another

example of how genome testing can influence clinical decisions. Researchers have identified a few hundred genes in an individual that are related to drug metabolism, and they are continuing to identify more. The Clinical Pharmacogenetics Implementation Consortium released guidelines for prescribing drug dosing or alternative drug recommendations for individuals expressing certain genetic variation. With a relatively inexpensive genome-based drug metabolism test (ranging from $200 to $500), a doctor can determine the rate at which an individual can metabolize specific classes of drugs, including cancer drugs.

Education and Overcoming Roadblocks

While genomic sequencing and big data analytics have started to change the way oncologists can treat cancer, many roadblocks remain. Researchers are still discovering new associations between genetics and disease, and while the sequencing itself can be completed within one day, processing and analysis can require a team of genetic researchers to manually map and interpret the data. The processing and analysis of genomic data has not yet been standardized, but the precision U.S. Food and Drug Administration program, currently in beta mode, provides a platform where researchers can validate their processing pipelines for genomics data. In addition, in certain situations, genome sequencing is covered by only some insurers or coverage exists for only a small number of specific genetic tests.

An Improved Sequence in Cancer Care

Despite these challenges, the potential for affordable genome sequencing tests and in-memory computing to revolutionize cancer treatment is enormous. Providing personalized care and individualized drug therapy for patients can significantly improve outcomes and reduce the overall cost of cancer care.

As the data pool grows, researchers and doctors will gain more insights from genome testing. They will be able to carve out precision-based treatments by making sense of vast amounts of available DNA data, ultimately improving the lives of millions of people fighting cancer around the world. ❖

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STEM CELL THERAPIES:

THE ERA OF REGENERATIVE MEDICINE?

Advancements in stem cell therapy may soon eliminate surgeries and cure disease, but first, the debate between two different schools of thought concerning how best to proceed needs to be resolved.

By Meredith Whitmore

MEDICINE THAT WAS once seen only in science-fiction fantasy is gradually becoming a reality. Tracheas have been generated in laboratories and successfully implanted in humans for several years. In clinical trials around the world, advances are being made against various diseases, including retinitis pigmentosa,[1] severe combined immunodeficiency (SCID)[2] and age-related macular degeneration.[3] There are hopeful signs that patients may one day prevail against these now-debilitating conditions. On other fronts, multiple sclerosis patients treated with stem cells are showing remarkable results as well,[4] and stroke and traumatic brain injury victims are beginning to gain a bit of the functionality they lost after their injuries.[5]

Thanks to stem cell research and therapies, all of these marvelous results are within our reach — and much more progress is expected in coming years within this still somewhat fledgling industry.

Advances in this field, however, require considerably more research and funding, and more often than not, both are limited. Debates about the ethics and proper use of stem cell therapies, meanwhile, abound.

A Revolutionary Treatment

It's no wonder disagreements exist among researchers, academics and physicians regarding regenerative medicine. Stem cell therapies are an entirely different ideology from anything used before, and protocols and methodologies are still being developed. With biologics and more traditional medical procedures, doctors are essentially trying to "patch up" harm done by a disease or a traumatic injury to ease symptoms — not wholly cure the illness or regenerate tissue itself. With stem cell therapies, however, the paradigm shifts to tissue restoration as the primary goal. In diseases such as cystic fibrosis, for example, physicians hope to eventually restore lung tissue within diseased lungs,[6] not merely rein in a patient's symptoms or try to keep a damaged lung functioning. The goal is to develop therapies to a point where physicians and researchers don't merely stop a disease from progressing, but actually turn back time in a sense and renew an organ so a patient has improved or even complete use of it.

The Basics of the Field

A bit of context lays the scaffolding for further discussion. First, at a most basic level, stem cells are crucial, unspecialized cells within every person's body. Capable of self-renewal (not merely duplication) and differentiation into other types of cells, stem cells continually repair and maintain all tissues in the body. Without them, we might live only a few hours because our other cells would have nothing to replenish them. When we exercise, for example, the microscopic tears made in our muscles are healed by stem cells, a process that gradually increases the muscle's strength as we exercise over time. Stem cells are, in fact, continually doing this type of healing in every tissue of a person's body. It's that type of regenerative power that doctors and researchers seek to harness and enhance to apply to diseased and wounded tissue. Our bodies are already reasonably effective at healing themselves in many cases, but researchers strive to focus and accelerate the process.[7]

It's their self-renewal and differentiation abilities that make stem cells so exciting to the medical field. Beyond these two features, various types of stem cells have different abilities. Embryonic cells, for example, are pluripotent (capable of becoming virtually any type of cell), while adult cells are multipotent (still capable of some differentiation, but more limited). Induced pluripotent stem cells (iPS) are relatively new and very exciting to researchers because they are reprogrammed adult cells that have already been differentiated into a specific cell. Once they are reprogrammed in a lab, iPS cells have virtually the same ability as embryonic cells to be pluripotent. Which cells are used for treatment in clinical trials depends largely on a patient's needs.[8]

In some cases, stem cells come autologously from a patient's own body, and in others, a donor offers allogeneic transplant. Increasingly, multipotent adult cells are used autologously, taken from a patient's own bone marrow, fat, skin, blood and even teeth. Once drawn through autologous or allogeneic means, stem cells are then enriched by methods as simple as centrifugation or cultivation through petri dishes and agar. The resulting product is then injected, infused or surgically transplanted into a patient's body at the site of disease or injury.[7]

Stem cell therapies are an entirely different ideology from anything used before, and protocols and methodologies are still being developed.

Two Schools of Thought

Dr. Kristin Comella, chief scientific officer and board member of U.S. Stem Cell, Sunrise, Fla., says there are two groups of scientists advancing stem cell therapy today. In one camp are the academic researchers, and in the other, the physicians who want to bring stem cell therapies directly to clinics without so much regulation. Comella claims the latter camp. "The university scientists," she explains, are "those who are very interested in doing extensive research and want a lot of animal testing before any stem cell therapy becomes mainstream and is brought to humans. But we want to bring stem cell therapy directly to clinics, using it through physicians rather than going through pharmaceutical companies. I want these therapies to be considered similar to surgeries or medical procedures as opposed to drugs in the hands of pharmaceutical companies."

"There's a debate right now about the safest and the best way to bring stem cell therapies forward," adds Dr. Comella. "In our camp, we say: 'We shouldn't withhold these therapies from patients. Patients have a right to use their own tissue and use

their own bodies' potential to heal them of diseases, especially diseases that have no other [treatment] option.' We see these patients' fear and illness and realize that, without using experimental stem cell therapies, there is little to nothing we can do to help them. We believe patients who are otherwise given a death sentence have a right to try an experimental procedure. And, they can provide informed consent and do it."

Kevin McCormack, senior director for public communications and patient advocate outreach at California Institute for Regenerative Medicine (CIRM), a stem cell research funding organization, explains: "The FDA [U.S. Food and Drug Administration] has very clear guidelines about what it considers a medicine or a treatment. And that is, if you take stem cells from someone, that usually involves taking some fat, putting it through a centrifuge to isolate the stem cells and then reintroducing those cells into them — say their knee to help repair damage. The FDA says that is something 'minimally manipulated' and allowable if the procedure is done at the same time. If, on the other hand, you take those same stem cells, isolate them through a centrifuge, and I return a week or so later to receive them somewhere other than my knee, then the FDA would say that's not the same procedure, so therefore it certainly counts as something inappropriate and unallowable. The FDA's rules are a little bit gray, which is why clinics have popped up all over the country offering all types of therapies that are unproven and unlicensed. So there's some confusion there. In terms of CIRM's standards, absolutely, we believe that stem cells are something that need to be regulated and thoroughly tested in a way that ensures the safety of patients, which is always our prime concern."

Though early stem cell researchers believed embryonic tissue was the most effective, science has since proved otherwise.

However, adds McCormack, "The FDA evolved regulating biologics, and stem cell therapies are an entirely new field. The FDA's rules haven't evolved at the same rate as medical development has, so they're trying to make the old system fit an entirely new paradigm, and it's not a good fit. That's why we think there needs to be reconsideration. There needs to be a re-evaluation of how this can best be done."

Current Uses and Research

Despite the excitement regarding clinical trials of stem cell therapies, it's crucial to remember that FDA has not yet approved any stem cell-based products for use beyond "cord blood-derived hematopoietic progenitor cells (blood-forming stem cells) for certain indications."[8] But current research truly is promising and exciting.

For example, as alluded to earlier, Canadian doctors Harold Atkins, a bone marrow transplant specialist, and Mark Freedman, a neurologist, were very aggressive in a clinical trial that involved killing multiple sclerosis patients' damaged immune systems with chemotherapy, then injecting modified autologous stem cells to "reboot" their bodies. *The Lancet* reports that the treatment "halted clinical relapses and development of new brain lesions in 23 of 24 patients with multiple sclerosis," and "eight of the 23 [remaining] patients had sustained improvement in their disability over 7.5 years."[4]

Besides this, University of California, Los Angeles stem cell researcher Dr. Don Kohn has cured 18 SCID children by removing stem cells from their bone marrow, genetically modifying them to correct the defect and reintroducing them to the children's bodies.[2]

And Dr. Damien Bates, chief medical officer and head of research at SanBio, Inc., says he is pleased with the findings from a recent clinical study on stroke and traumatic brain injury patients. Dubbed a Phase I/IIa clinical study, the dose escalation trial involved 12 subjects from Stanford University and six from the University of Pittsburg Medical Center.[5] The most-improved patients who regained impressive functionality overnight after receiving stem cell injections in their brains were interviewed on several news programs. The media quickly proclaimed the results "miraculous." Cautiously, however, Dr. Bates says, "I am excited that some patients have improved dramatically, but I think we all need to be careful not to overstate any claim at this stage; we've got a long way to go with these additional studies that are much more rigorous, and then mandated by the FDA, before we can make any definitive conclusions about the efficacy of the product."

It's important to note that Dr. Bates is not the only cautiously optimistic researcher. In his blog "The Niche," University of California, Davis stem cell scientist Paul Knoepfler, PhD, writes: "Stem cells are not a cure-all. I am as excited as anybody about the potential of stem cells to treat a whole bunch of diseases and injuries, but they are not some kind of miracle cure for everything."[9]

Dr. Comella has a different perspective entirely on research, however, because she is rarely able to do it. "To do large double-

blind placebo-controlled trials to determine whether or not these are safe and effective treatments for patients requires quite a bit of funding," explains Dr. Comella. "As an example, to do 100 patient trials would cost $10 million, and the FDA requires, typically, thousands of patients, which could cost hundreds of millions of dollars to bring these therapies forward in the traditional drug-approval process. Really, the only people who can afford those trials are big pharmaceutical companies. In this case, where physicians are getting stem cells from the patients themselves, there's no drug to patent, there's no drug to bottle, so Big Pharma is not going to be interested in paying for these clinical trials. As a result, there's no funding for us to do the clinical trials, and we're caught in a catch-22. Yes, I would love to do clinical trials to demonstrate that these therapies work, but I don't have the funding to do it, and Big Pharma's not going to do it because there's no product for them to sell at the end."

Ethical Questions

Embryonic and fetal tissues have been used in science for decades, yet many people remain uncomfortable with that fact for religious or moral beliefs. Induced pluripotent stem cells, of course, have the potential to lessen the ethical concern. It remains to be seen, though, whether iPS will be a long-term viable option that can completely replace embryonic cells. Still, the issue may be at least somewhat resolved since Dr. Robin Smith, president of the Stem for Life Foundation, says that, though early stem cell researchers believed embryonic tissue was the most effective, science has since proved otherwise. She adds that today there are more than 5,000 clinical trials using adult stem cells and fewer than 50 using embryonic cells.[10]

And, at a 2015 stem cell conference at the Vatican, at which CIRM president and CEO Randy Mills was invited to attend, the Pope himself expressed his belief that stem cell research is crucial to saving lives. Though the Catholic Church condemns use of embryonic stem cells, it upholds the belief that stem cell research is morally upright when using adult cells.[11]

Future Possibilities

Dr. Comella holds nothing back when she envisions stem cell therapies of the future: "I see a combination of all the different types of regenerative medicine, so cell and gene therapies combined, also incorporating stem cell therapies with any surgical procedures. One day, we might even be able to eliminate many surgical procedures. Many knee replacements that are happening today could be unnecessary because, in the future, we'll be able to just repair the tissue. Certainly, any arthroscopic surgeries on the knee will become outdated very rapidly. [Clinical data] is already indicating that the long-term effects of such surgeries are not good. We don't have to cut such tissue out. Leave it in. Repair it. That can be applied to not just orthopedics, but many different indications.

"We are doing a lot of these things right now, so the future of medicine is here. We're treating neurological disorders and getting some amazing results. We're treating orthopedic problems, autoimmune problems, different degenerative diseases. By placing stem cell therapy in the hands of physicians who are actually seeing the patients, and doing this day in and day out with patients, we can move rapidly into cures for patients."

Dr. Bates holds an equally optimistic view: "I think the future of stem cell therapy is really exciting, and I've basically devoted my life to it. I'm a plastic and reconstructive surgeon, so my whole life I've been involved with wound repair and tissue healing. Trying to understand the biology behind why some animals can regenerate entire limbs and eyes and we humans can't is fascinating. I think stem cells are the one potential avenue to try and trigger that regenerative potential that we have. I did my PhD in embryology, and we know that up to the third trimester, fetuses have the ability to, not regenerate entire limbs, but heal their wounds with no scarring, which is just phenomenal. Why do we lose that potential as we get older? We don't fully understand that, but if we can tap into that regenerative potential and heal our tissues so we can produce functional tissue without scarring, then that's amazing. I think that's the Holy Grail, and I think that most companies, including SanBio, are working toward that. Whether stem cells are the definite answer remains to be seen, but stem cells are an area of huge focus by a lot of different companies at the moment." ❖

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Real-Time Healthcare Monitoring

Mobile health technology is changing the way patient data is gathered and accessed, using real-time analytics to improve outcomes and quality of care.

By Trudie Mitschang

WHETHER A PATIENT is being discharged from the hospital, living with a chronic disease or simply expecting a baby, the need for ongoing healthcare monitoring is real, potentially inconvenient and often costly. While providers have typically relied on the patient or caregiver to gather data and provide progress reports, asking a recovering patient or family member to take and accurately report vitals like blood pressure and heart rate is a less-than-optimal follow-up plan. Thankfully, emerging mobile health technology is now allowing doctors to see real-time data on individuals in their care, often without the patient or caregiver having to manually record or transmit it. The rapidly expanding market for these monitoring systems is showing promise for use with patients who span the treatment spectrum from physical therapy, cardiac and stroke to the elderly and homebound. Some applications are even making strides in the area of infectious disease.

"Telemedicine and mobile health will truly change and enhance healthcare delivery in the long run," says George Tierney, co-founder of SnapMD, a virtual care management telemedicine software company. "These technologies are not a silver bullet for the many issues found with access and delivery of healthcare; however, they can play an enormous part in driving down costs and improving quality of care."[1] SnapMD helps healthcare providers extend their reach of care by leveraging secure one-on-one live video, audio and text message consultations between ambulatory patients and their primary care and specialty care physicians. The company was named one of the top-10 telemedicine technology solutions for healthcare providers and their patients by Healthcare Tech Outlook.

Exploring Real-Time Advantages

Remote healthcare monitoring with real-time data offers many advantages to both patient and provider. Used correctly, it can spot health patterns or areas of concern, allowing healthcare professionals to intervene more quickly than if there was a reporting delay. Predictive analytics also allow physicians to compare real-time patient data from monitoring devices to medical baselines, helping them predict which patients are likely to develop complications and need further intervention.

This type of preventive, at-home monitoring could be extremely beneficial not just for patients, but also for the healthcare industry as a whole. According to a recent Goldman Sachs report summarized by *Business Insider*,[2] remote patient monitoring could save more than $305 billion in healthcare costs, largely attributed to monitoring of patients with chronic diseases such as heart disease, asthma and diabetes. The report also states that the healthcare community has been surprisingly open-minded when it comes to exploring this initial wave of digital health solutions that are poised to bridge "the digital and physical worlds to change physician and patient behavior."

The report also addresses various obstacles to implementation of digital healthcare, patient and doctor acceptance, reimbursement concerns and U.S. Food and Drug Administration (FDA) regulations. "The FDA has laid out definitive guidelines surrounding regulation of digital health and pathways to approval," the report states. "In general, the organization will intervene in cases where mobile applications make medical recommendations and affect the treatment of various illness. The FDA has already approved over 100 digital health applications to date."[2]

Improving Quality of Care

Improving quality of care for patients is a significant benefit of real-time health monitoring. Flagstaff-based Northern Arizona Healthcare has pioneered a program called Care Beyond Walls and Wires that is expanding the reach of its healthcare services into underserved rural communities with outstanding results. The program monitors patients using a smartphone application and customized medical devices that vary by condition. Data from the devices is then captured in the app and automatically sent to the patient's medical providers, who can then review it for warning signs or concerning patterns. A controlled study of the first 50 patients in the program showed an estimated $92,000 in savings per patient over a six-month period, as well as significant decreases in the rate of hospitalizations and days spent in the hospital.[3] "This project launches a model of care that transcends traditional medicine, using state-of-the-art technology to care for patients beyond the walls of the hospital," says William Bradel, Flagstaff Medical Center (FMC) president and CEO. "Working with these technology companies and national health agencies will extend FMC's reach into outlying areas where healthcare is most needed."[4]

The idea for the program originated with the National Institutes of Health Office of Public and Private Partnerships, which was looking for better ways to monitor patients with congestive heart failure (CHF) in rural areas. The goal was to provide better care while keeping the patients out of the hospital, thus reducing healthcare costs. San Diego telecommunications company Qualcomm was chosen to lead the project, with Maryland-based Zephyr Technology and Verizon providing software, smartphones and remote-monitoring hardware. "Our mission is to transform the health of the communities we serve," says Bradel. "This program will dramatically extend the delivery of healthcare by giving our CHF patients the tools to stay connected to a nurse at FMC, regardless of how close they are to the hospital."[4]

Improving quality of care for patients is a significant benefit of real-time health monitoring.

Real-time healthcare monitoring is also being used by researchers at the Scripps Translational Science Institute (STSI) in La Jolla, Calif. In 2015, the institute launched a home-based clinical trial that used wearable sensor technology to identify people with asymptomatic atrial fibrillation (AFib). According to the Centers for Disease Control and Prevention, as many as six million Americans live with AFib, an irregular heartbeat that

can lead to a five-fold increased risk of stroke and other severe health-related complications. In fact, one in three people with AFib will have a stroke in their lifetime, making it a significant health burden worldwide. With as many as 30 percent of all cases of AFib undiagnosed, more effective methods of screening are needed to help reduce AFib-associated mortality, morbidity and costs.[5]

The purpose of the STSI study was to determine whether screening select individuals in their homes using wearable sensor technology could identify people with asymptomatic AFib more efficiently than routine care such as regular visits to a primary care physician to address general health issues. "This is a uniquely targeted and participant-centric trial that takes full advantage of digital technologies, including large medical data sets and wearable sensors," says Steven Steinhubl, MD, director of digital medicine at STSI and principal investigator of the trial. "Once completed, it has the potential to truly change the practice of screening and markedly improve outcomes."[5]

As telemedicine becomes increasingly common, universal access to data will prove to be a crucial element in future healthcare delivery systems.

Researchers say this type of technology is especially promising since it can be customized not only for specific patient needs, but also for unique conditions and infectious diseases. STSI is currently testing monitoring technology that will help workers provide quality care to Ebola patients without putting themselves at risk of contracting the disease. The project will use a sensor similar to an adhesive bandage to take patients' vital signs with two wireless monitors. Through this method, early signs of the disease can be detected while minimizing staff exposure to the virus.[6]

Big Data and the Changing Face of Healthcare

When it comes to healthcare, the increasingly popular term "big data" refers to a wide-ranging combination of clinical, genetic and genomic outcomes, claims, social and other data that are collected from multiple sources in an effort to give physicians a more comprehensive, detailed medical picture of their patient population. By most accounts, increased access to and use of big data is a decidedly big deal. According to an article published by Siemens Healthcare, "Big data will transform approaches in healthcare that have long defined the industry. No longer will we pool data from individuals to predict what happens at the population level. Instead, population data will be so comprehensive that it will accurately predict what happens to an individual patient."[7]

As telemedicine becomes increasingly common, universal access to data will prove to be a crucial element in future healthcare delivery systems. In a pilot study of postcolorectal surgery cases, the Mayo Clinic cut complications by half, decreased patient stays and saved $10 million by using a program that identified best care practices, then measured and monitored those metrics in real time.[7]

Big data is also being captured and analyzed for bedside use in the hospital setting. In some cases, analytics can identify a patient's risk of hospital readmission and divert staffing and resources to help prevent it. At SickKids Hospital in Toronto, Canada, infants in the neonatal intensive care unit wear biosensors that collect data thousands of times per second. These biosignals are uploaded and processed in real time for the fastest possible identification of hospital-acquired infections. This type of data access can help the hospital begin treatment as much as 24 hours sooner than if physicians waited until traditional biometrics indicated an infection.[7]

Smartwatches: The Future of Healthcare

The introduction several years ago of the smartwatch, a device that marries the practical advantages of a timepiece with the broad, app-centric benefits of a smartphone, initially limited its health-related content to wrist-based fitness tracking. Those capabilities have grown exponentially, with smartwatches now offering everything from fetal monitoring to the management of chronic conditions.

One device showing promise is the Oxitone watch, a wrist-worn, medical-grade pulse oximeter that continuously measures a person's oxygen saturation, heart rate and respiratory rate. Portable pulse oximeters that provide continuous oxygen saturation readings are already available from a variety of manufacturers, including one that works with an iPhone, but unlike the Oxitone, they all rely on a sensor that clips onto a fingertip or earlobe, presenting a challenge for continuous all-day monitoring. "After investigating the current market situation, we found that while oxygen circulation was being monitored continuously in the hospital, it was an incredibly uncomfortable experience for the patient," says Leon Eisen, PhD, founder and

chief executive officer of Israel-based Oxitone Medical. "At home, people are only capable of having episodic measurements using spot-check monitoring, which doesn't provide continuous measurement for oxygen circulation. People can't wear the fingertip sensor all the time, it's just impossible — it's not comfortable and falls off your finger too easily. Nobody knew how to continuously measure blood circulation, so we decided it was time to move forward."[8]

Dr. Eisen came up with the idea after experiencing a personal family tragedy: His father died from a heart attack just three hours after being released from the hospital. "Wearable devices are the future of monitoring health and will reduce the cost of healthcare," says Dr. Eisen.[9]

The Airstrip App for Apple Watch is another example of smartwatch technology that allows doctors to read a patient's heart rate and other acute health data. The app can also be used to view a patient's health information on the go, and experts say its implications for the healthcare industry could be vast. The AirStrip company founders believe it could help doctors better monitor patients with chronic illnesses, including heart disease, diabetes and even chronic obstructive pulmonary disease, from home. It could also increase the line of communication between doctors and patients, without having patients make a trip to the hospital. In addressing privacy concerns, Cameron Powell, MD, AirStrip's co-founder, says the app complies with HIPAA healthcare privacy laws by requiring users to authenticate themselves, similar to other doctor-to-patient messaging systems already in use.[10]

Another AirStrip app, the Sense4Baby, turns an average smartphone into a fetal monitoring tool for expectant mothers, enabling the mother to look at and hear her baby's heartbeat, then transmit that information in real time to her doctor. This allows the doctor to immediately determine if the unborn baby is in distress or if the mother needs to come in for additional monitoring.[11]

Companies like AirStrip are actively developing new uses for real-time healthcare technology, seeking to connect to a wider variety of medical devices such as blood pressure cuffs and glucose monitoring devices. According to AirStrip CEO Alan Portela, the ability to monitor this type of data in real time will not only help physicians better manage their patients with chronic diseases, but will empower the patients themselves to take control of their health. Next steps include connecting the sensors and smart devices to analytics, which would better enable both patients and physicians to monitor disease progress.[12]

Portela envisions the technology as a sort of go-between to allow doctors to monitor their patients on a more regular basis than the routine follow-ups that many patients with chronic illnesses currently follow. Instead, doctors could monitor patients in real time, and more quickly identify the individuals who are in need of immediate medical care. "It is not just about displaying [the information] in real time," Portela says. "It is really about which clinical problem are we trying to solve."[12]

Smartwatches now offer everything from fetal monitoring to the management of chronic conditions.

Reinventing How Care Is Delivered

Digital technologies have changed the way companies in every business sector innovate, interact and connect with customers. For the healthcare industry, adapting similar technologies has the potential to fundamentally reinvent how care is delivered. In a future where the healthcare delivery system is fully digitized, emerging trends such as telemedicine, portable data-recording devices and mobile apps will become the norm. Properly implemented, remote real-time healthcare monitoring can enhance patient-clinician communication, streamline coordination of care, promote self-management of chronic disease, reduce healthcare costs and improve patient outcomes. ❖

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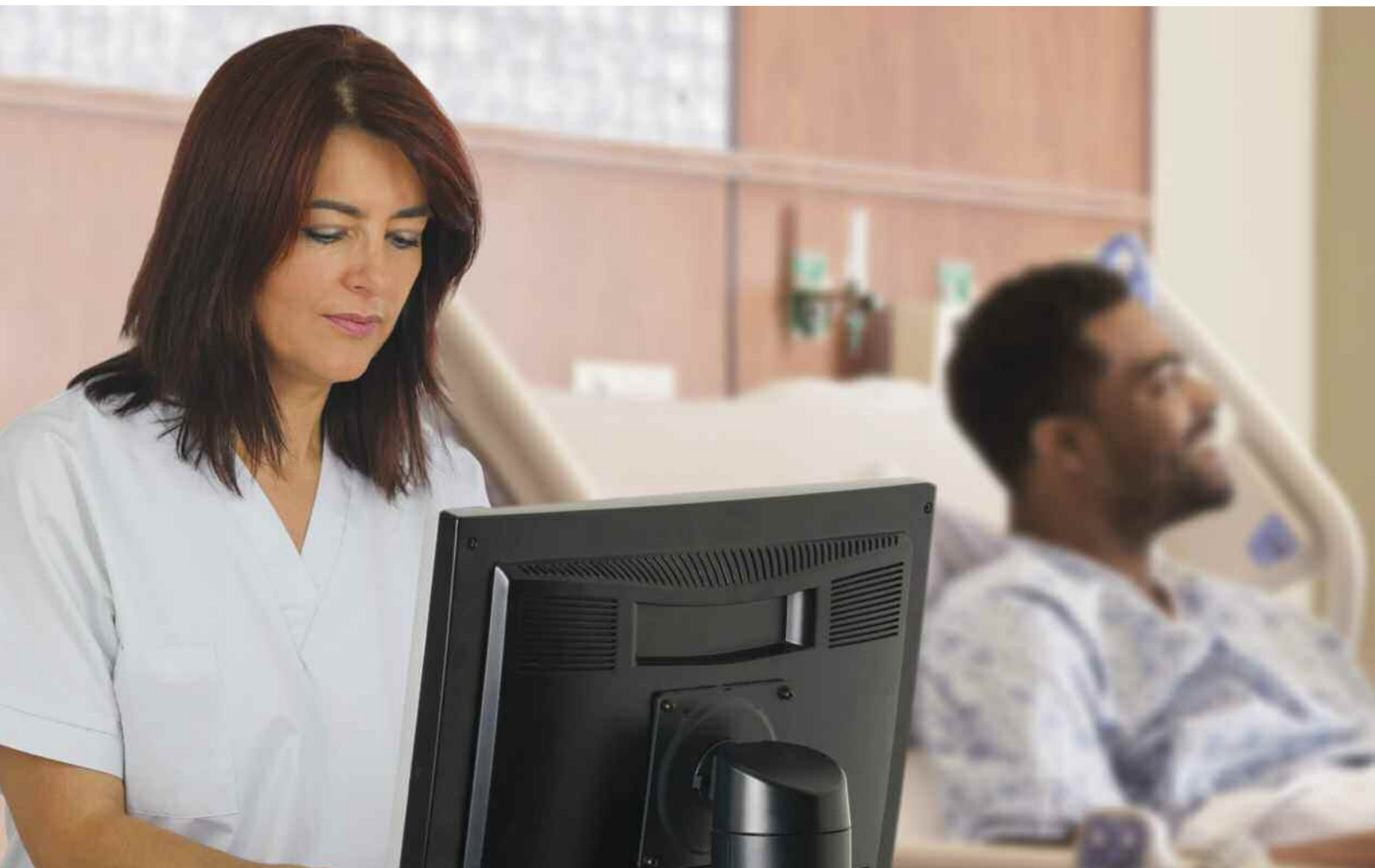
The Growing Profession of Medical Scribes

Medical scribes can help to improve patient and physician satisfaction by taking the focus off of electronic health records and putting it back on the patient.

By Amy Scanlin, MS

THE AMERICAN RECOVERY and Reinvestment Act's "meaningful use" incentives for outcomes and value in healthcare have fully kicked in and so, too, have the penalties for lack of compliance with use of electronic health records (EHRs). While EHRs have been widely touted as an opportunity to improve health record accuracy and patient satisfaction, some medical professionals are not entirely convinced. Complaints about the challenge of learning new software, the potential for distractions caused by data entry at the point of care and, worse, the potential for misremembering patient information should data be entered later are, for some, hindrances.



Enter the fairly new profession of medical scribe that helps bridge the barriers between EHR requirements and physician efforts to provide optimal patient care. Medical scribes, unlicensed clerical assistants, enter patient exam data into EHRs under supervision and typically during a patient's exam. From the first noted reference to scribes in 1974, to the "birth of the industry" in 2004, scribes have been used for decades in emergency rooms, and their numbers are increasing exponentially. The American College of Medical Scribe Specialists (ACMSS) estimated 15,000 scribes in the workplace in 2014, and expect more than 100,000 by 2020.[1] And, Kaiser Healthcare suggests that one in five physicians is now using a scribe.[2]

Scribes work in hospitals, doctor offices, emergency rooms and long-term care facilities, and they may be employed by the provider directly or the healthcare organization, or they may work as contractors. Scribe services are used not only by physicians but, state law permitting, by other licensed healthcare providers. "The greatest innovation for scribes is their use in the outpatient setting," says Kristin Hagen, executive director of ACMSS. "This is where we are working to improve health most proactively using a team-based approach."

Education Requirements

As one would expect, scribes are not authorized to make any independent determinations or enter any orders. Rather, they are clerical assistants, capturing data of patient visits as authorized by providers. They may also be requested by the provider to pull up previous notes or tests for review, assist in navigating through the EHR or simply input current information. Though the minimum education level generally is a high school degree or some college, in many cases, medical scribes are aspiring medical and nursing students who are working to gain experience before attending professional school. Tushar Kapoor, MD, FACEP, executive vice president of staff development and founder of CityMD, a practice that has used medical scribes since its inception, agrees, saying the majority of its applicants are prehealthcare specialists who want to go on to obtain other degrees. In speaking with other scribe companies, he explains, it is fairly standard across the U.S. for medical scribes to be seeking higher education.

While it is an unlicensed field, about one-third of medical scribes opt to obtain a voluntary certification.[2] ACMSS offers three paths to certification: education-based (through schools certified by the Commission on Accreditation of Allied Health Education Programs); work experience-based (a minimum of 200 hours of clinical instruction required or 50 hours for individuals who currently hold a license or certification); and via physician practice administrator, whereby a provider or hospital may refer a trusted staff member for certification testing. As EHRs have become commonplace, so too have the personnel requirements to meet the needs of that investment.

Increased Productivity, But at What Cost?

Should the volume and complexity of patients and the number of providers warrant, medical scribes can provide a valuable service while increasing efficiency. Proponents of scribes say their assistance leads to greater productivity, which leads to increased revenue. And, increased accuracy in the recording of EHR entries leads to greater accuracy in coding and billing. Scribes also enable more face-to-face time since providers are no longer typing notes during visits, which can lead to improved patient satisfaction.

Examples of scribes making positive contributions in the field are many. A John F. Kennedy Medical Center report states that the use of scribes contributed to an increase in revenue of 15 percent and improved patient satisfaction scores.[3] An article published in *Family Practice Management Journal* discusses a boost in productivity of 40 percent and a 23 percent increase in revenue when using assistants who provide transcription services.[4] And, a study published by the National Library of Medicine

showed both large increases in productivity (59 percent more patients seen in a relative hour) and additional downstream revenue with the assistance. Overall quality improvements in patient visits was also seen.[5]

Patient satisfaction can potentially be improved when patients feel their providers are listening closely and not distracted by technology. A study by researchers at the University of California, San Francisco found patients were less likely to rate their care as "excellent" when doctors spent more time on computers entering notes. It also found that doctors may miss nonverbal cues when not looking directly at patients,[6] which could change the course of patient conversation and care.

Providers using medical scribes say they have greater job satisfaction with fewer clerical tasks, and some report scribes provide more accurate notes, both in granularity and specificity, in a shorter amount of time due to greater familiarity with EHR software and its various screens and toggles. These improvements can be used to argue "meaningful use" for the EHR incentive program;[7] as ACMSS's Hagen explains, scribes must be certified to meet the definition of "meaningful use."

"Scribes have been an integral part of what we do since day one," says Dr. Kapoor. "There was never a question of scribe use in our company. From the patient perspective, they want my individualized attention with no distractions and to have all of their questions answered. As a physician, I want to provide the best quality care, and scribes eliminate me having to focus on charts and screens. Because of scribes, I am able to treat my patients physically and emotionally and educate them on issues that are current. Without scribes, half of my attention would go to the [EHR]."

While it is an unlicensed field, about one-third of medical scribes opt to obtain a voluntary certification.

Yet, despite the advantages, critics of scribes in the healthcare setting worry that they will potentially make patients uncomfortable and less forthcoming with information (although, patients always have the right to refuse the presence of additional staff in the exam room). However, as evidenced in an article published in the *American Association of Family Physicians*, when the role of an assistant is explained, patients are generally accepting of his or her presence. Patients also feel greater satisfaction since they view the assistant as an additional advocate who will allow more quality time for provider-patient interaction.[8]

Others worry that EHR software developers will have fewer incentives to continue making improvements to make their products easier to use. They argue the acceptance of an "inferior product" is one of the primary reasons practitioners hire scribes, and if EHRs were more user-friendly, the need for scribes would be lessened. In addition, critics claim providers who rely on scribes will have difficulty navigating the software in the event a scribe is unavailable.[9] Yet, an opposing argument suggests providers should always remain conversant in EHR software, even when using scribe services, because they maintain final responsibility for the medical chart and its content. Without an understanding of the system, their ownership of that content would be difficult at best. In any case, it would also be unwise to assume a scribe will always be available.

Critics also raise concerns that the defined lines between providers and scribes could become blurred in a busy practice. For instance, patient load and the requirement for provider authentication may actually slow down the process it is intended to speed up. Should providers not take the time to thoroughly review a scribe's work, errors could occur, and the time it takes to review the work could negate any initial time savings.

How Do Scribes Work?

In a busy practice with a high volume of patients, scribes can improve workflow. Medical scribes work alongside providers as they attend to patients. Working at a computer terminal, scribes enter data using their own security rights into the EHR. As alerts pop up, scribes share them with providers, and providers give the appropriate response. At the conclusion of the office visit, or as soon as possible thereafter, providers review and authenticate the scribes' entries.

Dr. Kapoor shares that, in his practice, scribes are an integral part of the medical team. So, in addition to performing traditional scribe duties, they also assist in bringing patients in, informing them of the status of their stay (for example, how many minutes until they can be seen in X-ray) and conducting similar duties. Scribes' close proximity to both patients and providers makes it imperative that they be flexible and adaptable to the workflow and a variety of personalities. "We are looking for scribes who are team players, enjoy healthcare and helping others," explains Dr. Kapoor. "They must also be well conversant in the [EHR], document quickly and efficiently, and grasp new concepts quickly." CityMD both sources and trains their scribes internally.

Since physicians are ultimately the responsible parties, and

scribes assist in nonclinical duties, there is no liability insurance requirement for medical scribes, nor do third-party payers reimburse for scribe services.

The CPOE Debate

In 2011, the Health Information Technology for Economic and Clinical Health Act mandated that unlicensed workers may not enter orders such as those for prescriptions and X-rays, meaning that these must be initiated by providers rather than scribes. However, in 2012, the Centers for Medicare and Medicaid Services (CMS) issued a ruling that in addition to licensed medical staff, only "credentialed medical assistants" may enter a computerized provider order entry (CPOE) to meet "meaningful use" under the EHR incentive program criteria. Assistants, according to CMS, must be credentialed outside the organization in which they work.

So, when providers have orders via CPOE, scribes may initially enter the data, but orders will not be placed until providers have authenticated and signed off on them, making providers ultimately responsible for the records.

The Scribe/Provider Electronic Record

In 2011, the American Health Information Management Association Joint Commission issued a guideline[7] on appropriate use of scribes that dictates the types of information they may input into an EHR:

- History of the patient's present illness
- Review of systems and physical examination
- Vital signs and lab values
- Results of imaging studies
- Progress notes
- Continued care plan and medication lists

The guideline also describes how scribes should notate their involvement in the EHR:

- Name of the provider providing the service
- Date and time the service was provided
- Name of the patient for whom the service was provided
- Authentication, including date and time

And, it provides authentication guidance for providers:

- Affirmation of the provider's presence during the time the encounter was recorded
- Verification that the provider reviewed the information
- Verification of the accuracy of the information
- Any additional information needed
- Authentication, including date and time

According to the guideline, scribes' and providers' signatures should be separate and clearly distinguishable.

It should be noted that security rights for scribes and providers are similar, which is not the case for clinical assistants. Those utilizing clinical assistants and/or scribes should clearly differentiate the duties of each job description to avoid any confusion in policy and workload. Also, third-party payers have various requirements for authentication of electronic signatures. As such, organizations using scribes should check to determine the specifics.

> Providers using medical scribes say they have greater job satisfaction with fewer clerical tasks.

Putting the Patient Back in Focus

Medical scribes provide a valued service and an often-needed reprieve from the newer technology requirements of medical care, enabling providers to tend more closely to patients' needs, while knowing office visits are being appropriately and thoroughly documented. For many, this addition to the care team is an enhancement and provides the opportunity to meet federal requirements and bring medicine's focus fully back to the patient. "Our goal is to provide excellent patient care, and we wanted to bring back for physicians what we were trained to do," says Dr. Kapoor. "For us, the only logical way to do that was to take away the IT component, and the next logical step was using scribes." Hagen echoes that sentiment: "Scribes give providers the ability to do what they got into medicine to do in the first place." ❖

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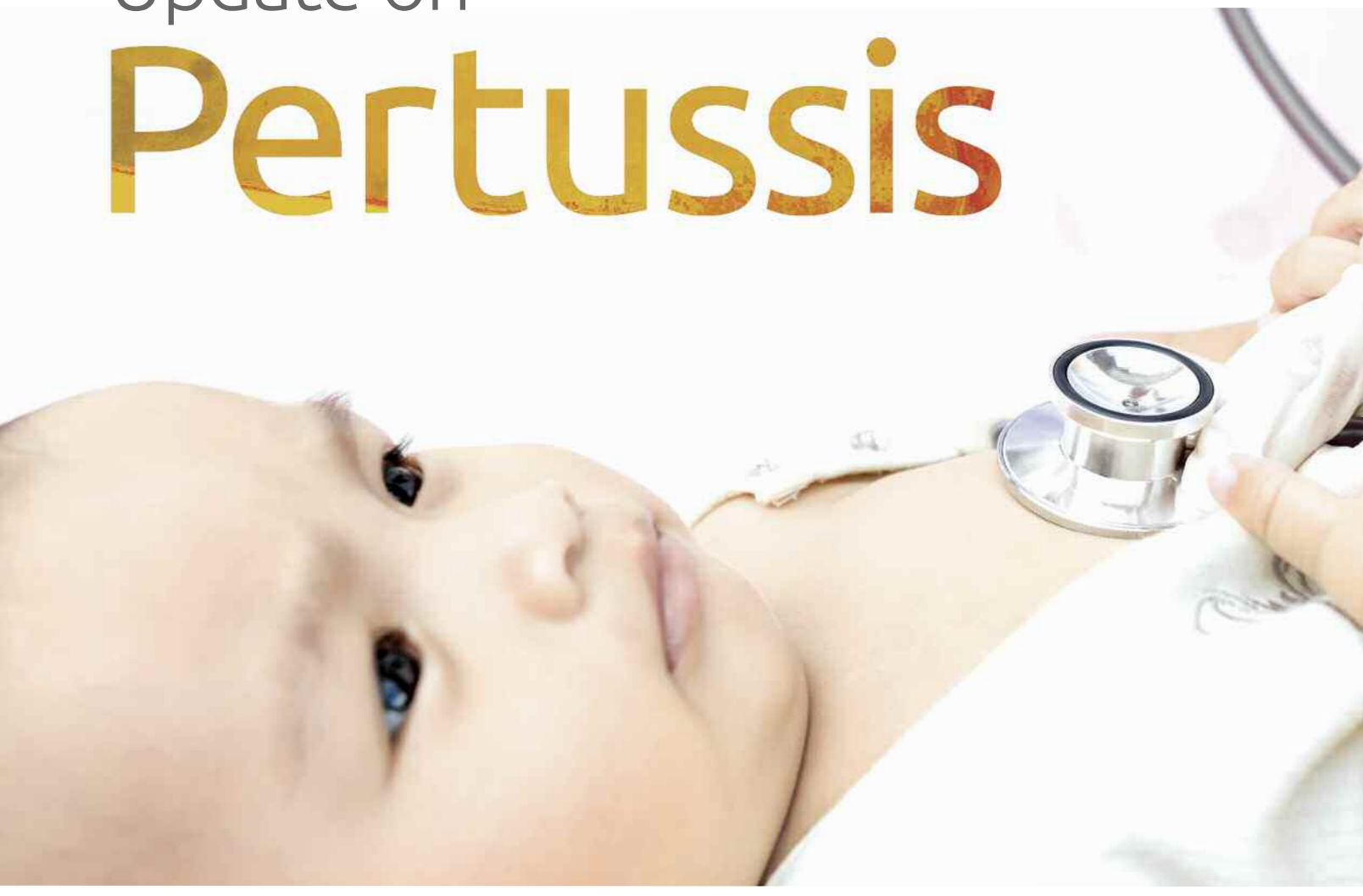
Update on Pertussis



Despite its near eradication in the U.S., whooping cough is making a comeback due to disproven claims and reduced vaccine effectiveness.

By Jim Trageser

BETTER KNOWN BY its descriptive nickname "whooping cough," pertussis was quite recently on its way to joining smallpox as an extinct disease. However, due to a combination of its own highly contagious nature, its evolving DNA and the increasing influence of anti-vaccine activists, pertussis not only persists, it has made a sadly dramatic comeback in recent years.

Not only can a case of whooping cough be frightening for the patient (and their family members), but in the very young — who are the most likely to contract it, before their immunizations are complete — it can be fatal. One report cites 36,000 deaths in the United States due to pertussis between 1926 and 1930, before the first vaccine was

introduced. By 1976, an effective vaccination campaign had brought the total number of pertussis cases in the U.S. down to 1,010.[1]

But after an inaccurate 1982 NBC television news report that falsely claimed the pertussis vaccine caused permanent brain damage, the public outcry was so strong that researchers devised a less-powerful vaccine that had fewer side effects. Unfortunately, it also seems to have a much shorter period of effectiveness. By 2012, pertussis infections had grown 40-fold from 1976 numbers to 48,277 cases in the U.S.,[1] resulting in 20 deaths,[2] while globally, there are an estimated 16 million cases per year, resulting in 195,000 fatalities — mostly children.[3]

What Is Pertussis?

Pertussis is a highly contagious infection of the upper respiratory tract. The bacteria that causes pertussis are inhaled, after which they attach themselves to the cilia along the respiratory tract, where they exude toxins that cause swelling and irritation in nearby tissue.[4] This irritation causes the violent coughing associated with the disease.

Unlike many other contagious diseases, there is no ancient history of pertussis; the first mention appeared in 1540 in England. In 1578, an epidemic in Paris was recorded. Thomas Sydenham, a British physician, gave the first detailed description of the disease in 1679, also giving it its modern name.[5]

It wasn't until 1900 that the bacterium that causes the disease was observed microscopically. Jules Bordet and Octave Gengou, working in Paris, identified the species in a patient's sputum. It took another six years before they isolated a sample.[6]

Causes of Pertussis

Pertussis is caused by the bacteria Bordetella pertussis.[4] It is distributed through the air by an infected person either through normal breathing or by coughing. The bacteria are very difficult to grow outside the human body, making development of vaccines challenging.

Symptoms and Progression of Pertussis

The early symptoms of pertussis are identical to those of everyday colds:

- Low-grade fever
- Mild, occasional cough
- Runny nose

These early symptoms can last for up to two weeks, and physicians will generally not have reason to suspect pertussis or to test for it based on these symptoms. After one to two weeks, the advanced symptoms of pertussis will manifest:[7]

- Numerous rapid coughs followed by a high-pitched "whoop" as the patient inhales
- Vomiting during or following a coughing spell
- Exhaustion following a coughing spell

These symptoms can last for up to 10 weeks. Indeed, the Chinese call pertussis the "100 day cough."[7] Coughing is often more prevalent at night. Gradually, coughing will ease, preceded by the "whoops" disappearing. Subsequent respiratory infections may cause the coughing to resume for up to six months following the initial infection. Patients may be more susceptible to pneumonia during or after whooping cough.[8]

Depending on the severity of coughing fits, patients can suffer secondary symptoms of trauma. These symptoms can include:[9]

- Broken capillaries in the eyes or skin
- Bruised and/or cracked ribs
- Hernias, particularly in the abdomen
- Apnea in infants

Diagnosing Pertussis

Pertussis can be diagnosed either by considering the distinctive late-stage symptoms or by testing a sample of mucus from the patient. A blood test for specific antigens can also be used.[10] X-rays may be appropriate if a secondary infection such as pneumonia is suspected.

Treating Pertussis

Antibiotics can help shorten the infection if started within the first three weeks. If the antibiotic treatment begins before the onset of spasmodic coughing fits, the treatment can also ease the severity of the infection. After three weeks, the bacteria are typically no longer in the body; however, the toxins produced by the bacteria will continue to produce the symptoms for weeks afterward.[11] Antibiotics are rarely prescribed after three weeks from onset of infection due to the bacteria already being absent from the patient.

Other treatments to ease symptoms throughout the course of the disease include:[11]

- Using a mister to help loosen the mucus and reduce the severity of coughing
- Keeping the environment free of dust, smoke and chemicals that can irritate the throat or lungs
- Providing regular liquids to the patient

Infants, particularly those who have not yet completed their immunizations, may require hospitalization[12] so they can be monitored continuously, and so mucus can be removed as it builds up. They may also receive fluids via IV, as well as oxygen to assist their breathing. Up to half of infants under the age of 1 who contract pertussis in Western nations will be hospitalized.

Depending on the severity of coughing fits, patients can suffer secondary symptoms of trauma.

For infants suffering a severe infection, pertussis immunoglobulin (P-IGIV) may prove effective at easing the symptoms caused by pertussis toxin. A 1991 study in Scandinavia showed remarkable improvements in a blind study, with coughing fits cut by two-thirds on average.[13] A 1999 study of mice in a laboratory environment also showed significant improvement.[14]

However, a 2014 follow-up analysis of these and other studies found little correlation between the use of P-IGIV and severity, frequency or length of coughing fits.[15] Still, the authors cautioned that the number of studies was too low to provide conclusive evidence, and the quality of the documentation associated with those studies was often incomplete. They concluded by encouraging additional studies on the efficacy of P-IGIV in treating symptoms of pertussis toxins.

Preventing Pertussis

Pertussis has been preventable by vaccine since the 1940s. Experiments to produce a pertussis vaccine had begun in the 1930s, and a whole-cell vaccine was adopted as the standard in 1944. The vaccine was developed by killing bacteria by solution or heat and then introducing them to the body via injection to stimulate production of antibodies. Side effects of the vaccine were generally mild, but some patients did report convulsions and blacking out,[16] although later studies showed no permanent effects from these episodes.

The efficacy of the vaccine was astonishing. Just 30 years after the pertussis vaccine was introduced, the disease stood on the brink of extinction, with just over 1,000 cases reported in the U.S. in 1976. But six years later, on April 19, 1982, the Washington, D.C., affiliate of the NBC television network aired a program that claimed the pertussis whole-cell vaccine caused permanent brain damage in some infants.[17] Afterward, understandably, parents were reluctant or outright refused to have their children immunized. While that report would eventually be wholly disproved and discredited, the damage was done: Parents did not trust the whole-cell vaccine.

To mitigate the widespread distrust, researchers developed a new vaccine that used broken pieces of the bacterium instead of dead whole cells. The new vaccine is today part of the DTaP vaccine (diphtheria, tetanus and pertussis) given to children in five doses. It is also part of the TDaP booster vaccine given to preteens, teenagers and adults.

Unfortunately, a 2012 study published in the *New England Journal of Medicine* showed that the acellular vaccine, developed in response to the ill-informed backlash against the whole-cell vaccine, does not provide the same long-lasting protection as the original formulation.[18] Specifically, the study found that immunity to pertussis waned within five years of the last dose of DTaP. *Scientific American* reported a year later that outbreaks in California were not just occurring among the unvaccinated. (California has among the highest number of children whose parents elect not to have them vaccinated, although a new law will make it almost impossible to opt out in the future.) A majority of children who contracted pertussis in California in 2010 were children who had received the acellular vaccine.[19] And, the U.S. Food and Drug Administration found that while the vaccine prevented those immunized from developing pertussis,

it did not necessarily prevent them from being infected — or from passing the infection on to unvaccinated people they encountered.[20]

While this evidence might seem to add up to a strong medical and scientific argument to return to the whole-cell vaccine, it's quite possible that the rise of the anti-vaccine political movement would make it very difficult to initiate a quick return to the whole-cell vaccine.[17]

Ongoing Research

Researchers are attacking pertussis from a variety of angles. They are looking at ways of crippling the bacteria that cause the disease, as well as ways of stimulating the body's own defenses to better fight the infection.

Among the promising lines of research are those that involve giving pregnant women the vaccine. Early studies show the vaccine stimulates the mother's body to produce antibodies that are passed to the child via the placenta. Another study is devoted to introducing minute quantities of pertussis toxins to stimulate the body to build up defenses against the poisons produced by the infectious bacteria. And, yet another study is seeking bioengineering drugs to attack specific molecules in the cell walls of the pertussis-causing bacteria while leaving healthy cells in the patient unaffected.[21]

However, the target is also changing. A recent study offers evidence that Bordetella pertussis has evolved to the point over the last 80 years that the current vaccines may no longer work against it. As the genetic code for the bacteria changes over time, the antibodies stimulated by the current vaccine may not be targeting the current bacteria, leaving many vaccinated children vulnerable.[22]

Looking Ahead

While the ongoing and unavoidable evolution of Bordetella pertussis may require an update to the vaccine, the largest hurdles to lowering incidences of pertussis outbreaks are political and cultural — not medical.

California's experience in going from enacting one of the most lenient state "opt-out" laws for preschool vaccinations to adopting one of the strictest for the current school year may offer some guidance. Under the old law and policy, California parents could simply declare a moral opposition to vaccination to have their children exempted. The new law no longer even allows for a formal religious exemption.

Nonetheless, the lingering autism scare of the late 1990s, ignited by British medical journal *The Lancet* publishing a paper alleging a link between vaccines and autism in young children (later wholly disproved), has made opposition to vaccines a cause célèbre in Western Europe and North America. As pointed out above, reverting to a whole-cell vaccine for pertussis would likely prove effective at stopping the disease and saving lives, but it would also generate tremendous opposition.

Pertussis has been preventable by vaccine since the 1940s.

And, with fewer than two dozen deaths a year due to pertussis in the U.S., changing vaccines is unlikely to be seen as a critical public health issue. In the rest of the world, with nearly 200,000 children a year still dying from a preventable disease, the issue isn't political so much as practical: an overt lack of resources to get every child vaccinated. That is perhaps where the focus should and will lie in the years to come. ❖

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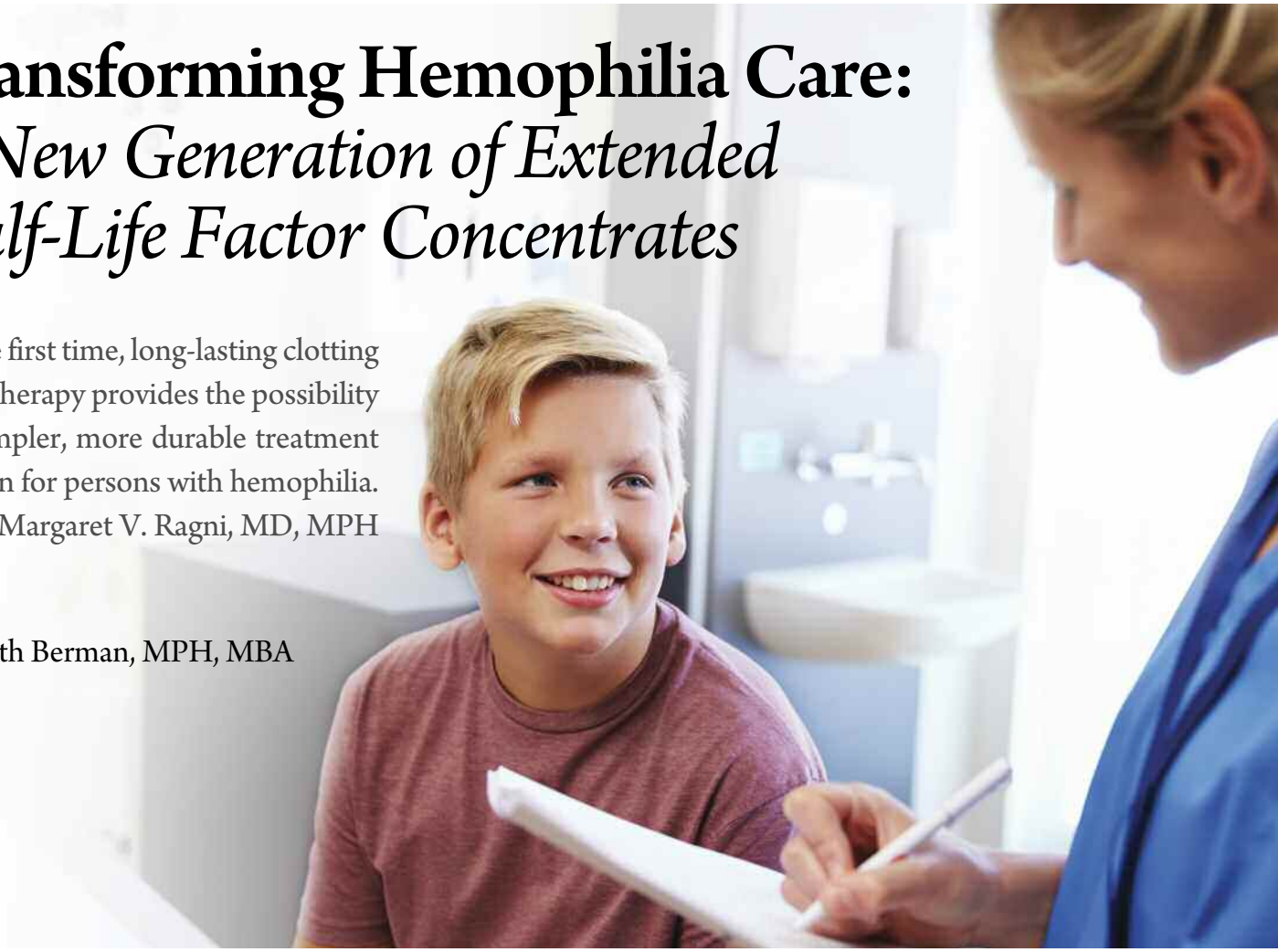
Transforming Hemophilia Care: *A New Generation of Extended Half-Life Factor Concentrates*



For the first time, long-lasting clotting factor therapy provides the possibility of a simpler, more durable treatment regimen for persons with hemophilia.
— Margaret V. Ragni, MD, MPH

By Keith Berman, MPH, MBA

FOR CHILDREN AND adults with hemophilia and a history of spontaneous bleeding episodes, the old "on-demand" strategy of reactively administering clotting factors to treat bleeds was displaced more than 20 years ago by a new standard of care: routine prophylactic infusions to maintain coagulation function and prevent bleeds from occurring in the first place. Prophylaxis is well-proven as a means to avoid development of crippling hemarthroses and normalizing the daily lives of persons with hemophilia, who can travel without fear and participate in previously off-limits physical activities.

But there is a catch. The very short circulating half-life of natural or recombinant coagulation factors necessitates frequent infusions. For children with hemophilia A, who metabolize infused factor VIII (FVIII) more rapidly than adults, dosing is typically necessary every other day to assure that the FVIII trough level remains above the critical lower threshold (1 to 3 percent or higher) required for protective hemostatic function. As factor IX (FIX) has a somewhat longer circulating half-life, it is most common for persons with hemophilia B to dose themselves twice per week.* This necessity to frequently infuse factor on a lifelong basis has created its own set of management challenges:

Problems with peripheral venous access in children. Many younger children have peripheral veins that are very small, hard to find or tend to roll away, making them very difficult to "hit" with the small-gauge needle on the first try. Repeated multiple times each week, this translates into much stress for both the child and

** The frequency of infusion is highly individual, depending on variables that include age (half-life of infused factors is shorter in children than adults), severity of the factor deficiency, dosage and experience with breakthrough bleeds.*

the parent caregiver. To address this problem, the physician will usually offer the option of surgically placing a central venous access device (CVAD), such as a port, to facilitate simple and reliable infusions.

CVAD-associated infection and thrombosis risks. Even with meticulous adherence to sterile technique, use of a CVAD to administer factor creates significant risks of a local or, more seriously, systemic sepsis. Each infusion additionally introduces the potential for thrombosis that clogs the port or other CVAD. The more frequently factor must be administered each week, the more likely it is that parents will give up on administering the product through peripheral veins — with negligible risk of infection or thrombosis — and opt instead for placement and use of a CVAD that entails both risks.

Treatment burden. Regardless of age, the need to prepare and administer factor multiple times each week on a chronic basis is unpleasant, and for some patients and caregivers can lead to treatment "exhaustion."

Poor adherence to a demanding prophylaxis regimen. This can pose a particular problem for adolescent and young adult males, at a life stage where it is commonplace to question authority and to underestimate the health risks of their behaviors and life choices. The more demanding and burdensome the prophylaxis regimen, the more likely it is not adhered to, with associated higher risks of hemarthroses and long-term joint damage.

The technical feasibility and obvious advantages of FVIII and FIX treatments able to persist longer in the circulation spurred a host of new product development programs, both by leading manufacturers of hemophilia therapies and by biopharmaceutical industry newcomers to hemophilia. For the most part, they have applied technologies already used successfully to produce other types of long-acting therapeutic proteins.

Multiple Means to Extend Factor Half-Life

Three fundamental approaches have been exploited to produce the five extended half-life (EHL) recombinant FVIII and FIX products now on the market, and several others currently in development (Table 1):

Table 1. Licensed and Investigational Extended Half-Life Factor VIII and Factor IX Products

		Product	Manufacturer	EHL Technology
FACTOR VIII	Licensed	ADYNOVATE Antihemophilic Factor (Recombinant), PEGylated	Shire	Covalent conjugation with polyethylene glycol (PEG)
		AFSTYLA Antihemophilic Factor (Recombinant), Single Chain	CSL Behring	Covalently bound light/heavy chains; increased von Willebrand factor affinity
		ELOCTATE Antihemophilic Factor (Recombinant), Fc Fusion Protein	Biogen	Covalent linkage to IgG1 Fc domain sequence
	Investigational	BAY 94-9027: PEGylated B-Domain-Deleted Recombinant Factor VIII	Bayer	Site-directed covalent conjugation with polyethylene glycol (PEG)
		N8-GP (NN7088): GlycoPEGylated Recombinant Factor VIII	Novo Nordisk	Site-directed glycoPEGylation selecting O-glycan in B-domain
		Product	**Manufacturer**	**EHL Technology**
FACTOR IX	Licensed	ALPROLIX Coagulation Factor IX [Recombinant], Fc Fusion Protein	Biogen	Covalent linkage to IgG1 Fc domain sequence
		IDELVION Coagulation Factor IX [Recombinant], Albumin Fusion Protein	CSL Behring	Genetic fusion of recombinant albumin
	Investigational	N9-GP (NN7999): GlycoPEGylated Recombinant Factor IX	Novo Nordisk	Site-directed glycoPEGylation

• Attachment of polyethylene glycol (PEG) to the molecule (PEGylation or glycoPEGylation);

• A natural vascular endothelial cell-mediated process that "recycles" immunoglobulin G (IgG) and albumin into the circulation; and

• Specifically for FVIII, molecular engineering to stabilize the protein and increase von Willebrand factor affinity.

Both PEGylation (applied by Shire and Bayer) and glycoPEGylation (Novo Nordisk) prolong intravascular half-life of FVIII and FIX by virtue of the ability of long protein-bound strands of PEG to 1) prevent uptake and clearance by reticuloendothelial cells, 2) decrease the formation of neutralizing antibodies by masking antigenic sites and 3) protect against proteolysis by enzymes such as trypsin, chymotrypsin and proteases.[1]

Products developed by Biogen and CSL Behring exploit a physiologic process that enables IgG antibodies and albumin — which together account for 80 percent to 90 percent of total plasma protein — to persist in the bloodstream for an average of about three weeks. Both proteins are bound by a neonatal Fc receptor (FcRn) on the surface of endothelial cells lining the blood vessels, then endocytosed and subsequently recycled into the bloodstream. The two companies employed chemistries to attach either the Fc receptor of IgG1 or recombinant human albumin to FVIII or FIX, which then piggyback on the natural endocytosis-mediated IgG or albumin recycling process.

And, in an entirely novel approach, CSL Behring covalently linked the light and heavy chains of FVIII to form a more intrinsically stable single chain. This single-chain FVIII variant has a roughly two-fold higher affinity for von Willebrand factor, whose primary role is to prevent the premature activation and clearance of the protein.

> "The technical feasibility and obvious advantages of FVIII and FIX treatments able to persist longer in the circulation spurred a host of new product development programs."

EHL Factor IX Persists Longer in Circulation

As different as these bioengineered clotting factors are, the half-life extension they achieve is surprisingly similar: roughly 1.5- to 1.6-fold for EHL FVIII products and three- to five-fold for EHL FIX products.

Accounting for roughly 80 percent of all persons with hemophilia, hemophilia A is around four times more prevalent than hemophilia B.[2] Yet thanks to the much longer half-life of EHL FIX — ranging from 80 to 110 hours in adults versus under 20 hours for EHL FVIII — the benefits of EHL technologies are more pronounced for the smaller hemophilia B population with a bleeding tendency severe enough to warrant prophylaxis.

While recommended starting dosages and infusion intervals differ somewhat for each of the three approved EHL FVIII products, prophylaxis is commonly started and maintained with twice-weekly dosing. In two pivotal Phase III clinical studies evaluating Shire's ADYNOVATE and Biogen's ELOCTATE, the median dosing interval for subjects assigned to an adaptable prophylaxis dosing regimen was about 3-1/2 days.[3,4]

By contrast, hemophilia B patients initiating EHL FIX prophylaxis typically start with once-weekly dosing. In 26 clinical study subjects on Biogen's ALPROLIX product,[5] whose treatment interval was adjusted to maintain FIX trough level between 1 percent and 3 percent above baseline or higher as clinically indicated to prevent bleeding, the median interval between infusions was just shy of 14 days. Similarly, the majority of 37 subjects who completed six months of prophylaxis therapy with CSL Behring's IDELVION FIX at a dose ≤40 IU/kg switched successfully to a 14-day interval at dose ranging from 50-75 IU/kg.[6]

The comparatively modest FVIII half-life extension attained with modifications similar to EHL FIX (e.g., PEGylation and FcRn-mediated endothelial recycling) can be attributed to the absence of von Willebrand factor (VWF) in the bioengineered FVIII protein; unfortunately, natural VWF that complexes with infused EHL FVIII has a relatively short half-life itself.[7]

Absent some entirely new bioengineering breakthrough, it is unlikely that EHL FVIII products will ever approach the

seven- to 14-day dosing interval now routinely enjoyed by hemophilia B patients on EHL FIX prophylaxis. Nevertheless, most children and nearly all adults on standard FVIII prophylaxis are able to reduce their number of infusions by at least one per week after switching to an EHL FVIII product.[8]

Adjusting the Regimen to Fit the Need

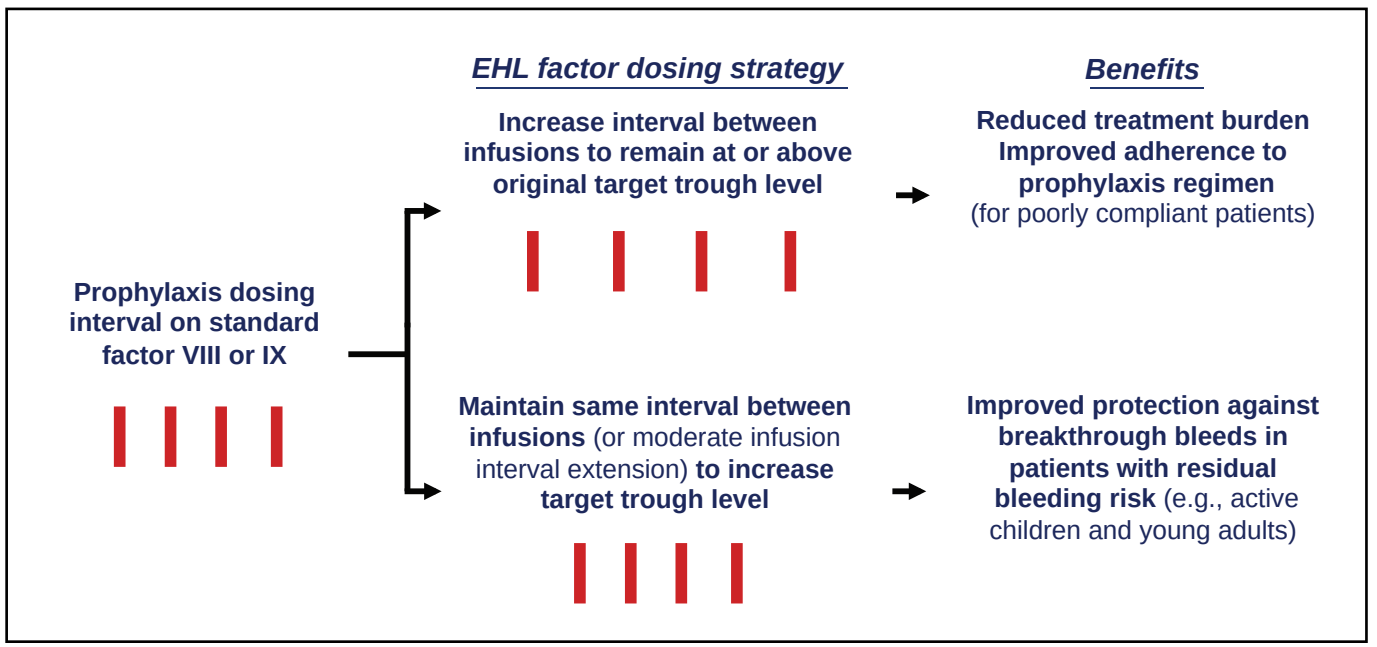
For many patients, it is quite satisfactory to adhere to the recommended dosing frequency — twice-weekly infusions of EHL FVIII, for example — with dose adjustments to achieve a trough level of 1 percent to 3 percent above baseline or as clinically indicated to prevent bleeding. But for some patients, it appears advantageous to individualize the regimen, adjusting the dose or the dosing interval based on their prior prophylaxis experience with standard factor concentrates, the trough level goal and actual breakthrough bleeding experience.

The vast majority of patients starting EHL factor prophylaxis were already on a prophylaxis regimen with standard recombinant factor concentrates. The presumptive justification to switch for most of these individuals is the reduced treatment burden of a prolonged interval between infusions. But converting to an EHL product also presents an additional opportunity for individualizing dosing frequency in a way that places a priority on protection from spontaneous bleeds.

Figure 1 outlines two optional strategies for prophylaxis-managed patients who make the switch to EHL products. For the majority of patients with a history of very good bleeding protection on standard factor prophylaxis, an EHL product allows the

> While recommended starting dosages and infusion intervals differ somewhat for each of the three approved EHL FVIII products, prophylaxis is commonly started and maintained with twice-weekly dosing.

Figure 1. Alternative Prophylaxis Dosing Frequency Strategies for Patients Switching from Standard to EHL Factor Products



physician to extend the interval between infusions, reducing the chronic treatment burden and potentially improving adherence for those with a poor treatment compliance history. But for patients with less-than-satisfactory control of spontaneous bleeds on their original prophylaxis regimen — physically active children and adolescents, for example — the physician may wish to opt for maintaining the same infusion interval (or reducing its extension) with the goal of attaining a higher, more protective trough level.[9]

The dose itself can also be adjusted to increase the trough level, but there are limits. This is true in particular for EHL FVIII products with their relatively modest half-life advantage over standard FVIII. There is a temptation for patients who still require twice or three times weekly infusions to simply boost the dose as a means to extend the dosing interval. Unfortunately, this strategy has a serious downside. The pharmacokinetics of this clotting factor dictates that, beyond a point, overall product utilization — and cost — escalates unacceptably when the interval between doses is stretched and the dose is increased to try to sustain a protective trough level. "Increasing the dose size rather than reducing dose frequency is an inherently inefficient approach to therapy," Professor Michael Laffan at London's Hammersmith Hospital pointed out in a recent review.[10]

Embracing the Payoffs of EHL Products

A survey of 25 hemophilia treatment centers (HTCs) conducted earlier this year by The Marketing Research Bureau (MRB)[11] revealed that 13 percent of hemophilia A patients on prophylaxis therapy now use an EHL FVIII product. Unsurprisingly, given their much longer seven- to 14-day dosing interval, nearly 37 percent of hemophilia B patients on a prophylaxis regimen are now administering an EHL FIX product.

> "The vast majority of patients starting EHL factor prophylaxis were already on a prophylaxis regimen with standard recombinant factor concentrates."

Demand for EHL products is expected to continue to grow as clinicians, patients and caregivers recognize their ability to:

- Reduce treatment burden on children and caregivers using peripheral veins for prophylaxis therapy;
- Offer a more acceptable alternative to use of CVADs in younger children, with their attendant risks of infection and line clogging;
- Improve adolescent/young adult compliance with their prescribed prophylaxis regimen, potentially translating into fewer hemarthroses and reduced risk of joint damage;
- Reduce patient resistance to switching from episodic treatment to prophylaxis, reducing bleeding event rates and long-term joint damage risk; and
- Facilitate targeting of higher, more protective trough levels, with attendant reduction in breakthrough bleeding risk.

There are already indications that EHL products are enjoying broadening appeal. In contrast to results from an earlier survey of HTCs conducted in late 2014, MRB's latest 2016 survey found that the reduced burden of administering EHL factors is now attracting significant numbers of patients who had been episodically treating spontaneous bleeding events.

In the near future, we can expect to see publication of patient studies quantifying the benefits of extended half-life factor concentrates and providing guidance on how to best integrate them into clinical practice. But in the meantime, all indications are that this new product class represents a powerful new tool for improving the care and quality of life for persons with hemophilia. ❖

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Angela Matthews met her ovarian cancer diagnosis head-on because she wants to "hold her grandchildren one day." Today, she is cancer-free.

Ovarian Cancer: *A Patient's Perspective*

By Trudie Mitschang

ANGELA MATTHEWS* WAS an active, healthy 43-year-old with four young children, a thriving career and busy social calendar when she first noticed the symptoms. Cramping, bloating, sporadic menstrual bleeding and unexplained weight loss prompted her OB-GYN to order an ultrasound. Angela was incorrectly diagnosed with a ruptured ovarian cyst, and over a period of four months, her symptoms escalated. "When I went back to my OB-GYN a month later, they did another ultrasound and also a CA125 blood test to check for cancer antigens," recalls Angela. "When the results came back, my CA125 was 4,400 (a normal one is under 35). I was immediately referred to an oncologist, who was 99 percent sure it was ovarian cancer."

Angela and her husband, Eric, were stunned. With no family history or other risk factors, a cancer diagnosis was the last thing they expected. "We had no idea I was that sick," says Angela. "We were just on a vacation, I was working full time, I was helping in my kids' classrooms and running all four of them around for after-school activities."

Angela's oncologist explained that although her symptoms seemed mild, she was actually in a small percentage of patients who even exhibit symptoms. Known as the silent killer, ovarian cancer is one of the most deadly cancers in women. According to the American Cancer Society, only 20 percent to 30 percent of women diagnosed with late-stage ovarian cancer are alive five years later.[1] "When I asked about survival rates, my oncologist said it was about 30 percent with a high rate of reoccurrence," says Angela. "She did explain, however, that the statistics tended to be outdated and not to pay attention to them. I told her I was going to fight this because I wanted to be able to hold my grandchildren. She looked straight at me and said, 'I hate cancer so much that I have made it my life's work so that women like you will be able to hold their grandchildren one day.'"

An Aggressive Treatment Plan

Angela's treatment plan began with a full hysterectomy that removed her ovaries, fallopian tubes, uterus and cervix. Before surgery, Angela was injected with a fluid that illuminates cancer in the body; during surgery, her organs "lit up like a Christmas tree." Her anticipated stage 2 cancer was actually diagnosed at stage 3, and surgeons proceeded to remove a portion of her colon, part of her intestines and the fat layer in her stomach during the nine-hour procedure.

Angela was also fitted with an intraperitoneal (IP) chemotherapy port; her 21-day cycles included intravenous (IV) treatment of Taxol and IP treatment of Cisplatin. "The chemo went directly into my abdomen," explains Angela. "I had to go through several hours of hydration, receive the chemo and then turn every 15 minutes for two hours so the drugs could reach all areas of my abdomen. My nurses and I called it 'marinating.' On days eight through 21, I would rest. This cycle continued for six rounds."

Angela considers herself fortunate to have been treated at a university hospital by an oncologist who specializes in ovarian cancer. While going through chemo, she learned that not many oncologists offer the IP chemotherapy option. "Because it allows the chemo to go directly into the abdomen, it's a game changer for patients and offers a much higher survival rate," she explains. "I was also very fortunate to have an IV portacath for my Taxol treatments instead of having to go the IV route. This saved my veins from collapsing or getting major scar tissue."

Beating the Odds

Today, Angela appears to have defied the statistics; she has been cancer-free since Dec. 9, 2015. A fighter by nature and a woman of faith, Angela says exceptional medical care and a positive attitude played huge roles in her outcome. "I never let myself think about dying, and I refused to read articles or look at statistics that talked about dying from my disease," she says. "So many people think they don't have control of their disease or their treatment, but healing starts first with your attitude and your willingness to fight. I have always been competitive, and I may have been surprised by cancer, but I refused to be defeated by it." ❖

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

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*Names have been changed at the patient's request.

Ovarian Cancer:
A Physician's Perspective

DR. LESLIE M. Randall is an obstetrician-gynecologist in Orange, Calif. She completed her fellowship training with University of California, Irvine's Division of Gynecologic Oncology and is skilled in the comprehensive medical and surgical care of women with all gynecologic cancers. Dr. Randall upholds many service commitments, including assistant professor at the University of California, Irvine, School of Medicine and director of education for gynecologic oncology.

BSTQ: Why is ovarian cancer frequently misdiagnosed?

Dr. Randall: In reality, it's somewhat rare, and the symptoms are very vague. Women complain of feeling bloated and getting full early, but these are symptoms that can occur with multiple benign diagnoses. Added to that is there's not a good screening method; you can't diagnose it early because it develops so quickly.

BSTQ: What are some of the most common risk factors?

Dr. Randall: Age is a risk factor. Postmenopause, the risk definitely goes up. Having a family history of breast cancer and ovarian cancer, or being a carrier of a gene mutation called BRCA1 or BRCA2, are known risk factors, as is having a condition called Lynch syndrome, an inherited condition that gives a person a higher risk of certain cancers of the digestive tract, gynecologic tract and other organs.

BSTQ: Are you seeing more women diagnosed with ovarian cancer at a younger age?

Dr. Randall: No. There are a certain number of women who are diagnosed pre-menopause, but most have some mutation. The mutations are definitely genetic; if we identify a mutation, we test blood relatives for that same mutation.

BSTQ: From a patient perspective, what are the advantages of being treated at a university hospital like the University of California, Irving (UCI)?

Dr. Randall: One advantage is the level of surgical expertise a patient has access to. At UCI, we have expertise in ovarian cancer surgery and various types of chemotherapy regimens. Ongoing clinical trials are also available. The other benefit is that we take a multidisciplinary approach to care that includes gynecological oncology, medical oncology, radiation oncology, genetics, nutrition counseling, nursing and interventional radiology. All of that is important to have with an ovarian cancer diagnosis.

BSTQ: Tell us about intraperitoneal (IP) chemotherapy. What are its advantages and risks?

Dr. Randall: This treatment is concentrated in the area where the cancer occurs. IP chemotherapy is delivered through an implanted subcutaneous port that drains into the cavity of the abdomen, allowing direct access for the drug to the peritoneal cavity where ovarian cancer is prevalent. Some clinical trials have shown that treatment with IP and intravenous (IV) chemotherapy extended median overall survival for patients with ovarian cancer by more than a year, compared with women treated with IV chemotherapy alone. IP use, however, can cause more frequent and more severe side effects than IV chemotherapy, including abdominal pain, nausea and vomiting.

BSTQ: Are there any new treatments or promising clinical trials?

Dr. Randall: The most promising trials include the PARP inhibitor, which stands for "poly (ADP-ribose) polymerase." PARP is a family of enzymes found throughout the body that are needed for a form of DNA repair known as break excision repair. PARP inhibitors offer a much more targeted attack on tumors whose self-repair is already under fire. Olaparib (Lynparza, AstraZeneca) is one of the current U.S. Food and Drug Administration-approved PARP inhibitors for cancer treatment. Immunotherapy is also showing promise. This treatment involves the development of monoclonal antibodies that specifically recognize and attack ovarian cancer cells. These antibodies are man-made versions of the natural antibodies the human body makes to fight infection.

BSTQ: What are some of the best resources for developments in ovarian cancer research and treatment?

Dr. Randall: A few of my trusted resources include the Society of Gynecologic Oncology (sgo.org), Foundation for Women's Cancer (foundationforwomenscancer.org) and the National Cancer Institute (cancer.gov). ❖

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

Healthcare Global Market Analytics Report 2016

Author: The Business Research Company

Healthcare Global Market Analytics provides strategists, marketers and senior management with the critical information to assess the global healthcare sector. It contains information on healthcare services, pharmaceutical and medical equipment, and includes an historic and forecast growth rate from 2011 to 2019 that analyzes expenditure per capita, expenditure per household, government expenditure, healthcare indicators and surgical procedures. The report covers Asia, Europe, the Americas, the Middle East, Africa and Oceania.

www.thebusinessresearchcompany.com/our-research/healthcare/healthcare-global-market-analytics-report-2016

Medicines Use and Spending in the U.S.: A Review of 2015 and Outlook to 2020

Author: IMS Institute

The outlook for medicine spending through 2020 is for mid-single digit growth driven by further clusters of innovative treatments, offset by a rising impact from brands facing generic or biosimilar competition. In this report, the IMS Institute highlights different aspects of the use of medicines in the U.S., spanning overall spending, key market segments, volumes, patient cost exposure and healthcare delivery changes, as well as the outlook to 2020.

www.imshealth.com/en/thought-leadership/ims-institute/reports/medicines-use-and-spending-in-the-us-a-review-of-2015-and-outlook-to-2020#form

State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars

Author: National Conference of State Legislatures

This report highlights legislation considered during the last four years in at least 36 states to establish state standards for substitution of a "biosimilar" prescription product to replace an original biologic product, as well as state roles in regulating safety and compounding, specialty drugs and clinical trial and "right-to-try" measures.

www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx

Observational Studies: Opportunities and Challenges for Drug and Devicemakers

Author: U.S. Food and Drug Administration

This report, based upon a webinar by 30-year industry veteran Jeff Trotter, explains the opportunities and pitfalls that observational studies can offer an organization. Drawing on a survey of more than 2,500 individuals representing a cross-section of the pharmaceutical, medical device and biotech industries, Trotter discusses how companies are using observational studies, including the role of observational studies in the pre-approval versus the post-market phase; using observational studies to establish baselines of real-world behavior and identify needs; understanding stakeholders and their different needs; and the importance of establishing standards of operating procedures specifically for observational studies rather than adapting clinical research procedures.

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Navigating HCT/P Regulations: Risks and Opportunities for Drug and Device Manufacturers

Author: U.S. Food and Drug Administration

Navigating HCT/P Regulations explains where and how FDA has set the medical product line and what practitioners of regenerative therapies must do to comply with the agency's regulations. This management report explains what uses of human cells and tissue are regulated and when FDA requires an HCT/P to go through the marketing approval process, including: 1) the three criteria FDA uses to determine whether an HCT/P falls under its jurisdiction; 2) the four draft guidances in which the agency establishes its regulatory policy; 3) two court cases that have helped shape regulation of regenerative medicine; 4) the distinction between two classes of HCT/Ps and which one is quickest to market; and 5) the steps involved in applying for a license to market.

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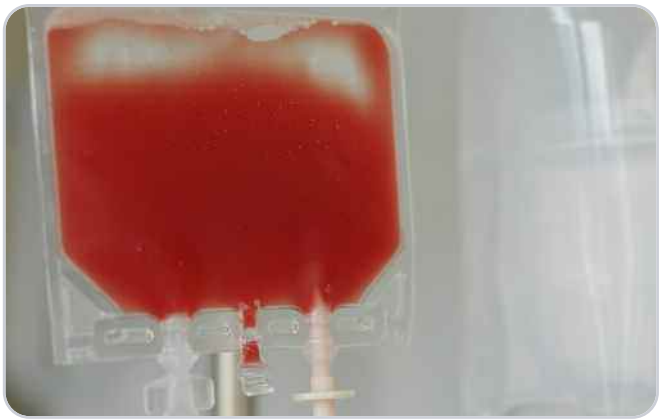
Recombinant Human Soluble Thrombomodulin May Improve Outcomes in Transplant-Associated Thrombotic Microangiopathy



Intravenous administration of recombinant soluble thrombomodulin (rTM) may improve recovery and survival compared to other treatments in patients with transplant-associated thrombotic microangiopathy (TA-TMA) after hematopoietic stem cell transplantation (HSCT), according to a retrospective analysis of 254 consecutive patients at a single Japanese institution. Transplant-associated TA-TMA is a severe complication that is attributed to underlying endothelial cell damage. As rTM has cytoprotective effects against calcineurin inhibitor-induced endothelial cell damage, the investigators hypothesized that patients receiving rTM as a first-line treatment would potentially realize a benefit.

Of 16 post-HSCT patients diagnosed with TA-TMA, nine were treated with rTM and seven received other treatments. Seven of the nine patients (78 percent) in the rTM group recovered from TA-TMA without addition of second-line therapy, while none recovered in the control group, who received various therapies including fresh frozen plasma (FFP) and therapeutic plasma exchange (p=0.003). In the entire cohort, three patients (33.3 percent) remained alive in the rTM group, while no patients survived in the control group after their TA-TMA diagnosis.

The investigators concluded that these data suggest that administration of rTM may improve clinical outcomes in patients with TA-TMA.

Fujiwara H, Maeda Y, Sando Y, et al. Treatment of thrombotic microangiopathy after hematopoietic stem cell transplantation with recombinant human soluble thrombomodulin. Transfusion *2016 Apr;56(4):886-92.*

Recombinant Human Prothrombin Prevents Bleeding in Hemophilia A and B Mice

Both a plasma-derived human factor II (pdhFII) and an investigational recombinant human prothrombin (MEDI8111) dose-dependently decreased blood loss and bleeding time in hemophilia A mice, according to Swedish investigators at AstraZeneca's CVMD IMED unit. Doses of MEDI8111 and pdhFII required to achieve a 50 percent reduction in blood loss and bleeding time were 37 and 87 mg/L, and 100 and 155 mg/L, respectively. In hemophilia B mice given MEDI8111, the doses required to achieve a 50 percent reduction in blood loss and bleeding time were 56 mg/L and 67 mg/L, respectively.

Plasma concentrations of both thrombin and thrombin-antithrombin complex (TAT) increased dose-dependently as well with administration of either MEDI8111 or pdhFII in hemophilia A mice. Similar results were observed in hemophilia B mice.

The investigators concluded that MEDI8111 was effective in dose-dependently decreasing bleeding in hemophilia A and B

mice, which supports a current hypothesis that factor II is one of the major components responsible for the efficacy of prothrombin complex concentrate (PCC) and activated prothrombin complex concentrate (aPCC) in hemophilia patients. The authors also concluded that "data suggest that MEDI8111 may be useful for preventing bleeding in patients with hemophilia A and B."

Hansson KM, Lidblom A, Elg M, et al. Recombinant human prothrombin (MEDI8111) prevents bleeding in haemophilia A and B mice. Haemophilia *2016 May;22(3):453-61.*

Medicare IVIG/SCIG Reimbursement Rates

Rates are effective Oct. 1, 2016, through Dec. 31, 2016.

Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
BIVIGAM IVIG	Kedrion	J1556	$79.04	$77.77
CARIMUNE IVIG	CSL Behring	J1566	$66.15	$65.09
FLEBOGAMMA IVIG	Grifols	J1572	$73.61	$72.43
GAMMAGARD SD IVIG	Shire	J1566	$66.15	$65.09
GAMMAPLEX IVIG	Bio Products Laboratory	J1557	$74.06	$72.88
OCTAGAM IVIG	Octapharma	J1568	$71.96	$70.81
PRIVIGEN IVIG	CSL Behring	J1459	$75.80	$74.58
HIZENTRA SCIG	CSL Behring	J1559	$98.29	$96.71
HYQVIA SCIG	Shire	J1575	$127.44	$125.40
GAMMAGARD LIQUID IVIG/SCIG	Shire	J1569	$79.99	$78.71
GAMMAKED IVIG/SCIG	Kedrion	J1561	$77.16	$75.93
GAMUNEX-C IVIG/SCIG	Grifols	J1561	$77.16	$75.93

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

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IVIG/SCIG Reference Table

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

2016-2017 Influenza Vaccine

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

Manufacturer	Product	Presentation	Age Group	Code
TRIVALENT				
SEQIRUS	AFLURIA (IIV3)	5 ML multi-dose vial	5 YEARS AND OLDER*	90658/Q2035
		0.5 ML prefilled syringe, 10-BX		90656
SEQIRUS	FLUVIRIN (IIV3)	5 ML multi-dose vial	4 YEARS AND OLDER	90658/Q2037
		0.5 ML prefilled syringe, 10-BX		90656
SEQIRUS	FLUAD (aIIV3)	0.5 ML prefilled syringe, 10-BX	65 YEARS AND OLDER	90653
PROTEIN SCIENCES	FLUBLOK (RIV3)	0.5 ML single-dose vial, 10-BX	18 YEARS AND OLDER	90673
SANOFI PASTEUR	FLUZONE HIGH-DOSE (IIV3)	0.5 ML prefilled syringe, 10-BX	65 YEARS AND OLDER	90662
QUADRIVALENT				
SEQIRUS	FLUCELVAX (ccIIV4)	0.5 ML prefilled syringe, 10-BX	4 YEARS AND OLDER	90674
GSK	FLUARIX (IIV4)	0.5 ML prefilled syringe, 10-BX	3 YEARS AND OLDER	90686
GSK	FLULAVAL (IIV4)	5 ML multi-dose vial	3 YEARS AND OLDER	90688
MEDIMMUNE	FLUMIST** (LAIV4)	0.2 ML live virus intranasal spray	2-49 YEARS	90672
SANOFI PASTEUR	FLUZONE (IIV4)	5 ML multi-dose vial	6-35 MONTHS	90687
			3 YEARS AND OLDER	90688
		0.5 ML prefilled syringe, 10-BX	3 YEARS AND OLDER	90686
		0.5 ML single-dose vial, 10-BX		90686
SANOFI PASTEUR	FLUZONE PEDIATRIC (IIV4)	0.25 ML prefilled syringe, 10-BX	6-35 MONTHS	90685
SANOFI PASTEUR	FLUZONE INTRADERMAL (IIV4)	0.1 ML prefilled microinjection, 10-BX	18-64 YEARS	90630

aIIV3 MF59-adjuvanted trivalent inactivated injectable
IIV3 Egg-based trivalent inactivated injectable
ccIIV4 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.

** As of June 22, 2016, the CDC's ACIP voted against using the live attenuated influenza vaccine (LAIV), also known as nasal spray, during the 2016-2017 flu season. According to the CDC, data from the U.S. Influenza Vaccine Effectiveness Network showed a 3 percent vaccine effectiveness (VE) in study participants between 2 years and 17 years of age. This 3 percent estimate means no protective benefit could be measured, compared to traditional flu shots (IIV), which demonstrated a 63 percent VE against any flu virus among children 2 years to 17 years of age.

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