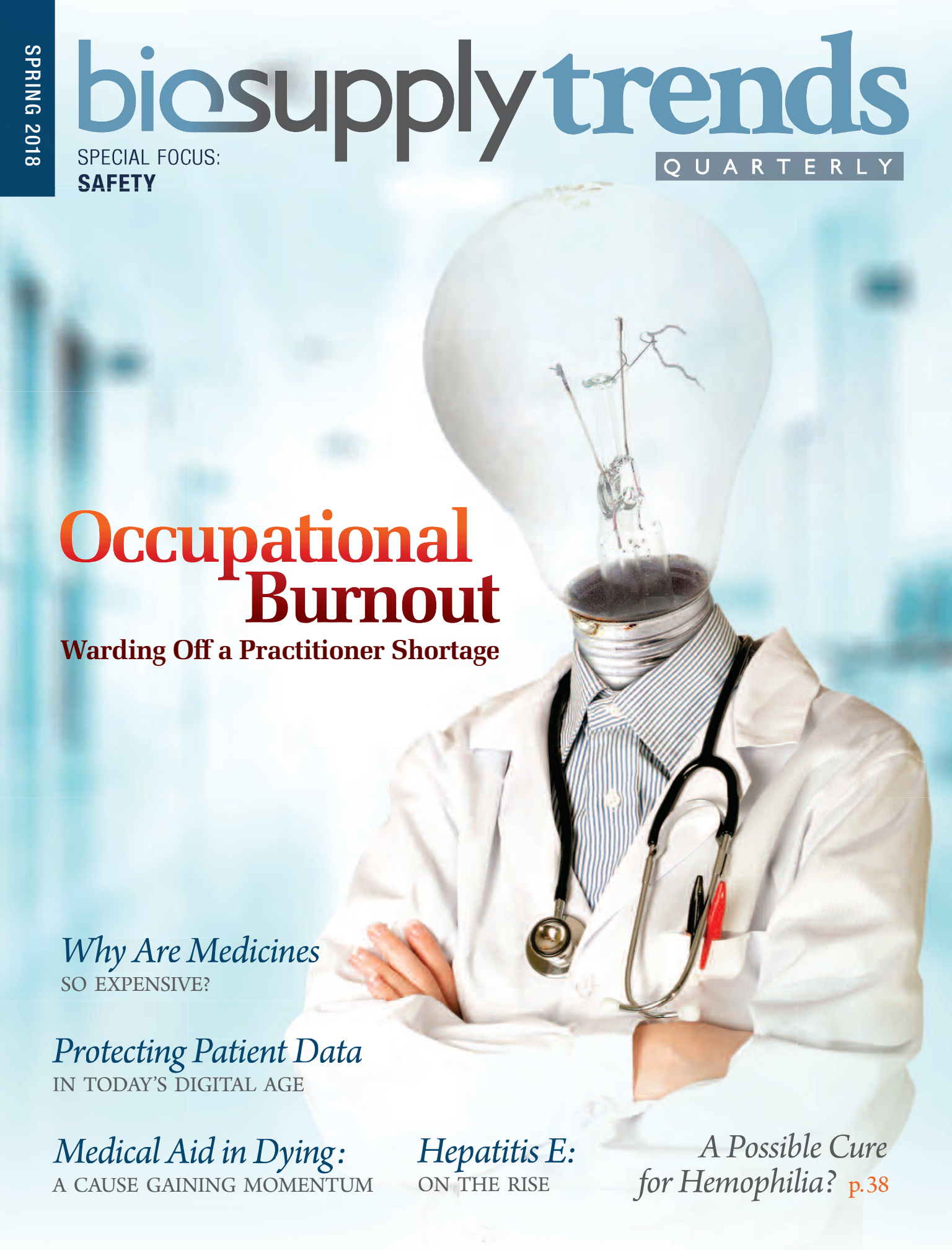
SPRING 2018

biosupply trends

QUARTERLY

SPECIAL FOCUS:
SAFETY



Occupational Burnout

Warding Off a Practitioner Shortage

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SO EXPENSIVE?

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IN TODAY'S DIGITAL AGE

Medical Aid in Dying:
A CAUSE GAINING MOMENTUM

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ON THE RISE

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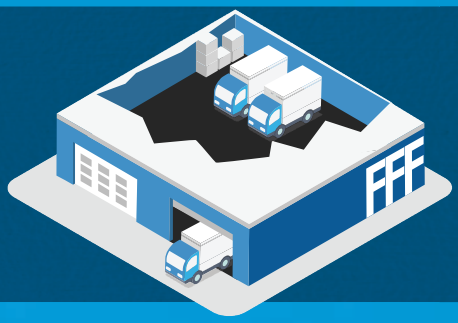
8 Critical Steps

Purchasing

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

Storage

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

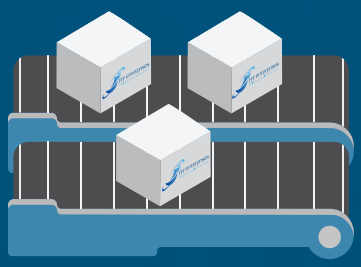


Specialty Packaging

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

Interactive Allocation

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



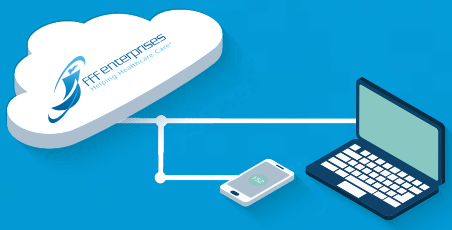
To Guaranteed Channel Integrity™

Delivery

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

Methods of Delivery

Monitoring and adjusting for extreme weather conditions allows time-sensitive delivery to ensure product integrity.



Verification

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

Tracking

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

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

FFF enterprises
Helping Healthcare Care®

More than 29 counterfeit-free years

Since 1988

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Features

Up Front

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BioSources

About BioSupply Trends Quarterly

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

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BioSupply Trends Quarterly has a circulation of 40,000, with an approximate readership of more than 100,000 decision-makers who are comprised of general practice physicians, hospital and clinic chiefs of staff and buyers, pharmacy managers and buyers, specialist physicians and other healthcare professionals.

For information about advertising in *BioSupply Trends Quarterly*, you may request a media kit from Ronale Tucker Rhodes at (800) 843-7477 x1362, rrhodes@bstquarterly.com.

Our Commitment to Safety

HELPING HEALTHCARE CARE remains the constant guiding principle behind FFF Enterprises' business model since its launch 30 years ago. We are committed to raising pharmaceutical industry standards, ensuring safe distribution of pharmaceuticals, and providing healthcare professionals with innovative solutions that promote the quality and safety of medical care. *BioSupply Trends Quarterly*, by design, is one way we further our mission to be a source of informative and timely material that covers events affecting our industry. Our focus this issue concentrates on several crucial safety concerns practitioners, patients and drug manufacturers face today.

With increasing administrative burdens placed on healthcare providers, there is growing evidence of occupational burnout among practitioners. Indeed, it is now known that more than half of physicians today have at least one sign of burnout such as feeling overextended, unsympathetic toward patients and lack of work achievement. This development, touted as a "national public health crisis" for its potential impact on patient safety, is covered in our article "Banishing Burnout in the Healthcare Setting" that points out how to identify ways to deal with burnout. To avoid a potential practitioner shortage, it seems clear that support in the form of improved workflow operations, reduced electronic health record (EHR) burdens and adequate allotted times to interact with patients can provide needed relief.

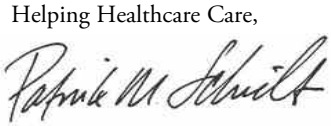
The recommendation to reduce EHR burdens is not meant to minimalize the importance of compliance to protect patients' safety. Importantly, updated Health Information Portability and Accountability Act (HIPAA) rules require healthcare organizations protect patients against data breaches made possible by today's digital age. As we explain in our article "Healthcare Data: Ensuring Regulatory Compliance," three additional rules must now be followed, including the privacy rule, security and enforcement rule and the Health Information Technology for Economic and Clinical Health Act. While the requirements can be complicated, organizations can best conform to these by assessing risk, making security part of their culture, understanding when information can be shared and following strict protocols when data is breached.

Of course, patient rights must continue to be protected in the event of terminal illness. As our article "The Evolution of Medical Aid in Dying" points out, while the right-to-die issue is controversial, existing laws call for adherence to strict criteria to ensure the process is safe. Oregon set the example with its Death with Dignity Act that now has 20 years of data showing the law is working as intended. Since its passage, five other states have enacted medical aid in dying laws, and 27 more states are considering them.

Lastly, lack of access to prescription medications is another safety concern for all involved, including patients, practitioners and drug manufacturers. One of the leading barriers to medication access is price, which can cause patients to go without medications or look for dangerous alternatives. It's no secret drug prices in the U.S. are high compared with other nations. The question, though, is: Who is responsible? We delve into this topic in our article, "Are Drugs Really Overpriced?" And, while some answers might surprise many, increased transparency is needed before the full account for high drug prices can be truly understood.

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

biosupply trends QUARTERLY

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

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CMS Launches Voluntary Bundled Payment Model

The Centers for Medicare and Medicaid Services (CMS) Center for Medicare and Medicaid Innovation has launched a new voluntary bundled payment model called Bundled Payments for Care Improvement Advanced (BPCI Advanced). Whereas Medicare pays providers for each individual service performed under traditional fee-for-service payment, under the BPCI Advanced model, participants can earn additional payment if all expenditures for a beneficiary's episode of care are under a spending target that factors in quality. Participants may receive payments for performance on 32 different clinical episodes such as major joint replacement of the lower extremity (inpatient) and percutaneous coronary intervention (inpatient or outpatient). The goal is to create incentives for providers and practitioners to work together to coordinate care and engage in continuous improvement to keep spending under a target amount. BPCI Advanced also qualifies as an Advanced Alternative Payment Model, under which providers take on financial risk to earn incentive payments.

According to CMS, the BPCI Advanced model takes into account rigorous evaluation results from previous models, industry experience with bundled payment, and stakeholder input from healthcare providers at acute care hospitals, physician group practices and other providers and suppliers. The model starts Oct. 1, 2018, and continues through Dec. 31, 2023. More information about the model, its requirements and application process can be found at innovation.cms.gov/initiatives/bpci-advanced. ❖

CMS Announces New Payment Model to Improve Quality, Coordination, and Cost-Effectiveness for Both Inpatient and Outpatient Care. Centers for Medicare and Medicaid Services press release, Jan. 9, 2018. Accessed at www.cms.gov/Newsroom/MediaReleaseDatabase/Press-releases/2018-Press-releases-items/2018-01-09.html.

Hike Proposed for Medicare Payments in 2019

The Centers for Medicare and Medicaid Services has proposed a 1.84 percent increase in 2019 Medicare payments to health insurers that manage Medicare Advantage insurance plans for more than 20 million elderly and disabled people. The proposed rate, which was near analyst expectations, affects how much insurers charge for monthly healthcare premiums, plan benefits and how much they profit. It also expands the benefits insurers can offer in the plans to include items such as wheelchair ramps and devices to diminish the impact of health conditions.

As of January, enrollment in Medicare Advantage plans was 20.9 million, accounting for 35 percent of overall Medicare enrollment. The largest sellers of these plans are UnitedHealth Group, Humana, Aetna and WellCare Health Plans. ❖

Humer C. U.S. Government Proposes 1.84 Percent Hike in 2019 Payments to Medicare Insurers. Reuters, Feb. 1, 2018. Accessed at www.reuters.com/article/us-usa-healthcare-medicare/u-s-government-proposes-1-84-percent-hike-in-2019-payments-to-medicare-insurers-idUSKBN1FL6K7.

HHS Forms Conscience and Religious Freedom Division

The U.S. Department of Health and Human Services (HHS) has formed a new Conscience and Religious Freedom Division in the HHS Office for Civil Rights (OCR) to restore federal enforcement of U.S. laws that protect the fundamental and unalienable rights of conscience and religious freedom. The new division will provide HHS with the focus it needs to more vigorously and effectively enforce existing laws protecting these rights. "Laws protecting religious freedom and conscience are just empty words on paper if they aren't enforced," said OCR Director Roger Severino. "No one should be forced to choose between helping sick people and living by one's deepest moral and religious convictions, and the new division will help guarantee that victims of unlawful discrimination find justice. For too long, governments big and small have treated conscience claims with hostility instead of protection, but change is coming and it begins here and now." ❖

HHS Announces New Conscience and Religious Freedom Division. U.S. Department of Health and Human Services press release, Jan. 18, 2018. Accessed at www.hhs.gov/about/news/2018/01/18/hhs-ocr-announces-new-conscience-and-religious-freedom-division.html.

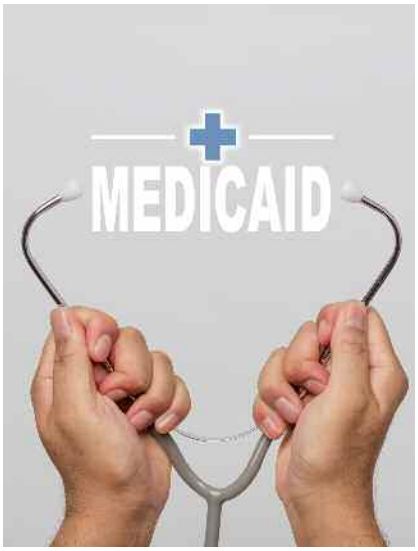
New Policy Guidance Issued to Improve Medicaid Beneficiary Enrollment

To support efforts to improve Medicaid enrollee health outcomes by incentivizing community engagement among able-bodied, working-age Medicaid beneficiaries, the Centers for Medicare and Medicaid Services (CMS) is providing new policy guidance to help states design demonstration projects that promote the objectives of the Medicaid program and are consistent with federal statutory requirements. The guidance is in response to state requests to test programs through these projects in which work or participation in other community engagement activities, including skills training, education, job search, volunteering or caregiving, would be a condition for Medicaid eligibility. However, this condition would not apply to individuals with a disability, elderly beneficiaries, children and pregnant women.

Specifically, CMS has identified a number of issues for states to consider:

• Because of areas of high unemployment or caregiving for young children or elderly family members, states will be required to describe strategies to assist eligible individuals in meeting work and community engagement requirements and to link individuals to additional resources for job training, provided they do not use federal Medicaid funding to finance those services.

• States should align their efforts with



Supplemental Nutrition Assistance Program or Temporary Assistance for Needy Families requirements, where appropriate.

• Federal disability and civil rights laws must be fully complied with to ensure all individuals with disabilities have the necessary protections to ensure they are not inappropriately denied coverage. In addition, states will be required to offer reasonable modifications to individuals with disabilities, and will be required to exempt individuals determined to be medically frail or who have an acute condition that a medical professional has determined will prevent them from complying with the requirements.

• States will be required to make reasonable modifications for individuals with opioid addiction and other substance use disorders. These modifications may include counting time spent in medical treatment toward an individual's community engagement requirements or exempting individuals participating in intensive inpatient or outpatient medical treatment, as well as supporting other state efforts.

• States are encouraged to consider a range of activities that could satisfy work and community engagement requirements such as career planning, job training, referral and volunteering opportunities, as well as job support services offered in connection with the requirement, and they should take into account people's employability and potential contributions to the labor market.

"States have the opportunity to help individuals improve and enhance the skills that employers truly value," said Seema Verma, CMS administrator. "People who participate in activities that increase their education and training are more likely to find sustainable employment, have higher earnings, a better quality of life, and, studies have shown, improved health outcomes." ❖

CMS Announces New Policy Guidance for States to Test Community Engagement for Able-Bodied Adults. Centers for Medicare and Medicaid Services press release, Jan. 11, 2018. Accessed at www.cms.gov/Newsroom/MediaReleaseDatabase/Press-releases/2018-Press-releases-items/2018-01-11.html.

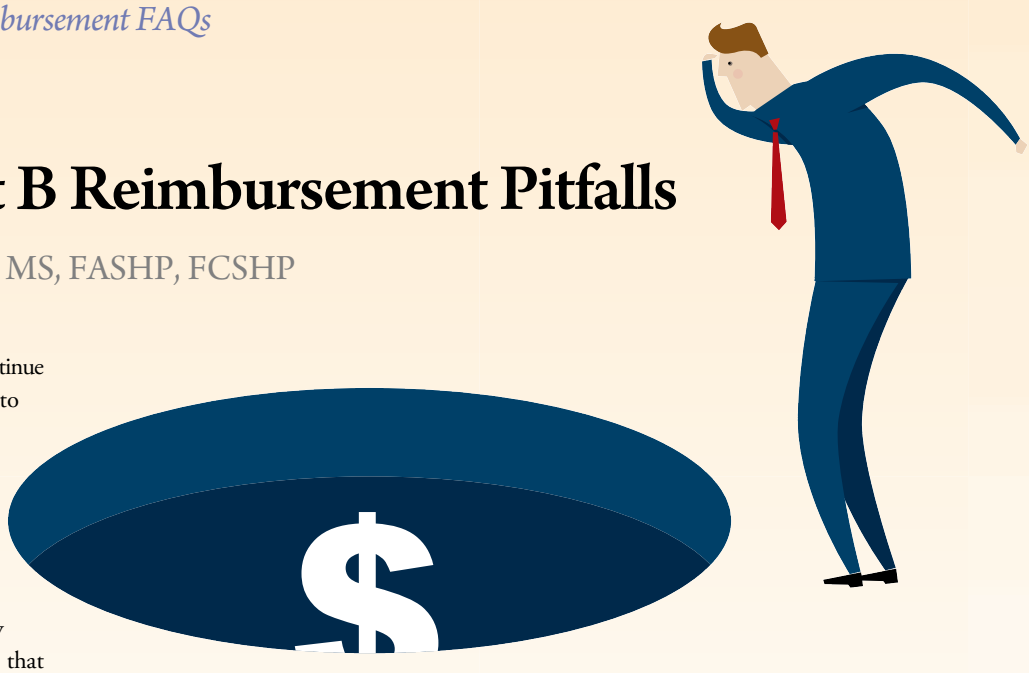
New Secretary of Health and Human Services Confirmed

On Jan. 24, Alex Michael Azar II was confirmed the 24th Secretary of Health and Human Services. Most recently, Azar was chairman of Seraphim Strategies, LLC. Prior to that, he was president of Lilly USA, LLC, the largest affiliate of global biopharmaceutical leader Eli Lilly and Company. During the George W. Bush administration, he served as the deputy secretary of the U.S. Department of Health and Human Services immediately after serving as its general counsel, receiving Senate confirmation for both presidential appointments by voice vote. He earned

his bachelor's degree from Dartmouth College and his juris doctorate from Yale University. ❖

Avoiding Part B Reimbursement Pitfalls

By Bonnie Kirschenbaum, MS, FASHP, FCSHP



AS HEALTHCARE PRICES continue to skyrocket, practitioners can help to mitigate the impact by fully meeting the reimbursement requirements for Part B drugs in outpatient settings. Providing all appropriate information for reimbursement ensures payment is forthcoming when a patient's story is told completely and accurately in a codeable fashion that describes what was done and what was used.

Review Documentation for Reimbursement

First, be sure the diagnosis that supports the drug use is charted completely for detailed ICD-10 assignment by the revenue cycle team. Next, verify the name of the drug is linked to a Healthcare Procedural Coding System (HCPCS) code. If a miscellaneous HCPCS code is used in the interim before permanent assignment, the national coverage determination (NCD) number must accompany it as well. Payment is for the actual dose of the drug administered, not for the amount of the drug in a vial or package. This actual dose is converted into billing units using the Centers for Medicare and Medicaid Services (CMS)-created values. The amount of drug waste, if applicable, is also converted into billing units and assigned the JW modifier. The CMS-assigned status indicator (SI) determines the payment classification. If the drug has been given by an intravenous (IV) infusion, then electronic health record (EHR) documentation supporting an injectable drug administration charge is essential.

Who, What and Why?

Where does all this information come from, and who is responsible for providing it? The diagnosis that supports the choice of the drug and its use is essential, and it must be documented completely and accurately in the EHR by the clinician ordering the drug. The use of a computerized physician order entry (CPOE) should support the requirements outlined in prior authorization (PA) requirements set by the payer and the local/national coverage determination (LCD/NCD) requirements set by Medicare.

How this is done and who is responsible for creating the appropriate order sets depends on core competency. Similarly, core competency is necessary for the correct assignment of the HCPCS code and the creation of the billing unit conversion crosswalk. Commercial resources may be available at the practitioner's site. If so, they should be used to their maximum potential. This also applies to recovering revenue for waste. Never assume the initial assignment is error-free. It must be checked and rechecked at each step of the transmission throughout the revenue cycle process. The SI assigned to the drug will signal what revenue to expect and the method of payment, either separate or bundled. Most expensive products used in the outpatient prospective payment system (OPPS) setting are given by IV infusion, which is reimbursed separately from the drug itself. EHR documentation supporting this charge is essential, so it should be incorporated into the EHR system to ensure the process is seamless and accurate with an automatic prompt for documentation of administration.

Examples of Documentation Gone Wrong

Examples of inappropriate paths a drug can take may provide some ideas of where problems could be encountered and how to correct them to ensure payment.

Example: A patient is registered appropriately, including payer information, but the payer information is not passed on to the pharmacy. Or, the prescriber charts scantily because he/she is not aware of what is necessary, and the revenue cycle team assigns codes that don't meet payer requirements.

Correction: Make payer information automatically available to the pharmacy. The CPOE file system should include PA/LCD/NCD information so payer requirements are available at the time of drug order entry. If this is not done, neither the prescriber nor the pharmacy is aware of the requirements.

Example: A place was not created in the EHR for the details of the PA to be documented.

Correction: The EHR should be retooled to accommodate payment requirements. To do otherwise risks claim denial due to lack of medical necessity. It's not that the

drug choice is wrong or the patient does not meet the criteria for its use. Payment refusal was due to a cascade of poor choices and actions by the clinical and IT teams in setting up the EHRs.

Example: A mismatch occurred between the pharmacy drug master (PDM)/charge description master (CDM) and the HCPCS billing units and SI.

Correction: Vigilance is essential with these two dynamic file sets. Regular review of the progression of charges through the various IT systems is necessary to identify glitches. It's unacceptable to follow a "set it, forget it and don't routinely check it" procedure.

Example: The pharmacy is unaware of how to bill for wasted payable injectable drugs from single-dose vials, amps and syringes.

Correction: Create a candidate list by identifying SI G- and K-eligible drugs, and update it quarterly. Billing unit conversions are essential for waste, as well as for the actual dose of the drug used. This can only be accomplished if an accurate crosswalk with the PDM/CDM is set up to accommodate required charting. Also, the pharmacy must continually follow up on this. It cannot opt for "robo-billing" in which the revenue cycle team has no idea what the clinician or IV preparation area actually did, but simply churned out bills based on an IT infrastructure. The ultimate test of success is a match between the actions of a clinician or IV prep area and what is actually charted and billed.

> "As practices move forward, they must stay alert to changes and recognize everyone shares the responsibility for reimbursement."

Example: A pharmacy is unaware of how to implement the 2018 OPPS 340B reimbursement changes, and it either overestimated or underestimated the financial impact.

Correction: Identifying the candidate drugs is an essential first step with the creation of a list of eligible SI K drugs purchased at 340B price that is updated quarterly. Modifier assignment is a CMS requirement. An accurate crosswalk must be provided to the revenue cycle team of SI K drugs bought at 340B price requiring the JG modifier and SI G drugs bought at 340B price requiring the TB modifier. Once again, reality must match billing. All 340B drugs must be accurately represented with the JG modifier on Medicare bills only for 340B-eligible patients.

A Shared Responsibility

As practices move forward, they must stay alert to changes and recognize everyone shares the responsibility for reimbursement. No one person has all the core competencies needed. Reimbursement can only be successful through teamwork and designating who is going to do what. This means the pharmacy and therapeutics committee makes wise progressive decisions, clinicians write complete orders, IT creates a favorable system, pharmacy, nursing and social services do their parts, and the revenue cycle team submits the code sets that tell the patient's story completely and accurately. ❖

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.

Vaccines

Study Finds 2017-18 Flu Vaccine More Protective Than Believed, Especially Among Children

With many reports about this year's influenza (flu) vaccine ineffectiveness, a new study shows it is more effective than thought, especially among children. Results of the preliminary study involving 4,600 people, which will be updated at the end of the flu season, show the vaccine is 25 percent effective against the most common strain, H3N2, 42 percent effective against influenza B viruses and 67 percent effective against H1N1 viruses. And, children age 6 months to 8 years responded significantly better to the vaccine than older adults. These results are in contrast with a study in Australia that suggested the vaccine would be only 10 percent effective against the H3N2 virus, as well as a Canadian study that put that figure at 17 percent. Also encouraging is that the H3N2 strain of flu is becoming less common relative to other strains more easily

curbed by the vaccine. "Even with current vaccine effectiveness estimates, vaccination will still prevent influenza illness, including thousands of hospitalizations and deaths," said scientists from the Centers for Disease Control and Prevention. ❖

Harris R. Young Kids Are Getting the Best Protection From Current Flu Vaccine. NPR, Feb. 15, 2018. Accessed at www.npr.org/sections/health-shots/2018/02/15/586041989/young-kids-are-getting-the-best-protection-from-current-flu-vaccine.

Vaccines

Influenza Vaccine Coverage Is Highest Among Workplaces with Vaccination Requirements

An Internet panel survey of healthcare personnel (HCP) from March 28, 2017, through April 19, 2017, showed the overall influenza vaccination coverage estimate among HCP was 78.6 percent in the 2016-17 season, an increase of 15 percentage points since the 2010-11 season, but similar to the 2013-14 through 2015-16 seasons, with the highest coverage among those whose workplace had vaccination requirements. In workplaces without vaccine requirements, HCP with vaccination available at the workplace had higher coverage than those without onsite vaccination. And, HCP working in hospital settings consistently reported higher vaccination coverage than those working in other settings, and they were most likely to report workplace vaccination requirements and onsite vaccination.

The survey, conducted by Abt Associations for the Centers for Disease Control and Prevention, included 2,438 HCP through Medscape or Survey Sampling International Internet panels. ❖

Black CL, Yue X, Ball SW, et al. Influenza Vaccination Coverage Among Health Care Personnel — United States, 2016-17 Influenza Season. *Morbidity and Mortality Weekly Report,* Sept. 29, 2017. Accessed at www.cdc.gov/mmwr/volumes/66/wr/mm6638a1.htm?s_cid=mm6638a1_w.

Medicines

Higher-Potency Rabies IG Vaccine Receives FDA Approval

Grifols' HyperRAB (rabies immune globulin [human]) has been approved by the U.S. Food and Drug Administration (FDA) to treat rabies postexposure prophylaxis. The new formulation is twice the potency (300 IU/mL) of currently available rabies immune globulin options, offering a greater concentration of anti-rabies virus antibodies within each mL of volume, as well as the potential for fewer injections by significantly reducing the volume of medication administered in each dose. It is manufactured using a caprylate chromatography process, which reduces procoagulant activity and product impurities such as IgG aggregates.

Each year, approximately 60,000 people in the U.S. are treated with postexposure prophylaxis following exposure to an animal that is known or believed to have rabies. The Advisory Committee on Immunization Practices and the Centers for Disease Control and Prevention (CDC) recommend immediate prophylaxis following exposure to rabies, including a rabies immune globulin injection directly into the wound site to prevent the virus from entering the central nervous system, which eventually leads to death.

"This is the first advancement in administration of human rabies immune globulin treatment in over 40 years," said Charles Rupprecht, VMD, MS, PhD, expert technical advisor on rabies for the Pan American Health Organization/World Health Organization, and former chief of the rabies program at CDC. "Because patients are required to be dosed by weight, the increased potency of this new formulation allows more rabies antibodies per mL to go directly into wounds in delicate areas such as the extremities or face. Administration in these areas has proven to be very uncomfortable for patients, especially children, and challenging for healthcare professionals in administration of the full dose." ❖

Grifols HyperRAB (Rabies Immune Globulin [Human]) 300 IU/mL Receives FDA Approval to Treat Patients Exposed to Rabies Virus Infection. Grifols press release, Feb. 6, 2018. Accessed at www.prnewswire.com/news-releases/grifols-hyperrab-rabies-immune-globulin-human-300-iuml-receives-fda-approval-to-treat-patients-exposed-to-rabies-virus-infection-300594182.html.

Medicines

FDA Approves First Biosimilar to Fight Cancer

In September, the U.S. Food and Drug Administration (FDA) approved the first biosimilar drug to treat cancer. Mvasi (bevacizumab-awwb) was approved as a biosimilar to Avastin (bevacizumab) for the treatment of adults with certain colon, lung, brain, kidney and cervical cancers. Specifically, the approved indications include:

- metastatic colorectal cancer in combination with IV 5-fluorouracil-based chemotherapy for first- or second-line treatment;
- metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for the second-line treatment of patients who have progressed on a first-line bevacizumab product-containing regimen;
- nonsquamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease;
- glioblastoma with progressive disease after prior therapy, based on improvement in objective response rate (no data available demonstrating improvement in disease-related symptoms/survival with bevacizumab products);
- metastatic renal cell carcinoma, in combination with interferon alfa; and
- cervical cancer that is persistent, recurrent or metastatic, in combination with paclitaxel and cisplatin or paclitaxel and topotecan.

Mvasi is marketed by Amgen. Like Avastin, the labeling for Mvasi has a boxed warning about an increased risk of holes in the stomach and intestines; surgery and wound-healing complications; and severe or fatal pulmonary, gastrointestinal, central nervous system and vaginal bleeding. Common side effects include nosebleeds, headache, high blood pressure, inflammation of the nasal cavity, high levels of protein in the urine, taste alteration, dry skin, rectal bleeding, excessive tear production, back pain and skin irritation. In addition, women who are pregnant should not take Mvasi because it may cause harm to a developing fetus. ❖

FDA OKs First 'Biosimilar' Drug to Fight Cancer. U.S. Food and Drug Administration press release, Sept. 14, 2017. Accessed at www.clinicalconnection.com/health-news/news-article/40900/fda-oks-first-biosimilar-drug-to-fight-cancer.

First-Ever Biosimilar to Fight Cancer Approved by FDA. *Pharmacy Practice News,* Sept. 15, 2017. Accessed at www.pharmacypracticenews.com/FDA-Approvals/Article/09-17/First-Ever-Biosimilar-to-Fight-Cancer-Approved-by-FDA/44607/ses=ogst?enl=true.

Medicines

Mylan's Ogivri Approved as Biosimilar to Herceptin

Mylan's Ogivri (trastuzumab-dkst) has been approved by the U.S. Food and Drug Administration as a biosimilar to Genentech's Herceptin (trastuzumab) for the treatment of patients with HER2-overexpressing breast or metastatic stomach cancer (gastric or gastroesophageal junction adenocarcinoma). Approval was based on comparisons of extensive structural and functional product characterization, animal data, human pharmacokinetic and pharmacodynamic data, and clinical studies, including clinical immunogenicity between Ogivri and Herceptin, which demonstrated Ogivri is highly similar to Herceptin and there are no clinically meaningful differences between the products. ❖

FDA Approves Ogivri as a Biosimilar to Herceptin. U.S. Food and Drug Administration press release, Dec. 1, 2017. Accessed at www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm587404.htm.

Vaccines

Universal Flu Vaccine Begins Two-Year Clinical Trial

Researchers at the University of Oxford have begun a two-year clinical trial to test a universal influenza (flu) vaccine in more than 2,000 patients. The vaccine, developed by Oxford University's Jenner Institute and Vaccitech, a biotech company founded by Jenner scientists, works by using proteins found in the core of the virus that remain stable, rather than those on its surface that mutate all the time. The vaccine stimulates the immune system to boost virus-killing T cells instead of antibodies. Previous research has shown that T cells can help fight more than one type of flu virus. The researchers are hoping the vaccine will provide better and longer-lasting protection when used along with the seasonal flu shot. "We're hoping it will last two to three years — maybe even four years — but we don't really know until we do the trials," said Tom Evans, Vaccitech's chief executive.

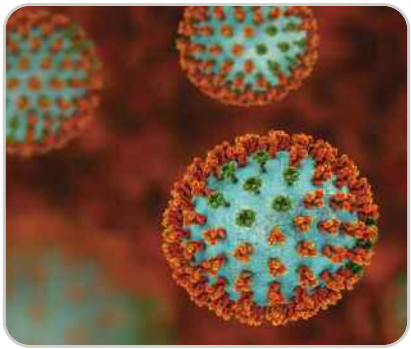
The vaccine has already been tested for safety in earlier trials. The new mid-stage Phase IIb testing will recruit at least 500 British subjects this season with the remainder to be recruited during the 2018-19 flu season. It is the first time a universal flu vaccine has progressed beyond Phase I clinical testing. ❖

Hirschler B. Oxford Team to Test Universal Flu Vaccine in World First. Reuters, Oct. 3, 2017. Accessed at www.reuters.com/article/us-health-flu-vaccine/oxford-team-to-test-universal-flu-vaccine-in-world-first-idUSKCN1C80NI.

Research

New Pill May Kill the Flu Virus in Patients in 24 Hours

Japanese drug maker Shionogi has created an experimental compound delivered via a single-dose pill that has been shown to effectively kill the influenza (flu) virus in patients within a single day. In a Phase III clinical trial of baloxavir marboxil, the average amount of time the compound took to kill the virus in otherwise healthy adults was just more than 24 hours. That is in contrast to participants treated with Tamiflu (oseltamivir), which took 72 hours to kill the flu virus, and those given a placebo, which took 96 hours to heal from the flu. The drug works by blocking an enzyme the virus uses to reproduce itself in infected cells. And, it targets both the A and B types of flu virus.



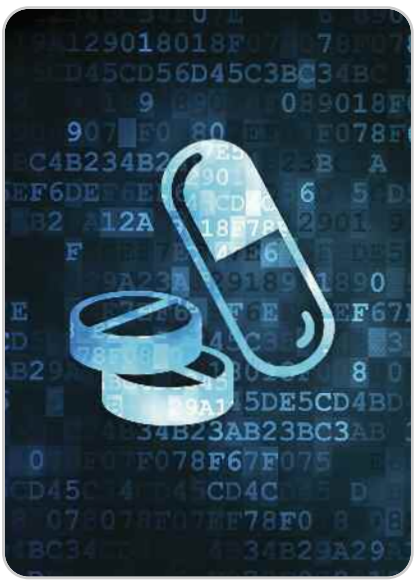
The advantages of the experimental compound are twofold: 1) The overall time to alleviate symptoms was similar with both baloxavir marboxil and oseltamivir, but the experimental drug provides immediate relief faster, which may help to curb the virus's contagiousness. 2) It is a single-dose delivery, compared with oseltamivir's 10-dose regimen (two doses daily for five days). "The advantage is that it's one pill once, versus a course of therapy, so particularly for pandemic planning, this could be an advantage," said the head of co-developer Roche's pharma unit, Daniel O'Day. (Roche is the manufacturer of Tamiflu.) "You don't have the potential resistance that comes with not completing your course of therapy."

In February, Japan's healthy ministry approved the drug, and it is expected to be available there in May. Roche, which will have the rights to distribute the drug internationally, will apply for approval to sell the drug in the U.S. this summer, with a decision expected sometime in 2019. ❖

Bedoya D. Japanese Company Claims Experimental Drug Kills Flu Virus in a Single Day. Infosurhoy, Feb. 13, 2018. Accessed at www.infosurhoy.com/cocoon/saii/xhtml/en_GB/health/japanese-company-claims-experimental-drug-kills-flu-virus-in-a-single-day.

Medicines

First Digital Pill for Mental Illness Approved by FDA



Abilify MyCite (aripiprazole tablets with sensor; Otsuka Pharmaceutical), the first digital ingestion tracking system, has been approved by the U.S. Food and Drug Administration (FDA). The drug, which is approved for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar 1 disorder and for use as an add-on treatment for depression in adults, has an ingestible sensor embedded in the pill that records that the medication was taken. The system works by sending a message from the pill's sensor to a wearable patch, which transmits the information to a mobile application so patients can track the ingestion of the medication on their smartphone. Patients can also permit their caregivers and physicians to access the information through a web-based portal.

"Being able to track ingestion of medications prescribed for mental illness may be useful for some patients," said Mitchell Mathis, MD, director of the Division of Psychiatry Products in the FDA's Center for Drug Evaluation and Research. "The FDA supports the development and use of new technology in prescription drugs and is committed to working with companies to understand how technology might benefit patients and prescribers."

According to Abilify MyCite's prescription labeling, the ability of the product to improve patients' compliance with their treatment regimen has not been shown, and the product should not be used to track ingestion in "real time" or during an emergency because detection may be delayed or may not occur. A boxed warning on the product alerts healthcare professionals that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death, and warns about an increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants. ❖

FDA Approves Pill with Sensor That Digitally Tracks If Patients Have Ingested Their Medication. U.S. Food and Drug Administration news release, Nov. 13, 2017. Accessed at www.fda.gov/newsevents/newsroom/pressannouncements/ucm584933.htm.

Medicines

FDA Issues Product Advisory for CSL Behring's AlbuRx

During routine inspection of retained AlbuRx 25% samples, CSL Behring noted the potential for fading print with more effect on the expiration dating on the patient tear-off portion of the vial label. The issue is limited to 50 mL and 100 mL vial sizes. While CSL Behring is taking no action with product on the market, it is addressing the print settings to ensure readability throughout the shelf life of the product. CSL Behring recommends inspecting vial labels for readability and fading. If fading is evident, the immediate carton can be referred to for lot number and expiration dating. In addition, the lot number is imprinted on the vial aluminum seal. If the lot number and expiration dating are not able to be verified, customers are asked to contact CSL customer support at (800) 683-1288. ❖

Albumin Human 25 Percent Solution (AlbuRx 25): Product Information Advisory — Fading Print On Label. U.S. Food and Drug Administration press release, Dec. 11, 2017. Accessed at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm587337.htm.

Research

Study Finds Antibiotics Can Weaken the Immune System

Researchers at Harvard, MIT, the Wyss Institute for Biologically Inspired Engineering and the Broad Institute have found antibiotics can be counterproductive and weaken the immune system's ability to fight off bacteria. In the study, mice were infected with E. coli bacteria and then treated with a common antibiotic called ciprofloxacin. Results showed the antibiotic directly affected the tissues of the mice, which changed the metabolites (cells released during metabolism), making the E. coli more resistant to the antibiotic. At the same time, the immune cells, called macrophages, were found to be less effective at fighting off infection because the antibiotic cut off their respiration. "You generally assume that antibiotics will significantly impact the bacterial cells, and yet here they seem to be triggering responses in mammalian cells," said James Collins, senior author of the study. "The drugs are producing changes that are actually counterproductive to the treatment effort. They reduce the bacterial susceptibility to antibiotics, and the drugs themselves reduce the functional benefit of the immune cells."

The researchers plan to conduct more detailed animal studies using other antibiotics. They may also study the metabolites in human patients who are already being treated with antibiotics to see how well the findings may translate. ❖

Yang JH, Bhargaca P, McCloskey D, et al. Antibiotic-Induced Changes to the Host Metabolic Environment Inhibit Drug Efficacy and Alter Immune Function. *Cell Host & Microbe*, Nov. 30, 2017. Accessed at www.cell.com/cell-host-microbe/fulltext/S1931-3128(17)30455-9.

Medicines

First Treatment Approved by FDA to Treat EGPA

Nucala (mepolizumab, GlaxoSmithKline) has been approved by the U.S. Food and Drug Administration (FDA) to treat eosinophilic granulomatosis with polyangiitis (EGPA), a rare autoimmune disease that causes vasculitis. Approval was based on data from a 52-week trial in which patients were randomized to receive either Nucala 300 mg or placebo subcutaneously once every four weeks while continuing oral corticosteroid (OCS) therapy (OCS was tapered at week four). Results showed that compared with placebo, Nucala-treated patients achieved a significantly greater accrued time in remission, with a higher proportion of patients in the Nucala group achieving remission at both week 36 and week 48. In addition, significantly more patients who received Nucala achieved remission within the first 24 weeks and remained in remission for the 52-week study.

"Prior to today's action, patients with this challenging, rare disease did not have an FDA-approved treatment option," said Badrul Chowdhury, MD, PhD, director of the division of pulmonary, allergy and rheumatology products in FDA's Center for Drug Evaluation and Research. "The expanded indication of Nucala meets a critical, unmet need for EGPA patients. It's notable that patients taking Nucala in clinical trials reported a significant improvement in their symptoms." ❖

Ernst D. Nucala Approved to Treat Rare Autoimmune Disease That Causes Vasculitis. MPR, Dec. 12, 2017. Accessed at www.empr.com/news/nucala-mepolizumab-eosinophilic-granulomatosis-polyangiitis-churg-strauss-syndrome/article/713564.

Research

Study Shows Fever During Pregnancy Increases Risk of Autism at Birth

Researchers at Columbia University in New York have found children born to mothers who experience fever, especially multiple fevers, during the second trimester of pregnancy are at increased risk for developing autism spectrum disorder (ASD). The study analyzed data on 95,754 women participating in the Norwegian Mother and Child Cohort Study that followed pregnant Norwegian women and their children born between 1999 and 2009. They found mothers who experienced a fever above 99 degrees Fahrenheit during the second trimester of pregnancy had a 40 percent increased risk of having a child with ASD compared to women who had no fevers. The chances of ASD rose with the number of maternal fevers, increasing by more than 300 percent if a mother had three or more fevers after the first trimester.

Mady Hornig, MD, of Columbia University's Mailman School of Public Health said that since fever is caused by acute inflammation, a longer exposure of the fetus to an inflammatory environment in the womb may cause a greater disruption of brain development. This increased risk of

ASD among women with prenatal fevers has been reported previously, say the researchers, but their study is the first large, prospective investigation showing a so-called dose-response effect. In addition, their study provides clues about which drug to use during pregnancy to control the fever. This is because not all of the mothers who took the nonsteroidal anti-inflammatory ibuprofen to treat the fever during the second trimester had a child who developed ASD, but mothers who took acetaminophen during that time had very little difference in their child's fever-related risk for ASD. The researchers note, however, that numbers of women who used ibuprofen during pregnancy are small, so they can't be confident that ibuprofen had mitigating effects.

"What is particularly important about our findings is that it not only strengthens the evidence for a particular pathway for ASD, but it also suggests that we may be very close to understanding how to safely mitigate or prevent some outcomes by directing prevention or intervention strategies toward this pathway," said Dr. Hornig.

Because the study didn't address the cause of fever, there is an ongoing study that is "testing blood samples collected at mid-pregnancy and at birth to explore the possible role of specific infectious agents and the contribution of distinctive patterns of immune response among mothers and children to understand the mechanisms creating vulnerability." ❖

Hornig M, Bresnahan MA, Che X, et al. Prenatal Fever and Autism Risk. *Molecular Psychiatry* advance online publication 13 June 2017; doi: 10.1038/mp.2017.119.

Insurance

Medicare Costs Pose Rising Financial Burden on Older Adults

According to a Kaiser Family Foundation study, more than one-third of people with traditional Medicare spent at least 20 percent of their total income on out-of-pocket healthcare costs in 2013, and it is projected that number will increase to 42 percent by 2030. Out-of-pocket healthcare costs included premiums, deductibles and cost-sharing for Medicare-covered services, as well as spending on services not covered by Medicare such as dental and long-term care. The analysis does not include enrollees in Medicare Advantage plans, who account for 19 million of the 59 million people with Medicare.

The study found that while some people with Medicare face relatively low out-of-pocket costs, the financial burden can be especially large for beneficiaries with modest incomes and significant medical needs. For instance, among beneficiaries in traditional Medicare, just over half with incomes below $20,000 and those ages 85 and older spent at least 20 percent of their total income on health expenditures in 2013, along with more than four in 10 beneficiaries in fair or poor health status. Among all Medicare beneficiaries, out-of-pocket costs consumed 41 percent of beneficiaries' per-person Social Security income in 2013, on average. Older women and beneficiaries ages 85 and older tended to have higher average out-of-pocket spending as a share of average Social Security income than others. ❖

Many People with Traditional Medicare Spent at Least 20 Percent of Their Income on Health Care in 2013. Kaiser Family Foundation, Jan. 29, 2018. Accessed at www.kff.org/medicare/press-release/more-than-one-third-of-people-with-traditional-medicare-spent-at-least-20-percent-of-their-total-income-on-health-care-in-2013.

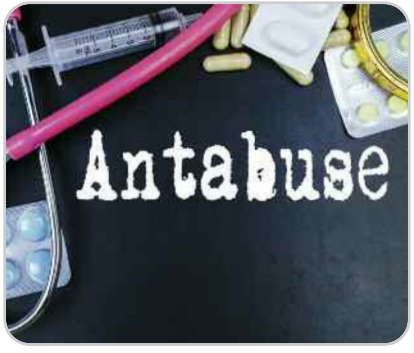
Research

Study Shows Antabuse Lowers Risk of Death from Cancer

A nationwide epidemiological study has shown cancer patients who continuously used disulfiram (Antabuse), a drug prescribed to alcoholics to prevent them from drinking, have a lower risk of death from cancer compared to those who stopped using the drug once diagnosed. In addition, the study's researchers identified the ditiocarb-copper complex as the metabolite of disulfiram responsible for its anticancer effects.

In the study, researchers observed the drug's effect on both living mice and on human cancer cells and noted that when the drug is metabolized, it causes the protein NPL4 to clump together with the enzyme P97, which immobilizes the protein and freezes cancer cells, thus preventing them from disposing of unnecessary proteins. This buildup stresses the cancer cells and eventually causes them to die. Moreover, results were even more pronounced when disulfiram was combined with copper, and the drug did not discriminate when it came to what type of cancer cells it killed. In fact, it was just as effective in killing prostate, breast and colon cancer. And, only cancer cells were affected, while normal cells seemed to be unharmed.

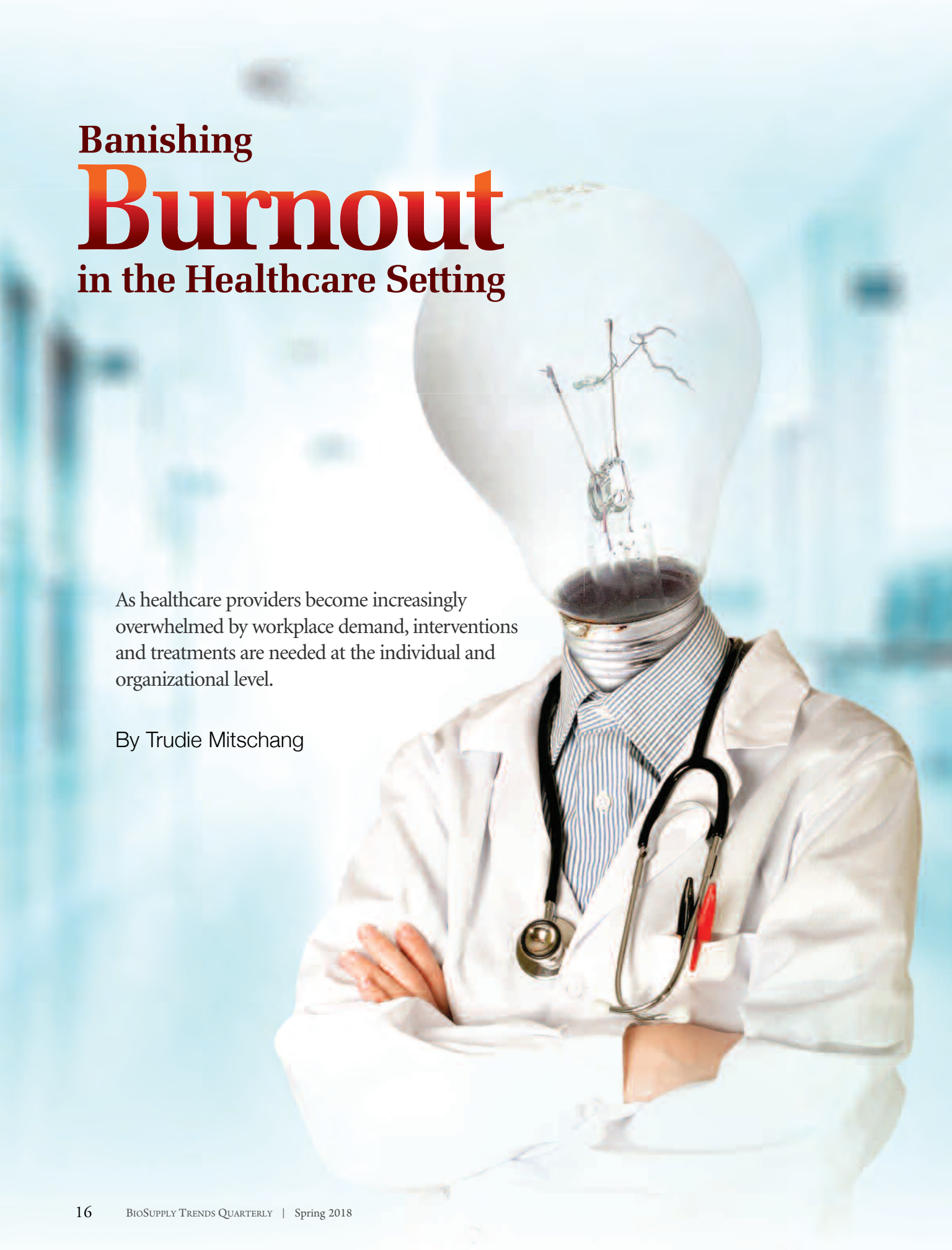
This is the first study to suggest a biological explanation for this side effect of disulfiram. However, Matthew Galsky, MD, an oncologist and professor of medicine at the Icahn School of Medicine at Mount Sinai, said it's too soon to consider this as a cancer cure because it is still unknown if the doses used to achieve these results in the laboratory can be safe and effective in human patients. "Unfortunately, we want advances quick when we are



treating cancer because this is a devastating disease, and repurposing drugs does shorten this time," said Dr. Galsky. "Still, we need to do a careful investigation in the clinic to make sure that it's safe to give adequate doses." ❖

Skrott Z, Mistrik M, Andersen KK, et al. Alcohol-Abuse Drug Disulfiram Targets Cancer Via P97 Segregase Adaptor NPL4. *Nature,* Dec. 6, 2017. Accessed at www.nature.com/articles/nature25016.

Banishing Burnout in the Healthcare Setting



As healthcare providers become increasingly overwhelmed by workplace demand, interventions and treatments are needed at the individual and organizational level.

By Trudie Mitschang

REGARDLESS OF THE profession, most people have likely experienced occupational burnout at some point in their careers. The syndrome, typically characterized by feelings of emotional exhaustion, increased apathy and fatigue, may also cause individuals to become short-tempered or irritable. In some instances, attention to detail may lag. Obviously, whether a person is an office manager, teacher or mechanic, these symptoms can be problematic and negatively impact job performance. But, if the person is a practicing physician, nurse or other healthcare provider, burnout syndrome can impact the quality of care provided and even patient safety.

So just how widespread is the problem in the healthcare sector? In late 2015, a study conducted by the Mayo Clinic, in partnership with the American Medical Association (AMA), found more than half of American physicians had at least one sign of burnout, a nearly 10 percent increase from prior study results conducted three years earlier.[1] In fact, a recent report written by a panel of prominent healthcare CEOs and presented at a 2017 AMA summit asserts burnout is becoming a "national public health crisis."[2] In addressing some of the root causes, the paper states doctors and nurses alike are working longer shifts, caring for more patients and completing more documentation for those patients. "The spike in reported burnout is directly attributable to loss of control over work, increased performance measurement (quality, cost, patient experience), the increasing complexity of medical care, the implementation of electronic health records [EHRs] and profound inefficiencies in the practice environment, all of which have altered workflows and patient interactions," the report says. "The result is that many previously well-adjusted and engaged physicians have been stressed to the point of burnout, prompting them to retire early, reduce the time they devote to clinical work, or leave the profession altogether."[2]

Diagnosing Burnout and Identifying Root Causes

In the healthcare setting, burnout is a concern with far-reaching ramifications. The syndrome can lead to reductions in focus, effort, empathy and bedside manner, which in turn may result in misdiagnoses, medical errors, suboptimal care and increased medical malpractice risk. Having an accurate means of diagnosis for this widespread problem is essential if practitioners are to receive the support and care they need.

Recognized as the leading measure of burnout among healthcare professionals, the Maslach Burnout Inventory[3] was created in 1981 by Christina Maslach, professor emerita of psychology at the University of California at Berkeley. The tool consists of 22 questions rated on a frequency and intensity scale, and is considered a go-to resource that identifies three levels or "scales" of burnout:

- Emotional exhaustion measures feelings of being emotionally overextended and exhausted by one's work.
- Depersonalization measures an unfeeling and impersonal response toward patients.
- Personal accomplishment measures feelings of competence and successful achievement in one's work.

According to Maslach, "Burnout is a negative state of physical, emotional and mental exhaustion that is the end result of a gradual process of disillusionment. It is typically found among highly motivated individuals who work over long periods of time in situations that are emotionally demanding."

Leading healthcare executives now say the way medicine is practiced in the United States is to blame, fueled in part by growing clerical demands that have doctors spending two hours on the computer for every one hour they spend seeing patients.

Changes in medicine resulting from healthcare reform have also introduced workplace pressures that threaten to further destroy the health and morale of America's healthcare providers. In the *Medscape Physician Lifestyle Report 2015*, physicians were asked to rank causes of burnout in order of significance.[4] Respondents cited:

- Excessive bureaucratic tasks
- Long hours at work
- Insufficient income
- Increasing computerization of practice
- Ramifications of the Affordable Care Act

Ann Whitehead, vice president of risk management and patient safety for CAPAssurance, notes, "Healthcare reform has dramatically changed the way medicine is delivered, and we're all in the process of transformation. Physicians are now asked and required to do much more to keep their practices going. Whereas in the past, physicians would call us with basic risk-management questions, it is now not uncommon to field calls with questions on a wide range of compliance and regulatory issues — MU2,

ICD-10, HIPAA, EHR, reimbursement issues, telehealth, CDS and many more. It is inevitable that this increase in responsibilities would detract from time spent with patients and career fulfillment."[4]

Some say the very culture of the medical field is also a culprit when it comes to burnout, citing an educational system and profession that have long rewarded self-denial, perseverance and expert performance in the face of enormous pressure. In assessing the problem, leading healthcare executives now say the way medicine is practiced in the United States is to blame, fueled in part by growing clerical demands that have doctors spending two hours on the computer for every one hour they spend seeing patients.[5]

According to Anthony Montgomery, MD, organizational psychologist and expert in physician burnout, the educational system is largely responsible for perpetuating burnout by neglecting to cultivate an essential set of skills in its learners. Dr. Montgomery explains that medical education is almost exclusively aimed at perfecting students' clinical and technical abilities — with little to no attention given to the development of the social, leadership and teamwork skills desperately needed to successfully interact with patients and colleagues.[5]

While burnout is said to be affecting all segments of the medical profession, certain areas of specialty seem to be more at risk.

Addressing Issues at the Organizational Level

In other professions, dealing with burnout can be handled with a variety of physical and mental health interventions. But, when it comes to the medical field, experts say the solutions are not so simple. "This really isn't just about exercise and getting enough sleep and having a life outside the hospital," says Tait Shanafelt, MD, a former Mayo Clinic researcher. "It has at least as much or more to do with the environment in which these folks are practicing."[5]

In a recent study, researchers conducted a meta-analysis evaluating existing randomized clinical trials and before-and-after studies of physician burnout interventions. Specifically, they assessed the effectiveness of two types of burnout interventions:

• Physician-directed, or approaches that target individuals, such as mindfulness or cognitive behavioral techniques to improve coping, communication and competence; and

• Organization-directed, or approaches that focus on improving the workplace environment, such as changes in scheduling, workload, practice operation and decision-making.

The study's takeaway was that while physician-directed interventions held merit, when it comes to actually beating and preventing physician burnout altogether, organization-directed interventions have a greater positive influence. "The first step to overcoming burnout at the organization level is to listen and understand the root causes. Then, offer institutional support, which can take many forms, including optimizing physician workflows, reducing EHR burdens and increasing physician time on direct patient care. These organization-directed interventions will have a greater effect on burnout among your physicians," says the study.[6]

Last July, the National Academy of Medicine called on researchers to identify specific organizational interventions intended to ease burnout; and, in the meantime, many hospitals and even health insurers have stepped in to do their part.[5]

In 2017, Cleveland Clinic increased the number of nurse practitioners and other highly trained providers by 25 percent to handle more routine tasks for its 3,600 physicians. It also hired eight pharmacists to assist with prescription refills.

Atrius Health, Massachusetts' largest independent physicians group, is addressing administrative "overload" by diverting email traffic away from doctors to other staffers and simplifying medical records. The goal, it says, is to cut 1.5 million "mouse clicks" per year.

Insurer UnitedHealth Group, which operates physician practices for more than 20,000 doctors through its Optum subsidiary, launched a program to help doctors quickly determine whether drugs are covered by a patient's insurance plan during the patient visit. It is also running a pilot program for Medicare plans in eight states to shrink the number of procedures that require prior authorization.

A Career in Crisis

While burnout is said to be affecting all segments of the medical profession, certain areas of specialty seem to be more at risk. In 2015, AMA and Mayo Clinic conducted a survey[7] of 6,880 doctors to assess the occurrence of burnout. The top five specialties with the highest rates of burnout were providers who practiced:

1) Emergency medicine
2) Urology
3) Physical medicine and rehabilitation
4) Family medicine
5) Radiology

Additional studies indicated, in some instances, practitioners were not only questioning their chosen area of expertise, but their entire career path. The Physicians Foundation 2016

Physicians Survey[8] revealed:

- 63 percent of its respondents had negative feelings about practicing medicine;
- 49 percent experienced feelings of burnout; and
- 49 percent would not recommend a career in medicine.

While much of the responsibility for addressing burnout is focused on organizational change, this can take time. In the interim, mental health professionals familiar with the problem say healthcare workers must become proactive about recognizing the symptoms of burnout and seek immediate support when needed. Jodi De Luca, PhD, a clinical psychologist at Boulder Community Hospital Emergency Department in Colorado, encourages practitioners to take advantage of the company's employee assistance program.[7] "Many healthcare organizations offer resources for employees that include free services such as short-term counseling sessions for personal and/or work-related issues such as alcohol and substance abuse; grief and bereavement counseling; individual, couples and/or family counseling sessions; treatment for psychological disorders; assessments; referrals to specialists; and much more," she says. "The healthcare industry is very active in educating employees about the signs and consequences of burnout. Support from managers, supervisors and fellow colleagues is essential in addressing the identification, prevention and treatment of burnout."

Still others assert prevention is key. Mark Linzer, MD, director of the division of general internal medicine at Hennepin County Medical Center in Minneapolis, has studied physician burnout since 1996. He understands why many physicians eventually feel exhausted practicing medicine, but believes the problem is avoidable.[9] "Burnout doesn't have to be highly expensive to fix," Dr. Linzer says. "The problem is that no one is listening. People always want to say that physician wellness and performance measures will cost a lot of money, but preventing burnout can actually save money in the long run on recruiting and training new practice staff."

Dr. Linzer cites at least seven warning signs of burnout, including a chaotic work environment, a disagreement between personal and organizational values, and a poor work/life balance. "Spending quality time with loved ones helps physicians perform better," he explains. "When they can't do those things, it's all they think about during the day, and the patient suffers."

Moving the Needle Toward Wellness

While the medical profession is just starting to grapple with the epidemic problem of burnout, hope is on the horizon with new and innovative approaches to overall wellness. "I think most healthcare leaders now realize this is a threat to their organization, but there is also uncertainty that they can do anything effective to address it," notes Dr. Shanafelt. "They say, 'It's a national epidemic, what can we do?'"

To address this question, Dr. Shanafelt is part of a pioneering program at Stanford Medicine where he now serves as its chief wellness officer. Stanford is the first U.S. academic medical center to create such a position, and Dr. Shanafelt hopes to build a model program other medical centers will emulate.[10] Currently, Stanford's WellMD Center offers programs that include peer support, stress reduction and guidance on how to cultivate compassion and resilience. The center also aims to relieve some of the burdens on physicians through organization-level changes such as increased efficiencies and simplified workplace systems. "My experience has shown that an individual organization that is committed to this at the highest level of leadership and that invests in well-designed interventions can move the needle and run counter to the national trend of physician distress and burnout," he says.[10] ❖

While the medical profession is just starting to grapple with the epidemic problem of burnout, hope is on the horizon with new and innovative approaches to overall wellness.

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

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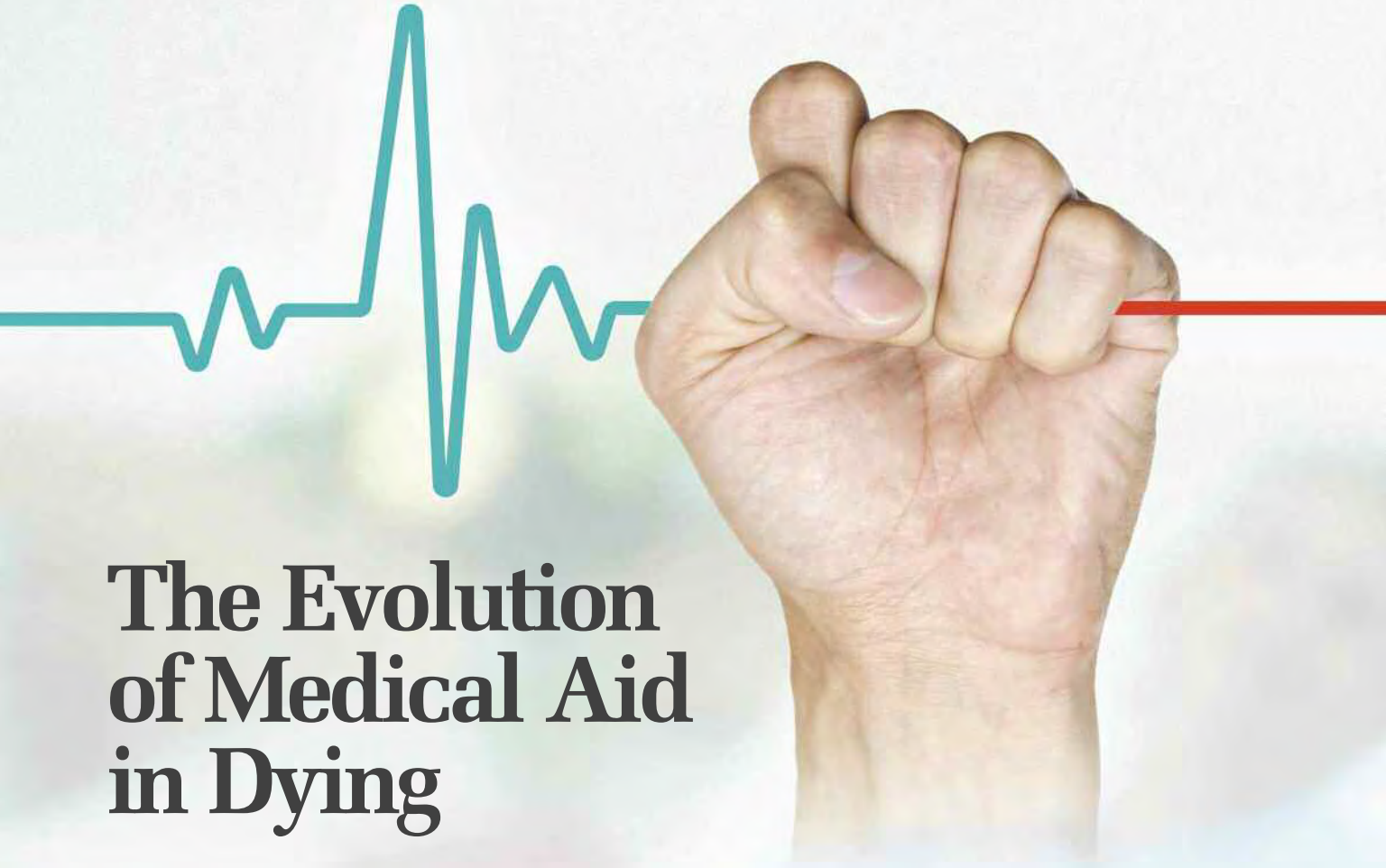

The Evolution of Medical Aid in Dying

The right-to-die movement advocating the passage of state legislation to allow medical aid in dying is gaining momentum.

By Diane L.M. Cook

THE RIGHT-TO-DIE movement started in the United States in the 1980s, when the Hemlock Society was formed and Jack Kevorkian, MD, offered his "death counseling" services. Prior to that, the movement had progressed very slowly. It took 91 years from the time the first euthanasia bill was drafted and subsequently defeated in Ohio in 1906,[1] until Oregon passed its Death with Dignity Act (DWDA) in 1994 that went into effect in 1997.[2] The DWDA was the first aid-in-dying statute in the United States.

Public support for the right-to-die movement has increased in the U.S., mainly due to a change in terminology. In 1996, the American College of Legal Medicine (ACLM) rejected the term "physician-assisted suicide," claiming it "unfairly colors the issue, and for some, evokes feelings of repugnance and immorality." In 2008, ACLM was the first organization to publicly advocate elimination of the word "suicide" from the term.[3] Today, mentally competent, terminally ill persons who choose to hasten their death with the assistance of their attending physician are no longer referred to as committing suicide or engaging in physician-assisted suicide, physician-assisted death, mercy killing or euthanasia. The medical practice is now referred to as medical aid in dying (MAID).

While public support for MAID has increased over the decades, as evidenced by a 2014 poll that showed three of four Americans (74 percent) agreed "individuals who are terminally ill, in great pain and who have no chance for recovery have the right to choose to end their own life,"[4] several groups continue to prevent states from passing MAID legislation. Indeed, political parties, religious groups and the medical community have all been instrumental in restricting the right-to-die movement. While MAID legislation is passed at the state level, in 2008, the federal Democratic Party position stated it is "silent on euthanasia and assisted suicide," and

the federal Republican Party position stated: "We believe medicines and treatments should be designed to prolong and enhance life, not destroy it. Therefore, federal funds should not be used for drugs that cause the destruction of human life. Furthermore, the Drug Enforcement Administration ban on use of controlled substances for physician-assisted suicide should be restored."[5]

A summary of religious groups' views on end-of-life issues, including physician-assisted suicide and euthanasia, released by the Pew Research Center in 2013, showed 14 of 16 major American religious groups opposed any form of euthanasia or physician-assisted suicide.[6] And, the June 2016 edition of the American Medical Association's Code of Medical Ethics states: "Permitting physicians to engage in assisted suicide/euthanasia would ultimately cause more harm than good." In addition, it continues: "Physician-assisted suicide/euthanasia is fundamentally incompatible with the physician's role as healer … and … instead of engaging in assisted suicide/euthanasia, physicians must aggressively respond to the needs of patients at the end of life."[7]

Even so, since Oregon's DWDA went into effect, individuals and right-to-die organizations have done much to change the landscape of MAID.

Brittany Maynard's Story

Brittany Maynard, a California resident, put a face on the right-to-die movement. Maynard was a teacher who loved to travel. She married Dan Diaz in September 2012, and she looked forward to starting a family. But in January 2014, Maynard was diagnosed with terminal brain cancer. In March 2014, she was given six months to live. She was only 29 years old.

At the time of Maynard's terminal diagnosis, California did not have MAID legislation. After she learned from her oncologist she would endure unremitting pain and seizures in her final days, which would cause terrible trauma to herself and her loved ones, Maynard and Diaz moved to Oregon to take advantage of the DWDA.

The DWDA allows terminally ill Oregon residents to apply for and receive from their attending physician a lethal prescription of medication, which they must consume themselves to hasten their death. The DWDA gave Maynard the option to end her life with dignity before it became unlivable.

Between the time Maynard and Diaz settled in Oregon, and her passing on Nov. 1, 2014, she became a strong advocate for the legalization of MAID. "During the last six months of Brittany's life, she spoke up and lent her voice to the issue of medical aid in dying because she felt it was an injustice that we had to move from our home for her to have the option of a gentle dying process," said Diaz. "Her message was aimed primarily at legislators so that no one else would have to endure leaving their home, like she did, after being told they have six months to live."

Three years after Maynard's passing, Diaz continues to advocate for MAID legislation and has traveled to more than a dozen state capitals to provide testimony at Senate hearings where MAID legislation is moving forward. "I share the reality of what medical aid in dying means to a terminally ill individual," he explains. "I also dispel the myths and false narratives that the opposition bring forward. Their campaign is based on fear and attempts to slow the passing of the legislation."

While public support for MAID has increased over the decades, several groups continue to prevent states from passing MAID legislation.

Diaz believes laws that govern medical issues should not be based on religious beliefs: "To be fair to persons of all religions, and those who may not subscribe to any religion, laws should not align with a particular religious doctrine. The strength of medical aid in dying legislation is that it's an option which a terminally ill person has to apply and qualify for by meeting strict criteria. The passage of medical aid in dying legislation does not affect terminally ill persons who are opposed to the practice for their own religious beliefs. A person who opposes medical aid in dying legislation would simply never avail themselves of the option."

Diaz says improvements in medical training are needed for end-of-life care that should include a clear understanding of MAID. "Medical professionals are trained to help patients

Oregon's Death with Dignity Act (DWDA)[12,13]

To request a prescription for lethal medications, the DWDA requires a patient be:
1) An adult (18 years of age or older);
2) A resident of Oregon;
3) Capable (defined as able to make and communicate healthcare decisions); and
4) Diagnosed with a terminal illness that will lead to death within six months.

Patients meeting these requirements are eligible to request a prescription for lethal medication from a licensed Oregon physician. To receive a prescription for lethal medication, the following steps must be fulfilled:
1) The patient must make two oral requests to his or her physician, separated by at least 15 days.
2) The patient must provide a written request to his or her physician, signed in the presence of two witnesses.
3) The prescribing physician and a consulting physician must confirm the diagnosis and prognosis.
4) The prescribing physician and a consulting physician must determine whether the patient is capable.
5) If either physician believes the patient's judgment is impaired by a psychiatric or psychological disorder, the patient must be referred for a psychological examination.
6) The prescribing physician must inform the patient of feasible alternatives to DWDA, including comfort care, hospice care and pain control.
7) The prescribing physician must request, but may not require, the patient to notify his or her next of kin of the prescription request.

According to a report titled "Oregon Death with Dignity Act: Data Summary 2016," which provides data on the law from 1998 to 2016, 1,749 people had prescriptions written under the act, and 1,127 patients have died from ingesting the prescription medications they received from their attending physicians. During 2016, the rate of DWDA deaths in Oregon was 3.72 per 1,000 deaths.

The report also shows characteristics of DWDA patients were similar in all years. Most patients were aged 65 years or older (80.5 percent) and had cancer (78.9 percent). The median age at death was 73 years, and decedents were commonly white (96.2 percent) and well-educated (50.0 percent had at least a bachelor's degree). Most patients died at home (88.6 percent), and most (88.7 percent) were enrolled in hospice care. The three most frequently mentioned end-of-life concerns were loss of autonomy (89.5 percent), decreased ability to participate in activities that made life enjoyable (89.5 percent) and loss of dignity (65.4 percent).

become well again, almost at any cost. They sometimes offer specific treatments to terminally ill patients they know will not work, but feel obligated to offer anyway," says Diaz. "Early in medical school, doctors in training need to be reminded that we're all mortal, and we will all eventually die. Therefore, terminally ill persons need to be provided with information on treatment options to make informed medical decisions for their end-of-life care. Unwanted or unnecessary treatment could prolong a person's dying process and cause them more suffering."

Oregon's DWDA

Oregon's DWDA is a death with dignity law written by founding members of the Death with Dignity National Center, a nonprofit organization that campaigns, lobbies and advocates for MAID legislation in states that currently lack it. Peg Sandeen, executive director of the organization, says not only was Oregon's DWDA the first law of its kind in the United States, it was the first law of its kind in the world, and it has the most restrictive requirements a terminally ill person must meet.

Sandeen explains the defining difference between the DWDA and euthanasia: "The Death with Dignity Act allows for terminally ill Oregon residents to obtain a lethal prescription from their physician for self-administration. In medical aid in dying, the terminally ill person controls their dying process from beginning to end. There are currently five states and Washington, D.C., that have medical aid in dying statutes. Euthanasia is where a physician or other person directly administers a medication to end another's life. Euthanasia is illegal in all 50 states in the United States.

"The Death with Dignity Act sets medical issues apart from dying issues, and allows a terminally ill person to live until they decide it's time for them to die. The Death with Dignity Act created a right for one special group, the terminally ill, but it

protected everyone else — including persons who are not terminally ill or who are not of sound mind or are unable to make end-of-life decisions for themselves."

According to Sandeen, the DWDA has helped to change everything about the landscape of MAID: "The DWDA codified the medical standard of care as it relates to what a physician does to help their terminally ill patients hasten their death. Physicians were already helping their terminally ill patients die, but the process was somewhat unregulated. In Oregon, we wrote down these steps for physicians to follow.

"The quality of dying has also improved since the Death with Dignity Act came into effect. There are more signed advanced directives and Provider Orders for Life-Sustaining Treatment, hospice usage is higher, there is more support for terminally ill patients' desire to hasten their death, and more terminally ill people are dying at home.

"Although the DWDA was originally passed under Oregon's Measure 16 ballot in 1994, the law did not come into effect until 1997. Oregon now has 20 years of irrefutable data that shows the law is working as it was intended to. There is also data now available from California and Washington state which show their respective death with dignity laws are working in those states as the law was intended, as well."

Since the DWDA came into effect, five more states and The District of Columbia have passed death with dignity laws. Washington passed the Death with Dignity Act in 2008, Vermont passed the Patient Choice and Control at the End of Life Act in 2013, California passed the End of Life Option Act in 2016, Colorado passed the End of Life Options Act in 2016, and the District of Columbia passed the Death with Dignity Act in 2017. Montana does not have a death with dignity statute. However, in 2009, Montana's Supreme Court ruled nothing in the state law prohibited a physician from fulfilling a terminally ill patient's request by prescribing lethal medication to hasten his or her death.[8]

Sandeen says the organization is currently working with grassroots groups and nonprofit organizations in Hawaii, Maine, New York, Ohio and Texas, as well as advocates in several other states to help pass death with dignity laws.

Compassion & Choices

As part of her advocacy for MAID legislation, Maynard partnered with Compassion & Choices. Predicated on the Seven Principles of Person-Centered Care, Compassion & Choices has worked for more than 30 years to improve healthcare and expand options for end-of-life care. The organization works to advance policies that allow people to make fully informed decisions about their healthcare, including to improve pain management, end unwanted or unnecessary medical treatment, improve hospice and palliative care, and help to enact MAID legislation.

Barbara Coombs Lee, president of Compassion & Choices, was an emergency room and intensive-care unit nurse and physician assistant for 25 years before she became a private attorney and counsel to the Oregon State Senate. Coombs Lee co-authored Oregon's DWDA and served as its chief spokesperson through its two statewide ballot campaigns in 1994 and 1997.

Brittany Maynard, a California resident, put a face on the right-to-die movement.

Coombs Lee says Compassion & Choices' most important accomplishment has been to put MAID into a medical context. "Intentional dying used to be considered separate from medical care," she says. "However, it's become a pivotal point for a terminally ill patient to approach their attending physician and ask for medical aid in dying. Doctors should be up-front with their patients in terms of their prognosis and their treatment. And if the doctor says, 'I can't help you,' it doesn't mean they can't help the patient at all. Rather, doctors should be able to help their patients through their dying process."

Compassion & Choices' Seven Principles of Person-Centered Care[14]

1) Focus: End-of-life care should focus on the individual's comfort.
2) Self-determination: Individual tolerance for pain and suffering varies dramatically.
3) Autonomy: Decisions about end-of-life care begin and end with the individual.
4) Personal values: You have the right to make decisions based on your own deeply held values and beliefs, without fear of moral condemnation or political interference.
5) Informed consent: You have the right to comprehensive, candid information to enable you to make valid decisions and give informed consent.
6) Balance: You must be empowered to make decisions based on your own assessment of the balance between quantity and quality of life.
7) Notice: You as the patient have the right to early, forthright and complete notice of institutional or personal policies or beliefs that could impact your end-of-life wishes.

Maynard was an example of the kinds of decisions a terminally ill patient is able to make if they ask questions about the course of their illness and peaceful death options available to them, says Coombs Lee. "Compassion & Choices developed the first national end-of-life consultancy program in 1993, which offers patient tools, information and emotional support for end-of-life options," she explains. "We also pioneered the use of and transformed advance directives from strictly legal documents to a values-based approach for communicating end-of-life priorities."

Maynard's partnership with Compassion & Choices began on Oct. 6, 2014, with the launch of her six-minute YouTube video explaining her decision to hasten her death and advocate for proposed legislative change in her home state of California.[9] Her video was watched by almost 12 million people, generated worldwide media attention and, eventually, led to California passing the End of Life Option Act in 2016.

There are now 27 more states considering enacting MAID legislation.

The partnership also resulted in the creation of the Brittany Maynard Fund,[9] an Internet site where people can go to donate to and lend their voice and support for the MAID cause. "People can make contributions to the fund," says Coombs Lee. "People can write letters to send to their government officials. People can feel like they are a part of a community of like-minded individuals. People can also see what's happening in the right-to-die movement and take meaningful action in their own communities."

A Growing Cause

According to Coombs Lee, Maynard was a worldwide voice for medical aid in dying. In the three weeks between Maynard's story that appeared in the media and her death, 38 percent of American adults (93 million people) heard her story.[10] Maynard's story was published on People.com on Sunday, Nov. 2, 2014, garnering more than 16.1 million unique visitors and reaching nearly 54 million people on Facebook. It was the biggest story in Time Inc.'s publication history.[11] "Brittany changed the perception of medical aid in dying. She made people understand her dilemma and her choices, and people of all ages related to her," says Coombs Lee.

Diaz says Brittany would feel a great sense of relief to know individuals in other states "now have the medical aid in dying option available to them so they, too, will have the option of a gentle dying process, and they won't have to move to a state that has medical aid in dying legislation like she had to."

There are now 27 more states considering enacting MAID legislation. However, says Diaz, it does not mean all 27 states will pass it: "The challenge with passing medical aid in dying legislation is that it can be subject to politicians' personal religious beliefs. It's easy for a senator to bring medical aid in dying legislation forward, but it can be hard to get the legislation passed by that state's legislative body."

Yet, Diaz believes those in the baby-boom generation who have navigated end-of-life care with their parents, and some of whom are faced with a terminal illness of their own or that of their spouse, will help the right-to-die movement. "Baby boomers won't tolerate anything less than having all options available to them," he says. "That determination will be a big benefit with medical aid in dying legislation and will help make headway in getting this legislation passed."

Sandeen is confident that once a certain number of states have enacted death with dignity legislation, the ball will start rolling, pick up speed and many more states will pass the legislation quickly: "Hopefully, more states will pass death with dignity legislation sooner, in the next 20 years or so, and we won't have to wait 14 years as we did between Oregon in 1994 and Washington in 2008." ❖

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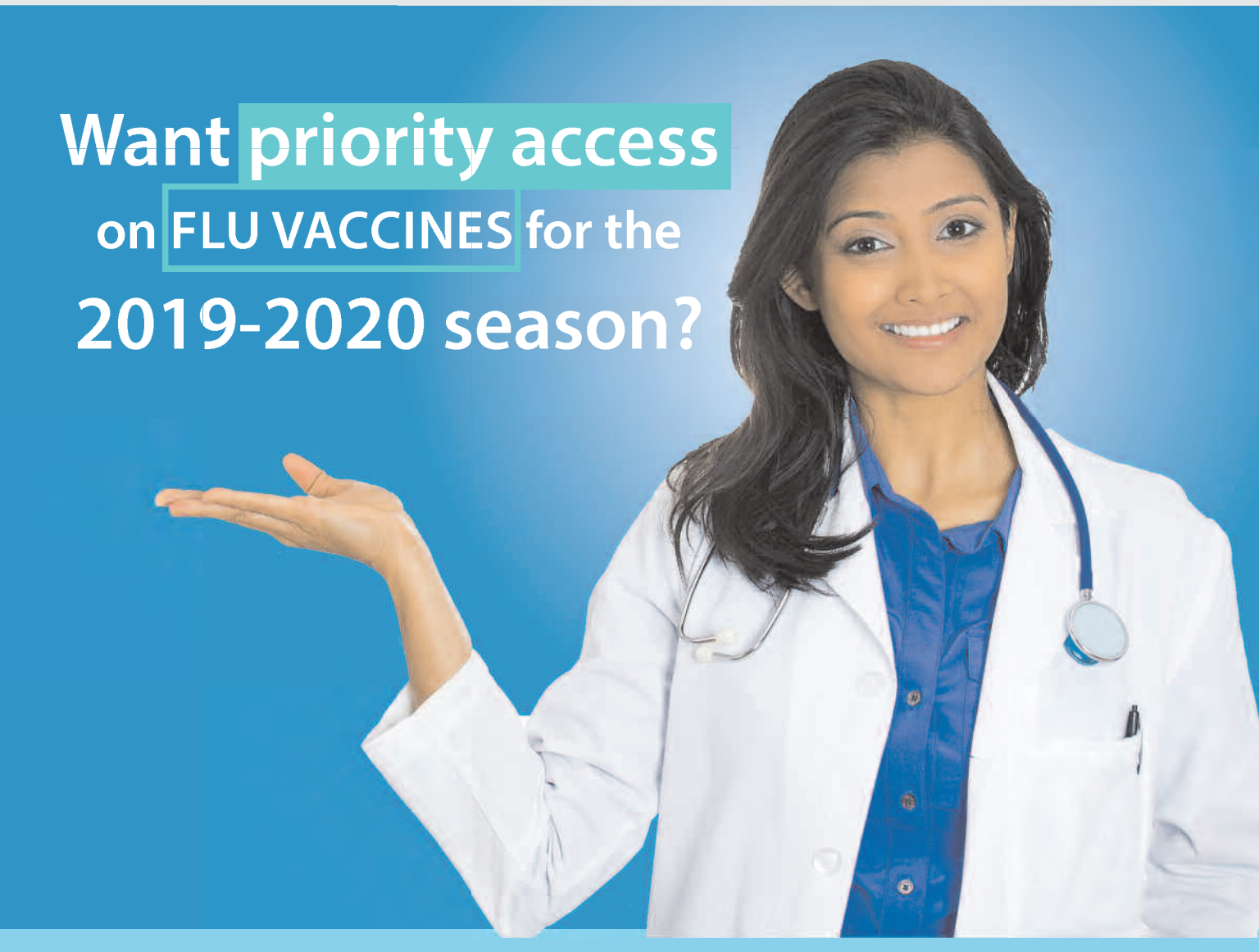

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Are Drugs Really Overpriced?

Pricing of drugs is far more complex than the big, bad pharma price-gouging narrative.

By Meredith Whitmore

TO SOMEONE LISTENING to the many reports on the state of drug prices in this country, the situation sounds like an ominous fairy tale in which at least one character gets eaten by a monster. The drug price tale, though, is less about scaring morals into children and more about understanding commerce — which can be just as frightening in its own way. What seems to be the most common story version goes like this: In one corner is the pharmaceutical industry, a menacing predator with teeth like the Big Bad Wolf's. In the other are the unsuspecting patients who simply need their prescriptions and have no recourse. There isn't even a fight. Big pharma crushes consumers by brute strength and unfair pricing.

But is this monster vs. helpless consumer metaphor accurate in all cases? In any? Some say, emphatically, yes. We all know the horror story of Martin Shkreli's unanticipated decision to raise the price of Daraprim from $13.50 per pill to $750 per pill, literally overnight — a 5,000 percent increase and a financial nightmare for those who depended on the drug.[1] Soon after was the EpiPen scandal, with Mylan Pharmaceuticals suddenly raising its price by a "mere" 400 percent. Allergy sufferers everywhere lamented this budget-breaker and searched for occasionally dangerous alternatives, all while Mylan's CEO's salary rose more than 600 percent.[2,3]

Based on these and other headline makers, the pharmaceutical industry does appear evil and greedy. But, like all things, one must dig deeper into the complexities to understand more than surface issues. And, there are plenty. So, is this Big Bad Wolf narrative missing something, or is the bad reputation justly deserved? Considering the fact Americans spend an average of $1,100 per person on prescription medications, it's a topic needing discussion.[4,5]

Understanding Drug Pricing

It seems so easy. Consumers simply pay the price the drug manufacturers set, right? Wrong. This isn't it at all. Nothing is as straightforward as most consumers believe. A quick review of the price system will help set the stage for recall and understanding:

Pharmaceutical companies do not set the drug prices patients will pay. Drug prices are actually determined less by the pharmaceutical industry and more by pharmacy benefit managers (PBMs), organizations providing educational services to help patients, logistics expertise and leverage to negotiate reimbursement rates for medications and patient care services. Their influence on pricing is considerable and unreported. These companies, such as Express Scripts, CVS Caremark and Argus, negotiate with pharmaceutical companies for discounts off the list price. Once a PBM has purchased the drug, it increases the drug's price and distributes it to pharmacies that have purchased it. Insurance companies come into play at this point. Employers are the biggest providers of health insurance, so chances are your patient's employer hired a PBM to negotiate rebates from the pharmaceutical companies. Depending on whether similar drugs are available from various other drug manufacturers, a PBM might negotiate a significant rebate and further reduce prices, which further decreases the pharmaceutical company's net price. This difference in price becomes the PBM's profit. Some PBMs keep all of the profit, and some rebate employers while retaining only part of it.[6] However, these transactions are not transparent and just what they keep is not disclosed.

Pharmaceutical companies do not set the drug prices patients will pay.

Based on how much an employer has agreed to pay for an employee's pharmaceuticals, and how much rebate its PBM has achieved, drugs are placed on co-pay tiers. The more preferred the drug and tier, the more an employee/consumer will pay out of pocket. This is why patient A might pay much more than patient B, and much less than patient C, and why the same drug might be on different tiers within different insurance companies.

Though we hear about list price most frequently in headlines, that price does not equate to the pharmaceutical company's profit. Its profit depends on its negotiations with a PBM. And a PBM's profit rests on its negotiations with insurance companies and drug makers.[6]

Generic Medications and Alleged Patent Abuse

The drug-pricing plot thickens when pharmaceutical companies are accused of patent abuse, or using ambiguous intellectual-property law to extend their patents, which purportedly keeps cheaper generic drugs from going to market. Regarding patent abuse, among other accusations, FDA Commissioner Scott Gottlieb went so far as to tell drug manufacturers to: "End the shenanigans."[7]

But, Holly Campbell, deputy vice president of public affairs at Pharmaceutical Research and Manufacturers of America (PhRMA), says patent abuse is not a true factor in high drug prices. "Despite claims from critics," she explains, "nearly 90 percent of all medicines dispensed in the United States are generic alternatives that cost a fraction of the original brand price. More than $140 billion of brand medicine sales are projected to face generic competition by 2021. Further, the number of generic medicines coming on the marketplace is actually increasing. The FDA [U.S. Food and Drug Administration]

approved a record-breaking number — more than 1,000 — generic medicines in 2017. This is evidence that the process is working."

However, People for Affordable Drugs founder David Mitchell adamantly asserts the process isn't working, and that it should do much more for patients. "It is very difficult to reform our drug pricing system," he says, "because the problem with our system is that everybody makes more money when prices go up, except consumers, taxpayers and patients. There's only one side [to this issue]: The system has to serve patients. If it doesn't serve patients, what good is it? It's not as though there are multiple sides. We need a system that serves the needs of patients, not business."

But the business aspect is crucial to the industry, according to one Biotechnology Innovation Organization (BIO) spokesman, who declined to be identified. "The strong intellectual property rights which innovators and investors rely upon here in America is one of the reasons why America's biopharmaceutical is the envy of the world, responsible for well over half of all new drugs developed worldwide," he explains. "Despite the risks of investing in biotechnology, the industry attracts billions of dollars annually in new private investments based on the promise of innovative and patented discoveries, which will only be translated into actual commercial products providing a return on investment after years, sometimes decades, of capital-intensive investment and research efforts."

For years, drug research and development has been said to result in justifiably high drug prices.

Campbell offers further perspective: "It is important to keep in mind that the marketplace for medicines works differently than the rest of the healthcare system. There are no generic hospitals and no generic physicians, but there are affordable generic medicines. This is what enables us to afford new lifesaving treatments."

Research and Development

For years, drug research and development (R&D) has been said to result in justifiably high drug prices. "Drug development is incredibly complex, risky and costly — a process that takes, on average, 10 to 15 years and over $2 billion, when accounting for the many failures along the way," says the BIO spokesman. "It's also important to consider the larger biomedical innovation ecosystem, where 90 percent of drug development programs fail. What's more, over 90 percent of drug companies report to be

unprofitable, and the biopharmaceutical industry ranks 36th (out of 126 industries) in terms of aggregate profitability — behind sectors such as food, retail, auto parts and apparel/footwear — yet we continue to drive the profits we make back into the important research and development process. In fact, the biopharmaceutical industry reinvests more of its revenues back into R&D than any other sector — to the tune of nearly 20 percent. For America to continue to serve as the world leader in biopharmaceutical innovation, revenue from the few successes are needed to reward past investments and to attract new investments to finance future research and development programs for patients in need."

Economist Avik S. A. Roy, however, has a vastly different perspective: "There is no correlation between drug prices and the cost of innovation. The costliest drugs to develop are those which require large Phase III clinical trials involving tens of thousands of patients. ... Such trials can cost several billion dollars per molecule. But, in fact, new drugs in these areas have little pricing power, because doctors have the ability to prescribe effective and inexpensive generics for these conditions. Indeed, the clinical effectiveness of generics makes them the standard of care for first-line therapy for most common metabolic and cardiovascular diseases.

"The cheapest drugs to develop are those which require small clinical trials involving dozens of patients such as drugs for ultra-rare, or ultra-orphan, conditions like Fabry disease and paroxysmal nocturnal hemoglobinuria (PNH). Phase III trials for these conditions, which only affect several thousand people in the United States, run in the tens of millions. But manufacturers of such drugs have generated billions in revenues from them. The pioneer in this area, Genzyme, was acquired by Sanofi-Aventis for over $20 billion in 2011, when it was garnering $4 billion in annual revenue for drugs, including a treatment for Fabry disease. Alexion, the developer of a treatment for PNH, recorded $3 billion in revenue in 2016. Annual revenues in this range exceed those of many drugs which were at least equally innovative but developed for more common disorders."[8]

Hospitals' Role in Price

Lest we believe high drug prices have only to do with the previously mentioned players, hospitals have their own implication. PhRMA's information resource "Let's Talk About Cost" reveals hospitals are responsible for, on average, a 500 percent increase in drug prices.[9,10]

"Hefty hospital markups for drugs are also to blame for high prices," said the BIO spokesman. "[Hospitals also] receive more than 250 percent of what they paid to obtain the treatment after negotiations with commercial payers were considered. This might also help explain why hospitals comprise by far the largest share of healthcare spending, at about 30 percent of U.S. healthcare expenditures, or close to $1 trillion annually."

Insurers themselves are problematic as well. "It's important to point out," explains the BIO spokesman, "that while net price and overall spending growth for drugs continue to level, insurers are under scrutiny for the role they play in driving up patient out-of-pocket costs for medicines. For example, lawsuits against UnitedHealth allege that their prescription benefit design can require that patients pay co-pays for more than the actual cost of the drug — with the insurer pocketing the difference. Insurers have also faced criticism for discriminatory formulary design, particularly against patients with high-cost health conditions such as HIV and hepatitis C."

Possible Solutions

Obviously, consumers suffer when their healthcare expenses exceed their incomes. High drug prices, whether justified or not, hurt consumers who desperately need affordable medications. What can be done to smooth the system intended to help patients?

Campbell says there is no magic wand to lowering drug prices. By getting all players to work together, however, she believes the goal can be achieved. Among her solutions is boosting competition. By bringing to market more generics and brand-name drugs, she believes prices will be driven down and consumer choice increased. She also believes rewarding patients' improved outcomes and reforming outdated laws that inhibit value-based arrangements for prescription drugs will lower prices, benefiting everyone. Rather than revamping the entire system, though, she wants to keep what works, which includes rejecting policies that hinder functioning markets, lessen innovation or threaten safety or access.

Mitchell firmly believes fixing patent abuse and government-granted monopolies, allowing Medicare to negotiate and requiring much-needed transparency from PBMs will help tremendously.

And, the BIO spokesman agrees with Mitchell, at least in part. He says a lack of transparency from PBMs makes it nearly impossible to determine how much of negotiated savings are passed along to patients or withheld as profits for PBMs or insurers. "Because PBMs generally refuse to disclose rebate information on a drug-by-drug basis, health plans are unable to determine whether its PBM is favoring the lowest net-cost drug in each therapeutic category, or whether, instead, it makes formulary decisions based upon which drug in a given class will net the PBM a higher rebate. This black box system drives up costs for both patients and insurers," he explains.

High drug prices, whether justified or not, hurt consumers who desperately need affordable medications.

No Magic Wand

No, there certainly is not a magic wand to solve problems in such a complex system. It would seem, however, that with all players working together — drug manufacturers, PBMs, insurers, pharmacies, hospitals, consumers and others — prices can begin to be lowered for the most expensive and least attainable drugs. In any case, consumers must realize that the big, bad pharma price-gouging narrative is only the tip of the iceberg, and often an erroneous one. What lies beneath it is more complicated, more difficult to remedy and much less about the aforementioned list price that is so often, and so wrongly, held responsible for every pricing problem. ❖

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Healthcare Data: Ensuring Regulatory Compliance

By Amy Scanlin, MS

Updated HIPAA rules require healthcare organizations stay vigilant in keeping patient data safe from threats in this ever-changing digital age.

ENSURING THE PRIVACY of patient health information is a required responsibility of healthcare providers under the Health Information Portability and Accountability Act (HIPAA). Signed into law in 1996, HIPAA continues to be updated and enhanced as new technology and privacy concerns lead to amended requirements about how data are protected. Some examples include requirements for how patient data are stored electronically and how health data are transported from portable devices to electronic health records (EHRs). Under HIPAA, providers are required to be compliant with the privacy rule, security and enforcement rule, and the Health Information Technology for Economic and Clinical Health (HITECH) Act that was part of the American Recovery and Reinvestment Act of 2009.

Briefly, the privacy rule protects identifiable health information, regulates circumstances under which protected health information may be disclosed and requires specific arrangements for business associates (such as health information organizations and e-prescription gateways) that provide services to covered entities.

The security rule builds on provisions of the privacy rule by requiring security risk assessments and appropriate safeguards for electronic data handling. Every healthcare setting must perform risk assessments and document its physical, administrative and technical safeguards. Because safeguards differ for entity types, the rule allows for flexibility and scalability in terms of what an organization needs to do to accomplish its tasks. The security rule applies to health plans, healthcare clearinghouses and any health-

care provider who transmits health information in electronic form in connection with a transaction for which the Secretary of Health and Human Services has adopted standards under HIPAA (the covered entities) and their business associates.

The HITECH rule further strengthens the privacy and security rule, including requiring subcontractors of business associates to have a comparable level of security. Subcontractors are deemed those that create, receive, maintain or transmit personal health information on behalf of business associates. Tougher penalties for data breaches are also authorized, particularly in cases of willful neglect.[1]

Today's Challenges

Balancing the need for privacy and security in an era of email and text communications, cloud storage and virtual appointments is one of today's newest challenges. According to M3 Technology Consultants in Centreville, Va., medical data are worth 10 times more than credit cards on the black market, and website malware that holds data hostage and seeks out password and privacy information accounts for 69 percent of all data breaches. Notably, these security vulnerabilities affect both personal and professional systems, whether they are digital operating systems, cloud storage or even old-fashioned paper storage systems. And, the more sensitive the information, the more at risk it may be.

Balancing the need for privacy and security in an era of email and text communications, cloud storage and virtual appointments is one of today's newest challenges.

Regrettably, no matter how robust security is, people are its weakest link. Staff members who neglect to install critical software updates, misplace mobile devices, create weak passwords that can be easily deciphered, or feel they have been unfairly terminated all present grave concerns. "In nearly every case, the people are a company's weakest link," says Joseph P. Migliozzi, PE, MCSE, CCNA, RHCSA, president of M3 Technology Consultants. "From dormant accounts of persons who have left [practices], to simple, repetitive passwords, these are the most obvious vulnerabilities. The big stuff is rare, though it gets a lot of press. But, when someone out on the Internet finds a connection to a server, then successfully guesses the administrator password or finds an employee name on the Internet and starts trying to guess their password (their wife's name or kid's name, etc.), once they are in, they can see whatever they want. Those big software exploits that you hear about are much harder to do."

And, these vulnerabilities create a number of considerations, including unique challenges that must be identified through assessments and managed via security plans, as well as responsibilities of providers and their business associates when a breach has been detected.

Understanding Risks

Federal law requires a risk assessment consistent with the HIPAA security rule to determine how electronic personal health information (ePHI) is protected within a system. This risk assessment should cover the most obvious points from who maintains keys to the physical building, to more in-depth questions such as who has access to what parts of a patient's digital records. "It all comes down to assessing risk," explains Lee Kim, BS, JD, CISSP,

CIPP/US, director of privacy and security at Healthcare Information and Management Systems Society, North America (HIMSS). "What are the critical or high-priority items to address? There is no such thing as 100 percent security, but if you address the high-impact items, you will go a long way."

A good starting point for assessing risk is the U.S. Department of Health and Human Services' free 156-question Security Risk Assessment Tool[2] available online, as well as a five-step tiered assessment of the risks of using mobile phones as a means of patient communication[3] and a seven-step approach for implementing a security management process.[4] Detailed information directed to both patients and providers about obtaining consent for exchanging health information electronically is also available.[5]

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A more robust security assessment by a qualified expert familiar with healthcare settings will provide more information regarding specific ePHI risks and greater analysis than can be gained through an in-house assessment. It's important to look at the size and complexity of an organization, its hardware and software security capabilities to determine the probability of ePHI risk at each level of data transmission while balancing the cost associated with the security measures. Kim recommends asking the following questions:

• Is this nascent technology reliable; have the "bugs" been worked out?

• What is the assessment of the risk as a result of adopting this new infrastructure for storage and transmission of data?

• What is the reputation of the manufacturer of the technology? Does it have a good track record for security?

• Where will the infrastructure be located? On premises? In the cloud? In the United States? Another country? (Each country/region has different data protection laws.)

• Will a third party the business associates with adopt and implement the same security policies and procedures? If not, why not, and what system does it have in place? Is it willing to provide information about its policies, procedures and design/architectural information?

• Who owns the third party? In which country is the third party located?

• If the third party will manage, control or have access to the organization's data, how will it report any incidents that may occur involving the organization's data?

• What is the reliability and availability of the remotely hosted resources?

Migliozzi suggests asking: "How is access to the network monitored and controlled? What can people see and not see on the network? How are devices controlled, tracked and monitored? What type of firewall security is there — from anti-spam to malware — and what tools are being used? What is the company's exposure on the Internet, and how is intrusion protection monitored?"

With the ever-changing nature of data and data transmission, documented policies should be thoroughly implemented, and any changes to the types of data, hardware, software or policies that affect security should be documented as well. And, according to federal requirements, these records must be kept for six years, although states may have even lengthier requirements.

"Being able to balance data security and the potential security implementation costs is one important goal in conducting a risk analysis, and is a requirement of the HIPAA security rule," says the Office of the National Coordinator for Health Information Technology (ONC). "It is important to evaluate the likelihood and impact of potential risks to ePHI, then implement security measures to address those identified risks and document the chosen security measures and, where required, the rationale for their adoption. The security measures must address the administrative, physical and technical safeguards included within the HIPAA security rule."

However and by whomever the risk assessment is undertaken, the ultimate success, outcome and responsibility for the results rest on the covered entity that is responsible for protecting the patient's information. Before and during the process of evaluating EHRs, software and IT providers must discuss HIPAA rules and how the company intends to use the software with developers, says Migliozzi. They also need to verify that the IT company under consideration has a proven track record of working with the software under consideration or in use.

Security as a Culture

Security must be part of an organization's culture. It must have an appointed security officer who receives appropriate training, including a thorough understanding of HIPAA compliance and oversight of risk assessment. The officer must document any security issues, and risks must be mitigated using the meaningful use security-related objectives set forth in the HIPAA security rule.[4]

All threats won't necessarily be cyber in nature. Other potential risks include theft, workforce errors, disgruntled employees and even natural disasters such as fires, floods and earthquakes. The

security officer must identify all risks and the likelihood of each to exploit vulnerabilities that would affect confidentiality, integrity and availability of ePHI.[4]

According to Kim, security must be accessible: "If employees and other workforce members cannot do their jobs, they will likely 'work around' policies, procedures and other restrictions that help keep the environment safe and secure. In other words, you cannot have such a restrictive and user-unfriendly security program that your workforce members are always trying to defeat it. In such a case, your program will either fail completely or have significant problems." She suggests making sure policies are user-friendly and easy to understand, and she emphasizes companies need to teach employees why rules are in place. For instance, she says, "maybe even demonstrate what happens if a password is 'shared' with others or if the password is just '123456' …, or if that strange PDF is opened up … what can happen to a computer, etc.? Get everyone involved and educated. Security is everyone's responsibility."

Everyone from staff to volunteers should be provided a copy of the security training manuals, and everyone should be involved in the conversation, not just those in charge of security. The organization should foster open communication and an opportunity for questions, and it should be open to suggestions for improvements from frontline staff who live the security operations daily.

Patients can also be involved in the protection of their information so they understand the seriousness and procedures in place to protect it. Invite them to ask questions, and help them understand how they can actively participate. "Patient education is an incredibly important part of meaningful consent," says Peter Ashkenaz, an ONC spokesperson.

Sharing Information

Under the HIPAA privacy rule, covered entities can use protected health information and disclose it to another covered entity or their business associates for certain healthcare operations and under certain circumstances without seeking patient consent or authorization, according to Ashkenaz. Those circumstances include when both entities have or have had a relationship with the patient. However, the PHI requested must pertain to that relationship, and only a minimum amount of information may be disclosed that pertains only to the healthcare operation at hand.

Some examples of when information can be shared include:[6]

- Conducting quality assessment and improvement activities;
- Conducting patient safety activities;
- Conducting population-based activities related to improving health or reducing healthcare costs;
- Conducting case management and care coordination;
- Contacting healthcare providers and patients with information about treatment alternatives; and
- Supporting fraud and abuse detection and compliance programs.

Practical Communication Steps and Strategies for Providers[9]

- Do not email electronic personal health information unless certain information is encrypted.
- Do not include personally identifiable information such as full names or Social Security numbers.
- Be clear and concise — no shorthand, emoticons, jokes or sarcasm.
- Proof messages thoroughly, and beware of autocorrect changes.
- Ensure the provider's full name and professional affiliation is in the signature line of each communication.
- Ask patients to confirm receipt of messages.
- Set limits on communication exchanges. If a patient's questions require detailed explanations, ask them to make an office visit so the information can be discussed in person to ensure better understanding.
- Archive all electronic communication records.

Communicating on Personal Devices

The ways in which people communicate are changing rapidly. From emails to texts between patients and providers to communication among providers via electronic health information exchanges, the opportunities for connections are advancing rapidly, as are the challenges of deciding how those communications will be conducted and maintained.

First, informed consent is an important aspect of these types of communications. Providers must do everything possible to ensure patients understand the various risks, from unsecured Wi-Fi connections to the vulnerabilities inherent to lost or stolen devices and unintended recipients of electronic communications. And, risks vary as do their potential severity.

While it is advised that providers get written consent from patients prior to engaging in electronic communications, under HIPAA guidelines, patients who initiate text conversations may be providing consent to communicate electronically.[7] Even so, extra care and concern should be taken to ensure certain patients understand the risks, and providers must ensure they are meeting federal requirements. The security and encryption of electronic data should never be taken for granted, no matter how robust the system.

Online communications, whether between providers and patients or between providers discussing patients' charts (including emails, texts and communications via patient portals), must meet

the security rule and meaningful-use standards for secure messaging of ePHI, and they must be encrypted.

The question of whether to allow providers to access ePHI via their personal mobile devices is sometimes raised to balance busy work schedules. The answer, says Migliozzi, is "no; having separate phones is better." While professionally managed security is generally updated automatically, the same may not be true for personal systems, which increase security risks. However, M3 Technology Consultants suggests that if a bring-your-own-device policy is allowed, organizations must tightly manage security and follow HIPAA compliance.

Security must be part of an organization's culture.

Another concern, says Migliozzi, is privilege misuse, which accounts for 5 percent of breaches. "Most often, this translates to current or former employees or contractors intentionally misusing administrative privileges for the purpose of harming the company," he says. So, he suggests granting access on a need-to-know basis to as few individuals as possible and creating and enforcing policies restricting access to sensitive data. He also suggests expediting the change of all usernames and passwords for accounts after employee terminations.

Notification of Data Breach

According to the U.S. Department of Health and Human Services Health Information Privacy for Professionals, unless otherwise requested by law enforcement, covered entities must notify affected individuals of a data breach as soon as is reasonably possible and no later than 60 days after the breach was first discovered or should have been discovered. Also, if covered entities have insufficient or out-of-date contact information for 10 or more individuals, they must provide substitute individual notice by either posting the notice on the homepage of its website for at least 90 days or by providing the notice in major print or broadcast media where the affected individuals likely reside.[7] However, covered entities generally have only a 30-day window to make corrective actions to modify a situation of willful neglect that allowed the breach to occur.[1]

"Breach notification requirements differ according to the jurisdiction," says Kim. "We have to be concerned not just with federal laws and regulations, but also local and state laws and regulations as well. These laws and regulations dictate who needs to be notified and when. As with any incident, you need to contain the incident. That's the way you can reduce or mitigate the outflow of information. Obviously, the incident must be contained quickly. The more quickly it can be contained, the better off one will be. We also need to create an environment which fosters information sharing [so that] people [aren't] afraid of [automatically] losing their jobs if an incident occurs (actual or suspected). Breaches can get very large in volume if people are hesitant to report … the problem just compounds."

Preparing for the Unexpected

Security requirements for healthcare organizations can be very confusing. What should be protected, how it should be protected and the best path forward are best described as a multitiered flow chart with many moving parts.

Organizations should keep security risk analysis reports, signed business associate agreements, EHR logs that demonstrate use of security features and safeguards, and notated efforts to monitor user actions. Importantly, they should also keep incident and breach information and make sure staff understands it is the policy to randomly monitor computer habits.

Hope is not a plan. The best way to protect against cyber incidents is to prepare for the unexpected. There are many resources available. The ONC and Office of Civil Rights have vast amounts of user-friendly information and guidance available online.[8] Organizations such as HIMSS can help promote understanding about sound policy and information practices. And, IT security companies such as M3 Technology Consultants can help provide workable solutions for safer online environments.

Ultimately, the responsibility of cyber security and following meaningful use falls on organizations, no matter where missteps may have occurred. ❖

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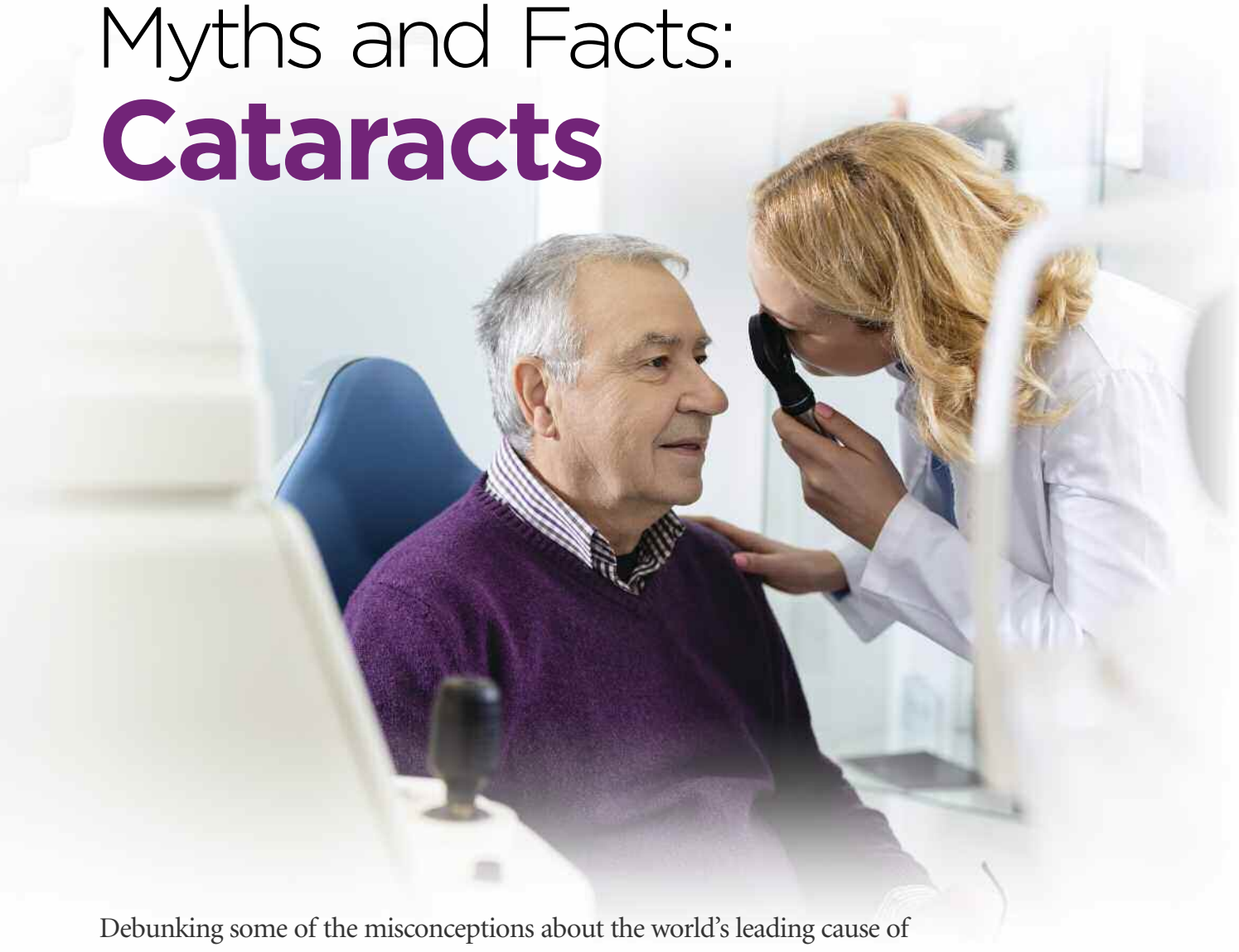
Myths and Facts: Cataracts



Debunking some of the misconceptions about the world's leading cause of blindness could help many people get the treatment they need.

By Ronale Tucker Rhodes, MS

CATARACTS HAVE BEEN around for centuries, dating back to the 5th dynasty (about 2457 to 2467 BCE). The term "cataract" comes from the Latin word "cataracta," meaning waterfall. It's believed the condition that causes vision to be cloudy was named because of the white appearance of rapidly running water.[1]

Cataracts are the leading cause of vision loss worldwide, affecting nearly 22 million Americans age 40 years and older. In fact, cataracts are a natural result of aging, and by age 80, more than half of all Americans will have cataracts, according to the National Eye Institute.[2] Worldwide, 51 percent of people who are blind are blind due to cataracts, mostly due to lack of resources and healthcare access, particularly in Asia and Africa. But, even in the Western world where treatment is safe and relatively accessible, myths persist about the cause of cataracts and their treatment, resulting in many people failing to seek treatment due to its perceived risks.[3] Clarifying the facts about cataracts, then, could help to curb preventable vision impairment and loss.

Separating Myth from Fact

Myth: Cataracts grow on top of the eyes.

Fact: Cataracts, which can occur in one or both eyes but cannot spread from one to the other, are a white or cloudy patch that develops on the eye lens, the part of the eye that helps to focus

light, or an image, on the retina (the light-sensitive tissue at the back of the eye). In a normal eye, the image is sharp, but if the lens is cloudy from a cataract, the image is blurred or yellowed.[4]

Cataracts are a natural result of aging. Age-related cataracts affect vision in two ways: cloudiness or color change. The lens consists mostly of water and protein. When the protein clumps up, it clouds the lens and reduces the light that reaches the retina; this is known as a cataract. When a cataract is small, only a small part of the lens is affected by cloudiness, and many don't notice any change in vision. However, because cataracts grow slowly, over time, the cloudy area in the lens gets larger, so vision gets worse. The lens can also slowly change to a yellowish/brownish color, which adds a brownish tint to vision. Again, while the discoloration may be small in the beginning, as it increases, it makes it more difficult to read or perform other routine activities.[4]

While cataract surgery once used to require a hospital stay and lengthy recovery period, that is not the case today.

Myth: Cataracts affect only the elderly.

Fact: While cataracts are most common among people in their 70s and 80s, they can occur in younger individuals due to conditions other than age: blunt injury to the eyes, radiation, treatment during chemotherapy with prednisone-like medications, diabetes, cigarette smoking, alcohol use, prolonged exposure to ultraviolet sunlight and family history.[4,6] Even infants can have cataracts at birth due to a congenital anomaly.[5]

In fact, about 1 percent to 2 percent of all cataract surgery patients are in their 40s, but it is believed many more people that age probably have cataracts already forming in one or both eyes and just don't know it yet. A recent study by the Mayo Clinic indicates an increasing number of people are having cataract surgery — and at younger ages. The study examined cataract surgeries performed from 2005 to 2011 in Minnesota's Olmsted County and found about 20 percent of those surgeries were in patients younger than 65.[7]

Myth: Close-up tasks can make cataracts worse.

Fact: A common misconception is that reading or tasks such as sewing can make cataracts worse. But, actually, the additional light needed by those activities is what is likely to make a person notice he or she has a cataract.[8]

Myth: Cataracts are reversible.

Fact: Once the lens begins to cloud, the process can't be reversed with any treatment; the lens can only be replaced. However, people can delay the progress of cataract formation by eating a well-balanced diet, limiting exposure to UVA and UVB rays and quitting smoking.[5]

Myth: Eye drops can prevent or dissolve cataracts.

Fact: While some products claim they can prevent cataracts, they can't, because cataract formation is a natural part of the eye's aging process. Nor can any products dissolve cataracts because they are not a substance. Moreover, the U.S. Food and Drug Administration (FDA) has not approved any drops that cure or delay cataracts.[8]

Myth: A cataract must be "ripe" before it can be removed.

Fact: Prior to the early 1990s, people were required to wait until their cataracts ripened (hardened) before they were surgically removed. That operation involved removing the lens intact through a fairly large incision in the eyeball, which had better results because the lens was solid and wouldn't fall apart during extraction. However, now, most cataracts are removed by breaking up the lens into small pieces and then suctioning them out. This way, the lens doesn't need to be hard to be removed, which means cataract surgery can be based on how much the cataract is affecting a person's vision rather than on whether it is ripe.[9]

Myth: Cataracts can be removed with a laser.

Fact: Cataracts are not removed with a laser. Rather, femtosecond lasers are now being used in the U.S. to "assist" in the surgical removal of them. In 2008, the first laser-assisted cataract surgery was performed in Hungary. After gaining FDA approval, the first laser-assisted cataract surgery was performed in the U.S. in 2010.

During surgery, the laser assists with the corneal incisions, opening of the capsule containing the cataract and the initial sectioning of the cataract into smaller pieces. Because of its incredible precision, it may prove to be superior to the current technique in which these steps are manually performed by the surgeon. However, further data and well-designed studies are needed to prove this method is associated with better outcomes and fewer complications. And, because insurance does not cover the cost of having laser-assisted cataract surgery, there is a significant out-of-pocket payment for patients.[10]

Myth: Cataract surgery is dangerous and requires months of recovery.

Fact: This unfortunate myth prevents people from getting the treatment they need. While cataract surgery once used to require a hospital stay and lengthy recovery period, that is not the case today. The surgical procedure most commonly used today, known as phacoemulsification, is highly sophisticated and reliable. It can be safely performed by an ophthalmologist in a hospital or an ambulatory surgery center on an outpatient basis in less than an hour with a 95 percent success rate.[3,4] Indeed, more than 3.3

million cataract surgeries are performed in the U.S. each year, according to David Chang, MD, clinical spokesman for the American Academy of Ophthalmology, who describes it as "the most common operation performed anywhere on the body."[7]

Phacoemulsification was introduced more than 40 years ago. During the procedure, the surgeon creates an opening in the natural "sac" that holds the lens in place, called the lens capsule, and the lens is separated from the capsule by using a balanced salt solution. Once the capsule is open and the lens can move freely inside the capsule, a special ultrasound device is used to break the lens into small pieces and suck it out of the eye. After removal, additional viscous material is injected into the lens capsule to hold it open to make room for the new artificial lens. The folded artificial lens is then inserted into the capsule, where it is then allowed to unfold. Because the two incisions usually self-seal, they do not require stitches.[10]

There are also two other types of surgical procedures used to remove cataracts. Extracapsular cataract surgery is used mainly for very advanced cataracts in which the lens is too dense to dissolve into fragments (phacoemulsify) or when phacoemulsification is impossible. It requires a larger incision so the cataract can be removed in one piece without being fragmented inside the eye. Intracapsular cataract surgery requires an even larger wound than extracapsular surgery, and the entire lens and surrounding capsule are removed together. This technique, which requires the intraocular lens to be placed in a different location (in front of the iris), is rarely used today but can still be useful in certain situations.[11]

There are now several lens replacement options. Monofocal intraocular lenses (IOLs) are the traditional lenses that offer fixed vision at one distance only, which is generally far vision. These are the lowest priced implants available and, generally, glasses still need to be prescribed after surgery for reading and computer use.

Three premium IOLs are available. Multifocal IOLs are the most common and contain different zones to give sharp vision at multiple distances. They work in a similar way to progressive lenses in eyeglasses. However, with the limited space on multifocal IOLs divided into zones, some advantages of seeing through just one zone in single vision monofocal lenses are lost, such as contrast sensitivity. Alternatively, accommodating IOLs shift position with the action of the eye muscles to give sharper vision at different ranges, much like the action of a person's natural lens. The ciliary muscle of the eye allows the lens to move forward and focus on images that are near. When the muscle relaxes, it allows the lens to reshape and focus on intermediate objects. As another option, toric IOLs correct for astigmatism.

There are also two additional types of IOLs. Aspheric IOLs are slightly flatter than traditional IOLs, providing contrast sensitivity, which allows images in a similar color to their background to be more clearly defined. Younger cataract patients benefit longer from this type of IOL, but older patients lose the ganglion cells of the retina, so over time contrast sensitivity declines anyway. Also, blue light filtering IOLs filter out ultraviolet and high energy blue light waves present in natural and artificial light.

Because premium IOLs are not considered essential to restore sight, patients may have to cover the additional cost of these lenses.[12]

Recovery after surgery can differ for each patient. However, typically, vision is blurry at first as the eye heals and adjusts, and colors may seem brighter because of the new, clear lens. In addition, itching and mild discomfort for a couple of days after surgery is normal. Eye drops or other medication are usually prescribed to prevent infection, reduce inflammation and control eye pressure. Follow-ups with the doctor are typically scheduled a day or two after surgery, the following week and then again in about a month to monitor healing. Most people need glasses, at least some of the time, after cataract surgery.[13]

Dispelling the Myths Now

With many doctors and scientists conducting cataract research, studies are aimed at discovering new treatment options, including controlling cataracts with drugs so corrective surgery will not be needed. Studies are also delving into how certain vitamins and minerals might prevent or slow the progress of cataracts, whether sunlight exposure may be associated with an increased risk of cataracts and how genetics contribute to cataract development.[14]

While cataracts have been recognized for centuries, our understanding of what causes them and how to correct the problem has progressed tremendously over the years. Today, cataract surgery is one of the safest surgeries performed with very few complications. By gaining clarity about this natural part of the aging process, it's hoped many more patients will receive the treatment they need to preserve their sight. ❖

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Gene Therapy for Hemophilia: *Edging Closer to Reality*

"Children today born with hemophilia are being born into an era where, due to these groundbreaking therapies, they should in all respects be able to live their lives to their fullest potential."

— Steven Pipe, MD, Chair, NHF Medical and Scientific Advisory Council

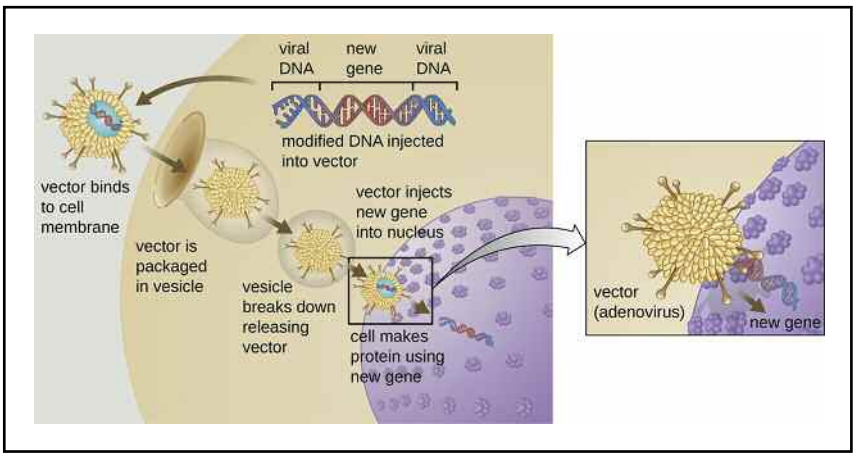
By Keith Berman, MPH, MBA

IN OUR LIFETIMES, no serious medical condition has had its prognosis more dramatically transformed by scientific advances than severe hemophilia. Prior to the first use of factor-enriched cryoprecipitate and plasma-based factor VIII (FVIII) and factor IX (FIX) concentrates in the 1960s, followed by recombinant factor products in the 1990s, clinicians were limited to transfusions of fresh frozen plasma to try to limit bleeds into joints, soft tissues and the central nervous system. Children with severe disease (defined as a FVIII or FIX level of less than 1 percent of normal) grew up experiencing frequent painful joint bleeds resulting in crippling joint hemarthroses. The ever-present risk of catastrophic spontaneous or trauma-induced hemorrhage translated into much-shortened lives. As recently as 1960, the average lifespan of a male with severe hemophilia was less than 20 years.[1]

By the mid-1990s, "on-demand" factor replacement therapy to manage frequent bleeds began to give way to a far more effective strategy: prophylactic dosing, typically every other day or three times weekly, of a sufficient dose of replacement factor to maintain circulating levels high enough to protect against spontaneous and excessive trauma-induced bleeding. Approved starting in 2014, the newest generation of FVIII and IX concentrates are structurally or chemically altered to extend their circulating half-life, significantly reducing the frequency of infusions to maintain protective levels. Today, a child with moderately severe or severe hemophilia A or B who is fully adherent to prophylactic treatment regimen has a much-reduced risk of serious bleeding episodes, with the potential to attain a normal life expectancy.[2]

The disease burden of severe hemophilia in the U.S. and other developed countries is now largely associated with 1) the demands of complying with regular prophylactic infusions of factor concentrate over a lifetime, 2) limitations on physical activities that can still induce joint, soft tissue or central nervous system bleeds and 3) a roughly 30 percent risk, usually in early childhood, of developing inhibitor alloantibodies that neutralize exogenously administrated clotting factor, leaving the patient exposed to potentially life-threatening

Figure 1. Direct Gene Therapy Using an Adenovirus Vector



Source: courses.lumenlearning.com/microbiology/chapter/gene-therapy

bleeds. A significant residual bleeding risk remains, however, as mean coagulation factor levels attained with prophylaxis are still far below the normal range and reach a nadir in the latter period prior to the next infusion. Finally, there are exceedingly high annual costs of prophylactic therapy with factor replacement therapies, which can amount to tens of millions of dollars over a lifetime. All of these considerations have encouraged the development of potentially curative gene therapy.

How Hemophilia Gene Therapy Works

The principle of gene therapy is straightforward: resolve or at least ameliorate disease caused by a defective gene by populating target cells with the normal gene that encodes and expresses therapeutic levels of functional protein. But there are two fundamentally different ways to do it. GlaxoSmithKline's Strimvelis gene therapy, approved in the European Union in 2016 for a variant of severe combined immunodeficiency, is a pioneering example of cell-based delivery, wherein the patient's bone marrow or circulating CD34+stem cells are harvested and cultured with a viral vector that inserts the corrective gene directly into the stem cell cDNA; these expanded gene-corrected stem cells are then reintroduced into the patient. Thus, the gene therapy "product" is the patient's own genetically engineered autologous cells.

But ex vivo genetic manipulation of harvested stem cells is complex and requires the cells be transported to a centralized laboratory with this expertise for processing. In addition to Strimvelis, investigational gene therapy programs addressing hematological disorders such as sickle cell disease and β-thalassemia are other examples of cell-based delivery of gene therapy involving stem cell harvesting and ex vivo manipulation.

In contrast, current development-stage hemophilia gene therapies deliver transgenes encoding FVIII or IX directly to the patient's target liver cells (Figure 1). Large numbers of these transgenes, which are ferried into target liver cells by an adeno-associated virus (AAV) vector containing a "liver-specific promoter," are intravenously infused in a single treatment session. The first approved gene therapy product in the U.S., Spark Therapeutics' LUXTURNA,* is a directly delivered gene therapy. Not unlike any other approved biotherapeutic, LUXTURNA is manufactured at a U.S. Food and Drug Administration (FDA)-licensed facility in Philadelphia. It is purchased by the hospital and supplied to the operating room, where it is injected subretinally. Similarly for a future hemophilia gene therapy, a manufactured AAV-FVIII or IX transgene would simply be supplied to the hospital and administered to the patient.

Hemophilia gene therapy differs in one other important respect from ex vivo-processed stem cell gene therapies. The AAV vector delivers the FVIII or IX gene to the liver cell nucleus, but in this instance, it typically does not integrate into the cellular DNA. Instead, the transgene-containing vector remains separate from the chromosomes. Because the AAV does not integrate itself into the cellular DNA with investigational hemophilia gene therapies, the risk of potentially creating cancer-inducing mutations (known as insertional mutagenesis) that has occurred with investigational ex vivo stem cell-based gene therapies is minimized.

A Head Start for Hemophilia B Gene Therapy

While there are six times as many individuals with severe hemophilia A than with severe hemophilia B, early gene therapy efforts focused on hemophilia B for the simple reason that the gene DNA encoding FIX is about half as large as the DNA encoding FVIII. Until very recently, the comparatively large size of FVIII DNA was widely thought to be problematic given the limited packaging capacity of AAV capsids.[3] The gene coding FIX is in fact easier to incorporate into various viral vectors with robust protein expression in vivo. By 2013, after advancing through preclinical testing, three investigational hemophilia B gene therapy products had entered early-stage clinical trials in patients with severe or moderate-severe

** Indicated for treatment of a mutation-associated retinal dystrophy disorder*

hemophilia B (Figure 2). While numbers of treated subjects are small, recently presented findings from these studies are very encouraging.

Spark Therapeutics/Pfizer (SPK-9001). This novel gene therapy product incorporates a FIX Padua transgene in its recombinant AAV vector. U.S., Canadian and Australian investigators infused SPK-9001 at a dose of 5 x 10^{11} vector genomes per kilogram (vg/kg) of body weight in 10 adult male subjects previously on prophylaxis, all of whom had baseline FIX coagulant activity of ≤2 percent of the normal value. On follow-up ranging from 28 weeks to 78 weeks, the annualized bleeding rate (ABR) was reduced from a mean of 11.1 events per year (range 0 to 48) to a mean of 0.4 events per year (range 0 to 4) after vector administration. All 10 subjects experienced sustained elevations in their FIX coagulant activity, with a mean steady-state of 33.7 ± 18.5 percent of normal (range 14 percent to 81 percent).

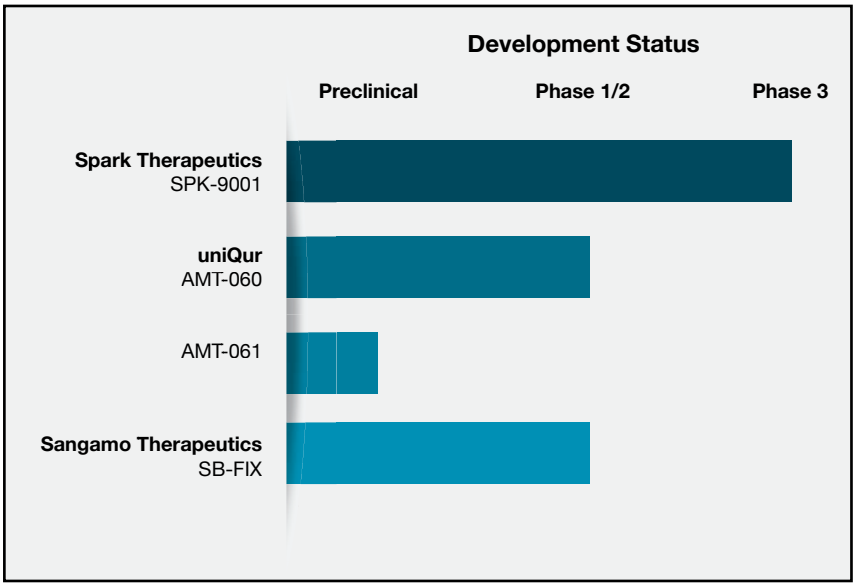
FIX concentrate use in these subjects correspondingly fell from a mean monthly dose of 2,908 IU per kg (range 0 IU to 8,098 IU) prior to SPK-9001 administration to just 49 IU per kg (range 0 IU to 376 IU) after administration. Eight of the 10 subjects didn't require any exogenous FIX, and nine of 10 experienced no bleeding events after vector administration. No clinically significant adverse events were observed.

In their report, investigators concluded that a single administration of SPK-9001 gene therapy "enabled the termination of baseline prophylaxis and the near elimination of bleeding and factor use."[4]

uniQure (AMT-060). A single administration of the higher of two evaluated doses (2 x 10^{13} genome copies) of uniQure's investigational AAV serotype 5 (AAV5)-human FIX hemophilia B gene therapy reduced the mean annualized spontaneous bleeding rate from 3.0 to 0.9 bleeds in five adult subjects with endogenous FIX levels ≤2 percent of normal and a severe bleeding phenotype.[5] Annualized FIX use decreased by 73 percent, and eight of nine participants receiving FIX at study entry were able to stop prophylaxis. FIX expression levels were stable over one-and-a-half years of follow-up, and there were no serious adverse events or development of inhibitors. However, at the highest tested dose, AMT-060 does not appear to effect as robust an elevation in endogenous FIX production as competitive hemophilia B gene therapies currently in clinical development.

In late 2017, this Netherlands-based biotechnology firm reported that AMT-061, a modified version of its original hemophilia B gene therapy, achieved an approximately 6.5-fold improvement in FIX activity in cynomolgus monkeys.[6] Like Spark Therapeutics' gene therapy product for hemophilia B, AMT-061 substitutes the high-activity FIX-Padua gene variant for wild-type FIX in the AAV5 capsid-based vector. While expression of FIX is similar to AMT-060, animals infused with a single dose of AMT-061 had approximately 6.5-fold higher FIX activity. Moreover, at a dose of 5 x 10^{12} vg/kg, FIX activity averaged 58.9 percent of normal from week 4 to week 13 postadministration, compared to an average of just 9.1 percent of normal for AMT-060. uniQure plans to advance AMT-061 into a pivotal clinical study in 2018.

Figure 2. Hemophilia B Gene Therapy Programs



Sangamo Therapeutics (SB-FIX). Sangamo has taken a unique "gene editing" approach to gene therapy for severe hemophilia B using a site-specific zinc finger nuclease (ZFN) to integrate the FIX transgene within the albumin gene of the liver cell genome.[7] An AAV vector is additionally used in vivo to deliver the FIX gene. Sangamo targeted the albumin gene because of liver cells' very large capacity to produce this blood protein — about 15 grams per day. The company believes that targeting and co-opting only a very small percentage of the albumin gene's capacity could potentially produce therapeutically relevant levels of FIX with no significant effect on albumin production.[8]

Sangamo's Phase I/II "FIXtendz" trial currently in progress will enroll 12 subjects with severe hemophilia B to evaluate the safety, tolerability and preliminary

efficacy of three escalating doses of SB-FIX.

Hemophilia A Gene Therapy Programs Advance

Despite the head start for investigational hemophilia B gene therapies to enter clinical trials, one U.S. competitor, BioMarin Pharmaceuticals, has managed to close the gap with its proprietary hemophilia A gene therapy, and is now enrolling the first subjects in a pivotal Phase III trial. Two others, Spark Therapeutics and Sangamo Therapeutics, are currently enrolling patients in Phase I/II studies (Figure 3).

BioMarin Pharmaceuticals (BMN 270). Founded 20 years ago, BioMarin has already secured FDA approval for several enzymes and drug compounds to treat rare congenital disorders, and has several others in the development pipeline. BMN 270 or valoctocogene roxaparvovec, intended for treatment of severe hemophilia A, is the company's sole gene therapy candidate. BMN 270 comprises an AAV5 vector encoding a B domain-deleted FVIII gene.

In initial mouse models of hemophilia A, BMN 270 restored FVIII plasma concentrations to levels projected to be adequate for normal clotting activity in humans. In Phase I/II clinical trial findings reported last December, BioMarin reported the sustained normalization of FVIII activity level over a period of one year in six of the seven study participants receiving the highest of three doses of BMN 270 (6×10^{13} vg/kg). All seven high-dose subjects experienced stabilization of hemostasis and a profound reduction in FVIII use.[9]

At 78 weeks following BMN 270 treatment, the mean and median circulating FVIII levels for the high-dose patient cohort were, respectively, 90 percent and 89 percent of normal. In all seven subjects, the median ABR dropped from 16.5 bleeds prior to BMN 270 therapy to zero bleeds (mean 16.3 to 0.5 bleeds). Annualized FVIII infusions per subject dropped from a median of 138.5 infusions prior to gene therapy to zero infusions (mean 136.7 to 6.1 infusions). Remarkably, none of the seven subjects in the high-dose cohort used any FVIII for self-reported bleeds between week 22 and the end of the study period. Prior to gene therapy, the median FVIII utilization in this cohort was about 400,000 IU per year.

As of mid-November 2017, no subject receiving BMN 270 developed inhibitors to FVIII. Adverse events were considered minor; eight of the nine study subjects experienced mild elevations in serum alanine aminotransferase that resolved without sequelae. While these results are obviously highly promising, the investigators caution that continued follow-up is needed to determine the long-term safety and efficacy of BMN 270.

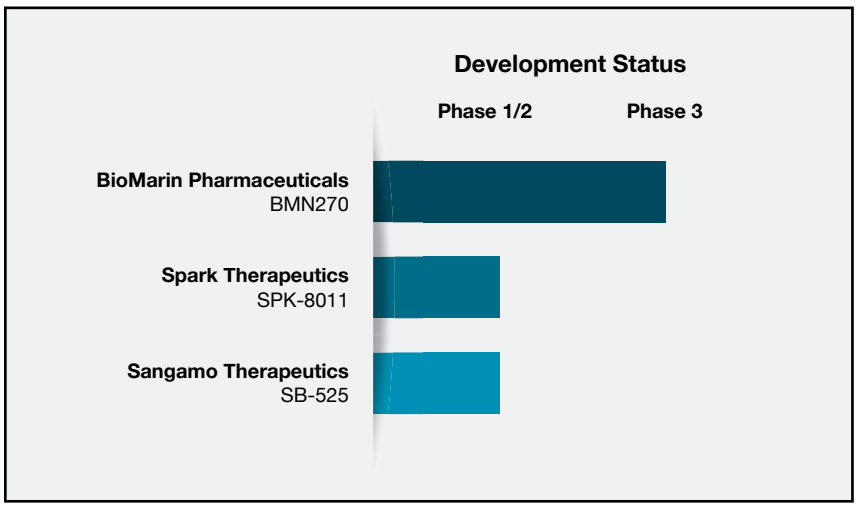
In December 2017, BioMarin enrolled the first of a planned 40 patients with severe hemophilia A in its global "GENEr8-1" Phase III clinical trial to evaluate the efficacy and safety of a single 6×10^{13} vg/kg dose of BMN 270. A second Phase III trial scheduled to start in early 2018, "GENEr8-2," will separately evaluate a single 4×10^{13} vg/kg dose of BMN 270.

Spark Therapeutics (SPK-8011). As of last December, early outcomes had been reported on seven severe hemophilia A patients dosed with a single infusion of 5×10^{11} vg/kg of this liver-targeted, human FVIII gene-containing AAV-LK03 capsid. After an initial four-week induction period, the overall annualized infusion rate of exogenous FVIII was reduced by approximately 98 percent, to a mean of just 1.2 infusions from a baseline mean of 57.8 infusions prior to gene therapy.

In two participants followed for more than 30 weeks, one has achieved sustained FVIII expression with a mean activity level of 10 percent of normal after week 12, while the other has demonstrated much more variable expression kinetics, with a mean FVIII level of 16 percent of normal, but with fluctuation ranging from 6 percent to 37 percent. Preliminary findings of this nature clearly underscore the importance of results from long-term follow-up of larger numbers of treated subjects for this and all other investigational gene therapies.

Sangamo Therapeutics (SB-525). Sangamo recently initiated a Phase I/II clinical trial of SB-525, a recombinant AAV2/6 vector

Figure 3. Hemophilia A Gene Therapy Programs



encoding the gene for B-domain deleted human FVIII. The expressed protein has the same amino acid sequence as Pfizer's XYNTHA, a recombinant FVIII product approved for the treatment of hemophilia A.

Potentially Favorable Cost Economics

Appropriately, enthusiasm for hemophilia gene therapy relates to its potential to translate into better protection against bleeding risks and an improved quality of life. But its eventual approval will bring an additional collateral benefit into focus: cost savings.

"For a 55 kilogram person with severe hemophilia A on prophylaxis, the average annual usage is around 330,000 IUs of standard FVIII per year, assuming he is 100 percent treatment-compliant," said Matthew Hotchko, PhD, vice president of research at the Connecticut-based Marketing Research Bureau. "At the current price, this translates into a cost of close to $300,000 per year. And, of course, the cost of prophylaxis increases in direct proportion to increased body weight." The annual average cost for extended half-life products is significantly higher due to the higher price of this new product class, Dr. Hotchko added — about $400,000 to $450,000 for a 55 kg individual with severe disease, again assuming he is 100 percent treatment-compliant.

Approved gene therapies will unquestionably be costly. But in the case of hemophilia, the presumption that these highly sophisticated treatments will boost healthcare spending on the disease is turned on its head. Because gene therapies promise to all but eliminate the need for extraordinarily costly chronic factor replacement therapy, these one-time treatments can be expected to importantly reduce the lifetime cost burden of severe hemophilia A and B.

> "While there are six times as many individuals with severe hemophilia A than with severe hemophilia B, early gene therapy efforts focused on hemophilia B."

Who Will Get Hemophilia Gene Therapy?

The task of defining appropriate candidates for a given hemophilia A or B gene therapy will obviously need to await the enrollment and long-term follow-up of a sufficient number of study subjects to provide acceptable clarity about its safety and efficacy. In particular, referral for a given gene therapy product will heavily depend on its success rate and the persistence of protective levels of clotting factor. These answers remain a number of years away.

But let's assume for a moment that one or more investigational gene therapies prove to be safe and reliably maintain factor activity well above the target levels that currently guide FVIII and FIX prophylaxis schedules. While prophylaxis has dramatically reduced the risk of spontaneous and traumatic bleeds, it is still far from an ideal therapy.

The shortcomings of prophylaxis with factor concentrates extend beyond the known risk of developing inhibitors and the adverse quality-of-life impact of having to regularly self-infuse the product for moderately severe or severe disease.

People on prophylaxis still cannot engage in so-called "high-risk" sports or other physical activities that could potentially induce serious bleeds into the joints, soft tissues or brain. As each scheduled factor infusion approaches, and the factor level drops to its nadir, the risk of an activity- or injury-related bleed, in particular, increases. And, of course, noncompliance or even occasional forgetfulness boosts the chances for a serious or life-threatening bleeding event.

It is widely acknowledged that while chronic prophylactic treatment with factor products has improved patient quality of life and protection against bleeds, it leaves much to be desired. If preliminary evidence is any indication, gene therapy could indeed prove to be the definitive cure that, at last, frees thousands of people with hemophilia to live a normal life. ❖

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In May 2012, Aimee Copeland was an active, 24-year-old University of West Georgia grad student. Her life changed in an instant following a freak zip line accident that exposed her to deadly flesh-eating bacteria. Although she lost all her limbs, this tenacious young woman retained her relentless optimism and drive, and today she runs a nonprofit foundation to help others overcome life-altering physical disabilities.

Necrotizing Fasciitis: *A Patient's Perspective*

By Trudie Mitschang

THE DAY IN late spring of 2012 that Aimee Copeland's life irrevocably changed began uneventfully. She'd finished classes for the semester and was hanging out with friends. Since the day was warm, the group decided to go swimming in a nearby creek. Noticing a homemade zip line, they began taking turns gleefully skimming across the water, but on Copeland's second run, the line suddenly snapped, sending her plummeting into the rocky creek bed below. The resulting gash on her calf required 22 staples, and over the next two days, Copeland suffered severe pain. Then, on May 4, she awoke in horror to find her injured leg had turned purple and was rotting all the way up to her hip. "I thought I was dying," she recalls.

Rushed back to the hospital, Copeland was diagnosed with necrotizing fasciitis.

What Is Necrotizing Fasciitis?

Necrotizing fasciitis is a bacterial infection often referred to as flesh-eating bacteria. It's a terrifying moniker, and for good reason. The bacteria attacks the skin and the tissue beneath it (fascia, which surrounds muscles, nerves, fat and blood vessels), often spreading quickly — sometimes at the rate of an inch per hour. Necrotizing fasciitis typically enters the body through an open wound or some sort of external injury, and according to the National Institutes of Health, up to 25 percent of patients die due to complications such as organ failure and blood poisoning.

Several different types of bacteria can cause necrotizing fasciitis, including Streptococcus, the bacteria that causes strep throat, and others found in soil, animals and nature. In Copeland's case, the infection was triggered by Aeromonas hydrophila, a bacteria found in fresh or brackish water.

A Brush with Death

By the time she was admitted to the hospital, Copeland's leg was too far gone to be saved, and with the infection rapidly spreading, her life was also in jeopardy. She was flown to a hospital in Augusta, Ga., where doctors amputated her left leg almost to her hip and cut skin from her abdomen to stop the bacteria's spread. "All my vital organs were also failing," she says. "I coded simply being moved from the stretcher to table and had to be resuscitated."

Following her surgery, Copeland required a respirator to breathe and was on full-time dialysis. Three days after her amputation, doctors told her parents that her chances of survival were slim to none. At that point, she was prescribed vasopressors. For days, they ensured blood flow to her vital organs, but eventually starved her extremities, tragically leading to further amputations. In addition to her left leg, Copeland lost both arms below the elbow and her right leg below the knee. But, she survived.

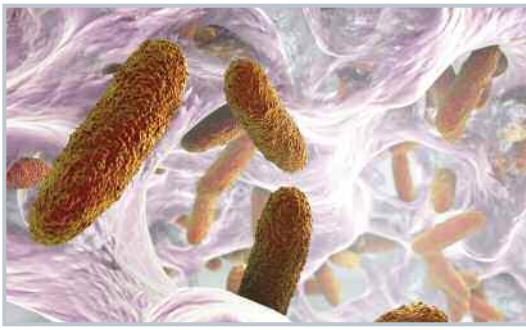
A Second Chance at Life

For Copeland, the road to recovery was a difficult one. Her long-term relationship with her college boyfriend ended, and she had to learn to accomplish even basic daily tasks using newly fitted prosthetics. Young and single, she also had to regain her self-confidence, eventually dating again. But, it was her frustration with her physical limitations that eventually led her to discover her new life's purpose. "Before the infection, I was extremely active," she explained. "You could often find me rock climbing, backpacking and trail running. So, I quickly became frustrated with what seemed to be my new situation — just sitting in a wheelchair. A huge part of who I was no longer seemed accessible to me. And I wasn't alone. People who use wheelchairs are often separated from the outdoors due to mobility and accessibility issues."

Determined to live life fully again, Copeland completed her second master's degree in social work, and through physical therapy, training and determination, she reconnected with her inner athlete. Today, she swims, kayaks and bikes, and she helps others with physical disabilities do the same. "Developing a safe space that promotes healing while providing accessible outdoor environments has become my passion and my goal. That's why I founded the Aimee Copeland Foundation, which will raise funds to build and run an inclusive wellness park and holistic therapy center — right here in metro Atlanta."

These days, Copeland is in a happy romantic relationship, loves cooking for friends in her open kitchen, working out and adding to the 80,000 miles she's already driven in her customized van. With her whole life ahead of her, she says, "My self-confidence has never been higher. I've let go of the girl I was before — I've completely embraced who I am." ❖

Flesh-Eating Bacteria:
Fear vs. Facts



AN UNSTOPPABLE and often lethal bacteria that feeds on human flesh? Sounds like some futuristic plague from a science fiction plot. But, as numerous tragic headlines attest, not only is flesh-eating bacteria a very current medical malady, incidents of this rare disease may be on the rise.

This term is a bit of a misnomer; the bacteria don't actually eat flesh, but instead release toxins that liquefy tissue (no less horrific). The medical name for the disease is necrotizing fasciitis, or death of the fascia. According to the Centers for Disease Control and Prevention (CDC), roughly a thousand cases are reported annually in the U.S., although this number is likely an underestimate due to misdiagnosis.[1]

The Evolution of a Killer Bacteria

Necrotizing fasciitis is an infection from not one but actually several strains of bacterium. These include group A Streptococcus, Klebsiella, Clostridium, Escherichia coli, Staphylococcus aureus and Aeromonas hydrophila. Public health experts consider group A strep to be the most common cause of necrotizing fasciitis,[1] despite that infections from it are typically mild and easy to treat, as in the case with strep throat. But what we're learning is people infected with a rare strain of it can develop life-threatening infections. Researchers say the reason is the bacteria known as group A strep has undergone four major genetic changes, transforming it into the type that causes necrotizing fasciitis.[2]

In a 2014 study, James Musser, MD, PhD, a genomic pathologist at Houston Methodist Research Institute in Texas, investigated how changes in the genetic sequence of flesh-eating bacteria enabled it to trigger an epidemic in the late 1980s to early 1990s. He and colleagues discovered four major steps in the microbe's transition from harmless to potentially fatal. They traced the emergence of the bacterium, identified the toxin that makes it deadly and uncovered the final steps that led to an epidemic.[2] "For the first time, we really understand precisely the molecular evolutionary genetic events that gave rise to creating a new pathogen, which then caused an epidemic disease," explains Musser.[2]

Assessing Points of Entry

Understanding how these bacteria penetrate the body can lead to faster and more accurate diagnosis, and potentially save lives. The most commonly identified way of getting necrotizing fasciitis occurs when the bacteria enter the body through a break in the skin, including cuts, scrapes, burns, insect bites or puncture wounds. "There are often points of entry — a cut that gets the bug through the skin to the deep areas; or sometimes it's a poke, like a thorn or a needle stick; or on other occasions, it might be an insect bite," says William Schaffner, an infectious disease specialist at Vanderbilt University Medical Center who has spent decades studying these pathogens. He adds there are times when doctors can't find a point of entry, making it possible the bacteria can get through nonpunctured skin.[3] "These bugs move fast," he adds. "Infections can spread an inch an hour and quickly cause sepsis, multi-organ failure and even death in as many as one in three of those infected."

Who Is at Risk?

While deaths from necrotizing fasciitis tend to be highly publicized, it is important to remember that chances of contracting the infection are extremely low. According to CDC, most people who are afflicted with necrotizing fasciitis have other health problems that may lower their body's ability to fight infection. Some of these conditions include diabetes, kidney disease, cancer and chronic conditions that weaken the body's immune system.

People with necrotizing fasciitis often display symptoms within a few hours following an injury. The skin may be warm with red or purplish areas of swelling that spread rapidly. Some people get ulcers, blisters or black spots on the skin. Patients often describe their pain as severe. Additional symptoms include fever, chills, fatigue and vomiting. Anyone displaying symptoms of necrotizing fasciitis should seek immediate medical attention.

Is a Vaccine on the Horizon?

Armed with knowledge regarding the evolution of this pathogen, researchers hope to develop vaccines, treatments and improved public health initiatives to combat this frightening disease. While researchers note that one vaccine won't work against all bacterial strains that can cause necrotizing fasciitis, scientists are currently working on a group A strep vaccine because of the many other health complications these bacteria can cause. If successful, it could potentially prevent certain cases of flesh-eating disease, and move us one step closer to curbing these aggressive infections.[3] ❖

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

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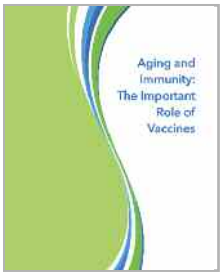
Aging and Immunity: The Important Role of Vaccines

Authors: American College of Physicians, American Pharmacists Association and Gerontological Society of America



Aging and Immunity: The Important Role of Vaccines is a new resource highlighting the biological impact of aging on immunity. Funded by GlaxoSmith Kline, the guidebook is designed to help healthcare professionals understand the biological impact of aging on immunity and reinforce the importance of adult immunization, especially for vaccine-preventable diseases such as shingles, pneumonia and influenza. The guidebook also offers practical tips and strategies for supporting aging patients' health and overcoming barriers to vaccination. "As we age, our immune system declines, making older adults more susceptible to serious conditions," said Jack Ende, MD, MACP, president of the American College of Physicians. "Understanding the aging immune system is becoming increasingly important for clinicians because vaccination is an effective solution to overcoming some of this age-related decline in immunity."

www.acponline.org/system/files/documents/clinical_information/resources/adult_immunization/aging_and_immunity_guide.pdf

ICD-10-CM Code Book for Physicians, 2018 (1st Edition)

Author: American Health Information Management Association

The *ICD-10-CM Code Book for Physicians, 2018* is written to help physicians and clinicians execute the International Classification of Diseases, Tenth Revision, Clinical Modification specifically in an outpatient setting. Key features include all 2018 updates to codes and coding guidelines, hierarchical condition category codes, color-coded tabs to align with section colors, coding guidelines in the introduction and before each section for quick reference, color-coded navigation to make code selection easier, references to coding guidelines, American Hospital Association coding clinic references, anatomical art and identification of diagnoses that impact Medicare Code Editor version 34 edits.

my.ahima.org/store/product?id=64468

Snapshots of Recent State Initiatives in Medicaid Prescription Drug Cost Control

Author: Kaiser Family Foundation

A new issue brief from the Kaiser Family Foundation highlights the range of issues and recent initiatives states are considering in this policy area. The state actions come at a time of increasing attention among policymakers to the cost of prescription drugs in health programs like Medicaid and Medicare and growing public concern about spending for prescription drugs. The brief reviews the structure of the prescription drug benefit in Medicaid and the traditional policy levers states have used to control drug spending. It also highlights new state strategies to contain costs such as efforts to obtain greater rebates, actions concerning generic drugs and biosimilar alternatives, transparency laws and new efforts to draw on federal resources.

www.kff.org/medicaid/issue-brief/snapshots-of-recent-state-initiatives-in-medicaid-prescription-drug-cost-control

Guide to FDA Drug Safety Regulation, 2018 Edition

Author: U.S. Food and Drug Administration (FDA)

This guide is written to help drug manufacturers keep up with FDA's evolving drug safety requirements as the agency tries to speed drug development and lower prices. The guide covers what information must be reported to FDA, how to prepare postmarket benefit-risk evaluation reports, requirements for electronic submission of adverse event data, best practices for conducting pharmacoepidemiologic safety studies, how to develop risk minimization action plans, how FDA determines if a risk evaluation and mitigation strategy is necessary and how to conduct nonclinical safety research.

www.fdanews.com/products/category/57-pharmaceuticals/product/55340-guide-to-fda-drug-safety-regulation-2018-edition

Subcutaneous Immune Globulin Effective as Maintenance Treatment in Chronic Inflammatory Demyelinating Polyneuropathy

A pivotal multinational, Phase III, placebo-controlled study demonstrated both low-dose and high-dose therapy with a licensed, self-administered subcutaneous immune globulin (SCIG) product was efficacious and well-tolerated as maintenance treatment for patients with chronic inflammatory demyelinating polyneuropathy (CIDP). Approximately two-thirds of patients with CIDP currently need long-term intravenous IG (IVIG) therapy.

One hundred and seventy two adults with definite or probable CIDP who responded to IVIG treatment were randomly allocated in a 1:1:1 ratio to weekly maintenance treatment with 0.2 g/kg or 0.4 g/kg of CSL Behring's Hizentra 20% SCIG product or placebo (2% human albumin solution). The Polyneuropathy And Treatment with Hizentra (PATH) study met its primary end-point, with 39 percent and 33 percent of patients on low- and high-dose Hizentra regimens experiencing a CIDP relapse or withdrawing from the study over a 24-week treatment period, compared with 63 percent of patients on placebo ($p = 0.007$ and 0.001, respectively). Additionally, the study found that 81 percent and 67 percent of high- and low-dose patients, respectively, remained relapse-free for up to 24 weeks.

Both SCIG dose regimens were well-tolerated. Local reactions accounted for most adverse events, and all were either mild (95 percent) or moderate (5 percent). "Hizentra maintained stable disease and prevented relapse, suggesting that subcutaneous immunoglobulin may be used as an alternative maintenance therapy to intravenous immunoglobulin in CIDP patients," said lead author Dr. Ivo N. van Schaik.

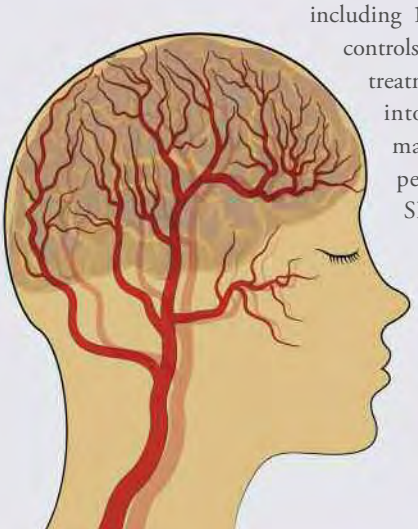
Van Schaik IN, Bril V, van Geloven N, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2018 Jan;17(1):35-46.

Editor's note: In March, CSL Behring's Hizentra was approved by the U.S. Food and Drug Administration for the treatment of CIDP as maintenance therapy to prevent relapse of neuromuscular disability and impairment.

Plasma Exchange with 5% Albumin Associated with Marked Stabilization of Brain Perfusion in Alzheimer's

Plasma exchange (PE) with 5% albumin replacement was associated with marked stabilization of brain perfusion in patients with mild to moderate Alzheimer's disease during a 21-week treatment period and reduced perfusion loss compared to control subjects at six-month follow-up, according to findings from a sham-controlled Phase II clinical trial.

Of 42 patients recruited for this study, 37 were analyzed, including 18 treated with PE and 19 controls. Evaluable patients received treatment for 21 weeks, divided into one intensive and two maintenance periods. Brain perfusion was assessed by SPECT scans using an automated software program, and brain structural changes were assessed by MRI, at weeks 0 (baseline), 21 and 44.



After six months, PE-treated patients experienced less cerebral perfusion loss than controls in frontal, temporal and parietal areas. Notably, perfusion was stabilized in the language-related Brodmann area BA38-R during the PE treatment period ($p<0.05$). Statistical parametric mapping analysis showed stabilization or absence of progression of perfusion loss in PE-treated patients until week 21, in contrast to significant worsening of perfusion in the control group at all time points. There was a trend toward decreasing hippocampal and total intracranial volume for both patient groups during the study.

The investigators noted that these brain perfusion findings could be related to previously documented mobilization of amyloid-β peptide in CSF and plasma and improved cognitive performance in this same PE-treated group compared to controls. They anticipate that the ongoing Phase III AMBAR (Alzheimer Management by Albumin Replacement) trial sponsored by Grifols will help shed further light on these relationships.

Cuberas-Borrós G, Roc I, Boada M, et al. Longitudinal neuroimaging analysis in mild-moderate Alzheimer's disease patients treated with plasma exchange with 5% human albumin. *J Alzheimers Dis* 2018;61(1):321-32.

Medicare Immune Globulin Reimbursement Rates

Rates are effective April 1, 2018, through June 30, 2018

	Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
IVIG	CARIMUNE NF	CSL Behring	J1566	$71.06	$69.92
IVIG	FLEBOGAMMA	Grifols	J1572	$70.29	$69.16
IVIG	GAMMAGARD SD	Shire	J1566	$71.06	$69.92
IVIG	GAMMAPLEX	BPL	J1557	$78.19	$76.93
IVIG	OCTAGAM	Octapharma	J1568	$82.81	$81.49
IVIG	PRIVIGEN	CSL Behring	J1459	$79.30	$78.03
IVIG/SCIG	GAMMAGARD LIQUID	Shire	J1569	$79.38	$78.10
IVIG/SCIG	GAMMAKED	Kedrion	J1561	$78.29	$77.03
IVIG/SCIG	GAMUNEX-C	Grifols	J1561	$78.29	$77.03
SCIG	CUVITRU	Shire	J1555	$135.25	$133.08
SCIG	HIZENTRA	CSL Behring	J1559	$98.33	$96.75
SCIG	HYQVIA	Shire	J1575	$138.59	$136.37

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

Calculate your reimbursement online at www.FFFenterprises.com.

Immune Globulin Reference Table

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

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

2018–2019 Influenza Vaccine

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

Product	Manufacturer	Presentation	Age Group	Code
Trivalent				
FLUAD (aIIV3)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90653
FLUZONE HIGH-DOSE (IIV3)	SANOFI PASTEUR	0.5 mL PFS 10-BX	65 years and older	90662
Quadrivalent				
AFLURIA (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	5 years and older*	90686
AFLURIA (IIV4)	SEQIRUS	5 mL MDV	5 years and older*	90688
FLUARIX (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUBLOK (ccIIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	18 years and older	90682
FLUCELVAX (ccIIV4)	SEQIRUS	0.5 mL PFS 10-BX	4 years and older	90674
FLUCELVAX (ccIIV4)	SEQIRUS	5 mL MDV	4 years and older	90756**
FLULAVAL (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLULAVAL (IIV4)	GSK	5 mL MDV	6 months and older	90688
FLUMIST (LAIV4)	MEDIMMUNE	0.2 mL nasal spray 10-BX	2-49 years	90672
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	3 years and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL SDV 10-BX	3 years and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	5 mL MDV	6 months and older	90688
FLUZONE PEDIATRIC (IIV4)	SANOFI PASTEUR	0.25 mL PFS 10-BX	6-35 months	90685/90687

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

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

Afluria may be used in persons aged ≥9 years.

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

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