SUMMER 2018

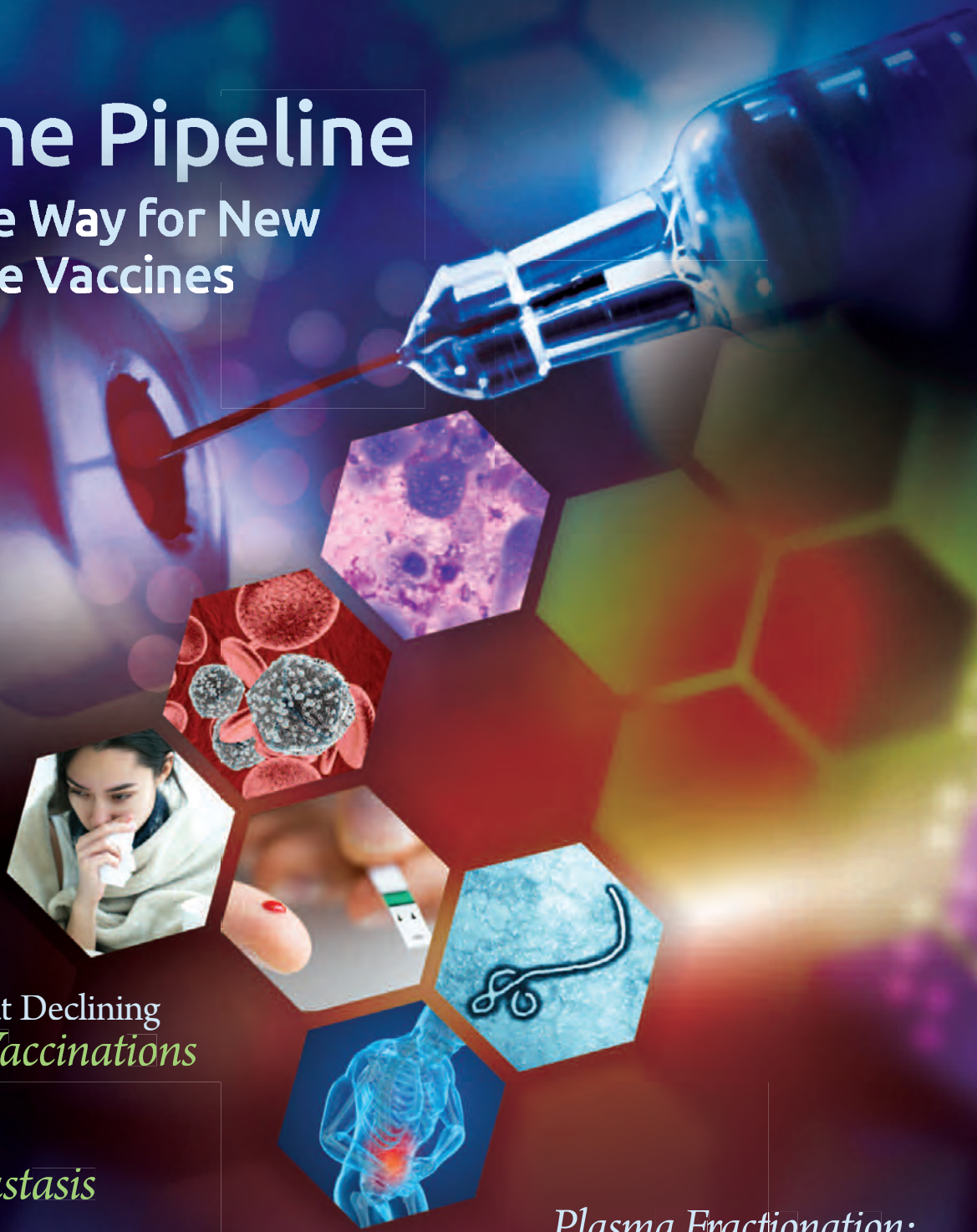
biosupply trends

QUARTERLY

SPECIAL FOCUS:
VACCINES

Vaccine Pipeline

Paving the Way for New Preventive Vaccines



How to Combat Declining
Childhood Vaccinations

Understanding
Cancer Metastasis

Medicine Storage and Inventory:
Using Smart Technology

Plasma Fractionation: Keeping Pace with Demand p.38

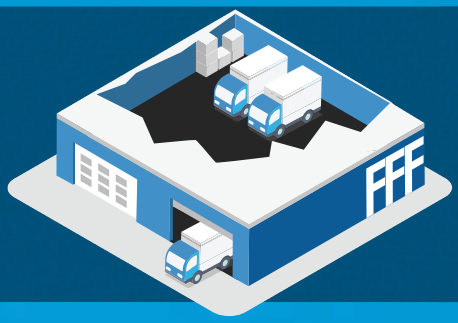
8 Critical Steps

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.

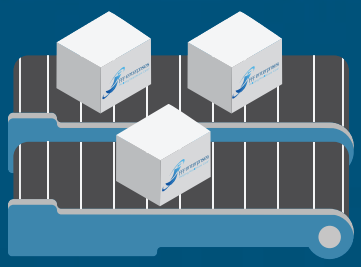


Specialty Packaging

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.



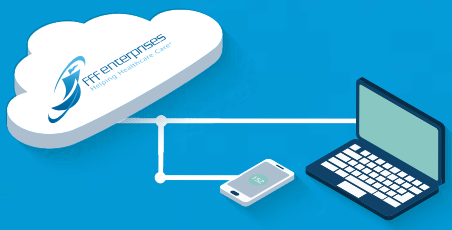
To Guaranteed Channel Integrity™

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.

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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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The Benefits of Vaccine Development and Safety

IN NOVEMBER, during the opening presentation at the Vaccines + Immunity: Examining Modern Medicine meeting, Leonard Friedland, MD, vice president, director of scientific affairs and public health, Vaccines, North America, at GlaxoSmithKline, remarked: "We are at the golden age right now in vaccinology. The opportunities that we have to take advantage of the knowledge we have gained from immunology, biology, microbiology and genomics, and to translate this into advances in patient care — this is absolutely incredible." His statement could not have been more spot-on, with some 264 vaccines in the pipeline in the U.S., and several recently approved vaccines to prevent infectious diseases in adults, including Flublok Quadrivalent (influenza), Shingrix (shingles) and HEPLISAV-B (hepatitis B).[1]

Indeed, it seems we are at a high point in vaccine development, with research over the past couple of years paving the way for some exciting new developments. In our article "Vaccines in the Pipeline," we touch on new vaccines that seek to prevent threatening diseases, including HIV, type 1 diabetes, influenza, cancer, Clostridium difficile and Ebola.

While it is well-known vaccines are one of the best preventive measures universally recommended today, some 50,000 adults die each year in the U.S. from vaccine-preventable diseases such as influenza and measles, which is more than from HIV/AIDS, breast cancer or traffic accidents.[2] Also disheartening, as we explain in our article "The Consequences of Declining Childhood Vaccination," this is due in part to the recent phenomenon of parents failing to vaccinate their children for various reasons such as a fear of giving their children too many vaccines too soon, concern about vaccine ingredients and the misconception that they cause autism — all of which have been discredited. And, without the protection of recommended vaccines comes declining community immunity, resulting in the resurgence of preventable diseases that can be deadly. Fortunately, as we outline, healthcare professionals can clear up parents' misconceptions about vaccine safety and emphasize the overwhelming benefits of vaccinating children.

Because of the high value and fragile nature of these essential vaccines and other biologics, protecting them is a serious concern. Strict guidelines for their storage and inventory — especially those that rely on cold-chain logistics — are governed by several different agencies, requiring time-intensive processes by healthcare facility staff to maintain supply and reduce potential damage and waste. We detail the Centers for Disease Control and Prevention's guidelines for storage and inventory in our article "Managing Medicines: Mitigating the Risks of Inventory and Storage." And, to assist facilities with simplifying and automating these complex tasks, we highlight two smart systems — Verified Inventory Program-Consignment and MinibarRx — that can greatly ease this burden on healthcare facilities.

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

1. Mroz D. The U.S. Is in the Golden Age of Vaccine Development. ContagionLive, Nov. 13, 2017. Accessed at www.contagionlive.com/news/golden-age-of-vaccine-development.
2. National Foundation for Infectious Diseases. Top Reasons to Get Vaccinated. Accessed at nfid.org/about-vaccines/reasons.

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

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CMS Issues Final 2019 Payment Notice Rule

The Health and Human Services (HHS) Notice of Benefit and Payment Parameters for 2019, issued by the Centers for Medicare and Medicaid Services (CMS), aims to increase state flexibility, improve affordability, strengthen program integrity, empower consumers, promote stability and reduce unnecessary regulatory burdens imposed by the Patient Protection and Affordable Care Act. The final rule includes these key provisions:

• *Essential health benefits (EHBs).* Instead of being limited to 10 options, states will be able to choose from the 50 EHB-benchmark plan used for the 2017 plan year in other states or select specific EHB categories such as drug coverage or hospitalization from among the categories used for the 2017 year in other states. States will also be able to build their own set of benefits that could potentially become their EHB-benchmark plan, subject to certain scope of benefits.

• *Qualified health plan (QHP) certification standards.* Oversight authority will be returned to states regarding state review of network adequacy, and will ease the burden on issuers related to essential community providers. It will also eliminate the meaningful difference requirement for QHPs to give insurers more flexibility in designing plans.

• *Exemptions.* Exchanges will be able to make a determination of lack of affordable coverage based on projected income using the lowest cost exchange metal level plan when there is no bronze level plan available in the service area.

• *Risk adjustment.* The HHS-operated risk adjustment data validation program will be amended to reduce burdens on issuers. In addition, the HHS-operated risk adjustment program will be recalibrated for the 2019 benefit year to incorporate new data that reflects the actual experience of individual and small group market enrollees, which should more closely reflect the risk within markets. In states where HHS operates the risk adjustment program, CMS will also provide states with the flexibility to request a reduction to the otherwise applicable risk adjustment transfers in the individual, small group or merged market by up to 50 percent beginning with the 2020 benefit year, which may be helpful in attracting and retaining insurers and more precisely accounting for relative risk differences in the state market.

• *Advanced premium tax credit (APTC) program integrity.* Exchanges will be required to implement stronger checks to verify applicants actually earn the income they claim to qualify for APTCs. And, it will require exchanges to discontinue APTCs for enrollees who fail to file taxes and reconcile past APTCs, even if the exchange does not first send notice directly to the tax filer.

• *Special enrollment periods (SEPs).* For consumers newly gaining or becoming a dependent and enrolling through the birth, adoption, foster care placement or court order SEPs, the alternate coverage start date options available under all of these SEPs will be amended and standardized. Pregnant women who are receiving healthcare services through Children's Health Insurance Program coverage for their unborn child will qualify for a loss of coverage SEP upon losing access to this coverage. Finally, consumers will be exempted from the prior coverage requirement that applies to certain special enrollment periods if they lived in a service area without qualified health plans available through an exchange.

• *Medical loss ratio (MLR).* MLR requirements will be amended to reduce quality improvement activity reporting burdens on insurers and allows states to request reasonable adjustments to the MLR standard for the individual market if the state shows a lower MLR standard could help stabilize its individual insurance market.

• *Small business health options program (SHOP).* SHOPs will be allowed to eliminate the online enrollment process and employers will be allowed to enroll directly with an exchange-registered agent, broker or issuer.

• *Rate review.* The primary role of state regulators in the rate review process will be increased, while the regulatory burden for states and issuers will be reduced. The rule will exempt student health insurance coverage from federal rate review requirements, and will raise the default threshold for review of reasonableness from 10 percent to 15 percent.

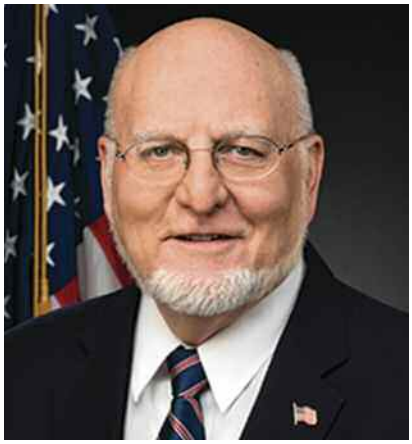
For additional information about the final rule, go to www.cms.gov/CCIIO/Resources/Regulations-and-Guidance/Downloads/2019-Letter-to-Issuers.pdf. ❖

CMS Issues Final 2019 Payment Notice Rule to Increase Access to Affordable Health Plans for Americans Suffering from High Obamacare Premiums. Centers for Medicare and Medicaid Services press release, April 9, 2018. Accessed at www.pressreleasepoint.com/cms-issues-final-2019-payment-notice-rule-increase-access-affordable-health-plans-americans.

Redfield Named Head of CDC

HIV/AIDS researcher Robert Redfield, MD, has been named the next head of the Centers for Disease Control and Prevention (CDC). Dr. Redfield is a professor of medicine at the University of Maryland School of Medicine and cofounder and associate director of the school's Institute of Human Virology (IHV). In his role at IHV, Dr. Redfield oversees a clinical program that provides HIV care and treatment to more than 6,000 patients annually in the Baltimore-Washington, D.C., area. In that work, he has become expert in treating heroin addiction, since intravenous drug use carries a higher risk of transmitting infectious diseases such as HIV and hepatitis.

"The AIDS epidemic in the United States, particularly in cities like Baltimore, is infinitely tied up with substance use and substance abuse," said James Curran, MD, dean of the Rollins School of Public Health at Emory University. "I think that experience he has in Baltimore is very, very relevant to the opioid epidemic that we've been seeing over the past two decades." ❖



Johnson SR. Redfield Named to Lead CDC. *Modern Healthcare*, March 21, 2018. Accessed at www.modernhealthcare.com/article/20180321/NEWS/180329976.

Work Requirements Can Be Used as a Basis for Medicaid Eligibility

New guidance from the Centers for Medicare and Medicaid Services (CMS) allows work requirements to be used as a basis for eligibility for certain Medicaid beneficiaries through 1115 waivers. Those who can be subject to work requirements include nonelderly, nonpregnant adult Medicaid beneficiaries who are eligible for Medicaid on a basis other than disability. The guidance also outlines that exemptions/protections from work requirements must be made for individuals who are medically frail or have substance abuse disorders. And, it says states should outline how they would support beneficiaries with limited employment opportunities such as in economically depressed areas, rural areas, with transportation limitations, etc.

Currently, nine states (Arizona, Arkansas, Indiana, Kansas, Maine, Mississippi, New Hampshire, Utah and Wisconsin) have applications pending asking for permission to include some type of work requirements. Kentucky recently had its waiver, which included work requirements, approved by CMS. The Kaiser Family Foundation found approximately 40 percent of non-SSI Medicaid adults are not working, and these individuals are most likely to be affected by this policy. The remaining 60 percent of non-SSI Medicaid adults who either work part time or full time would, presumably, meet any work requirement policy. ❖

Weider K and Whitlock R. CMS Guidance on Work Requirements for Medicaid Eligibility. *Health Law & Policy Matters*, Jan. 11, 2018. Accessed at www.healthlawpolicymatters.com/2018/01/11/cms-guidance-work-requirements-medicaid-eligibility.

CMS Finalizes Medicare Advantage Rates for 2019

The finalized 2019 Medicare Advantage plan rates will rise an average of 3.4 percent, and with another 3.1 percent adjustment from a change in risk scores (a measure of the sickness or health of the population served), the payment increase could be as high as 6.5 percent. According to the Centers for Medicare and Medicaid Services Administrator Seema Verma, the agency is changing how it uses encounter data (created by healthcare providers during visits with patients) to set risk scores by boosting the percentage of such data to 25 percent, up from 15 percent. The remaining 75 percent will come from Medicare fee-for-service data. The agency is also adding additional mental health, substance use disorder and chronic kidney disease conditions to its risk adjustment model. ❖

Inserro A. CMS Raises Medicare Advantage Payments, Tweaks Opioid Language for Patients with Pain. AJMC, April 3, 2018. Accessed at www.ajmc.com/newsroom/cms-raises-medicare-advantage-payments-tweaks-opioid-language-for-pain-patients.

Basic Concepts Driving Drug Payment

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

PAYMENT RULES for medications are changing with multiple new ideas being proposed and/or enacted. Many of these changes hinge on where drugs are dispensed, prescribed and used. This column will lay the groundwork for understanding drug payment through an explanation of terms and a review of the enacted or proposed rule changes.

Understanding Drug Payment

Medicare remains the single largest payer of medical care and prescription drugs in the United States. Private payer or insurance carriers often emulate Medicare's payment decisions or at least use them as the basis for programs they institute.

From a medication payment standpoint, drugs fall into three basic Medicare categories based on prescribing location and use: Part A covers drugs for inpatients, Part B covers drugs for outpatients, Part C covers drugs under Medicare Advantage (MA) plans, and Part D covers drugs in the ambulatory setting, which may be the home or some type of residential or long-term care facility. Part A drugs, which are part of the inpatient medical benefit, and Part B drugs, which are considered incident to a physician visit or procedure and are on a well-defined list, fall under the medical benefit. Part D drugs are considered part of the pharmacy benefit, and their use is often under the control of the pharmacy benefit manager.

For Part B drugs covered by the outpatient prospective payment system (OPPS), Medicare assigns a status indicator (SI) to each to provide information about how they will be paid. The relevant SIs are G, K and N. SI G is assigned to new drugs or new uses of drugs that have been given pass-through status based on an application from the manufacturer. By statute, this three-year status protects payment for these drugs at average sales price plus 6 percent, and they will be seen as line items on the patient's bill. SI K is assigned to separately payable drugs based on a minimum cost ($120 per day for 2018) and also will be seen as line items on the bill. SI N is interesting because it straddles both a cost threshold and a statute requirement for drugs that are bundled into payments for procedures or outpatient visits. Although they are not seen as line items on the bill, billing as if they were is essential to represent the true cost of the bundle and to justify separately payable drug administration fees, if applicable. Don't strip these out of the bill!

The physician office setting is covered under the physician fee schedule, and rates may differ from OPPS for both drugs and services. There is significant discussion surrounding the site-of-service topic, and 2019 may very well bring some degree of normalization in payment rates.

2019 Changes to Medicare Advantage and Part D Plans

In early April, the Centers for Medicare and Medicaid Services (CMS) finalized policies for Medicare health and Part D drug plans that are designed to save Medicare beneficiaries money on prescription drugs, while at the same time offering additional plan choices. These comprehensive rule changes make programmatic and operational changes to the Medicare Advantage and prescription drug benefit programs for 2019, so they should be reviewed in their entirety. These changes are part of the continuing quest to save money on prescription drugs.

Lowering out-of-pocket drug prices is addressed in a number of ways, including:

• A reduction in the maximum amount low-income beneficiaries pay for certain biosimilars. The provision "Similar Treatment

of Biosimilar and Interchangeable Biological Products and Generic Drugs for Purposes of Low Income Subsidy (LIS) Cost Sharing" further encourages the use of lower-cost alternatives by applying generic cost-sharing to biosimilar and interchangeable biological products for LIS Part D enrollees throughout all phases of the benefit.

- Allowing certain low-cost generic drugs to be substituted onto plan formularies at any point during the year so beneficiaries immediately benefit and have lower cost-sharing.
- Increasing competition among plans by removing the requirement that certain Part D plans have to "meaningfully differ" from each other, making more plan options available.
- Increasing competition among pharmacies by clarifying the "any willing provider" requirement to increase the number of pharmacy options beneficiaries have.

Another example of lowering out-of-pocket drug prices can be seen in the 2018 OPPS rules that helped Medicare beneficiaries save on coinsurance on Part B SI K drugs administered in hospital outpatient departments participating in the 340B program. By reducing the amount Medicare pays facilities for those drugs by almost 30 percent, the 20 percent co-pay for which Medicare beneficiaries are responsible also has been reduced by approximately 30 percent.

Clarification of how hospitals implement these changes and how they apply to MA Part C plans that also provide Medicare benefits through private insurance is being made available to participating facilities. Namely, there will be a change in plan design and cost-sharing. MA plans will receive a 3.4 percent pay raise in 2019, well above the initial proposed 1.84 percent increase and higher than the 2018 increase of 2.95 percent.

Less red tape and the "Patients Over Paperwork" initiative (an effort aimed at removing regulatory obstacles and empowering patients to make informed healthcare decisions; developing innovative approaches to improving quality, accessibility and affordability; and improving beneficiaries' customer experience) are included in the sweeping changes. Included will be a streamlined review and approval process of materials that electronically communicate Medicare health and drug plan information to beneficiaries and improve transparency.

> "In early April, the Centers for Medicare and Medicaid Services (CMS) finalized policies for Medicare health and Part D drug plans that are designed to save Medicare beneficiaries money on prescription drugs, while at the same time offering additional plan choices."

CMS also included several changes to combat opioid overuse. Program regulations were revised to implement certain provisions of the Comprehensive Addiction and Recovery Act and the 21st Century Cures Act that direct Part D plan sponsors to establish a drug management program for beneficiaries at risk for prescription drug abuse or misuse. This includes a policy to prevent Medicare beneficiaries who are deemed at risk for opioid misuse or abuse from obtaining prescription drugs from multiple doctors or pharmacies. Instead, these beneficiaries will be limited to one pharmacy or prescriber for Medicare Part D benefits. This will limit an at-risk beneficiary's access to coverage for frequently abused drugs to those that are prescribed by a specified pharmacy or provider. Exempted beneficiaries are those who are being treated for active cancer-related pain, are receiving palliative or end-of-life care, or are in hospice or long-term care from drug management programs.

A fact sheet on the 2019 rate announcement and final call letter can be obtained at www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2018-Fact-sheets-items/2018-04-02-2.html. A fact sheet on the final rule (CMS-4182-F) can be obtained at www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2018-Fact-sheets-items/2018-04-02.html. The final rule can also be downloaded from the federal register at www.federalregister.gov/public-inspection/current.

This column will continue discussions of other proposed 2019 changes in the next issue. ❖

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

CDC OKs FluMist for 2018-19 Influenza Season

The Centers for Disease Control and Prevention advisory committee has voted 12-2 to recommend FluMist, the nasal spray version of the influenza vaccine, be used during the 2018-19 influenza (flu) season. FluMist is a live attenuated influenza vaccine licensed for use in otherwise healthy, nonpregnant people ages 2 years through 49 years. For the past two flu seasons, FluMist has not been recommended because of poor performance compared with the flu vaccine.

The decision was based on data from AstraZeneca, manufacturer of FluMist, that addressed a possible root cause of poor effectiveness against the influenza AH1N1 virus and a potential solution to address it, which includes using a different type of influenza AH1N1 virus in the vaccine. Specifically, AstraZeneca presented positive results from a U.S. study in children ages 2 years to 4 years that evaluated their responses to the H1N1 strain in the quadrivalent formula of the spray, which protects against four different influenza viruses. Results showed the H1N1 strain in the 2017-18 vaccine performed significantly better than the H1N1 strain in the 2015-16 vaccine.

Even though FluMist has not been recommended for the past two flu seasons, the U.S. Food and Drug Administration (FDA) has still approved it. The availability of FluMist in the U.S. for the 2018-19 influenza season is pending annual strain approval from FDA. ❖

Scutti S. FluMist Set to Return for Next Flu Season. CNN, Feb. 21, 2018. Accessed at www.cnn.com/2018/02/21/health/flumist-returns-cdc-bn/index.html.

Medicines

CSL Behring Will Discontinue Carimune NF in Third Quarter 2018

CSL Behring is discontinuing the production of Carimune NF (immune globulin [human] nanofiltered) in the third quarter of 2018. Discontinuation of the product is due to the preference among healthcare professionals and patients for newer, more advanced immune globulin options. In a letter to providers of the product, the company wrote: "Consideration of yield is especially important when dealing with a resource as precious as human plasma. Discontinuation of Carimune NF will allow CSL Behring to dedicate more resources to Privigen and Hizentra, which yield higher rates of immunoglobulin. Over the long term, CSL Behring will be able to supply more immunoglobulin to the market due to greater yield and manufacturing efficiencies."

Providers who have questions are asked to contact their local CSL Behring representative. ❖

Carimune Immune Globulin Intravenous (Human), Nonofiltered Product Discontinuation Notice. CSL Behring letter, February 2018.

Influenza

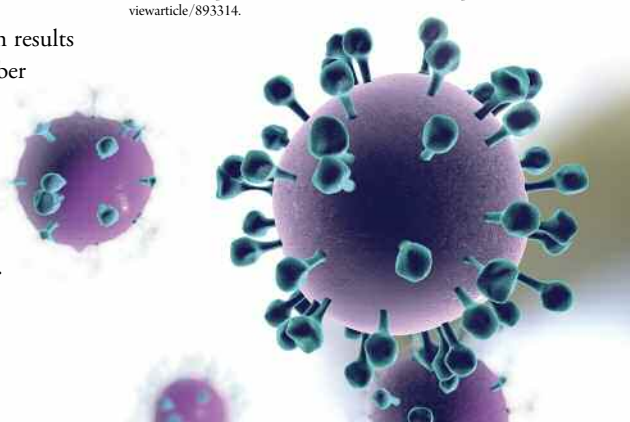
FDA Chooses Influenza Vaccine Strains for the 2018-19 Seasons

In March, the U.S. Food and Drug Administration's (FDA) Vaccines and Related Biological Products Advisory Committee chose the Northern Hemisphere's 2018-19 influenza (flu) vaccine strains based on the World Health Organization's recommendations. For the trivalent vaccine, the committee voted unanimously to include an A/Michigan/45/2015 (H1N1)pdm09-like virus and an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus, the latter of which is a change from the 2017-18 vaccine. And, the committee voted 11-1 to include a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage), which is also a change from the 2017-18 vaccine. The committee also voted unanimously to include a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage) as the second influenza B strain in the quadrivalent vaccine.

For the 2017-18 season, interim results show the vaccine lowered the number of cases of medically attended flu illness by 36 percent. Vaccine effectiveness against influenza A(H3N2) was 25 percent for all ages and 51 percent for children aged 6 months to 8 years. The vaccine was 67 percent effective against A(H1N1)pdm09, and 42 percent effective against influenza B (mostly B/Yamagata, not in inactivated influenza vaccine, trivalent).

"In terms of last year's vaccine … even though we've had a bad flu year, the strains that were selected … were really good selections," said Jack Bennink, PhD, a temporary voting member on the committee and senior managing epidemiologist at the National Institute of Allergy and Infectious Diseases. "They were as good as one could guess and make at the time. I don't think we could've done any better, and I'm encouraged by the fact that particularly [in children aged 6 months] to 8 years old it's almost 60 percent effective." ❖

Brown T. FDA Committee Recommends 2018-2019 Influenza Vaccine Strains. Medscape, March 1, 2018. Accessed at www.medscape.com/viewarticle/893314.



Medicines

Grifols' Higher-Potency Rabies Immune Globulin Is Now Available

In May, Grifols' higher-potency rabies immune globulin (RIG), HyperRAB S/D, was made available to healthcare providers. While HyperRAB has been on the market for 40 years, this improved immune globulin was approved by the U.S. Food and Drug Administration in April as a more effective and tolerable rabies treatment for patients. It is one of three RIGs approved as rabies postexposure prophylaxis. But, this new version is twice the potency (300 IU/mL) of currently available RIG options, offering a greater concentration of anti-rabies virus antibodies within each mL of volume. This means clinicians can administer fewer injections because each dose contains twice the concentration of anti-rabies virus antibodies.

Manufactured using a sophisticated caprylate chromatography process, which significantly reduces procoagulant activity and product impurities such as IgG aggregates, the new HyperRAB is available to U.S. patients in two sizes: 1 mL/300 IU and 5 mL/1500 IU. What's more, even though this new product is a big advancement for patient care, the cost of treatment remains the same as the original product.

Approximately 30,000 to 60,000 individuals are administered RIG each year after possible exposure to suspect animals. According to the Centers for Disease Control and Prevention (CDC) guidelines, patients with normal immune systems should receive a rabies vaccine on days 0, 3, 7 and 14 after exposure. If they are immunosuppressed, an additional vaccine is recommended on day 28.

CDC also recommends administering as much RIG into and around the wound site as possible. With the lower-potency immune globulins, it is often difficult for physicians to administer a large volume of RIG into a wound and around it. But, the new HyperRAB makes it easier to facilitate delivery of a better dose at the wound site. ❖

Research

Study Finds Mumps Vaccine Protection Wanes Over Time

A recent meta-analysis of six studies of mumps vaccine effectiveness conducted in the U.S. found protection against mumps lasts an average of 27 years after the last dose of the vaccine. In addition, researchers estimated 25 percent of Americans who were vaccinated against mumps as children may lose protection within about eight years, 50 percent within 19 years and 75 percent within 38 years. They also found weakening immunity to mumps played a major role in the recent reemergence of mumps among young adults. The findings suggest that in addition to the recommended two doses of mumps vaccine in childhood, adding a third dose or booster shot at age 18 could help maintain protection. ❖

Mumps Vaccine Protection May Be Waning, Driving Rise in U.S. Cases. United Press International, March 21, 2018. Accessed at www.upi.com/Health_News/2018/03/21/Mumps-vaccine-protection-may-be-waning-driving-rise-in-US-cases/2411521663206.

Research

Study Finds Vaccines Don't Weaken Babies' Immune Systems

In response to concerns from parents about whether multiple vaccines in early childhood could weaken their children's immune system, researchers conducted a study that examined whether the vaccine schedule was associated with an increased risk of infections not targeted by vaccines (referred to as "nontargeted infections"). They found no statistically significant differences in estimated cumulative vaccine antigen exposure through the first 23 months of life.

The nested case-control study examined 193 children with nonvaccine-targeted infections and 751 controls without nonvaccine-targeted infections in six U.S. healthcare organizations participating in the Vaccine Safety Datalink. Participants were children ages 24 months through 47 months born between Jan. 1, 2003, and Sept. 31, 2013, who were followed until Dec. 31, 2015. Cases of nonvaccine-targeted infection were matched to controls by age, sex, healthcare organization site and chronic disease status. Cumulative vaccine antigen exposure was estimated by adding the number of antigens in each vaccine dose received from birth through age 23 months.

Among the 944 participants (mean age 32.5 months; 45 percent female), the estimated mean cumulative vaccine antigen exposure was 240.6 for cases and 242.9 for controls, with a between-group difference for estimated cumulative antigen exposure -2.3. The researchers concluded that "among children from 24 through 47 months of age with emergency department and inpatient visits for infectious disease not targeted by vaccines, compared with children without such visits, there was no significant difference in estimated cumulative vaccine antigen exposure through the first 23 months of life." ❖

Glanz JM, Newcomer SR, Daley MF, et al. Association Between Estimated Cumulative Vaccine Antigen Exposure Through the First 23 Months of Life and Non-Vaccine-Targeted Infections From 24 Through 47 Months of Age. *JAMA*, 2018;319(9):906-913. Accessed at jamanetwork.com/journals/jama/article-abstract/2673970?redirect=true.

Guidelines

Updated C. Diff Guidelines Reflect New Treatment Options and Recommendations

The Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) have updated guidelines for diagnosis and management of Clostridium difficile (C. diff), which has become the leading cause of diarrhea in hospital patients and one of the most common healthcare-associated infections that sickens nearly 500,000 Americans and is associated with 15,000 to 30,000 deaths annually. The last IDSA/SHEA guidelines for C. diff were issued in 2010. And, while many of the recommendations remain the same, the updated guidelines reflect new treatment options and recommendations for who should be tested and which diagnostic tests are most appropriate.

The previous guidelines recommended metronidazole as first-line therapy for initial cases of mild-to-moderate C. diff and vancomycin for more severe cases. But, the updated guidelines recommend either vancomycin or fidaxomicin as the drug of choice for all initial episodes based on high-quality evidence that both drugs are superior to metronidazole. They also recommend both drugs for a first and

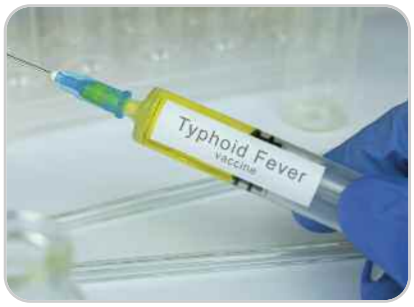
second recurrence of C. diff. But, for patients who have had several bouts and have failed all appropriate antibiotic treatments, the guidelines recommend fecal microbiota transplantation (FMT), a procedure that involves the transfer of stool from a healthy donor into the colon of an infected patient. FMT is still considered an investigational treatment by the U.S. Food and Drug Administration, but it has produced strong results in anecdotal reports and in randomized clinical trials. "An important aspect of susceptibility to C. difficile, if not the majority of susceptibility, is due to disruption of the microbiota by antibiotics," said Clifford McDonald, MD, senior advisor with the Centers for Disease Control and Prevention. "These patients can have multiple recurrent C. diff, they're failing over and over again, and that's where FMT is now another tool in the toolbox."

The new guidelines also recommend testing be limited to those patients with more than three episodes of new-onset diarrhea within 24 hours, specifically patients whose symptoms aren't attributable to underlying conditions or use of laxatives. In addition, it is recommended molecular tests, which have become increasingly popular in recent years due to their high sensitivity and quick diagnosis, be used on their own only when hospitals have established criteria for patients who are most likely to be at risk for C. diff. When the criteria don't exist, a two- to three-step process that includes a toxin immunoassay plus a molecular test and/or an antigen test are recommended. ❖

Dall C. New C Diff Guidelines Incorporate Fecal Transplant. Center for Infectious Disease Research and Policy, Feb. 16, 2018. Accessed at www.cidrap.umn.edu/news-perspective/2018/02/new-c-diff-guidelines-incorporate-fecal-transplant.

Guidelines

WHO Recommends Typhoid Vaccine in Children in Endemic Countries



The World Health Organization (WHO) is recommending a single dose of the typhoid conjugate vaccine (Typbar-TCV) for use in infants and children older than 6 months and a catch-up vaccine in children up to 15 years in countries where the infection is endemic. The recommendation is a result of a review of the vaccine by WHO's Strategic Advisory Group of Experts on Immunization in October 2017 that considered data on vaccine safety, efficacy, feasibility and affordability, as well as growing rates of drug-resistant typhoid. The Typbar-TCV vaccine provides longer-lasting protection and fewer doses than previous vaccines.

"Studies have shown that TCV is safe, effective and can provide protection for infants and children under 2 years of age, unlike the previous available typhoid vaccines," said Adwoa Bentsi-Enchill, MD, medical officer of the Department of Immunization, Vaccines and Biologicals at WHO. "The recommendation for the typhoid conjugate vaccine to be included in routine immunization programs will help pave the way for national authorities to introduce this vaccine in countries where they are needed most." ❖

First Typhoid Conjugate Vaccine Recommended by WHO. Contagion Live, April 3, 2018. Accessed at www.contagionlive.com/news/first-typhoid-conjugate-vaccine-recommended-by-who.

Medicines

VONVENDI Approved to Treat Von Willebrand Disease

The U.S. Food and Drug Administration has approved Shire's VONVENDI, a recombinant von Willebrand factor treatment for perioperative management of bleeding in adults 18 years and older with von Willebrand disease (VWD). VONVENDI is also indicated for on-demand treatment and control of bleeding episodes, and it is the first and only recombinant treatment for adults living with VWD, the most common inherited bleeding disorder.

Approval is based on results from a Phase III prospective, open-label, multicenter trial that evaluated the efficacy and safety of VONVENDI with or without recombinant factor VIII treatment in elective surgical procedures in adults 18 years and older diagnosed with severe VWD. Results showed VONVENDI met its primary endpoint demonstrating overall hemostatic efficacy assessed 24 hours after the last perioperative VONVENDI infusion or at completion of study visit, whichever occurred earlier. The overall median dosing frequency of once-daily was demonstrated to normalize hemostasis in appropriate patients. One study participant developed deep vein thrombosis three days after undergoing hip replacement surgery while receiving VONVENDI.

In addition to the expanded use of VONVENDI, the updated prescribing information states the product can be stored at refrigerated temperature 2 degrees Celsius (36 degrees Fahrenheit to 46 degrees Fahrenheit) or room temperature not to exceed 30 degrees Celsius (86 degrees Fahrenheit).

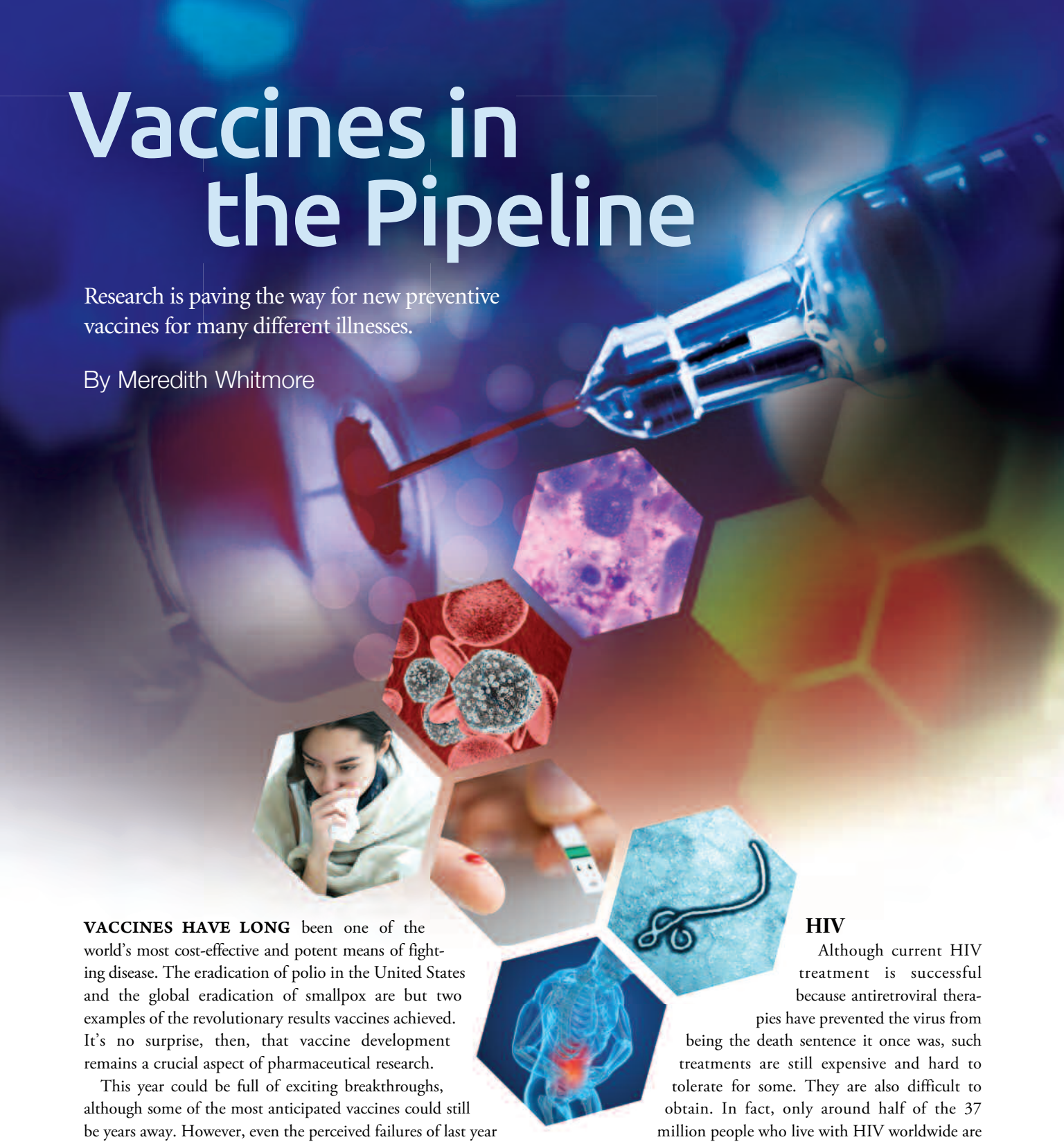
"Persons with von Willebrand disease face a heightened risk of bleeding during surgery and may require factor treatment before, during or after surgery," said Michael Tarantino, MD, professor of pediatrics and medicine at the University of Illinois College of Medicine and medical director and president of the Bleeding and Clotting Disorders Institute. "For surgeries requiring repeated, frequent infusions with combined von Willebrand factor and factor VIII concentrates, an excessive rise in factor VIII levels may increase the risk of thromboembolic complications such as blood clots. The expanded use of VONVENDI in surgical settings gives healthcare professionals flexibility in treating von Willebrand disease with an appropriate dose of von Willebrand factor, with or without recombinant factor VIII, based on each patient's unique needs." ❖

FDA Approves VONVENDI [Von Willebrand Factor (Recombinant)] for Perioperative Management of Bleeding in Adult Patients with Von Willebrand Disease. Shire Pharmaceuticals Group press release, April 17, 2018. Accessed at globenewswire.com/news-release/2018/04/17/1480207/0/en/Shire-plc-FDA-APPROVES-VONVENDI-FOR-PERIOPERATIVE-MANAGEMENT-OF-BLEEDING-IN-ADULT-PATIENTS-WITH-VON-WILLEBRAND-DISEASE.html.

Vaccines in the Pipeline

Research is paving the way for new preventive vaccines for many different illnesses.

By Meredith Whitmore



VACCINES HAVE LONG been one of the world's most cost-effective and potent means of fighting disease. The eradication of polio in the United States and the global eradication of smallpox are but two examples of the revolutionary results vaccines achieved. It's no surprise, then, that vaccine development remains a crucial aspect of pharmaceutical research.

This year could be full of exciting breakthroughs, although some of the most anticipated vaccines could still be years away. However, even the perceived failures of last year can further researchers' knowledge and experience. And, most researchers, among others who long for disease prevention, are hopeful past letdowns will fuel 2018's successes.

Here are a few of the most promising vaccines in the pipeline for HIV, type 1 diabetes, influenza, cancer, Clostridium difficile (C. diff) and Ebola. Time will tell whether the current trials will result in a tried-and-true product, but several studies look positive so far.

HIV

Although current HIV treatment is successful because antiretroviral therapies have prevented the virus from being the death sentence it once was, such treatments are still expensive and hard to tolerate for some. They are also difficult to obtain. In fact, only around half of the 37 million people who live with HIV worldwide are able to obtain therapy. Many who suffer from the illness are not even aware they have it, and around two million new cases are reported globally each year.[1] Having a vaccine to prevent HIV would be ideal because it could eliminate the need for long-term treatment and the disease entirely.

But developing such a vaccine is not easy, as several failed attempts have shown over the years. Still, there is always hope. In

Seattle, Wash., last year, scientists at Fred Hutchinson Cancer Research Center launched an investigational study of a "mosaic" HIV-1 preventive vaccine on World AIDS Day. The human trials began after successful animal trials, and much excitement revolves around the project. The HIV Vaccine Trials Network (HVTN), headquartered at the Fred Hutchinson Seattle campus and affiliated with the research, has launched a record four HIV vaccine clinical trials over the last year.[1]

Among these was the Imbokodo clinical trial in South Africa, which is a site using the HIV-1 vaccine. Sponsored by Janssen Pharmaceutical Companies, a division of Johnson & Johnson, and funded in part through the Bill and Melinda Gates Foundation and the National Institutes of Health's (NIH) National Institute of Allergy and Infectious Diseases (NIAID),[1] the vaccine offers perhaps the most promising research to end the HIV pandemic. It has reduced the risk of infection by 94 percent during each exposure and resulted in 66 percent complete protection after six exposures.[2]

The term "mosaic" stems from the variety of genes taken globally from several HIV subtypes. The study's goal is to initiate a far-reaching immune response that could fight any variety of the virus regardless of its origin in the world. Through the mosaic concept, Frank Tomaka, MD, a study co-chair, says, "what we're aiming for is a global vaccine. HIV preventative vaccines are difficult because the immune responses that may protect against one subtype may not work against another. Our goal is to produce one vaccine that can be shipped everywhere and can be efficacious everywhere."[1]

Another outstanding HIV vaccine trial underway is HVTN 702, which began in November 2016, enrolling 5,400 HIV-negative South African men and women. Results are slated for late 2020. Should the vaccine provide at least 50 percent protection against the HIV virus, it could become the first licensed vaccine used against the disease.[1] These and several smaller studies are providing researchers with increasing hope that HIV will soon be a thing of the past.

According to HVTN founder and leader Larry Corey, MD, "We are in the midst of an unprecedented time in HIV vaccine research. We have four concurrent efficacy trials underway, which will collectively enroll 12,200 volunteers in the search for an HIV vaccine over the next few years. With the support of our funders and research partners, we are doing all that we can to honor loved ones taken from us too soon and drive the progress that will secure a future without HIV."[1]

Type 1 Diabetes

More than two decades of research at the University of Tampere in Finland has demonstrated evidence linking a type of enterovirus called coxsackievirus B1 with an autoimmune reaction that causes the body to destroy cells in its own pancreas, leading to the development of type 1 diabetes.[3]

In one study on mice, researchers at Tampere and at Swedish medical university Karolinska Institutet have shown the enterovirus vaccine can protect against this virus-induced type 1 diabetes. Although the exact origin of type 1 diabetes is yet unclear, enteroviruses have long been thought to be a potential cause. In the study, researchers tested the virus's involvement in diabetes development by testing a prototype vaccine. At-risk individuals who are vaccinated are monitored for the onset of diabetes. If enteroviruses are involved and the vaccine is successful in preventing disease onset, such a vaccine will become a preventive treatment for virus-induced diabetes. It could also lead to the development of other vaccines for the non-virus-induced form of the illness.

So far, the data seem hopeful. Professor Malin Flodström-Tullberg at the Karolinska Institutet says, "These exciting results showing that the vaccine completely protects against virus-induced diabetes indicate the potential that such a vaccine has for elucidating the role of enteroviruses in human type 1 diabetes." Vesa Hytönen, MD, a prototype vaccine developer, adds that "the model described in this paper provides an excellent platform to test further enterovirus vaccines which contain a greater number of potential diabetogenic viruses. Through these proof-of-concept studies, we hope to develop and experimentally validate an enterovirus vaccine similar to the commonly used poliovirus vaccine, which has the potential to establish whether enteroviruses play a role in type 1 diabetes."[3]

Having a vaccine to prevent HIV would be ideal because it could eliminate the need for long-term treatment and the disease entirely.

Tampere professor Heikki Hyöty, another study author and a pioneer in such research, explains: "The experiments here are important steps toward the clinical use of novel enterovirus vaccines. Such a vaccine is under further development by Vactech Ltd. and its collaborator Provention Bio for testing in a clinical setting." Professor Hyöty adds that the investigational vaccine is not a cure for those who already have diabetes, but researchers are hopeful if trials are successful the vaccine could be preventive.[3] "Already now it is known that the vaccine is effective and safe on mice," explains Hyöty. "The developing process has now taken a significant leap forward, as the next phase is to study the vaccine in humans."[4]

Beyond preventing virus-induced type I diabetes, the vaccine could also help to prevent other enterovirus infections. "Additionally, the vaccine would protect from infections caused

by enteroviruses such as the common cold, myocarditis, meningitis and ear infections," says Hyöty.[4]

Researchers at the University of Tampere are also working to create a vaccine that targets a greater number of viruses thought to cause type 1 diabetes, beyond enterovirus. They are slowly providing more proof that viruses are implicated in the development of diabetes, and they are excited to begin clinical studies in humans.[3] And, while the leap from mice to humans is great, researchers are hopeful because of what they've experienced thus far.

In one study on mice, researchers at Tampere and at Swedish medical university Karolinska Institutet have shown the enterovirus vaccine can protect against this virus-induced type 1 diabetes.

Universal Flu Vaccine

The 2017-18 influenza (flu) season was one of the worst on record.[5,6] Each year, the flu virus takes its toll on patients and caregivers, and vaccines to date seem hit-or-miss at best in their efficacy since the number of strains they are designed to prevent is limited. But, that could soon change. Knowing the financial and personal damage the flu causes, finding a vaccine that could prevent all of its strains is a never-ending quest for some researchers. And, it seems they are moving closer to a solution.

Scientists at the University of California, Los Angeles (UCLA) claim they may have discovered a so-called "Goldilocks" flu vaccine. Studies so far indicate a strong immune response in animal subjects, but without causing the illness. The developmental vaccine rallies T cells to fight the disease, which is crucial because, unlike previous vaccines that employ only antibodies specific to certain strains, T cells will fight any form of flu virus.[7]

The vaccine is also different from others because it uses a live virus that elicits an antibody response and a T cell immunity in mice and ferrets, and it's hoped this finding will transfer to humans. Typically, flu vaccines use a dead virus that causes no T cell response. "This is really exciting," said Kathleen Sullivan, chief of the division of allergy and immunology at the Children's Hospital of Philadelphia. "It has the magic of both great antibody response and inducing a strong, strong T cell response that will be a safety net — so if a virus breaks through the first line of defense, you will have T cells to make sure you don't get very sick."[7]

UCLA is not alone in its quest. NIAID is also pursuing a multi-strain flu vaccine "that provides robust, long-lasting protection against multiple subtypes of flu, rather than a select few." According to the NIAID website, "Such a vaccine would eliminate the need to update and administer the seasonal flu vaccine each year and could provide protection against newly emerging flu strains, potentially including those that could cause a flu pandemic."[8,9]

Cancer

Researchers at Stanford University are thrilled by recent studies in mice that show a human cancer vaccine could actually be possible, although it will take much more time and effort. They found "injecting trace amounts of immune-stimulating agents into solid tumors in mice can eliminate all traces of cancer in the animals, including distant, untreated metastases." The method, which activates T cells, could work for multiple kinds of cancer, including those that occur spontaneously.

Currently, the researchers are recruiting lymphoma patients for human clinical trials. They believe applying the agents locally in small amounts could be a fast-acting and cost-effective cancer therapy that will not cause adverse side effects caused by current cancer treatments. "When we use these two agents together, we see the elimination of tumors all over the body," said Ronald Levy, MD, professor of oncology. "This approach bypasses the need to identify tumor-specific immune targets and doesn't require wholesale activation of the immune system or customization of a patient's immune cells. All of these immunotherapy advances are changing medical practice. Our approach uses a one-time application of very small amounts of two agents to stimulate the immune cells only within the tumor itself. In the mice, we saw amazing, body-wide effects, including the elimination of tumors all over the animal."[10]

Beyond this trial, there is even more hope for a cancer vaccine, though a somewhat different type. Researchers at the University of Pennsylvania and the Lausanne Branch of the Ludwig Institute for Cancer Research in Switzerland, among other institutions, are making progress toward a cancer vaccine that is specifically designed for each patient's disease and tumors. While the research is fledgling, the results are impressive so far.[11]

Lead study author Janos L. Tanyi, MD, PhD, and his team examined immune cells in patients' blood to develop the vaccines, extracting patients' dendritic cells, combining them with pieces of patients' tumors and activating them with interferon gamma. The cells were then injected into patients' lymph nodes. Twenty-five advanced ovarian cancer patients underwent this procedure, each getting a dose of the dendritic cell mixture every three weeks, with some study participants in the program for two years. The study's

purpose was merely to determine whether the treatment was possible and safe, but the scientists are still encouraged by the results.[11]

One participant, a 46-year-old woman who had already received five courses of chemotherapy for her cancer prior to the study, received 28 doses of the personalized vaccine over the course of two years and remained in remission for five years. "The two-year overall survival rate of these responder patients was 100 percent, whereas the rate for nonresponders was just 25 percent," said Dr. Tanyi. "The idea is to mobilize an immune response that will target the tumor very broadly, hitting a variety of markers, including some that would be found only on that particular tumor."[11] The vaccine appears to be safe and merits much more research and testing in larger clinical trials.

C. Diff

Most often contracted in hospitals and other medical settings, C. diff can mean a brutal, if not life-threatening, bout with intestinal inflammation, fever, nausea and diarrhea for those who contract it. Thankfully, Pfizer has had success with its experimental C. diff vaccine in the recent past. The company's vaccine candidate is designed to help prevent C. diff infection by inducing a functional antibody response capable of neutralizing the two main disease-causing toxins produced by the infection (toxins A and B).[12]

Today, because of the vaccine's good initial results, the Clover trial, a clinical research study on humans for the developmental vaccine, is recruiting adults 50 years and older who are at risk of developing the infection. The study will determine how well-tolerated and efficacious the vaccine is. Each subject who is admitted to the study will receive the vaccine, then three doses of the C. diff vaccine or a placebo. They will then be followed for up to three years as researchers watch for potential C. diff infection.[13]

While the vaccine's efficacy is obviously still uncertain, researchers are very hopeful. Kathrin Jansen, PhD, senior vice president and head of vaccine research and development for Pfizer Inc., said, "We are very encouraged by these interim immunogenicity and safety results demonstrating robust increases in vaccine-elicited neutralizing antibodies to both toxins that we believe could provide protection against C. difficile disease."[12]

Ebola

Just recently, a study published in *The Lancet Infectious Diseases* indicates participants inoculated with an experimental Ebola vaccine still maintain high and stable levels of antibodies to the Ebola Zaire virus two years after vaccination (there are other strains of Ebola). Participants who received a high dose of vaccine typically had higher antibody levels, but even those who received a lower dose showed promising levels that could potentially resist the disease.

The vaccine, V920, is from Merck and is given in a single shot, which is easiest for many African regions. "The ideal vaccine in these regions would have long-term durability," explains Angela Huttner, MD, lead author of the paper and an infectious diseases specialist at Switzerland's University Hospitals of Geneva. "This is really good news because this vaccine is destined for places where logistics are very difficult. Having to do booster shots would be very impractical in these regions."

Merck is working to obtain a 2018 licensure filing with the U.S. Food and Drug Administration for V920. It is also pleased with the results: "This publication is the first demonstration of the durability of the antibody responses induced by V920 out to two years. We are encouraged by these important results, and testing of long-term follow-up samples from additional trials is planned or ongoing to corroborate these findings."[14]

It is too early to know whether the vaccine will offer lifelong immunity, but research is certainly inching closer to that goal.

The Coming Results

While no one can predict success or failure in vaccine development, or any type of research for that matter, the mere fact scientists are tirelessly pursuing answers is heartening. No research is wasted, although not all research results in a viable vaccine. Let's hope 2018 and 2019 bring a wealth of knowledge and disease prevention alike, as well as some newly licensed vaccines that will improve, or even save, many lives. ❖

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

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The Consequences of Declining Childhood Vaccination

Parents who choose not to vaccinate their children reduce the community immunity threshold that can result in a return of preventable diseases.

By Diane L.M. Cook

ACCORDING TO THE Centers for Disease Control and Prevention (CDC), 20 percent of the nation's 2-year-olds are missing one or more recommended vaccinations,[1] and vaccination rates for kindergarteners are low enough in some areas to put communities at risk of losing community immunity.[2] Medical experts say the community immunity threshold, the proportion of the population that must be immunized to prevent diseases from spreading, is considered to be 95 percent. Once immunization rates fall below this level, diseases start to return and transmission rates dramatically increase, which can result in outbreaks and epidemics. So, why are childhood vaccination rates decreasing, and what can be done to prevent it?

Ensuring Vaccines' Safety

The U.S. Food and Drug Administration (FDA) approves and regulates all vaccines in the United States to ensure their safety, purity, potency and effectiveness. Before a vaccine is approved by FDA, results of studies on safety and efficacy are evaluated by highly trained FDA scientists and doctors. According to FDA, "Like any medicine, vaccines have benefits and risks, and although highly effective, no vaccine is 100 percent effective in preventing disease or 100 percent safe in all individuals. Most side effects of vaccines are usually minor and short-lived. For example, a person may feel soreness at the injection site or experience a mild fever. Serious vaccine reactions are extremely rare, but they can happen."[3]

"The United States' long-standing vaccine safety system ensures that vaccines are as safe as possible," says the Immunization Action Coalition. "In fact, currently, the United States has the safest, most effective vaccine supply in its history."[4] CDC's current immunization schedule lists 14 diseases for which vaccinations are recommended for babies and young children,

including hepatitis B; rotavirus; diphtheria, tetanus, and acellular pertussis; Haemophilus influenzae type b; pneumococcal conjugate; inactivated poliovirus; influenza; measles, mumps, rubella (MMR); varicella (VAR); and hepatitis A.[5]

More Parents Opting Out

According to a CDC report, more parents are opting out of having their children vaccinated in certain communities, with the median rate for nonmedical vaccination exemptions as high as 7 percent in Oregon.[2]

Three waivers allow parents to exempt their children from vaccinations. The first is a medical exemption for children who are severely allergic to a vaccine component; children who have an acute illness (this is only temporary until the child is well again); children who have compromised immune systems; and babies who are too young for their first immunization (younger than 2 months old). The second is a philosophical exemption for parents who do not believe in immunization due to personal beliefs. And, the third is a religious exemption for parents who refuse immunization due to religious reasons.[6] To curb increasing exemption rates, three states — California, West Virginia and Mississippi — have passed bills to eliminate religious and personal exemptions for vaccinations.[7]

The 2016 National Immunization Survey-Child (NIS-Child), which includes data on 14,988 children aged 19 to 35 months, also suggests childhood vaccination rates are declining, with vaccine/dose rates lower in 2016 compared to 2015, except for the first and second doses of hepatitis A and rotavirus.[8] According to the survey's report, "For most vaccines, coverage was lower among black children, children living below the federal poverty level, and children who were uninsured or covered by Medicaid compared with white children, children living at or above the federal poverty level, and children with private insurance. Coverage with recommended vaccines for children aged 19-35 months continues to be high and stable but remains below 90 percent for vaccines that require booster doses during the second year of life and for other recommended vaccines."[8]

And, while vaccines have been scientifically proven safe, the NIS-Child data show parents who choose to either delay vaccinating their children in accordance with the CDC's immunization schedule, or not to vaccinate their children at all, has been gaining ground.

Common Parental Vaccine Concerns

According to the American Academy of Pediatrics (APA), parents have expressed several concerns about vaccinating their children:

1. *Too many/too soon.* Parents worry giving too many vaccines too soon may overwhelm a baby's immune system. But, APA states that although infants do receive a lot of vaccines, they are given at the time babies are most at risk of illness and serious complications from the disease. And, vaccines are well-studied to ensure they are safe to give all at once. In addition, although children receive more vaccines today than they did in the past, the number of antigens is fewer.

2. *Nonstandard schedules.* Some parents would prefer to spread out the timing of vaccines and believe an alternative or nonstandard schedule is safer. But, APA states the recommended schedule is designed to protect children when they are most vulnerable to the diseases vaccines prevent.

3. *Vaccine ingredients.* Parents worry about vaccines' ingredients, including antigens, adjuvants, aluminum and thimerosal. But, according to APA:

• Antigens stimulate the body's immune response to make antibodies (cells that protect against infection). Antigens in vaccines cause the immune system to make antibodies that will protect the body if it comes into contact with a bacteria or virus that can cause illnesses.

• Adjuvants help increase the body's immune response to the antigen in the vaccine. Adjuvants make it possible to use smaller amounts of antigens and decrease the number of doses needed.

• Aluminum salts or gels have been used safely in vaccines for more than 70 years. The amount of aluminum in vaccines is similar to that found in a 33-ounce can of infant formula.

Vaccination is one of the best ways parents can protect their babies and young children from 14 potentially harmful diseases.

• Thimerosal is a mercury-based preservative that has been used to prevent contamination of vaccines with bacteria and fungi. Most childhood vaccines do not contain thimerosal, with two exceptions: the manufacturing process and multi-dose vials. Many studies have shown no link between thimerosal and autism. In fact, rates of autism have actually increased since thimerosal was removed from vaccines in 2001.

4. *Autism.* Some parents correlate the relationship of vaccines and autism. In 1998, *The Lancet* published an article by Andrew Wakefield, MD, and colleagues, that reported on a study of eight children who reportedly developed autism after receiving the MMR vaccine. In 2010, *The Lancet* retracted the study, citing ethical misconduct on the part of Dr. Wakefield. And, over the

past decade, 10 of the 13 authors of that article have retracted the findings. Since then, scientific studies comparing thousands of children who have and have not received the vaccine have not found a relationship between the vaccine and autism. Studies investigating a link between thimerosal and autism have also been completed, and they have reported no link between thimerosal and autism. The MMR vaccine has never contained thimerosal.[9]

One reason parents continue to correlate the relationship between the MMR vaccine and autism is many children are diagnosed with autism around the same age as when the MMR vaccine is given. "One of the criteria used to make a diagnosis of autism is a language delay. Because children do not have significant expressive language under a year of age, doctors have to wait until 15 to 18 months to confirm a language delay and make the diagnosis. That's about the same time as the MMR vaccination [around 2 to 3 years old], which leads some parents to wonder about autism and vaccination," states an excerpt published by the Immunization Action Coalition.[10]

Consequences of Not Vaccinating

According to CDC, the consequences of declining childhood vaccination can result in a resurgence of many of the vaccine-preventable diseases. An outbreak can result in thousands, or even tens of thousands, of people to suffer, and in many cases, die. In addition, current very low rates of vaccine-preventable diseases would drastically increase because the bacteria that cause these diseases are still prevalent throughout the world. If childhood vaccination rates decline in the United States, only one case of a vaccine-preventable disease could trigger an outbreak. And, unvaccinated travelers and immigrants can easily bring diseases into the United States. What's more, vaccine protection extends to all people in all communities. Not only are unvaccinated babies and young children at a much greater risk for contracting serious vaccine-preventable diseases, but they can transmit vaccine-preventable diseases and infect other people in the community.[11]

Maintaining Community Immunity Threshold

To increase vaccination rates to maintain the community immunity threshold of at least 95 percent or higher, CDC and the 2016 NIS-Child survey recommend several actions health practitioners can implement:[1]

- Educating parents about the importance of immunization and what can happen if children are not vaccinated;
- Informing parents that vaccine-preventable diseases caused hundreds of thousands of cases of illnesses and thousands of deaths every year in the United States before the 1920s when vaccines were not available;
- Reassuring parents that we can now protect children from 14 diseases (polio has not circulated in the United States since 1979, and smallpox has been eradicated worldwide); and
- Reminding parents that children should not have to suffer and possibly die from a vaccine-preventable disease, and advising them on childhood immunization schedules beginning within the first year of life.

The 2016 NIS-Child results indicate the immunization safety net is not reaching all children early in life. According to the survey report, coverage could be increased if health practitioners implemented evidence-based interventions such as:[8]

- Reminders for parents to eliminate missed opportunities to vaccinate their children;
- Standing orders to provide vaccinations whenever appropriate; and
- Immunization information systems to track vaccination administration.

Vaccines Offer the Best Protection Against Diseases

Vaccination is one of the best ways parents can protect their babies and young children from 14 potentially harmful diseases. "For children born between 1994 and 2016 in the United States, the CDC estimates that routine vaccinations will prevent an estimated 381 million illnesses, 24.5 million hospitalizations, and 855,000 deaths over the course of their lifetimes," said Bertram Kelly, public affairs team lead in the Office of the Associate Director for Communications of CDC. Unfortunately, too many parents continue to opt out of vaccines for their children, increasing the chances of an outbreak of diseases that have been mostly eradicated in the U.S. As an authority parents of young children look to for advice, healthcare professionals must take every opportunity to clear up any misconceptions parents may have regarding vaccines' safety and urge the timely vaccination of their little ones. ❖

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HyperRAB®
Rabies Immune Globulin (Human)
300 IU/mL

Indication and Usage

HYPERRAB® (rabies immune globulin [human]) is indicated for postexposure prophylaxis, along with rabies vaccine, for all persons suspected of exposure to rabies.

Limitations of Use

Persons who have been previously immunized with rabies vaccine and have a confirmed adequate rabies antibody titer should receive only vaccine.

For unvaccinated persons, the combination of HYPERRAB and vaccine is recommended for both bite and nonbite exposures regardless of the time interval between exposure and initiation of postexposure prophylaxis.

Beyond 7 days (after the first vaccine dose), HYPERRAB is not indicated since an antibody response to vaccine is presumed to have occurred.

Important Safety Information

For infiltration and intramuscular use only.

Severe hypersensitivity reactions may occur with HYPERRAB. Patients with a history of prior systemic allergic reactions to human immunoglobulin preparations are at a greater risk of developing severe hypersensitivity and anaphylactic reactions. Have epinephrine available for treatment of acute allergic symptoms, should they occur.

HYPERRAB is made from human blood and may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

The most common adverse reactions in >5% of subjects during clinical trials were injection-site pain, headache, injection-site nodule, abdominal pain, diarrhea, flatulence, nasal congestion, and oropharyngeal pain.

Do not administer repeated doses of HYPERRAB once vaccine treatment has been initiated as this could prevent the full expression of active immunity expected from the rabies vaccine.

Other antibodies in the HYPERRAB preparation may interfere with the response to live vaccines such as measles, mumps, polio, or rubella. Defer immunization with live vaccines for 4 months after HYPERRAB administration.

Please see brief summary of Prescribing Information on adjacent page or visit HyperRAB.com for full Prescribing Information.

GRIFOLS

HYPERRAB®
Rabies Immune Globulin (Human)

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

HYPERRAB [rabies immune globulin (human)] solution for infiltration and intramuscular injection

Initial U.S. Approval: 1974

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

HYPERRAB is a human rabies immune globulin indicated for postexposure prophylaxis, along with rabies vaccine, for all persons suspected of exposure to rabies.

Limitations of Use:

Persons previously immunized with rabies vaccine that have a confirmed adequate rabies antibody titer should receive only vaccine.

For unvaccinated persons, the combination of HYPERRAB and vaccine is recommended for both bite and nonbite exposures regardless of the time interval between exposure and initiation of post-exposure prophylaxis.

Beyond 7 days (after the first vaccine dose), HYPERRAB is not indicated since an antibody response to vaccine is presumed to have occurred.

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

For infiltration and intramuscular use only.

Administer HYPERRAB within 7 days after the first dose of rabies vaccine.

Postexposure prophylaxis, along with rabies vaccine, after suspected exposure to rabies	HYPERRAB 20 IU/kg body weight OR 0.0665 mL/kg body weight Single dose	• Administer as soon as possible after exposure, preferably at the time of the first rabies vaccine dose. • Infiltrate the full dose of HYPERRAB thoroughly in the area around and into the wound(s), if anatomically feasible. • Inject the remainder, if any, intramuscularly.

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

300 IU/mL solution for injection supplied in 1 mL and 5 mL single-dose vials.

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

None.

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

- Severe hypersensitivity reactions, including anaphylaxis, may occur with HYPERRAB. Have epinephrine available immediately to treat any acute severe hypersensitivity reactions.
- HYPERRAB is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

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

The most common adverse reactions in >5% of subjects in clinical trials were injection site pain, headache, injection site nodule, abdominal pain, diarrhea, flatulence, nasal congestion, and oropharyngeal pain.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Therapeutics Inc. at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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- Repeated dosing after administration of rabies vaccine may suppress the immune response to the vaccine.
- Defer live vaccine (measles, mumps, rubella) administration for 4 months.

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Managing Medicines: Mitigating the Risks of Inventory and Storage

The time-intensive and costly job of storing and inventorying medicines is eased with smart technology systems.

By Ronale Tucker Rhodes, MS

THE NUMBER OF prescription drugs ordered and provided in the U.S. each year is staggering. Between 2011 and 2014, data provided by the Centers for Disease Control and Prevention (CDC) showed 48.9 percent of the U.S. population (more than 326 million[1]) used at least one prescription drug in the past 30 days. The number of drugs ordered or provided was 3.7 billion in physician offices, with 76.2 percent of visits involving drug therapy. In hospital outpatient departments, the number of drugs ordered or provided was 329.2 million, with 72.5 percent of visits involving drug therapy. And, in hospital emergency departments, the number of drugs ordered or provided was 317.6 million, with 79.6 percent of visits involving drug therapy.[2]

For this magnitude of prescription drugs, there are strict guidelines for their storage and handling established by the U.S. Food and Drug Administration.[3] In hospitals, those guidelines are governed by the Centers for Medicare and Medicaid Services and The Joint Commission (TJC) to ensure consistency and that the processes are followed for patient safety, ethical decision-making and quality care.[4] In physician offices and clinics, storage guidelines are governed by states' pharmacy and medical licensing board regulations. It is also recommended physician offices and clinics follow policies set forth by TJC and the Institute for Safe Medication Practices.[5]

Meeting medication management requirements can be a challenge. Adequate lighting, ventilation, temperature, sanitation, space and security are of paramount concern for proper storage. And, drug waste due to product expiration can be extremely costly. For example, according to sources at Newton-Wellesley Hospital in Massachusetts, the facility is able to return some expired drugs for credit, but in 2017, it had to destroy about $200,000 worth of outdated medication. And, a commentary in the *Mayo Clinic Proceedings* cited comparable losses at Tufts Medical Center in Boston. In fact, similar scenarios are replicated in hospitals across the country, and the cost is significant: About $800 million per year of drugs is lost due to expiry, and this does not include the costs of expired drugs at long-term-care and retail pharmacies.[6]

Adhering to safe protocols for storage and inventory of medicines can be extremely labor intensive, requiring strict policies are in place that are overseen by dedicated staff. Fortunately, over the past decade, many smart technology solutions have become available for healthcare facilities to expedite compliance.

The Complexities of the Cold Chain

Product safety is heavily reliant on cold-chain logistics to manage temperature-sensitive products as they move through the supply chain. Products requiring cold-chain handling are predominantly biologics (blood products and vaccines) derived from living cells, delivered in liquid form by injection or infusion and packaged in vials or syringes.[7] Projected growth of cold-chain biopharma products is twice that of the industry overall,[7] placing added emphasis and increased regulatory scrutiny on proper storage and dispensing.

Some drugs that require cold-chain management need to be stored at controlled room temperature. Vaccines need to be stored at between 2 degrees and 8 degrees Celsius,[8] whereas other drugs need to be stored at between 20 degrees and 25 degrees Celsius, with allowable excursion between 15 degrees Celsius and 30 degrees Celsius, as long as the mean kinetic temperature remains in the defined range.[9] Too much exposure to heat, cold or light at any step in the cold chain can damage drugs and result in loss of potency. In addition, exposure to freezing temperatures could destroy some drugs.[8]

CDC Storage and Inventory Guidelines

According to a 2011 survey by TJC, not storing medications per the manufacturer's recommendations and failing to remove expired drugs are top reasons for noncompliance in medication storage.[10] To help mitigate problems with cold storage of biologics, CDC has written step-by-step guidelines. An overview of these are:[8]

1) Medicine packages should be opened immediately to assess for damage and temperature. Damaged or incorrect temperature drugs should be segregated in a separate location, and the supplier should be contacted for advice on how to proceed.

Adhering to safe protocols for storage and inventory of medicines can be extremely labor intensive, requiring strict policies are in place that are overseen by dedicated staff.

2) Medicines should immediately be stored at the recommended storage temperature. To assist with this, it is recommended a sign be placed on the refrigerator that lists the appropriate storage temperatures.

3) Medicines should be stored in the middle of refrigerators and never in doors that are exposed to warm temperatures when units are opened. They should be stored in their original packaging inside designated storage trays positioned 2 inches to 3 inches

from refrigerator walls. And, when new product arrives, the stock should be rotated by placing newer medicines behind older ones. To help stabilize and maintain proper temperatures, two or three containers of water should be placed in areas of the refrigerators where medicines cannot be stored such as in doors.

4) Temperature inside refrigerators should be monitored and recorded at least twice a day to ensure they are within the proper range. Since a drug's appearance is not a reliable indicator that it has been stored in appropriate conditions, it is critical to monitor closely. And, gasket seals should be periodically checked to ensure doors close completely.

5) It is recommended to place temperature log sheets on refrigerators and document the twice-daily checks. Celsius and Fahrenheit log sheets are available at www.immunize.org/catg.d/p3037C.pdf and www.immunize.org/catg.d/p3037F.pdf, respectively.

6) If it is suspected medicines have been exposed to out-of-range temperatures or have been left out of refrigerators, they should be marked with "Do Not Use" and transferred to a functional refrigerator at the proper storage temperature while determining whether the medicine is still viable.

CDC also has step-by-step guidelines for inventorying medicines. Briefly described, these include:[8]

According to a 2011 survey by TJC, not storing medications per the manufacturer's recommendations and failing to remove expired drugs are top reasons for noncompliance in medication storage.

1) Expiration dates, printed on vials, manufacturer-filled syringes and packages, indicate when the product must be discarded if it has not been used. If an expiration date has only a month and year, the product may be used up to and including the last day of that month. If a day is included with the month and year, the product may only be used through the end of that day.

2) In some cases, products must be used before their expiration. In these cases, the product will have a beyond use date (BUD) that is calculated based on the date the vial is first entered and the storage information in the package insert. The BUD replaces the expiration date and should be noted on the label along with the initials of the person making the change.

3) A stock record should be used to keep track of inventory. The record can be in paper or electronic form, or it can be part of an immunization information system with the capacity to manage vaccine inventory. The stock record should be updated weekly, and it should account for and document every dose of the medicine, including:

- Date of delivery (and initials of the person who unpacked the delivery)
- Medication and diluent name and manufacturer
- Number and expiration date for each lot (including expiration dates based on BUD guidance in the product information)
- Number of doses received
- Condition of each medication and diluent upon arrival (i.e., did it arrive in good condition at the proper temperature?)
- Center for Comparative Medicine reading if included in the shipping container (and actions taken if the monitor was triggered, signaling a possible temperature excursion)
- Number of doses used (i.e., administered, wasted, compromised, expired or transferred [and destination])
- Balance of remaining doses after subtracting the amount used

Multiple doses of the same medication in the same presentation from the same lot with the same expiration date can be documented as one entry on the stock record. However, the total number of doses received should be indicated, regardless of how many vials or syringes the doses came in. Doses of diluents that come with lyophilized medications should be documented on a separate stock record.

4) At least once a month and before placing any order, all medications and diluent doses should be counted to ensure the number of doses in the storage unit matches the number of doses documented in the stock record. If the numbers don't match, the correct number should be entered based on the count on a separate line below the old balance, and the corrected balance should be used for calculating stock quantities in the future.

At the end of each month, the total number of medications and diluent doses used during the month and the amount of stock still available should be determined. And, at the end of the year, the stock record should be used to determine the number of doses received and used during the year to help minimize future waste.

5) Expiration dates on medications and diluents should be checked at least once a week. And, expired medications should be immediately removed to avoid inadvertently administering them. Expired medications should be documented on the stock record.

Simplifying Storage and Inventory with Smart Technology

Without a doubt, safely storing and inventorying medicines can be time-intensive. While many facilities establish their own systems to follow recommended guidelines, there are a number of simplified options that automate most of the required tasks. Below are just two examples of such smart systems.

Verified Inventory Program-Consignment (VIPc). VIPc is a streamlined inventory management solution designed for high-value and critical-care products. Developed by FFF Enterprises, a major distributor of plasma products, vaccines and biopharmaceuticals, the system is a radio-frequency identification (RFID)-based consignment solution that tracks and monitors products and the conditions in which they are stored. The cabinets are monitored by FFF Enterprises' VIPc team on a 24/7 basis for both temperature and inventory. In the event of a temperature excursion, the team responds immediately to ensure product integrity is not compromised. When product is loaded or removed from the cabinet, the RFID technology updates the inventory of the cabinet without any manual intervention on the part of the customer.

Throughout each day, the facility's staff can dispense product from the cabinet as it is needed for patient dosing, and once a minimum par level (a minimum quantity of a given item that must be kept on hand) is reached, an alert will go to the VIPc team, and replenishment will arrive the next day. When it arrives, the facility's staff can simply open the box, load the products into the cabinet and close the door. RFID scanning and updating of the inventory will happen automatically. And, since it is a consignment program, the facility is invoiced only for products dispensed from the cabinet, which occurs at the end of each week.

What's more, the VIPc team proactively monitors product expiration to ensure these high-cost critical-care products don't go to waste. In the event a customer is unable to use product and it becomes short-dated, the team will reach out to facilitate a return of the product well before it reaches its expiration date so it can be sent to a customer who can immediately use it. The team then replenishes that facility's cabinet with longer-dated product.

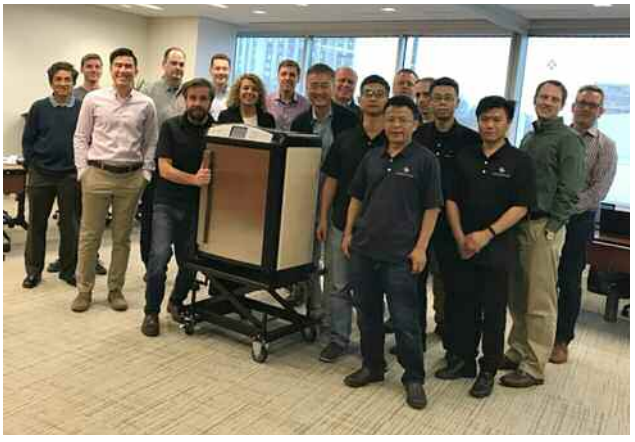
VIPc has been placed primarily in acute facilities and hospital pharmacies. Products most frequently stored in the VIPc cabinets are coagulation factors, which are costly and have unpredictable usage, but are critical to have on hand to save patients' lives when need arises. In addition, facilities store specialty products such as those used to treat snake bites, heart attacks and strokes. The cabinets are also in place in many ophthalmology surgery centers to store a product used in cataract surgeries. According to Karen Sasscer, senior director, product and contract management for VIPc, most customers have the system set up for refrigerated storage (between 2 degrees and 8 degrees Celsius), but the cabinets can also be configured for controlled room temperature storage (between 20 degrees and 25 degrees Celsius), which brings versatility to support products with varying storage requirements.

"One of the great things about the VIPc program is it is more than just a consignment program," says Sasscer. "The RFID technology gives remote visibility into real-time inventory levels and VIPc cabinet activity. With this, our team is able to automatically replenish product based on par levels, which eliminates the need for the customer to manually count inventory and call in orders. For any product carried in VIPc, once the inventory level has reached the minimum par level, an alert is triggered to the VIPc team that ensures a replenishment order is placed to get the customer back up to its normal stocking level. These replenishment orders are always shipped for overnight delivery."

VIPc is a streamlined inventory management solution designed for high-value and critical-care products.

MinibarRx (MBRx). MBRx is a smart refrigerator designed specifically for vaccine storage, handling and inventory management. Developed in 2013 as a stand-alone joint venture of affiliates of Minibar Systems (the world's largest maker of refrigerated platforms to the hospitality industry) and InstantDx (a pioneer in electronic prescribing and healthcare-transaction services), the system is designed to improve the process of purchasing, storing, administering and billing for refrigerated vaccines in physician offices, retail pharmacies and non-acute, ambulatory surgery centers and urgent care facilities.

As an affiliate, FFF Enterprises provides the MBRx refrigerators with the vaccines it distributes and automates the MBRx process using its proprietary software that sets a reorder point for each refrigerated vaccine at each location based on average usage. Reports are received each day with all refrigerated vaccines that have reached a reorder point, and then orders are placed for those items up to the maximum capacity/par level for that medication. To avoid product expiry, electronic notifications are communicated to providers starting 45 days prior to the medication's expiration date. An LCD screen on the unit also displays all vaccines close to expiring for proper management. If a product does expire before being used, the LED indicator light on the dispenser will turn red to indicate not to use the product. And, if the product is removed



The MBRx team is working around the world to provide an efficient solution to drug management and storage.

for use, an alarm will sound and an email notification will be sent. At this point, the product would then be returned for possible credit based on the manufacturer's guidelines.

The MBRx system works as follows at the provider's location: To remove a product, a staff member logs in with a unique four-digit code, an LED light illuminates green alerting the member to pull from a particular cartridge to manage expiry, and then the user removes what is needed and closes the door. When a vaccine is removed, it is automatically recorded and reordered when a minimum par level is reached. When orders are shipped to the practice, the medication information (product, lot number, expiration) are pushed to the machine to aid in the refill process. A staff member then enters a six-digit refill code, selects the product to refill, verifies the information matches, and the unit tells the member which dispenser the product goes in. Temperature readings are recorded automatically by the unit every 10 seconds, and they are uploaded to FFF's portal every 10 minutes. If a temperature reading is out of the designated range, it triggers an alarm at the unit and sends an email notification to all MBRx internal support staff and any designated practice managers.

MBRx greatly reduces the labor-intensive activity to comply with guidelines for storage and handling.

According to Tim Mikac, general manager and executive vice president of the MBRx division at FFF Enterprises, "Alerts of expiry are rare, as the reorder points are based on actual usage data and we only order when those thresholds are hit. However, when an expiration alert comes through, the office will work to schedule patients who could use that product, if possible. A wasted vaccine is unfortunate."

MBRx greatly reduces the labor-intensive activity to comply with guidelines for storage and handling. "The MBRx unit reduces the amount of time spent ordering, rearranging and stocking product," explains Mikac. "We provide 24/7 monitoring of temperature and power, and there are multiple temperature sensors integrated throughout the unit to provide a more accurate indication of the temperature at any point in the unit. Sensing built into the dispensers allows providers to know exactly when a product was taken out and who took it, and the current inventory can be accessed at any time via the screen or the physician portal. Reordering is done automatically via daily reorder reports, which eliminates the need to count inventory and place orders for anticipated usage. All of this offers reassurance that product is stored safely, offering optimal clinical outcomes."

Easing the Burden

Considering the enormity of medicines — especially biologics requiring cold-chain-logistics — stored in healthcare practices, hospitals and pharmacies in the U.S., safe handling and dispensing is a serious concern. Rightly so, the many regulatory agencies overseeing healthcare facilities demand adherence to strict storage and inventorying guidelines to ensure patient safety. Since following those guidelines can be very time-consuming and costly, smart technology systems offer a valuable option to ease the burden and promote optimal outcomes for providers and patients. ❖

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

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Integrating Behavioral Health and Primary Care

Amid growing recognition that physical, mental and social challenges are interrelated, the collaborative care model is experiencing renewed interest. The good news is new global payment options and electronic health record technology are making this innovative practice model an achievable goal.

By Trudie Mitschang

INTEGRATING CARE FOR mental, behavioral and psychosocial issues into primary care has become increasingly important in recent years. From depression, eating disorders and anxiety to substance abuse, nearly one in five Americans has been diagnosed with some type of behavioral health condition, leading to healthcare costs estimated as high as $57 billion a year, on par with cancer.[1] In fact, the innate connection between mental and physical health is well-documented; while many patients come to primary care seeking relief for physical symptoms, those symptoms often have their root in mental or behavioral problems. Inversely, chronic illness can lead to depression, stress or other behavioral health challenges. The complexity of these issues results in myriad obstacles for the primary care provider, while also impacting patient outcomes and healthcare costs.

"If we are going to look to develop a high-performing healthcare system that deals with the totality of medical costs, ignoring mental health and substance use as drivers of costs and human suffering will not work. These illnesses are too big to ignore and too important," says Paul Summergrad, MD, past president of the American Psychiatric Association.[2]

Assessing Current Integration Models

The concept of integrating primary care and behavioral health is not new. Some of the most successful care models focus on training primary care providers to use evidence-based practices in screening for depression, anxiety and other conditions that can be effectively managed in primary care settings. These models often incorporate a care manager or behavioral health specialist who follows up with patients and monitors their response and adherence to treatment. The main goal of most integrated care programs is to improve communication between behavioral health and primary care providers and thereby improve care coordination.

Two of the best-known approaches, the Collaborative Care and TEAMcare models, were developed at the University of Washington.[3] A key aspect of the Collaborative Care model is the strategic use of psychiatrists who are tasked with providing consultations to primary care providers, with a focus on patients who don't make progress or who have more serious mental illnesses.

Collaborative Care focuses on defined patient populations tracked in a registry, measurement-based practice and treatment to target. Trained primary care providers and embedded behavioral health professionals provide evidence-based medication or psychosocial treatments, supported by regular psychiatric case consultation and treatment adjustment for patients who are not improving as expected. The approach originated in a research culture and has now been tested in more than 80 randomized controlled trials in the U.S. and abroad. Several recent meta-analyses suggest that Collaborative Care consistently leads to better patient outcomes, better patient and provider satisfaction, improved functioning and reductions in healthcare costs.[4]

The concept of integrating primary care and behavioral health is not new.

TEAMcare, another approach that is rapidly attracting interest, offers the simultaneous treatment of mental conditions such as depression and medical conditions such as diabetes using teams of behavioral health and primary care providers. The model is designed to prevent situations in which one poorly controlled chronic condition lessens the effective treatment of another.[3] According to the National Institute of Mental Health (NIMH), this model provides significant benefits: "Addressing the whole person and his or her physical and behavioral health is essential for positive health outcomes and cost-effective care. Many people may not have access to mental healthcare or may prefer to visit their primary healthcare provider. Although most primary care providers can treat mental disorders, particularly through medication, that may not be enough for some patients."[3] And, says NIMH, historically, it has been difficult for primary care providers to offer effective, high-quality mental healthcare when working alone. Supporting these providers with mental health services and expertise has the potential to reduce costs, increase quality of care and, ultimately, save lives.

EHR technology plays a pivotal role in bringing behavioral and medical teams into closer collaboration.

Counting the Costs

Despite efforts to create successful integrative care models, widespread behavioral health integration is still rare, and the integration of substance abuse services is even rarer. Lack of integration is due, in part, to little or no financial incentive or administrative advantage to bringing what are now stand-alone medical and behavioral health operations together. Payers use separate provider networks, billing and coding practices, accreditation metrics and record-keeping requirements. This makes a team-based approach to care difficult to finance and structure — whether it's achieved by including behavioral health professionals in primary care settings or medical practitioners in behavioral health settings. Primary care practices that seek to enhance behavioral health services face restrictions on the types of services for which they can bill, and reimbursement rates are often low. And, sometimes there are pre-approval requirements or other restrictions that make it difficult for behavioral healthcare providers to work side-by-side with primary care clinicians.[5]

"Payment is the heart of the problem," says Roger Kathol, MD, president of Cartesian Solutions Inc., a Burnsville, Minn.–based consulting firm that advises health systems, health plans and other purchasers on sustainable strategies for integrating behavioral health and physical health services. Benjamin Miller, PsyD, director of the Eugene S. Farley, Jr. Health Policy Center at the University of Colorado School of Medicine, agrees: "Healthcare as a system has not evolved to align financial mechanisms, practice delivery, training and education, and even our community expectation, to support a model of care that integrates behavioral health."[2]

To address these concerns, some organizations are testing whether a global payment model can support the provision of behavioral services in local primary care practices. In 2012, the Colorado-based Rocky Mountain Health Plans — in partnership with the family medicine department at the University of Colorado, Denver, and the Collaborative Family Healthcare Association, a nonprofit that promotes collaborative models of primary care — launched a pilot titled SHAPE (Sustaining Healthcare Across integrated Primary care Efforts). In the pilot, three practices in Western Colorado that have already integrated behavioral healthcare are receiving global payments to fund team-based care, with three integrated practices that earn fee-for-service payments serving as controls.[2]

Under the pilot guidelines, instead of offering supplementary per-member/per-month payments to reimburse practices for delivering behavioral healthcare, as some insurers have done, SHAPE's leaders opt for a global payment approach to reimburse practices for the full costs of providing behavioral healthcare — taking into account staffing resources and the number and complexity of patients served. The global payment also provides practices with flexibility to determine which services will produce the best results, as well as to dedicate time to panel management, care coordination and other "in-between-visit" activities that may lead to big health gains. "We don't want behavioral health providers to be trapped by requirements to demonstrate productivity by the volume of traditional mental health services they render or to earn their 'keep' through a fee-for-service revenue model," says Patrick Gordon, associate vice president at Rocky Mountain Health Plans. "We think that pulls them away from the care team, pulls them away from activity that might add value but can't easily be coded."[2]

Participating practices are held accountable for patients' total costs of care: They stand to lose part of their payment if they do not meet certain budgetary and quality benchmarks, and they can also earn incentive payments for demonstrating improvement in health outcomes. The long-term goal is "to show what's possible when you can actually create a global budget," Gordon adds. "You can allocate resources to create value, and set up aligned gain-sharing mechanisms. It's accountability and gain-sharing mechanisms that pull people together."[2]

Incorporating Electronic Health Record (EHR) Technology

Of the many stakeholders in the discussions surrounding behavioral health and primary care integration, the role of healthcare information technology (IT) can be significant. Health IT tools ranging from shared electronic medical records to patient registries can be utilized to facilitate the integration of behavioral health into primary care. When used effectively, health IT helps providers communicate and can promote systematic screenings through clinical decision support mechanisms.

EHR technology plays a pivotal role in bringing behavioral and medical teams into closer collaboration. An EHR that successfully connects primary care physicians, behavioral health providers and care coordinators can ensure all parties are in sync, working to develop a patient-focused, holistic plan of care. One of the challenges historically has been the methods used for sharing vital information commonly depended on traditional mail and fax services. To reinvent the care model, automated IT is key to successfully integrating the behavioral and medical disciplines for enhanced collaborative care. By utilizing EHR technology, behavioral health and primary care providers can help bring the two worlds closer and foster a new spirit of teamwork.[6]

In addition to improving communication, an EHR that fully integrates behavioral and medical health modules can help eliminate redundant testing and reduce the risk of contraindicated care. It's important to keep in mind that while many EHR systems are adept at meeting the needs of hospitals and medical specialties, they may be less familiar with the unique needs of behavioral health providers. For example, behavioral healthcare often requires more repeat visits than primary care. It is not unusual for a patient who sees a primary care doctor twice a year to see a behavioral health therapist weekly. In addition, documentation requirements are distinctly different, as are coding issues. The ICD-10 diagnosis codes used by medical providers give way to DSM-5 in behavioral health.

A 2017 study published in the *Journal of the American Board of Family Medicine* states that as integrated primary care and behavioral healthcare services come to the forefront, healthcare organization leaders must establish strong EHR use to enable better care coordination between the two specialties. The study's research team conducted feedback interviews with 11 Colorado-based primary care practices integrating behavioral health into their workflows. Following a three-year test period and retrospective qualitative interviews, the researchers identified five common themes to effective care, with one of those themes the need to use targeted data collection pertinent to integrated care to drive improvement and impart accountability.[7]

Specifically, the research team found strong EHR use was critical to care coordination between patients and primary care and behavioral health providers. Creating a substantial health IT infrastructure was among one of the primary suggestions between each of the participating healthcare organizations. "Establish standard processes and infrastructure necessary for your integrated care approach: workflows, protocols for scheduling and staffing, documentation procedures and an integrated EHR," the researchers said, citing one of the common recommendations for integrated primary and behavioral healthcare.[7]

As healthcare organizations move toward collaborative care to combat behavioral/medical comorbidity, EHR technology can play a vital role. However, harnessing the full power of this technology requires a new mind-set by recognizing all providers need equal input and access to patient records. To accomplish this, health professionals must work together and learn to rely on the power of instant communication instead of sending notes via mail or fax. With that in mind, the study concluded an integrated EHR platform can be a powerful ally in uniting behavioral and medical providers to better meet the complex needs of multi-condition patients.

A Worthwhile Pursuit

The idea of a practice model that successfully integrates behavioral and primary care is a topic worthy of further discussion. Forward-thinking primary care practices that successfully implement collaborative care for depression and other chronic mental health disorders are shown to report much higher rates of remission and recovery. Readily available and predictable crisis management services for distressed patients, whether by full integration, colocation or via agreement with community-based behavioral health service providers, can give patients timely access to mental health expertise and provide relief for busy primary care teams. While numerous collaborative care obstacles still exist, the benefits to both patient and provider make this innovative healthcare model a worthwhile pursuit in our evolving healthcare landscape. ❖

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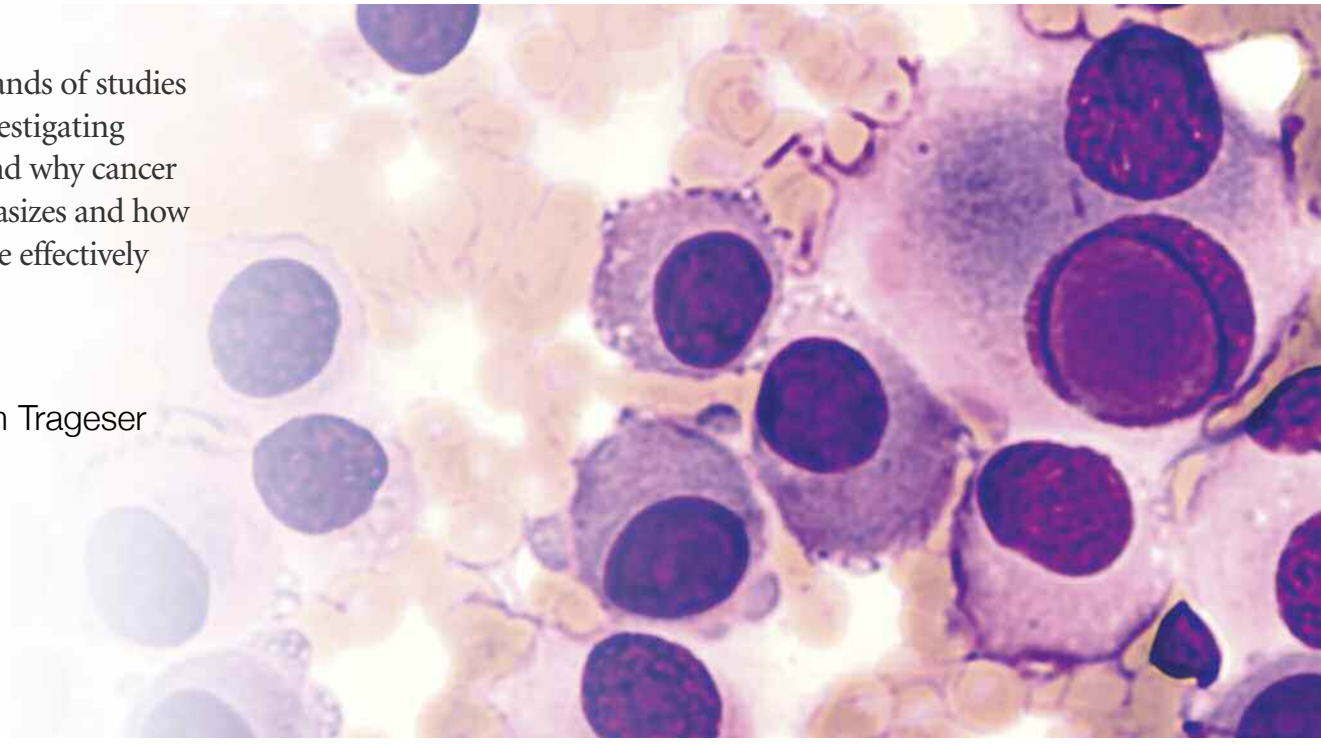
Update on Metastatic Cancer

Thousands of studies are investigating how and why cancer metastasizes and how to more effectively treat it.

By Jim Trageser



CANCER IS A two-headed monster, and it's hard to say which is the more lethal. The malignancy itself can, depending on where it forms, quickly become life-threatening since the out-of-control growth of cancer cells can interfere with core bodily functions. But, the other threat is perhaps even more dire: Individual cancer cells can break away from the original growth and spread to other parts of the body, where they start new tumors in a process known as metastasis.

Having malignant tumors spread throughout the body is obviously a much more challenging situation to treat. In fact, the National Cancer Institute reports cancer overall is the second-leading cause of death in the Western world, trailing only cardiovascular disease, with most cancer deaths caused by metastatic cancer.[1] In 2016, there were approximately 1.7 million new cases of cancer diagnosed in the United States (out of a population of roughly 326 million), and 596,000 cancer-caused deaths.[2] The most prevalent forms of cancer in this country are breast, lung and prostate cancer.[3]

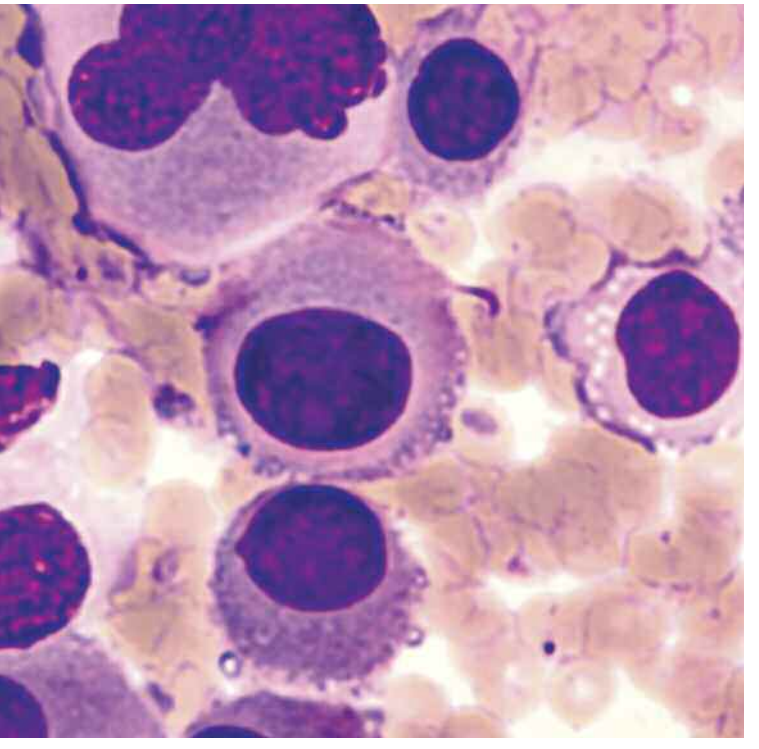
What Is Cancer Metastasis?

Metastatic cancer is any cancer that has spread to a distant part of the body through the blood or lymphatic systems.[4] Metastasis is understood to be a different process than the one observed when cancer spreads from its original location to contiguous tissue.[5]

Cancer has been known since antiquity. The Edwin Smith Papyrus, an Egyptian artifact dated to about 3,000 B.C., describes tumors of the breast and notes there was no effective treatment. Two and a half millennia later, Hippocrates used the word "carcinoma" (crab) to refer to ulcer-causing tumors, the name likely based on the pattern that noticeable tumors made under the skin of patients.[6] In the Middle Ages and Renaissance, autopsies (often illegal) helped further our understanding of many diseases, including cancer. In this last century, there have been dramatic advances in our knowledge of what cancer is and how it operates on cellular and molecular levels. Today, physicians and researchers have identified some 200 different types of cancer.

Despite all this, many of the specific mechanisms of metastasis have not yet been discovered.[5] And, in spite of all our advances in knowledge, diagnosis and treatment, cancer continues to be the

second-leading cause of death in the United States. However, a recent study did show cancer survival rates are increasing. Since 1990, cancer deaths in this country have fallen by 25 percent. And, more recently, from 2004 to 2013, cancer deaths for men declined by 1.8 percent, and for women and children by 1.3 percent.[2]



Survival rates vary widely from one form of cancer to another, and the National Cancer Institute emphasizes that statistics have little bearing on any individual patient. Breast cancer five-year survival rates from 1975 to 2012 increased from 75 percent to 91 percent, while lung cancer rates increased from 12 percent to 19 percent. Other forms such as bladder, prostate and colon cancers improved at a rate somewhere in between.[7]

Once cancer has spread, however, survival rates go down — often significantly. Those diagnosed with early stage lung cancer have an overall five-year survival rate of 56 percent; those whose lung cancer has spread have only a 5 percent five-year survival rate.[8] The good news is even those with metastatic cancer are seeing improved long-term survival as treatment improves.[7] Nevertheless, researchers estimate 90 percent of all cancer deaths result from metastatic tumors, not the original tumor.[9]

Causes of Cancer Metastasis

While today we have a more complete picture of how and why cells become cancerous (i.e., damage to the genetic codes that regulate cellular reproduction), the exact how and why of metastasis are not as well understood. The reasons some malignant cells break away from their tumor are not known. And, while scientists know these rogue cells penetrate the walls of blood and lymphatic vessels, the specific method used is not entirely understood, nor is it known how some of these cancer cells in the bloodstream and lymph nodes evade elimination by the body's immune system.[5] Researchers are also unsure what causes the cells to eventually stop their journey and once again begin their unregulated division and growth, although certain types of cancers have shown a tendency to metastasize in the same places (i.e., breast cancer metastasizing in the liver and testicular cancer in the bones).[10]

Symptoms and Progression of Metastatic Cancer

As with primary tumors, or even non-tumor-causing cancers such as leukemia and lymphoma, metastatic cancer does not always cause immediate symptoms. Symptoms vary depending on where the tumors develop. In fact, symptoms of a metastatic (or secondary) tumor are no different from those of a primary tumor:

- Sudden change in weight
- Noticeable lump or thickening of tissue under the skin
- Change in bowel movements
- Change in frequency or ease of urination
- Persistent indigestion
- Persistent joint or abdominal pain
- Difficulty breathing or swallowing
- Unexplained bleeding
- Fatigue
- Bone fractures
- Seizures or headaches
- Unexplained skin changes, including sores

Metastasis is understood to be a different process than the one observed when cancer spreads from its original location to contiguous tissue.

Patients should be coached to report any of these symptoms to their physician.[11]

As with a primary tumor, secondary tumors have a wide range of growth rates. Some can be dormant for years before resuming

growth; others spread so rapidly they are basically beyond treatment before they are discovered.[4]

Typically, the progression of metastatic cancer will mirror that of the primary tumor where it originated. A fast-growing cancer that has spread will remain a fast-growing cancer in its secondary tumors as well. Since slow-growing forms are less likely to metastasize than more aggressive types, metastasized cancers are statistically more likely to be of a type that presents a faster progression schedule. Many cases of metastasized cancers will be categorized as advanced cancer due to the seriousness of disease progression and the resistance of malignancy to treatment.[12]

Diagnosing Metastatic Cancer

In most cases, a patient will already have been diagnosed with cancer before being diagnosed with a metastatic tumor. Depending on the type of cancer diagnosed and how far it has progressed, an oncologist may already be regularly testing for metastasization. At other times, it will only be symptoms from the metastatic tumors that alert the physician and patient to the presence of cancer, rather than making a diagnosis until after the malignancy has spread.

Typically, the progression of metastatic cancer will mirror that of the primary tumor where it originated.

Metastatic cancers are known and treated as the original type of cancer. For example, breast cancer that has spread to the liver is still referred to and treated as metastatic breast cancer. A biopsy and examination of the tissue can confirm the secondary tumors are metastasized from the already known cancer. In some cases, the metastatic growths can't be traced back to a previous tumor. These are referred to as cancer of unknown primary origin.[4]

An initial cancer diagnosis can be made from blood work looking for specific markers, or from an imaging procedure such as a CT scan, MRI or X-ray. However, a biopsy is generally considered the only definitive method to confirm a diagnosis as serious as cancer.[13]

Treating Metastatic Cancer

Until recently, treatment for a metastatic cancer almost always took the form of a continuation of the regimen being used to treat the primary tumor, although the the urgency related to treatment increased significantly.

However, researchers are finding metastasized cancer cells are often resistant to drugs used to successfully attack primary tumors. The cells found in secondary tumors are often even less genetically stable than primary malignancy cells, with wildly different membrane properties, making existing drugs ineffective against them.[5] (And, in one recently reported case, a lung cancer tumor whose cells had lost the NKX2-1 gene that acts as master switch had grown into a miniature stomach and duodenum, reflecting the genetic instability researchers and physicians face in treating all malignancies.[14])

Depending on how broadly the cancer has spread, treatment may consist primarily of systemic therapy: chemotherapy drugs that move through the bloodstream to attack cancer cells throughout the body. Surgery, ablation or radiation therapy may be used to try to remove or reduce new growths, or to provide pain relief in affected areas.[12] In other cases, because the metastasized cancer can be so different from the primary cancer that created it, new treatments specifically targeting metastasized tumors are being introduced.

One new treatment that has shown promise in the past few years in treating metastatic melanoma and non-small cell lung cancer is immunotherapy in which the body's own immune system is harnessed to help attack cancer:

- One class of drugs known as PD-1 inhibitors (pembrolizumab [Keytruda]; nivolumab [Opdivo]; ipilimumab [Yervoy]) allow the body's immune system to recognize malignant cells more easily by suppressing a specific protein on T cells that normally prevent those cells from targeting other cells.[15] However, patients being administered these drugs must also be monitored for side effects that can be caused by the immune system — now unleashed — attacking healthy, noncancerous cells. Because of this, certain pre-existing conditions such as colitis, hepatitis, diabetes and others may preclude use of PD-1 inhibitors.

These drugs are administered intravenously every three to four weeks on an outpatient basis, and regular blood tests are conducted to check for possible side effects.[16] Treatment typically continues until the tumors shrink beyond detection, or there is an adverse reaction. A newly released study shows Keytruda showed improved survival rates in half of lung cancer patients, and delayed the development of advanced cancer.[17]

- Stereotactic radiosurgery, performed by aiming multiple, highly focused radiation beams directly at tumors, is now being used to treat brain and spinal metastases.[18] The radiation beams destroy the DNA in the nucleus of the targeted cells, preventing them from reproducing.[19] When multiple beams meet at the tumor, the healthy tissue through which all the beams pass is relatively unscathed, whereas the tumor receives a high dose of radiation that can not only destroy the DNA of the malignant cells, but also cause blood vessels to shrivel and close, denying the malignancy needed nutrients.[18]

During stereotactic radiosurgery, a head frame or specialized mask immobilizes the patient's head to assist in maintaining high accuracy of the beams so only malignant cells are struck and damaged by the radiation. Two main types of machines are used. Linear accelerators use X-rays, and require only a single session for a small tumor or several visits for larger growths or multiple tumors, and they are used to treat tumors throughout the body. Gamma Knife machines use gamma rays, which are even higher energy photons than X-rays, and are generally limited to treating conditions in the brain, including secondary malignancies. Treatment consists of one to several visits depending on the size and number of growths.[18] Follow-up care includes blood tests and radiological imaging to see if the treatment was successful in shrinking the secondary growths, and monitoring of the patient with possible chemotherapy or follow-up radiation treatment.

• Proton therapy is similar to stereotactic radiosurgery, but rather than using highly charged photons (the same particles as in visible light or radio waves), much heavier protons are used. Where an X-ray or gamma ray beam continues on after hitting the tumor, a proton beam stops at its target, doing no further damage to the tissue behind the tumor. With increased accuracy and less secondary damage to nearby healthy tissue, proton therapy is preferred for malignancies in the brain and spinal cord, as well as in children.[20]

The proton therapy treatment regimen is much the same as radiation therapy: One or more visits to the radiation center, depending on the size and number of tumors. Follow-up care includes blood tests and subsequent imaging to determine the effectiveness of treatment.

Additional care to any of the above three treatment regimens includes long-term monitoring by an oncologist and primary care physician, and may include additional chemotherapy tailored to the original cancer.

The newest treatment is not yet available for most metastasized cancers, but its implications for all cancers are revolutionary. Last summer, the U.S. Food and Drug Administration approved Novartis' CAR-T therapy, the first anti-cancer gene therapy approved in the U.S., to treat acute lymphoblastic leukemia. With CAR-T therapy, a physician extracts T cells from the patient, freezes them cryogenically and sends them to Novartis. At the company's lab, the patient's T cells are reprogrammed to produce a new protein called a chimeric antigen receptor. This protein causes the T cells, which are refrozen and shipped back to the physician for injection into the patient, to identify and kill any cells with that specific antigen, which is unique to this type of leukemia, on their membrane. Early studies showed more than 80 percent of patients in a CAR-T study had their cancer enter remission within three months of treatment.[21]

Whether the care plan is to eliminate the cancer, slow its growth or provide palliative relief to the patient, the American Cancer Society recommends the patient must always know what the goal of each step is in the treatment plan, what the options are and be included in decisions regarding treatment.[12]

When a cure is no longer an option, the oncologist and primary care physician will work with the patient and his or her family or other inner circle to ensure the highest quality of life. Pain relief, mobility and mental acuity are all goals to be balanced in planning the best course of treatment.[12]

Preventing Metastatic Cancer

Since the triggers that cause some tumors to metastasize are not fully understood, there is no way to prevent an existing cancer from metastasizing other than successfully treating it — whether through surgery, radiation or chemotherapy. Preventing the initial development of cancer is the best method to preventing cancer metastasis.

Healthy eating, avoiding tobacco use and maintaining an active lifestyle remain the best, most widely accepted methods of reducing the risk of developing a malignancy in the first place.

One new treatment that has shown promise in the past few years in treating metastatic melanoma and non-small cell lung cancer is immunotherapy in which the body's own immune system is harnessed to help attack cancer.

Ongoing Research

Cancer is likely the most-studied medical condition on Earth. Of the more than 60,000 studies listed on ClinicalTrials.gov, there are quite a few focusing specifically on cancer metastasis. Given that there are more than 200 types of cancer, and that it is likely each of them is capable of metastasis, it is not surprising there are more than 9,000 studies on cancer metastasis listed.

Among the thousands of studies listed, these are some of the more intriguing:

• A 2017 study conducted at Samsung Medical Center in South Korea is building a database of genomes of metastatic cancerous cells to cross-reference them against all registered drugs that target specific cellular molecules.[22]

• The Mayo Clinic's Jacksonville, Fla., facility is expected to issue its findings this fall on a 10-year study it is conducting in conjunction with the National Cancer Institute on stereotactic radiation therapy on patients with liver metastases. While stereotactic radiation therapy is already being clinically employed, it remains a young technology. This study is looking at determining ideal dosage to balance effectiveness versus side effects in a field of 18 participants, and the final report will include post-treatment measurements of both survival rates and the patients' reported quality of life.[23]

Curing cancer has been the top goal of the Western medical profession for nearly a half century.

• At the Moores Cancer Center at the University of California, San Diego, researchers are roughly two years into a five-year study comparing survival and quality of life rates among patients whose metastatic cancers are treated with checkpoint blockade immunotherapy (CBI) alone versus those whose CBI treatment is supplemented by stereotactic body radiation therapy. The 146 participants were randomly assigned to two treatment regimens. Half will have their advanced metastasized cancer treated with an anti-PD-1/PD-L1 immunotherapy only, and the other half will receive immunotherapy plus have their metastasized tumors treated with SBRT at 9.5Gy x3 fractions within three weeks of the beginning of immunotherapy. Results are expected to be posted in January 2021.[24]

• Eli Lilly is in the midst of a three-year study set to conclude in September 2018 studying the efficacy of a new fibroblast growth factor receptor 3 (FGFR3) antibody-drug, LY3076226, in both advanced cancer and metastatic cancer patients. The 37 study subjects receive an intravenous dose of the drug every three weeks, with follow-up study measuring residual amounts of the drug in the bloodstream, and its effectiveness in treating the tumor(s).[25]

• Massachusetts General Hospital and Merck Sharp and Dohme Corp. are collaborating on a study investigating whether pembrolizumab (Keytruda) is effective in fighting metastases in the central nervous system. The 102 participants are currently fighting either a previously untreated brain metastasis, a progressive brain metastasis, multiple brain metastases from melanoma, or a neoplastic meningitis with a solid malignancy. Patients will be examined with a cranial MRI every six weeks to study the efficacy of the treatment. The study began in 2016, and is expected to be completed in 2024.[26]

Looking Ahead

Curing cancer has been the No. 1 goal of the Western medical profession for nearly a half century, with massive government subsidies since at least the Nixon administration with the signing of the National Cancer Act of 1971. While tremendous progress has been made, cancer remains the second-leading cause of death in the developed world. Some studies suggest that as advances in treating and preventing cardiovascular disease continue to show results, cancer will become the leading cause of death in North America and Western Europe.

Metastasis seems to be endemic to what cancer is. Since cancer will sadly remain with us for the foreseeable future, physicians will continue to work with patients to attack these diseases when possible, and provide quality-of-life care when it is not. ❖

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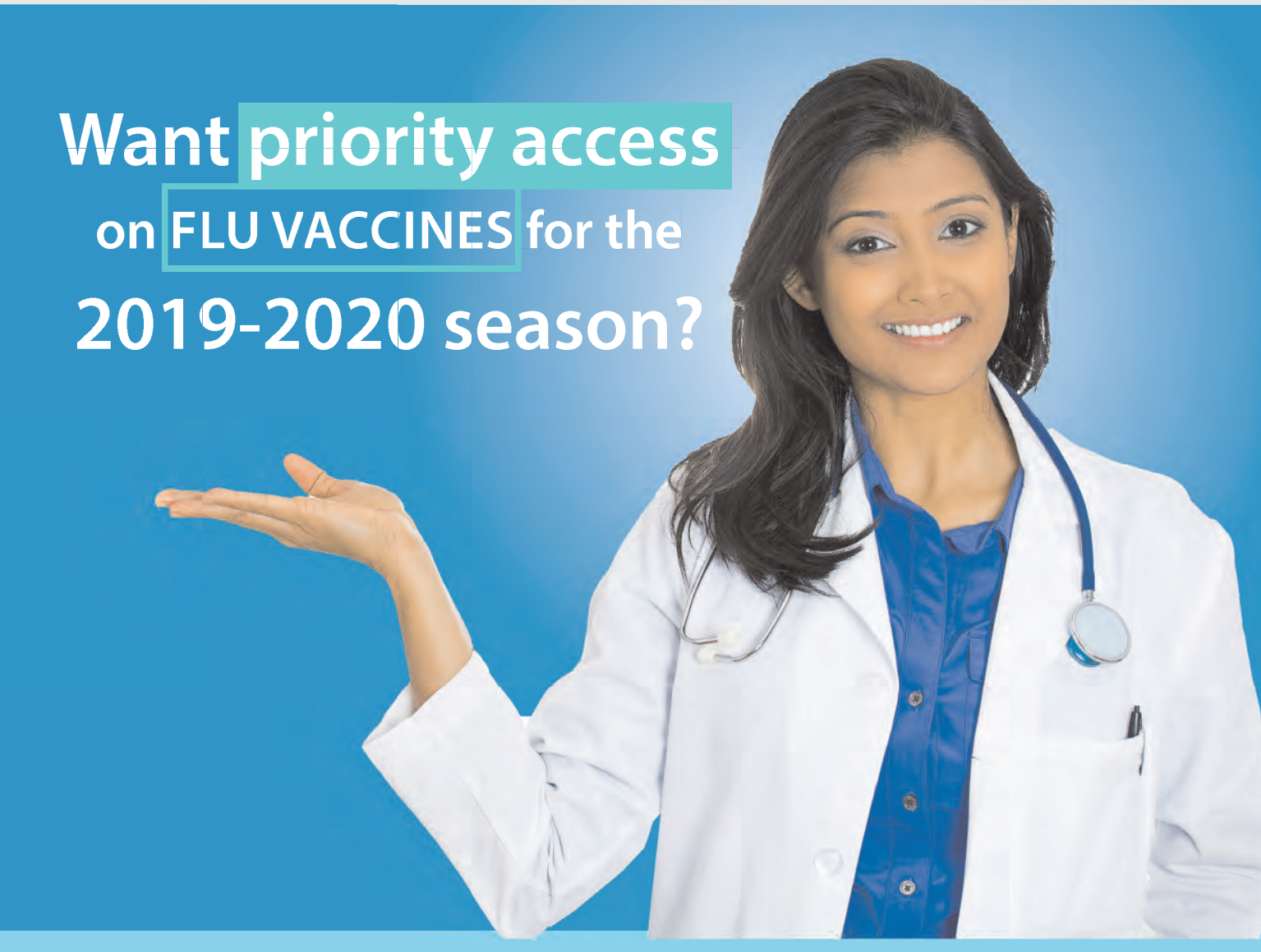

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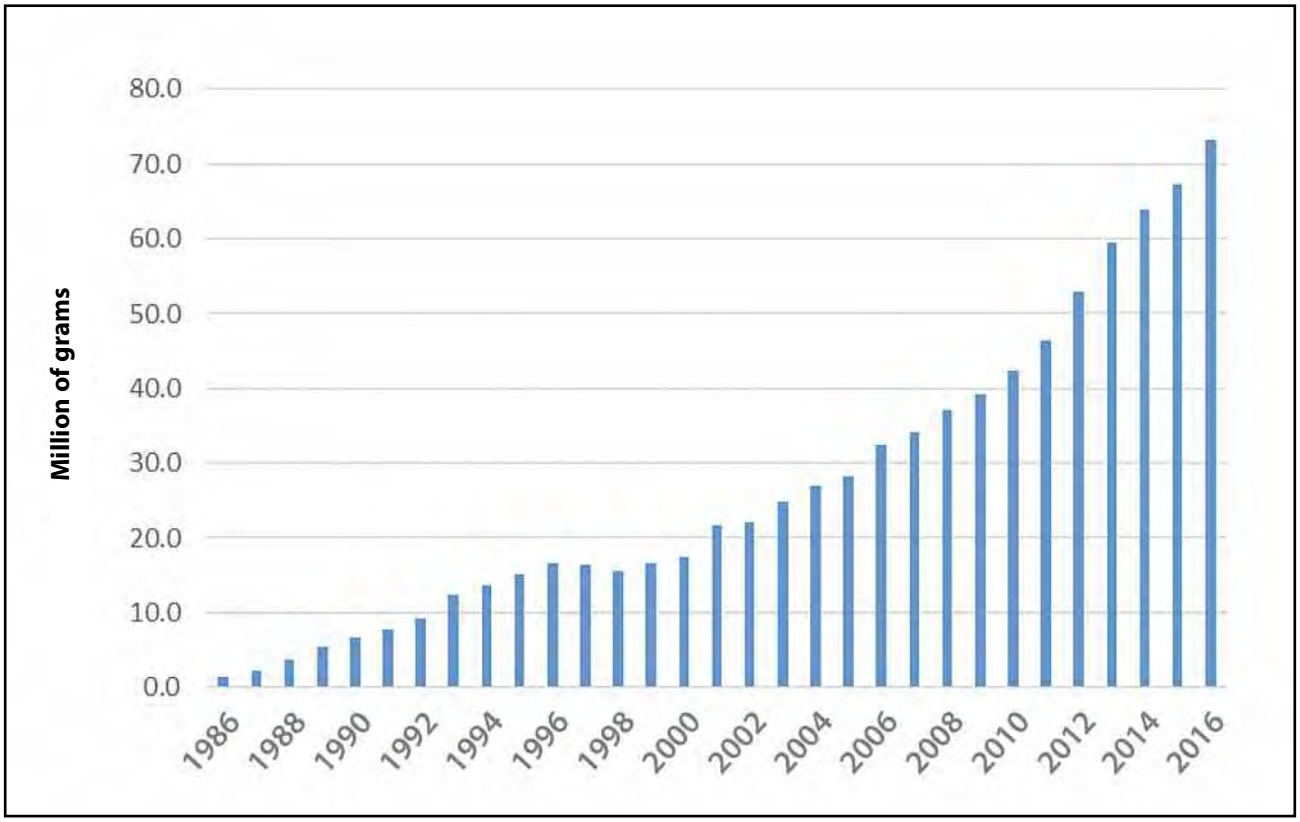
Plasma Fractionation: *The Challenge of Keeping Pace with Global IG Demand*

By Keith Berman, MPH, MBA

TRY TO NAME an injectable drug or biopharmaceutical available more than 30 years, whose prescribing activity has increased year after year without interruption — including a doubling in demand over the last decade. If you came up with polyvalent human immune globulin (IG) — which comprises intravenous immune globulin (IVIG) and essentially the same product formulated for subcutaneous delivery (SCIG) — you are correct.

If no others come to mind, it is because no other U.S. Food and Drug Administration (FDA)-approved drug entity has experienced anything resembling this sustained record of near-continuous demand growth* since FDA approved the first IVIG product in 1981 (Figure 1). Today, 15 IVIG and SCIG products (Table) compete for a share of a

Figure 1. The U.S. Polyvalent IG Market (IVIG/SCIG) from 1986 to 2016



Source: The Marketing Research Bureau, Inc. (Orange, CT)

** Excepting a product supply shortage period that extended from 1998 through 2001.*

U.S. hospital, clinic and home infusion market currently growing at more than 8 percent annually.

After a new drug is introduced, it typically goes through a market life cycle that culminates either with market *maturity* — demand stagnation once a product reaches its clinical applicability and market size limits — or with market *decline*, as providers switch to better new drug alternatives. Why has this not been the case with polyvalent IG? Industry experts have identified at least four reasons:

1) IG is essentially a concentrate of the most critical portion of the humoral immune systems of not one but thousands of individual plasma donors. Unlike single molecular entities, IVIG and SCIG products contain many thousands of highly specific IgG antibodies with a diversity of incompletely understood immunoregulatory, anti-inflammatory and infectious disease-targeting functions.

2) The clinical utility of IG across an ever-broadening spectrum of serious or life-threatening autoimmune, inflammatory, immunodeficiency and other immune-mediated disorders continues to be documented in patient studies and case reports now numbering in the thousands.

3) There is a trend toward more aggressive treatment with high-dose IG — 1 to 2 grams per kilogram of body weight or more per month — in autoimmune neurologic diseases in particular, based on evidence of superior effectiveness in relation to lower-dose regimens.[1,2] Additionally, long-term IG usage appears to account for a steadily increasing proportion of patients.[3]

4) While per capita utilization lags far behind North America and Europe, there has been a recent surge in IG demand in many countries in southeastern Asia. From 13 percent of global IG demand in 2008, just six years later, Asia accounted for 18 percent of the global IG market.[4]

Table. Available FDA-Approved IG Products*

Manufacturer	*Product*	*Administration*
CSL Behring	Privigen Immune Globulin Intravenous (Human) 10%	Intravenous
	Carimune NF Immune Globulin Intravenous (Human) Nanofiltered**	
	HIZENTRA Immune Globulin Subcutaneous (Human) 20%	Subcutaneous
Grifols	Flebogamma 5% DIF Immune Globulin Intravenous (Human)	Intravenous
	Flebogamma 10% DIF Immune Globulin Intravenous (Human)	
	GAMUNEX-C Immune Globulin Injection (Human) 10%	Intravenous Subcutaneous
Shire	GAMMAGARD LIQUID Immune Globulin Infusion (Human) 10%	Intravenous Subcutaneous
	GAMMAGARD S/D Immune Globulin Intravenous (Human) 5%, less than 1 mcg of IgA per mL	Intravenous
	HyQvia Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase	Subcutaneous
	CUVITRU Immune Globulin Subcutaneous (Human) 20%	
Octapharma	Octagam Immune Globulin Intravenous (Human) 5%	Intravenous
	Octagam Immune Globulin Intravenous (Human) 10%	
Bio Products Laboratory (BPL)	Gammaplex Immune Globulin Intravenous (Human) 5%	Intravenous
	Gammaplex Immune Globulin Intravenous (Human) 10%	
Kedrion Biopharma	GAMMAKED Immune Globulin Injection (Human) 10%	Intravenous Subcutaneous

* All products are supplied in liquid form, except for Carimune NF and Gammagard S/D, which are supplied in lyophilized form.
** Production of Carimune NF is scheduled to be discontinued in Q3 2018.

In 2016, 35 years after IVIG was first introduced, U.S. demand for polyvalent IG products grew 8.7 percent, from 67.3 million grams to just over 73 million grams. Preliminary data indicate this trend continued through 2017, with product shipments exceeding 80 million grams. The global IG market mirrors this growth pattern: Over the eight years between 2008 and 2016, worldwide demand for IVIG and SCIG more than doubled, with an average annual growth rate of 9 percent (Figure 2).

IG demand growth on this scale presents two special challenges for the plasma fractionation industry. The first is to forecast and invest in plasma collection facilities to assure sufficient additional IgG-containing donor plasma is available to process into IG products. The second

Figure 2. The Global Polyvalent IG Market (IVIG/SCIG) from 1986 to 2016, with Projected Global Demand Through 2024

Source: The Marketing Research Bureau, Inc. (Orange, CT)

challenge is to plan, invest and provide adequate lead time to construct and secure regulatory approval to operate new or expanded fractionation and related IG production facilities.

It All Starts with the Plasma

Pooled donor plasma contains an average of around 9 grams of IgG per liter, but historically, most of that IgG was unrecoverable as a result of the process used to isolate it. The original Cohn plasma fractionation process, first developed in the 1940s to purify albumin, relied on sequential precipitation steps using increasing concentrations of cold ethanol, at the cost of a significant IgG yield loss.

As IVIG demand climbed in the 1990s, manufacturers began modifying their purification processes to try to improve the yield of IgG per liter of plasma. Today, most manufacturers employ just a single cold ethanol precipitation, substituting anion exchange chromatography and processing with agents such as caprylic acid to remove impurities.[5,6] "Over the last 25 years, plasma processing advances have improved IgG yield by roughly 60 percent on average, from 2.5 grams per liter to 4 grams or more per liter today," said plasma industry analyst Patrick Robert, PhD.[7]

While improved IgG yield per plasma liter has certainly helped moderate plasma requirements, manufacturers still must expand plasma collections at a pace to stay ahead of growing IG product demand. Consider the industry's four leading global manufacturers — Grifols, CSL Behring, Shire and Octapharma — which collectively supply nearly 70 percent of the world demand for IG products[4] and a similar share of the roughly 12 million additional IG grams purchased each successive year since 2012.

Assuming an IgG yield of 4 grams per liter, simple mathematics dictates that, in 2018, these four leading manufacturers will need to increase their combined plasma collections by approximately two million liters. As each individual plasma donation averages about two-thirds of a liter in volume, this translates into some three million additional plasma donations needed this year to keep up with growing global IG demand. That, in turn, translates into substantial investments in design and construction of new or expanded plasma collection centers, and additional equipment purchases and staffing.

Between 2004 and 2014, the global supply of plasma intended for fractionation

doubled to nearly 40 million liters (Figure 3). Looking forward, continuing investments in collection center construction, equipment and staffing will be needed to generate the additional three million or more liters of additional plasma required each year to meet the global IG demand forecast into the next decade.

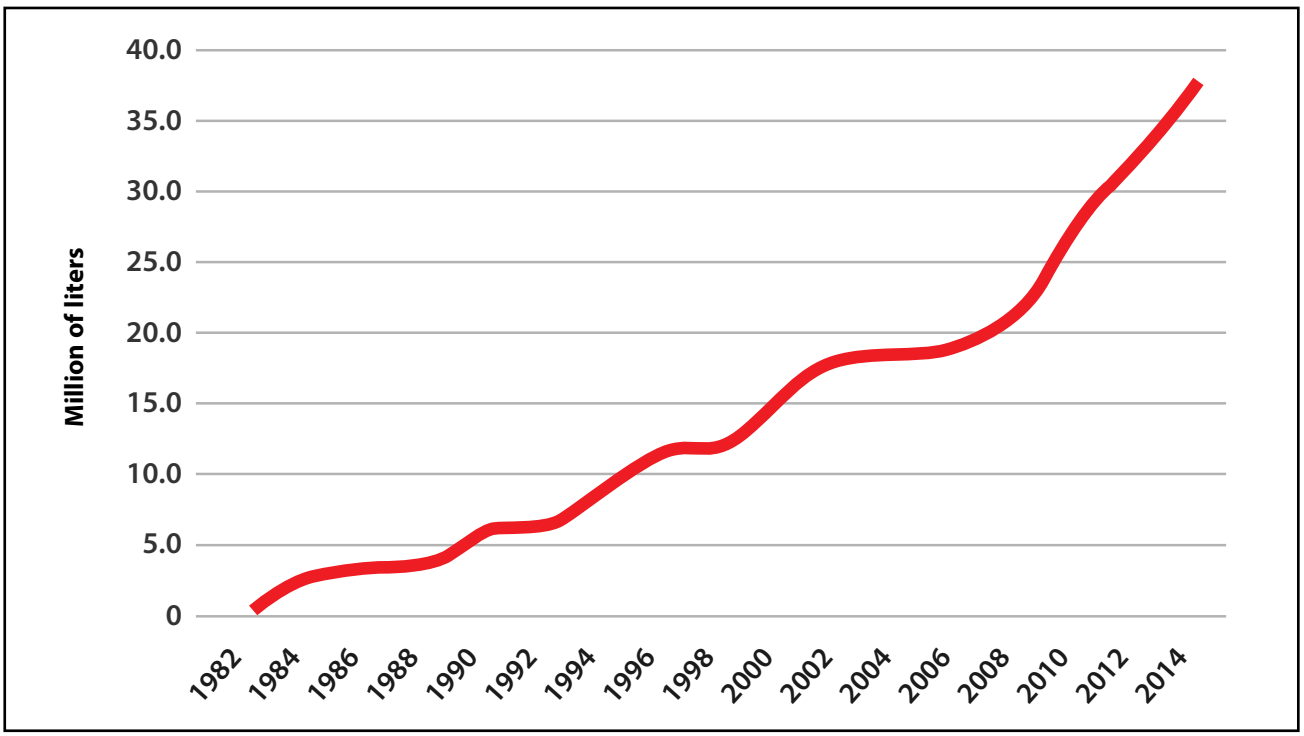
Major Investments in New Fractionation Capacity

At least two studies have compared the cost structure of plasma protein therapeutics and various chemical-based pharmaceuticals. For pharmaceuticals, manufacturing and raw material costs on average account for only about 15 percent to 20 percent of total costs, dwarfed by sales and marketing, research and development and other costs unrelated to production. The picture is entirely different for plasma protein therapeutics: Raw materials and manufacturing expense account for roughly 60 percent to 70 percent of total costs.[8,9]

> While improved IgG yield per plasma liter has certainly helped moderate plasma requirements, manufacturers still must expand plasma collections at a pace to stay ahead of growing IG product demand.

Fractionating and purifying IgG from starting batches of thousands of liters of plasma requires custom-designed, scaled-up equipment housed in large physical plants operated by hundreds of specialized, highly skilled

Figure 3. Growth in Global Donor Plasma Requirements to Manufacture IVIG and SCIG



Source: The Marketing Research Bureau, Inc. (Orange, CT)

Left: CSL Behring Immune Globulin Production Facility at Bern, Switzerland[12]
Right: Grifols Plasma Fractionation Facility Under Construction at Clayton, North Carolina[13]

personnel (Figure 4). Often depending where existing production capabilities are located, a manufacturer may decide, in order to maximize operating efficiency, to situate all components of its IG manufacturing expansion — plasma fractionation, IgG purification, filling/finishing and final product testing — at a single facility or at multiple sites commonly spread across different continents. In scale, complexity and lead time, this investment dwarfs the typically $2 million to $3 million per-facility cost and two to three years to plan and open a plasma collection center.

Every major plasma fractionator is actively investing in new production capacity to keep ahead of forecasted future IG demand growth. One example of the scope and long planning time horizons involved is a nearly complete U.S.-based fractionation plant first announced in April 2012 by Baxter International,[10] prior to the spinoff of its plasma products division and eventual acquisition by Shire.

Baxter budgeted a capital investment in excess of $1 billion over a five-year period to build a facility with up to three million liters of annual plasma fractionation capacity when fully operational. In August 2012, ground was broken on the company's new state-of-the-art manufacturing facility in Covington, Ga., near Atlanta.[11] In December 2017, on schedule five years later, Shire filed for approval to manufacture its IVIG product, Gammagard Liquid, at the new facility. Commercial production is expected to start at the new Covington facility sometime in 2018.

A Commitment with a Higher Purpose

It's difficult to overstate the importance of the industry's commitment to proactively plan and invest in new plasma collection and IG production capacity. With the global IG market forecast to grow about 7 percent — nearly 15 million grams — annually through the year 2024, inadequate raw material or capacity, or both, could lead to a significant product shortage. A shortage would inevitably drive up prices and, more importantly, jeopardize the health of many thousands of thousands of patients who rely on IVIG and SCIG, both in the U.S. and across the globe.

In addition to the "big four" of Shire, Grifols, CSL Behring and Octapharma, a number of other experienced fractionators are stepping up their efforts to capture a piece of the growing IG market. South Korea-based Green Cross, for example, is completing construction of a plasma fractionation plant in Canada that will expand its 1.7 million-liter fractionation capacity by one million liters. Biotest in Germany is engaged in a project anticipated to double its current plasma processing capacity.

IG manufacturing is a costly, complex and globalized enterprise, but in the end, its success serves one higher purpose: assuring that today and in the future, patients in need have access to this unique therapeutic. ❖

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

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13. Accessed at siteselection.com/LifeSciences/2014/apr/briefly-bio.cfm.

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Val Bias has been living with hemophilia since birth, a survivor of the odds of a short life-span prior to better treatments, as well as contracting HIV from factor infusion. Today, he is CEO of the National Hemophilia Foundation advocating for improving quality of life for hemophilia patients.

Hemophilia: *A Patient's Perspective*

By Trudie Mitschang

VAL BIAS, CEO of the National Hemophilia Foundation (NHF), has lived with hemophilia his entire life, beating odds almost from the start. At the time of his birth, every male member of his family with hemophilia had already died. When Val was in the fourth grade, he came across a hemophilia section in a school textbook and learned the average life expectancy for someone with his condition was 20 years. At age 10, Val came to the shocking realization his life was already half over. Despite predictions to the contrary, Val survived well past the anticipated two decades, only to find his life threatened again by an equally formidable foe: human immunodeficiency virus (HIV).

Understanding Hemophilia

More than three million Americans have a bleeding disorder such as hemophilia, von Willebrand disease or rare factor deficiencies. These disorders prevent the blood from clotting normally, can result in extended bleeding after injury, surgery or trauma, and can be fatal if not treated effectively. Because of this, people with hemophilia depend heavily on clotting factor replacement therapy derived from human blood or a recombinant developed in the lab.

It was through an infusion of clotting factor concentrate derived from human plasma that Val contracted HIV and hepatitis C. It's well documented from the late 1970s to the mid-1980s (prior to more stringent blood safety measures) HIV, hepatitis C and hepatitis B from infected blood donors made its way into blood products. As a result, nearly half of all people with hemophilia became infected with HIV, many developed acquired immunodeficiency syndrome and thousands died, including many of Val's friends, colleagues and his beloved first wife, Katie, who unknowingly contracted the virus from Val.

The year Katie died, Val attended the NHF annual meeting, and his subsequent involvement led to him being elected chairman of the board. "We began a crusade to help people who developed HIV from tainted blood products," he remembers. The work culminated in the passage of the Ricky Ray Hemophilia Relief Act of 1998. Ten years later, in 2008, Val became NHF's CEO.

Since stepping into the role of CEO, Val has led the organization to the forefront of the healthcare reform debate on such issues as the elimination of lifetime caps on insurance benefits and coverage for pre-existing conditions with insurers. In addition, he has greatly expanded NHF's research agenda and created the Women's Health and Bleeding Disorders Institute to address the growing need for awareness and treatment for women with bleeding disorders. "In recent years, great strides have been made in treatment, public policy and advocacy for the bleeding disorders community," says Val. "When I came on board, we had a three-quarter million [dollar] deficit. Today, we have a $25 million budget and $14 million in reserves. We had 35 chapters in 2008, and now we have 52 and a staff of almost 80."

Advocating for Quality of Life

Today, this seasoned survivor and advocate is focused on helping NHF expand its research agenda, with an emphasis not just on bleeding disorder cures but also quality of life for this diverse community. "Life expectancy for people with bleeding disorders is normal today," he explains. "But, it's not just about how long you live but also about the quality of your life. You might live to be 70 years old, but if you get up and go to work every day and come home to your family and have no energy to engage socially, your quality of life is not what it could be."

Val has also concentrated his efforts on raising national awareness regarding bleeding disorders. In 2016, he led a successful effort to have the month of March designated by the U.S. Department of Health and Human Services as the first-ever Bleeding Disorders Awareness Month. He also helped launch the Red Tie Challenge, a movement intended to start a national conversation about bleeding disorders.

Val notes current research is shifting its focus to products in the pipeline that can potentially increase people's ability to live fuller and more active lives. "Some of the most promising trials are demonstrating the possibility that many patients could live very normal lives," he explains. "There are questions, of course, about the costs. What remains to be seen is if these products will be accessible and reimbursable for everyone who needs them." ❖

Dr. Steven Pipe, who specializes in inherited and acquired bleeding and thrombotic disorders, explains the many promising therapies for hemophilia patients today.

Hemophilia:
A Physician's Perspective

STEVEN PIPE, MD, medical director of the Pediatric Hemophilia and Coagulation Disorders Program at the University of Michigan, has been researching the structure and function of the factor VIII (FVIII) protein and its secretion pathway to improve the manufacture of its recombinant form. He is a member of the National Hemophilia Foundation's Medical and Scientific Advisory Council.

BSTQ: What are the most significant health challenges for individuals living with severe hemophilia?

Dr. Pipe: The primary complication is recurrent bleeding, primarily into joints (hemarthrosis). Though acute bleeding can be arrested by replacing missing clotting factor through intravenous infusions, repeated bleeding leads to progressive joint injury and, ultimately, a crippling and painful chronic arthropathy. Bleeding can be effectively prevented through prophylactic infusions of the clotting factors; preventing bleeding preserves joint health over subsequent decades.

An important complication of clotting factor replacement therapy is up to 30 percent of patients with severe hemophilia A (FVIII deficiency) will develop an immune response and make an antibody that inhibits the function of the clotting FVIII. This makes it impossible to treat or prevent their bleeding with FVIII replacement. Their acute bleeding has to be managed with alternative clotting factors (bypassing agents) that are less effective for acute bleed management and prophylaxis. Thus, developing inhibitors increases a patient's risk for serious acute bleeding, including death, and leads to increased hospitalizations and a higher incidence of joint disease.

Finally, our older patients (older than 35 years) still suffer from the legacy of blood contamination from HIV and hepatitis C in the early 1980s. This affected up to 90 percent of the severe hemophilia population, and it remains a significant comorbidity affecting the health of the older population of patients.

BSTQ: How have treatment options evolved?

Dr. Pipe: In part, due to infections associated with clotting factors obtained through plasma fractionation, recombinant technologies led to the development of recombinant clotting factors. These synthetic facsimiles of FVIII and factor IX (FIX) have proved to be safe and efficacious, and in the developed world have become the standard of care for replacement therapy. Moreover, the recombinant platform has allowed for targeted bioengineering of the molecules to alter the properties of the FVIII or FIX. The most successful innovations have resulted in longer half-lives of clotting factors. These extended half-life factors have led to improved joint outcomes, increased physical activity levels and reduced infusion frequency.

BSTQ: Tell us about your work with gene therapy and why it holds significant promise.

Dr. Pipe: Because hemophilia is a monogenic disease — that is, it is due to a mutation in a single gene resulting in loss of a single protein, either FVIII or FIX — it is amenable for genetic therapies that effectively replace a working copy of the gene. This has made hemophilia an attractive candidate for gene therapy. Many avenues have been explored over the past 30 years. However, the most promising platform is packaging of the gene coding for either FVIII or FIX protein into a recombinant viral vector. The virus serves as the vehicle to deliver the gene into the target cell, typically the liver, where the gene remains and accesses the normal machinery to produce the proteins and restore plasma levels of either FVIII or FIX to levels sufficient to prevent bleeding.

The proof-of-principle clinical trial was reported in 2011 using an adeno-associated virus vector to deliver the gene for FIX in severe hemophilia B. Men achieved durable expression of FIX such that they no longer required clotting factor prophylaxis and have maintained low bleeding rates. Since then, additional Phase I/IIb clinical trials have shown the ability to produce levels of FVIII or FIX that are in the "curative" range. These programs are now moving to Phase III trials.

BSTQ: What's next in terms of bleeding disorder research?

Dr. Pipe: Besides the novel substitution therapy, emicizumab, several additional research programs aim to treat hemophilia through alternative methodologies. Each of these pipeline programs is targeting the inhibitory pathways for coagulation. By targeting these pathways, blood clotting can be restored without needing to administer FVIII or FIX. These would have broad application for hemophilia A or B with and without inhibitors. It will be interesting to see in the years ahead how these will compare in safety and efficacy with gene therapy programs. ❖

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

Medicare Beneficiaries' Out-of-Pocket Health Care Spending as a Share of Income Now and Projections for the Future

Author: Henry J. Kaiser Family Foundation

In this report, the Kaiser Family Foundation assesses the current and projected out-of-pocket healthcare spending burden among Medicare beneficiaries using two approaches. First, it analyzes average total per capita out-of-pocket healthcare spending as a share of average per capita Social Security income, building upon the analysis conducted annually by the Medicare Trustees. Second, it estimates the median ratio of total per capita out-of-pocket spending to per capita total income, an approach that addresses the distortion of average estimates by outlier values for spending and income. Under both approaches, the foundation uses a broad measure of Medicare beneficiaries' total out-of-pocket spending that includes spending on health insurance premiums, cost sharing for Medicare-covered services and costs for services not covered by Medicare such as dental and long-term care. Also presented are estimates of the out-of-pocket spending burden for Medicare beneficiaries overall, and by demographic, socioeconomic and health status measures, for 2013 and projections for 2030, in constant 2016 dollars.
files.kff.org/attachment/Report-Medicare-Beneficiaries-Out-of-Pocket-Health-Care-Spending-as-a-Share-of-Income-Now-and-Projections-for-the-Future

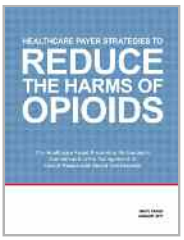
Dreams That Can Save Your Life: Early Warning Signs of Cancer and Other Diseases

Authors: Larry Burk, MD, CEHP, and Kathleen O'Keefe-Kanavos

Showcasing the important role of dreams and their power to detect and heal illness, Dr. Larry Burk and Kathleen O'Keefe-Kanavos share research and true stories of physical and emotional healings triggered by dreams. The authors explore medical studies and ongoing research on the diagnostic power of precognitive dreams, including Dr. Burk's own research on dreams that come true and can be medically validated. They share detailed stories confirmed by pathology reports from subjects in medical research projects whose dreams diagnosed illness and helped heal their lives, including Kathleen's own story as a three-time breast cancer survivor whose dreams diagnosed her cancer even when it was missed by her doctors.
www.findhornpress.com/dreams-that-can-save-your-life.html

Healthcare Payer Strategies to Reduce the Harms of Opioids

Author: Healthcare Fraud Prevention Partnership (HFPP)



This HFPP white paper describes best practices for serious consideration by all healthcare payers and other relevant stakeholders to effectively address and minimize the harms of opioids while ensuring access to medically necessary therapies and reducing fraud, waste and abuse. The HFPP focuses on three approaches: 1) Sharing resources, policies and practices that connect patients to care that is best suited to their needs and achieves optimal outcomes, ultimately reducing opportunities for fraud, waste and abuse related to opioids; 2) Identifying and mitigating potentially fraudulent, abusive or wasteful activities related to opioids; and 3) Engaging in innovative studies and information sharing techniques within the HFPP to identify and share effective opioid misuse and opioid use disorder mitigation strategies.
downloads.cms.gov/files/hfpp/hfpp-opioid-white-paper.pdf

The Fast Track to Drug Approval: Five FDA Pathways for Expedited Review

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

In its report *The Fast Track to Drug Approval*, FDA has established five application pathways — Fast-Track Designation, Breakthrough Therapy Designation, Regenerative Advanced Therapy Designation, Priority Review and Accelerated Approval — that can get new products through review and onto the market more quickly and with fewer hoops to jump through. The report explains the general criteria for applying under the expedited approval pathways, key elements and requirements of each pathway, content of submissions for each pathway, how to work with FDA to increase chance of success, and how to strategically align research and development functions with the expedited approval pathways.
www.fdanews.com/products/55624

Cognitive, Behavioral and Neuroinflammatory Parameters Improve in Autistic Children Treated with Intravenous Immune Globulin

Significant improvements in cognitive and behavioral function were observed in 14 children with autism spectrum disorder and evidence of immune dysfunction, who were administered high-dose intravenous immune globulin (IVIG) treatment over a period of 30 weeks, according to a pilot study conducted by U.S. investigators.

A select group of autistic children with a diagnosis of autistic disorder, Asperger's disorder or pervasive developmental disorder and evidence of a dysregulated immune system received 1 g/kg of 5 percent IVIG (Gammaplex, Bio Products Laboratory) for 10 21-day treatment cycles. The primary endpoint was pre- and posttreatment disease improvement assessed using standardized cognitive and behavioral tests (e.g., Children's Communication Checklist [CCC-2], Social Responsiveness Scale [SRS], Aberrant Behavior Checklist [ABC], Clinical Global Impressions-Severity [CGI-S] and Improvement [CGI-I], and Autism Diagnostic Observation Schedule [ADOS]). A number of experimental biomarkers associated with neuroinflammation were also captured.

Significant improvements from baseline to study endpoint were observed in several sub-scales of the CCC-2, SRS, CGI-I, CGI-S and ADOS, including associated maladaptive behavior ($P \leq 0.043$), reciprocal social interaction ($P \leq 0.015$), communication ($P \leq 0.001$) and stereotyped behaviors and repetitive

interests ($P \leq 0.013$). Statistically significant reductions were also seen in numerous immunological biomarkers indicative of neuroinflammation. IVIG treatments were well-tolerated. These findings suggest inflammatory etiologies may play a role in some cases of autism, and IVIG treatment may, through an anti-inflammatory effect, exert a positive impact on its behavioral manifestations.

Melamed IR, Heffron M, Testori A, et al. A pilot study of high-dose intravenous immunoglobulin 5% for autism: impact on autism spectrum and markers of neuroinflammation. Autism Res *2018 Mar;11(3):421-33.*

SCIG Therapy Is Cost-Saving Versus IVIG in Canadian Study of Primary Immunodeficiency Patients

This first-ever prospective economic analysis by Canadian investigators found that, from both hospital- and health system-based perspectives, home-based subcutaneous immune globulin (SCIG) therapy was associated with significantly lower average total nondrug costs than hospital-based intravenous immune globulin (IVIG) therapy for patients with primary immunodeficiency disorders.

The analysis included 30 adult patients in the IVIG group and 27 patients in the SCIG group. The average age and baseline weight were not significantly different between the two groups. Patients on IVIG therapy typically came to the hospital every three to four weeks where a nurse inserted an intravenous line for infusions that generally required about two to three hours. Initiation of SCIG treatment required training by a qualified nurse, generally in a single one-on-one visit. Once patients had been trained, they infused the product on their own at home, generally in small volumes ranging from one to seven times per week. For patients transitioning from IVIG to SCIG at the beginning of the study, treatment was initiated at a dose equivalent to the previous IVIG dose, given once a week.

Over the 12-month study period, all nondrug hospital costs (including hospital nurses and technicians) and physician visit costs were respectively $1,836 and $84 for the SCIG group, and $4,187 and $744 for the IVIG group. "SCIG has significantly decreased costs for the Canadian health care system compared with IVIG," the investigators concluded. "It should be considered in patients who are currently on IVIG and in those who are to start immunoglobulin replacement therapy."

Fu LW, Song C, Isarunuwatchai W, et al. Home-based subcutaneous immunoglobulin therapy vs hospital-based intravenous immunoglobulin therapy: A prospective economic analysis. Ann Allergy Asthma Immunol *2018 Feb;120(2):195-9.*

Medicare Immune Globulin Reimbursement Rates

Rates are effective July 1, 2018, through September 30, 2018

	Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
IVIG	CARIMUNE NF	CSL Behring	J1566	$82.81	$81.48
	FLEBOGAMMA	Grifols	J1572	$72.15	$71.00
	GAMMAGARD SD	Shire	J1566	$82.81	$81.48
	GAMMAPLEX	BPL	J1557	$111.54	$109.75
	OCTAGAM	Octapharma	J1568	$66.32	$65.25
	PRIVIGEN	CSL Behring	J1459	$79.34	$78.07
IVIG/SCIG	GAMMAGARD LIQUID	Shire	J1569	$101.11	$99.49
	GAMMAKED	Kedrion	J1561	$82.42	$81.09
	GAMUNEX-C	Grifols	J1561	$82.42	$81.09
SCIG	CUVITRU	Shire	J1555	$135.01	$132.84
	HIZENTRA	CSL Behring	J1559	$98.50	$96.92
	HYQVIA	Shire	J1575	$145.38	$143.05

* 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.FFEnterprises.com.

Immune Globulin Reference Table

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

* 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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