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QUARTERLY
SUMMER 2022 VACCINES

mRNA Vaccines

The Future of Disease Prevention?

Vaccine Passports:
ARGUMENTS FOR AND AGAINST

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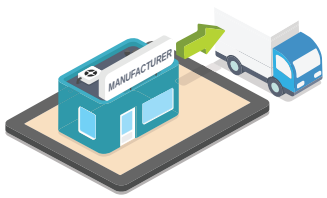
Guaranteed Channel Integrity®
8 Critical Steps

STEP 1

Purchasing

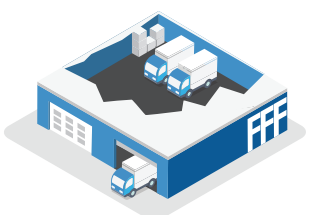
At FFF, we only purchase product from the manufacturer–never from another distributor or source–so the integrity of our products is never in question.



STEP 2

Storage

The healthcare products we store and transport are sensitive to temperature variations. Our state-of-the-art warehouse is temperature-controlled, monitored 24/7, and supported with backup generators in the event of power loss. In addition, we only stack products double-high to minimize pressure on fragile bottles and containers.



STEP 3

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STEP 4

Interactive Allocation

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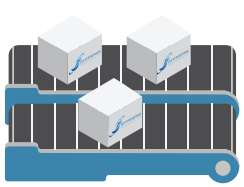

Our commitment to a secure pharmaceutical supply chain is demonstrated by our flawless safety record. The 8 Critical Steps to Guaranteed Channel Integrity have resulted in more than 11,600 counterfeit-free days of safe product distribution.

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STEP 5

Delivery

Our delivery guidelines are in compliance with the State Board of Pharmacy requirements. Products we deliver must only be transported to facilities with a state-issued license, and only to the address on the license. We make no exceptions. And we will not ship to customers known to have a distributor's license.

STEP 6

Methods of Delivery

We monitor for extreme weather conditions, and when the need arises, we ship overnight to maintain product efficacy. We also track patient need during life-threatening storms to make sure products are delivered when and where patients need them most.

STEP 7

Verification

In compliance with U.S. Drug Supply Chain Security Act (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.

STEP 8

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.

Up Front

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

Publisher: FFF Enterprises, Inc., 44000 Winchester Road, Temecula, CA 92590

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

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Far-Reaching Effects of the Pandemic

AT LONG last, COVID-19 appears to be changing from a pandemic to being endemic. Still, there is no question that our more than two-year ordeal has profoundly impacted the world and has cost millions of lives. Now, with the trend in vaccine uptake (75 percent, according to McKinsey & Company's Consumer Health Insights Survey conducted in February) and the ending of lockdowns, it might seem the impacts of the COVID-19 pandemic are coming to an end. But that would be far from reality. In fact, both positive and negative effects on society will be far-reaching, especially for healthcare. In this issue, we highlight three that are notable.

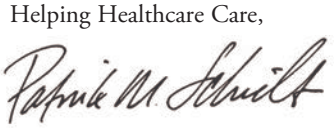
One negative outcome of the pandemic was created by the swift development of effective vaccines to prevent the SARS-CoV-2 virus, which initiated a societal divide between those who trusted the science behind the rushed vaccines and those who mistrusted it. What's more, the use of vaccine passports, which have been adopted in some areas and proposed in others, widened this divide. In our article "Vaccine Passports: Vaccination Confirmation or a Privacy Concern?" (p.16), we define vaccine passports, as well as discuss the views of proponents and opponents.

No matter the side individuals take in the vaccine passport debate, there's no question that the speed at which COVID-19 vaccines were developed was a monumental scientific achievement. According to McKinsey & Company's COVID-19: Implications for Business briefing note #98, "The effort to develop and distribute vaccines demonstrated how much can be achieved with global collaboration, lessons that can be applied to ambitious improvements in well-being." Of course, what made it possible to develop these first vaccines so quickly was mRNA technology. And, as we note in our article "The Promise of mRNA Vaccines for Disease Prevention" (p.22), while this technology was still in development, the pandemic served as the catalyst scientists needed to complete their research. Now, in addition to yielding COVID-19 vaccines, the technology is a viable method to produce novel vaccines for many deadly diseases, including influenza, shingles, cytomegalovirus, respiratory syncytial virus, Epstein-Barr virus, HIV and cancer.

Conversely, lockdowns put in place to curb the spread of the SARS-CoV-2 virus resulted in a host of negative consequences now being referred to as "immunity debt." As we explain in our article "Immunity Debt: A Catalyst for the Development of Infections and Autoimmune Disease?" (p.26), unprecedented reductions in routine care visits, as well as nonemergency community-acquired viral and bacterial infections, resulted in the loss of herd immunity, which could have repercussions for years to come. In fact, it is hypothesized that reduced and delayed infections may eventually result in higher incidences of autoimmune disease.

As always, we hope you enjoy the additional articles in this issue of *BioSupply Trends Quarterly*, and find them both relevant and helpful to your practice.

Helping Healthcare Care,



Patrick M. Schmidt
Publisher

biosupplytrends QUARTERLY

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

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How the No Surprises Act Protects Consumers

With the No Surprises Act that went into effect Jan. 1, new federal protections shield millions of consumers from surprise medical bills, which are unexpected bills from out-of-network providers, out-of-network facilities or out-of-network air ambulance providers. The protections ban surprise billing in private insurance for most emergency care and many instances of nonemergency care. They also require that uninsured and self-pay patients receive key information, including overviews of anticipated costs and details about their rights.

These protections will also promote competition in healthcare and other sectors of the American economy. "The No Surprises Act is the most critical consumer protection law since the Affordable Care Act," said Health and Human Services (HHS) Secretary Xavier Becerra. "After years of bipartisan effort, we are finally providing hardworking Americans with the federal guardrails needed to shield them from surprise medical bills. We are taking patients out of the middle of the food fight between insurers and providers and ensuring they aren't met with eye-popping, bankruptcy-inducing medical bills. This is the right thing to do, and it supports President Biden's vision of creating a more transparent, competitive and fair healthcare system."

A recent report from the HHS Office of the Assistant Secretary for Planning and Evaluation reviewed key evidence on surprise billing and the need for the consumer protections in the No Surprises Act. The report showed surprise billing is common among those with private insurance. Nearly one in five patients who go to the emergency room, have an elective surgery or give birth in a hospital receive surprise bills, with average costs ranging from $750 to $2,600 per episode.

For people who have health coverage through an employer, a Health Insurance Marketplace or an individual health plan purchased directly from an insurer, the rules took effect Jan. 1. These rules:

- Ban surprise bills any time emergency care is received, and require cost-sharing for these services such as co-pays that are always based on in-network rates, even when care is received without prior authorization.
- Ban surprise bills from certain out-of-network providers if an individual goes to an in-network hospital for a procedure. This means cost-sharing for certain additional services during the visit will generally be based on in-network rates.
- Require providers and facilities to share with patients easy-to-understand notices that explain the applicable billing protections and who to contact if they have concerns that a provider or facility has violated the new surprise billing protections.

For people who do not have health insurance or pay for care on their own (also known as "self-paying"), the rules that took effect Jan. 1 require most providers to give a "good faith estimate" of costs before providing nonemergency care. The good faith estimate must include expected charges for the primary item or service, as well as any other items or services that would reasonably be expected. For example, for an uninsured or self-pay consumer getting surgery, the estimate would include the cost of the surgery, as well as any labs, other tests and anesthesia that might be administered during the procedure. Uninsured or self-pay consumers who receive a final bill that exceeds the good faith estimate by $400 or more can dispute the final charges.

Both insured and uninsured/self-pay individuals who are concerned their rights have been violated now have access to a host of tools, including a help desk (available at 800-985-3059 from 8 a.m. to 8 p.m. EST seven days a week; TTY 800-985-3059) and webpage (CMS.gov/nosurprises), where more details on registering potential violations can be found. ❖

Bunis D. Biggest Medicare Changes for 2022. American Association of Retired Persons, Jan. 3, 2022. Accessed at www.aarp.org/health/medicare-insurance/info-2022/changes-in-2022.html.

HHS Provides More COVID-19 Relief Funds to Healthcare Providers

The Department of Health and Human Services (HHS) announced more than $413 million in Provider Relief Fund (PRF) payments to more than 3,600 providers across the country. This is the fourth round of PRF Phase 4 payments, totaling nearly $12 billion that has been distributed to more than 82,000 providers in all 50 states, Washington D.C. and five territories since November 2021. This is in addition to the Health Resources and Services Administration's (HRSA) distribution of American Rescue Plan (ARP) rural payments totaling nearly $7.5 billion in funding to more than 44,000 providers across the country over the past four months. "These funds have helped save lives throughout the pandemic," said HHS Secretary Xavier Becerra. "As we continue to make progress in

defeating COVID-19, it's important to keep supporting our providers with the resources they need so we can all build back better and healthier than before."

In September 2021, HHS opened applications for $25.5 billion in COVID-19 provider funding. With this latest installment, more than $19 billion of this funding has been awarded. Phase 4 payments reimburse smaller providers for a higher percentage of losses during the pandemic and include bonus payments for providers who serve Medicaid, Children's Health Insurance Program and Medicare beneficiaries.

PRF payments received in the first half of 2022 can be used until June 30, 2023. With these payments, approximately 89 percent of all Phase 4 applications have been processed. Remaining applications require additional manual review, and HRSA is working to process them as quickly as possible.

For additional information, visit www.hrsa.gov/provider-relief. ❖

HHS Distributing an Additional $413 Million in Provider Relief Fund Payments to Health Care Providers Impacted by the COVID-19 Pandemic. HHS.gov press release, March 22, 2022. Accessed at www.hhs.gov/about/news/2022/03/22/hhs-distributing-additional-413-million-provider-relief-fund-payments-health-care-providers-impacted-by-covid-19-pandemic.html.

HHS Expands Funding for Mental Health and Substance Use Services

The Department of Health and Human Services (HHS) through the Substance Abuse and Mental Health Services Administration (SAMHSA) announced two Certified Community Behavioral Health Clinics (CCBHCs) funding opportunities totaling $312 million over four years for up to 156 awards to expand and increase access to evidence-based mental health and substance use services for Americans. This includes providing essential mental health services such as 24-hour mobile crisis teams, screening and case management to vulnerable communities that would otherwise lack access to services.

The two CCBHC grant programs are:

- Planning, Development and Implementation grants will assist clinics to establish and implement new CCBHC programs.
- Improvement and Advancement grants will support existing CCBHCs to enhance and improve their programs.

"Over the past several years, CCBHCs have been instrumental in transforming behavioral healthcare in their respective communities," said Miriam Delphin-Rittmon, PhD, HHS, assistant secretary for mental health and substance use and the leader of SAMHSA. "But we know now that much more support is needed to ensure that everyone who needs help can access care when and where they seek it."

CCBHCs must meet federal standards for the range of services they provide, and they are required to get people into care quickly. An important feature of the CCBHC model is that it requires crisis services that are available 24 hours a day, seven days a week. CCBHCs must also provide routine outpatient care within 10 business days after an initial contact so people don't languish on waiting lists. Equally important, CCBHCs are required to serve anyone who requests care for mental health or substance use, regardless of their ability to pay, place of residence or age, including developmentally appropriate care for children and youth. ❖

HHS Announces Dramatic Increase in Funding to Expand the Availability of Certified Community Behavioral Health Clinics Across the Nation. U.S. Department of Health and Human Services press release, March 24, 2022. Accessed at www.hhs.gov/about/news/2022/03/24/hhs-announces-dramatic-increase-funding-expand-availability-certified-community-behavioral-health-clinics-across-nation.html?utm_source=news-releases-email&utm_medium=email&utm_campaign=march-27-2022.

Drug Vial Sizes, Waste and Recovering Costs

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

FOR SEVERAL years, payers and providers have discussed how to remedy the issue of unused or wasted drugs from single-use vials, but manufacturers have mainly stayed on the periphery. Some of the points raised include oversized vials with excess drug compared to common and usual doses, the lack of a variety of single-use vial sizes to better accommodate dosing, and manufacturers' reluctance to innovate these vial sizes after initial U.S. Food and Drug Administration (FDA) approval. What's more, frustration continues to grow since most of these medications already are available in other countries in vials containing smaller quantities.

How Single-Use Vials Are Billed

Many years ago, rather than allowing for the common practice of billing on an entire single-use vial, the Centers for Medicare and Medicaid Services (CMS) moved to mandatory billing for the actual dose administered expressed in billing units with a billing unit assigned to each product. This benefited patients who no longer were paying for the excess amount in the single-use container.

To accomplish this, each facility created or acquired from a vendor a crosswalk that linked the healthcare common procedure coding system (HCPCS) code/CMS assigned billing unit to the actual dose of the drug to calculate the number of billing units to be submitted. This allowed pharmacies to choose whatever type/size packaging they wanted to use and provided them flexibility in operating their IV rooms, used pooling or other methods of preparation. Other payers followed suit and since then, billing for an entire single-dose vial when the entire number of billing units in that vial totaled more than the actual dose was considered overbilling.

However, shortly thereafter, a barrage of complaints were filed by facilities, clinics, physician offices, etc., claiming they were being financially penalized either when there was only a single-use product available or they didn't have enough use to warrant a multidose container. The compromise was to allow the payer to bill for the unused remainder of the single-use labeled amount as waste (billing for overfills as waste is forbidden) with no impact for the patients who were not charged for the wasted amount.

Remember that CMS reimburses facilities for 80 percent of the payment, and patients (co-insurers) are responsible for 20 percent. Using that logic, CMS reimburses for 80 percent of the waste dollars, but patients are not charged a co-pay for waste.

The REFUND Act

Making the change to more appropriate-sized vials is easier said than done since each change to packaging and labeling, materials used, etc., needs to be reapproved by FDA, as does any rewording on a package insert.

Frustrated that no concrete action had been taken to make pharmaceutical manufacturers change the single-use vial size closer to usual patient doses, in 2019, U.S. Senators Dick Durbin (D-IL) and Rob Portman (R-Ohio) took action. They introduced a bipartisan bill designed to reduce egregious wasted spending on discarded medications that result from excessively large, single-use drug vials. This effort eventually progressed to the Recovering Excessive Funds for Unused and Needless Drugs (REFUND) Act of 2021, which requires drug manufacturers to issue rebates to CMS for discarded amounts (i.e., amounts remaining after administration) of single-dose vial drugs that are covered under Medicare. Manufacturers that fail to comply are subject to civil penalties. CMS must determine rebate amounts based on payment claims from providers. (Currently, providers may receive payment under Medicare for discarded amounts of single-dose vial drugs through the use of a specific claims modifier.)

Thereafter, the infrastructure bill (H.R.3684 — Infrastructure Investment and Jobs Act) that passed on Nov. 15, 2021, included a drug waste provision from the REFUND Act that requires manufacturers to rebate the amount wasted back to CMS effective Jan. 1, 2023. Specifically, this bill requires drug companies/manufacturers to reimburse Medicare for certain single-dose container/package drugs payable under Part B of the Medicare program for discarded amounts (leftover portions) of the drugs. Exclusions to this include 1) drugs or biologicals that are either radiopharmaceuticals or imaging agents; 2) drugs or biologicals

approved by FDA for which dosage and administration instructions included in the labeling require filtration during the drug preparation process, prior to dilution and during administration, and require any unused portion of such drugs after the filtration process be discarded after completing the filtration process; or 3) drugs or biologicals approved by FDA on or after the date of enactment of the provision for which payment has been made under the provision for fewer than 18 months.

Further provisions require the U.S. Department of Health and Human Services (HHS) to aggregate the total amount of discarded Part B drugs quarterly using Medicare Part B claims and calculate refunds using the average sales price (ASP) (or wholesale acquisition cost if ASP is not available). Drug manufacturers will be required to provide a rebate to HHS for the total amount of discarded medication recorded, above a 10 percent low-volume threshold. Noncompliance to provide a timely rebate could incur civil monetary penalties.

Complying with the REFUND Act

To ensure compliance with this Act, audits are a guarantee. Audits may be of the manufacturers' compliance, the accuracy of the aggregated amount calculated, comparisons of billed doses and billed wastage with the number of units sold, or any number of other methods to determine data accuracy and rule out fraud.

Therefore, facilities must review their waste billing programs. Many facilities may not have paid much attention to their programs since Medicare created billing for expensive waste in the outpatient prospective payment system shortly after switching to "billing units representing actual dose given" for reimbursement and away from the "whole vial" method of billing. While Medicare does not mandate billing for waste, it makes it possible to recoup lost dollars if a facility chooses to bill for it. To determine if a drug can be billed for waste, four questions must be answered: 1) Is the drug being used for a Medicare outpatient? 2) Is it a single-dose vial/package? 3) Does the product have an HCPCS code? 4) Only when the answer is yes to all these questions can the facility bill for waste. If any answer is no, then it cannot bill.

> While Medicare does not mandate billing for waste, it makes it possible to recoup lost dollars if a facility chooses to bill for it.

Facilities can avoid pitfalls by not creating an automatic bill situation that doesn't represent true actions. For example, if the vial contains 1 gram of the drug, and the infusion center uses 500 mg for each of two patients, nothing is wasted. But without carefully building this calculation into the system, the revenue cycle could assume two vials had been used and would erroneously process two waste charges, which would be fraudulent.

Zero-priced products (patient assistance and white bag/specialty pharmacy drugs) don't qualify for waste billing since there is no charge for these products. Staff must understand the difference, know when a zero-priced product is being used and use the correct line item on the order entry.

Additional Billing Tips

- Facilities must understand their systems and its limitations. For instance, a system can be set up so the computer will calculate the amount given and the amount wasted, but how does this information become a line item on the medication administration record for the nurse to chart the waste? And, how does this information get converted into a waste line item bill with the appropriate modifier that accompanies the drug line item bill so the two are charged together on the same day? Documentation must be in the patient charts; automated dispensing records or other internal pharmacy records aren't sufficient. Additionally, if facilities charge for a drug that is automatically dispensed from a cabinet, a system must be set up to consistently chart it in the medical record.
- Facilities must pay attention to revenue cycle orientation. Waste billing means there are two lines of billing for the same patient on the same day with the waste identified by the JW modifier. Consequently, the hard stops built into many of the revenue cycle processes that prevent this from happening must be adjusted. ❖

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.

Implementing Personal Touch in the Healthcare Environment

By Ronale Tucker Rhodes, MS

HEALTHCARE PROFESSIONALS (HCPs) must have the right technical skills, medical knowledge and experience, but they are also expected to be empathetic, compassionate and trustworthy. Sadly, empathy may be eroding in the medical profession under the pressures of stress-inducing factors such as time demands and bureaucracy, not to mention the added weight of the COVID-19 pandemic that has impacted many physicians' bedside manner. But as researchers of a study that examined changes in medical students' empathy during medical school explain, "Medicine at its core is a human service profession. Cultivating humanistic values in general and enhancing interpersonal skills and empathy in particular are of paramount importance in any human service endeavor."[1]

So, how can facilities improve the HCP-patient experience? One way is by implementing patient-centered care with a personal touch.

What Patients Want

When patients experience the complex emotions associated with their healthcare needs, what they need most is compassionate, personalized care from a person who is concerned about and understands their unique situation. In fact, research shows that despite the technical quality of care delivered, provider empathy is the main indicator of whether a patient will be satisfied. Patients also perceive empathic care as technically better than less personal care.

A survey published in the *New England Journal of Medicine* showed 59 percent of patients reported that face-to-face time with their providers increased their engagement and satisfaction. Another study, published in *JAMA Internal Medicine*, showed patients reported more satisfaction when providers took a minute to look away from their computers during patient visits. A total of 48 percent of patients in an encounter with high computer usage reported high satisfaction scores, while 81 percent of patients in an encounter with low computer usage reported the same scores.[2]

In the 2020 Deloitte Survey of U.S. Health Care Consumers, the top four factors determining "an ideal healthcare experience," which mirrored findings in a similar study on consumer priorities in 2016, were as follows:[3]

- 44 percent: Providers who listen to me and show they care about me
- 42 percent: Providers who spend time with me and do not rush through the exam
- 39 percent: Providers who clearly explain what they are doing during the exam and what I need to do after the visit
- 25 percent: Providers who communicate with each other and coordinate treatment

Challenges in the Healthcare Setting

The first step to improving the HCP-patient relationship is gaining a thorough understanding of the day-to-day challenges healthcare professionals face.

Today, HCPs feel pressured to forgo the "human" aspect of interactions and focus solely on meeting the physical needs of the patient in quick, efficient interactions. Despite their appreciation of the roller coaster of emotions patients experience, which is why they do their jobs (to make a positive difference in patients' lives), HCPs are overworked and underpaid in an industry that's underfunded and overused (some would even say abused). Worse, they are often pushed to the limits of their coping skills, as we have seen throughout the COVID-19 pandemic.[4]

Other factors they face today that impact the HCP-patient relationship include caring for the growing number of chronically ill patients; managing patients with anxiety, depression and mental illness; keeping up with technology and its costs; using technology to engage patients; and getting paid what they're worth as payment models shift from fee-for-service to pay-for-performance.[5]

Changes That Can Make a Difference: Modeling Other Programs

Communication and organizational culture play key roles in providing HCPs with the tools they need to improve the way they interact with patients.

One study published in the *American Journal of Medical Quality* examined a hospital-wide communication training program outlining best practices for doctors to follow in interactions with patients. The

study found that by implementing the training program, the percentage of patients who "always" felt doctors carefully listened to them, treated them with respect and courtesy, and explained things in a way they could understand improved by 9 percent. Communication practices provided to the doctors included:[6]

- Basic courtesies such as knocking prior to entering exam rooms, closing door/curtain to ensure privacy, washing hands after entering the room, muting the TV, shaking hands with patients, sitting at eye level with patients, introducing team members to patients and family members, asking open-ended questions and more
- A format for bedside discussions that included getting observations from patients (e.g., pain levels, symptoms), checking patients' vital signs and reporting relevant results of any exams or tests taken, and summarizing patients' major health problems, their statuses (stable/improving/worsening) and treatment plans
- Summarizing findings and treatment plans in simple language, including the reason for their hospital admission, the plan for the day and when patients will come in again
- Scripted questions to ensure patients don't have any questions or concerns about managing their condition or following their treatment plans

Equally if not more impressive is The Sharp Experience. In 1998, Sonia Rhodes, an executive at Sharp HealthCare where her father was being treated, "became an aggressive advocate for improving the patient experience — not the medical treatment, which was top-notch, but the service experience." Working with a team of executives, they agreed on "The Sharp Experience: Creating the best place for employees to work, for physicians to practice and for patients to receive care — and ultimately the best healthcare system in the universe." Seven years later, Sharp hospitals' unit patient satisfaction scores increased in the national percentile rankings from as low as the teens to as high as the 90s. Physician satisfaction rose to the 80th percentile, employee satisfaction rose by 13 percent, turnover declined by 14 percent and net revenue increased by a half-billion dollars.

Today, The Sharp Experience consists of five elements: AIDET, behavior standards, five must-haves, leadership tools and pillars of excellence.

AIDET provides a framework for Sharp's staff to communicate with patients and their families, as well as with each other. The acronym stands for Acknowledge: Greet people with a smile and use their names if you know them; Introduce: Introduce yourself to others politely, tell them who you are and how you are going to help them, and escort people where they need to go rather than pointing or giving directions; Duration: Keep in touch to ease waiting times, and let others know if there is a delay and how long it will be; Explanation: Advise others what you are doing, how procedures work and whom to contact if they need assistance, and communicate any steps they may need to take; Thank you: Foster an attitude of gratitude. Thank people for their patronage, help or assistance.

The 12 behavior standards — attitude is everything; reward and recognition; courteous communication; teamwork; service recovery; zero harm; appearance matters; service excellence; privacy and confidentiality; electronic communication matters; mutual respect; and diversity — provide a clear and simple description of exactly what is expected of every Sharp employee.

To ensure Sharp HealthCare is the best place to work, the best place to practice medicine and the best place to receive care, employees must exemplify the must-haves, five essential behaviors and actions in the workplace: 1) Greet people with a smile and "Hello," using their name when possible; 2) Take people where they are going, rather than point or give directions; 3) Use key words at key times: "Is there anything else I can do for you? I have the time."; 4) Foster an attitude of gratitude. Send thank-you notes to deserving employees; and 5) Round with reason to better connect with staff, patients, family and other customers.

The leadership tools are designed to inspire employees to stage their own meaningful experiences for their customers. And, lastly, the pillars of excellence — quality, safety, service, people, finance, growth, community — are the foundation to transform the healthcare experience.

Benefits of Personal Touch

Without a doubt, there are many challenges that can prevent unique HCP-patient experiences. But, by following the direction of others who have managed to overcome those challenges, gratification is likely to be gained by both HCPs and their patients. ❖

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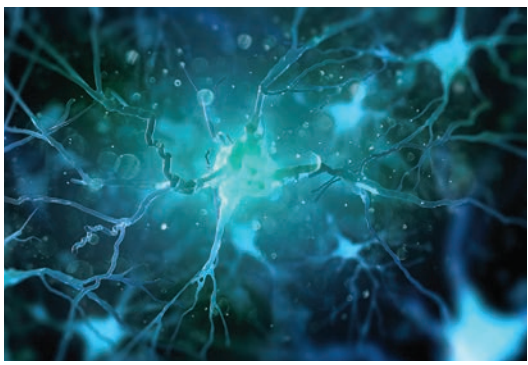
Medicines

FDA Approves Argenx's Vyvgart to Treat MG



The U.S. Food and Drug Administration (FDA) has approved Vyvgart (efgartigimod) to treat generalized myasthenia gravis (gMG) in adults who test positive for the anti-acetylcholine receptor (AChR) antibody. In MG, the immune system produces AChR antibodies that interfere with communication between nerves and muscles, resulting in weakness. Severe attacks of weakness can cause breathing and swallowing problems that can be life-threatening.

Vyvgart is the first approval of a new class of medication. It is an antibody fragment that binds to the neonatal Fc receptor (FcRn), preventing FcRn from recycling immunoglobulin G (IgG) back into the blood. The medication causes a reduction in overall levels of IgG, including the abnormal AChR antibodies present in MG.

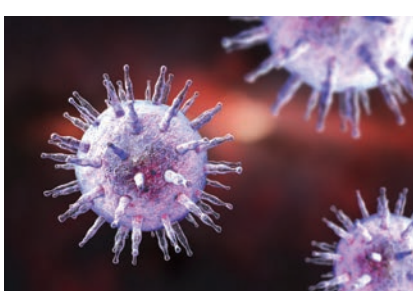
The safety and efficacy of Vyvgart were evaluated in a 26-week clinical study of 167 patients with MG who were randomized to receive either Vyvgart or placebo. The study showed that more patients with MG with antibodies responded to treatment during the first cycle of Vyvgart (68 percent) compared to those who received placebo (30 percent) on a measure that assesses the impact of MG on daily function. More patients receiving Vyvgart also demonstrated response on a measure of muscle weakness compared to placebo.

The most common side effects associated with the use of Vyvgart include respiratory tract infections, headache and urinary tract infections. Since Vyvgart causes a reduction in IgG levels, the risk of infections may increase. Hypersensitivity reactions such as eyelid swelling, shortness of breath and rash have occurred. ❖

FDA Approves New Treatment for Myasthenia Gravis. U.S. Food and Drug Administration press release, Dec. 17, 2021. Accessed at www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-myasthenia-gravis.

Research

Virus Identified as Cause of Multiple Sclerosis



A new study shows the Epstein-Barr virus (EBV) is essential for the development of multiple sclerosis (MS), although not all individuals who have EBV develop MS. According to this study, the risk of MS infection increased 32-fold after EBV infection, but remained unchanged after infection with other viruses.

"The hypothesis that EBV causes MS has been investigated by our group and others for several years, but this is the first study providing compelling evidence of causality," said Alberto Ascherio, MD, DrPH, professor of epidemiology and nutrition at Harvard Chan School and senior author of the study. "This is a big step because it suggests that most MS cases could be prevented by stopping EBV infection, and that targeting EBV could lead to the discovery of a cure for MS."

In the study, the researchers analyzed serum samples taken biennially by the military and determined the soldiers' EBV status at time of first sample and the relationship between EBV infection and MS onset during the period of active duty. In this cohort, the risk of MS increased 32-fold after infection with EBV but was unchanged after infection with other viruses. Serum levels of neurofilament light chain, a biomarker of the nerve degeneration typical in MS, increased only after EBV infection. The findings cannot be explained by any known risk factor for MS and suggest EBV as the leading cause of MS.

According to Dr. Ascherio, the delay between EBV infection and the onset of MS may be partially due to the disease's symptoms being undetected during the earliest stages and partially due to the evolving relationship between EBV and the host's immune system, which is repeatedly stimulated whenever latent virus reactivates.

The discovery raises hopes for the future development of a cure for MS, which affects nearly 2.8 million people worldwide. "Currently there is no way to effectively prevent or treat EBV infection, but an EBV vaccine or targeting the virus with EBV-specific antiviral drugs could ultimately prevent or cure MS," said Dr. Ascherio.

Moderna recently announced it had begun clinical trials in humans for a vaccine against EBV. ❖

Epstein-Barr Virus May Be Leading Cause of Multiple Sclerosis. Harvard T.H. Chan School of Public Health press release, Jan. 13, 2022. Accessed at www.hsph.harvard.edu/news/press-releases/epstein-barr-virus-may-be-leading-cause-of-multiple-sclerosis.

Medicines

New Drug Approved by FDA to Treat Eczema

AbbVie's Rinvoq and Pfizer's Cibinqo have been approved by the U.S. Food and Drug Administration (FDA) to treat moderate-to-severe atopic dermatitis, or eczema, in patients who do not respond to previous treatment or when use of other treatments is not recommended. Rinvoq's approval was expanded from rheumatoid arthritis to treat eczema for patients 12 years and older, while Cibinqo was approved for use in only adults.

Both drugs belong to a class called JAK inhibitors, which block inflammation-causing enzymes known as Janus kinases and target a range of autoimmune diseases. FDA in December added its strictest warning to labels of JAK inhibitor drugs from Pfizer, Eli Lilly and AbbVie following a review of Pfizer's Xeljanz, another JAK inhibitor. Both Pfizer and AbbVie cited risks of serious infections and cardiovascular events, among others. The expanded approval for Rinvoq follows significant delays amid concerns over safety. Initial results from a trial of Cibinqo showed an increased risk of serious heart-related problems and cancer in some patients being treated with the drug. ❖

U.S. FDA Approves Drugs from AbbVie, Pfizer to Treat Eczema. Reuters, Jan. 14, 2022. Accessed at financialpost.com/pmn/business-pmn/u-s-fda-approves-drugs-from-abbvie-pfizer-to-treat-eczema.

Research

Scientists Are Developing Cheaper, Patent-Free and Easier-to-Make COVID Vaccine

Researchers at the Texas Children's Hospital Center for Vaccine Development at Baylor College of Medicine are developing a COVID-19 vaccine using a conventional method that will make the production and distribution cheaper and more accessible for countries most affected by the pandemic and where new variants are likely to originate due to low inoculation rates. The team, led by Peter Hotez, MD, PhD, and Maria Bottazzi, PhD, has been developing vaccine prototypes for SARS and MERS since 2011, which they reconstructed to create the new COVID vaccine, dubbed Corbevax, or "the world's COVID-19 vaccine." And, while more than 60 other vaccines are in development using the same technology, Dr. Bottazzi said their vaccine is unique because they do not intend to patent it, allowing anyone with the capacity to reproduce it.

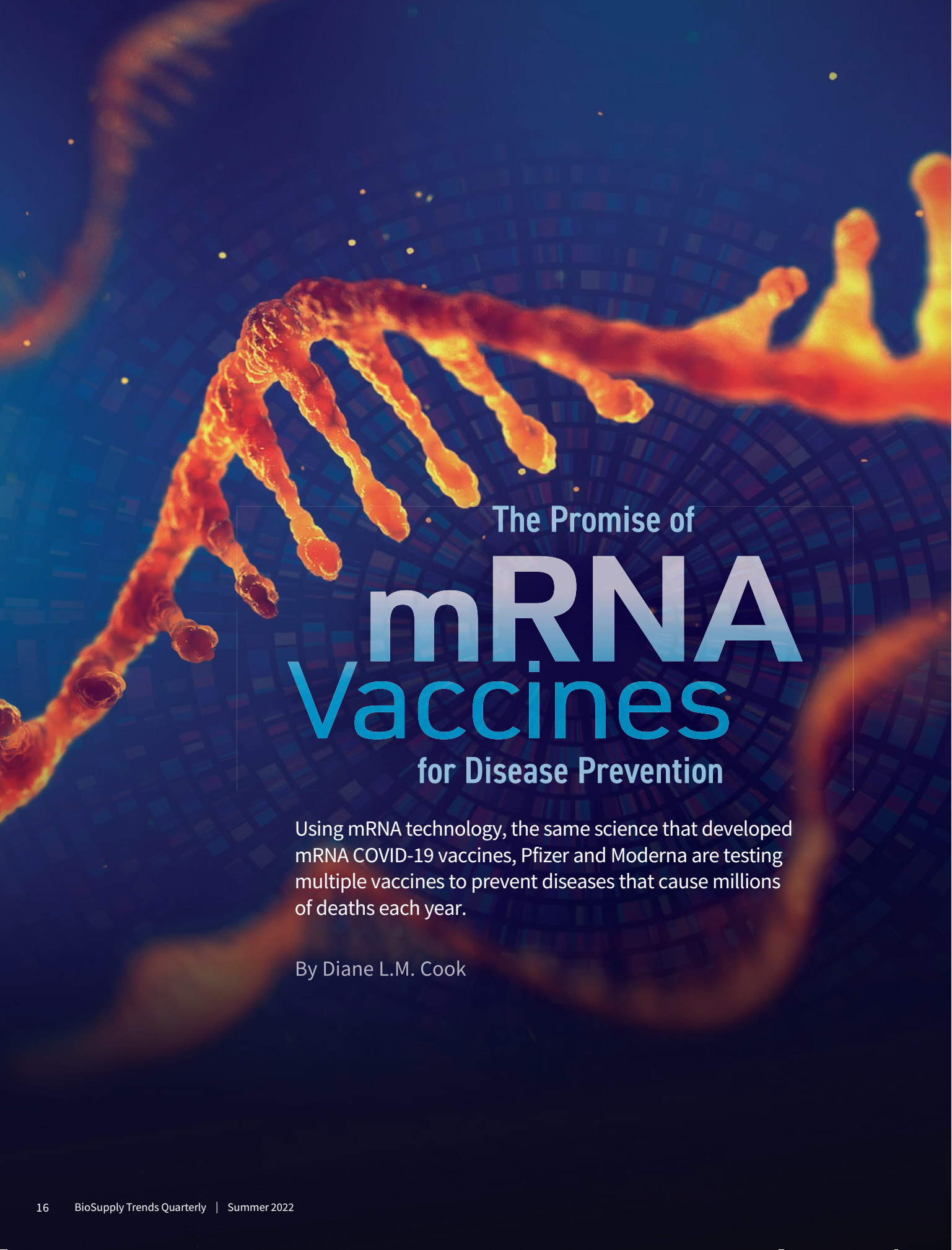
Corbevax's clinical trial data has yet to be released due to resource constraints, but Texas Children's hospital said the vaccine was more than 90 percent effective against the original COVID-19 strain and more than 80 percent effective against the Delta variant. The vaccine's efficacy against the Omicron variant is currently being tested.

The process to create the vaccine involves the use of yeast, called recombinant protein sub-unit technology, which places an actual piece of COVID-19's spike protein in yeast cells. The yeast cells then copy the vital protein and the protein is introduced to the immune system. This is the same method by which hepatitis B vaccines are produced. "Pretty much anybody that can make hepatitis B vaccines or has the capacity to produce microbial-based protein-like bacteria or yeast, can replicate what we do," Dr. Bottazzi said. In contrast, the Moderna, Pfizer and Johnson & Johnson vaccines currently authorized in the U.S. use different technologies that are not shared with other companies. Crucially, storing the Corbevax vaccine only requires standard refrigeration, unlike the Pfizer vaccine, which requires ultra-cold storage in transit.

According to Dr. Bottazzi, the reason she and her team did not patent the vaccine was because of her team's shared philosophy of humanitarianism and to engage in collaboration with the wider scientific community: "We want to do good in the world. This was the right thing to do, and this is what we morally had to do. We didn't even blink. We didn't think, 'how can we take advantage of this?' You see now that if more like us would have been more attuned to how the world is so inequitable and how we could have helped from the beginning so many places around the world without thinking 'what's going to be in it for me?' we could have basically not even seen these variants arise."

Dr. Bottazzi hopes her move will incentivize others to follow suit and make affordable and accessible vaccines for other diseases and viruses such as hookworm. ❖

Salam E. Texas Scientists' New Covid-19 Vaccine Is Cheaper, Easier to Make and Patent-Free. Yahoo!News, Jan. 15, 2022. Accessed at news.yahoo.com/texas-scientists-covid-19-vaccine-100019383.html.



The Promise of mRNA Vaccines for Disease Prevention

Using mRNA technology, the same science that developed mRNA COVID-19 vaccines, Pfizer and Moderna are testing multiple vaccines to prevent diseases that cause millions of deaths each year.

By Diane L.M. Cook

THE COVID-19 PANDEMIC was the catalyst scientists needed to complete their messenger Ribonucleic Acid (mRNA) research to develop the first mRNA-based vaccine. Now, vaccine manufacturers are using this new technology to produce novel vaccines for disease prevention of respiratory, tropical and latent viruses — and potentially cancer.

mRNA Vaccine Technology

Messenger RNA, also known as mRNA, is one of the types of RNA found in a cell. Like most RNA, it is made in the nucleus and then exported to the cytoplasm where the translation machinery, the machinery that makes proteins, binds to these mRNA molecules and reads the code on the mRNA to make a specific protein. In essence, the DNA for one gene can be transcribed into an mRNA molecule that will make one specific protein.[1]

mRNA vaccines instruct the body to produce specific antigens called spike proteins that look physically similar to those of viruses. The antigens trigger the body's immune system to create specific antibodies that fight off the real viruses should a body become exposed to them.

Research surrounding mRNA began decades ago, between 1947 and 1961, by several scientists around the world, separately but simultaneously.[2] However, mRNA research plateaued for approximately 30 years because it was unstable and caused a harmful inflammatory immune response. In 1994, James Eberwine, PhD, and his colleagues, were the first to "transfect" RNA into cells when they put RNA into a region of a neuron to determine what the protein made from that RNA did in that region. According to Dr. Eberwine, "We saw that if you put the RNA from cell A into cell B, then cell B will become cell A. RNA and mRNAs have a figurative cellular memory and a literal transformational quality."

Then, in 2005, Drew Weissman, MD, PhD, and Katalin Kariko, PhD, made a breakthrough in their mRNA research. They altered one of mRNA's four building blocks, known as nucleosides, and discovered that their modified synthetic mRNA no longer caused inflammation. This discovery solved the instability and inflammation challenges and allowed the mRNA research to continue. "mRNA vaccines are essentially plug and play," explained Dr. Weissman. "We believe you can change the part of the mRNA that encodes a protein, plugging in new code specific to the virus we hope to protect against, and cause one's body to produce proteins that match that virus' proteins. We do not have to develop and manufacture an entirely new formula."[3]

Pfizer and Moderna were the first vaccine manufacturers to utilize this novel mRNA vaccine technology to develop mRNA-based vaccines, both of which are COVID-19 vaccines.

Pfizer and Moderna were the first vaccine manufacturers to utilize this novel mRNA vaccine technology to develop mRNA-based vaccines, both of which are COVID-19 vaccines. Initially recognized in Wuhan, China, in December 2019, China released the genome sequence for the SARS-CoV-2 virus on Jan. 11, 2020. Moderna then used this genome sequence to develop its COVID-19 vaccine (Spikevax) within two days, and Pfizer and BioNTech announced their partnership in March 2020 to develop their COVID-19 vaccine (Comirnaty), which moved into Phase I clinical trials by May 2020.[4]

Now that the first mRNA-based COVID-19 vaccines have been in use for more than a year, Pfizer and Moderna are moving forward with developing other mRNA-based vaccines for several well-known viruses.

Pfizer

Pfizer Inc., an American multinational pharmaceutical and biotechnology corporation, develops and produces vaccines for diseases using many technological platforms. Currently, Pfizer is developing two new mRNA-based vaccines and is investigating lipid nanoparticle (LPN) formulation technology for vaccine development.

In partnership with BioNTech, Pfizer was the first vaccine manufacturer to enter the marketplace with an mRNA-based COVID-19 vaccine, BNT162b2 (Comirnaty), to prevent infection with the SARS-CoV2 virus. Their COVID-19 vaccine received emergency use authorization from the U.S. Food and Drug Administration (FDA) on Dec. 11, 2020, and it received full approval on Aug. 23, 2021.[5]

In September 2021, Pfizer also started a Phase I study to evaluate the safety, tolerability and immunogenicity of an mRNA vaccine to prevent influenza. The trial included 615 healthy adults aged 65 years to 85 years old, with an FDA-approved standard quadrivalent influenza vaccine as a control. The completion date for this study is estimated to be July 26, 2022.[6]

In January 2022, Pfizer and BioNTech partnered to research, develop and commercialize a potential first mRNA-based shingles vaccine. Shingles is caused

by the varicella zoster virus (VZV), the virus that causes chicken pox. VZV is a latent virus that can reactivate later in life, causing shingles. Adults aged 50 years and older, as well as vulnerable populations such as cancer patients, are at an increased risk of shingles, a debilitating, disfiguring and painful disease that impacts approximately one in three people in the United States. Pfizer and BioNTech's clinical trials for its mRNA-based shingles vaccine are set to start in the second half of 2022. According to Pfizer, while there are currently approved vaccines for shingles, there is an opportunity to develop an improved vaccine that potentially shows high efficacy and better tolerability and is more efficient to produce globally by utilizing mRNA technology."[7]

Also in January 2022, Pfizer announced its agreement with Acuitas Therapeutics that will expand its access to LPN formulation technology for up to 10 targets for vaccine or therapeutic development, which offers a strong strategic fit with Pfizer's mRNA strategy to develop potential new breakthrough vaccines. Acuitas' mRNA-LNP technology is used in Pfizer's COVID-19 vaccine.[8]

Moderna

Moderna Inc., an American pharmaceutical biotechnology company, is focused on developing RNA therapeutics, primarily mRNA vaccines and therapies spanning several therapeutic areas.

Cytomegalovirus (CMV), a type of herpes virus that usually produces very mild symptoms in an infected person, may cause severe neurological damage in people with weakened immune systems and newborns. CMV is a latent virus that remains in the body for life after infection. The Centers for Disease Control and Prevention (CDC) estimates more than half of adults have been infected with CMV by age 40.[9] In addition, CMV is the most common infectious cause of birth defects in the United States. CDC estimates about one out of every 200 babies is born with congenital CMV and approximately one out of five of these babies will have long-term health problems such as hearing loss, intellectual disability, vision loss, seizures and lack of coordination or weakness.[10]

Moderna's vaccine candidate, CMV mRNA-1647, combines six mRNAs in one vaccine that encode for two proteins located on the surface of CMV: five mRNAs encoding the subunits that form the membrane-bound pentamer complex and one mRNA encoding the full-length membrane-bound glycoprotein B (gB). Both the pentamer and gB are essential for CMV to infect barrier epithelial surfaces and gain access to the body, which is the first step in CMV infection. The vaccine is designed to produce an immune response against both the pentamer and gB to prevent CMV infection. Moderna believes a vaccine that protects women from CMV infection should protect against congenital CMV infection. Currently, there is no approved CMV vaccine.

The Phase I and II studies of CMV mRNA-1647 vaccine demonstrated functional antigen-specific responses that support the vaccine's potential to prevent CMV infection. Interim seven-month data from the Phase II study at 50 ug, 100 ug and 150 ug dose levels showed the vaccine was generally well-tolerated. The most common local adverse reaction was injection site pain, and the most common systemic adverse reactions were headache, fatigue, myalgia, arthralgia and chills. Based on the interim analysis of the Phase II study, the 100 ug dose was chosen for the Phase III study.

Moderna is currently recruiting participants for its Phase III study, known as CMVictory, to evaluate the safety and efficacy of the CMV mRNA-1647 vaccine against primary CMV infection in women aged 16 years to 40 years old. This study is anticipated to enroll up to 8,000 participants, including 6,900 women of child-bearing age, from approximately 150 global sites beginning in the United States. The U.S. demographic will include 58 percent white women and 42 percent persons of color.[11]

Respiratory syncytial virus (RSV) is one of the most widespread respiratory viruses in young children and older adults in the United States. In children younger than 1 year old, RSV is the most common cause of bronchiolitis and pneumonia. In older adults, RSV can result in pneumonia and respiratory distress. There is currently no approved vaccine for RSV.

Moderna's vaccine candidate, RSV mRNA-1345, encodes for a stabilized profusion F glycoprotein that elicits a superior neutralizing antibody response compared to the postfusion state. This vaccine candidate uses the same LNP as Moderna's COVID-19 vaccine and contains optimized protein and codon sequences.

The Phase I study of RSV mRNA-1345 enrolled participants aged 65 years to 79 years. Results released in September 2021 showed neutralizing antibodies were confirmed to be present at baseline in all participants and that a single vaccine of 50 ug, 100 ug or 200 ug boosted neutralizing antibody titers against RSV-A by approximately 14-fold and against RSV-B by approximately 10-fold. In addition, it was well-tolerated in older adults through the first month.

The Phase II/III study, known as ConquerRSV, commenced in November 2021 and expects to enroll approximately 34,000 participants. Conducted in multiple countries with locations selected by RSV epidemiology, the primary purpose of the Phase II study is to evaluate the safety of the RSV mRNA-1345 vaccine in adults older than 60 years of age for initiation

of the large-scale Phase III study.[12] In February 2022, the National Institute of Allergy and Infectious Diseases' Data and Safety Monitoring Board endorsed the start of the Phase III study after an independent review of preliminary Phase II data, which suggests the vaccine has an acceptable safety profile in older adults at the selected dose. The primary purpose of the Phase III study is to establish the safety and efficacy of the vaccine in support of licensure. According to a Moderna spokesperson, "An mRNA vaccine against RSV could have a positive impact on individuals, communities and global public health. Our ultimate goal is to combine our RSV vaccine with our COVID-19 and flu boosters into a single-dose booster."[13]

Epstein-Barr virus (EBV) is a member of the herpes virus family, which includes CMV, herpes simplex virus (HSV) and VZV. EBV is a major cause of infectious mononucleosis and can lead to lifelong medical conditions. It is also associated with an increased risk of developing multiple sclerosis, certain lymphoproliferative disorders, cancers, autoimmune diseases and long COVID. Currently, there is no approved vaccine to prevent EBV.

Moderna's EBV mRNA-1189 vaccine candidate contains four mRNAs that encode EBV envelope glycoproteins — gH, gL, gp42 and gp220 — that mediate viral entry into B cells and epithelial surface cells, the major targets of EBV infection. In January 2022, Moderna dosed its first participant in its Eclipse study, which will be conducted at 15 sites in the United States and will enroll 270 participants. The primary purpose of the study is to assess the safety and tolerability of the EBV mRNA-1189 vaccine candidate in healthy adults aged 18 years to 30 years. The study aims to demonstrate whether the vaccine has the potential to induce protection from both cell types — inhibiting viral entry into B cells and epithelial cells.[14]

Also in January 2022, Moderna, and its partner IAVI — a nonprofit scientific research organization dedicated to addressing urgent, unmet global health challenges, including HIV, tuberculosis and emerging infectious diseases — announced first doses were administered in a Phase I clinical trial of its experimental mRNA-based HIV vaccine. The Phase I trial, IAVI G002, will test the hypothesis that sequential administration of priming and boosting HIV immunogens delivered by mRNA can induce specific classes of B-cell responses and guide their early maturation toward broadly neutralizing antibody (bnAb) development. The induction of bnAbs is widely considered to be a goal of HIV vaccination, and this is the first step in that process. The immunogens being tested in IAVI G002 were developed by scientific teams at IAVI and Scripps Research and will be delivered via Moderna's mRNA technology. The primary purpose of the Phase I trial is to build on the response seen in a proof-of-concept trial. Participants will be monitored for safety for six months after their last vaccination. Participants' immune responses to the vaccine candidates will then be examined in molecular detail to evaluate whether the targeted responses were achieved.[15]

Under Moderna's intra-tumoral immune-oncology program, the company has two investigational cancer vaccines currently in clinical trials. These vaccines are designed to stimulate a patient's immune system with antigens derived from tumor-specific mutations to enable the immune system to elicit a more effective anti-tumor response. Through next-generation sequencing, the mRNA-based personalized cancer vaccines have the potential to direct a patient's cells to express the selected neoepitopes (mutations found on a patient's cancer cells) that might help a patient's immune system better recognize cancer cells as foreign and destroy them. Using algorithms developed by its in-house bioinformatics team, Moderna predicts 20 neoepitopes present on a patient's cancer should elicit the strongest immune response based on unique characteristics of a patient's immune system and the cancer's particular mutations.

In January 2022, Pfizer and BioNTech partnered to research, develop and commercialize a potential first mRNA-based shingles vaccine.

The randomized, placebo-controlled Phase II study investigating a 1 mg dose of the mRNA-4157 vaccine in combination with Merck's pembrolizumab (KEYTRUDA), compared to pembrolizumab alone, for the adjuvant treatment of high-risk resected melanoma is fully enrolled. The primary endpoint of the Phase II study is recurrence-free survival at 12 months. Moderna expects the Phase II data results in the fourth quarter of 2022. The Phase I study in multiple cohorts is ongoing, including in the expanded head and neck cohort.[16]

Moderna's mRNA-2752 vaccine candidate is currently in a Phase I study to evaluate it as a single agent in patients with advanced solid tumor malignancies and lymphoma. Enrollment in additional cohorts is ongoing. Interim data from the ongoing Phase I study showed mRNA-2752 in combination with AstraZeneca's durvalumab (IMFINZI) was tolerated at all dose levels tested and elicited evidence

of anti-tumor activity.[17]

In February 2022, Moderna announced it is expanding its mRNA-based vaccine pipeline with three new development programs: mRNA-1608 vaccine candidate for HSV, mRNA-1468 vaccine candidate for VZV and mRNA-4359, a new checkpoint cancer vaccine to explore initial indications for advanced or metastatic cutaneous melanoma and non-small cell lung carcinoma.[18]

cycles. We create our mRNA vaccines and mRNA therapeutics using the same, cell-free manufacturing processes and facilities. Other benefits include low fixed costs and flexible resource allocation."

Moderna also believes the potential implications of using mRNA as a drug are significant and far-reaching and could meaningfully improve how medicines are discovered, developed and manufactured: "For Moderna, priority one is our pan-respiratory annual single-dose booster vaccine. Respiratory viruses are a major cause of mortality worldwide, with an estimated 2.7 million deaths in 2015, and many more millions hospitalized and sick at home. Building on our continued focus on mRNA-1273, our COVID-19 vaccine, we want to prevent people who are at high risk — 50 years of age and older, healthcare workers and the immunocompromised — from being hospitalized due to respiratory infection. We will not stop until that goal is achieved."

Priority two for Moderna is to go after the most impactful latent viruses and develop first-in-class vaccines against them: "We want to protect our fellow human beings from suffering from the long-term damage caused by these viruses. Too many people have the quality of their health impacted because, decades before, they were infected with a latent virus. We envision a world where vaccines against all the most important latent viruses are available to all." ❖

Under Moderna's intra-tumoral immune-oncology program, the company has two investigational cancer vaccines currently in clinical trials.

A New Vaccine Landscape

Although the mRNA-based vaccine technology is still novel, the research behind the science has existed for several decades and shows great promise for disease prevention. Both Pfizer and Moderna are excited about this new vaccine landscape — with its multiple benefits over traditional vaccine technology — that they believe could prevent diseases, as well as reduce suffering and death around the world.

According to Pfizer, "mRNA-based influenza vaccine design requires only the genetic sequence of the virus. The flexibility of mRNA technology and its rapid manufacturing could potentially allow better strain match, greater reliability of supply and the potential opportunity to improve upon the efficacy of current flu vaccines. Furthermore, in a pandemic influenza situation, mRNA technology could allow rapid, large-scale manufacturing of effective vaccines."[19]

According to Moderna, "mRNA provides many competitive advantages to other methods of vaccine development. For one, it allows for accelerated research and development timelines and rapid iteration

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Vaccine Passports:

Vaccination Confirmation or a Privacy Concern?

The implementation of vaccine passports in response to the COVID-19 pandemic has raised arguments for and against them.

By Meredith Whitmore

IF TWO-PLUS years of a pandemic have reinforced old adages, one standout would be that you can't please all people all the time. A clear example of this is Americans' reactions to the COVID-19 vaccine and the much-publicized topic of vaccine "passports." Rifts between groups for and against the vaccines and passports are such a point of contention that factions now belittle one another. A particularly vocal writer said in one article, "I too want to eat in a restaurant, away from the unvaccinated. But to be honest, it's not just because I don't want to get sick. It's because I despise them — whoever they are — the sans-papiers. I am not proud of this."[1]

A polarizing perspective is clearly unhelpful. However, insight and wisdom can come from examining the main issues: public health, civil liberties and privacy.

Defining a Vaccine Passport

First, it's helpful to understand what a vaccine passport is — or what it could be. With no national standard, states and companies are implementing their own rules to identify those who are vaccinated, and definitions seem fast and loose as authorities stumble toward a solution. This is particularly true with regard to international tourism. As infectious disease specialist Scott Weisenberg, MD, states, "Right now, the definition [of vaccine passport] that matters is the definition of the person in front of you helping you go through immigration."[2]

In generally accepted terms, vaccine passports are a form of identifying whether a person has been vaccinated against or tested negative for COVID-19 and, therefore, may enter businesses, attend cultural events or access public venues that require such proof. A passport could be similar to a phone app, a small paper card, a smart card or something else. Many businesses and even U.S. and international cities require some form of identification already.[3]

Vaccine passports do (sort of) have a history. Schoolchildren are required to show proof of vaccination for classes and activities. People who travel overseas are sometimes mandated to bring a medical passport, otherwise known as the Yellow Card, created by the World Health Organization (WHO). For example, multiple countries in Africa and South America require this card to ensure the safety of international travelers, as well as nationals, against yellow fever.

Most people agree some type of safety measure is necessary to prevent COVID-19 transmission, but few agree on what that measure should be. For many, the global vaccine passport movement has seemed ominous and monumental enough to spark fear, division and confusion. And, perhaps, these reactions

are to be expected. After all, information, misinformation and no information are common frustrations for physicians and the general public.[4,5,6]

Passports Already Established

In December 2021, former New York City Mayor Bill de Blasio announced the Key to NYC Pass, a vaccine ID to grant New Yorkers access to various businesses. "This approach is going to make clear that: You want to enjoy everything great in the summer of New York City? Go get vaccinated. When you hear those words, I want you to imagine the notion that because someone's vaccinated, they can do all the amazing things that are available in the city," said de Blasio. "If you're unvaccinated, unfortunately, you will not be able to participate in many things. That's the point we're trying to get across. It's time for people to see vaccination as literally necessary to living a good, full and healthy life." de Blasio is also a proponent of New York State's Excelsior Pass, a free, voluntary platform that provides secure, digital proof of COVID-19 vaccination or negative test results.[7]

Most people agree some type of safety measure is necessary to prevent COVID-19 transmission, but few agree on what that measure should be.

From a proponent's perspective, de Blasio's statement is a matter of life, quality of life and death. From an opponent's perspective, it more or less boils things down to being vaccinated or being denied a fuller life. It feels like coercion. So where is the balance? Some would say there is none, but a quick breakdown of varying perspectives can highlight what's at stake for both sides.

Arguments by Proponents

Many proponents' cases are very distinct. One Canadian writer states frankly: "The direct benefit of vaccine passports is clear: They would allow us to safely lift restrictions on indoor gatherings, with all the attendant benefits to the economy, culture, sports and education. They also incentivize people to get fully vaccinated."[8]

Others are concerned about more obvious public health and safety issues. One study found that, "The benefits of vaccine mandates and vaccine passports are clear. They should increase the rate of vaccination and almost eliminate severe outcomes/hospitalizations in the general population. It has also been shown that vaccines reduce the risk of transmission to their closest contacts by about 41 percent among infected persons."[9]

Katherine Ginsbach, JD, and Anastasia Vernikou, JD, of Georgetown University agree, stating that a vaccinated individual is far likelier to have a mild case of the illness: "Vaccine passport proponents argue that vaccine passports and immunization certificates encourage

people to get vaccinated and allow a gradual reopening of the economy, and the lifting of restrictive public health measures such as quarantines, business closures and stay-at-home orders. Industries such as retail, travel and entertainment particularly benefit from a mandatory vaccine passport scheme as they will be able to resume their commercial activities in a manner that protects both their customers and employees."[10]

people who sometimes are hesitant or complacent. In countries that restricted entry to nightclubs or events with more than 1,000 people, vaccinations increased among people younger than 20 years. When countries established requirements for a wider array of settings, vaccinations also increased among adults aged 30 years to 49 years.[12]

An important fact is that vaccinated individuals are much more likely to

Through use of vaccine passports, a *British Medical Journal* study optimistically found that only 28 cases of COVID-19 were detected in 7,764 participants who completed the full testing requirements.

Through use of vaccine passports, a *British Medical Journal* study optimistically found that only 28 cases of COVID-19 were detected in 7,764 participants who completed the full testing requirements. Another study found that had the British government decided to mandate COVID-19 passports for crowded events, it could have reduced cases and deaths by as much as 30 percent in subsequent weeks.[11]

Policies that require people to show proof they've been vaccinated against COVID-19, recovered from the illness or recently tested negative for SARS-CoV-2 before they can travel internationally or go to public places that require vaccination or recovery could increase vaccination rates in countries with low uptake, according to a study of these policies in six European countries. Indeed, people younger than 30 years had the largest increase in vaccinations after these policies were enacted, suggesting restrictions might help improve vaccine uptake in younger

have only mild illness. "So they may be more likely to be out and about, despite being infected," said family physician and epidemiologist Jeff Kwong of the University of Toronto. "By excluding all the unvaccinated people from these places, we are in essence keeping them safer from the vaccinated people who may be asymptomatically or presymptomatically infected with COVID, but still able to transmit, especially when everyone is unmasked. If we drop the vaccine passports, the unvaccinated are going to go into those spaces. Right now, they may be living the life of a hermit, and have managed to stay safe that way. But if we get rid of vaccine certificates, they're like sitting ducks."[12]

Arguments by Opponents

There are people who question who they can trust and to whom they safely grant authority. Simply following the proposals of media, corporations and even

healthcare is considered blind trust to many. Much is at stake, and questions beget understanding for both sides of the vaccine passport issue. Listed are some opposing arguments.

One concern is vaccine inequality. Albert Fox Cahn, founder of the Surveillance Technology Oversight Project (STOP) and a *Wired* contributor, says, "Let's look at who's been vaccinated. Here in New York City and New York State, nearly every state in the country, it's overwhelmingly wealthier, whiter communities that have been able to get vaccinated first. I am so worried that this vaccine passport drive will transform medical segregation into digital segregation in nearly every public space. We're talking about something that could exclude millions of people from the necessities of basic life and compound the injustices that defined our healthcare response to this entire pandemic. Those communities hardest hit hard by the pandemic, who have died at the highest rates, who have suffered the most, are the ones who are going to be the least able to benefit from the purported benefits of this vaccine passport."[13]

Many vaccine passport opponents foresee a two-tiered society of segregation — the haves and the have-nots. WHO is also concerned about racial discrimination because of vaccine rollout inequality. The organization believes that because the supply of COVID-19 vaccines is still limited, "preferential vaccination of travelers" could lead to a shortage of vaccinations for people who need them most. This is especially worrisome since the bulk of the vaccines are going to countries with higher socioeconomic status.[3]

Aaron Prosser, a researcher at McMaster University in Hamilton, Ont., Canada, found that, "the first cost [of mandated vaccines and vaccine passports]

is healthcare-specific. Staffing shortages (loss of unvaccinated workers) may occur, leading to adverse effects on patient care."[9]

Of course, there are also concerns about privacy and security and profits. A digital COVID-19 vaccination certification, or "passport," is a mobile app that instantaneously affirms the vaccinated status, COVID test results, birth date, gender and/or other identifiers of its holder. The information is usually mosaicked in a QR code, read by a proprietary scanner and linked to a government registry. Unfortunately, there have been repeated incidents of security breaches. Numerous and very serious breaks have occurred at healthcare institutions and high-tech corporations, despite these companies demanding respect and promising healthcare records safety. Hundreds of millions of health records have been exposed, and it's likely more will be unprotected in the future. This is especially concerning with the dark web and rampant fraud.[14]

What's more, vaccine apps are not being produced by public health experts, but by large high-tech corporations. "The yellow international medical passports," says Cahn, who believes the emerging surveillance technologies pose an unprecedented threat to civil rights and the promise of a free society, "are not the same thing at all as a digitalized vaccine ID. What we see and hear in New York City and other cities around the U.S. is a movement to expand a very different technology — a type of vaccine passport that wouldn't be used when you fly internationally, but used when you go to work, go to school, even go to the local grocery store. And from my perspective as a civil rights lawyer and a technologist, this is really disturbing. Both because of privacy and equity impacts, but because of the fact that for all of the surveillance we're now being sold, there's no evidence that it actually will work. And I'm quite worried that it will actually be a step back for the rollout of our vaccines — these desperately needed vaccines."[14]

Job losses are also a concern. One longtime Brooklyn public school teacher, Casey McFadden, joined the growing list of workers refusing the vaccination out of personal preference. Her fear, specifically, was a severe allergic reaction because of underlying health conditions. "Many of us are not against the vaccine," explains McFadden. "We just don't like the idea of someone forcing us to do something. It is about civil liberties and our rights. We are treading on some dangerous waters." McFadden, who had retired, returned to teaching to increase her retirement income and to help decrease the teacher shortage during the beginning of the COVID-19 crisis. "I risked my life returning because the city wasn't even testing children then," she says. "Why are they being so mean-spirited and putting people out of work when all they had to do is bring back the weekly COVID testing?"[15]

Although not a vaccine passport argument, per se, safety is a concern that prevents some people from being vaccinated. From many healthcare workers' perspectives, the vaccine is clearly helpful, not harmful, even if no vaccine is 100 percent safe. However, many citizens look back, however rightly or wrongly, on the U.S. Food and Drug Administration's short history of major mistakes. Although the organization has many more successes, some of its errors fail to engender trust.[16]

Summing It Up

It's likely that no one will ever fully comprehend how to expertly navigate the tension of the COVID-19 vaccines and passports. The arguments by each side will continue to tease and evade, just like light on a cut gem. But, it would benefit everyone, regardless of their stance, to discuss, educate, empathize and actually hear one another whether for or against. With time, further information will be gained and protocols ironed out. But for now, regardless of decisions and progress made, not all people on either side will be pleased all the time. ❖

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Immunity Debt: A Catalyst for the Development of Infections and Autoimmune Disease?

Are precautions to stop the spread of COVID-19 now causing other widespread illness?

By Amy Scanlin, MS

IF THE COVID-19 pandemic taught us anything, it is to expect the unexpected. Unfortunately, that unexpected could be happening now with increasing risks of severe infections thanks to an unintended consequence of social distancing, hypervigilant cleaning and fewer doctor visits and vaccinations. It seems these important measures put in place by necessity to help stem the spread of the SARS-CoV-2 virus may also have had the unintended consequence of causing a backlash of infections — a concern known as "immunity debt."

Natural, or innate, immunity is a frontline defense against invasive pathogens, prompting the immune system to develop an adaptive response. With more exposure to pathogens and viral loads, innate immunity theoretically increases in effectiveness, spurring immune stimulation. Much like early exposure to peanuts may ward off the development of a peanut allergy, early exposure to pathogens and viral loads can lead to a robust immune system.

But during the COVID-19 lockdowns, hospitals saw unprecedented reductions in routine care visits, as well as nonemergency community-acquired viral and bacterial infections such as viral gastroenteritis, chicken pox, upper and lower respiratory tract infections, Streptococcus pneumonia and Haemophilus influenza b. Despite this, infections initially remained lower post-lockdown than during prepandemic levels. And, while that sounds positive, mathematical models suggest the loss of herd immunity for these and other diseases has the potential to cause more intense and widespread infections — possibly for years to come.[1]

Immunity Debt on a Worldwide Scale

As the world began to reopen after two-plus years of minimal exposure to microbes, scientists in some parts of the world saw a rebound in infection rates for conditions such as respiratory syncytial virus (RSV) and influenza, as well as atopic inflammatory diseases. Particularly

at risk for these infections were children, the elderly and the immunocompromised.

Now, the implications of immunity debt on world health are becoming reality, particularly for some early childhood infections. For example, New Zealand saw very low levels of RSV (usually a significant cause of hospitalizations) while under lockdown, but a rapid increase in the number of cases after a partial border reopening in April 2021 — five times higher, in fact, than the 2015 through 2019 peak average.[2] Australia also saw a virtual absence of both RSV and influenza during the pandemic, but even larger outbreaks than usual by October 2020.[1] In the U.S., RSV cases spiked in the summer of 2021, particularly in southern states, even though infection rates are usually higher in the winter.

Without the natural protection that exposure to RSV provides, and without a vaccine to protect against it, immunity debt and rebounding post-epidemic infections may make future epidemics even more severe.

Hygiene Hypothesis and the Rise of Autoimmune Disease

Extrapolating this hygiene hypothesis to the use of protective measures put in place during the pandemic, questions remain as to whether reduced and delayed infections may have a larger eventual impact on the incidence of autoimmune and allergic disease.

As rates of bacterial infections decrease, a coincidental increase is often seen in autoimmune and allergic diseases, a phenomenon often found in developed countries where use of antibiotics and antimicrobials is high. This is explained by the hygiene hypothesis, which proposes an overzealous use of antibiotics and antimicrobials and subsequent limited exposure to pathogens lead to a compromised immune system, suggesting an imbalance of microbiota, particularly in the gut, may be affecting immunoregulation.

Currently, antinuclear antibody biomarkers for autoimmune diseases are on the rise in the U.S., particularly in males, non-Hispanic whites, adults 50 years and older and adolescents. And, since this phenomenon cannot be explained by genetics, investigators are considering environmental factors[3] since, as populations move from one place to the next, they tend to be affected by immune diseases at the same incidence as their adopted homeland.[4]

There is also a rise in immunocompromised states, which could be caused by cleanliness. When the environment is too clean, the immune system doesn't have the opportunity to fully develop, causing its defenses to become inadequate. Remarkably, exposure to germs is beneficial. Early childhood exposure to germs helps the immune system to develop and recognize the good from the bad. Even in utero, a mother's exposure to germs can help to strengthen the fetus' immune system and gut microbiome.

An increase in autoimmunity can be further explained by the use of antibiotics, particularly in childhood, which may prevent colonization of beneficial microbiota and cause the immune system to attack harmless bacteria.

There are numerous examples that strengthen the case for the hygiene hypothesis. Chronic allergic diseases and asthma are more likely to occur when early exposure to immune-stimulating endotoxins that trigger the molecular "switch" TLR4 are low. It is also thought that a weakened immune system could be a contributing factor for the development of asthma in infants exposed to viral RSV pathogens. In more robust immune systems, RSV will trigger the same TLR4 "switch"; however, for reasons still unclear, when the immune system is lacking, exposure to RSV may instead trigger asthma rather than protect against infection.[5]

Asthma and allergies are being studied through the lens of the hygiene hypothesis relating to hepatitis A. The long form of the TIM-1 gene acts as a receptor for hepatitis A on the immune system. It is also critical to the development of asthma and allergies. The rates of hepatitis A have fallen dramatically since the 1950s, but since then, the rates of asthma and allergies have been on the increase. Perhaps not coincidentally, since that time, sanitation has also improved. The longer version of TIM-1 seems to act as a protector against asthma and allergies, but particularly so in those who have been infected with hepatitis A. It is theorized that the binding of hepatitis A to immune cells and efficacy of the killing of T cells may be enhanced by the long form of TIM-1, ultimately providing protection against asthma and allergies.[6]

Microflora Hypothesis

More recently, the microflora hypothesis links early exposure to a variety of environmental influences on immune system development. The more robust the intestinal microbiota, the more robust the microbiome development, and less propensity toward inflammatory states, including food allergies and allergic diseases. For example, infants with less gut microbial diversity between 3 months to 1 year of age, measured by enterobacteriaceae/bacteroidaceae ratios, have an increased rate of food sensitivity, suggesting the first year of development is crucial to precluding immune hypersensitivities later in life.[7] Of course, a host of factors are at play when it comes to influencing whether one is susceptible to allergies, including genetics. It is too early to know with certainty what role, if any, microflora play, although it appears a promising area of research.

There is also a rise in immunocompromised states, which could be caused by cleanliness.

Immunity Debt or Vaccination Crisis?

In addition to a decline in natural immunity, a decrease in vaccination coverage is a real concern. Prior to the pandemic, vaccination rates were relatively high, particularly in developed countries, thanks to mandatory childhood vaccinations and generally good adherence to vaccine recommendations in other age groups. However, during the pandemic, a reduction in doctor visits, including well-baby visits, resulted in reduced vaccination rates, in some cases sharply. "Availability of the vaccine was not a problem during the pandemic, but access was," says Teale Ryan, MSN, RN, a PhD student at the University of Kansas Medical Center. "Just like routine preventive care was missed during the first year of the pandemic, so were routine vaccines. People in lockdown, especially in larger cities, didn't want to leave their homes. Healthcare providers were also doing large amounts of their work through telehealth." These factors have not yet returned to normal.

As such, some people question whether the greater challenge is immunity debit or a vaccination crisis. According to Ryan, there is a lot of COVID-19 vaccine misinformation, including that the vaccines don't prevent the disease, causing vaccine hesitancy. But, of course, research shows that the vaccines greatly reduce the chances individuals will become infected with the SARS-CoV-2 virus if they are vaccinated. And, they are greatly protected against severe disease. In fact, according to Stanford researchers, vaccinated persons had better immunity against future COVID-19 strains than those whose only immunity was a previous infection. In their study, vaccinated participants who became infected with alpha or delta variants began to generate antibody panels that recognized and bound to the viral spike protein (in this case, the Wuhan-Hu-1 virus), as well as the viral spike protein of other variants. On the other hand, antibodies produced in unvaccinated individuals would bind to the viral spike protein of only the alpha or delta variants. In addition, the antibodies produced solely through past infection showed bias toward the strain of the original infection and a lowered ability to bind to the spike proteins of other variants. The researchers speculated that the reason for this could be germinal centers in the lymph nodes that actively amplify antibodies for weeks after a vaccination. In contrast, antibodies generated by the unvaccinated but previously infected were variable and dropped steadily once the infection passed.[8]

The World Ahead

Although the risks of immunity debt are real, from a practical standpoint, the usual and universal precautions may be all that is necessary to lead a life well-lived in as safe an environment as possible. Enabling the best immune response through vaccinations, drug treatments and lifestyle choices is the best course of protection against current and future infections. ❖

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An Update on Treating PTSD

While not a new condition, PTSD continues to affect many people who require new treatments to allow them to lead as normal a life as possible.

By Jim Trageser

WHILE MODERN understanding of post-traumatic stress disorder (PTSD) originally grew primarily out of attempts to treat affected combat veterans from World War I, World War II and, most pivotally, Vietnam, we now know that anyone who has endured a severe, traumatic event can be affected by its lingering symptoms that are debilitating and affect patients' ability to function in everyday life due to flashbacks, avoidance, reactivity and/or mood imbalances.

Today, it is not just military combat veterans who are diagnosed with PTSD, nor even just first-responders among civilians. Victims of violent crime and even witnesses to those crimes or to horrific accidents can develop PTSD. In fact, it is estimated approximately 7 percent to 8 percent of the U.S. population will suffer from PTSD at some point in life.[1]

Ironically, it was PTSD skeptic Lt. Gen. George Patton who inadvertently helped bring public attention to the psychiatric conditions that exposure to intense or sustained traumatic stress can induce, which began the slow process of lowering prejudice toward PTSD and mental illness in general. During the Allied campaign in Sicily in August 1943, Patton angrily slapped two enlisted men under his command during a tour of field hospitals. During one visit, Patton encountered a patient who had been admitted despite not suffering any physical wounds. Pvt. Charles Kuhl had been sent to the hospital for what was then called battle fatigue or exhaustion. Seeing a soldier with no visible wounds in a hospital enraged Patton, who accused the man of cowardice while attacking him. A few days later, Patton again lost his temper at another military field hospital and slapped Pvt. Paul Bennet, whose superior officers had sent him to the

hospital to recover from exhaustion and dehydration.[2]

Following these incidents, Patton initially issued orders that only those with physical wounds were to be sent to hospitals, and those suffering from combat fatigue must stay on the front lines. However, once theater commander Gen. Dwight Eisenhower got word of the incidents through the Medical Corps chain of command, he countermanded that directive and ordered Patton to apologize. (Later that year, when news of the two slapping incidents reached stateside newspapers, the political uproar was so great that Patton was relieved of his command. He would not return to combat duty until nearly a year later, following D-Day.)

Even if Patton was not yet aware of how "battle fatigue" or "exhaustion" was being diagnosed and treated, Army and Navy doctors certainly were. In the North African campaign that preceded the invasion of Sicily, Maj. Gen. Omar Bradley had, on the advisement of psychiatrist Frederick Hanson, issued orders that psychiatric casualties were to be treated at forward areas rather than being sent to the rear. Studies following World War I had shown that quick intervention near combat areas had been the most effective treatment for what was then called "shell shock," a term for soldiers who exhibited a range of psychological symptoms after prolonged exposure to artillery fire or other high-stress combat. Field commanders had noted soldiers becoming unresponsive, even catatonic, slow to react or process orders, unable to communicate lucidly and wandering aimlessly around the battlefield. These men were obviously a danger both to themselves and to their comrades and, thus, had been removed from the front lines and handed over to medical staff for evaluation and treatment. Under Bradley's order, more than half of all such patients were able to be successfully returned to their units after treatment.[3]

However, not all units or commands saw that same level of success. In the Pacific Theater, physicians and medics employed a similar treatment regimen at forward field hospitals. During the Battle of Biak off the north coast of New Guinea, Lt. Col. William Shaw, chief division surgeon, reported that only about one-third of battle fatigue casualties were able to return to combat duty with their units after a period of rest and restoration.[4]

It was the Vietnam War, however, that truly brought PTSD to the public's attention, with nearly a quarter of all deployed military personnel requiring some form of psychological treatment either in theater or in the years following their return home.[3] Rather than many combat veterans suffering the severe, disabling symptoms seen among combat commanders, they were suffering from a different manifestation: frequent nightmares, a heightened alertness, avoidance of anything that could remind them of the war and increased moodiness.

It was this public attention that brought to bear the resources and research leading to PTSD as a recognized diagnosis, as well as new and more-effective treatments. Today, along with an improved understanding of the causes and manifestations of PTSD, there are improved treatment options that provide clinicians with additional tools to help patients.

What Is PTSD?

PTSD was made an official diagnosis in 1980 with its inclusion in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* by the American Psychiatric Association. It is defined as a condition caused by "a dominating psychological experience that retains its power to evoke panic, terror, dread, grief or despair."[5]

PTSD is marked by a constellation of symptoms:[6]

- Intrusive or re-experiencing symptoms: flashbacks, nightmares, intrusive memories
- Avoidance of reminders of the trauma
- Hyperarousal: easily startled, sleep disturbances
- Negative emotions
- Significant distress or dysfunction

Key to a PTSD diagnosis is exposure to an extreme form of trauma. Initially, a traumatic event was defined as a catastrophic stressor that was outside the range of usual human experience. But today, there is an existing classification of "adjustment disorders" for those unable to cope with the sorts of normal challenges and disappointments of life, including divorce, unemployment, death of a loved one, etc.[5]

Many forms and models of psychotherapy can be employed depending on the severity and type of PTSD symptoms.

Diagnosing PTSD

The National Institute of Mental Health defines the criteria for a PTSD diagnosis as:[7]

- At least one re-experiencing or intrusive symptom
- At least one avoidance symptom
- At least two arousal and reactivity symptoms

• At least two cognition and mood symptoms

A diagnosis is typically made by a psychiatrist or psychologist, generally one with experience treating patients with PTSD.

Current Treatment Protocols

Two main interventions are available for treating PTSD: psychotherapy and medication.[5] They may be used together, or one or the other may be used alone depending on specific symptoms, their severity and the overall health of the patient.

Many forms and models of psychotherapy can be employed depending on the severity and type of PTSD symptoms. These can be provided in group or private sessions or in a combination of the two.

Clinicaltrials.gov lists more than 1,500 ongoing, recent or pending studies of PTSD treatment.

The American Psychological Association (APA) lists four therapies as "strongly recommended" for treating PTSD:

- Cognitive behavioral therapy (CBT)
- Cognitive processing therapy
- Cognitive therapy
- Prolonged exposure

CBT is a form of psychotherapy that focuses on modifying dysfunctional emotions, behaviors and thoughts. Considered a "solutions-oriented" form of talk therapy, CBT rests on the idea that by changing how patients consciously think about an event, improvements can be made in how they react to it.[8] In addition to sessions with a therapist, additional work is completed by patients on their own.

Cognitive processing therapy is a subset of CBT that provides patients with tools to allow them to review their emotions and thoughts regarding the trauma they experienced in an effort to assist them in returning to a nonimpaired day-to-day life.[9]

Cognitive therapy is another subset of CBT that focuses on changing pessimistic interpretations of a trauma to allow for a resumption of normal daily activities.[8]

Prolonged exposure involves both revisiting previously avoided memories of a trauma, as well as engaging in activities that have been avoided due to their association with that trauma. The goal is to help patients realize that the memories themselves are not dangerous, and that normal activities can be resumed.[10]

In addition, three other therapies are "conditionally recommended" by APA that have proved effective, but are not as well-proven as the four strongly recommended therapies:

- Brief eclectic psychotherapy
- Eye movement desensitization and reprocessing therapy
- Narrative exposure therapy

Brief eclectic psychotherapy blends CBT with other therapies with the goal of helping patients confront and then discard their feelings of shame and guilt arising from the trauma.[8]

With eye movement desensitization and reprocessing therapy, patients recall the traumatic memory while following an object with their eyes, which allows their brains to remap the memory without triggering the normal stressful response.[11]

In narrative exposure therapy, a therapist leads patients through a process of recounting their entire life story, including the traumatic event. Patients tell the story in great detail to allow them to take control of their own life history.[12]

In addition to therapy, specific medications may be prescribed by a physician to assist patients' recovery — either in concert with therapy or as a stand-alone treatment.[13]

Certain antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), have been shown to help relieve many PTSD symptoms. Two SSRIs approved by FDA to treat PTSD are sertraline (Zoloft) and paroxetine (Paxil).[14] Venlafaxine (Effexor) is an SNRI that has shown promise in treating PTSD symptoms.[15] And, prazosin (Minipress), which is often used to treat symptoms of an enlarged prostate, has shown some potential for preventing nightmares associated with PTSD.[14]

Lastly, anti-anxiety medications may be used to treat some PTSD symptoms, although these generally have significant side effects and are typically only prescribed for a set duration.

Ongoing Research

Clinicaltrials.gov lists more than 1,500 ongoing, recent or pending studies of PTSD treatment.

One study being conducted at the Minneapolis VA Health Care System is investigating the use of the drug ketamine in concert with prolonged exposure therapy. A similar study at the Depression and Anxiety Center at the Icahn School of Medicine in Mount Sinai, N.Y., is looking at adding trauma-focused psychotherapy to ketamine treatment. Researchers at Tel Aviv University are studying whether attention control treatment can treat symptoms of PTSD, while a team at the New York State Psychiatric Institute is looking at interpersonal psychotherapy

PTSD Symptoms

Physical	Cognitive and Emotional	Behavioral
Difficulty breathing	Easily agitated	Avoidance of feelings, thoughts, people, places or events related to the potentially traumatic experience
Profuse sweating	Trouble concentrating	Hyperalert
Rapid heart rate	Negative expectations about oneself or distorted blame	Detached and withdrawn
Elevated blood pressure	Inability to experience positive emotions	Alcohol consumption
Migraines	Nightmares or flashbacks of the potentially traumatic experience with a strong emotional response	Drug use
Exaggerated startle response	Feeling overwhelmed	Change in activities or loss of interest in hobbies
Difficulty sleeping		Disciplinary issues

Adapted from: Geraci J, Baker M, Bonanno G, Tussenbroek B and Sutton L. Understanding and Mitigating Post-Traumatic Stress Disorder (2011). US Army Research. 344. Accessed at digitalcommons.unl.edu/cgi/viewcontent.cgi?article=1343&context=usarmyresearch.

for adolescents who suffer from PTSD. And, the Stress, Trauma, and Anxiety Research Clinic at Wayne State University in Detroit has been utilizing dance therapy and yoga with some promising results, although more study is needed to quantify any benefit.[6]

On the pharmacological side, the Connecticut VA is studying whether intranasal insulin might help calm hyperactivity in the amygdala region of the brain. And, other studies are investigating whether already approved drugs, including oxytocin, the antipsychotic brexpiprazole (Rexulti), the blood pressure medication clonidine (Catapres) and the epilepsy-treating pregabalin (Lyrica), can be used to treat PTSD.

There are also a handful of new drugs in the clinical trials pipeline. A new allosteric modulator of NMDA receptor, NYX-783, is in recruitment stage for clinical trials. And, the Danish company H. Lundbeck A/S is conducting trials on a proposed monoacylglycerol lipase inhibitor, Lu AG06466, for its effectiveness in relieving PTSD. It is also being tested for efficacy in treating multiple sclerosis and epilepsy.[16]

Finally, medical devices are being proposed to treat PTSD. Butler Hospital in Providence, R.I., is studying the use of transcranial direct current stimulation. The Eastern Colorado Health Care System is testing Apollo Neuro, a stress relief wearable device that fits on the wrist or ankle, to see if its use of vibration can help ease PTSD symptoms. And, the U.S. Army and the University of Arizona are collaborating on a study using bright light therapy to attempt to improve sleep among PTSD patients.

Looking Ahead

While the United States recently withdrew its military forces from Afghanistan, military veterans from that and earlier conflicts will be dealing with PTSD for decades to come. And as seen in Ukraine, warfare seems quite far from extinction; with reports of widespread attacks on civilians, survivors of that conflict will also be dealing with PTSD for the foreseeable future.

In the United States, rising murder and assault rates in many urban areas have erased decades of progress in lowering the incidence of violent crime, leaving traumatized victims in their wake. And modern industrial society continues to cause horrific trauma unimaginable to our ancestors, maiming and killing victims in traffic and workplace accidents as powerful machines inadvertently meet very vulnerable human flesh.

With these realities, physicians and therapists will have no shortage of patients needing PTSD treatment in this lifetime. But, thankfully, ongoing research seems likely to yield more effective treatments to allow those affected to resume lives as normal as possible. ❖

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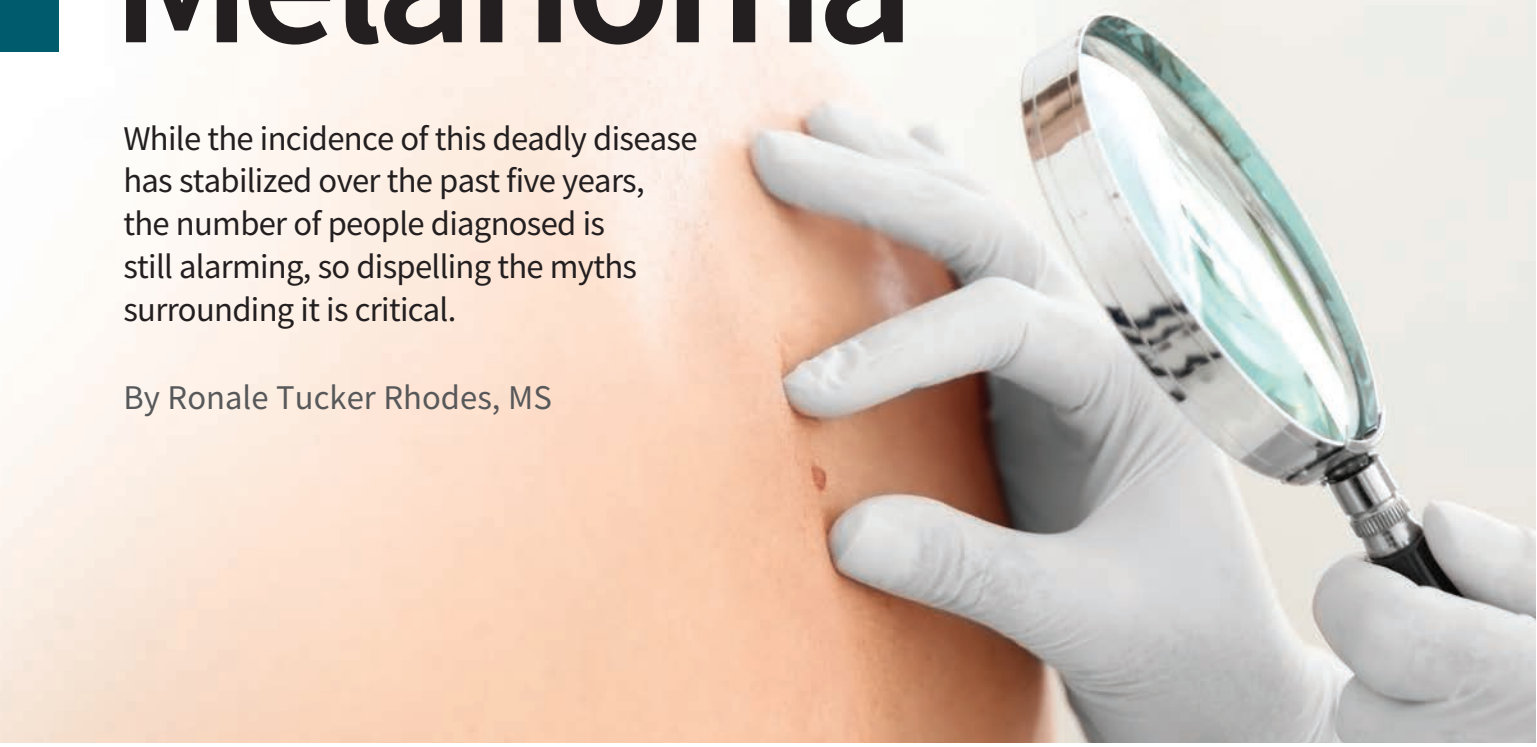
Myths & Facts: Melanoma



While the incidence of this deadly disease has stabilized over the past five years, the number of people diagnosed is still alarming, so dispelling the myths surrounding it is critical.

By Ronale Tucker Rhodes, MS

ACCORDING TO THE Centers for Disease Control and Prevention (CDC), cancer is the second leading cause of death in the United States, exceeded only by heart disease, and one of every four deaths in the U.S. is due to cancer. Also in the U.S., skin cancer is the most common form of cancer.[1] Melanoma, one of three major types of skin cancer, accounts for only about 1 percent of skin cancers, but it causes a large majority of skin cancer deaths.[2] In 2018, the latest year for which incidence data are available, 83,996 new cases of melanoma were reported, and 8,199 people died. For every 100,000 people, 22 new melanoma cases are reported, and two people die (Figure 1).[1]

The rates of melanoma have been rising rapidly over the past few decades, but have stabilized in the last five years and vary by age. In 2022, the American Cancer Society estimates about 99,780 new melanoma cases will be diagnosed (about 57,180 in men and 42,600 in women) and about 7,650 people are expected to die of melanoma (about 5,080 men and 2,570 women).[2]

Melanoma is more than 20 times more common in whites than in African Americans. Overall, the lifetime risk of melanoma is about 2.6 percent (one in 38) for whites, 0.1 percent (one in 1,000) for Blacks and 0.6 percent (one in 167) for Hispanics. However, the risk for each person can be affected by a number of different factors. Melanoma is more common in men overall, but before age 50, the rates are higher in women.[2] It is the fifth most common cancer among men and women.[3] And, the risk of melanoma increases as people age. The average age at diagnosis is 65, but melanoma is not uncommon even among those younger than 30. In fact, it's one of the most common cancers in young adults (especially young women).[2]

The underlying cause of these grim statistics could lie in the fact that so many people disbelieve melanoma is a serious disease. Yet, the reality is this misunderstood deadly and costly disease (treatment is estimated to cost approximately $3.3 billion each year in the U.S.[4]) can often be prevented. So dispelling the many myths surrounding it could potentially help to save millions of lives.

Separating Myth from Fact

Myth: Only adults get melanoma; it doesn't affect children.

Fact: Melanoma can develop from the day an individual is born until the day he or she dies.[5] While it is the most common form of cancer in young adults ages 25 years to 29 years, it is also increasing faster in younger women ages 15 years to 29 years.[6] Yes, melanoma is rare in children, but between 300 and 400 cases are diagnosed in the United States each year.[7] In fact, pediatric melanoma has increased on average 2 percent per year since 1973, although its incidence seems to have decreased over the last few years.[8] And, because it is so rare, many childhood melanomas are found in the later stages when treatment becomes more involved.[7] What's important to know is that among children and teenagers, melanoma often looks different and may grow faster than it does in adults.[8]

Myth: Individuals who tan easily and rarely burn won't get melanoma.

Fact: Cases of melanoma are more prevalent in individuals with fair skin, freckles, blue or green eyes, and blond, red or light brown hair, but everyone is at risk. What's more, melanoma is less frequently diagnosed among Blacks, Hispanics or Asians, and when it is found in these ethnicities, it is often in its late stages.[9] As such, the death rates are higher in darker-skinned people. "It is often diagnosed later, at a more advanced stage, because both doctors and patients may not even be considering the possibility of skin cancer developing on darker skin until it's too late," says Saira George, MD, a dermatologist at MD Anderson Cancer Center.[10]

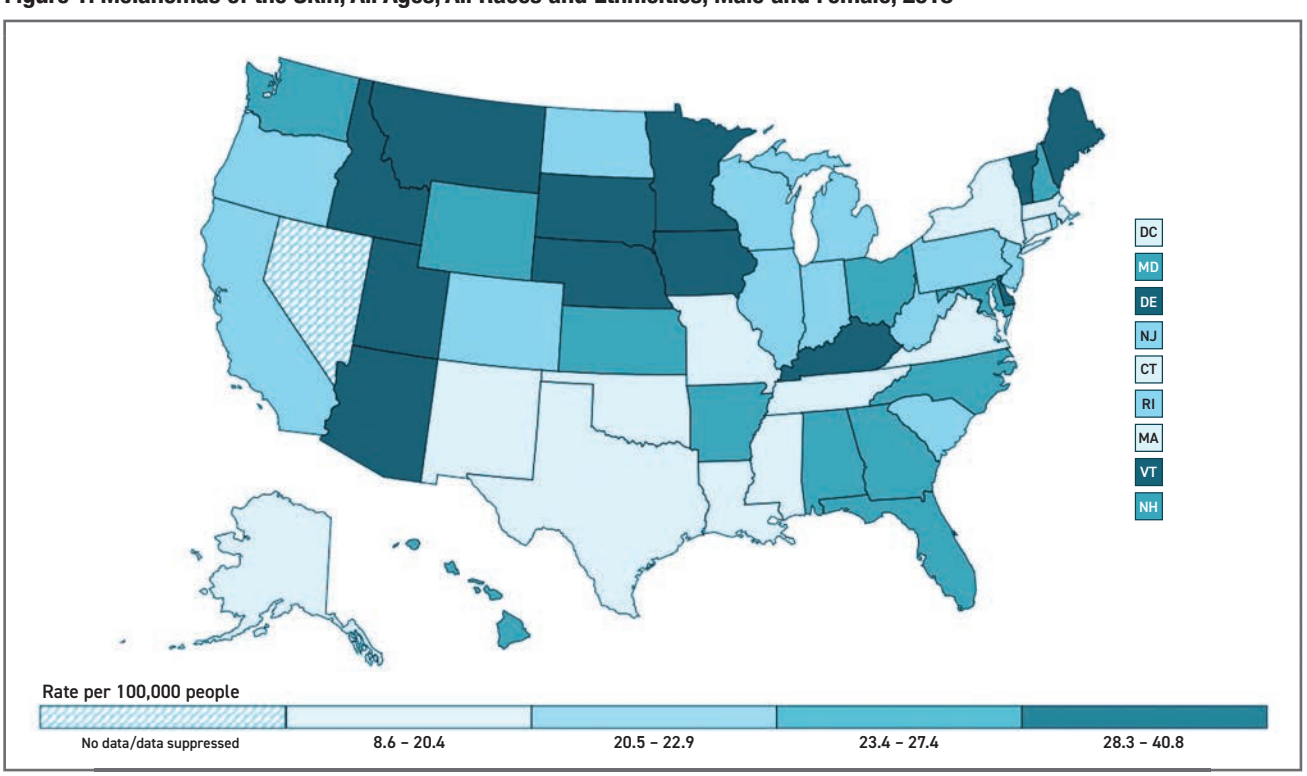
Myth: A mole has to be raised and turn color to be a possible melanoma.

Fact: It doesn't matter whether a mole is flat or raised. In fact, a lesion's texture is less important than its color or changes in either color or shape. "In my experience, it's just the opposite — 90 percent of melanomas I've treated in moles were flat," explains Jenny Nelson, MD, a dermatological surgeon at Avera Medical Group in Sioux Falls, S.D. In addition, oddly shaped moles, especially ones that may not be circular should be sampled. For example, a mole that has a "tail" shooting off in one direction is indicative of melanoma.[11]

There are four main types of melanoma: superficial spreading, nodular, lentigo maligna and acral lentiginous.[12]

1) Superficial spreading melanoma is the most common type of melanoma skin cancer, occurring in approximately 70 percent of cases. This melanoma tends to grow outward (called radial growth) and spread across the surface of the skin, but

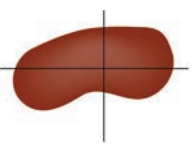
Figure 1. Melanomas of the Skin, All Ages, All Races and Ethnicities, Male and Female, 2018



Melanoma Warning Signs

The first five letters of the alphabet are a guide to help individuals recognize the warning signs of melanoma:

Asymmetry



Most melanomas are asymmetrical. If a line is drawn through the middle of the lesion, the two halves don't match, so it looks different from a round to oval and symmetrical common mole.

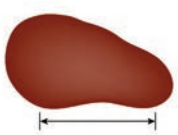
Border

Melanoma borders tend to be uneven and may have scalloped or notched edges, while common moles tend to have smoother, more even borders.

Color

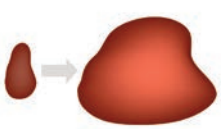
Multiple colors are a warning sign. While benign moles are usually a single shade of brown, a melanoma may have different shades of brown, tan or black. As it grows, the colors red, white or blue may also appear.

Diameter or Dark



While it's ideal to detect a melanoma when it is small, it's a warning sign if a lesion is the size of a pencil eraser (about 6 mm, or ¼ inch in diameter) or larger. Some experts say it is also important to look for any lesion, no matter what size, that is darker than others. Rare, amelanotic melanomas are colorless.

Evolving



Any change in size, shape, color or elevation of a spot on the skin, or any new symptom in it such as bleeding, itching or crusting may be a warning sign of melanoma.

it can also start to grow down into the skin (called vertical growth). It is often flat and thin (less than 1 mm thick) with an uneven border. It varies in color and may have different shades of red, blue, brown, black, grey and white. It usually develops on the central part of the body (trunk), arms and legs, and it tends to happen on the back in men and the legs in women.

2) Nodular melanoma is the second most common type, making up about 15 percent to 20 percent of cases. It grows down into the skin and spreads more quickly than other types. It is a raised growth that sticks out from the skin (polypoid), and the growth may be shaped like a mushroom with a stem or stalk (pedunculated). It is usually black, but sometimes can be red, pink or the same color as skin. It usually develops on the face, chest or back, and it can be found on areas of skin not exposed to the sun.

3) Lentigo maligna melanoma most often develops in older people, and it makes up about 10 percent to 15 percent of all melanoma skin cancers. It usually appears as a large, flat tan or brown patch with an uneven border, and it tends to get darker as it grows and has many shades of brown or black. It often starts from an in situ tumor called lentigo maligna, which is an early form of the growth only in the top or outer layer of the skin (epidermis). Lentigo maligna melanoma usually grows outward across the surface of the skin for many years before it starts to grow down into the skin. It usually develops on areas of skin that are regularly exposed to the sun without protection such as the face, ears and arms.

4) Acral lentiginous melanoma is most common in people with dark skin such Africans, Asians and Hispanics. It is not related to being exposed to the sun, and it makes up less than 5 percent of all melanoma skin cancers. Acral lentiginous melanoma appears as a small, flat spot of discolored skin that is often dark brown or black. It usually grows outward across the surface of the skin for a long time before it starts to grow down into the skin. And, it usually develops on the soles of the feet, palms of the hands or under the nails.

It's important to note that many melanomas occur in pre-existing spots or moles, so a doctor should evaluate all moles, lesions or spots that have changed.

And, individuals with multiple moles should undergo routine full-body exams by a dermatologist.[13]

Myth: Melanoma is only possible if the body is regularly exposed to the sun.

Fact: Sun exposure can be a primary cause of melanoma, but there are many other risk factors. Exposure to ultraviolet (UV) radiation from the sun plays a major role. People who live at high altitudes or in areas with bright sunlight year-round have a higher risk of developing skin cancer, and those who spend a lot of time outside during the midday hours also have a higher risk.

Exposure to UVB radiation from the sun appears more closely associated with melanoma, but newer information suggests UVA may also play a role. While UVB radiation causes sunburn and does not penetrate through car windows or other types of glass, UVA can pass through glass and may cause aging and wrinkling of the skin in addition to skin cancer.

People who use tanning beds, tanning parlors or sun lamps have an increased risk of developing all types of skin cancer.

Other risk factors for melanoma include many moles or unusual moles, fair skin, family history (about 10 percent of people with melanoma have a family history of the disease), familial melanoma caused by mutations in specific genes, other inherited conditions, including xeroderma pigmentosum, retinoblastoma, Li-Fraumeni syndrome, Werner syndrome and certain hereditary breast and ovarian cancer syndromes, previous skin cancer, race or ethnicity, age and a weakened or suppressed immune system.[14]

Also, melanoma can develop over time. So, regular or extreme exposure to sunlight may not lead to immediate skin cancer. "It could take months or years to see a lesion develop. Extreme exposure does add to the overall toll," explains Dr. Nelson, but "the damage and risk add up over time."[11]

Importantly, some types of melanoma are not related to sun exposure and can occur in unexpected places such as the vagina, rectum, inside the mouth, the soles of the feet and the palms of the hands.[13] "I've removed melanomas from armpits and feet; they can develop anywhere and are more related to skin type than sun exposure," says Dr. Nelson. "Your genetics play a big role, too, and while cancers develop on the hands and face, they can happen anywhere."[11]

Myth: Getting a base tan will protect against melanoma.

Fact: There's no such thing as a safe tan or a tan that prevents sunburns. When exposed to UV rays from the sun or tanning booth, they damage the DNA of skin cells. To protect the cells, the body sends melanin, or pigment, to the surface of the skin, and the skin turns color at the expense of health. The minor protective effect of a tan can easily be wiped out by additional UV exposure, leading to more damage.[10]

The underlying cause of these grim statistics could lie in the fact that so many people disbelieve melanoma is a serious disease.

Myth: Sunscreen with a high SPF will protect against melanoma.

Fact: SPF protection doesn't increase proportionately with the designated SPF number. For example, SPF 30 absorbs 97 percent of UV rays, while SPF 50 absorbs just slightly more — 98 percent — and SPF 100 absorbs 99 percent. Therefore, an SPF of at least 30 should be applied.[10] Also, sunscreen must be applied correctly. Most people use only 25 percent of what is needed to obtain protection. For instance, an SPF 100 sunscreen applied at 25 percent has an effective SPF of only 3.1. And, sunscreen must be reapplied every two hours or according to the product label. Water-resistant sunscreens should be reapplied every 40 minutes to 80 minutes. Sunscreen should also be reapplied after swimming or participating in any activity that causes perspiration. Just to note, the U.S. Food and Drug Administration prohibits the labeling of sunscreen as "waterproof," "sweatproof" or "sunblock."[9]

Myth: Sunscreen isn't necessary in the winter.

Fact: Harmful UV rays are present year-round and can reach and damage skin even on hazy days or days with light or broken cloud cover or shade.[9]

Myth: Primary care doctors can diagnose melanoma.

Fact: General practitioners can suspect melanoma, but they usually lack sufficient training to accurately diagnose melanoma. Even dermatologists can't always tell if a suspicious skin growth is cancerous just by looking, but they do have the experience, diagnostic technology and resources general practitioners don't have.[5]

Melanoma is typically diagnosed by pathologists, doctors who specialize in interpreting laboratory tests and evaluating cells, tissues and organs to diagnose disease, or dermatopathologists, pathologists with specialty training in diagnosing skin cancer and other disorders of the skin using a microscope and other laboratory tests. To diagnose melanoma, a biopsy of the suspicious skin area,

called a lesion, is tested in a laboratory. The pathologist or dermatopathologist will then write a pathology report that notes the thickness of the melanoma, the presence or absence of ulceration, whether the cells are dividing (called the mitotic rate), the type/subtype of melanoma, the presence of immune cells called tumor-infiltrating lymphocytes, margin status (which describes whether melanoma cells can be seen at the deep and/or peripheral [side] edges of the biopsy sample), and presence or absence of certain markers associated with prognosis and/or response to different therapies.[15]

Myth: There are very few treatments for melanoma.

Fact: Actually, while the incidence of melanoma has increased, treatment and survival for patients with localized or metastatic melanoma have improved dramatically in the past 10 years with improved management.

Treatment recommendations depend on many factors, including the thickness of the primary melanoma, whether the cancer has spread, the stage of the melanoma, the presence of specific genetic changes in melanoma cells, rate of melanoma growth and the patient's other medical conditions. Other factors used in making treatment decisions include possible side effects, as well as the patient's preferences and overall health.

Skin cancer *can* kill you, especially melanoma, which can be fatal if not treated promptly.

Doctors will also test whether the melanoma has spread beyond the original site. If there's a risk that the cancer has spread to the lymph nodes, a procedure known as a sentinel node biopsy is performed. During a sentinel node biopsy, a dye is injected in the area where the melanoma was removed, and the dye flows to the nearby lymph nodes. The first lymph nodes to take up the dye are removed and tested for cancer cells. If these first lymph nodes (sentinel lymph nodes) are cancer-free, there's a good chance the melanoma has not spread beyond the area where it was first discovered.

For people with more advanced melanomas, imaging tests can look for signs that the cancer has spread to other areas of the body. These tests include X-rays, CT scans, MRIs and PET scans. However, these imaging tests generally aren't recommended for smaller melanomas with a lower risk of spreading beyond the skin.[16]

Surgery is first performed to remove the original melanoma. If it is determined the cancer has spread to the lymph nodes and beyond, a number of other therapies can be tried. These include:[17]

- Radiation therapy uses high-energy X-rays or other particles to destroy cancer cells. In some instances, adjuvant radiation therapy is recommended after surgery to prevent the cancer from recurring.
- Systemic therapy is given through the bloodstream to destroy cancer cells. Systemic therapies used for melanoma include: immunotherapy, targeted therapy and chemotherapy.

Immunotherapy, also called biologic therapy, is designed to boost the body's natural defenses to fight the cancer. In recent years, major advances have been made in treating stage III and stage IV melanoma with immunotherapy. Both nivolumab (Opdivo) and pembrolizumab (Keytruda) have been shown to shrink melanoma for 25 percent to 45 percent of patients with unresectable or stage IV melanoma, depending on when treatment is given. Both drugs also have been shown to reduce the risk of the cancer coming back after surgery for stage III melanoma. More recently, pembrolizumab has been shown to reduce the risk of cancer coming back after surgery for higher risk stage II melanoma (stage IIB and stage IIC).

Other immunotherapy treatments include ipilimumab (Yervoy) that targets a molecule called cytotoxic T-lymphocyte associated molecule-4 (CTLA-4) and has been shown to shrink melanoma for 10 percent to 15 percent of patients; a combination of ipilimumab and nivolumab may be used for the treatment of unresectable stage III or stage IV melanoma; interleukin-2, which activates T cells; Talimogene laherparepvec (T-VEC; Imlygic), a herpes virus therapy designed in a laboratory to make an immune-stimulating hormone to treat unresectable stage III and stage IV melanoma; and interferon, including high-dose interferon alfa-2b (Intron A) and pegylated interferon alfa-2b (Sylatron).

Targeted therapy is a treatment that targets the cancer's specific genes, proteins or the tissue environment that contributes to cancer growth and survival. These include BRAF inhibitors to treat individuals with melanomas that have a mutated or activated BRAF gene; MEK inhibitors for unresectable or metastatic melanoma with a BRAF V600E or V600K mutation; combination BRAF-MEK inhibitors; KIT inhibitors that treat the KIT gene, which is mutated or present in increased numbers (extra copies of the gene) in some tumors in certain subtypes of melanoma; and tumor-agnostic treatment that is not specific to a certain

type of cancer but focuses on a specific genetic change called an NTRK fusion.

• Chemotherapy is the use of drugs to destroy cancer cells, usually by keeping the cancer cells from growing, dividing and making more cells. However, because immunotherapy and targeted therapy have been more effective at treating melanoma, chemotherapy is used much less often.

Myth: Melanoma can be prevented.

Fact: There is no proven way to completely prevent melanoma, but individuals may be able to lower their risk by reducing exposure to UV radiation, limiting or avoiding direct exposure to the sun between 10:00 a.m. and 4:00 p.m., wearing sun-protective clothing, using a broad-spectrum sunscreen throughout the year that protects against both UVA and UVB radiation and has an SPF of at least 30, avoiding recreational outdoor sunbathing, not using sun lamps, tanning beds or tanning salons, and examining skin regularly.[14]

Myth: Melanoma can't kill you.

Fact: Skin cancer *can* kill you, especially melanoma, which can be fatal if not treated promptly. Life expectancy for skin cancer depends on the type and stage of cancer and whether it has metastasized. Fortunately, with new treatments available today, survival rates are increasing.

Survival rates provide an idea of what percentage of people with the same type and stage of cancer are still alive a certain amount of time (usually five years) after diagnosis.[19] For people with melanoma that is less than 1 mm in maximal thickness and has not spread to lymph nodes or other distant sites, the five-year survival is 99 percent. For people with thicker melanoma, the five-year survival may be 80 percent or higher. Survival rates at five years for people with melanoma that has spread to the nearby lymph nodes is 68 percent. But this number differs for every patient and depends on the number of lymph nodes involved, genetic changes, the amount of tumor in the involved lymph nodes and the features of the primary melanoma. If melanoma has spread to other parts of the body, the survival rate is lower, about 30 percent. The good news is treatment advances have doubled this survival rate since 2004, and only approximately 5 percent of cases are diagnosed at this stage.[3]

It should be noted that survival rates are estimates and are often based on previous outcomes of large numbers of people who had a specific cancer, but they can't predict what will happen in any particular person's case.[19]

Dispelling the Myths Now

Without a doubt, melanoma is a serious and often deadly disease. The good news for people diagnosed with melanoma today is they have a better outlook than ever before due to diagnostics and treatment. The bad news is that too many people are still being diagnosed with melanoma simply because they don't understand the gravity of the disease and its risks, and they don't take the necessary precautions to try to prevent it. Clearly, it's imperative that we reverse the toll this disease is taking on the American public. In 2019, the U.S. Department of Health and Human Services published *The Surgeon General's Call to Action to Prevent Skin Cancer*, which outlines action steps we can all take — as individuals, parents, educators, employers, policymakers, healthcare professionals and communities. This publication is a Call to Action to partners in prevention from various sectors across the nation to address skin cancer as a major public health problem.[20] ❖

Resources for Melanoma Information

- American Melanoma Foundation: www.myamf.org, (858) 882-7712
- Melanoma International Foundation: www.melanomainternational.org, (866) 463-6663
- Melanoma Research Foundation: www.melanoma.org, (800) 673-1290
- Patient Access Network Foundation: www.PANFoundation.org, (866) 316-7263
- Patient Services Incorporated: www.patientservicesinc.org, (800) 366-7741

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After suffering for years with PTSD and contemplating suicide, Dan Jarvis turned his life around after he encountered a breakthrough treatment called the Reconsolidation of Traumatic Memories, a protocol he now uses to help others through his 22Zero nonprofit.

PTSD: *A Patient's Perspective*

By Trudie Mitschang

RETIRED ARMY SFC Dan Jarvis deployed to a combat zone in Afghanistan in 2011. Shortly after his arrival, he stepped on a pressure plate and detonated an improvised explosive device (IED) that inflicted a traumatic brain injury. Although he insisted on continuing to lead his troops, the battalion surgeon ordered him out for a week before rejoining his soldiers. Following weeks of no sleep, he led his squad on a mission to escort an explosive team to defuse a bomb found by another platoon. When an undetected IED exploded under the fourth vehicle in the convoy, taking the life of SPC Doug Cordo, Jarvis felt responsible.

Near the end of his deployment, Jarvis received a Red Cross message informing him that his mother was deathly ill. He left Afghanistan and headed to the United States in hopes of seeing his mom before she took her last breath. Unfortunately, he did not make it in time. After her funeral, Jarvis returned to his assigned duty station in Fairbanks, Alaska, at Fort Wainwright. Burdened by guilt and still unable to sleep, Jarvis sought an escape by binge drinking nightly.

The combined trauma of these experiences led Jarvis to contemplate suicide. But, when a solider from his former platoon took his own life, he resolved not to follow the same path. After retiring from active duty in 2014, he reentered the law enforcement profession, married, but continued to suffer in silence. "The symptoms of post-traumatic stress disorder became more pronounced, including drinking, depression, nightmares, night sweats and a negative outlook," he recalls. "My wife strongly encouraged me to seek help, and I contacted the local VA."

After his diagnosis of PTSD, Jarvis underwent prolonged exposure therapy that tormented him nearly as much as the trauma he had experienced. He opted not to continue this line of treatment, and that's when he encountered the breakthrough treatment that changed his life for the better. "The Reconsolidation of Traumatic Memories Protocol (RTM) developed by the Research and Recognition Project was the most effective clinical treatment I experienced," explains Jarvis. "I also benefited from Accelerated Resolution Therapy that helped me process my survivor guilt."

According to the Research and Recognition Project, RTM is defined as a novel, nontraumatizing, brief therapy for PTSD characterized by intrusive symptoms. RTM works by restructuring the visual representations of a trauma memory as a past, nonthreatening memory by changing elements of the memory. These changes include, from a dissociated perspective, the loss of color, the loss of depth cues, increased distance and visual and temporal distortions.[1]

Jarvis says his experience with RTM was so life-changing that he was compelled to help others find the same relief from traumatic memories. Today, he is the founder of 22Zero, a nonprofit organization that does just that. Jarvis notes the name is powerfully symbolic: The number 22 is the commonly accepted number of suicides per day in the U.S. The goal, says Jarvis, is to take the number 22 a day to zero. "Originally, we were raising money to fund trainings using the RTM protocol with licensed counselors," says Jarvis. "Then, when COVID hit, we had to regroup and reorganize. We changed our own paradigm by going to the roots of the RTM, which is neuro-linguistic programming. Our process is called Trauma Resiliency Protocol (TRP), which is modeled after an earlier protocol called visual/kinesthetic dissociation."

When asked about his mental health today, Jarvis describes it as "fantastic," and says he is free of night terrors, anxiety and anger outbursts: "I'm still human and feel the pressures of daily living. I went through a divorce during COVID, but I've recovered from that. I still felt sad and abandoned, but lucky for me I have many coaches to support me."

Today, Jarvis works with others who are battling PTSD, and he emphasizes that he wants people to know it is 100 percent healable. Based on his experience, he's seen success with clients typically after one to four sessions using TRP. "Our program is free for veterans, active duty and first responders," says Jarvis. "We also work with civilians and family members. I encourage people not to hold onto their trauma. Help is available." ❖

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Dr. Phil Baquie is a mental health professional who developed and teaches Tactical Presilience training that provides proactive, preemptive and preventive training to help law enforcement and military personnel defeat PTSD.

PTSD: *A Physician's Perspective*

ORIGINALLY FROM Australia, Phil Baquie, PsyD, LPC, is a licensed mental health professional who specializes in working with law enforcement and military personnel. He has trained Army Special Forces personnel, Navy SEALs, U.S. Marshals and other federal and state law enforcement agents. Part of his passion comes from his own background in the military, law enforcement and private security contracting professions. He holds a master's degree in counseling and a doctor of psychology degree, with advanced certifications in treating trauma and post-traumatic stress disorder (PTSD). Dr. Baquie serves as a board member at 22Zero, a nonprofit that specializes in alternative treatment options for PTSD.

BSTQ: What is PTSD?

Dr. Baquie: PTSD is a psychiatric disorder that may occur in people who have experienced or witnessed a traumatic event such as a natural disaster, a serious accident, a terrorist act, war/combat or rape.

BSTQ: Tell us about your work with PTSD patients and the 22Zero nonprofit.

Dr. Baquie: My training is as a traditional licensed counselor, and I am also a certified clinical trauma professional. Of course, you can have all the letters after your name, but it's my personal experience, including 12,000 hours working with patients, that has been most beneficial. I've seen the suffering people go through, and I wanted to find better treatment options for them. That's how I connected with 22Zero. After learning about their treatment protocols, I developed my own program called Tactical Presilience, a program specifically for first responders.

BSTQ: What intrigued you about the 22Zero approach?

Dr. Baquie: I was conducting research for my Tactical Presilience program when I came across the work 22Zero is doing for veterans and first responders suffering with PTSD. After flying to Florida to observe a peer-to-peer training for law enforcement, I was astounded by the way police officers were being trained in this technique and were able to dramatically reduce traumatic symptoms in one session with two days of training. As a mental health professional with years of training, it was a real paradigm shift to see how these techniques were redefining the treatment of trauma. Since then, I have incorporated the treatment into my own practice with remarkable results. I continue to maintain a small caseload of patients at my clinics, and I now spend around 70 percent of my time developing, researching and teaching Tactical Presilience and consulting with 22Zero.

BSTQ: Why did you want to focus on preemptive trauma training?

Dr. Baquie: Many programs are reactive and help agencies deal with the weight of critical incidents after they occur; however, there is very little proactive and preemptive training that provides tools for first responders and military personnel prior to critical incidents occurring. Tactical Presilience training is the missing link to provide needed proactive, preemptive and preventive training for first responders and military. It equips their minds with practical tools they can use, so when critical incidents are experienced, they have the resources to deal with them.

BSTQ: How does the treatment approach at 22Zero differ from traditional PTSD treatment?

Dr. Baquie: The most common PTSD treatment is called exposure therapy; it has patients relive and talk through the trauma. It's considered the gold standard, although more recent studies have begun to question actual success rates using this approach. The treatment protocol at 22Zero is called Reconsolidation of Traumatic Memories Protocol, which utilizes powerful visualization techniques to help clients disassociate from the trauma.

BSTQ: What are common misperceptions about PTSD?

Dr. Baquie: In my experience, PTSD tends to be highly overdiagnosed. A trauma diagnosis does not always meet the criteria for PTSD. Temperament, personality and personal experience in childhood all influence whether a traumatic event leads to PTSD. Also, a controversial assumption is that PTSD is permanent. But, techniques like the ones we're employing at 22Zero are helping people get their lives back. Studies are using biomarkers and brain mapping to document progress, and neuroscience is revealing insights about the ability of the brain to heal itself. Trauma does not need to be something someone is stuck with for life. ❖

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

Ryplazim:
The First Definitive Treatment for Congenital Plasminogen Deficiency

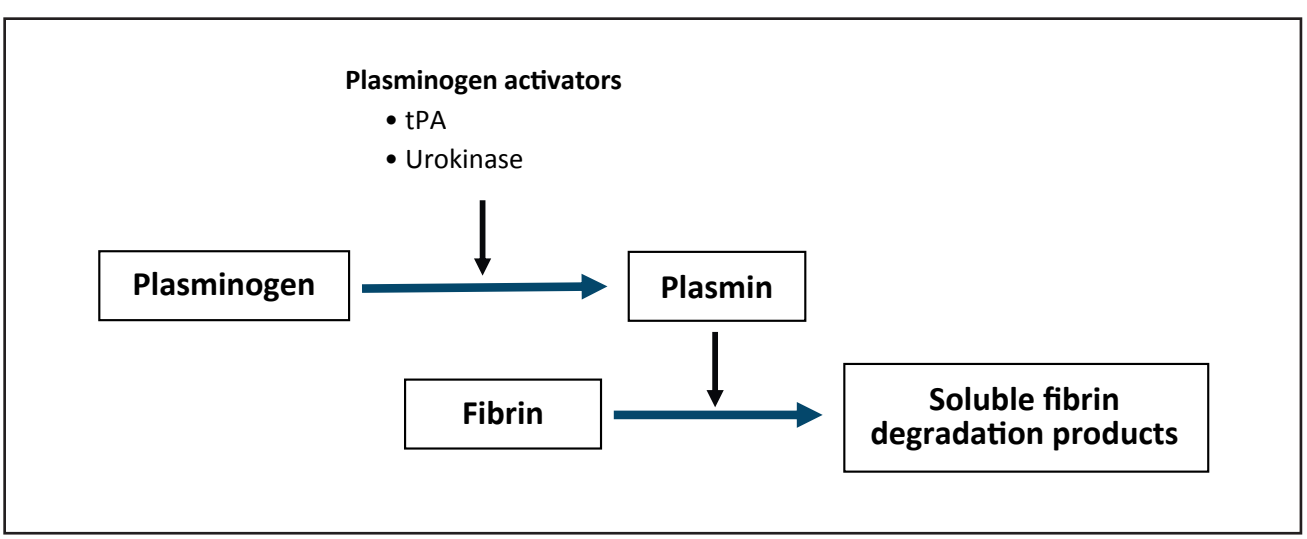
By Keith Berman, MPH, MBA

IT'S AN ultrarare autosomal recessive disorder that occurs in fewer than two of every million individuals,[1] but congenital plasminogen deficiency (PLGD) is known by several names, including type I plasminogen deficiency,* plasminogen deficiency and hypoplasminogenemia. PLGD results from inheritance of defective copies of both alleles of the PLG gene, which yields dysfunctional or too little plasminogen, the key mediator of fibrinolysis following its conversion to enzymatically active plasmin (Figure 1). The end result is impaired extracellular fibrin clearance during wound healing, presenting on affected mucous membranes throughout the body as accumulations of nondegraded fibrin as pseudomembranous ligneous — "woody" — growths. In most cases, the disease is diagnosed within the first year of life.

Ligneous conjunctivitis is by far the most common clinical manifestation of PLGD, occurring in more than 80 percent of diagnosed cases. It is usually triggered by an eye infection or other event that causes ocular inflammation. In the one-third of cases with corneal involvement, ligneous conjunctivitis can result in vision impairment or blindness (Figure 2).[1] These thick, fibrous pseudomembranous lesions can be surgically excised, but invariably they quickly return; in fact, the surgical procedure itself acts to accelerate or trigger lesion regrowth.

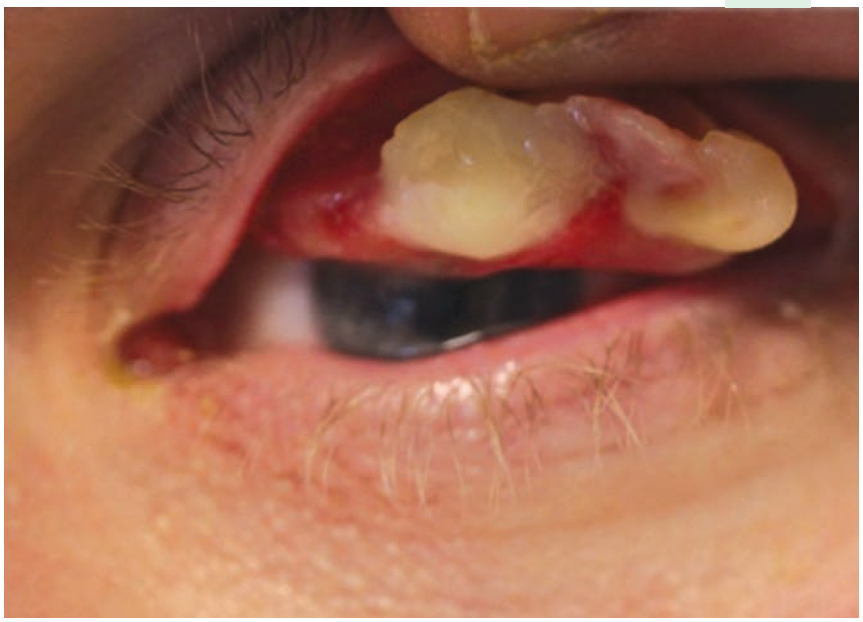
Ligneous growths can occur as well in the mouth, nasopharynx, duodenum, middle ear, brain, respiratory tract and female genital tract, resulting in a host of serious complications. The roughly 30 percent of patients who present with ligneous gingivitis experience both periodontal destruction and tooth loss.[1] Lesions involving the respiratory tract, reported in 20 percent of patients in one large case series,[2] can cause acute, life-threatening airway obstruction and death. Lesions in the middle ear may result in hearing loss. In roughly one in eight children, fibrin deposition in the cerebral ventricular

Figure 1. The Role of Plasminogen and Plasmin in Fibrinolysis



* In type I plasminogen deficiency (hypoplasminogenemia), a variety of nonsense and missense mutations, or a specific deletion, result in parallel reductions in the level of the protein's immunoreactivity and functional activity. In type II plasminogen deficiency (dysplasminogenemia), plasminogen immunoreactivity is normal or near-normal, whereas its specific functional activity is markedly reduced; however, dysfibrinogenemia in isolation is not associated with any disease and may be considered a polymorphic variation in the general population.

Figure 2. Ligneous Conjunctivitis



Source: Wong TA. Woody Eyes, Be Gone! *Blood*, 2018 Mar 22;131(12). Accessed at ashpublications.org/blood/article/131/12/1266/36610/Woody-eyes-be-gone.

system results in occlusive hydrocephalus.[3] In general, a lower residual plasminogen activity level corresponds with a more severe disease burden.

For ligneous conjunctival lesions in particular, various treatments have been tried in an attempt to prevent them from recurring following surgical excision. Trials of nonspecific topical drugs, including corticosteroids, heparin and cyclosporine, have been disappointing.[4,5] A number of case reports have shown that topically administered donor fresh frozen plasma (FFP) eye drops has prevented recurrence over a period of many months or even years.[6,7,8,9] But the FFP must be readministered multiple times each day, and of course it offers no benefit for any other problematic ligneous lesions present elsewhere in the body.

In the late 1990s, several case reports described effective treatment of ligneous conjunctivitis with an investigational Lys-plasminogen product[10,11,12] that was developed by European plasma derivatives manufacturers for potential use as an adjunctive fibrinolytic therapy for vascular thromboses in combination with plasminogen activators.[13] Accounting for less than 10 percent of circulating plasminogen, Lys-plasminogen is a modified form of the zymogen that binds more avidly to fibrin;** most circulating plasminogen is present as Glu-plasminogen. Unfortunately, with a very brief half-life of just 20 hours,[14] Lys-plasminogen did not prove to be practical as a chronic treatment for this lifelong disease.

Clinicians would have to wait more than 20 years for a small Canadian company to develop, test and finally secure U.S. regulatory approval last year for RYPLAZIM, the first definitive treatment for ligneous lesions and their complications in patients afflicted with PLGD.[15] RYPLAZIM is now produced and commercialized by Kedrion Biopharma.[16]

Plasminogen Replacement Therapy with RYPLAZIM

RYPLAZIM is a concentrate of native circulating Glu-plasminogen, purified to greater than a 95 percent purity level using a series of chromatographic adsorbents from large pools of donor human plasma. Any potentially contaminating enveloped and nonenveloped viruses that might have evaded screening tests are removed both by affinity chromatography and 20 nanometer nanofiltration; enveloped viruses, including HIV and hepatitis viruses, are additionally inactivated by solvent/detergent treatment. The mean in vivo half-life of this pooled Glu-plasminogen concentrate is 38 hours to 40 hours, roughly twice that of the Lys form.

> Ligneous conjunctivitis is by far the most common clinical manifestation of PLGD, occurring in more than 80 percent of diagnosed cases.

Dosing frequency with RYPLAZIM plasminogen replacement therapy is individualized over the initial 12 weeks of therapy as dictated by post-infusion

•• The theoretical advantage of Lys-plasminogen in clot thrombolysis is its higher affinity for fibrin and its more rapid conversion to the active fibrinolytic enzyme plasmin than native Glu-plasminogen.

plasminogen activity level testing, and subsequently in accordance with its efficacy in resolving or stabilizing ligneous lesions. The first standard 6.6 mg/kg intravenous dose is administered after a blood draw to measure the patient's baseline plasminogen activity level. If the 72-hour post-infusion trough plasminogen activity level is between 10 percent and 20 percent above baseline, the patient is maintained on an every-three-days (Q3D) dosing frequency over the next 12 weeks. Dosing is increased to Q2D if the 72-hour post-infusion plasminogen level is less than 10 percent above baseline or reduced to Q4D if it is more than 20 percent above baseline.

If lesions resolve by 12 weeks, the patient can remain on the same dosing frequency with monitoring for new or recurrent lesions every 12 weeks thereafter. If they do not resolve by 12 weeks, or there are new or recurrent lesions, the dosing frequency can be increased in one-day increments every four weeks to eight weeks up to Q2D while reassessing clinical improvement until the lesions improve or stabilize without further worsening. However, if the desired outcome does not occur by 12 weeks and the trough plasminogen activity level is more than or equal to 10 percent above the baseline trough level, clinicians are advised to consider other treatment options such as surgical removal of the lesion in addition to plasminogen treatment.

This regimen was put to the test in an open-label Phase II/III study in 14 pediatric and adult patients who completed at least 12 weeks of RYPLAZIM treatment and had a plasminogen activity level less than or equal to 45 percent and documented history of lesions and symptoms consistent with a diagnosis of congenital plasminogen deficiency.[17] Clinical manifestations at presentation ranged in duration from one year to 42 years, with the most extensive disease histories observed in patients with plasminogen activity less than 5 percent of normal.

Clinically visible lesions involving the eyes and gingiva were imaged and their length and width analyzed at baseline, weeks four, eight and 12 and every 12 weeks thereafter. Nonvisible lesions of the nasopharynx, bronchus, colon, kidney, cervix and vagina were variously assessed using medical imaging studies (e.g., ultrasound, magnetic resonance imaging), functional assessments (e.g., spirometry, audiogram, oximetry) or reported clinical symptoms.

All 14 study patients achieved and generally maintained their target trough pre-infusion plasminogen activity levels of more than or equal to 10 percent above baseline across the initial 12-week treatment period. Nine patients had 23 clinically visible lesions in the conjunctiva and gingiva, 18 of which completely resolved and five of which improved by week 12. Six of seven nonvisible internal lesions resolved by week 12, and the seventh resolved by week 24. All three patients who presented with manifestations of abnormal wound healing at baseline (wounds, scars, acne and palmar/plantar warts) showed improvement by week 12. Finally, no new lesions were observed, nor did any existing lesions recur over the study period.[17] "Both the rapidity and the magnitude of the improvement has been remarkable, knowing that in many cases the lesions have been present for years," noted co-investigator John Moran, MD, who helped to design the study.

RYPLAZIM was well-tolerated in both children and adults; there were no serious adverse events and no patient permanently discontinued treatment due to an adverse event. Headache and nasopharyngitis were the most commonly reported adverse events. Several patients experienced nonserious adverse events, including epistaxis, hematuria, dysmenorrhea and/or elevated D-dimer level, which were consistent with fibrinogen's physiologic fibrinolytic and lesion dissolution activity. Reassuringly, no antiplasminogen antibodies were detected in any patient.

RYPLAZIM "represents a pivotal breakthrough in the treatment of this very rare coagulation deficiency and an important therapeutic advance for affected patients who have suffered under the burden of their disease due to lack of an available efficacious therapy," the study authors concluded.[17]

While PLGD affects only an estimated 500 U.S. children and adults, its health toll can be profound.

The Newest Rare Disease Plasma Protein Therapy

While PLGD affects only an estimated 500 U.S. children and adults,[1] its health toll can be profound. "Congenital plasminogen deficiency can impact self-image, quality of life and ability to achieve

full potential in school and/or work," said Amy Shapiro, MD, who served as principal investigator on the pivotal Phase II/III trial. For these individuals, for whom no specific treatment was available until now, RYPLAZIM therapy can be transformative.

But Dr. Shapiro points out one final potential obstacle for PLGD patients: Its extreme rarity "results in frequent mis- and delayed diagnoses by professionals lacking specialist knowledge."[1] This, in turn, has limited our understanding of the disease's natural history, and to date has thwarted development of clinical guidelines.

To address this, Dr. Shapiro and collaborators have established a registry called the Plasminogen Deficiency Study, which will capture data from an international population of people with PLGD and their immediate family members over a four-year period. Those who know of or care for anyone with PLGD are encouraged to visit the Plasminogen Deficiency Study website (www.plgdeficiency.com) or contact Dr. Shapiro directly (ashapiro@ihtc.org) at the Indiana Hemophilia & Thrombosis Center. ❖

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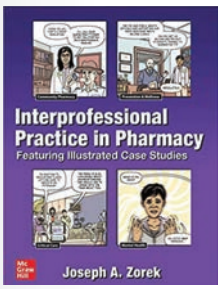
KEITH BERMAN, MPH, MBA, is the founder of Health Research Associates, providing reimbursement consulting, business development and market research services to biopharmaceutical, blood product and medical device manufacturers and suppliers. He also serves as editor of *International Blood/Plasma News*,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



Interprofessional Practice in Pharmacy: Featuring Illustrated Case Studies, 1st Edition

Author: Joseph A. Zorek

This book presents an accessible, in-depth exploration of pharmacists working to advance the safe and effective use of medications. Descriptions demonstrate how pharmacists work within interprofessional teams and contribute to the interprofessional care of patients in multiple healthcare settings. Illustrated case studies provide a window into the profession of pharmacy. Readers will enjoy exploring healthcare through the lens of pharmacists, including contemporary issues such as infectious disease outbreaks and the opioid crisis.

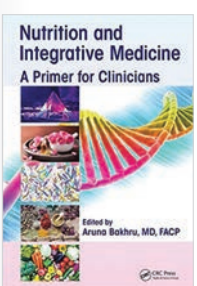
www.amazon.com/dp/1260462420

Nutrition and Integrative Medicine: A Primer for Clinicians, 1st Edition

Author: Aruna Bakhru, MD, FACP

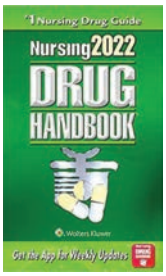
This book offers insights on the microbiome of the human body, examines the relationship of human health to the microbiome and food, and introduces the concept of "food as information." It provides enlightenment on anti-aging and healing modalities, mind-body medicine and an investigation of psychological trauma related to disease causation. Integrative therapies, including water, light and sound therapy, are explored, and information on healing chronic disease through nutrition, the tooth-body connection, the role of toxins in disease causation, and electromagnetic field hypersensitivity, as well as its management, is presented.

www.amazon.com/dp/1032094885



Nursing 2022 Drug Handbook, Forty-Second North American Edition

Author: Lippincott, Williams & Wilkins



This handbook is a completely updated nursing-focused drug monograph featuring 3,500 generic, brand-name and combination drugs in an easy A-to-Z format. This edition includes 32 new U.S. Food and Drug Administration-approved drugs, including the COVID-19 drug remdesivir, as well as thousands of clinical updates, including new dosages and indications, black box warnings, genetic-related information, adverse reactions, nursing considerations, clinical alerts and patient teaching information. There is a special focus on U.S. and Canadian drug safety issues and concerns, as well as a photoguide insert with images of 439 commonly prescribed tablets and capsules. Also included is a free online companion toolkit.

www.amazon.com/Nursing2022-Drug-Handbook-Nursing/dp/1975158881

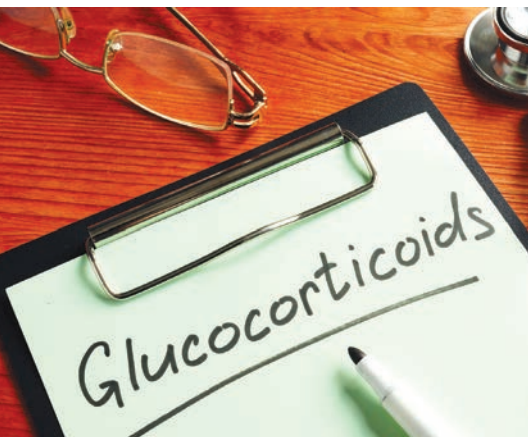
Top 300 Drugs Pocket Reference Guide

Author: Coventry House Publishing

The *Top 300 Drugs Pocket Reference Guide* serves as a portable reference to learn the essential information for the most commonly prescribed drugs. This on-the-go resource details the brand name, pharmacologic class, mechanism of action, dosage form, common use and other clinical details for each drug. This guide serves as an effective resource to learn the basic characteristics of the most popular drugs.

www.amazon.com/dp/1736696157

IVIG Plus Glucocorticoids Superior to IVIG Alone for MIS-C Associated with COVID-19: Review and Meta-Analysis



While the etiology and pathogenesis of multisystem inflammatory syndrome (MIS-C) in children associated with SARS-CoV-2 infection remains unclear, the resemblance of its manifestations to Kawasaki disease has prompted use of intravenous immune globulin (IVIG) alone or in combination with glucocorticoids. Given the absence of a consensus or guidelines to guide optimal treatment of MIS-C with these agents, U.S. and Nepalese collaborators performed a systematic review and meta-analysis of qualifying studies conducted from January 2020 to August 2021.

Three studies, which cumulatively enrolled 756 pediatric patients less than 21 years of age, were included in the final quantitative analysis. Initial therapy with IVIG plus glucocorticoids significantly lowered the risk of treatment failure relative to IVIG therapy alone (odds ratio [OR] 0.57; 95% confidence interval [CI] 0.42 to 0.79; I2 45.36%) and the need for adjunctive immunomodulatory therapy (OR 0.27; 95% CI 0.20, 0.37; I2 0.0%). The combination therapy was not associated with a reduction in occurrence of ventricular dysfunction (OR 0.79; 95% CI 0.34 to 1.87, I2 58.44%) or the need for inotropic support (OR 0.83; 95% CI, 0.35 to 1.99, I2 75.40%).

"This study supports the use of IVIG with glucocorticoids compared to IVIG alone, as the combination therapy significantly lowered the risk of treatment failure and the need for adjunctive immunomodulatory therapy," the investigators concluded. ❖

Rauniyar R, Mishra A, Kharel S, et al. IVIG plus glucocorticoids versus IVIG alone in multi-system inflammatory syndrome in children (MIS-C) associated with COVID-19: A systematic review and meta-analysis. *Can J Infect Dis Med Microbiol* 2022 Mar 29:9458653.

Plasma Prekallikrein Inhibition by Antisense Oligonucleotide Reduces Hereditary Angioedema Disease Burden

An investigational antisense oligonucleotide (donidalorsen) that acts by degrading plasma prekallikrein messenger RNA was evaluated in patients with hereditary angioedema (HAE) and C1 inhibitor deficiency to assess whether this agent can reduce the frequency of angioedema attacks and the burden of disease.

In this Phase II trial, 20 HAE patients were randomized in a 2:1 ratio to receive four subcutaneous 80 mg doses of either donidalorsen or placebo, with one dose administered every four weeks. The primary endpoint was the time-normalized number of investigator-confirmed angioedema attacks per month between week 1 (baseline) and week 17.

From baseline, prekallikrein activity in the donidalorsen group decreased by 61 percent by the end of the study. The mean monthly angioedema attack rate was 0.23 (95% confidence interval [CI] 0.08 to 0.39), compared to 2.21 in those receiving placebo (95% CI 0.58 to 3.85), a mean difference of 90 percent. This closely corresponded with a 95 percent reduction in the number of attacks per month that required on-demand therapy between week 5 and week 17 (95% CI -99% to -52%). Beyond week 5, just one of 14 patients in the donidalorsen group experienced an attack, versus all six subjects in the placebo group.

The mean change in the 100-point Angioedema Quality of Life Questionnaire was -26.8 points in the donidalorsen group and -6.2 points in the placebo group. No serious adverse events were reported in either group. The investigators concluded that, in this small Phase II trial, donidalorsen treatment resulted in a significantly lower rate of angioedema attacks than placebo. [Study funded by Ionis Pharmaceuticals.] ❖

Fijen LM, Riedl MA, Bordone L, et al. Inhibition of prekallikrein for hereditary angioedema. *New Engl J Med* 2022 Mar 17; 386(11):1026-33.

Medicare Immune Globulin Reimbursement Rates

Rates are effective July 1, 2022, through Sept. 30, 2022

	Product	Manufacturer	J Codes	ASP + 6% (before sequestration)	ASP + 4.3% (after sequestration)
IVIG	ASCENIV	ADMA Biologics	J1554	$963.54	$948.09
	BIVIGAM	ADMA Biologics	J1556	$140.98	$138.72
	FLEBOGAMMA DIF	Grifols	J1572	$81.04	$79.74
	GAMMAGARD SD	Takeda	J1566	$146.35	$144.00
	GAMMAPLEX	BPL	J1557	$96.68	$95.13
	OCTAGAM	Octapharma	J1568	$84.04	$82.69
	PANZYGA	Octapharma/Pfizer	90283/J1599	$138.70	$136.48
	PRIVIGEN	CSL Behring	J1459	$93.87	$92.36
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$89.99	$88.55
	GAMMAKED	Kedrion	J1561	$86.78	$85.39
	GAMUNEX-C	Grifols	J1561	$86.78	$85.39
SCIG	CUTAQUIG	Octapharma	J1551	$120.28	$118.35
	CUVITRU	Takeda	J1555	$149.71	$147.31
	HIZENTRA	CSL Behring	J1559	$123.47	$121.49
	HYQVIA	Takeda	J1575	$158.94	$156.39
	XEMBIFY	Grifols	J1558	$135.69	$133.51

Calculate your reimbursement online at www.FFFenterprises.com.

Immune Globulin Reference Table

	Product	Manufacturer	Indication	Size
IVIG	ASCENIV LIQUID, 10%	ADMA Biologics	PI	5 g
	BIVIGAM LIQUID, 10%	ADMA Biologics	PI	5 g, 10 g
	FLEBOGAMMA 5% DIF Liquid	Grifols	PI	0.5 g, 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)	Takeda	PI, ITP, B-cell CLL, KD	2.5 g, 5 g, 10 g
	GAMMAPLEX Liquid, 5%	BPL	PI, ITP	2.5 g, 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, 25 g
	OCTAGAM Liquid, 10%	Octapharma	ITP, DM	2 g, 5 g, 10 g, 20 g, 30 g
	PANZYGA Liquid, 10%	Octapharma/Pfizer	PI, ITP, CIDP	2.5 g, 5 g, 10 g, 20 g, 30 g
	PRIVIGEN Liquid, 10%	CSL Behring	PI, ITP, CIDP	5 g, 10 g, 20 g, 40 g
IVIG/SCIG	GAMMAGARD Liquid, 10%	Takeda	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, 2.5 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	CUTAQUIG Liquid, 16.5%	Octapharma	PI	1 g, 1.65 g, 2 g, 3.3 g, 4 g, 8 g
	CUVITRU Liquid, 20%	Takeda	PI	1 g, 2 g, 4 g, 8 g, 10 g
	HIZENTRA Liquid, 20%	CSL Behring	PI, CIDP	1 g, 2 g, 4 g, 10 g 1 g PFS, 2 g PFS, 4 g PFS
	HYQVIA Liquid, 10%	Takeda	PI	2.5 g, 5 g, 10 g, 20 g, 30 g
	XEMBIFY Liquid, 20%	Grifols	PI	1 g, 2 g, 4 g, 10 g

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

2022-2023 Influenza Vaccine

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

Product	Manufacturer	Presentation	Age Group	Code
Quadrivalent				
AFLURIA (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	3 years and older	90686
AFLURIA (IIV4)	SEQIRUS	5 mL MDV	6 months and older	90687/90688
FLUAD (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90694
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	6 months and older	90674
FLUCELVAX (ccIIV4)	SEQIRUS	5 mL MDV	6 months and older	90756*
FLULAVAL (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUMIST (LAIV4)	ASTRAZENECA	0.2 mL nasal spray 10-BX	2-49 years	90672
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL SDV 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	5 mL MDV	6 months and older	90688
FLUZONE HIGH-DOSE (IIV4)	SANOFI PASTEUR	0.7 mL PFS 10-BX	65 years and older	90662

ccIIV4 Cell culture-based quadrivalent inactivated injectable
IIV4 Egg-based quadrivalent inactivated injectable
LAIV4 Egg-based live attenuated quadrivalent nasal spray

* 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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