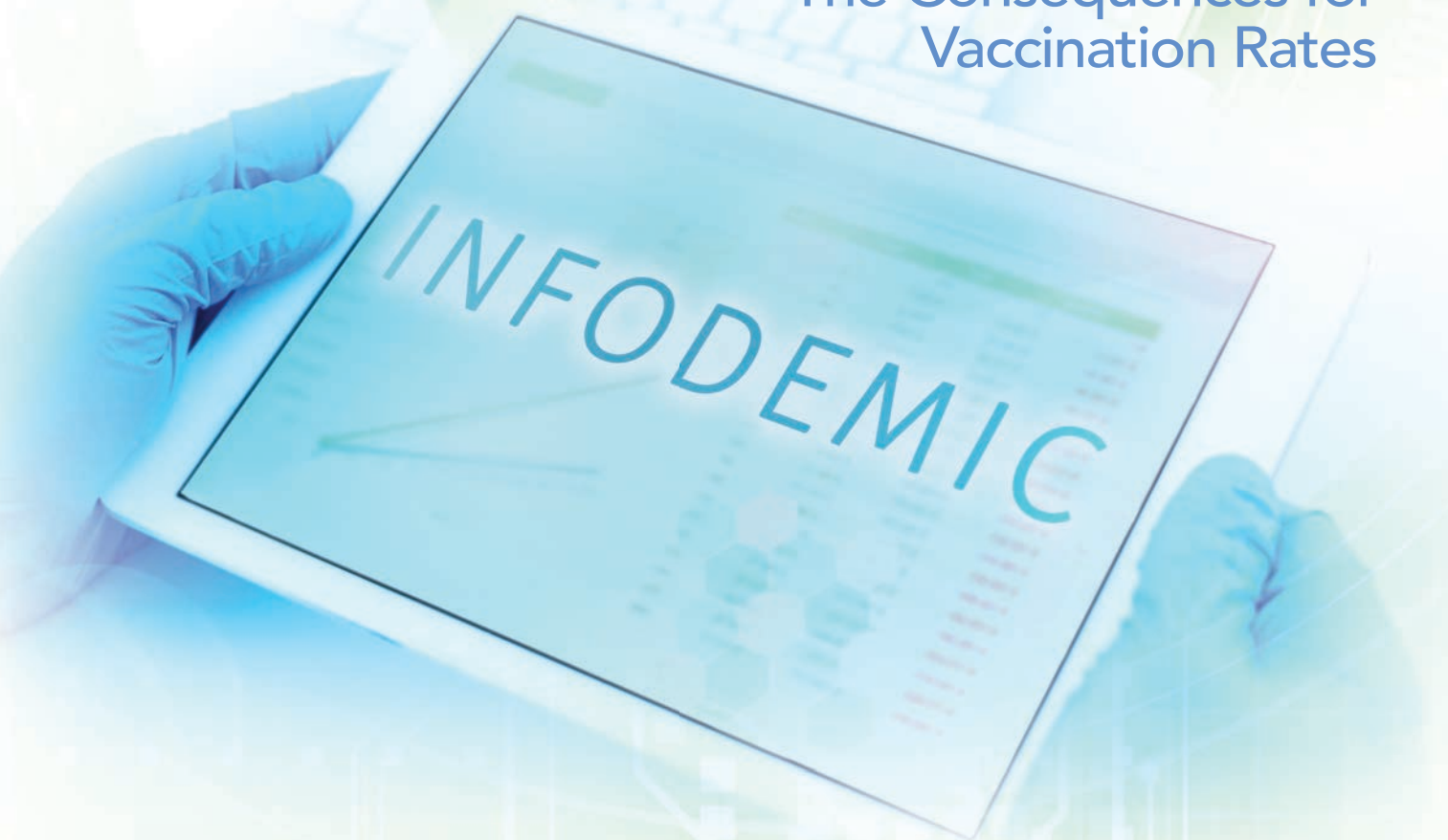
biosupplytrends
QUARTERLY
SUMMER 2023 VACCINES

Medical Misinformation

The Consequences for Vaccination Rates



ADDRESSING MISCONCEPTIONS ABOUT Adult Vaccines

Personalized Cancer Vaccines: PROMISING OUTCOMES ON THE HORIZON

WHAT NEW Biosimilar Legislation MEANS FOR DRUG ACCESS

MYTHS AND FACTS ABOUT Autism

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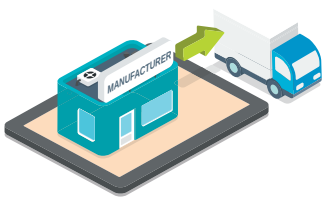
GuaranteedChannelIntegrity®

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

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STEP 3

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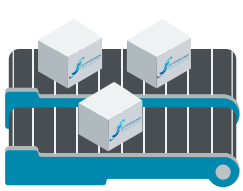

Our commitment to a secure pharmaceutical supply chain is demonstrated by our flawless safety record. The 8 Critical Steps to Guaranteed Channel Integrity have resulted in more than 11,600 counterfeit-free days of safe product distribution.

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STEP 5

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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

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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

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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.

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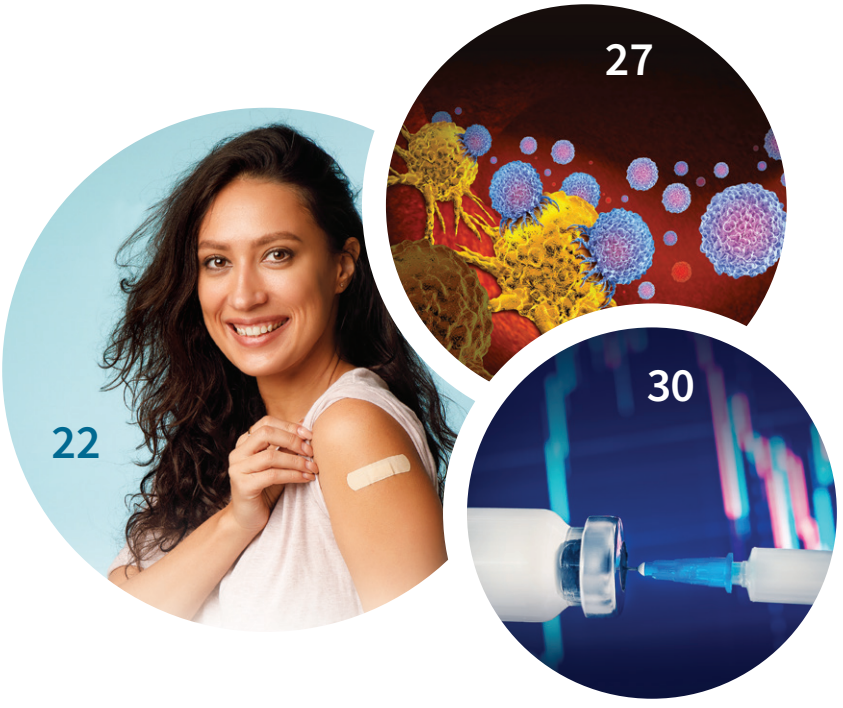

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About BioSupply Trends Quarterly
BioSupply Trends Quarterly is the definitive source for industry trends, news and information for healthcare professionals in the biopharmaceuticals marketplace.

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The Spread of Misinformation and Its Effects on Vaccines

THE SPREAD of misinformation regarding vaccines is nothing new. In fact, some form of vaccine hesitancy has been occurring since the first vaccine was administered more than 200 years ago. Today, however, the effects of exposure to misinformation about vaccines has been exacerbated by the COVID-19 pandemic. Prior to the pandemic, social media platforms had few policies that addressed vaccine misinformation. But now, with increasing public and political pressure, most of the major platforms all have explicit policies regarding COVID-19 and vaccine misinformation more broadly. Nevertheless, misinformation continues to flourish with damaging consequences.

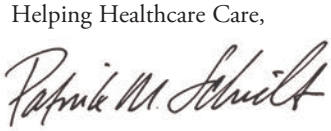
Political motivation rather than scientific data and research is perhaps one of the most problematic issues surrounding vaccine misinformation. And, as we explain in our article "How Medical Misinformation About Vaccines Is Spread" (p.16), while social media is often considered the main driver of misinformation, healthcare professionals, websites, blogs, media outlets and celebrities also contribute to its spread. Regrettably, the serious consequences arising from vaccine misinformation such as lack of herd immunity that is resulting in disease outbreaks are increasingly being felt. Therefore, it can't be overstressed that healthcare professionals are key to combating the spread of misinformation by learning how to recognize it and sharing accurate, up-to-date, evidence-based information.

While a majority of the public attributes vaccine misinformation to childhood, influenza and COVID-19 vaccines, what seldom gets attention is how misinformation, conflicting information and lack of access contribute to adult vaccine hesitancy. We report in our article "Adult Vaccines: Fact vs. Fiction" (p.22) that at least three out of four adults are missing one or more recommended vaccines. Indeed, it's often overlooked that adults need a Tdap booster every 10 years in addition to annual influenza and COVID-19 vaccines, and some adults with various health issues also require pneumococcal, hepatitis B and herpes zoster vaccines, but most don't receive them. This is mainly a result of five misconceptions that we address, as well as lack of provider-patient communication. Fortunately, organizations such as the American Academy of Family Physicians and the Centers for Disease Control and Prevention, among others, have developed campaigns to encourage adult vaccine compliance and have outlined specific steps providers can take to ensure their patients get vaccinated.

With cancer now the second-leading cause of death worldwide, it's no surprise that research to develop vaccines that prevent and/or cure cancer, which have been in development for decades, are now rapidly progressing with the success of the mRNA COVID-19 vaccines. In our article "Personalized Cancer Vaccine Development" (p.27), we describe the research behind many of these vaccines, which utilize mRNA, DNA and tumor antigen peptide technologies. It is projected that by controlling the costs of developing these vaccines, one may be available soon. It can only be hoped that misinformation won't foil their promise.

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

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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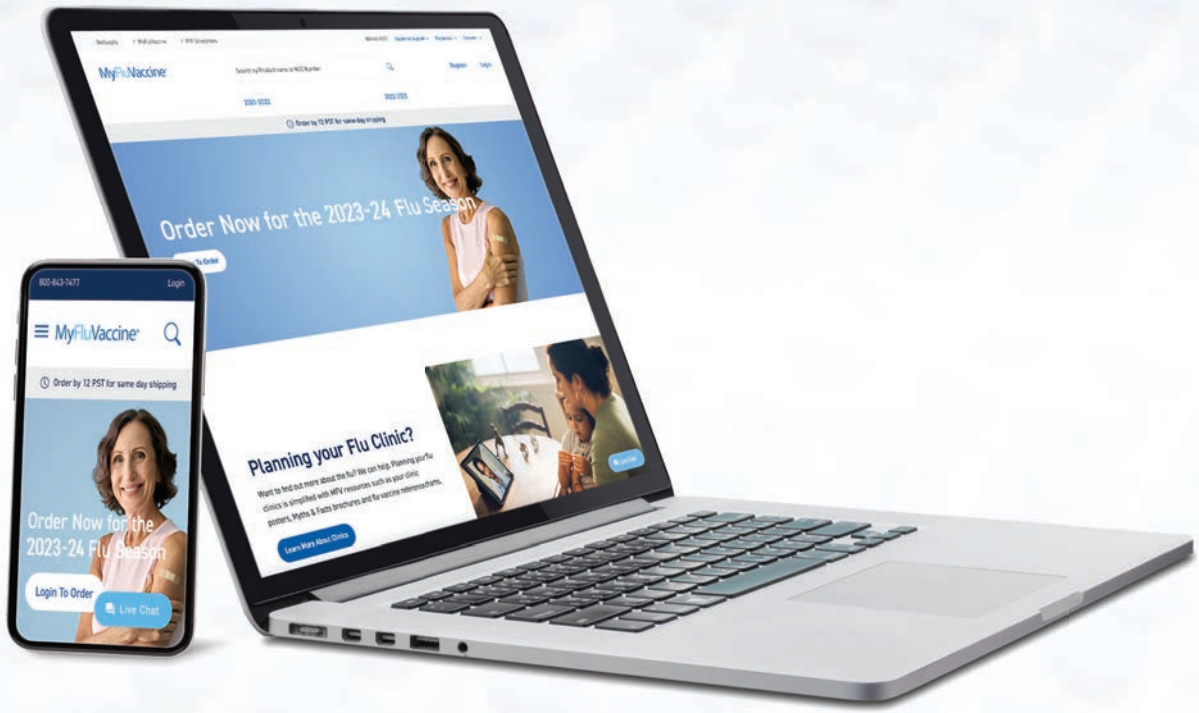

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HHS Issues Amendment to PREP Act for Medical Countermeasures Against COVID-19

The U.S. Department of Health and Human Services (HHS) has issued an amendment to the declaration under the Public Readiness and Emergency Preparedness (PREP) Act for medical countermeasures against COVID-19. The PREP Act declaration ensures Americans have broad access to critical COVID-19 countermeasures, including vaccines, tests and treatments, and has provided flexibilities and protections for those individuals and entities who have been involved in providing the tools that have helped the United States get to a better place with COVID-19.

For the past three years, much of the healthcare landscape — including pharmacies — has relied on these flexibilities and liability protections. By issuing this amendment, the Secretary of HHS intends to allow pharmacies to continue their critical roles, even after certain products transition to traditional healthcare pathways. However, the end of the COVID-19 public health emergency alone does not automatically terminate PREP Act coverage for countermeasures.

Key changes to the PREP Act include:

- Extending coverage for COVID-19 vaccines, seasonal influenza vaccines and COVID-19 tests.
- Extending coverage through December 2024 for federal agreements, including all activities related to the provision of COVID-19 countermeasures that are 1) provided based on a federal agreement (including the vaccines and treatments purchased and provided by the United States government [USG]), or 2) directly conducted by the USG, including by federal employees, contractors or volunteers.
- Ending coverage for certain activities. Once products are no longer distributed under a USG agreement, PREP Act coverage will no longer extend to COVID-19 vaccination by nontraditional providers (e.g., recently retired providers and students) and COVID-19 vaccinations across state lines by licensed providers and pharmacists and pharmacy interns.
- Ending coverage for routine childhood vaccinations. ❖

HHS Announces Intent to Amend the Declaration Under the PREP Act for Medical Countermeasures Against COVID-19. U.S. Department of Health and Human Services press release, April 14, 2023. Accessed at www.hhs.gov/about/news/2023/04/14/factsheet-hhs-announces-amend-declaration-prep-act-medical-countermeasures-against-covid19.html?utm_source=news-releases-email&utm_medium=email&utm_campaign=april-16-2023.

Grants Provided for Certified Behavioral Health Clinics

Two funding opportunities for Certified Community Behavioral Health Clinic (CCBHC) expansion, totaling $123.6 million, were made available by the U.S. Department of Health and Human Services. The CCBHC Planning, Development and Implementation grant aims to assist clinics to establish and implement new CCBHC programs, and the CCBHC Improvement and Advancement grant seeks to enhance and support existing CCBHCs that currently meet the CCBHC Certification Criteria.

Made possible through the Bipartisan Safer Communities Act, HHS awarded 15 states each with $1 million, one-year CCBHC planning grants, the first time these planning grants have been available since the program began in 2015. In 2024, up to 10 of those will participate in the CCBHC Medicaid demonstration program and receive enhanced Medicaid reimbursement. The full CCBHC demonstration program provides reimbursement through Medicaid for the full cost of services that CCBHCs provide, at higher, more competitive rates than community mental health centers previously received. This sustainable funding also ensures they can provide a more comprehensive range of services rather than fragmented services driven by billing codes.

CCBHCs were created to transform mental health and substance use treatment across the country and provide sustainable funding for robust community outpatient mental health treatment. CCBHCs are required to provide a range of services, including crisis services that are available 24 hours a day, seven days a week. ❖

HHS Announces Over $120 Million In Funding Opportunity for Certified Community Behavioral Health Clinics Providing Mental Health and Substance Use Disorder Care Across the Country. U.S. Department of Health and Human Services press release, March 24, 2023. Accessed at www.hhs.gov/about/news/2023/03/24/hhs-announces-over-120-million-funding-opportunity-certified-community-behavioral-health-clinics-providing-mental-health-substance-use-disorder-care-across-country.html?utm_source=news-releases-email&utm_medium=email&utm_campaign=march-26-2023.

HHS Creates New Office of Family Violence Prevention and Services

The U.S. Department of Health and Human Services (HHS) has announced a new Office of Family Violence Prevention and Services (OFVPS) under the Administration for Children and Families (ACF). Three of the priority goals of the new OFVPS will be to:

• Develop an ACF-wide strategy and action plan for the prevention of and response to domestic violence across social service programs. This ACF-wide strategy will better leverage existing services available for survivors of domestic violence, intimate partner violence and dating violence; maximize public-private partnerships; and strengthen coordination with other federal and state government funding mechanisms for survivors.

• Maintain and lead coordination and collaboration efforts across agency partners, including continued and strengthened partnerships with the new HHS Office of Assistant Secretary for Health's Director of Sexual & Gender-Based Violence, the Department of Justice, the Department of Housing and Urban Development and more.

• Prioritize the continued implementation appropriations to support survivors of domestic violence and sexual assault.

"This new office underlines ACF's commitment to prevention programs, survivor services and a whole family approach to serving families when they need it most," said ACF Assistant Secretary January Contreras. "ACF will continue to implement a comprehensive strategy to promote violence prevention through programs and resources that impact survivors' physical and behavioral health, safety, well-being, housing, economic mobility and family stability." ❖

HHS Strengthens Response to Domestic Violence Through the New Office of Family Violence Prevention and Services. U.S. Department of Health and Human Services press release, March 20, 2023. Accessed at www.hhs.gov/about/news/2023/03/20/hhs-strengthens-response-domestic-violence-through-new-office-family-violence-prevention-services.html.

Initial Guidance Established for Medicare Drug Price Negotiation Program for Price Applicability Year 2026

For the first time, Medicare will have the ability to negotiate lower prescription drug prices because of the Inflation Reduction Act, a law that lowers healthcare and prescription drug costs after the U.S. Department of Health and Human Services, through the Centers for Medicare and Medicaid Services (CMS), issued initial guidance detailing the requirements and parameters on key elements of the new Medicare Drug Price Negotiation Program for 2026, the first year the negotiated prices will apply. Alongside other provisions in the new drug law, the Medicare Drug Price Negotiation Program will strengthen Medicare's ability to serve people currently in Medicare and for generations to come.

This initial guidance is one of a number of steps CMS laid out in the Medicare Drug Price Negotiation Program timeline for the first year of negotiation. The initial program guidance

details the requirements and procedures for implementing the new program for the first set of negotiations, which will occur during 2023 and 2024 and result in prices effective in 2026. Key dates for implementation include:

• By Sept. 1, 2023, CMS will publish the first 10 Medicare Part D drugs selected for initial price applicability for year 2026.

• The negotiated maximum fair prices for these drugs will be published by Sept. 1, 2024, and prices will be in effect starting Jan. 1, 2026.

• In future years, CMS will select for negotiation up to 15 more Part D drugs for 2027, up to 15 more Part B or Part D drugs for 2028, and up to 20 more Part B or Part D drugs for each year after that, as outlined in the Inflation Reduction Act.

"Drug price negotiation is a critical piece of how this historic law improves the Medicare program," said CMS Administrator Chiquita Brooks-LaSure. "By considering factors such as clinical benefit and unmet medical need, drug price negotiation intends to increase access to innovative treatments for people with Medicare." ❖

HHS Releases Initial Guidance for Historic Medicare Drug Price Negotiation Program for Price Applicability Year 2026. U.S. Department of Health and Human Services press release, March 15, 2023. Accessed at www.hhs.gov/about/news/2023/03/15/hhs-releases-initial-guidance-historic-medicare-drug-price-negotiation-program-price-applicability-year-2026.html?utm_source=news-releases-email&utm_medium=email&utm_campaign=march-12-2023.

Tips for Operating on Razor-Thin Margins

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

HEALTHCARE PROVIDERS across the nation have marked well more than a year of consecutive negative margins as they experience the effects of higher expenses. Many currently risk closing without some type of legislative support or other financial lifeline. When examining budgets, the direction often given is to concentrate on driving down expenses for drug costs and reducing personnel and other overhead. Yet, at the same time, providers often neglect to highlight their potential for a tremendous revenue contribution or even bring this to the attention of the C-suite. It's a simple concept: Every budget has an expense side and a revenue side. One could argue that if expenses (e.g., personnel) were driven down precipitously and revenue opportunities were ignored, providers would not have met their potential for mitigating those negative margins.

Payer Tools and Tactics

Of course, payers hold the keys to payments, and denials for submitted claims are rampant. From the payers' perspective, they must appropriately plan and manage benefit coverage for the many expensive high-investment drugs in the pipeline. This includes specialty drugs, biologics, immunotherapy products and biosimilars. The tools/tactics they use include prior authorization, bundled payments, moving drug products out of the medical and into the pharmacy benefit, mandating treatment pathways and closed formularies, stipulating site of care, and even creating "payvider" risk-sharing collaborations between payers and providers.

But, there's a difference between the prospective approach of denials prevention and denials management, which often is the fruitless, time- and resource-consuming quest to overturn the denial and collect revenue. Prevention hinges on telling the patient's story completely and accurately with appropriate documentation that is codable. This hinges on proving the medical necessity of both the service and the treatment. The outpatient/ambulatory environment is ripe with opportunities to do this in the infusion clinic, oncology clinic and other areas that dispense biologics and immunotherapy products.

Working in tandem with the revenue cycle team, facilities are responsible for knowing the payers and their requirements; understanding site-of-care stipulations; completing prior authorizations (PAs); understanding local and national coverage determination requirements; following mandated step therapy; confirming ICD-10 code matches; and ensuring electronic health record and coding accuracy. Failure of any one of these multiple steps results in payment denial!

Moving forward, Congress is reforming the PA process and is considering mandating real-time prior authorization decisions, among other approaches. Whether or not these reductions will apply to specialty pharmaceuticals, including biologics and biosimilars, remains to be seen.

On April 5, the Centers for Medicare and Medicaid Services (CMS) finalized the Prior Authorization Rule to help ensure beneficiaries in both Medicare Advantage (MA) and traditional Medicare programs receive access to the same medically necessary care. MA plans must comply with national and local coverage determinatons (NCDs and LCDs) and the general coverage/benefit of traditional Medicare regulations. But, coverage criteria has not been fully established: MA may create internal coverage criteria based on publicly available current evidence in widely used treatment guidelines or clinical literature. In full transparency, MA plans must explicitly state circumstances when they may apply internal coverage criteria. Streamlining PA requirements is designed to ensure continuity of care and reduce disruption for beneficiaries. As part of a coordinated care plan, PAs can be used only to confirm the diagnoses or other medical criteria and/or ensure an item or service is medically necessary. Plans must provide a minimum 90-day transition period if enrollees currently undergoing treatment switch MA plans (new plans can't require PA). The PA request of approval for a course of treatment must be valid for as long as medically reasonable and necessary to avoid disruptions in care in accordance with applicable coverage criteria, the patient's medical history and the treating provider's recommendation. The MA plan also must establish a Utilization

Management Committee, review policies annually and ensure consistency with traditional Medicare NCDs/LCDs.

At the same time, payers are altering their approach, with some reducing the number of required authorizations. Each payer handles PAs differently, and many are accused of using this delay/refusal tactic strictly as a financial measure. It's frustrating for healthcare providers and deleterious to patients, especially if the nature of the illness is life-threatening. It also can be seen as a control issue. Who's making the decision about appropriate treatment: the provider or the payer?

Site of care can enter into reimbursement as well. For instance, a claim can be approved for drug A if given in a free-standing nonhospital-based location to decrease the cost and not pay up-charging facility fees. On the other hand, a claim can be denied for drug A if given in an inpatient setting or even a hospital-based infusion center.

Being aware of who the payer is before proceeding forward with providing the drug or biologic is a key step. Indeed, knowing who the primary and secondary payers are, as well as their requirements for payment, is essential to ensuring a complete clean claim can be submitted.

There are four different types of medical necessity:

1) Medical necessity for the service itself (The patient has a diagnosed cancer and would like to be treated at the facility; does the payer coverage include the facility for that diagnosis?)

2) Medical necessity for the status (This includes inpatient vs. outpatient and initial and continuing therapy.)

3) Medical necessity for the setting (Has the payer mandated site of care and, if so, is the facility authorized? If site of care mandates a free-standing center, a hospital-based infusion center will not likely be paid.)

4) Medical necessity for the product (If a payer mandates PA, how is this confirmed *before* the patient arrives for treatment?)

Whomever is responsible for handling each of these types of medical necessity must have the appropriate skill levels. And, that person must know each patient's specific medical benefit plan.

Self-Administered Drugs

Each Medicare Administrative Contractor (MAC) publishes its own self-administered drug (SAD) exclusion list. Providers must be aware of what products are on the list and how those products are to be used, documented and accounted for.

SADs excluded from payment are those administered by patients to themselves; they don't include administration by spouses, nursing aides, allied health professionals or physicians. A rare exception may include payment for an oral anticancer drug or an antiemetic given with chemotherapy treatments.

While each MAC makes its own list, many follow standard CMS listings and definitions, including:

Route of administration

- Drugs delivered intravenously are presumed to be *not usually* self-administered.
- Drugs injected intramuscularly are presumed to be *not usually* self-administered, although depth and nature of the drug may be considered.
- Drugs administered subcutaneously are considered to be *usually* self-administered.

Status of the condition

- Acute: any condition that the expected course of treatment is less than two weeks
- Chronic: any condition that requires treatment for more than two weeks

Frequency of administration

- Infrequent injections: drugs given monthly or less than once per month
- Frequent injections: drugs given one or more times per week or more than once per month

Route-of-administration modifiers are now required by some MACs. The JA and JB modifiers apply to drugs that have multiple routes of administration but only one HCPCS Level II code (J or Q). The JA modifier applies to intravenous administration of drugs and the JB modifier applies to subcutaneous administration. Payment for subcutaneously administered drugs on the SAD list will be denied, as will claims for drugs on the list that are billed without the modifiers.

Providers should search the SAD list on their MAC's website and develop a protocol for handling medications that will not be paid for, rather than letting them be a trigger for a denied claim. ❖

Resource

1. Centers for Medicare and Medicaid Services. 2024 Medicare Advantage and Part D Final Rule (CMS-4201-F), April 5, 2023. Accessed at www.cms.gov/newsroom/fact-sheets/2024-medicare-advantage-and-part-d-final-rule-cms-4201-f.
2. Centers for Medicare and Medicaid Services. CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, Sections 50.5.3 and 50.5.4. Accessed at www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=53127&ver=119&bc=0.

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.

Reducing Healthcare Costs for Patients

With economic burdens continuing to pressure the American people, easing the financial strain of healthcare is more important than ever.

By Meredith Whitmore

THE EVER-RISING expense of healthcare is not only a patient's concern — it's also the healthcare system's responsibility to lower costs. Part of a healthcare provider's duty is to protect patients from exorbitant fees for even routine procedures. In 2020, U.S. healthcare costs totaled $4.1 trillion, making it one of the country's costliest expenses.[1] Health spending accounted for 19.7 percent of the nation's gross domestic product that same year.[2] That equals an annual healthcare cost of $12,530 per person in 2020 versus roughly $150 per person in 1960.[3,4]

The United States' dependence on the health insurance model has increased administration expenses. Studies have found such expenditures make up about 15 to 25 percent of U.S. healthcare costs. Roughly half of those costs are due to the complexity of billing alone. For example, a 2018 *Journal of the American Medical Association* study found that American physicians used 14.5 percent of their primary care revenue just on administrative billing costs.[5]

Add to this the expense of high-tech equipment, treatments, facilities and other indispensable and costly necessities. According to Molly Cooke, MD, FACP, professor of medicine at the University of California, San Francisco, "Our country is remarkably generative in the development of new diagnostic tests, drugs and procedures — and remarkably undisciplined in their deployment."[5]

Such financial quandaries and bloat have caused healthcare systems to look at ways to reduce costs without compromising patients' safety or quality of care, requiring strategy. It's difficult, however, to know where to start, since so many financial strains affect expenses. The following ideas could give providers and hospital systems direction to begin the process of easing the burden on patients.

Prevent Burnout and Turnover Among Healthcare Staff

When it comes to preventing employee burnout and turnover, the major question is: "How can we improve our staff's work experience?" The answer is to support healthcare staff by empowering them to succeed, equipping them to work more effectively and fostering a positive workplace culture to help everyone, including the patients for whom healthcare workers provide care, by:[6,7]

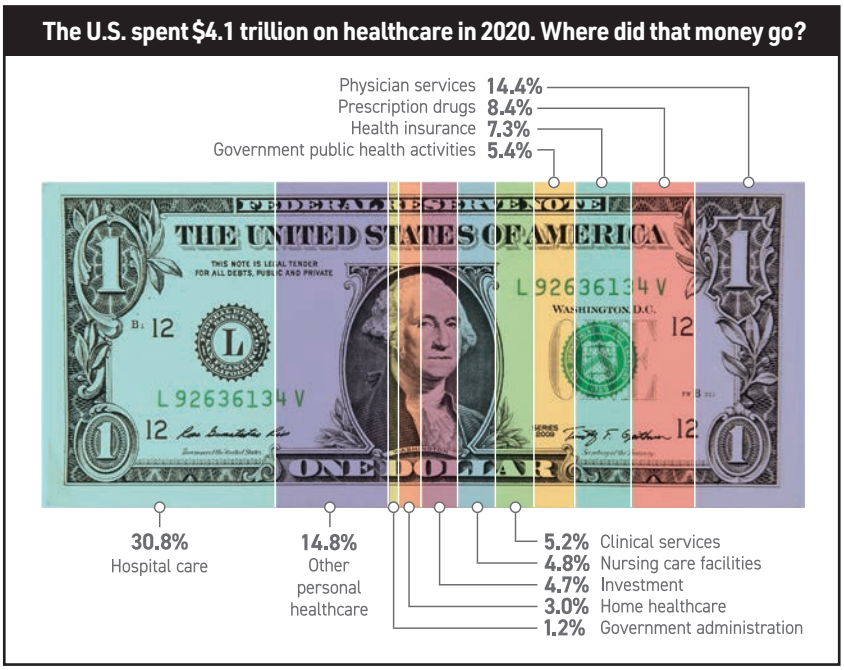
- Offering training and development opportunities such as communication training, cross-training between jobs and team building activities. This not only equips workers to perform their jobs more effectively, but it also decreases worker frustration and offers incentive to stay with the organization. This, in turn, reduces the costs of recruitment and promotes team efficiency and satisfaction.
- Keeping track of overtime and scheduling, and offering breaks when workload is intense. This fights burnout and increases efficiency because staff is better able to complete tasks when they are less strained.
- Providing a positive work environment. Offer fun perks and activities like fitness competitions, holiday parties and other beneficial yet interesting events. Show staff they are appreciated and celebrated because of their hard work. Employees who feel supported and valuable are more likely to perform better and desire to work longer term.[8]

Streamline Scheduling and Patient Flow

Improving scheduling and patient flow is another way to reduce the cost of healthcare without sacrificing patients' health and safety. Clinics and hospitals can monitor how patients move throughout facilities, then create a standardized plan for managing patient flow. This decreases delays and wait times for patients, saves staff resources and ensures maximum occupancy for each exam room and/or bed. Healthcare institutions can also monitor where and how required staff work at any given time. Such analysis can determine the best staffing strategy for all departments to increase or decrease staff according to the patient census.[7,8]

Outsource and Bundle Contracts with One Partner

Outsourcing provides another way for hospitals to reduce the cost of healthcare without compromising patients' health and safety. Specialty support services such as food service, information technology, environmental services and lab services can be outsourced and standardized to reduce overhead, which means more funding is freed up for other necessities. These changes should be implemented strategically, since



Source: Pie graph on page 17 of the following document: www.ama-assn.org/system/files/prp-annual-spending-2020.pdf.

having too many contracts and protocols with vendors can waste money and diminish patient satisfaction. Carefully standardizing support services with one quality vendor enhances an institution's culture and ensures streamlined and efficient hospital services.[7,8,9]

Create a Patient Satisfaction Strategy

Providing patients with quality care even beyond medical procedures can help prevent operational costs, while also improving patient outcomes. Think about what's important to patients beyond medical care. Focus on patient facilities, personalized care and friendly staff. Use regular surveys and feedback forms, then follow up with patients about their input to inform your strategy for making improvements. Consider adopting new methods such as using a telehealth platform to offer remote care (which can improve patient satisfaction because it spares patients commute time and costs while improving access to care) or implementing an online portal. Clients appreciate the ease of being able to check their billing, appointments and doctor instructions online.[9]

Implement Technologies to Reduce Operational Costs

Consider automating technology (e.g., for billing, appointment scheduling and appointment reminders). This not only simplifies processes, but also saves time and contributes to overall improved patient care. Using technology such as electronic health records and electronic medical records can also reduce overhead. Restructuring and utilizing these technologies means staff has more time to focus on providing quality care. It also helps decrease administrative costs and increase staff satisfaction.[9]

Explore Value-Based Care

Value-based care is a new delivery model that accentuates quality instead of quantity. An analogy of this might be the old adage: "Work smarter, not harder."

In this model, providers must research the most cost-effective and promising treatment paths and procedures.[9] They can focus on providing patients with the most effective treatments at the best price. For example, oncologists can deliver improved outcomes at lower costs by considering various treatments in light of effectiveness versus price. They can concurrently provide access to other support services as needed such as telehealth appointments for conditions and treatments that do not always require in-person visits such as psychiatry services, lab result reviews or follow-up appointments. When physicians offer patients strategic and cost-effective treatment, they can use resources more efficiently and effectively.

Reimagine and Redesign to Reduce Cost

Certainly, major changes like these take effort to research and implement effectively. A learning curve might be in a staff's future should healthcare facilities choose to restructure their services to provide better patient care at a more reasonable and responsible cost. But such a redesign can also improve overall staff satisfaction by making their work more efficient and patient-focused. ❖

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Research

Study Finds Experimental Alzheimer's Drug Slows Cognitive Decline

A large clinical trial of Eli Lilly's experimental Alzheimer's medication, donanemab, found the drug slowed declines in patients' ability to think clearly and perform daily tasks by more than a third. The drug, which is given by infusion once a month, works by removing plaque buildups in the brain known as amyloid that are a hallmark of Alzheimer's disease. In the trial, donanemab cleared amyloid so effectively that a majority of patients in the trial — 52 percent — were able to stop taking the medicine by one year, and 72 percent were able to do so by a year and a half.

In the trial that ran for 18 months and included 1,700 patients, researchers looked at the participants in two groups, separated by levels of a brain protein known as tau. A 35 percent slowing in cognitive and functional decline was seen in the group with intermediate levels of tau, whose disease hadn't progressed as far. When this intermediate group was combined with the group with higher levels of tau, the figure was 22 percent. However, there were some side effects reported; there were three deaths in the trial among people taking the drug, two of which were attributed to adverse events such as brain swelling or microhemorrhages, known as amyloid-related imaging abnormalities.

"For every medicine, for every disease, there are potential risks and potential benefits," said Eli Lilly's Chief Scientific and Medical Officer Daniel Skovronsky, MD, PhD. But he noted that almost half of the participants taking the drug, 47 percent, showed no decline on a key measure of cognition over the course of a year, compared with 29 percent of people taking a placebo. "That's the kind of efficacy that's never been seen before in Alzheimer's disease," said Dr. Skovronsky.

Eli Lilly filed for accelerated approval with the U.S. Food and Drug Administration (FDA) for donanemab based on earlier results but was rejected in January as the agency sought more data. Based on these results, in people with early symptomatic Alzheimer's disease, Eli Lilly says it plans to file for approval from FDA by the end of June. ❖

Tirrell, M. Experimental Alzheimer's Drug Slows Cognitive Declines in Large Trial, Drugmaker Eli Lilly says. CNN Health, May 3, 2023. Accessed at www.cnn.com/2023/05/03/health/alzheimers-drug-donanemab-eli-lilly/index.html?utm_term=16831973707662d657b80f989&utm_source=cnn_Five+Things+for+Thursday%2C+May+4%2C+2023&utm_medium=email&bt_ee=2HY93T7rFQvbZXoZ5H%2BlUEgyoz%2BBylJ1aug6m58vZBOfc3Nem14%2F%2F419CFppnf9O&bt_ts=1683197370768.

Medicines

FDA Retires Monovalent COVID-19 Vaccines

The U.S. Food and Drug Administration (FDA) has amended the emergency use authorizations of the Moderna and Pfizer-BioNTech COVID-19 bivalent mRNA vaccines to simplify the vaccination schedule for most individuals. This action includes authorizing the current bivalent vaccines (original and omicron BA.4/BA.5 strains) to be used for all doses administered to individuals 6 months of age and older, including for an additional dose or doses for certain populations. The monovalent Moderna and Pfizer-BioNTech COVID-19 vaccines are no longer authorized for use in the United States.

"At this stage of the pandemic, data support simplifying the use of the authorized mRNA bivalent COVID-19 vaccines and the agency believes that this approach will help encourage future vaccination," said Peter Marks, MD, PhD, director of the FDA's Center for Biologics Evaluation and Research. "Evidence is now available that most of the U.S. population 5 years of age and older has antibodies to SARS-CoV-2, the virus that causes COVID-19, either from vaccination or infection that can serve as a foundation for the protection provided by the bivalent vaccines. COVID-19 continues to be a very real risk for many people, and we encourage individuals to consider staying current with vaccination, including with a bivalent COVID-19 vaccine. The available data continue to demonstrate that vaccines prevent the most serious outcomes of COVID-19, which are severe illness, hospitalization and death." ❖

Coronavirus (COVID-19) Update: FDA Authorizes Changes to Simplify Use of Bivalent mRNA COVID-19 Vaccines. U.S. Food and Drug Administration press release, April 18, 2023. Accessed at www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-changes-simplify-use-bivalent-mrna-covid-19-vaccines.

Research

Experimental mRNA Vaccine Plus Keytruda Delays Melanoma Recurrence

A new study shows that a personalized messenger RNA (mRNA) cancer vaccine plus the checkpoint inhibitor Keytruda (pembrolizumab) reduced the risk of recurrence or death in people with high-risk advanced melanoma. The vaccine, mRNA-4157 (V940, being jointly developed by Moderna and Merck), uses the same mRNA technology as the Moderna and Pfizer-BioNTech COVID-19 vaccines.

With promising early results, a version of the vaccine called mRNA-4157 (V940) was evaluated in the Phase IIb KEYNOTE-942 trial as a treatment for advanced melanoma. The study included 157 participants with stage III or IV cutaneous melanoma that had been completely removed within the prior 13 weeks, but it had spread to a lymph node, so they were considered at high risk for recurrence. They were randomly assigned to receive Keytruda for up to a year either alone (50 patients) or with the vaccine administered every three weeks for up to nine doses (107 patients).

Over two years of follow-up, the vaccine combination demonstrated "statistically significant and clinically meaningful improvement" over Keytruda alone. Recurrence-free survival rates at one year were 83.4 percent in the vaccine group versus 77.1 percent in the Keytruda monotherapy group. At 18 months, the corresponding rates were 78.6 percent versus 62.2 percent — a 44 percent reduction in the risk of recurrence or death.

Treatment was generally safe, but adverse events were common. Side effects were consistent with those observed in previous studies of Keytruda, and adding the vaccine did not substantially increase severe adverse events (25 percent in the vaccine group versus 18 percent in the Keytruda monotherapy group). Just over half of vaccine recipients reported mild or moderate injection site pain. "The novel mechanism of action of mRNA-4157 may both deepen the activity of pembrolizumab and broaden the population of patients that can benefit from immune therapy," Ryan Sullivan, MD, of Mass General Cancer Center, and colleagues concluded. ❖

Highleyman, L. Experimental mRNA Vaccine Plus Keytruda Delays Melanoma Recurrence. Cancer Health, April 16, 2023. Accessed at www.cancerhealth.com/article/mrna-vaccine-plus-keytruda-delays-melanoma-recurrence.

How Medical Misinformation About Vaccines Is Spread

Politicization and polarization have made finding credible information online harder than ever.

By Abbie Cornett, MBA

THE DEVELOPMENT of vaccines is arguably one of the most important advances in the history of medicine, but in recent years, vaccination rates have significantly declined.[1] This decline can be largely attributed to the politicization of medical information and subsequent vaccine hesitancy. Vaccine hesitancy refers to a person's concerns about the decision to vaccinate oneself or one's child(ren) that result in a delay in acceptance or refusal of vaccines despite their availability. Other factors such as differing individual beliefs and attitudes, social norms and access to and confidence in accurate vaccine information have only exacerbated the issue.[2] The politicization of medical information — and vaccines, in particular — is a complex issue, one that has caused political polarization, rampant misinformation and an inherent lack of trust of both the government and pharmaceutical companies, but determining what's true and what's not remains important.

What Is Politicization?

Political motivations have always been somewhat involved in determining policy regarding public health. Balancing the allocation of government resources with the differing values of political parties isn't new, but until recently, it was not necessarily a problem. However, when public policy decisions are based on ideology instead of scientific data and research, the situation becomes politicized.[2] Politicization is "the action

of causing an activity or event to become political in character."[3]

In recent years, thanks in large part to the COVID-19 pandemic, politicians and political parties have largely taken a position on vaccines or medical treatments based on their ideologies rather than solely on scientific evidence.[4] Tying political ideology to medicine has resulted in public opinions on vaccines becoming intertwined with political identity rather than purely on facts. And, unfortunately, this politicization has led to the spread of misinformation that has negatively affected vaccine rates.

The most recent example of this was the controversy surrounding the COVID-19 vaccines, which directly led to millions of Americans delaying getting the vaccine or not getting it at all. In fact, in 2021, the Kaiser Family Foundation conducted a study on misinformation about COVID-19 and found that more than three-quarters (78 percent) of U.S. adults either believed or were not sure about at least one of eight false statements about the COVID-19 pandemic or COVID-19 vaccines.[5]

While it is true that Democrats were more likely to receive a COVID-19 vaccine than Republicans, and a number of Republicans remained unvaccinated, the politicization of vaccines was not one-sided. In fact, according to a 2021 article in *The Atlantic*, party lines seem to have less to do with politicization than vaccine status. "While most state and national GOP leaders focused on defending the rights of unvaccinated Americans, polling showed that the majority of vaccinated adults — including a substantial portion of Republicans — supported tougher measures against those who refused COVID-19 shots," the article stated.[6] The vaccine itself seems to pit the vaccinated against the unvaccinated, with some on the far left calling for imposing vaccine mandates across the board and some on the far right outright vilifying the vaccine.

Drivers of Misinformation

Both sides post information online about vaccines, and both accurate and inaccurate information can be found there. Unfortunately, social media often drives misinformation. Platforms such as Facebook, Twitter and Instagram have made it easier for individuals to spread misinformation and even conspiracy theories about vaccines and other medical issues. False narratives can quickly gain traction through viral posts and memes shared and reshared by users on both sides of the political aisle. In fact, according to cognitive scientist and humanistic psychologist Scott Barry Kauffman, PhD, founder and director of the Center for Human Potential, a recent study showed that "people on both sides of the traditional left-right divide are equally likely to believe political news that is consistent with their ideology, and to disbelieve news that is inconsistent with their side."[7] Viral posts with information that aligns with one political ideology or another can influence public opinion, which can lead to both vaccine hesitancy and other adverse health outcomes both at an individual and a population level. When looking at medical information on social media, it is essential to remember that because platforms are usually free and accessible to anyone, information is not vetted by experts as it is when posted on the website of a credible news source.[8]

Additionally, it is important to remember that just because a healthcare worker posts medical information does not mean it is true! Not all healthcare workers on social media are reliable sources of information. There are notable instances of physicians with a political agenda deliberately spreading misinformation, as in the case of the founder of America's Frontline Doctors Simone Gold, MD, JD, a Los Angeles physician. Dr. Gold is known for both her nurturing of medical conspiracies popular in some right-wing circles and her involvement in the storming of the U.S. Capitol building on Jan. 6, 2021.[9]

Unfortunately, social media often drives misinformation. Platforms such as Facebook, Twitter and Instagram have made it easier for individuals to spread misinformation and even conspiracy theories about vaccines and other medical issues.

Social Media Is Not the Only Way Misinformation Is Spread

While social media is a significant driver, it is not the only way misinformation is spread. There are many websites and blogs devoted to promoting medical misinformation and anti-vaccine beliefs, and political agendas are not the only reason for sharing misinformation. Some healthcare professionals seem to do it for fame and personal gain. An example is Joseph Mercola, DO, an osteopath in

Cape Coral, Fla., who has been dubbed the most influential spreader of COVID-19 misinformation.

In February 2021, Dr. Mercola published an online article that declared the COVID-19 vaccines were a medical fraud and permanently altered a person's genetic coding. The article went viral, reaching more than 400,000 people.[10] His medical misinformation about the COVID-19 vaccine was nothing new: Dr. Mercola has amassed a net worth of more than $100 million in the past 10 years by pushing unproven natural remedies and disseminating anti-vaccine content.

Questionable healthcare providers spread misinformation, but they are not the only ones. There are many other websites and blogs devoted to the spread of medical misinformation, too. These types of sites appear to be credible sources of information to the public, but they either lack scientific evidence or they rely on cherry-picked data that is used out of context to misinform their audience.

One of the best ways to combat medical misinformation on the Internet is for responsible healthcare providers to post accurate, up-to-date, evidence-based information.

This cherry-picking of data is part of what makes the misinformation so convincing. Wrapping fictitious or misleading information around a kernel of truth makes it more believable. The myth that drinking bleach prevents COVID-19 is a good example. While it is true that bleach can be used on surfaces as a disinfectant, it can cause severe bodily harm if drunk. This kernel of truth makes it more believable for people who may not understand the dangers of the practice.[11]

Misinformation is also spread by traditional media outlets, influencers and celebrities. Traditional media outlets usually report accurate information, but unfortunately, they are not immune to politicization. It has been well-documented (in particular by the Pew Research Center) that the U.S. media environment has become increasingly polarized in recent years, with Democrats and Republicans placing trust in completely different news sources.[12] Politicization can lead to the spread of misinformation through sensationalized headlines or incomplete reporting that does not provide a complete picture of the scientific evidence, and it can happen on either side of the aisle.

Besides traditional media outlets, social influencers and celebrities can significantly impact public opinion, too. Recently, many celebrities have used their platforms to spread misinformation about vaccines. This trend is particularly concerning. Because of their popularity, the public may be more likely to trust them and treat what they say as a reliable source rather than listen to medical professionals.

Consequences of Misinformation

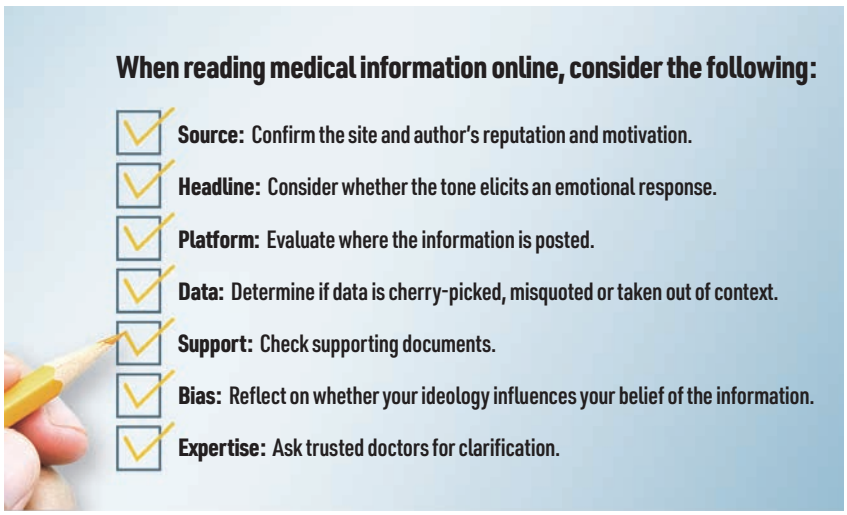
The politicization of vaccines and the spreading of misinformation can have serious consequences for public health. With low vaccination rates, diseases can spread more easily and quickly within communities. It is important to understand that vaccines not only protect individuals who receive them but also contribute to what is known as herd immunity.

Herd immunity occurs when a large portion of a community (the herd) becomes immune to a particular disease through vaccination or previous exposure. The spread of disease from person to person becomes unlikely when herd immunity is achieved. The whole community becomes protected, not just those who are immune.[13] Additionally, when herd immunity is achieved, it helps protect vulnerable individuals who may not be able to receive a vaccine. The consequence for individuals and the spreading of disease outbreaks are not the only repercussions. The spreading of disease also strains healthcare systems and increases healthcare costs for everyone. Further, outbreaks lead to lost work productivity and missed school.

Detecting Misinformation

To combat misinformation, one must first learn how to spot it. When determining whether a piece of information is credible, the following items should be looked at:[11]

- *Source*: Examine the source to determine if it is reputable. This can be done by researching the author's credentials. Additionally, decide the motivation of the author. Is it political in nature? Is it posted on a trusted domain like .edu or .gov?
- *Headline*: Does the headline appear sensationalized or designed to elicit an emotional response?
- *Platform*: If it is on social media,



determine if the information is posted as a prank (much of what is posted is meant to be a joke). Unfortunately, people may believe the joke to be true when they do not look further into its claim.

- *Data*: Carefully read the article to determine if the data has been cherry-picked or if the research is misquoted or taken out of context.
- *Support*: Carefully research the supporting documents. Do the cited sources share the same conclusions as the article?
- *Bias*: Check your own biases and ideology regardless of which political party you belong to. Do you believe the article because it supports what you want to think?
- *Expertise*: If you have questions, ask someone who is an expert in the medical field. An excellent place to start is a trusted doctor.

Combating Misinformation

Because vaccine hesitancy has multifactorial and complex causes, combating it requires a broad range of approaches. One of the best ways to combat medical misinformation on the Internet is for responsible healthcare providers to post accurate, up-to-date, evidence-based information.

Unfortunately, actively engaging on social media is not something academics are typically good at. In an article by Stanford Medicine, Vin Gupta, MD, a pulmonary critical care physician at the University of Washington, points out that this is an area in which the medical community needs improvement. "Much of academia doesn't effectively engage with social media," Dr. Gupta said. "We're not taught how to do that."[14] He stresses the importance of promoting reliable content to combat misinformation, suggesting the use of storytelling and compelling images to deliver powerful public health messages. "Make it less about you; cut through partisanship," Dr. Gupta emphasizes.

While combating medical misinformation on social media is important, misinformation must also be addressed by healthcare workers at a community and societal level. This must be done by building people's trust in public health infrastructure, addressing misinformation and reducing the distribution of false or misleading posts on social media.

Politicization of Medicine = Poorer Population Health

Overall, politicizing vaccines can severely affect public health by decreasing vaccination rates and increasing the risk of disease outbreaks. It is vital to combat medical misinformation on social media, traditional media outlets and the Internet at large by providing accurate information about vaccines through reliable healthcare professionals and public agencies. ❖

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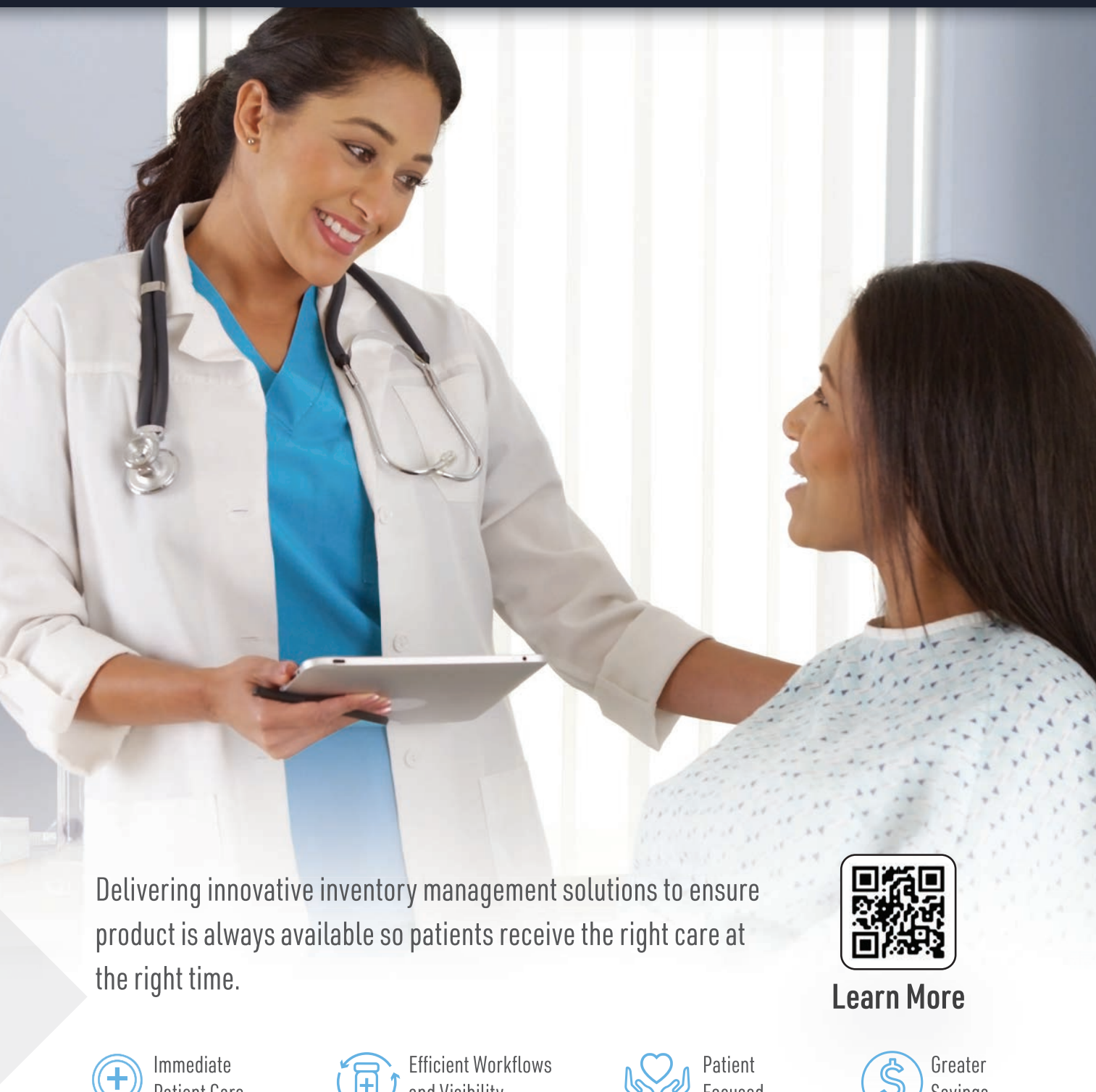

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Adult Vaccines: Fact vs. Fiction

Addressing patient misconceptions and uncertainty remains important to help get routine adult vaccinations back on schedule.

By Diane L.M. Cook

VACCINES ARE critical components of routine healthcare for adults, providing protection against vaccine-preventable severe illness, disability and death from 15 infectious diseases. But, the Centers for Disease Control and Prevention (CDC) says at least three out of four adults are missing one or more recommended vaccines.[1] According to CDC, approximately 63 percent of adults ages 19 years or older have received a tetanus-containing vaccine in the past 10 years; about 14 percent of adults ages 50 years or older have received at least one dose of recombinant zoster vaccine; and almost 24 percent of at-risk adults ages 19 through 64 years have received a pneumococcal vaccine.[2] Any lapse in routine vaccination can result in waning community immunity and pose a real risk that previously eradicated viruses could return to the general population.

But many people do not know they need vaccines in adulthood, nor do they know which vaccines are recommended throughout adulthood. Others do not get vaccinated due to conflicting information, misinformation, hesitancy or lack of access. As trusted health experts, healthcare providers can play a critical role in helping adults understand their need to get vaccinated. Research shows most adults believe vaccines are important and that a recommendation from their healthcare provider is a key predictor of whether they get their recommended vaccines.[3]

To assist healthcare professionals, several medical associations provide information and resources to assist in

dispelling any misconceptions adult patients might believe about vaccines. These resources can help to educate their patients about choosing the appropriate vaccines for their circumstances at the correct time in adulthood.

Adults Need Vaccines Too

According to the American Academy of Family Physicians (AAFP), the only medical society devoted solely to primary care, most vaccines recommended by CDC are given to children during routine pediatric visits. However, adults need them too because protection from childhood vaccinations may wane as people age, and adults may need additional vaccines every year.

As the president of AAFP, Tochi Iroku-Malize, MD, MPH, MBA, FAAFP, explains, "Vaccines are safe, effective and save lives. The best way to prevent getting seriously ill, being hospitalized or even dying is to get vaccinated. Immunizations are among the most cost-effective and successful ways to create communities of immunity. Family physicians play an important role in administering vaccines to adults, as well as to help adults overcome vaccine hesitancy and determine a vaccination schedule."

Annual check-ups are an opportunity to discuss which vaccines adult patients might need; remind patients that family doctors are the best source of health information for patients; and recommend the right vaccines that can protect from illness based on patients' age, job, travel plans and health risks.[4]

Recommended Adult Immunization Schedule

Every year, CDC publishes the Recommended Adult Immunization Schedule, which outlines recommended adult vaccines, along with when and why adults should get them (Table). As well as yearly influenza vaccines and staying up-to-date on COVID-19 vaccines, CDC's current recommendations for adults ages 19 years and older includes:[5]

- Tdap (tetanus, diphtheria and pertussis) vaccine once if not received as an adolescent, and then a Td (tetanus, diphtheria) booster every 10 years. Women should also get one Tdap dose each time they are pregnant.
- Hepatitis B vaccine for all adults ages 19 through 59 years, as well as adults ages 60 years or older who have risk factors for hepatitis B infection.
- Herpes zoster (shingles) vaccine for healthy adults ages 50 years and older, as well as adults ages 19 years and older who have weakened immune systems.
- Pneumococcal vaccine for all adults ages 65 years and older, or ages 19 through 64 with certain medical conditions or risk factors.

CDC encourages healthcare providers to talk to their adult patients about which vaccines are recommended for them since these patients might need other vaccines based on age, health conditions, job, lifestyle or travel habits.

Adults need vaccines too because protection from childhood vaccinations may wane as people age, and adults may need additional vaccines every year.

Addressing Misconceptions

According to AAFP, there are many misconceptions regarding vaccines, which can lead to some adults not getting their recommended vaccinations. Working hard to rectify the problem, the following are five common misconceptions about vaccines identified by AAFP, followed by the facts:[6]

1) *Vaccines don't work.* The fact is, vaccines prevent many diseases that used to make people very sick. Now that people are being vaccinated for those diseases, the diseases are not common anymore. However, for vaccines to work properly, they need to be given at certain times.

2) *Vaccines aren't safe.* The fact is, when a vaccine is developed, it goes through a strict and detailed process overseen by the U.S. Food and Drug Administration (FDA). Manufacturers must prove to FDA the vaccine is safe before it can be administered to people. CDC and FDA also monitor the vaccine production facilities to make sure vaccines are being produced safely. Each batch of vaccines is checked before it is distributed to the public to make sure it is safe.

3) *Vaccines aren't necessary because natural immunity is better.* The fact is, many preventable diseases are dangerous and can cause lasting side effects. It is much safer and easier to get the vaccine instead of contracting the disease. Getting vaccinated also helps people from spreading the disease to people who can't get vaccinated.

4) *Vaccines include a live version of the virus.* Although some vaccines contain live versions of the bacteria or virus that cause the disease, the fact is they have been so weakened during the vaccine creation process that they cannot make a person sick. Most vaccines contain a pretend version of the infection that causes the body to produce antibodies to defend itself as if the infection were real. It is this reaction, along with the creation of

antibodies in a person's system, that makes the body immune to the disease.

5) *Vaccines have negative side effects.* The fact is, severe side effects of vaccines are rare. Minor side effects of vaccines commonly include pain, redness and swelling near the injection site. The benefits of getting vaccines outweigh the possibility of side effects.

Efforts to Boost Vaccine Confidence

To help combat vaccine hesitancy, AAFP is calling upon its members who are passionate about vaccines to emphasize the critical role they play in keeping the community healthy. "Vaccines are one of the best preventive health tools we have," AAFP maintains. "But vaccine misinformation is a real threat to public health, and with increased patient hesitancy, potentially deadly disease outbreaks will happen." Therefore, emphasizes AAFP, "More education is needed to improve vaccination rates."[7]

In November 2021, AAFP collaborated with its vaccine partners to develop materials for family physicians to use at the point of care. These materials are intended to build vaccine confidence, disseminate accurate vaccination information and provide recommendations and guidance on routine vaccination. Recommendations include:

- Vaccinating all age groups, as per CDC's recommendations, regardless of economic and insurance status;
- Vaccinating patients during routine, annual well-check appointments;
- Educating physicians and healthcare teams about CDC-recommended vaccinations;
- Addressing misinformation and myths about vaccinations; and
- Implementing evidence-based interventions to improve vaccination rates.

Standards for Adult Immunization Practice

To assist family physicians in educating their adult patients on recommended adult vaccines, CDC has prepared standards, fact sheets and initiatives, including "Standards for Adult Immunization Practice," which emphasizes the role of all healthcare professionals to ensure adult patients are fully immunized. To make immunization a standard of patient care, CDC recommends providers do the following:[8]

1) Assess the immunization status of all patients at every clinical encounter.

2) Strongly recommend vaccines patients need.

3) Administer needed vaccines or refer patients to a vaccination provider.

4) Document vaccines received by patients.

In addition, CDC created a series of six fact sheets for healthcare professionals with information and tips on how to improve vaccination practice, including assessment, recommendation, administration, referral and documentation.

The Let's RISE Initiative

Further, to help specifically address pandemic-related declines in routine immunizations, CDC launched the Routine Immunization on-Schedule for Everyone campaign, known as the "Let's RISE" initiative, in January 2023. (RISE is an acronym for routine immunizations on schedule for everyone.) Let's RISE equips partners and healthcare providers with strategies, resources and data to support getting adults back on schedule with their routine immunizations. "During the COVID-19 pandemic, we saw a concerning drop in routine immunizations for adults," reports CDC. "Routine vaccination is rebounding, but unevenly, and has not yet recovered among all groups." CDC recommends healthcare professionals help get adults get back on schedule with their routine immunizations by:[9]

- Prioritizing ensuring everyone catches up on routine vaccination.
- Identifying individuals who are behind on their vaccinations.
- Encouraging vaccination catch-up through reminders, recall and outreach.
- Making strong vaccine recommendations.
- Making vaccines easy for everyone to find and afford.

Changes to the Recommended Adult Immunization Schedule

The American Medical Association (AMA) provides information about immunizations to physicians through a variety of media (e.g., website, webinars, blog and social media). AMA supports the immunization recommendations of the Advisory Council on Immunization Practices (ACIP).

According to Sandra Adamson Fryhofer, MD, AMA board chair, "The AMA encourages all eligible adults to receive their routine vaccinations according to [ACIP's] latest adult immunization schedule. Making sure you're up-to-date on your vaccines is vitally important to help protect yourself and your loved ones from vaccine-preventable diseases. As a result of the COVID-19 pandemic, reports show adults are behind on routine vaccinations."[10]

To achieve this, providers must be aware that there are important changes to the 2023 Recommended Adult Immunization Schedule. According to Dr. Fryhofer, the three most important changes are as follows:[10]

1) The recent case of paralytic polio in New York emphasized the importance of the polio vaccination in childhood and raises questions about the need for polio vaccine boosters.

2) For the first time, the Recommended

Table. Adult Immunization Schedule by Age

Legend

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection	Recommended vaccination for adults with an additional risk factor or another indication	Recommended vaccination based on shared clinical decision-making	No recommendation/Not applicable

Vaccine	19-26 years	27-49 years	50-64 years	≥65 years
COVID-19	2- or 3- dose primary series and booster (see notes)			
Influenza inactivated (IIV4) or Influenza recombinant (RIV4)	1 dose annually			
or Influenza live attenuated (LAIV4)		or 1 dose annually		
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap each pregnancy; 1 dose Td/Tdap for wound management (see notes)			
	1 dose Tdap, then Td or Tdap booster every 10 years			
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)			For healthcare personnel, (see notes)
Varicella (VAR)	2 doses (if born in 1980 or later)		2 doses	
Zoster recombinant (RZV)	2 doses for immunocompromising conditions (see notes)		2 doses	
Human papillomavirus (HPV)	2 or 3 doses depending on age at initial vaccination or condition	27 through 45 years		
Pneumococcal (PCV15, PCV20, PPSV23)	1 dose PCV15 followed by PPSV23 OR 1 dose PCV20 (see notes)			See Notes
				See Notes
Hepatitis A (HepA)	2, 3, or 4 doses depending on vaccine			
Hepatitis B (HepB)	2, 3, or 4 doses depending on vaccine or condition			
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication, see notes for booster recommendations			
Meningococcal B (MenB)	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations			
	19 through 23 years			
Haemophilus influenzae type b (Hib)	1 or 3 doses depending on indication			

Source: www.cdc.gov/vaccines/schedules/hcp/imz/adult.html

Adult Immunization Schedule has been approved by the American Pharmacists Association, which validates pharmacists as established partners in vaccine administration.

3) There is a new, shared clinical decision-making option for pneumococcal vaccines.

"We encourage everyone to talk with their physician to ensure they're up-to-date on their vaccinations," encourages Dr. Fryhofer.[10]

I Raise the Rates Program

The American College of Physicians (ACP), an organization of internal medicine physicians, specializes in the diagnosis, treatment and care of adults. With support from CDC and Sanofi

Pasteur, and previous support from GSK, Merck and Pfizer, ACP created the I Raise the Rates program, which is an initiative that provides adult immunization resources and vaccination information to help clinicians increase adult immunization rates in their practices.

As part of the initiative, ACP developed an adult immunization resource hub to assist physicians and their teams to assess, understand and improve adult immunization rates and patient outcomes in their clinical settings. Featured resources available via the hub include:[11]

Research shows most adults believe vaccines are important and that a recommendation from their healthcare provider is a key predictor of whether they get their recommended vaccines.

- 2023 ACIP Adult Immunization Recommendation Videos
- Practical Immunization Tips: Microlearning Resources
- High Value Care Immunization Referral Toolkit
- Increasing Adult Vaccinations: A Subspecialist's Perspective

Underscoring the Need for Updated Adult Vaccines

The National Foundation of Infectious Diseases (NFID), a nonprofit organization that educates the public and healthcare professionals about the prevention and treatment of infectious diseases, works to raise awareness about the importance of vaccination across the lifespan, from infancy to adulthood.

NFID says that every year in the United States prior to the COVID-19 pandemic, approximately 50,000 adults died from vaccine-preventable diseases, yet overall vaccination rates remain low. NFID Medical Director William Schaffner, MD, professor of medicine in the division of infectious diseases at Vanderbilt University Medical Center, says vaccines are not just for babies and kids anymore: "Adults are eligible for several vaccines that can prevent a series of serious infections. Doctors and pharmacists can advise their patients and customers about which vaccines are appropriate for them — some vaccines are recommended for all adults and other vaccines are recommended for adults with various occupations or chronic medical conditions."[12]

Dr. Schaffner says two vaccine examples underscore the importance of recommended adult vaccinations: the pneumococcal vaccine and the shingles vaccine.

Pneumococcal vaccine: "All adults should receive the pneumococcal vaccine when they reach age 65, but those with certain chronic medical conditions are eligible when they are younger." Pneumonia can be very serious and even deadly. Older adults are more likely to suffer from complications if they have certain chronic health conditions or a weakened immune system.[13]

Shingles vaccine: "The risk of shingles increases as a person ages. To prevent shingles, a vaccine is recommended for all adults starting at age 50." Shingles causes a painful rash that can be severe. The shingles rash usually develops on one side of the face or body. Before the rash appears, adults can experience pain, itching or tingling in the areas where the rash will develop. The virus can cause nerve pain that can last for weeks or months.[14]

Vaccines Remain Important in Adulthood

Dispelling misconceptions about adult vaccines remains important. With help from these medical associations and the resources they offer, healthcare professionals can continue the important work of addressing misconceptions about recommended vaccines and easing fears patients may have about getting them. These efforts will help adult patients get their immunizations back on schedule, which in turn will help return community immunity to the levels that existed before the COVID-19 pandemic erupted. ❖

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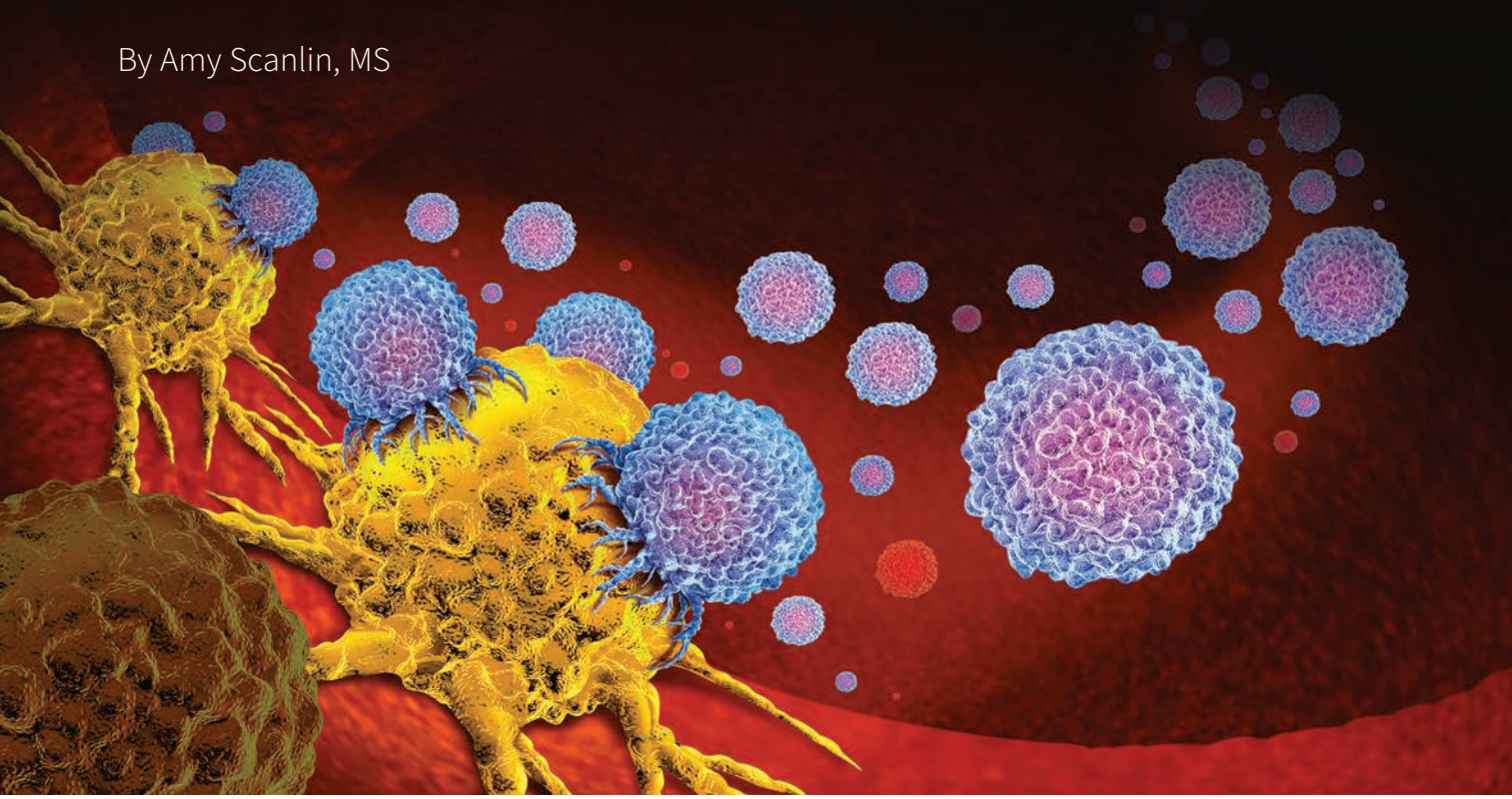
Personalized Cancer Vaccine Development

Research into targeted, effective vaccines for cancer remains ongoing.

By Amy Scanlin, MS



ALTHOUGH IMMUNOTHERAPY has recently revolutionized many cancer treatments, the concept of an effective personalized cancer vaccine has been in the making for decades. Today, strides in the efficacy of such treatments have produced a number of experimental vaccines in a variety of platforms.

Provisionally successful outcomes in mice and human clinical trials have demonstrated the potential viability of tailor-made vaccines using a patient's own cancer cells. Just as no two people are alike, neither are their cancer cells, nor are those cells' number and unique genetic mutations. As understanding of how to identify tumor-specific mutations that enable successful targeting of T-cell responses continues to grow, personalized cancer vaccines may one day be within reach.

Research is hoping to stimulate the immune system to effectively target tumor-specific proteins, or neoantigens, via cytotoxic CD8+ T cells supported by CD4+ T cells. Some believe that neoantigen-specific personalized cancer vaccines may be advantageous compared to tumor-associated antigen therapies due to their ability to trigger specific T-cell responses against abnormal or mutated cells, thereby lessening the risk of damage to healthy cells. Neoantigens also have the potential to prompt immunological memory, which may improve long-term protection against tumor reoccurrence.[1]

The higher the number of tumor mutations, the greater the number of possible neoantigen vaccine candidates. That's good news. However, those cell mutations must be weighed against the type of mutations and to what extent they are expressed. For example, a study of patients with pancreatic cancer showed that although overall survival was not affected by neoantigen load, the quality of neoantigens did have a positive effect. Additionally, this same study also found that survival rates were positively affected by the combination of neoantigen load and diversity of CD8+ T cells. The ability of T cells to specifically target tumors and the potential of Treg cell-mediated vaccine suppression must all be considered as studies continue.[2]

Vaccine Considerations

Early clinical trials of neoantigen-based cancer vaccines were conducted primarily postsurgery when no additional treatments were indicated. Today, however, researchers are considering not

only the types of tumors against which a personalized vaccine might be more effective, but whether a vaccine would be most effective when administered in the earlier stages of tumor activity when the immune system is more robust, or later postsurgery and in conjunction with immunotherapy when a greater number of available antigens might enable a multipronged approach.

Additional lines of research are considering whether personalized cancer vaccines would be most effective in combination with immune checkpoint inhibitors for an enhanced immune response, particularly in cancers with a lower number of mutations and fewer neoantigens. Indeed, numerous viable candidates exist for a personalized cancer vaccine approach.

For a personalized cancer vaccine to be efficacious, it must be produced quickly and be cost-effective. The time necessary to manufacture the vaccine will be dependent on the vaccine platform and drive treatment decisions toward those with the greatest chance for success. It is also possible that starting the patient on adjuvant treatment postbiopsy while the vaccine is in development could provide additional benefit in conjunction with the vaccine itself.

Tumor Cell Identification and Targeting

To identify target cancer cell mutations, whole exome sequencing of a biopsied tumor and surrounding nonmalignant cells is performed to compare the tumor and DNA. RNA sequencing can further identify the type of mutation, although some mutations may not result in recognized neoepitopes, which would necessitate prediction through human leukocyte antigen (HLA) typing.[2]

In theory, once vaccinated, a robust immune response should kick in as the uptake antigens prompt lymph node draining. As antigen-specific T cells grow, cancerous tumors expressed in neoantigens are targeted and killed, leaving only the memory T cells, central (TCM), effector (TEM), resident (TRM) and peripheral memory (TPM), a subset of CD8+ T cells. It is hoped that these memory T cells may be able to help to prevent future cancer reoccurrences by quickly responding to new antigen threats.

While there are numerous lines of study in the field of personalized cancer vaccines, three in particular are showing promise: those using messenger RNA (mRNA), DNA and tumor antigen peptides.

mRNA Vaccines

After 30 years of research into the deliverability of stable forms of mRNA-based vaccinations, excitement of mRNA as a possible cancer vaccine is growing thanks to the success of the COVID-19 vaccine.[3] mRNA vaccines are being evaluated in multiple clinical trials on a variety of cancer types.

Once tumor cell mutations are identified, algorithms can be used to predict which neoantigens are most likely to bind with T cells. Functionally, mRNA is taken up by dendritic cells, which, via nucleotides, instruct the manufacturing and sequencing of spike proteins that will deliver antigens to T cells. The T cells are then able to use this information to recognize the foreign invaders and trigger production of protective antibodies specific to the molecular features of the cancer cells.[3]

But, determining how to effectively deliver an mRNA vaccine has been a challenge since it is less stable than, for instance, a DNA-based vaccine that requires special storage and handling. One solution may be to encase mRNA inside lipid nanoparticles. This seems to function as a protector of the mRNA, making it invisible to the immune system and thereby potentially enhancing the vaccine's effectiveness.

However, despite the limited success of mRNA vaccines to date, multiple clinical trials are underway looking for new opportunities to increase their effectiveness. One such trial uses an mRNA cancer vaccine in conjunction with a PD-1 inhibitor. This particular trial is moving onto Phase III after a Phase IIb trial showed a reduction in tumor reoccurrence by 44 percent in stage III and stage IV melanoma patients postsurgery.[1]

Another study showed provisional success delivering mRNA vaccines to melanoma patients with T-cell response developed against multiple neoepitopes, with most patients remaining disease-free for 26 months posttreatment. One patient who relapsed received an anti-PD-1 antibody combination therapy and was again determined to be disease-free.[4]

Most recently, BioNTech tested its individualized neoantigen mRNA vaccine in 16 patients with pancreatic cancer in a Phase I clinical trial. Its vaccine was also tested in conjunction with atezolizumab (an anti-PD-L1 immunotherapy), autogene cevumeran (a maximum of 20 neoantigens per patient) and a modified version of a four-drug chemotherapy regimen. After 18 months, none of the eight who responded to the vaccine had their cancer return, whereas the usual time for a person's pancreatic cancer to return without the mRNA treatment is eight to 13 months. All eight who responded to the vaccine made T cells against their tumors, and those T cells have persisted for at least two years. Six of the eight participants who did not respond to the vaccine have seen their cancer return.[5]

DNA Vaccines

There are more than 200 trials evaluating the efficacy of DNA as a viable

personalized cancer vaccine alternative. DNA vaccines are stable, with no need for strict cold-chain requirements.[4] They can be engineered to include multiple neoantigens; be combined with immunotherapies and immune modulators; and possibly lower the risk of side effects such as damage to healthy tissues and vaccine intolerance that are sometimes seen in patients who receive an mRNA vaccine.[6]

DNA vaccines can be optimized, including amino acid sequencing and lengthening of neoantigen fragments, so that they can be introduced into the tumor in a precise format that maximizes an immune response. Longer epitopes seem to prompt a lengthier immune response and thus increased immune system recognition. However, immune modulators such as anti-PD-L1 checkpoint blockades would likely be needed to boost their chance of success.[6]

DNA vaccines targeting breast cancer studied in mice at the Washington University School of Medicine in St. Louis have demonstrated they can prompt an immune response that effectively shrinks tumors. However, a human study conducted on a single patient with pancreatic cancer showed no change in tumor size even though a measurable immune response was noted.[6]

Tumor Antigen Peptide Vaccines

Long peptide-based vaccines are being studied in a variety of cancers, albeit also with mixed results. In a small Phase I study, NeoVax (with 20 different long peptides) was administered to patients with stage III and stage IV melanoma postsurgery, along with CD4+ and CD8+ T cells. After 25 months, the stage III patients remained disease-free; however, the stage IV patient saw reoccurrence within a few months. After treatment with an anti-PD 1 antibody, T-cell response was broadened, and the tumor showed signs of regression. A second slightly larger Phase I study combined mRNA-encoded melanoma antigens and personalized neoantigen peptides resulting in CD8+ T cells that were comprised of both TCM and TEM cells, as well as CD4+ T cells, in even greater numbers.[2]

Conversely, two studies in patients with glioblastoma, a cancer with a typically low mutational burden, showed no clear benefits attributed to peptide-based vaccines. Both studies did, however, demonstrate the potential of neoantigen-based vaccines to stimulate T-cell response on tumors with low mutational burdens, warranting further study.[2]

Cost and Benefit

The costs associated with development, including clinical trials, of a personalized cancer vaccine is prohibitive, a fact that further complicates the already immense challenge of identifying viable options.

Researchers at Mount Sinai are looking to develop cancer vaccines based on common mutations seen across many patients, and testing a shared neoantigen vaccine for myeloproliferative neoplasms that allows for the development of vaccine peptides that target a calreticulin gene mutation that affects nearly one-third of patients.[7]

As researchers continue to study how personalized cancer vaccines may best activate T-cell response, particularly CD8+T, the addition of complementary therapies may be a strong treatment component. To date, clinical trials of personalized vaccines in conjunction with immune-checkpoint inhibitors have demonstrated only modest improvements over immune-checkpoint inhibitor monotherapy alone. Testing of personalized vaccines in combination with PD-1 or PD-L1 inhibition and CTLA4 inhibitors may be a logical next step to explore the possibility of an anti-PD-1-mediated response using a combination therapy.[2]

Vaccine Boosters

Whatever personalized approach is taken, there is a high likelihood that patients will need additional booster vaccines so that T-cell memory can be continually stimulated, particularly given the gradual challenge of T-cell exhaustion. Timing of booster vaccines should be considered in conjunction with any other treatments for a maximal therapeutic approach. In the case of a reoccurrence, DNA sequencing may offer an assessment of T cells and alternative neoantigens, as well as possible information as to why the vaccine did not perform as hoped, all of which would inform future treatments.[2]

As research into personalized cancer vaccines continues, optimizing delivery routes and timing in combination with any supportive immunotherapies will drive future success. ❖

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Biosimilars
and the Fight Against Inflation

By Rachel Maier, MS

New legislation promises to increase patient access to critical drug products by lowering costs. Will it work?

MEDICINE IS MEANT to ease symptoms, cure or prevent disease and promote overall health — but at what cost?

On average, Americans spend more than $1,500 per person on prescription drugs every year.[1] Drug prices in the United States are 2.56 times higher than prices in 32 comparable countries and 1.90 times as high when rebates and other discounts are considered, according to the office of the assistant secretary for planning and evaluation (ASPE), the principal advisory group to the United States Secretary of the Department of Health and Human Services (HHS).[2] While part of the spending can be attributed to patients' taking multiple medications at once (and thus, the expenditures are collective among many medicines), the fact remains that prices for prescription drugs are far higher in the United States than they are in any comparable nation, and it's a problem.[1]

A recent poll conducted by the Kaiser Family Foundation, a nonprofit organization focusing on national health issues, found that while most Americans (83 percent) say prescription drug prices in the United States are "unreasonable," 69 percent of people taking prescription drugs say affording them is easy.[3] The poll showed that while one in five adults currently taking three or fewer prescription medications say they have problems paying for their medications, 32 percent of those taking four or more medications struggle to afford them. The poll also indicated that some groups are much more likely to report difficulty paying for prescriptions, specifically "those who take four or more prescription medications, those who have chronic conditions in their household and those with an annual household income of less than $40,000."[3]

The price difference between biologic medications and small molecule drugs seems to be directly related to affordability. In 2017, only 2 percent of U.S. prescriptions were for biologic medications, but that small percentage accounted for $120 billion, or 37 percent, of net drug spending. An average, daily dose of a biologic costs 22 times more than that of a small molecule drug.[4] The reason for and solution to exorbitant drug prices isn't straightforward or simple. Various factors such as research and development, marketing and launch expenses, exclusivity, patents and lack of competition, among others, all contribute to the complicated nature of pharmaceutical pricing for both small molecule and biologic medications.[5]

Inflation doesn't make affordability any easier: Reduced consumer purchasing power forces patients to make the hard choice between paying for everyday essentials (such as food and gas) and critical medications. Inflation soared from 1.4 percent in 2020 to 8.5 percent in 2021, and as of this writing, it is still hovering at 6 percent, but sharp rises in drug prices have been an ongoing problem for the past several decades. Drug prices were five times higher in 2021 than they

were in 1984, according to a USAFacts report analyzing data collected by the Bureau of Labor Statistics. The same analysis showed the rise in drug prices was three times greater than the rate of inflation for all other goods during the same time period.[6]

In an attempt to address these exorbitant pharmaceutical prices in the United States, the Inflation Reduction Act (IRA) of 2022 signed provisions into law that are meant to make critical medications, especially biologic medications, more affordable, but the question remains whether or not the act will accomplish its goals.

Rising Drug Prices Outpace Inflation

Inflation is the rate at which the price of goods and services increases, but it doesn't directly drive up the price of prescription drugs. In fact, drug prices seem to operate independently from inflation.

Between 1989 and 2019, the average annual inflation rate in the United States was 2.5 percent; more recently, the inflation rate was 6.0 percent for the 12-month period between February 2022 and February 2023.[7] According to a 2021 report conducted by the American Association of Retired Persons, between January 2006 and December 2020, retail prices for 65 chronic-use brand-name drugs increased cumulatively by an average of 276.8 percent; the cumulative general inflation rate was 32 percent during that same 15-year period.[8]

Between 2019 and 2020, retail prices for 260 widely used brand-name prescription drugs increased by 2.9 percent, more than two times faster than general inflation increased the same year (1.3 percent). The average annual cost for one brand-name medication used on a chronic basis was more than $6,600 in 2020, more than $1,500 higher than the average annual cost of therapy in 2015. To put this in perspective, an average adult taking 4.7 prescription drugs per month in 2020 paid more than $31,000 for them that year, which is $17,000 more than the same therapy cost in 2015.[8]

According to HHS, between July 2021 and July 2022, there were 1,216 prescription drugs whose price increases exceeded the inflation rate of 8.5 percent for that time period. The average price increase for these drugs was 31.6 percent. Some drugs in 2022 increased by more than $20,000 (or 500 percent).[2]

The upward trend is thought to continue: Vizient, Inc.'s Winter 2023 Pharmacy Market Outlook forecasted a 3.78 percent overall drug price inflation rate for the calendar year beginning July 1, 2023.[9]

To make matters worse, drug prices routinely increase in January or July every year anyway. In January 2022, the average price increase was nearly $150 per drug (a 10 percent increase), and by July 2022, it was $250 (a 7.8 percent increase). These increases were larger than for the same months in previous years, according to ASPE.[2]

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What About Generics? Don't They Help?

Brand-name drugs are expensive when they first enter the market for many reasons, one of which is market exclusivity. Exclusivity is a period of time when the brand-name drug is protected from generic drug competition; it is designed to promote a balance between new drug innovation and generic drug competition. After branded drugs lose their exclusivity, generic versions can enter the marketplace after receiving approval from the U.S. Food and Drug Administration (FDA) and if a patent no longer blocks generic approval.[9] (Drug patents typically last for about 20 years.)

Once exclusivity ends, generic versions of small molecule, chemically-based drugs ("generics") are created to provide the same clinical therapies as existing brand-name counterparts at a lower price to consumers. They contain the same active ingredient; have the same strength, dosage and administration; and are equally safe and effective. Although some inactive ingredients might differ, generics yield the same therapeutic effects as brand names, so they can be substituted easily without the intervention of the prescriber. Generics are relatively easy and inexpensive to produce, especially since they do not have to repeat animal or clinical studies required of the original brand names to demonstrate their safety or efficacy.[10] Lower upfront costs make generics more affordable: They are typically sold for 80 to 85 percent less than brand-name medicines. It often takes many generic competitors entering the market to make any meaningful difference in price. The more competition, the lower the prices.[5]

Generics help offset costs — no doubt about it. In fact, according to the IMS

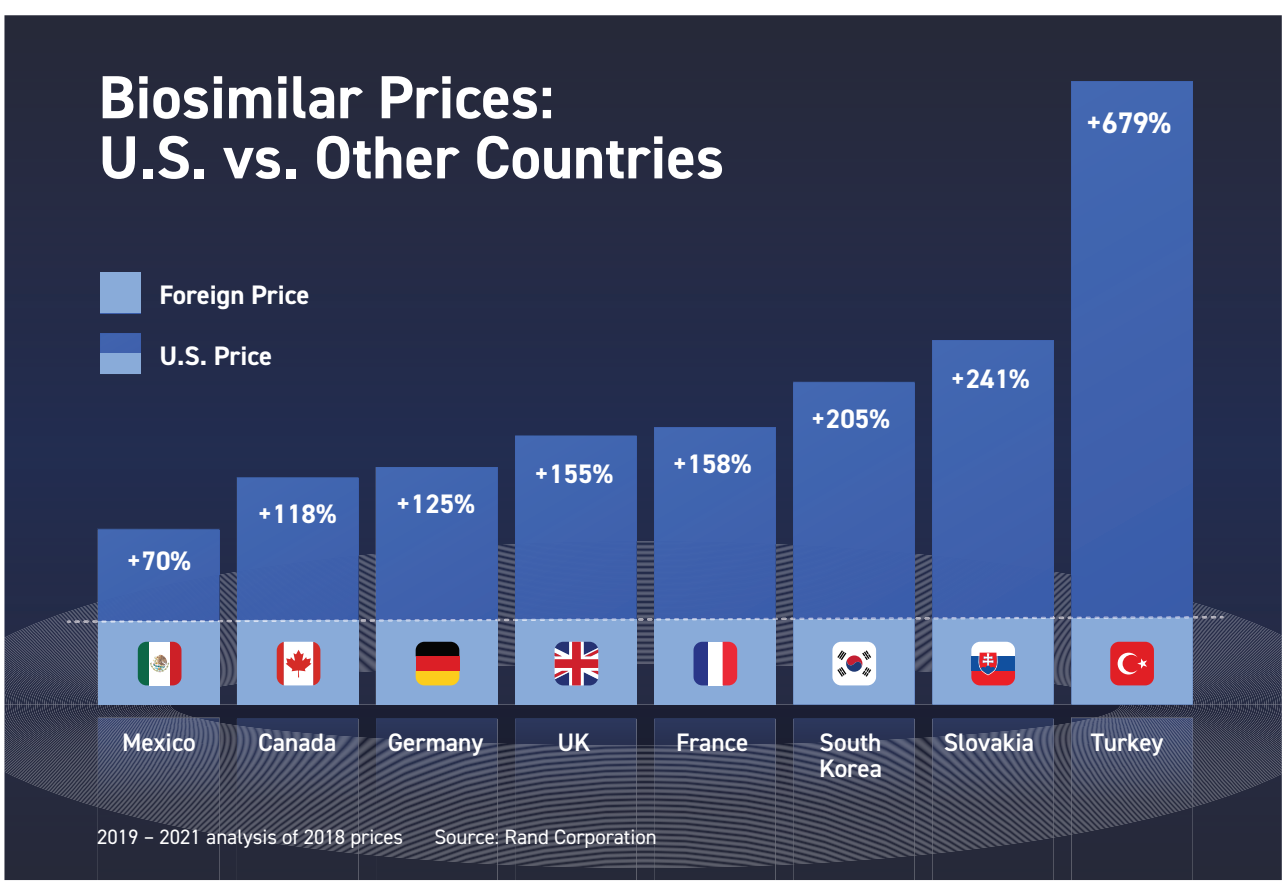
Health Institute, generic drugs saved the U.S. healthcare system almost $2.2 trillion between 2009 and 2019.[10]

How Biosimilars Factor In

But generics are only part of the solution. Replicating chemically based medicines is one thing, but replicating highly complex biologic medicines is another. Biologic drugs (commonly called "biologics") are the most expensive prescription medications on the market, costing $10,000 to $30,000 per year on average, and exceeding $500,000 per year for the most expensive biologics.[4] Unlike small molecule drugs, biologics are highly specialized, complex medicines that are generally derived from living organisms, including animal cells or microorganisms such as yeast and bacteria. Their nature varies and their structures are more complex, which makes their production far more complicated — and expensive — to reproduce than chemically based medicines, and as such, biologics don't have true generics.[11]

However, biosimilars are comparable to generics, and they may indeed be a game changer when it comes to affordability of biologic medications. Like generics, biosimilars are secondary iterations of an original drug product, and they carry the potential for lower consumer price tags. However, biosimilars aren't exact copies of originator biologic products (or "reference products"). Instead, they are highly similar to them and therefore require clinical studies to show they have no clinically meaningful differences from their brand-name counterparts that are already FDA-approved. Biosimilars have the same route of administration, strength, dosage form and potential side effects as the reference product, and they provide the same potential treatment benefits. They are rigorously and thoroughly evaluated by FDA before approval.[11] If biosimilar products go through an additional FDA approval process for interchangeability, they can be dispensed in place of the brand-name originator product without involvement of the prescriber.

Biosimilars offer comparable treatment options to patients with many chronic, debilitating diseases such as multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, psoriasis, some forms of cancer and rare genetic diseases, among others. Like biologics, their therapeutic



effects can significantly improve quality of life, prolong life — or both.

Biosimilars are exciting because they present an opportunity to reduce costs by creating competition for originator products that currently have market exclusivity.[12] According to FDA, "Biologics are among the fastest growing segments of the prescription product market. The FDA approval of additional biosimilar and interchangeable biosimilar medications may help stimulate competition. Patients will have more treatment options and potentially less expensive alternatives."[11] The savings would be immense: Using biosimilars instead of biologics could drive down the cost of medicines used to treat rare diseases with an estimated savings of $38.4 billion, or 5.9 percent of the projected U.S. spending on biologics between 2021 and 2025, according to the RAND Corp.[4]

But there aren't many biosimilars available in the United States yet; 40 have been approved as of this writing, and only 27 have been launched despite being widely available in other countries.[13] For example, 75 biosimilars have been approved in the European Union (EU); as of July 2022, they are interchangeable there, meaning that a prescribed reference product can be replaced by a biosimilar without provider approval.[13,14] Interchangeability is only possible in the United States when biosimilars meet additional FDA requirements.

But the United States is moving in that direction. The Biologics Price Competition and Innovation Act (BPCIA) of 2009 shortened the pathway to licensure for products that are shown to be biosimilar to, or interchangeable with, a previously approved reference product. The BPCIA promised to reduce the price of biologics while also promoting innovation.

Fourteen years later, we are starting to see the fruit of the BPCIA, as many biosimilars are in the pipeline for approval, several of which are expected to be approved this year. In January 2023, Amgen introduced the first of many promising biosimilar releases with its introduction of Amjevita (adalimumab-atto), a biosimilar to Humira (adalimumab).[15] At least seven other adalimumab biosimilars will follow later this year.[16] The patent for Stelara (ustekinumab) expires in September of this year, and nine biosimilars are currently in development, with two of them pending FDA approval (expected in late 2023). Biosimilars for Actemra (tociluzumab) are expected to seek FDA approval in 2023 as well. Extended exclusivity for Enbrel (etanecept) pushed the launch of two already FDA-approved biosimilars [Erelzi (etanercept-szzs) and Eticovo (etanercept-ykro)] to 2029. Xolair (omalizumab) and Tysabri (natalizumab) will both face biosimilar competition in the coming years, and development of biosimilar alternatives are already well under way.[17]

Advocates for U.S. price negotiations say implementing them between the government and drug makers would bring prices down here, too. But critics of price negotiations say too much government involvement will stifle innovation and competition, which will lead to fewer drugs in the future.

Competition vs. Price Controls

Despite the promise of savings, biosimilars remain expensive. Again, small molecule generic medications cost 80 to 85 percent less than their brand-name counterparts, but the savings from biosimilars doesn't come close to that. For example, Remicade, a biologic that treats autoimmune conditions such as rheumatoid arthritis, Crohn's disease, ulcerative colitis and severe psoriasis, has a list price of $4,671 per month, whereas Inflectra, Remicade's first biosimilar, has a list price of $3,785 per month (19 percent less than Remicade). Renflexis, another biosimilar for Remicade, has a list price of $3,014 per month (35 percent less than Remicade).[18]

Critical treatments remain out of reach because the patients still simply can't afford them, and dramatic increases in cost of living due to inflation makes an already precarious situation worse. Financial and co-pay assistance programs help, but patients are nevertheless often forced to pick between paying for everyday essentials such as food and gas, or spending their money on the specialized medicines they need. How to make them more affordable has been a point of contention for quite some time. Debate concerning what to do about it seems to come down to two strategies: Encourage competition to bring prices down naturally, or enforce price controls to bring prices down forcefully.

"At this point, there is likely nothing more critical to lower drug prices than encouraging biosimilar consideration and adoption," said Steven Lucio, senior principal of pharmacy solutions at

Vizient.[1] Increased competition among biologic products are thought to make vital medications 15 to 35 percent less expensive than reference products and grant patients more treatment options, generating close to $7 billion in savings every year.[1] Since biosimilars present a substantial opportunity for cost savings, Lucio emphasizes government must continue to support the biosimilar pathway and limit excessive patenting as a strategy to promote competition.

However, others emphasize that giving the federal government power to negotiate prices with drug companies is a better avenue to lower prices. Supporters of price negotiations in the United States point to the lower prices in other comparable countries as proof that government price regulations work. For example, countries in the EU deal directly with pharmaceutical companies to regulate prices; when a new drug enters the market, EU member states decide on its price. In Canada, the Patented Medicine Prices Review Board caps prices based on what medicines cost in other countries. In countries that have single-payers (government pays for most healthcare costs), the government negotiates prices with drug companies.[19] Advocates for U.S. price negotiations say implementing price negotiations between the government and drug makers would bring prices down here, too. But critics say too much government involvement will stifle innovation and competition, which will lead to fewer drugs in the future.[20]

Inflation Reduction Act to the Rescue?

President Joe Biden signed the IRA into law on Aug. 16, 2022, legislation that supporters say will provide both competition and price negotiations. Several provisions in the act aim to address drug prices, including:[21]

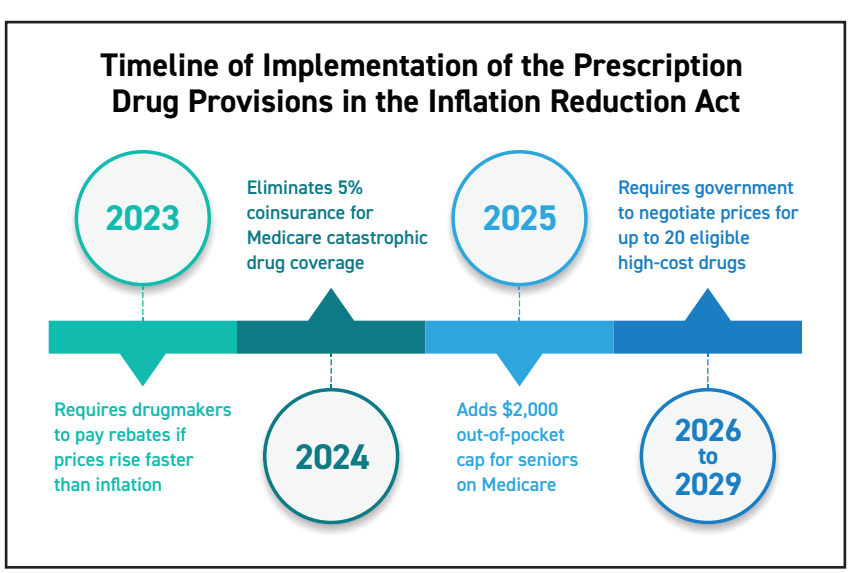
- Establishing a new program for Medicare to directly negotiate prices with pharmaceutical companies for some of the costliest drugs on the market, and implement penalties for companies that refuse to do so;
- Requiring manufacturers to pay rebates on drugs reimbursed under Medicare Parts B or D for which average prices increase faster than inflation;
- Eliminating the 5 percent coinsurance for Medicare catastrophic drug coverage;
- Increasing the add-on fee for healthcare providers prescribing biosimilars from 6 percent to 8 percent for five years;
- Establishing price caps on insulin;
- Providing free shingles vaccines for people covered by Medicare Part D;
- Limiting out-of-pocket drug costs for Medicare beneficiaries at $2,000 annually.

According to HHS, the IRA will deliver lower healthcare costs and much-needed relief from exorbitant prescription drug prices to millions of Americans covered by Medicare. "In recent years, prescription drug prices have skyrocketed, but thanks to the [IRA], America's families will soon start seeing relief," said HHS Secretary Xavier Becerra.[21] According to the Centers for Medicare and Medicaid Services, "By reducing coinsurance for some people with Part B coverage and discouraging drug companies from increasing prices faster than inflation, this policy may lower out-of-pocket costs for some people with Medicare and reduce Medicare program spending for costly drugs."[22]

Senate Finance Committee Chair Ron Wyden echoed these sentiments when he said, "For too long, Medicare has been forced to contend with Big Pharma with one hand tied behind its back."[23] The IRA fundamentally changes that with provisions that "[lower] prices in a way that is fair and designed to promote innovation, not stifle it." Executive Director of the Biosimilars Forum Julie Reed agreed, saying the IRA "will increase competition, promote access and ultimately save American taxpayers and patients money."[24]

But praise for the IRA's price-cutting promises isn't ubiquitous.

Some opponents to price negotiations claim the drug pricing plan is based on false promises, and that price negotiations are euphemisms for price controls. "They



say they're fighting inflation, but the Biden administration's own data show that prescription medicines are not fueling inflation," argues Stephen J. Ubl, president and CEO of the Pharmaceutical Research and Manufacturers of America. "They say this is 'negotiation,' but the bill gives the government unchecked authority to set the price of medicines. And they say the bill won't harm innovation, but various experts, biotech investors and patient advocates agree that this bill will lead to fewer new cures and treatments for patients."[25]

Other critics agree, saying price negotiations are really a way of imposing price controls. Wayne Winegarden, PhD, senior fellow in business and economics at the Pacific Research Institute, argues the IRA's provision for price negotiations actually discourages the competitive process. "Price controls can only generate savings by sacrificing innovation," Dr. Winegarden claims, and will create a risk that investors will not be able to recoup their capital costs when investing in biosimilar development. According to Dr. Winegarden, competition among biosimilars actually preserves incentive for innovation while generating savings because it provides the developers of the reference products an opportunity to recoup their initial investment. The result of price negotiations, he says, will be less competition and higher prices.[26]

Douglas Holtz-Eaken, a former top economic adviser to President George W. Bush and former director of the Congressional Budget Office (CBO), argues that provisions in the IRA may lower some costs of Medicare drugs, but it would also discourage new drug development or reduce venture capital investment in start-up pharmaceutical companies.[27] And, Representative Jason Smith of Missouri says "the prescription drug price controls included in the plan will — according to the [CBO] — increase the cost of new drugs, while simultaneously preventing new cures from coming to market. With the way that policy will also stifle generic drug competition, it will increasingly become only the wealthy who can afford innovative cures and medications."[28]

Time Will Tell

Inflation continues to hover at a higher-than-average rate, crippling the purchasing power of everyday Americans and making already high prescription drug costs even more difficult to afford. For patients needing critical biologic treatments, the problem is even more dire. The promise of biosimilars is encouraging: With lower list prices than their reference products, they may indeed increase affordability and access to these medications. But the jury's still out on whether the IRA will be a help or hindrance in this endeavor. Time will tell whether or not the American people will find financial relief anytime soon. ❖

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A Primer on Mpox

Most human cases of this zoonotic virus are mild, but knowing the signs, symptoms and preventive measures for transmitting this disease remains important for public health.

By Jim Trageser

ONE OF SHAKESPEARE'S most memorable (and lasting) lines from "Romeo and Juliet" is "A plague o' both your houses." While his cleverly dismissive insult is still remembered more than 420 years after the play's premiere, these days that line is more likely to be misquoted as "a pox on both your houses" — speaking to the fact that while the word "plague" has lost much of its power to convey fear, "pox" has not.

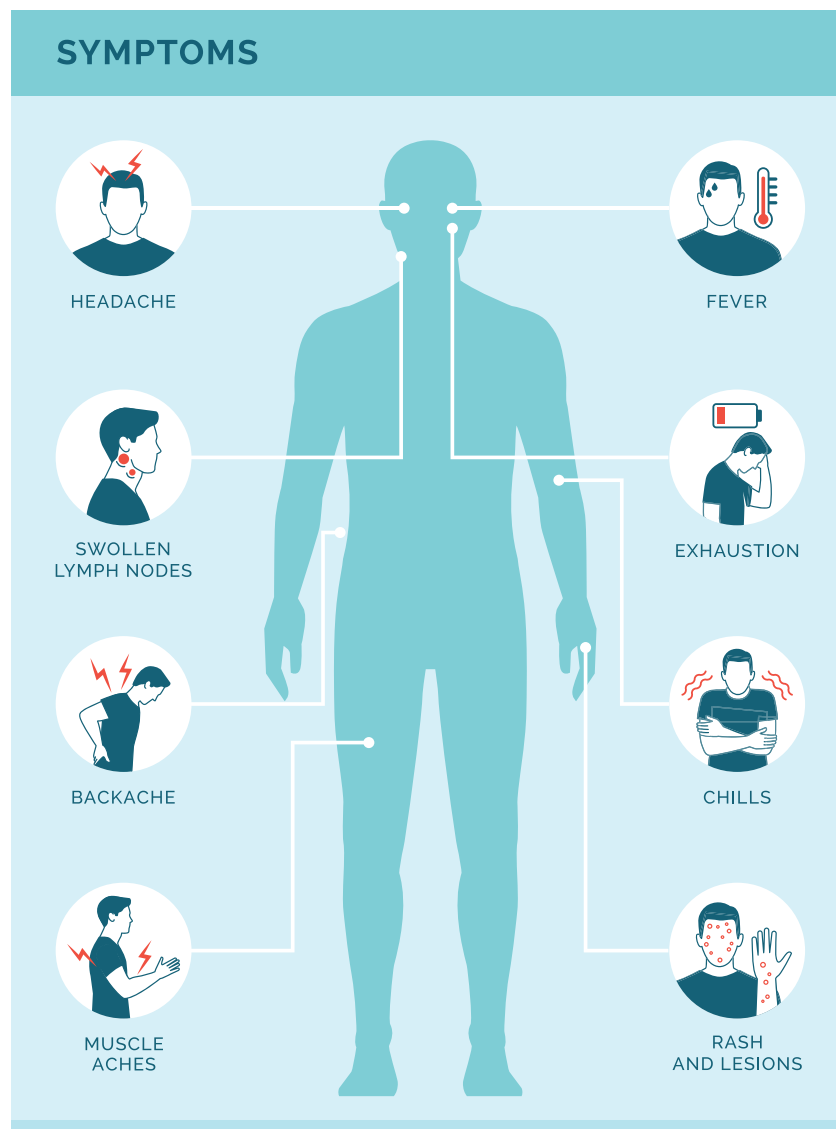
That etymological development may be due to the fact that bubonic plague is curable and we haven't had a major outbreak in more than a century (the United States has an average of only seven cases per year), whereas the equally deadly smallpox wasn't eradicated until 1977.[1] And chickenpox, while unrelated to smallpox and generally a much milder and less dangerous disease, remained a common childhood ailment until introduction of a vaccine just 35 years ago. The idea of a "pox" became more alarming than a "plague."

Thus, when outbreaks of monkeypox were reported in various places around the world beginning a couple of years ago, yet another generation of English speakers was reminded that a "pox" is nothing you want wished upon your house.

What Is Monkeypox (Mpox)?

Mpox is an infectious disease caused by the monkeypox virus.[2] However, the term "monkeypox" is being phased out and replaced with the term "mpox" upon a recommendation by the World Health Organization (WHO).[3]

The current outbreak in the United States has infected just more than 30,000 people in this country as of this writing.[4] Another 57,000 cases have been reported around the world during the past year, ranging from Brazil (more than 10,000) to Spain (7,500), Great Britain (3,700) to Germany (3,700). Other nations that have reported lower case numbers range from Australia to Japan, Iceland to South Africa. Overall, cases have been reported in more than 110 nations — with close to 100 of them reporting mpox for the first time.



Still, in the past few years, with more than 87,000 cases worldwide, there have been fewer than 120 deaths — and many of those who died had other underlying health conditions such as a weakened immune system, so mpox is clearly a far less virulent disease than smallpox.

The mpox virus is a member of the Orthopoxvirus genus, which also includes the viruses that cause cowpox and smallpox in humans. It was first described and isolated in 1958 by Preben von Magnus, MD, who noticed an outbreak of a skin infection among cynomolgus macaques (a type of long-tailed monkey) in a research laboratory in Copenhagen.[6]

The first time a human case was documented was in 1970 in a 9-year-old patient who lived in what is now the Democratic Republic of Congo. Since the patient lived in an area where there had not been any cases of smallpox for more than nine months, researchers conducted additional tests and eventually discovered the patient had mpox, not smallpox.[7]

There are two known strains, or variants, of mpox: Clade I and Clade II. Clade I is found primarily in the Congo Basin in Central Africa. Clade II was originally found in West Africa. Clade II has two subvariants, Clade IIa and Clade IIb. Clade IIb is the variant that has mostly been found outside of Africa.[8]

Symptoms, Diagnosis and Treatment

As with cowpox and smallpox, mpox symptoms include a distinctive rash (pox) that progresses from small, flat spots to pus-filled lesions that eventually dry out and fall off. The lesions appear in a pattern that generally includes the face, arms and legs.

After an incubation period of one to two weeks,[9] initial symptoms will appear prior to the appearance of skin lesions and will generally include fever, severe headache, muscle pain and heavy fatigue, along with swollen lymph nodes.[2]

Patients are contagious throughout the time they have symptoms and should isolate as much as possible during that time. Recent research suggests patients may begin shedding viruses even before symptoms occur.[10]

In rare cases, the virus will travel through the body to the genitals, eyes (causing vision issues or even blindness) or lungs (which can lead to pneumonia). If it spreads to the brain, it can cause encephalitis.

The Centers for Disease Control and Prevention recommends a vaccine for immunocompromised patients, as well as those who engage in certain types of risky sexual activity.

Diagnosis is generally made by polymerase chain reaction from a sample taken from an active skin lesion. The sample is sent to a qualified laboratory in a cold, dry tube.[10] It is important to note that WHO notes that antigen and antibody tests cannot differentiate between mpox and other orthopoxviruses.

While the disease can, in rare cases, prove deadly (about a 1 percent mortality rate for the mpox variant, Clade II, found most often in the United States[4]), most patients will recover on their own in two to four weeks. Antiviral medications can be used in severe cases. Otherwise, treatment is generally targeted to control the symptoms of fever and pain.[11]

Although fatalities have been rare in the United States, the mortality rate has run as high as 10 percent for those who contract the variant Clade I found most often in Central Africa, where mpox is thought to have originated and where it is now endemic.[12]

Other serious side effects can include severe facial or other scarring (from heavy lesions or scratching of lesions) and secondary bacterial infections from scratching of lesions.[11]

How Is Mpox Transmitted?

Much is still not known about mpox, including its natural reservoir and the most common modes of transmission. It is thought that mpox rates have been increasing in the past few years due to the cessation of the smallpox vaccines after the successful extermination of smallpox. It is known that at least some of the types of smallpox vaccine also conferred mpox immunity, since the two viruses are so closely related.[7]

Zoonotic transmission (transmission between species) likely occurs from exposure to infected animals (including scratches and bites, or airborne droplets from their breath), cuddling with infected pets or from eating infected meat that is not properly cooked.[2] While the original host of mpox is not yet known, numerous species of rodents have been found with the mpox virus, leading researchers to identify them as the likely natural reservoir. (One of the earliest human outbreaks in the United States involved pet prairie dogs that were temporarily housed next to a shipment of Gambian pouched rats being imported from West Africa in 2003.[13])

Human-to-human transmission is thought to be rare, but it is being increasingly documented. Researchers are unsure whether this represents a mutation in the virus' gene, or if it is simply the result of more opportunity due to greater numbers of infected patients contracting mpox from animals. Human-to-human transmission is most likely accomplished in some of the same ways people get it from animals: touching an infected lesion or breathing in microscopic droplets from someone who has mpox in the lungs. Mpox can also spread through exposure to contaminated bedding or clothing and, increasingly, via unprotected sex.[11] Pregnant women can transmit mpox to their unborn child, as well as after birth by cuddling with the baby.

Prevention

As noted above, several existing smallpox vaccines can help prevent mpox as well, including the ACAM2000 and Jynneos vaccines. Healthcare workers treating mpox patients or lab workers handling suspected mpox samples may consider receiving one of these vaccines. In addition, the Centers for Disease Control and Prevention recommends a vaccine for immunocompromised patients, as well as those who engage in certain types of risky sexual activity.[14]

For those who lack access to a vaccine, prevention comes down to basic precautions:

- Avoiding physical contact with anyone who displays symptoms of mpox
- Avoiding handling bedding or clothing of anyone who has had mpox (or bedding or toys of an infected animal)
- If contact is accidentally made, or unavoidable, washing hands with hot water and soap immediately after
- Self-isolating from an infected family member or roommate until symptoms have cleared

Research

Because existing smallpox vaccines already confer protection against mpox, and because most cases of Clade II mpox are fairly mild, there is relatively little research going on into mpox at this time. A search for both "monkeypox" and "mpox" on the U.S. Food and Drug Administration's Clinical Trials website (clinicaltrials.gov) revealed fewer than three dozen current or recent trials.

One study being jointly conducted by the University of California, San Diego, George Washington University and Emory University is looking at whether the dose of one of the existing vaccines (MVA-BN) can be reduced and still confer protection.

Other studies are looking at whether administering a smallpox vaccine after exposure to mpox can still help the body fight off infection, or perhaps reduce the severity of symptoms. And, still other studies are looking at the efficacy of existing antiviral drugs in lowering the severity of an mpox infection.

Looking Ahead

Because homo sapiens were the one and only reservoir for smallpox, eradicating smallpox was scientifically straightforward — if financially expensive and politically challenging. But once the last human being with smallpox was inoculated, there was nowhere else for the smallpox virus to live. But mpox is zoonotic, living in the tissue of unknown numbers of species of wild animals, so eradicating it is impossible with current technology.

Widespread inoculation — particularly against the more lethal Clade I variant — may be the best hope of reducing deaths due to mpox. Treatment of symptoms, including reducing pain and itching of the lesions, can help reduce scarring, as well as decrease the chances of a secondary infection. Those diagnosed with the Clade I variant might be candidates for antivirals to reduce the severity of the infection.

It is likely that mpox remained a largely local disease in Africa due to the lack of modern transportation infrastructure in that part of the world. Now that modern road, air, rail and sea travel are bringing those once-remote areas more fully into the global community, we are seeing mpox showing up in more than 100 nations. With mpox having been diagnosed everywhere from Iowa to Los Angeles in the United States, physicians in every community will need to be familiar with the symptoms and be ready to diagnose and treat mpox for the foreseeable future. ❖

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Myths & Facts: Autism

Dispelling the myths surrounding this condition can help parents and caregivers support individuals with ASD, as well as clear up stereotypes and misunderstandings often associated with it.

By Ronale Tucker Rhodes, MS

AFFECTING AN estimated one in 36 children in the United States in 2023,[1] autism spectrum disorder (ASD) is a developmental disability caused by differences in the brain. While a genetic condition is the cause of ASD in some people, in others, the cause is unknown. It typically begins before 3 years of age, and it can last throughout the person's life.[2]

The earliest description of a child now known to have autism was written in 1799;[3] however, it wasn't until 1943 and 1944 when the first "accepted" descriptions of autism were published by two men known as the "pioneers of autism research." In 1943, Leo Kanner, MD, published a paper titled "Autistic Disturbances of Affective Contact" that dubbed the condition as "early infantile autism" and later became known as autism of Kanner's syndrome. In 1944, Hans Asperger, MD, published a paper that presented case studies of four children he and his colleagues had seen in his clinic in Vienna, Austria. Although scholars debated how much the conditions described by Drs. Kanner and Asperger were different and the doctors themselves considered them different, the descriptions were eventually merged in 1981 in an influential paper titled "Asperger's Syndrome: A Clinical Account" by British psychiatrist Lorna Wing, MD. Dr. Wing argued that Dr. Kanner's autistic clients and those Dr. Asperger described "were part of a wider range of people — soon known as 'the spectrum' — who shared some mix of impairments in social interaction; deficits in comprehension and use of language; and the presence of 'repetitive, stereotyped pursuits.'"[4]

Today, it is known that most children can be diagnosed with ASD as young as 2 years old, but it is often diagnosed

after 4 years of age. It affects boys four times more often than girls. And, while it affects all ethnic and socioeconomic groups, minority groups tend to be diagnosed later and less often.[5]

Raising children with ASD and understanding how to deal with individuals with ASD is challenging for most. Unfortunately, this challenge is exacerbated by the misconceptions circulating about the condition, which is why dispelling the myths surrounding ASD can help to clear up stereotypes and misunderstandings, and serve as a form of emotional support for parents and caregivers.

Separating Myth from Fact

Myth: ASD is a disease.

Fact: ASD is not a disease, but rather a neurodevelopmental disorder that impairs a person's ability to communicate and interact with others.[6] Simply put, these individuals' brains work differently from other people's brains.[7]

Myth: ASD is a mental health disorder.

Fact: Again, ASD is a neurological disorder with abnormalities in brain structure and neurotransmitter levels. However, it's not uncommon for people, particularly adults, to be misdiagnosed with a mental illness before receiving a diagnosis of ASD. Importantly, though, mental illness and developmental disabilities such as ASD are not the same things, although studies have shown that many people with ASD also have a mental illness. In fact, anxiety and depression, in particular, occur at a higher rate among people with autism than in the general population.[8] In a study conducted in 2019 that evaluated the utility of the Mini International Neuropsychiatric Interview (MINI) in assessing co-occurring psychiatric disorders in children, adolescents and young adults with ASD, researchers found 91 percent of children/adolescents and 31 percent of young adults were diagnosed with one or more co-occurring diagnoses.[9] When someone with autism also has a mental illness, it's known as a dual diagnosis.

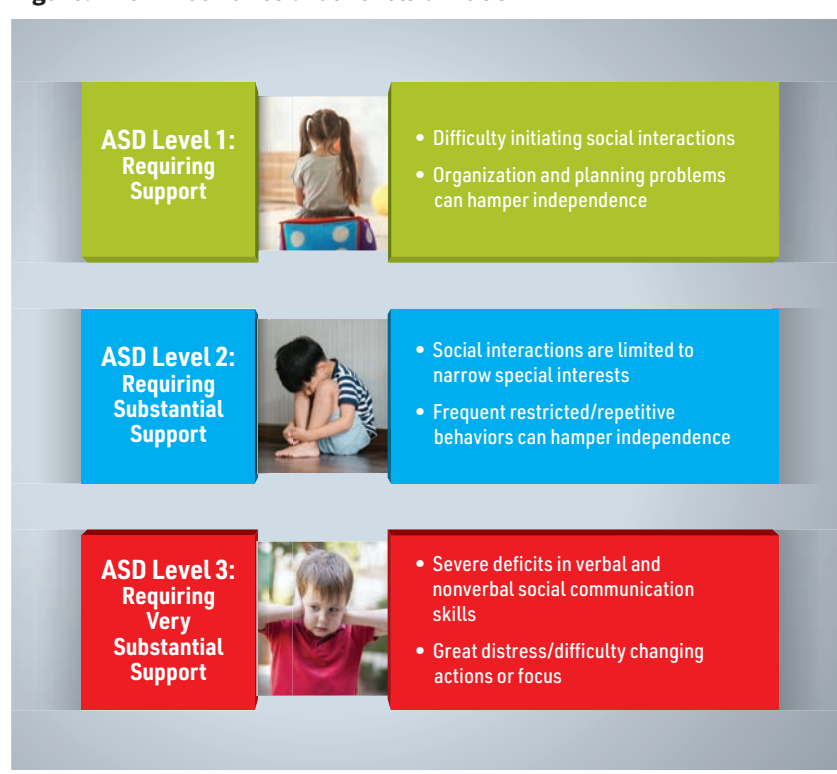
Myth: ASD affects all people the same.

Fact: Autism is a spectrum disorder, and individuals with ASD differ widely in their intellectual abilities. According to the Centers for Disease Control and Prevention, 31 percent of children with ASD have an intellectual disability (intelligence quotient [IQ] less than 70), 25 percent are in the borderline range (IQ of 71 to 85) and 44 percent have IQ scores in the average to above average range (IQ greater than 85).[5]

There are three levels of ASD described in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*: level 1, level 2 and level 3. Individuals are diagnosed with either level 1, 2 or 3 depending on how severe their disorder is and how much support they need in daily life. The levels range from least to most severe, with ASD level 3 describing an individual who has the most severe level of ASD symptoms, and ASD level 1 describing someone with symptoms on the milder end of the spectrum (Figure). Importantly, though, while the ASD levels are useful for diagnosing autism severity and support needs, they don't provide a full picture of the strengths and limitations of each level. And, the three levels are not entirely inclusive of the symptoms and needs of all people with ASD.[10]

Also, individuals with ASD can be hard to test, and IQ levels are often under- or overestimated unless testing is performed by an expert in intellectual and developmental disabilities and

Figure. The Three Functional Levels of Autism



autism. In fact, tests designed to include language and interpersonal analyses can misrepresent the intelligence of people with ASD.[3]

Myth: Individuals with ASD have savant abilities.

Fact: Only approximately one in 10 persons with autistic disorder has some savant skills, known as savant syndrome, a rare condition in which persons with various developmental disorders have an amazing ability and talent. In the case of intellectual and/or developmental disabilities, as well as brain injuries, savant skills occur at a rate of less than one percent. Therefore, not all savants are autistic, and not all people with autism are savants.[11]

Myth: Individuals with ASD are emotionally detached.

Fact: Studies show that people with ASD express emotion in different ways, they direct their emotions to others less frequently with eye contact and they sometimes get emotional about different things, but they do have emotion.

In fact, according to Kenneth Roberson, PhD, an adult autism psychologist in San Francisco, Calif., some people with ASD have difficulty perceiving emotions and responding to them, while others with ASD respond normally. But, trouble processing emotions is not universal among adults with ASD, says Dr. Roberson. Other psychological conditions result in trouble understanding and responding to emotions. What's more, adults with ASD who find it hard to recognize emotional reactions and express them have a specific pattern of processing emotions. For example, they find it difficult to understand emotions expressed directly by other people, as opposed to emotional information that is nonsocial such as music or written words. In addition, they have a hard time grasping emotional information that is complex such as a state of vague, nonspecific frustration. Finally, when someone on the spectrum notices an emotional reaction, either from within themselves or from someone else, it's likely he or she will respond inappropriately since the intuitive, ingrained strategies to process emotions that help neurotypical people react automatically and appropriately to emotional experiences are less developed and accurate in those with ASD.[12]

Recent studies conducted by the Olga Tennison Autism Research Centre have found a pattern suggesting that children with autism need a longer time to process and react to emotional facial expressions such as happy, angry, fear, etc., which is consistent with previous work. This means that in everyday social contexts, which are fast-paced and ever-changing, people with ASD can have difficulty because they can sometimes be emotionally "out of sync" or "out of time" with their social partners.

In general, the organization says, "emotions expressed by the human face, voice and body are more difficult for people with ASD to understand and react to than emotions expressed through nonhuman or nonbodily forms such as music or written words. However, it depends on who the person expressing the emotion is, that is, whether they are a stranger or someone familiar." Another recent study conducted by the organization "found more typical emotional reactions in children with autism to emotions expressed by people they knew, compared to people they didn't know."[13]

Myth: All individuals with ASD are violent.

Fact: There have been news stories relating ASD to violence, but aggressive acts by these individuals are usually in response to sensory overload or emotional

Associated Challenges of ASD[5]

- 25-30 percent of people with ASD are nonverbal or minimally verbal (fewer than 30 words or unable to use speech alone to communicate).
- 31 percent of children with ASD have an intellectual disability.
- Nearly half of people with ASD wander or bolt from safety.
- Nearly two-thirds of children with ASD between ages 6 years and 15 years have been bullied.
- Nearly 28 percent of 8-year-olds with ASD have self-injurious behaviors such as head banging, arm biting and skin scratching.
- Drowning remains a leading cause of death for children with ASD and accounts for approximately 90 percent of deaths associated with wandering or bolting by those age 14 years and younger.

Economic Costs of ASD[5]

- In 2015, the cost of caring for Americans with ASD was $268 billion, and it is predicted to rise to $461 billion by 2025.
- It costs an estimated $175 billion to $196 billion a year to care for adults with ASD in the U.S., compared to $61 billion a year for children.
- On average, medical expenditures for children and adolescents with ASD are 4.1 to 6.2 times greater than for those without ASD.
- Passage of the 2014 Achieving a Better Life Experience (ABLE) Act allows tax-preferred savings accounts for people with disabilities, including ASD, to be established by states.
- Passage of autism insurance legislation in all 50 states is providing access to medical treatment and therapies.

stress. In fact, it's unusual for individuals with ASD to act violently out of malice or pose any danger to society.[3] Indeed, a small body of literature has suggested that, rather than being more likely to engage in offending or violent behavior, individuals with ASD may actually have an increased risk of being the victim rather than the perpetrator of violence.[14]

However, it isn't uncommon for individuals with ASD to exhibit aggression. Hitting, biting, scratching, hair-pulling or kicking another person is relatively common in children on the autism spectrum. In a study of children and teenagers with autism, the researchers found that 68 percent had been aggressive to a caregiver and 49 percent had been aggressive to someone else at some point. More than half of the youth studied were currently having mild to severe aggressive behavior. According to Micah Mazurek, PhD, an associate professor at the University of Virginia where she directs the Supporting Transformative Autism Research program, in the general population, young children often become less aggressive as they get older and learn better ways to express themselves. But this aggression persists in some individuals with ASD through the teen years into adulthood. One study found that 15 to 18 percent of adults who have autism and intellectual disability showed aggression, and another study of autistic adults found that five percent of women and 14 percent of men had aggressive behavior over time, said Dr. Mazurek.[15]

Myth: ASD is caused by vaccines.

Fact: In 1998, *The Lancet* published an article linking vaccines to autism that triggered a great deal of fear, but after an investigation, the article was later retracted by the publisher. In 2010, the General Medical Counsel declared that the paper was not only based on bad science, but was deliberate fraud and falsification by the head researcher, Andrew Wakefield, MD, whose medical license was then revoked. Investigators learned that a lawyer looking for a link between the vaccine and autism had paid Dr. Wakefield more than £435,000 (equal to more than a half-million dollars).

Only approximately one in 10 persons with autistic disorder has some savant skills, known as savant syndrome, a rare condition in which persons with various developmental disorders have an amazing ability and talent.

The paper's findings led other doctors to conduct their own research into the link between the measles, mumps and rubella vaccine and autism. At least 12 follow-up studies were performed, and none found any evidence the vaccine caused autism.[16]

Myth: It is unknown what causes ASD.

Fact: Causes of ASD are not well-understood. However, research shows that genetics are involved in the vast majority of cases.[5] For instance, scientists have found rare gene changes, or mutations, as well as small common genetic variations in people with autism, implying a genetic component. In fact, a growing area of research focuses on interaction of genetic and environmental factors.[17]

According to Spectrum, a leading source of news and expert opinion on autism research, the most widely accepted environmental risk factors occur during gestation or around the time of birth. Various pregnancy and birth complications are associated with an increased risk of autism. These include preterm birth, low birth weight and maternal diabetes or high blood pressure during pregnancy. However, scientists are unsure of the mechanisms underlying these associations.

The maternal immune system also appears to play a role in autism risk. Infections, serious illnesses such as a bad case of influenza and hospitalizations during pregnancy are all linked to an increased risk of autism in a child. Women with autoimmune diseases, in which the body attacks its own tissues, are also at an elevated risk of having an autistic child. And, animal studies suggest that certain immune molecules can alter gene expression and brain development in ways that may be relevant to autism.

Exposure to the drug valproate, which is used to treat bipolar disorder and epilepsy, in the womb is also known to increase the risk of autism, as well as a variety of birth defects.[18]

In addition, according to Autism Speaks, several other factors are known to cause ASD, including:[5]

- Children born to older parents are at a higher risk for having autism.
- Parents who have a child with ASD have a two to 18 percent chance of having a second child who is also affected.
- Studies have shown that among identical twins, if one child has autism, the other will be affected about 36 to 95 percent of the time. In non-identical twins, if one child has autism, then the

other is affected about 31 percent of the time.

Myth: ASD can be diagnosed only in children.

Fact: Some individuals are not diagnosed with ASD until they are adolescents or adults. Unfortunately, diagnosing ASD can be difficult because there is no medical test such as a blood test to diagnose the disorder. Instead, doctors look at the child's developmental history and behavior to make a diagnosis using a variety of tools (see Example of Diagnostic Tools to Diagnose ASD); however, no single tool by itself should serve as the basis for a diagnosis.

ASD can sometimes be detected at 18 months of age or younger. By age 2, a diagnosis by an experienced professional can be considered reliable. However, many do not receive a final diagnosis until they are adolescents or adults, and the delay means they might not get the early help they need.[19]

Myth: ASD can be treated with a special diet.

Fact: While there is no scientific proof that diet helps to treat individuals with ASD, some parents believe it does. For instance, some believe in the specific carbohydrate diet, a restrictive eating plan that forbids carbohydrates with more than one molecule structure, including all grains, sugar, some dairy products and even certain vegetables. The diet was originally developed to treat gastrointestinal conditions such as celiac disease and ulcerative colitis. But, according to an article published in *U.S. News & World Report*, no strong evidence supports any diet to treat autism. For example, it says, "early research and plenty of parents' experiences have supported a gluten-free, casein-free diet — or one that eliminates all foods containing gluten (including wheat, barley and rye, among others) and casein (namely, milk and dairy products) — as helpful for autism symptoms, but recent, stronger research found no difference between children with autism on the plan and those on a placebo."[20]

The research the article is referring to is a study conducted to examine the safety and efficacy of the gluten-free/casein-free (GFCF) diet. In the study, researchers placed 14 children with autism, age 3 to 5 years, on the diet for four to six weeks and then conducted a double-blind, placebo-controlled challenge study for 12 weeks while continuing the diet, with a 12-week follow-up. Dietary challenges were delivered via weekly snacks that contained gluten, casein, gluten and casein, or placebo. With nutritional counseling, the diet was safe and well-tolerated. However, dietary challenges did not have statistically significant effects on measures of physiologic functioning, behavior problems or autism symptoms. The researchers do note that these findings must be interpreted with caution because of the small sample size; however, the study does not provide evidence to support general use of the GFCF diet.[21]

It is important to note, though, that many children with autism have digestive issues, so a particular diet might work for individual kids with autism, and specific food choices might help to manage autism symptoms, experts say. "Dietary intervention can be life-changing by helping to alleviate symptoms and physical pain that can contribute to behaviors often associated with autism," says Wendy Fournier, president of the National Autism Association.[20]

Some parents also have had their kids try certain medications such as chelation to remove mercury from their blood based on unsubstantiated reports that mercury can cause autism. However, these medications haven't been proven safe and could have serious side effects, including kidney damage. Very high doses of vitamin A are also believed by some to be very beneficial, but that can cause vomiting, bone thinning and liver damage, among other complications.[22]

Myth: ASD has become an epidemic.

Fact: Actually, it's only awareness about ASD that has increased since the 1980s and early 1990s, which has resulted in more parents, pediatricians and educators learning to recognize the signs of autism. As a result, more individuals are being diagnosed, causing people to believe that the condition has become an epidemic.[6]

Myth: ASD can be cured.

Fact: Unfortunately, ASD is a life-long condition, and there is no cure, even with medication. However, individuals with ASD can live independent, productive lives. Early and intensive behavioral treatment can reduce the severity of symptoms and help individuals develop adaptive skills for daily living, emotion and behavior regulation, and social engagement.[3] Types of treatments include:[23]

- Behavior and communication therapies that address the range of social, language and behavioral difficulties associated with ASD
- Highly structured educational therapies that typically include a team of specialists and a variety of activities to improve social skills, communication and behavior

Some individuals are not diagnosed with ASD until they are adolescents or adults.

Examples of Diagnostic Tools to Diagnose ASD[28]

- Childhood Autism Rating Scale (CARS)
- Autism Diagnosis Interview–Revised (ADI-R)
- Gilliam Autism Rating Scale–Second Edition (GARS-2)
- Autism Diagnostic Observation Schedule–Generic (ADOS-G)
- American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*

Note: These tools rely on a healthcare provider's observation of the child's behavior and/or the parent or caregiver's description of their child's development and behavior.

• Family therapies such as learning how to play and interact with children in ways that promote social interaction skills, manage problem behaviors and teach daily living skills and communication

• Speech therapy to improve communication skills

• Occupational therapy to teach activities of daily living

• Physical therapy to improve movement and balance

While there are no medications that can improve the core signs of ASD, some medications can improve symptoms. For example, certain medications may be prescribed for hyperactivity; antipsychotic drugs are sometimes prescribed to treat severe behavioral problems; and antidepressants may be prescribed for anxiety.[23]

Dispelling the Myths Now

Over the years, legislation has been enacted to help families of children with ASD. In 2014, the Achieving a Better Life Experience (ABLE) Act was enacted to allow states to create tax-advantaged savings programs for eligible people with disabilities (designated beneficiaries). Funds from these 529A ABLE accounts can help designated beneficiaries pay for qualified disability expenses, and distributions are tax-free if used for qualified disability expenses.[24]

In 2019, the Autism Collaboration, Accountability, Research, Education and Support (CARES) Act reauthorized and expanded the provisions first introduced in the Combating Autism Act of 2006. The Autism CARES Act ensures support for research, services, prevalence tracking and other government activities, as well as increases the annual authorized federal spending on autism efforts to $369.7 million through 2024.[25] Also in 2019, all 50 states and Washington, D.C., enacted mandates requiring some level of insurance coverage for the treatment of ASD.[26]

In 2022, both chambers of Congress passed the Autism Family Caregivers Act of 2022 that would give autism families the support and training needed to provide quality caregiving to their children. Specifically, the act would establish a five-year caregiver skills pilot program to award grants to nonprofits, community health centers or hospitals to provide skills training to family caregivers of children with autism. The grants will provide for 25 pilot programs in at least 15 states. However, as of this writing, the act has not yet been signed into law.[27]

Along with legislation, greater public awareness about ASD can help not just individuals with autism, but also make lives easier for families and caregivers. With the rising rates of diagnoses of ASD in the United States, it is increasingly important for parents, pediatricians and educators to recognize the signs of the condition so individuals can be diagnosed early and receive the support they need. ❖

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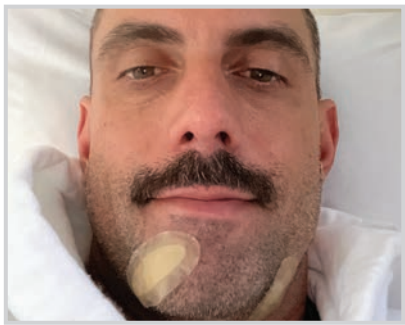

After several months of trying to get an appointment to get an mpox vaccine during the 2022 outbreak, Jeffrey Galaise finally got vaccinated right as he began experiencing symptoms of the disease.

Mpox: *A Patient's Perspective*

By Trudie Mitschang

DURING THE HEIGHT of last year's monkeypox (mpox) outbreak, New York resident Jeffrey Galaise, 42, had been navigating the city's overrun online appointment system desperate to get vaccinated. "I finally got an appointment in June, but had to cancel after contracting COVID," he said. Jeffrey did eventually get the mpox vaccine, but the timing could not have been worse: He was just beginning to feel ill. As his symptoms escalated, he experienced fatigue, achiness, low-grade fever, swollen glands, a headache and an overall dizzy, lethargic feeling, but he did not have any of the telltale pox blisters.

"Initially I went to my local urgent care, that has always been very helpful, and they confirmed that they couldn't test me for mpox without any lesions, which I didn't have at the time," he said. They were able to test him for everything else, and he tested negative for COVID-19, influenza and strep. After several more days, Jeffrey's fever spiked and he noticed several lesions on his body. That's when he went back to his primary care physician (PCP) and obtained an official diagnosis of mpox. From there, the real health challenges began.

"My [PCP] told me that based on what he saw in the lesions, my case was going to be severe, and he wanted me to get into the clinical trial for TPOXX, an antiviral previously used for smallpox that was in the process of FDA approval for mpox," explained Jeffrey. "At the time, only certain hospitals and doctors were able to administer it."

Jeffrey's PCP contacted a colleague at New York University Langone who admitted Jeffrey into the trial, but by the time they were able to get him the needed medication, his symptoms had worsened significantly. "By the time I was able to get TPOXX, I had at least 65 lesions all over my body and severe pain," explained Jeffrey. "If I had gotten the medication on the day I saw my doctor, I don't know how [the disease] would have progressed, but I would assume it would not have been as aggressive or severe."

From Victim to Advocate

The stigma associated with mpox (it is perceived by many as a sexually transmitted disease due to primarily spreading through sexual contact during the 2022 outbreak[1]) coupled with the unsightly appearance of the disease symptoms meant Jeffrey was left to primarily fight the virus in isolation. Determined to empower himself and help others, Jeffrey decided to go public about his experience via social media. "I felt like nobody had answers, and I needed people to talk to," he said. "I began posting online about my symptoms and looking for support groups, but I couldn't find anything. So I decided to start a Zoom support group of my own."

As word got out about the support group, more and more people began contacting Jeffrey. Gay men from all over the country logged on to his hour-long Zoom sessions to share their struggles and resources. "Because I was posting on Instagram, people were coming to me for information because they said their doctors just turned them away," he said. "They would go from one doctor to another doctor to another doctor. I'm not a therapist and I'm not a doctor, but it helped to talk to other people going through similar experiences and share coping strategies."

Jeffrey remained ill with mpox for nearly a month, and he says once he was diagnosed, there was limited information about how to best treat the symptoms. And, health experts acknowledge that the stigma associated with mpox, particularly within the LGBTQ community, means the pain and anguish do not always go away when the scabs heal. "I think it's important to be aware of the effect of the stigma regarding the route of mpox transmission, at-risk groups and disfiguring skin lesions — all of which could contribute to psychological distress," said James Badenoch, MBChB, academic foundation doctor at the Queen Mary University of Medicine in London and the co-lead author of a 2022 review and meta-analysis published in *eClinical Medicine* exploring neurological and psychiatric conditions linked to mpox.[2]

Today, Jeffrey has recovered physically, and thankfully, only suffered minimal scarring from the unsightly lesions. But he says he still has persistent nightmares about the infection. "It's a very traumatic experience. I'm a different person having been through this," he says. "If you haven't lived through it, you have no idea the kind of pain that this is, and the red tape that's attached to trying to get help and support." ❖

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Mpox: *Lessons Learned*

THE U.S. MONKEYPOX (mpox) public health emergency formally ended in early 2023. Yet, while mpox isn't completely gone, the average number of daily new cases has dwindled to the single digits. Still, many questions for public health officials remain.

Ambiguous Messaging

The 2022 outbreak of mpox in the United States primarily affected men who have sex with men.[1] This led to a difficult time for U.S. public health officials in terms of messaging, which needed to be geared toward an at-risk population that had previously been stigmatized during the HIV/AIDs crises. The Centers for Disease Control and Prevention (CDC) released a statement saying "infection could occur during close physical contact, and also through contact with contaminated surfaces like sheets or towels." They stopped short of naming mpox a sexually transmitted disease (STD).[1]

"People felt that if they called it an STD from the get-go, it was going to create stigma, and because of the type of sex that was occurring — oral sex, anal sex, anal sex between same-sex male partners — there may not have been the same kind of federal response," said Jeffrey Klausner, MD, MPH, a clinical professor of public health at the University of Southern California's Keck School of Medicine. "It was actually a political calculation to garner the resources necessary to have a substantial response to be vague about how it spread."[2]

However well-intentioned, the purposeful ambiguous messaging created confusion that likely led those in the impacted populations to continue engaging in risky sexual behavior during the height of the outbreak. "I think there was a balancing dance of not wanting to create stigma, in terms of who is actually the highest rates of transmission without being forthright," added Tony Hoang, executive director of Equality California, a nonprofit advocacy group for LGBTQ civil rights.[2] Hoang's group eventually launched its own public information campaign, stressing that sex was the risky behavior and clarifying that light brushes or touches weren't likely to pass the infection.

Vaccines Versus Behavior Change

According to CDC, people who were unvaccinated were almost 10 times more likely to be diagnosed with the infection than those who got the recommended two doses of the Jynneos vaccine.[3] During the summer of 2022, demand for the vaccine escalated in the gay community amid widespread reports of vaccine shortages. In the end, CDC estimates that while two million people in the United States were eligible for mpox vaccination, only about 700,000 received even a single dose.[1] Looking back at the trajectory and dramatic tapering off of the virus, experts say inoculation is almost certainly not the entire reason for decline, simply because not enough people were vaccinated. Instead, CDC suggests behavior change may have played a substantial role in curbing the spread.

In an online survey of men who have sex with men conducted last year, half of participants indicated they had changed their behavior out of fear of infection.[4] If that shift proves to be a significant factor in curbing the spread of mpox, some worry the United States could see another surge when behavior patterns shift once again.

A Look at What's Next

Education about mpox and access to vaccination seem to be key to curbing a future outbreak. Since nearly 40 percent of cases in the United States were diagnosed in people who also have HIV, CDC plans to ensure mpox vaccines are available as a routine part of care at HIV and STD clinics. Officials are also planning to attend LGBTQ events to offer onsite vaccinations and study people who've been vaccinated and/or infected to see whether they remain immune.[1]

"We're starting to see some data that suggests asymptomatic infection and transmission is possible, and that certainly will change how we think about this virus," said Anne Rimoin, PhD, MPH, an epidemiologist at the Fielding School of Public Health at the University of California, Los Angeles.[1]

In terms of addressing disparities, Hoang says Equality California is pushing for change: "We've learned that we have to take health into our own hands, and I do think that we will remain vigilant as a community for this outbreak and future outbreaks." ❖

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FcRn Antagonists: A Panoply of Autoimmune Disorders Now in the Development Pipeline

By Keith Berman, MPH, MBA

SPECIFICALLY DESIGNED to blockade the physiologic IgG recycling function of endothelial cell neonatal crystallizable fragment receptor (FcRn), FcRn antagonists represent a new class of monoclonal antibody (mAb)-based drugs that have been shown to mediate a sharp, dose-dependent reduction in circulating IgG levels. Thanks to this unique immunomodulatory functionality, FcRn antagonists are now recognized as among the most promising — and intensively competitive — new therapeutic modalities to emerge in years.

One product recently secured U.S. Food and Drug Administration (FDA) approval for the treatment of generalized myasthenia gravis (gMG), a classic autoantibody-mediated neuromuscular disorder. In total, four investigational FcRn antagonists are currently being clinically evaluated as potential treatments for a remarkable range of mostly rare autoantibody-mediated neurological, hematological, rheumatologic, endocrinologic, dermatologic and renal disorders.

First identified for its role in the facilitated transport of IgG from mother to fetus or neonate (thus its name), FcRn complexes with the constant tail (Fc) region of endocytosed plasma IgG and internalizes it into recycling endosomes, thus protecting IgG from degradation by cellular lysosomes. Endosomal FcRn-bound IgG is rereleased into the circulation by exocytosis, while unbound IgG is trafficked to lysosomes for degradation (Figure).

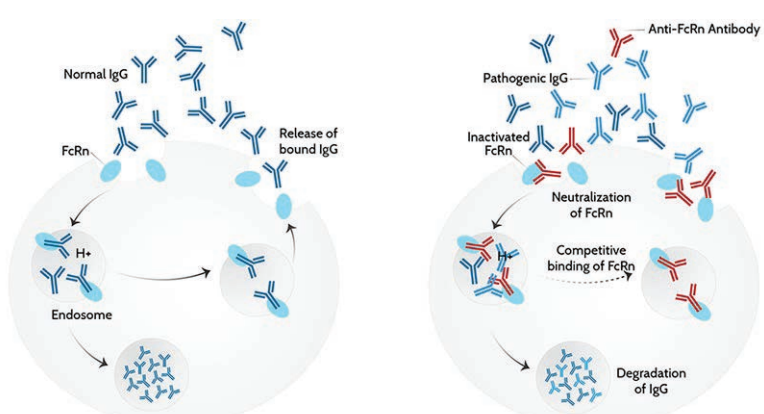
In essence, FcRn rescues IgG from cellular catabolism, which accounts for the prolonged 19- to 23-day average IgG half-life in the circulation. The functionality of FcRn is also indiscriminate: The half-lives of both physiologic and pathogenic IgG antibodies are extended by this endothelial recycling mechanism.

FcRn antagonists are designed to outcompete IgG for the Fc receptor epitope on FcRn. As a result of this blockade of FcRn functionality, more IgG is degraded in lysosomes and less is protected within endosomes and recycled into the circulation. At clinically tested doses, FcRn antagonists can reduce circulating IgG — including pathogenic IgG autoantibodies — by as much as 80 percent or more.

While the FcRn-targeted mechanism of action is novel, the therapeutic principle of reducing pathophysiologic IgG levels to ameliorate disease symptoms or induce remission is not new at all: Therapeutic plasma exchange (TPE or PLEX), generally with five percent albumin replacement, has been used as first- or second-line therapy for decades to acutely reduce serum IgG levels in a diverse spectrum of disorders that are known or thought to be IgG-mediated.[1] But serious clinical investigation of potential indications for

Figure. 1) Endothelial Cell FcRn-Mediated Recycling of Plasma IgG and 2) Blockade of Plasma IgG Recycling by FcRn Antagonist (Anti-FcRn Antibody)

(1) Plasma IgG taken up by endothelial cells binds to FcRn, which protects the IgG from lysosomal degradation and recycles it back to the circulation



(2) Anti-FcRn antibody competitively binds FcRn, resulting in IgG degradation (including pathogenic IgG autoantibodies) and reduced rate of return to the circulation

Table. Current Clinical Trials with Investigational and Approved FcRn Antagonists

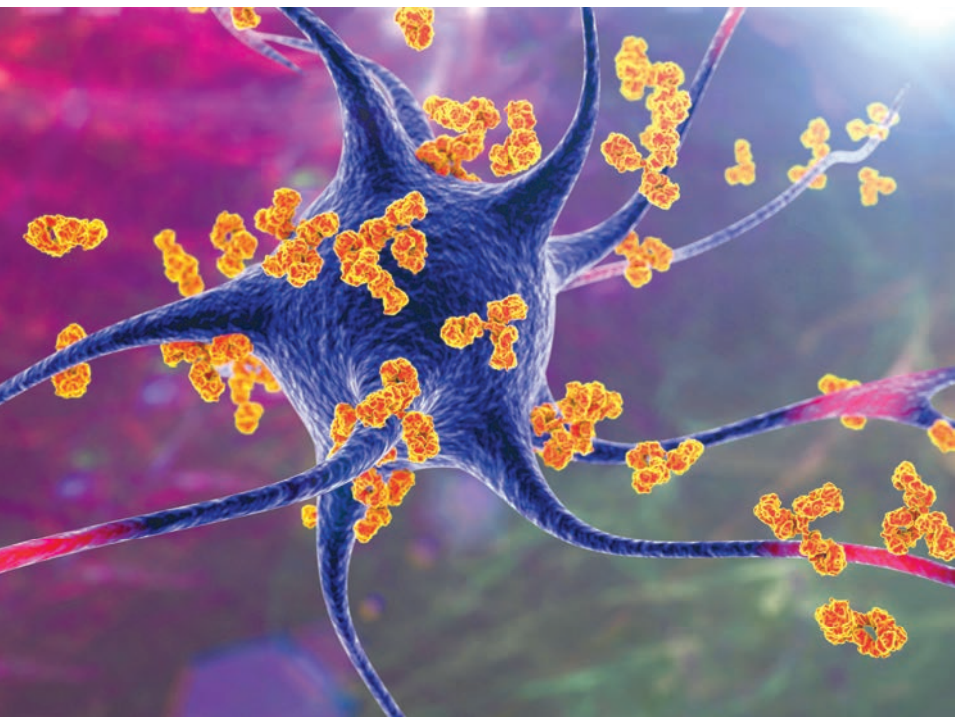
Neurological/neuromuscular	FcRn antagonist (sponsor) – Development status
Myasthenia gravis	Efgartigimod SC (argenx) — Phase III completed[1] Batoclimab SC (Immunovant) — Phase III Nipocalimab IV (Janssen) — Phase III Rozanolixizumab SC (UCB) — BLA accepted[2]
Chronic inflammatory demyelinating polyneuropathy (CIDP)	Efgartigimod SC (argenx) — Phase III Batoclimab SC (Immunovant) — Phase II Nipocalimab IV (Janssen) — Phase II/III Rozanolixizumab SC (UCB) — Phase II completed
Guillain-Barré syndrome	Efgartigimod IV[4] (argenx) — Phase II
Idiopathic inflammatory myopathies (myositis)	Efgartigimod SC (argenx) — Phase II/III Nipocalimab IV (Janssen) — Phase II
Autoimmune encephalitis[3]	Rozanolixizumab SC (UCB) — Phase II
Myelin oligodendrocyte glycoprotein antibody-associated disease (MOG-AD)	Rozanolixizumab SC (UCB) — Phase III
Post-COVID-19 postural orthostatic tachycardia syndrome (POTS)	Efgartigimod IV[4] (argenx) — Phase II
Hematological	
Primary immune thrombocytopenia (ITP)	Efgartigimod SC (argenx) — Phase III Rozanolixizumab SC (UCB) — Phase II completed
Warm autoimmune hemolytic anemia (wAIHA)	Nipocalimab IV (Janssen) — Phase II/III
Hemolytic disease of the fetus and newborn (HDFN)	Nipocalimab IV (Janssen) — Phase II/III
Rheumatologic	
Sjögren's syndrome	Efgartigimod IV[4] (argenx) — Phase II Nipocalimab IV (Janssen) — Phase II
Systemic lupus erythematosus (SLE)	Nipocalimab IV (Janssen) — Phase II
Rheumatoid arthritis	Nipocalimab IV (Janssen) — Phase II
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis	Efgartigimod (argenx) — Proof-of-concept trial pending
Severe fibromyalgia syndrome	Rozanolixizumab (UCB) — Phase II
Dermatologic	
Pemphigus vulgaris/foliaceus	Efgartigimod SC (argenx) — Phase III
Bullous pemphigoid	Efgartigimod SC (argenx) — Phase II/III
Endocrinological	
Thyroid eye disease (TED)	Efgartigimod (argenx) — Registrational trial pending Batoclimab SC (Immunovant) — Phase III
Graves' disease	Batoclimab SC (Immunovant) — Phase II
Renal	
Lupus nephritis	Efgartigimod IV[4] (argenx) — Phase II Nipocalimab IV (Janssen) — Phase II
Membranous nephropathy	Efgartigimod IV[4] (argenx) — Phase II
Antibody-mediated renal allograft rejection	Efgartigimod (argenx) — Proof-of-concept trial pending

1. Intravenously administered VYVGART (efgartigimod) received FDA approval for MG in December 2021.
2. LA decision by the FDA is expected in the second half of 2023.
3. Leucine-rich glioma inactivated 1 autoimmune encephalitis.
4. VYVGART (efgartigimod alfa-fcab) injection, for intravenous use.

BLA = biologics license application
IV = intravenous
SC = subcutaneous

TPE has never happened, largely due to challenges relating to vascular access, limited availability of equipment and trained nurse operators and, perhaps most importantly, a lack of adequate financial return potential to justify the large investments required to organize and conduct well-controlled trials.

None of these barriers apply with FcRn antagonists. As of early 2023, four well-financed drug developers are collectively investigating their proprietary FcRn antagonists for the treatment of at least 22 known or presumptive antibody-mediated autoimmune disorders (Table).



Argenx (efgartigimod)

By now, most clinicians who manage gMG patients are familiar with argenx' intravenously administered VYVGART (efgartigimod), approved for treatment of this indication in December 2021 and currently the only available FcRn antagonist. Efgartigimod is a human IgG1 fragment specifically engineered to increase its affinity to FcRn and thus outcompete endogenous IgG and prevent IgG recycling.

A more convenient self-administered subcutaneous (SC) delivery form of efgartigimod is currently being clinically evaluated in a 360-subject trial for the treatment of gMG. SC efgartigimod incorporates Halozyme Therapeutics' patented recombinant human hyaluronidase (rHuPH20) enzyme, which is incorporated into a number of approved biologics to facilitate their dispersion and absorption in circumstances where rapid, high-volume SC infusion is desirable.

Intravenous or SC efgartigimod is additionally being tested for the treatment of a dozen other rare or uncommon autoimmune disorders, including chronic inflammatory demyelinating polyneuropathy (CIDP), immune thrombocytopenic purpura (ITP), pemphigus vulgaris or foliaceus, bullous pemphigoid, myositis, post-COVID-19 postural orthostatic tachycardia syndrome (PC-POTS), primary Sjögren's syndrome, membranous nephropathy, thyroid eye disease (TED), lupus nephritis, ANCA-associated vasculitis, and antibody-mediated renal allograft rejection. The company anticipates data readouts from its late-stage CIDP, ITP and pemphigus trials later this year, and its myositis and bullous pemphigoid trials in 2024.

"Efgartigimod is a once-in-a-decade drug, the type of drug which builds companies," argenx Chief Financial Officer Karl Gubitz told attendees at a recent investor conference. Numerous investors clearly agree with his assessment: Solely on the strength of efgartigimod's anticipated commercial potential, to date this Dutch/Belgian biotechnology firm has raised more than $4.3 billion from offerings of equity securities, and currently boasts a market capitalization that exceeds $20 billion.

Janssen Pharmaceutical (nipocalimab)

This Johnson & Johnson company acquired nipocalimab, a fully human anti-FcRn IgG1 mAb, in its $6.5 billion acquisition of Momenta Pharmaceuticals in 2020. Janssen's clinical development program is no less ambitious than that of argenx, with nipocalimab currently being clinically tested for the treatment of at least 10 rare autoimmune disorders, including gMG, CIDP, idiopathic inflammatory myopathies, Sjögren's syndrome and warm autoimmune hemolytic anemia (wAIHA). Phase III trial results from the gMG and wAIHA studies are expected in the fourth quarter of 2023.

"We have seen in clinical trials that nipocalimab can remove [pathogenic autoantibody] IgG without interfering with cellular immunity or other antibodies such as IgM or IgA, which are important immune protectors," said Janssen's Senior Director and Global Compound Development Team Leader Hong Sun, MD, PhD.

In February, Janssen announced positive topline results from its proof-of-concept Phase II open-label clinical trial of once-weekly nipocalimab for the treatment of pregnant women at high risk for severe hemolytic disease of the fetus and newborn (HDFN); the trial met the primary endpoint, with the majority of pregnant patients who received nipocalimab achieving a live birth at ≥32 weeks of gestational age, without the

need for risky intrauterine transfusion throughout their entire pregnancy.[2]

Janssen also believes its FcRn antagonist may be an effective treatment for selected subgroups of two other relatively common autoimmune disorders: rheumatoid arthritis (RA), which affects well over one million U.S. adults,[3] and systemic lupus erythematosus (SLE), which is believed to affect more than 200,000 Americans.[4] Results from its Phase II RA and SLE proof-of-concept trials are expected in the second half of 2023.

Immunovant (batoclimab and IMVT-1402)

This clinical-stage biopharmaceutical company has raised more than $900 million to develop its lead product batoclimab (IMVT-1401), a fully human IgG1-based FcRn antagonist. Expected to shortly follow batoclimab into the clinic is a second product (IMVT-1402), which has been engineered to minimize interference with albumin recycling.*

Of particular interest, Immunovant has initiated the first anti-FcRn treatment program targeting Grave's disease. A significant share of the more than 100,000 persons diagnosed each year with Graves' disease remain difficult to control and symptomatic with anti-thyroid drug (ATD) therapy. Other treatment options, including radioiodine and surgery, present their own significant risks, primarily the risk of hypothyroidism and fatigue. Pathogenic autoantibodies are the known etiologic agent in most cases, in particular autoantibodies causing overstimulation of the thyroid stimulating hormone receptor (TSHR).[5]

Graves' patients on ATD therapy with elevated stimulatory TSHR antibodies and active disease are receiving weekly batoclimab over 24 weeks. The primary endpoint is the proportion of participants who achieve normalization of T3 and T4 with an ATD dose less than the baseline dose. Preliminary results from this Phase II trial are expected in the second half of 2023.

Clinical trials are additionally in progress to evaluate SC batoclimab for the treatment of CIDP, gMG and TED. A dose-dependent response was documented in a post-hoc analysis of findings from a placebo-controlled Phase IIb trial, with more than 40 percent of patients at the highest 680 mg weekly dose experiencing a ≥2 mm proptosis reduction in the study eye without a corresponding increase in proptosis of the nonstudy eye. Currently underway are a pair of Phase III trials in patients with moderate to severe TED, or Graves' disease evidenced by positive anti-TSHR antibody titers, with initial findings expected in the first half of 2025.

Immunovant expects to release new topline results from its currently ongoing studies about every six months between the second half of 2023 and the first half of 2025. Subject to demonstration of favorable safety and IgG-lowering activity in Phase I trials, the company also plans to evaluate its second-generation, albumin-sparing FcRn antagonist (IMVT-1402) for treatment of several of these and potentially other indications.

UCB (rozanolixizumab; UCB7665)

With annual sales of $6 billion, this Belgian biopharmaceutical company is developing its own fully humanized IgG4 FcRn antagonist product, rozanolixizumab (UCB7665). Earlier this year, a biologics license application was submitted to FDA seeking approval for an SC delivery form of UCB7665 for the treatment of moderate to severe gMG, anchored by results from a randomized, double-blinded, placebo-controlled Phase III trial in 200 subjects enrolled at more than 90 sites in 17 countries. UCB is additionally enrolling 30 gMG patients in a study to evaluate two alternative methods of self-administering UCB7665 subcutaneously — by syringe driver or manual push.

> As of early 2023, four well-financed drug developers are collectively investigating their proprietary FcRn antagonists for the treatment of at least 22 known or presumptive antibody-mediated autoimmune disorders.

The company has also recently completed a 43-subject Phase III trial evaluating the long-term safety, tolerability and efficacy of UCB7665 for the treatment of persistent or chronic ITP. A prior Phase II study documented good tolerability and clinically relevant improvements in platelet count (≥50 x

* In addition to IgG, FcRn complexes with circulating albumin to mediate albumin recycling.

10^9/liter) in all UCB7665 dosage groups. "These data build on the growing body of evidence that targeting the FcRn pathway has the potential to treat people with rare IgG autoantibody-mediated diseases such as primary ITP," said co-investigator and noted ITP research authority James Bussel, MD.[6]

In addition, UCB is investigating UCB7665 for the treatment of myelin oligodendrocyte glycoprotein (MOG) antibody disease (Phase III), as well as autoimmune encephalitis and severe fibromyalgia syndrome (both Phase II). Topline results from all three trials are expected in 2024.

A Promising Future for FcRn Antagonists

In a recent review article, one apheresis therapy expert astutely described FcRn antagonists as "plasma exchange in a bottle."[8] As both treatment modalities act by acutely reducing titers of pathologic IgG, it is not surprising that FcRn antagonists are being investigated for a few clinical indications for which TPE is long-established as first- or second-line therapy, most notably gMG and CIDP.

In a recent review article, one apheresis therapy expert astutely described FcRn antagonists as "plasma exchange in a bottle."

Of all the prospective clinical uses for FcRn antagonists now in clinical development, fibromyalgia syndrome is particularly interesting because historically no clear underlying cause had been identified to explain the characteristic widespread musculoskeletal pain that is typically accompanied by fatigue, sleep, memory and mood issues. What is known is that fibromyalgia tends to run in families, and is sometimes triggered or aggravated by an infection or a traumatic physical or emotional event.

However, very recent research has identified a subset of fibromyalgia patients with elevated levels of anti-satellite glial cell IgG, and these antibodies appear to be associated with more severe fibromyalgia symptomology.[7] UCB's randomized, placebo-controlled, double-blind proof-of-concept fibromyalgia study incorporates a crossover design and will enroll a total of 60 subjects. The primary outcome measure is the average score on the Brief Pain Inventory short form after 12 weeks of treatment.

But advancement of clinical research on FcRn antagonists is not constrained by the inherent limitations that have discouraged broader investigation of potential TPE uses. TPE is a roughly two-hour procedure involving the use of sophisticated equipment positioned in dedicated hospital spaces and operated by specially trained nurses. Vascular access is often challenging and can require surgical placement of ports. And perhaps the biggest barrier to TPE clinical research of the sophistication and scale needed to secure FDA approvals is a manufacturer revenue stream from sale of the enabling technology that simply cannot justify the very high cost of these trials.

The converse is true for FcRn antagonists, which are simple to administer in an outpatient setting (or may be self-administered by the patient at home), and whose potential to generate hundreds of millions or even billions of dollars in revenue can easily justify the large investments required to design, conduct and analyze clinical trial findings.

The impressive development pipelines of each of the four major competitors speak volumes about their belief that diseases mediated by pathophysiologic IgG autoantibodies, including many for which these "bad" autoantibodies haven't yet been identified, can be effectively managed by simply reducing their circulating titers. The global medical community will soon learn if this confidence bears out in real-world results. ❖

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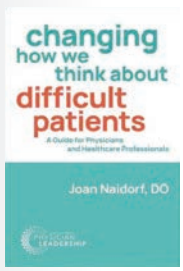
Changing How We Think About Difficult Patients: A Guide for Physicians and Healthcare Professionals

Author: Joan Naidorf, DO



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Author: Frank J. Domino

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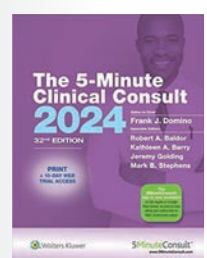

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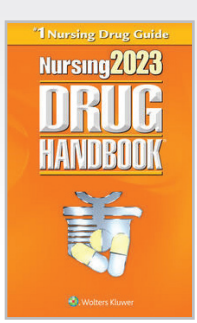

Nursing 2023 Drug Handbook (Nursing Drug Handbook), 43rd North American Edition

Author: Lippincott Williams & Wilkins

This handbook delivers evidence-based, nursing-focused drug monographs for nearly 3,700 generic, brand-name and combination drugs. With a tabbed, alphabetical organization and a "New Drugs" section, it makes it easy to check drug facts on the spot. The handbook includes 27 monographs of newly U.S. Food and Drug Administration-approved drugs; revisions of the 3,691 drug monographs that provide dosages, indications, boxed warnings, genetic-related information, adverse reactions, clinical alerts and patient teaching information; a pill guide insert; and 30 appendices covering topics such as serotonin syndrome, pregnancy risk categories and understanding biosimilar drugs.

www.amazon.com/Nursing2023-Drug-Handbook-Nursing/dp/1975183363

High-Dose IVIG Reduces Mortality Risk in Hospitalized Patients with Severe COVID-19: Systematic Review and Meta-Analysis

A systematic search of leading databases and registries by Chinese collaborators identified a total of 17 clinical trials and observational studies, including 1,925 intravenous immune globulin (IVIG)-treated and 2,786 control patients, that compared the efficacy of IVIG to routine care for hospitalized COVID-19 patients.

Administration of IVIG was not associated with a significant reduction in all-cause mortality across all COVID-19 patients receiving any dosage of IVIG (relative risk [RR], 0.89; 95% confidence interval [CI], 0.63 to 1.26; P – 0.53). There were similarly no significant differences compared to standard care with respect to length of hospital stay (mean difference, 0.29 days; 95% CI, -3.40 to 6.44 days; P = 0.88), need for mechanical ventilation (RR, 0.93; 95% CI, 0.73 to 1.19; P = 0.31) or incidence of adverse events (RR, 1.15; 95% CI, 0.99 to 1.33; P = 0.06).

However, a subgroup analysis focusing on the mortality-related impact of variable IVIG daily dosage and disease severity found significantly reduced overall mortality in the patient subgroup with severe COVID-19 that received high-dose IVIG (RR, 0.33; 95% CI, 0.13 to 0.86; P = 0.02; very low certainty). High-dose IVIG therapy was defined as 0.3 to 0.5 grams per kilogram of body weight per day for five days.

"High-dose IVIG might reduce mortality in patients with severe COVID-19," the authors concluded. "However, [due to the] combination of low quality of certainty due to the limited number of studies and the high risk [of] methodological heterogeneity, the results should be interpreted with great caution, and more research is needed to understand its specific effects." ❖

Liu, X, Zhang, Y, Lu, L, et al. Benefits of High-Dose Intravenous Immunoglobulin on Mortality in Patients with Severe COVID-19: An Updated Systematic Review and Meta-Analysis. *Frontiers in Immunology*, 2023 Jan 23;14:1116738.

Albumin Administration Linked to Lower Risk of Hyponatremia in Hospitalized Cirrhosis Patients: Single-Center Study

Short-term human albumin (HA) infusion significantly reduced the incidence of hyponatremia and increased the rate of improvement of hyponatremia in hospitalized hepatic cirrhosis patients, according to a retrospective study of 2,414 patients consecutively admitted to a single Chinese hospital between 2010 and 2014 (the "hospitalization outcome" cohort), and another 339 patients admitted between 2014 and 2021 (the "long-term outcome" cohort).

In the hospitalization outcome cohort, the HA group was found to have a significantly lower incidence of hyponatremia than the control group (16.3% versus 41.9%; p < 0.001). Logistical regression analysis also showed HA infusion (median total dosage: 30 g; range: 10-530 g) was associated with decreased risk of developing hyponatremia during hospitalization

(odds ratio [OR], 0.27; 95% confidence interval [CI], 0.184-0.396; p < 0.001). Patients who developed hyponatremia during hospitalization had a significantly higher in-hospital mortality than those who did not (7.1% versus 3.0%, p < 0.001), a mortality divergence seen in both the HA (10.4% versus 4.3%) and control (5.6% versus 2.3%; p = 0.003) groups.

Among the 291 patients in the long-term outcome cohort with normal serum sodium level at admission, those assigned to receive HA have a significantly lower incidence of hyponatremia than controls (7.7% versus 30.8%); the median total dosage of HA was again 30 g (range: 10-150 g). Again, HA infusion was significantly associated with reduced risk of developing hyponatremia during hospitalization (OR, 0.188; p = 0.016). Consistent with the hospitalization outcome cohort, development of hyponatremia during hospitalization was found to be associated with decreased long-term survival (HR, 0.400; 95% CI, 0.26-0.616; p < 0.001). ❖

Bai, Z, Xu, W, Chai, L, et al. Effects of Short-Term Human Albumin Infusion for the Prevention and Treatment of Hyponatremia in Patients with Liver Cirrhosis. *Journal of Clinical Medicine*, 2022 Dec 23; 12(1):107.

Medicare Immune Globulin Reimbursement Rates

Rates are effective July 1, 2023, through Sept. 30, 2023

	Product	Manufacturer	J Codes	ASP + 6% (before sequestration)	ASP + 4.3% (after sequestration)
IVIG	ASCENIV	ADMA Biologics	J1554	$982.81	$967.05
	BIVIGAM	ADMA Biologics	J1556	$145.93	$143.59
	FLEBOGAMMA DIF	Grifols	J1572	$112.23	$110.43
	GAMMAGARD SD	Takeda	J1566	$155.53	$153.04
	GAMMAPLEX	BPL	J1557	$118.97	$117.06
	OCTAGAM	Octapharma	J1568	$88.24	$86.82
	PANZYGA	Octapharma/Pfizer	J1576	$131.48	$129.37
	PRIVIGEN	CSL Behring	J1459	$95.98	$94.44
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$92.06	$90.59
	GAMMAKED	Kedrion	J1561	$101.28	$99.66
	GAMUNEX-C	Grifols	J1561	$101.28	$99.66
SCIG	CUTAQUIG	Octapharma	J1551	$143.86	$141.55
	CUVITRU	Takeda	J1555	$162.75	$160.14
	HIZENTRA	CSL Behring	J1559	$128.03	$125.98
	HYQVIA	Takeda	J1575	$166.55	$163.88
	XEMBIFY	Grifols	J1558	$139.99	$137.74

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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	5 g, 10 g
	GAMMAPLEX Liquid, 5%	BPL	PI, ITP	5 g, 10 g, 20 g
	GAMMAPLEX Liquid, 10%	BPL	PI, ITP	5 g, 10 g, 20 g
	OCTAGAM Liquid, 5%	Octapharma	PI	1 g, 2.5 g, 5 g, 10 g, 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	1 g, 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, 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

2023-2024 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	90685
AFLURIA (IIV4)	SEQIRUS	5 mL MDV	6 months and older	90685
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	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	0.5 mL PFS 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI	5 mL MDV	6 months and older	90685
FLUZONE HIGH-DOSE (IIV4)	SANOFI	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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