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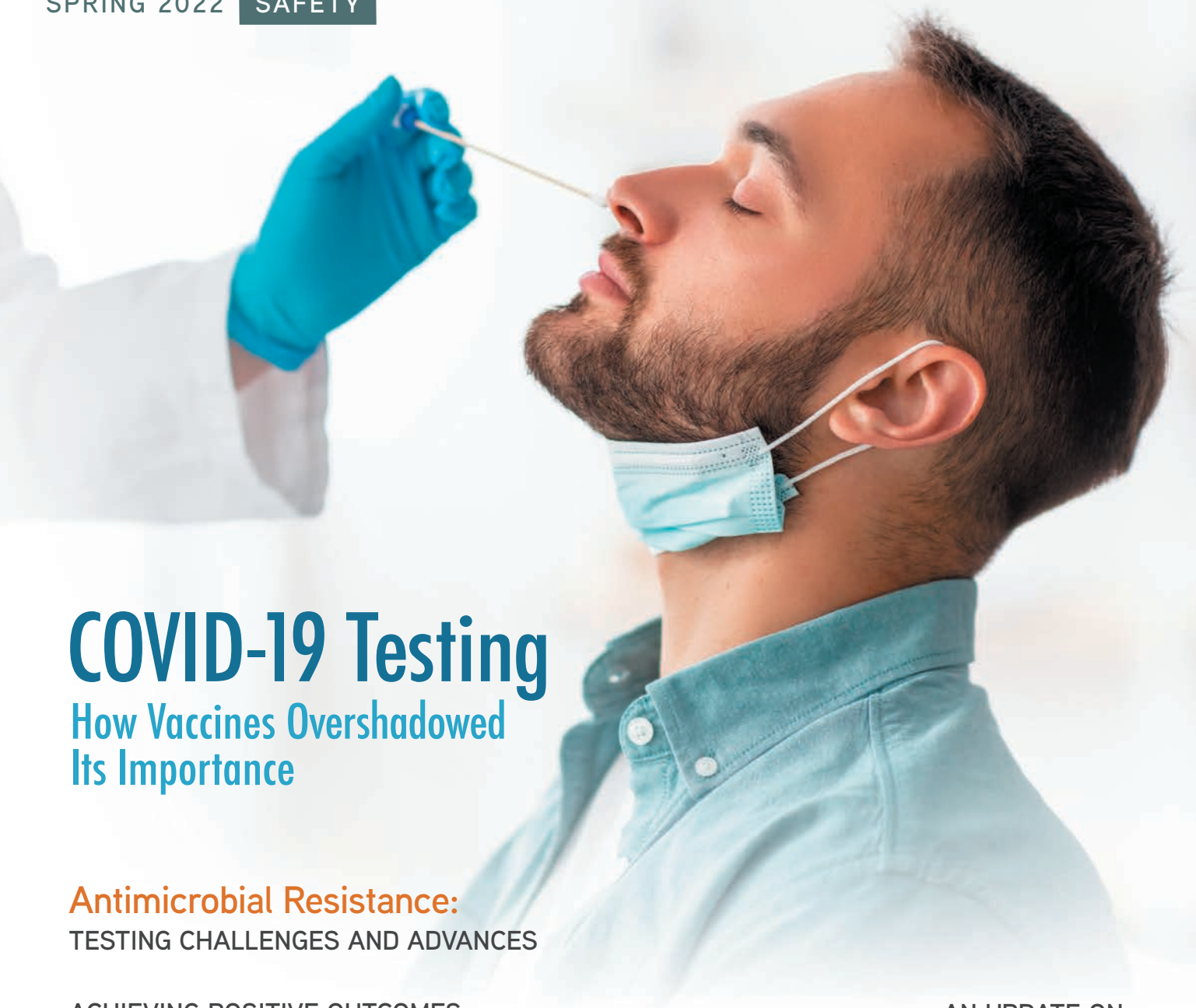
QUARTERLY
SPRING 2022 SAFETY



# COVID-19 Testing
## How Vaccines Overshadowed Its Importance

## Antimicrobial Resistance:
TESTING CHALLENGES AND ADVANCES

ACHIEVING POSITIVE OUTCOMES WITH Value-Based Healthcare

AN UPDATE ON Migraine Prophylaxis

## Intermittent Fasting:
A SOLUTION FOR WEIGHT LOSS?

MYTHS AND FACTS ABOUT Aging

A NEW TREATMENT FOR MYASTHENIA GRAVIS | PAGE 42

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# 8 Critical Steps

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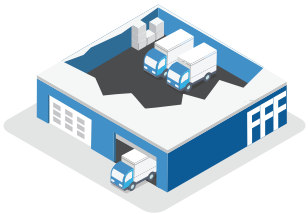

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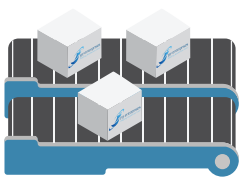

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# Curbing Disease Through Testing

**DURING THE** past several years, the U.S. has seen significant increases in the rate of new infectious disease cases. For instance, since 2015, rates of new chlamydia infections have risen by 19 percent, gonorrhea by 56 percent, syphilis by 74 percent and hepatitis A infection by an unprecedented 1,325 percent, and rates of new hepatitis B and C infections are rising as well.[1] This trend is alarming, especially as we enter the third year of the COVID-19 pandemic and as the threat of antimicrobial resistance (AMR) surges, intensified by the SARS-CoV-2 virus. But these infections and their associated treatment costs are preventable with vaccines, medications and, importantly, testing.

While there was obvious need to focus heavily on the manufacture of preventive vaccines and treatments for COVID-19 during the initial phases of the pandemic to minimize the human toll, this sole focal point has lent less credence to and awareness of the importance of testing. As we explain in our article "COVID-19 Testing: Vitally Important Despite Vaccines" (p.16), testing is crucial to give researchers the necessary firm data on how many people have contracted it, and they need to know how current (and likely future) variants spread and how many people have some natural immunity to the disease. But, as the number of people who are vaccinated continues to climb, convincing people to test for a current or past infection is easier said than done because the guided message has been to "get vaccinated" rather than "get tested," leaving many to wonder why testing is necessary once they are vaccinated. Indeed, it remains a steep challenge to convince the nation this continued vigilance is needed as people grow weary of this seemingly never-ending era of COVID-19. Nonetheless, healthcare professionals must make the case to persuade people to get used to this new-normal way of protecting the public from this infectious disease.

A lesser-known consequence of COVID-19 is the accelerated rise in AMR, the result of a majority of hospitalized COVID-19 patients receiving antibiotics even though only a small percentage of them had a bacterial coinfection. This recent misuse exacerbates the overuse of antibiotics in previous decades. In answer, our article "Advances in Diagnostic Testing for Antimicrobial Resistance" (p.20) discusses how AMR can be mitigated by testing to establish conclusively that an antibiotic is needed and the right treatment for the individual. As we explain, much can be determined by the type of bacteria and each individual's gut microbiota. Nevertheless, many challenges must be overcome, but it is hoped that federal efforts will provide meaningful intervention.

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

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

## Reference

1. Severance-Medaris C. Curbing Rising Rates of Infectious Diseases. National Conference of State Legislatures, July 2021. Accessed at www.ncsl.org/research/health/curbing-rising-rates-of-infectious-diseases.aspx.

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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# HHS Study Shows 63-Fold Increase in Medicare Telehealth Utilization During the Pandemic

A report from the U.S. Department of Health and Human Services (HHS) has found that considerable increases in the use of telehealth helped maintain some healthcare access during the COVID-19 pandemic, with specialists such as behavioral health providers seeing the highest telehealth utilization. The report, which was produced by researchers in HHS's Office of the Assistant Secretary for Planning and Evaluation (ASPE) and analyzes Medicare fee-for-service (FFS) data in 2019 and 2020, also shows that telehealth services were accessed more in urban areas than rural communities, and Black Medicare beneficiaries were less likely than white beneficiaries to utilize telehealth. "During the COVID-19 pandemic, various telehealth flexibilities enabled patient access to their providers," said HHS Acting Assistant Secretary for Planning and Evaluation Rebecca Haffajee. "Prepandemic telehealth visits for Medicare beneficiaries went from hundreds of thousands to tens of millions, with many utilizing telehealth for the first time."

The ASPE report found the share of Medicare visits conducted through telehealth in 2020 increased 63-fold, from approximately 840,000 in 2019 to 52.7 million. States with the highest use of telehealth in 2020 included Massachusetts, Vermont, Rhode Island, New Hampshire and Connecticut. States with the lowest use of telehealth in 2020 included Tennessee, Nebraska, Kansas, North Dakota and Wyoming. The report also found insightful trends on the kinds of services Medicare beneficiaries sought through telehealth. While overall healthcare visits for Medicare beneficiaries declined in 2020 compared to 2019, telehealth was particularly helpful in offsetting potential foregone behavioral healthcare. In 2020, telehealth visits comprised a third of total visits to behavioral health specialists, compared to 8 percent of visits to primary care providers and 3 percent of visits to other specialists. These findings prominently show an increased interest in seeking behavioral healthcare through telehealth.

To help protect access to care, the Centers for Medicare and Medicaid (CMS) recently announced that for the first time outside of the COVID-19 public health emergency (PHE), Medicare will pay for mental health visits furnished by rural health clinics and federally qualified health centers via interactive video-based telehealth, including audio-only telephone calls. Additionally, CMS is permanently eliminating geographic barriers and allowing patients in their homes to access telehealth services for diagnosis, evaluation and treatment of mental health disorders, including via audio-only communications technology. These provisions were included in the Consolidated Appropriations Act of 2021.

Other Medicare services added to the telehealth services list temporarily during the PHE will remain in place through Dec. 31, 2023, while CMS continues to evaluate whether these services should be permanently added to the Medicare telehealth services list. And to provide more transparency and visibility into telemedicine usage, CMS is also releasing a new snapshot showing the number of people with Medicare who utilized telemedicine services between March 1, 2020, and Feb. 28, 2021. The snapshot includes Medicare FFS claims data, Medicare Advantage encounter data and Medicare enrollment information. ❖

New HHS Study Shows 63-Fold Increase in Medicare Telehealth Utilization During the Pandemic. U.S. Department of Health and Human Services press release, Dec. 3, 2021. Accessed at www.hhs.gov/about/news/2021/12/03/new-hhs-study-shows-63-fold-increase-in-medicare-telehealth-utilization-during-pandemic.html?utm_source=news-releases-email&utm_medium=email&utm_campaign=dec-5-2021.

## Researchers at Emory University Awarded Grant to Pursue a Cure for HIV

An Emory University-led research collaboration has been awarded a five-year $23.8 million grant from the National Institutes of Health (NIH) to fast-track research to cure HIV infection or put it in permanent remission. The Enterprise for Research and Advocacy to Stop and Eradicate HIV (ERASE HIV) is one of the 10 newly NIH-funded Martin Delaney Collaboratories for HIV Cure and the only one researchers at a National Primate Research Center (NPRC) are leading.

The Emory/Yerkes NPRC study leaders include Deanna Kulpa, PhD, Mirko Paiardini, PhD, and Guido Silvestri, MD, who along with their team members are renowned for their HIV cure research. As part of ERASE HIV, they will characterize the key immune system functions that control persistent HIV infection and design innovative, immune-based therapies to eliminate or control the virus in the absence of antiretroviral


therapy (ART).

"It's been 40 years since the first case of what we now know as HIV/AIDS was reported in the United States," said Dr. Paiardini. "Since then, more than 700,000 people in America have died from HIV-related illness, and a similar number died worldwide just in the last year. Our work and the work of the other Martin Delaney Collaboratories will bring us closer to a cure, a goal now regarded as possible based on recent research advancements and the continuing dedication of HIV/AIDS researchers and advocates."

While ART has been successful in reducing HIV to undetectable levels and halting the progression to AIDS, the treatment does not eliminate HIV. The virus hides in the body and rebounds when people with HIV stop taking ART. "Antiretroviral therapy has literally been a lifesaver for millions of people living with HIV around the world, but our work is not finished," said Dr. Kulpa. "This NIH funding gives us the opportunity to build on Emory's eminence as a worldwide leader in HIV/AIDS research and to assemble an incredible team of researchers and community advocates for the ERASE HIV Collaboratory. ❖

A Cure for HIV: Emory Receives $23.8 Million NIH Grant to Accelerate Research. Emory University Woodruff Health Sciences Center press release, Sept. 9, 2021. Accessed at news.emory.edu/stories/2021/09/nih_grant_hiv_research_kulpa_paiardini_silvestri/index.html.

## Two Major Changes in Medicare in 2022

Aside from the Medicare premiums increase ($170.10 in 2022, up $21.60 from the 2021 monthly charge) and higher deductibles ($233 in 2022, an increase of $30), two other significant changes are expected in 2022 for Medicare beneficiaries:

1) Enrollees in every state will be able to sign up for a Part D "enhanced" plan that is participating in a Centers for Medicare and Medicaid (CMS) program that caps the cost of some insulins at $35 a month. The program began in 2021, but the number of plans available is expanding, with 2,159 Part D plans participating this year. Beneficiaries who are enrolled in original Medicare or a Medicare Advantage plan can sign up for this program.

2) Medicare is continuing to focus more attention on telehealth, especially during the pandemic. For 2022, the agency is increasing the availability of mental health services via telehealth. New features include providing certain mental and behavioral health services over the phone. CMS officials say this means counseling and therapy services, including the treatment of substance use disorders, will be more available, especially in areas where not everyone has access to broadband.

"The COVID-19 pandemic has highlighted the gaps in our current healthcare system and the need for new solutions to bring treatments to patients, wherever they are," said CMS Administrator Chiquita Brooks-LaSure. "This is especially true for people who need behavioral health services, and the improvements we are enacting will give people greater access to telehealth and other care delivery options."

Also in 2022, Medicare will pay for mental health visits outside of the rules governing the pandemic, which means mental health telehealth visits provided by rural health clinics and federally qualified health centers will be covered. ❖

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

# Rules and Regulations Affecting Revenue

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

**FOR PRACTICES** managing diverse patient populations covered by a variety of payers, a number of payment rule changes and unknown future federal and state regulations loom ahead.

## Code Sets

Code sets aren't static one-time creations; they often go through numerous updates and revisions. As living documents, they must continually be incorporated into healthcare practices' multiple electronic or computerized systems. Through its *MedLearn Matters* publications, software downloads and revenue cycle financial systems, the Centers for Medicare and Medicaid Services (CMS) conveys this information automatically at no cost. Following are some recent small changes to reimbursement that can have significant revenue implications for healthcare practices:

April 1, 2022: The Centers for Disease Control and Prevention (CDC) implemented three new ICD-10-CM diagnosis codes for reporting COVID-19 vaccination status: Z28.310 (unvaccinated for COVID-19 nonCC 23 95); Z28.311 (partially vaccinated for COVID-19 nonCC 23 951); and Z28.39 (other underimmunization status nonCC 23 95). Consequently, it is important for healthcare to determine which of the many computerized and tracking systems are affected by these new or changed codes.

April 1, 2022: CMS implemented seven new ICD-10-PCS procedure codes to describe the introduction or infusion of therapeutics, including vaccines for COVID-19 treatment (Table). Medicare pays for inpatient COVID-19 vaccines and their administration separately from the diagnosis-related group rate. Therefore, a mechanism must be in place to ensure claims for these separate payments are processed correctly.

A cascade of activities are related to adding new drugs to financial systems regardless of formulary status. As quickly as possible, facilities should add them to the drug master files with applicable Healthcare Common Procedure Coding System (HCPCS) codes and National Drug Code numbers, as well as create a billing unit crosswalk. A charge description master entry and link are also essential. In addition, prior authorization and other payer requirements need to be noted/linked, as well as appropriate drug administration codes.

Jan. 7, 2022: CMS created a new HCPCS code for Veklury (HCPCS code J0248; long descriptor: injection, remdesivir, 1 mg; short descriptor: injection, remdesivir, 1 mg), an antiviral medication, when administered in an outpatient setting that can be used by all payers for dates of service on or after Dec. 23, 2021. This drug is a classic example of revenue generated from drug administration fees. With 2021 sales of $5.6 billion, it had the largest drug spend.

According to Novitas, a Medicare Administrative Contractor that provides administrative services for government-sponsored healthcare programs, when billing for monoclonal antibody (mAb) infusions, the beneficiary coinsurance and deductible will be waived. When mAb doses are provided by the government without charge, facilities must bill for the drug along with the administration, with the billed amount as $0.01. And, while infusion claims for Medicare Advantage (MA) plan patients were submitted to original Medicare for 2020 and 2021, effective Jan. 1, 2022, they must be billed to the MA plan.

## Billing for Injectable Drugs in the Outpatient Setting

Although under the outpatient prospective payment system, reimbursement for the Part B/medical drug products may be decreased or incorporated into a bundled or packaged payment (or even provided free of charge), drug administration payments may cover some of the costs of required products and supplies. This may also be true for reimbursement from private insurers. Drug administration reimbursed as a bundled payment involves both nursing and pharmacy, and includes use of local anesthesia, starting the IV, accessing the IV, catheter or port, routine tubing, syringe, preparation of drug, flushing at completion and hydration fluid. To ensure reimbursement, data must be captured related to drug administration with the requisite charting to substantiate the charges.

Injectable drugs can arrive at a facility in a variety of different ways from a variety of sources when they are purchased or when obtained at no cost:

- Shipped directly to the facility from a specialty pharmacy for a specific patient
- Shipped directly to the facility for a specific patient or a group of patients as patient assistance drugs or government supplied drugs
- Brought to the facility by the patient to allow continuance of a specific regimen of a biologic or immunologic or other specialty product

Regardless of how they are received, when a drug is zero-priced, the facility/physician should bill the HCPCS code

**Table. New ICD-10-PCS Procedure Codes for Introduction or Infusion of Therapeutics, Including COVID-19 Vaccines**

| Procedure Code | Description | OR* |
|---|---|---|
| XW013V7 | Introduction of COVID-19 vaccine dose 3 into subcutaneous tissue, percutaneous approach, new technology group 7 | N |
| XW013W7 | Introduction of COVID-19 vaccine booster into subcutaneous tissue, percutaneous approach, new technology group 7 | N |
| XW023V7 | Introduction of COVID-19 vaccine dose 3 into muscle, percutaneous approach, new technology group 7 | N |
| XW023W7 | Introduction of COVID-19 vaccine booster into muscle, percutaneous approach, new technology group 7 | N |
| XW0DXR7 | Introduction of fostamatinib into mouth and pharynx, external approach, new technology group 7 | N |
| XW0G7R7 | Introduction of fostamatinib into upper GI, via natural or artificial opening, new technology group 7 | N |
| XW0H7R7 | Introduction of fostamatinib into lower GI, via natural or artificial opening, new technology group 7 | N |

** Because the procedure codes are designated as non-operating room (OR) procedures, there is no assigned MDC or MS-DRG.*

for the drug administered with the correct quantity (according to the dose per unit specified in HCPCS) and a zero charge.

## The Waste REFUND Act

The Infrastructure Investment and Jobs Act (H.R.3684), which passed on Nov. 15, 2021, includes a drug waste provision from the Recovering Excessive Funds for Unused and Needless Drugs (REFUND) Act that requires manufacturers to rebate the amount wasted back to CMS effective Jan. 1, 2023.

The bill requires drug companies and manufacturers to reimburse Medicare for certain wasted medications, specifically leftover portions of drugs packaged in single-dose containers or single-use packages payable under Medicare Part B. Exclusions to this are 1) drugs or biologicals that are either a radiopharmaceutical or imaging agent; 2) drugs or biologicals approved by the U.S. Food and Drug Administration (FDA) for which dosage and administration instructions included in the labeling require filtration during the drug preparation process prior to dilution and administration, and that require any unused portion of such drugs after the filtration process be discarded; or 3) drugs or biologicals approved by FDA on or after the date of enactment of the bill and for which payment has been made for fewer than 18 months.

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

Compliance audits are intended to rule out fraud. These audits could include manufacturer's compliance, accuracy of aggregated amount calculated, comparisons of billed doses and billed wastage with the number of units sold, or any other methods of determining data accuracy.

Medicare created billing for expensive waste in the OPPS shortly after switching to "billing units representing actual dose given" for reimbursement and away from the "whole vial" method of billing. While Medicare does not mandate billing for waste, it makes it possible to recoup lost dollars if a facility chooses to bill for it. To determine whether a drug can be billed for waste, answer these four questions: 1) Is the drug being used for a Medicare outpatient? 2) Is it a single-dose vial/package? 3) Does the product have an HCPCS code? 4) Does the product have a status indicator G or K designation? Only if the answer is yes to these questions can the facility bill for waste. If the answer is no, then it cannot bill.

Of course, it's important to avoid creating an auto bill situation that doesn't represent true actions. For example, if the vial contains 1 gram of the drug, and the infusion center uses 500 mg for each of two patients, nothing is wasted. But without carefully building this calculation into the system, the revenue cycle could assume two vials had been used and would erroneously process two waste charges, which is fraud.

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

**BONNIE KIRSCHENBAUM**, MS, FASHP, FCSHP, is a freelance healthcare consultant with senior management experience in both the pharmaceutical industry and the pharmacy section of large corporate healthcare organizations and teaching hospitals. She has an interest in reimbursement issues and in using technology to solve them. Kirschenbaum is a recognized industry leader in forging effective alliances among hospitals, physicians, pharmaceutical companies and distributors and has written and spoken extensively in these areas.

# Implementing Stringent Cleaning and Disinfecting Policies in the Healthcare Setting

By Ronale Tucker Rhodes, MS

**AFTER DEALING WITH** the COVID-19 pandemic for more than two years, many establishments are loosening precautionary restrictions. In healthcare facilities, these revised measures include allowing family and friends to accompany patients to care visits and hospital stays, thus increasing the possible spread of the SARS-CoV-2 virus. As a consequence, it is increasingly important for management to implement stringent cleanliness policies to curb the spread of infection.

## How the SARS-CoV-2 Virus Spreads

COVID-19, a respiratory infection caused by the SARS-CoV-2 virus, is transmitted mainly through exposure to respiratory droplets. This spread typically occurs through close physical contact within closed settings such as healthcare facilities, but it is also possible for the virus to be transmitted via surface contamination.[1]

According to the World Health Organization (WHO), environmental surfaces are more likely to be contaminated in healthcare settings where medical care is performed. Environmental surfaces include furniture and other fixed items inside and outside of patient rooms and bathrooms such as tables, chairs, walls, light switches, computer peripherals, electronic equipment, sinks and toilets, as well as the surfaces of noncritical medical equipment such as blood pressure cuffs, stethoscopes, wheelchairs and incubators.[2]

The SARS-CoV-2 virus, according to WHO, "is an enveloped virus with a fragile outer lipid envelope that makes it more susceptible to disinfectants compared to nonenveloped viruses such as rotavirus, norovirus and poliovirus." In studies that have evaluated the persistence of the COVID-19 virus on different surfaces, one found that the COVID-19 virus remained viable up to one day on cloth and wood, up to two days on glass, four days on stainless steel and plastic, and up to seven days on the outer layer of a medical mask. Another study found the COVID-19 virus survived four hours on copper, 24 hours on cardboard and up to 72 hours on plastic and stainless steel. In addition, WHO found, "the COVID-19 virus also survives in a wide range of pH values and ambient temperatures, but is susceptible to heat and standard disinfection methods." Yet, while WHO cautions that these studies "were conducted under laboratory conditions in absence of cleaning and disinfection practices and should be interpreted with caution in the real-world environment,"[2] it would seem prudent in light of the ever-persistent and constantly mutating virus that sanitizing and disinfecting cleaning protocols should be strictly followed.

## Cleaning Protocols

Chavaun LeBlanc, manager of environmental health and safety at MD Anderson Cancer Center in Houston, Texas, reports she frequently hears questions about cleaning high-touch objects to reduce the spread of COVID-19, including "What's the difference between cleaning and disinfecting?" Cleaning, she explains is removing all visible traces of dust or dirt such as laundering a shirt or wiping a shelf with a cloth. Disinfecting is killing the germs that may be living on the surfaces by using heat, light and chemicals. The distinction, says LeBlanc, is that "dirt-free does not equal germ-free."[3]

In healthcare environments, it is imperative that disinfecting measures be put in place, which is in addition to cleaning and sanitizing. The difference between sanitizing and disinfecting is sanitizing kills bacteria on surfaces using chemicals, whereas disinfecting kills viruses and bacteria on surfaces using chemicals. According to the U.S. Environmental Protection Agency (EPA), surface disinfectant products are subject to more rigorous EPA testing requirements and must clear a higher bar for effectiveness than surface sanitizing products.[4]

Currently, five main EPA-registered chemicals that hospitals use for disinfectants include quaternary ammonium, hypochlorite, accelerated hydrogen peroxide, phenolics and peracetic acid. And, choosing which chemical to use can often be a complicated process.[5]

*Quaternary ammonium compounds* are used broadly in routine cleaning, and the Centers for Disease Control and Prevention considers them to be a low-level disinfectant effective against most bacteria, enveloped viruses and some fungi. They are best used on noncritical surfaces such as floors, bed rails, tray tables, blood pressure cuffs, walls and partitions.

*Hypochlorite* is the most commonly used chlorine disinfectant. Sodium hypochlorite is commercially available as household bleach, and can be used in hospitals for bathrooms, food prep zones

**Table. Recommended Frequency of Cleaning of Environment Surfaces in Areas with Suspected or Confirmed COVID-19 Patients**

| Patient Area | Frequency | Additional Guidance |
|---|---|---|
| Screening/triage area | At least twice daily | Focus on high-touch surfaces, then floors (last) |
| Inpatient rooms — occupied | At least twice daily, preferably three times daily, in particular for high-touch surfaces | Focus on high-touch surfaces, starting with shared/common surfaces, then move to each patient bed; use new cloth for each bed if possible; then floors (last) |
| Inpatient rooms — unoccupied | Upon discharge/transfer | Focus on low-touch surfaces, high-touch surfaces, floors (in that order); waste and linens should be removed, and the bed thoroughly cleaned and disinfected |
| Outpatient/ambulatory care rooms | After each patient visit and at least one daily terminal clean | Focus on high-touch surfaces and disinfect after each patient visit; once daily, focus on low-touch surfaces, high-touch surfaces, floors (in that order); waste and linens should be removed, and beds should be thoroughly cleaned and disinfected |
| Hallways/corridors | At least twice daily | Focus on high-touch surfaces, including railings and equipment in hallways, then floors (last) |
| Patient bathrooms/ toilets | At least twice daily in private patient rooms and three times daily in shared toilets | Focus on high-touch areas, including door handles, light switches, counters, faucets, then sink bowls, toilets and finally floors (in that order); avoid sharing toilets between staff and patients |

Source: Adapted from: World Health Organization. Cleaning and Disinfection of Environmental Surfaces in the Context of COVID-19, Interim Guidance, May 15, 2020. Accessed at www.who.int/publications/i/item/cleaning-and-disinfection-of-environmental-surfaces-inthe-context-of-covid-19.

and blood spills. However, all areas must be precleaned to remove organic matter before disinfection.

*Accelerated hydrogen peroxide*, a more recent breakthrough in hospital disinfectants, is a blend of safe, active cleaning agents with hydrogen peroxide. It is safe for the cleaning staff and the environment with the lowest EPA toxicity category. These one-step cleaners disinfect in the presence of organic matter and blood, and they kill bacteria, viruses, mycobacteria, pathogenic fungi and blood-borne pathogens.

*Phenolics*, which have been around for a long time, are best for disinfection of nonporous surfaces and noncritical devices.

*Peracetic acid preparations*, which are rapid-acting disinfectants, are bactericidal, fungicidal, virucidal, mycobactericidal and sporicidal. Hospitals often use these in automated machines to sterilize medical instruments and to disinfect hemodialyzers.

Of course, it's always preferable to choose products that contain less-hazardous ingredients if possible. For instance, sodium hypochlorite (bleach) and quaternary ammonium compounds can cause asthma, so they should be used with caution in certain areas. Further, when using these products, they should be left wet on the surface or air dried for the correct dwell or contact time to ensure they kill resistant germs.[6]

## Best Practices

Employing the best strategies to disinfect surfaces in the healthcare environment is crucial. Following these steps achieves maximum results:[6]

1) *Create a plan.* A set of written standard operating procedures for cleaning and criteria for when to sanitize or disinfect should be developed.

2) *Routinely clean all frequently touched surfaces.* Particular attention should be paid to high-touch surfaces and items such as light switches, bed rails, door handles, intravenous pumps, tables, water/beverage pitchers, trays and mobile cart rails. Clearly, this is critical in areas where there are suspected or confirmed COVID-19 patients (Table).

3) *Provide information and training.* Workers must be informed about the hazards of the cleaning chemicals used in accordance with OSHA's Hazard Communication Standard, and they should wear appropriate protective equipment such as gloves. In addition, cleaning should follow accepted best practices that include cleaning from high to low, toward the doorway, and with dry cleaning tasks performed prior to wet cleaning tasks.

4) *Evaluate.* Last, continually reassess the plan, and seek feedback from people using the products and from those in spaces where they are used.

## Proper Implementation Is Essential

As the COVID-19 pandemic persists, properly implementing effective and responsible cleaning and disinfecting practices is essential to protect the wellness of both healthcare staff and patients. ❖

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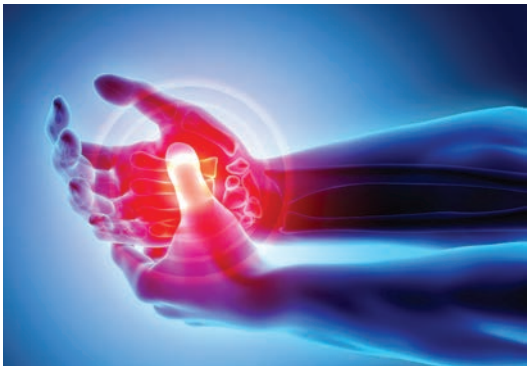
Research

## Experimental Vaccine Developed to Prevent Rheumatoid Arthritis



Researchers at the University of Toledo have developed an experimental vaccine to prevent rheumatoid arthritis, one of the most common autoimmune disorders that occurs when the body's immune system attacks and destroys healthy tissues, especially the medial joints of the hands, wrists, ankles and knees.

The researchers had been studying the protein 14-3-3 zeta's role in immunopathology such as aortic aneurysm and interleukin-17 autoimmune disease. Based on their previous work, they focused on proteins as potential triggers for rheumatoid arthritis. Instead, they found that removing proteins by gene-editing techniques causes severe early-onset arthritis in animal models, rather than preventing rheumatoid arthritis. Based on the new theory that 14-3-3 zeta protein prevents rheumatoid arthritis, the team has developed a protein-based vaccine using purified 14-3-3 zeta protein grown in bacterial cells. According to the researchers, the vaccine promotes a strong, immediate, but long-term response from the body's innate immune system. In addition to suppressing the development of arthritis, the vaccine also significantly improved bone quality, suggesting there should be long-term benefits after immunization.

"Despite the high prevalence, there is no cure [for rheumatoid arthritis] and it is not entirely clear what is causing it. This is true for almost all autoimmune diseases, making it very difficult to treat and prevent," said Ritu Chakravarti, PhD, an assistant professor at the University of Toledo College of Medicine and Life Sciences and the lead author of the study. "Fortunately, rheumatoid arthritis has completely disappeared in the vaccinated animals. If we could get this vaccine into the clinic, it would be revolutionary."

The researchers have applied for patents on their findings and are looking for partners in the pharmaceutical industry to support safety and toxicity studies in the hope of establishing preclinical studies. ❖

Kim J, Chun K, McGowan J, et al. 14-3-3ζ: A Suppressor of Inflammatory Arthritis. *PNAS*, Aug. 24, 2021 118 (34) e2025257118. Accessed at www.pnas.org/content/118/34/e2025257118.

Research

## IG Treatment May Reduce Acute Exacerbations of COPD

Observational studies suggest immune globulin (IG) treatment may reduce the frequency of acute exacerbations of chronic obstructive pulmonary disease (AECOPD). In the randomized controlled trial, the researchers recruited patients with COPD hospitalized for AECOPD or from ambulatory clinics with one severe or two moderate AECOPD in the previous year regardless of their serum IgG level. Patients were allocated in a 1:1 ratio with balanced randomization to monthly intravenous IG (IVIG) or normal saline for one year. The primary outcome was feasibility defined as prespecified accrual, adherence and follow-up rates. Secondary outcomes included safety, tolerance, AECOPD rates, time to first AECOPD, quality of life and healthcare costs.

Seventy patients were randomized (37 female; mean age 67.7) of which 34 (49 percent) adhered to at least 80 percent of planned treatments, and four (5.7 percent) were lost to follow-up. There were 35 serious adverse events, including seven deaths and one thromboembolism, none of which were related to IVIG. There were 56 and 48 moderate and severe AECOPD in the IVIG versus control groups. In patients with at least 80 percent treatment adherence, median time to first moderate or severe AECOPD was 275 versus 114 days, favoring the IVIG group.

According to the researchers, the study met feasibility criteria for recruitment and retention, but adherence was low. As such, a trend toward more robust treatment efficacy in adherent patients supports further study, but future trials must address treatment adherence. ❖

Cowan J, Mulpuru S, Abdallah SJ, et al. A Randomized Double-Blind Placebo-Control Feasibility Trial of Immunoglobulin Treatment for Prevention of Recurrent Acute Exacerbations of COPD. *International Journal of Chronic Obstructive Pulmonary Disease*, 2021;16:3275-3284. Accessed at www.dovepress.com/a-randomized-double-blind-placebo-control-feasibility-trial-of-immunog-peer-reviewed-fulltext-article-COPD.

Medicines

## FDA Approves Novartis' Cosentyx to Treat Arthritis in Children and Adolescents

Novartis has received U.S. Food and Drug Administration (FDA) approval for its Cosentyx (secukinumab) to treat children and adolescents with enthesitis-related arthritis and psoriatic arthritis. The human biologic was developed to directly target interleukin-17A, a cytokine involved in the inflammation of plaque psoriasis, psoriatic arthritis (PsA), ankylosing spondylitis, moderate to severe plaque psoriasis and nonradiographic axial spondyloarthritis.

Cosentyx is indicated to treat active enthesitis-related arthritis (ERA) in individuals aged 4 years and above, and active juvenile psoriatic arthritis (JPsA) in patients aged 2 years and above. It is the only biologic treatment approved for pediatric patients for both ERA and JPsA in the U.S. The approved pediatric dosing of Cosentyx is 75 mg (15 kg or more to less than 50 kg) or 150 mg (50 kg or more) injection, administered every four weeks for children and adolescents.

"This marks the second and third U.S. pediatric approval this year for Cosentyx, following pediatric psoriasis approval, and further reinforces the proven efficacy and safety of the therapy," said Todd Fox, Novartis' medical affairs immunology, hepatology and dermatology global head. "With more than 500,000 adult and pediatric patients treated worldwide since launch, healthcare professionals and patients can feel confident in Cosentyx." ❖

FDA Approves Novartis' Cosentyx to Treat Arthritis in Children and Adolescents. Pharmaceutical Business Review, Dec. 24, 2021. Accessed at www.pharmaceutical-business-review.com/news/fda-novartis-cosentyx-arthritis-children-adolescents.

Research

## COVID-19 Infection Alters Pregnant Mothers' and Their Newborns' Immunity

In a study conducted at the Cleveland Clinic that sought to understand the clinical and immunological implications of COVID-19 on maternal-to-fetal health, investigators found COVID-19 infection altered the mothers' immunity at delivery, and gestational COVID-19 exposure alters the immunity of newborns.

The study included 93 mothers with COVID-19 and 45 of their infants who were exposed to the virus. Investigators compared maternal blood specimens collected close to the original date of COVID-19 infection and throughout pregnancy and delivery, as well as studied immune profiles for more than 1,400 cytokines and other inflammatory proteins from the subjects' peripheral and cord blood samples. At delivery, the women had dysregulated levels of many cytokines associated with pregnancy complications such as MMP7, MDK, ESM1, BGN and CD209. The infants expressed induction of T cell-associated cytokines IL33, NFATC3 and CCL21. While most births

were healthy, there were high incidents of certain complications such as fetal growth restriction and preeclampsia.

According to Jae Jung, PhD, director of the Cleveland Clinic Global Center for Pathogen and Human Health Research, the "findings show that COVID-19 infection during pregnancy leads to distinct immune alterations in mothers and babies, highlighting how important it will be for long-term follow-up after pregnancy to catch and hopefully prevent any unforeseen long-term health conditions related to prenatal infection."

The investigators also found different immune signatures between pregnant women with asymptomatic and severe COVID-19 infection. The mothers with severe disease had significantly more inflammation and elevated levels of the protein interferon lambda 1 (IFNL1) and its binding receptor, IFNLR1. "This increase in interferon lambda signaling may help explain why we see relatively little direct transmission of COVID-19 between mother and baby during the period right before or after birth — what we call vertical transmission," said Suan-Sin (Jolin) Foo, PhD, the study's co-first author.

According to Dr. Foo, "More research will be necessary to determine if increased expression of IFNL1 and IFNLR1 does in fact block vertical transmission." ❖

Cosdon N. Immune Changes in Mothers, Infants Linked to COVID-19 Infection. Infection Control Today, Nov. 25, 2021. Accessed at www.infectioncontroltoday.com/view/going-deep-cleaning-potential-of-electrostatic-sprayers.

# COVID-19 Testing:
## Vitally Important Despite Vaccines

Due to the urgency in encouraging the public to get vaccinated against the SARS-CoV-2 virus, the message concerning the importance of widespread testing has been neglected, creating a lack of data needed for study by scientists.

By Jim Trageser

**GIVEN THE UNIQUENESS** of the severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2, and the COVID-19 disease it causes, it is little surprise to those on the front lines of medical care that there is considerable confusion among patients regarding vaccines and testing. The rapid ramp-up of research into the then-novel coronavirus inevitably led to equally rapid updates to our understanding of the virus, in turn leading to often jarring shifts in government policies regarding the pandemic. In addition, the messy, imperfect and all-too-human reality of scientific research led to both a sincere misunderstanding and calculated mercenaryism on the part of elected

officials charged with minimizing the human toll of the pandemic.

A century of towering medical advances led much of the public (and the mainstream media) to view medical research as an unwavering straight line forward. However, the highly contagious nature of the SARS-CoV-2 virus brought the haphazard reality of science into the average person's daily life in a tangible way not seen since polio was conquered more than six decades ago. More troubling, those for whom political affiliation is a defining part of their self-identity have divided themselves into two camps, neither of which is particularly open to a physician's counsel: 1) Those who think their belief in and support for science lends them an expertise they don't actually have, and 2) those who are predisposed to distrust almost anything attributed to science.

It is a situation that puts physicians in the discomfiting position of having to provide guidance to patients residing on a spectrum ranging from angry denial to the contentedly self-diagnosed merely looking for affirmation. And when it comes to convincing patients of the importance of being tested for COVID-19 following a confirmed exposure or exhibition of symptoms, that can be a steep challenge.

## Types of Testing

Two main categories of tests look for COVID-19: viral and antibody (Figure).[1] Viral tests ascertain whether patients are currently infected with the SARS-CoV-2 virus. Antibody tests determine if patients had a past infection.

The most common tests currently in use are viral tests that help identify contagious patients so they can self-isolate to prevent further spread of the infection. Viral tests work with samples taken from the throat or nose, and look for molecules unique to the COVID-19 virus.

**Figure. Types of COVID-19 Tests and When to Use Them**

| | |
|---|---|
| **Test in the Healthcare Provider's Office or Testing Site** | |
| **Polymerase Chain Reaction (PCR) Test Nasal Swab (24-72 Hours)** | This test looks for the virus' RNA in a patient's sample. A sample is collected by inserting a swab into a person's nostril and taking cells from the back of the nose. Some lab tests allow for patients to spit into a tube to get a saliva sample.<br>**When to use:** Make an appointment with a healthcare provider if exposed to the virus or if experiencing symptoms. |
| **At-Home Tests** | |
| **At-Home Nasal Swab with Lab-Based PCR Test (2-4 Days)** | This test is similar to the one provided at the healthcare provider's office, but the nasal swab is collected by the individual and mailed to a laboratory to be analyzed.<br>**When to use:** Use after exposure to the virus or when symptoms begin. |
| **Saliva PCR Test (2-4 Days)** | This test is similar to the one provided at the healthcare provider's office, but the saliva sample is collected by the individual and mailed to a laboratory to be analyzed.<br>**When to use:** Use after exposure to the virus or when symptoms begin. |
| **Rapid At-Home Antigen Tests (15 Minutes)** | This test detects a viral protein in the nasal sample.<br>**When to use:** Take this test when symptoms begin to get the best information about whether there are high amounts of the virus in an individual's system. |

*Adapted from: Balzer D. COVID-19 Tests: Different Types and When to Use Them. Mayo Clinic, Jan. 7, 2022. Accessed at newsnetwork.mayoclinic.org/discussion/covid-19-tests-different-types-and-when-to-use-them.*

There are two types of viral tests: rapid and laboratory. Rapid tests include home tests that can be self-administered and provide results in less than 20 minutes. These tests, including the newly available self-administered home tests, are generally antigen tests. Antigens are substances in a virus or bacteria that trigger the body's immune response. Rapid tests take approximately 15 minutes once the sample is applied, and they cost about $10 to $15 each. In these tests, the test strip is coated with laboratory-created antibodies specific to the body's response to a COVID-19 infection. If these antibodies encounter any antigens from the SARS-CoV-2 virus in the sample from patients, they will react and a colored line will appear on the strip indicating a positive result. However, these tests are not as accurate as lab tests, and they can provide false-negative results if patients are early in their infection.[2] Follow-up studies have found rapid tests are between 64 percent to 79 percent accurate.[3]

Laboratory tests use a technique called polymerase chain reaction, in which any RNA is amplified 30 or 40 times before the sample is tested for the SARS genes. It is considered to be 100 percent accurate,[2] but it can take several days from when a sample is taken until patients and/or their ordering physicians receive the results. And, they cost up to $100 per test.

Antibody tests are different from antigen tests that look for the presence of pieces of a virus. Antibody tests, or serology tests, seek out the immune system cells produced by the body to fight a COVID-19 infection. These tests can't indicate a current infection; they can indicate only if patients have been infected in the past.[4]

While some antibody tests can detect antibodies from a vaccine in addition to a previous infection, researchers caution that because there are different tests employing differing technologies, some tests will only indicate a previous infection, while others will also show antibodies from vaccines.[5] In addition,

tests may be inaccurate for those whose immune systems are weakened. For these reasons, the Centers for Disease Control and Prevention (CDC) currently recommends against using an antibody test to determine if a vaccine is offering protection.[6]

infection. Tetanus and chicken pox/shingles are just two diseases to which most patients are already accustomed to having regular booster shots to restimulate the body's immune response.

For this pandemic's virus, the flu is a more fitting example, since influenza viruses are prone to the kind of rapid mutations researchers are seeing with SARS-CoV-2. Obviously, every virus has its own genetic makeup that makes it more or less susceptible to chance random mutations, and unfortunately, SARS-CoV-2 is higher on the list than relatively stable viruses such as measles and poliovirus. Further, having tens or hundreds of millions of infected hosts also increases the odds of a chance random mutation just through the sheer number of SARS-CoV-2 viruses mutating in the bodies of the infected. Even if the odds of a chance mutation during any individual replication are low, when there could be multiple billions of replications in a single patient[7] and we calculate that against a global pandemic, clearly there are going to be mutations. And we can only find and track those through testing.

Once patients understand that not all viruses are alike, and thus not all vaccines work alike, they may be more receptive to the notion that getting tested is a common-sense step to protect their health — even after going to the trouble of getting vaccinated.

And, now that researchers have found that SARS-CoV-2 has had at least three significant mutations (Delta, Omicron and BA.2) that are not fully addressed by the earlier vaccines, it is likely more mutations will follow. This means vaccines will need updating, and people will need boosters, as well as ongoing testing, since we have experienced that even those who have received all the vaccines can still become infected and contagious.[8]

As such, even those already vaccinated should undergo testing if they have a confirmed exposure or are exhibiting symptoms consistent with COVID-19 — particularly if they live or work with people with compromised immune systems or are in another high-risk category. Even for the previously vaccinated, a positive COVID-19 test should be followed up with the latest isolation recommendations from CDC.[9] Unfortunately, this is news nobody wants to hear, especially now when COVID-19 fatigue is running nearly as strong as the pandemic itself.

**Major resistance to getting tested often comes from patients who have received both the two initial COVID-19 vaccines, as well as the booster.**

## 'But I'm Already Vaccinated!'

Major resistance to getting tested often comes from patients who have received both the two initial COVID-19 vaccines, as well as the booster.

Undeniably, the 20th century was the century of medical miracles. From eradicating smallpox to nearly eliminating polio, the development of the modern vaccine removed huge swaths of human suffering from our lives. However, those earlier vaccines also gave the public an unrealistic expectation of vaccine invincibility. This was compounded, unfortunately, by politicians (and not a few public health officials) who initially touted the COVID-19 vaccines as a sort of magic bullet that would end the pandemic — making promises before we had had enough time to measure the efficacy of these brand-new vaccines. As the primary face of the medical industry, physicians and other front-line personnel have found themselves bearing the brunt of the public's frustration. Saying "no" to further testing seems the only way for some patients to register that frustration.

Patients often need reminders that many familiar vaccines require multiple doses, or boosters, to help the body's immune system continue to fight an

## Long COVID-19

Every new infectious disease brings with it a host of unanticipated health challenges, and COVID-19 is no different. While most people apparently recover fully and quickly from COVID-19, a small percentage develop lingering symptoms of varying severity and type following infection. This is referred to as "long COVID-19."[10]

With recent research suggesting long COVID-19 in many patients is likely the result of the body's immune system overreacting to a COVID-19 infection,[11] testing to determine whether a patient has had COVID-19 can assist in determining whether the observed and reported symptoms are, indeed, consistent with a diagnosis of long COVID-19. The antibody, or serology, test would be the appropriate test in this instance.

A positive result might then lead to further testing since a lupus-like condition seems behind these cases of long COVID-19. Specific cells known as autoantibodies,

which attack the patient's body instead of the virus, are the suspected cause. Other patients seem to suffer a resurgence of Epstein-Barr virus, which may have been dormant but can become active again during COVID-19 infections while the body is busy fighting the virus.[12]

Because that same research shows other patients have long COVID-19 caused by a lingering COVID-19 infection, a negative antibody test can be followed up with an antigen test to look for a current infection. Many of these patients have found relief from long COVID-19 by receiving a vaccine, which seems to help the body eliminate the remaining SARS-CoV-2 virus.

Diabetes seems to be the underlying cause in the remaining patients with long COVID-19.

## Other Diseases

Another new syndrome associated with COVID-19 in children is multisystem inflammatory syndrome. An antibody test can determine if patients have had a past infection of COVID-19.[4]

In addition, any patients with a heightened risk factor — untreated high blood pressure, diabetes, obesity, a compromised immune system — should be tested after exposure or exhibiting symptoms consistent with COVID-19. These patients have a higher chance of developing serious health problems, and knowing if they have been infected will allow their physicians to monitor them and quickly begin aggressive treatment in the case of a positive test result.

## Body of Knowledge

Due to the high toll COVID-19 has taken around the world, and the necessity of focusing on producing vaccines, widespread antibody testing for COVID-19 has not been accomplished in most jurisdictions. We do know that for many people, perhaps a majority, a COVID-19 infection is accompanied by relatively minor symptoms that mimic other less-serious diseases such as the flu or a common cold. And another significant number of people who contract COVID-19 are wholly asymptomatic.

Therefore, researchers working on treatments for COVID-19 still lack a firm data set on how many people have contracted it. This is an important piece of information for epidemiologists studying how COVID-19 spread initially, and how current (and likely future) variants spread, as well as how many people have some natural immunity from having previously contracted the disease.

When patients use a home test, they should be encouraged to share the results with their physicians to assist in building a fuller picture of the pandemic.

## The Road Ahead

Despite the mainstream media's often polarized reporting, the percentage of the population that is vaccinated continues to increase. If, as many researchers now believe, COVID-19 is here to stay and will become endemic, much like influenza, then getting an annual COVID-19 booster will become just another medical discussion patients have with their doctors each year — with the decision based on the medical profile of each individual patient, rather than the raging political debates of the day.

Getting patients into the habit of being regularly tested, however, may be a tougher sell — simply because there is no existing program against which patients can compare. Regular testing for an infectious disease on a large scale is a new phenomenon, unique to COVID-19, and it may well take months and years of gentle, consistent persuasion to convince patients that testing is merely another necessary, if annoying, fact of life. ❖

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# Advances in Diagnostic Testing for **Antimicrobial Resistance**

The threat of antimicrobial resistance has increased substantially since the start of the COVID-19 pandemic, and while a host of diagnostic tools are available, these life-threatening infections still pose a threat due to limitations of tests, especially those that are rapid.

By Amy Scanlin, MS

**ANTIMICROBIALS HAVE** been revolutionizing medicine since their discovery in the 20th century, decreasing mortality and morbidity across the globe. However, their recent use and overuse have created an endemic of antimicrobial resistance (AMR) that now threatens the health that these drugs were designed to protect — intensified by nearly every aspect of the world in which we live: international travel, healthcare settings, wastewater and ground soil, food-producing animals and even the COVID-19 pandemic.

Although COVID-19 has dominated headlines in the past couple of years, its likely contribution to worsening the AMR endemic has not widely been discussed. Prior to the pandemic, AMR was estimated to kill more than 68,000 people annually in the European Union and United States alone. Looking ahead, the global threat of AMR is projected to cause more deaths than all cancers combined by 2050,[1] and complications from antibiotic resistant infections will cost as much as $100 trillion.[2] The financial ramifications of AMR could be comparable to those of climate change by the year 2030.[3]

Efforts to treat the real-time threat of COVID-19, compounded by threats of AMR, have been herculean. Particularly in the early days of the pandemic when there were far more unknowns about this virus, empiric administration of antibiotics to prevent secondary bacterial infections were commonplace. Still today, anywhere from 56 percent to 92 percent of hospitalized COVID-19 patients receive antibiotics throughout their course of treatment even though only 6 percent to 15 percent are suffering from a bacterial coinfection. Further, a retrospective study shows some patients with secondary bacterial infections are now acquiring AMR infection strains.[1]

In the U.S. alone, the Centers for Disease Control and Prevention (CDC) acknowledges the burden of deaths and infections from antibiotic resistance is actually greater than initially thought, with estimates of more than 2.8 million antibiotic-resistant infections annually and more than 35,000 deaths.[4]

The challenge of AMR is nothing new. Four years after the introduction of commercially available penicillin in 1943, resistance was observed for Staphylococcus aureus. However, the urgency and

proliferation of AMR, with genes developing singular and multiple resistance, has resulted in stepped-up efforts at mitigation, as well as development of more targeted therapies. Regrettably, innovation and production of new antibiotics are hampered by huge costs, including the expense of clinical trials and the risk that new drugs will soon be met with AMR, rendering them all but ineffective.

Healthcare associated infections, a major source of AMR infections, are stratified by the World Health Organization into three groups based on urgency of pathogens. High-priority bacteria include penicillin-resistant Streptococcus pneumoniae and so-called ESKAPE pathogens that are resistant to many antibiotics, including those considered last resort such as methicillin-resistant Staphylococcus aureus.

Through testing, antibiotic sensitivity can largely be determined, but results can take as long as a week. This delay perpetuates the problem of AMR since doctors may begin precautionary broad-spectrum antibiotics while awaiting results. It is estimated 50 percent of antibiotics are prescribed for the wrong strains due to incomplete or nonexistent testing.[5]

It is believed improved diagnostic testing, particularly rapid tests, will help to better identify infection strains and concurrent AMR.

## AMR Diagnostics: The Current Marketplace

AMR can occur in a number of ways, including intrinsically or through development of mutations by the very bacterial strains these antibiotics target. The chance of AMR occurrence and the severity of a subsequent infection are directly related to the affected individual's immune status.

Effectiveness of antimicrobial drugs are best tested using pure culture isolates with several cultivation rounds. According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical Laboratory Standards Institute (CLSI) guidelines, phenotype testing provides the most reliable diagnostic because it answers which antibiotic should be used and at what dose regardless of the resistance mechanism.[5] Minimum inhibitory concentrations (MIC) of antibiotic susceptibility tests (ASTs) under the EUCAST guidelines are generally higher than those of CLSI, even though CLSI's are more widely used.[6]

Disk diffusion is considered the gold standard of phenotype AST. It is simple and cost-effective, but it requires an overnight incubation and bacteria susceptibility confirmation between 16 hours and 24 hours, so it is less than ideal for analyzing slow-growing and fastidious bacteria. Dilution, both micro and macro, are other options for AST, although for both, it is difficult to maintain the recommended testing parameters such as pH and temperature. Likewise, for both diffusion and dilution, laborious testing requirements, length of incubation time and high risk of cross contamination provide significant challenges. On the other hand, epsilometer testing is preferred over disk diffusion and dilution for assessing AST because it is reliable across a range of antibiotics, particularly slow-growing and fastidious bacteria.[6]

Rapid ASTs can benefit patient outcomes through more timely identification and administration of targeted treatments, resulting in shortened hospital stays and reduced overall healthcare expense, although the implementation costs are vast, which include test kits, instruments and reagents, and required laboratory staff.

A number of commercially available rapid AST systems are on the market today, with reported result times in about four hours and susceptibility testing in six hours to eight hours, including broth dilution-based systems that use ready-made AST cassettes or cards. However, these are expensive and oftentimes don't take into account the total time needed for culture enrichment and isolation. There are also some doubts about whether accelerated cultures can fully substitute for traditional growth-based cultures. Therefore, in clinical settings, a more likely approach is the collection of pure isolates via culture samples followed by AST.

Genotype tests, with their sensitivity and specificity, make them generally better suited for rapid detection methods, with the polymerase chain reaction tests the most efficient. Genotype tests require shorter incubation times and have a reduced risk of contamination. However, they do have drawbacks, including specific assays for individual antimicrobial agents, and less sensitivity for latent infections. They also require skilled personnel to perform the tests.[6]

**A network of Antibiotic Resistance Laboratories, established in 2016, routinely tests and tracks emerging antibiotic resistance.**

Most rapid AST diagnostics today offer end-point analysis only and, therefore, may not be ideal in outpatient settings.[5] That said, diagnostic innovation continues, particularly for outpatient care settings where antibiotics are often prescribed.

Microfluidics-based diagnostics are some of the most promising devices on

the horizon because they are portable, cost-effective and reproducible, and they use a minimal number of samples. When coupled with optical sensors, AST tests can detect MIC in just a few hours and, in one reported case using a single bacterial cell analysis, within 30 minutes.

ATP bioluminescence assay is an enzyme-based approach to AST in which resistant bacteria result in bioluminescence, whereas susceptible bacteria stay neutral and can produce identification and susceptibility results of urinary infections within three hours to six hours.

Simplified blood culture system (SBCS) can be used for testing blood infections. These samples require no processing and can provide susceptibility within eight hours to 12 hours compared to a standard blood culture turnaround of up to 48 hours.[6]

## The Microbiome

The human microbiome is an important area of research as a harbinger of AMR bacteria. Even in the absence of antibiotic exposure, some studies show multidrug resistance in as much as 20 percent to 30 percent of the human gut microbiota, and drug-resistant genes have been detected in newborn meconium (the first feces or stool of the newborn), in some cases in rates higher than their mother's. Determining a predictive likelihood of carrying AMR bacteria, as well as becoming infected with one, is being looked at via high throughput DNA sequencing and bioinformatics. For example, homology-based methods can be used to predict antimicrobial-resistant genes using computers. The taxonomy of antimicrobial-resistant genes can also be studied to determine the source (i.e., whether it was passed vertically as part of microbial cell divide or horizontally by unrelated groups).[7]

Of course, the optimal antimicrobial testing mechanism will differ by healthcare setting based on availability, cost (including staffing) and accuracy. This may be particularly true in outpatient settings. However AST is assessed, communication of results and countering the effects of AMR infections are key.

## Federal Efforts and Innovations

The Antibiotic Resistance Solutions Initiative, part of the CDC's One Health approach under the National Action Plan for Combating Antibiotic-Resistant Bacteria, is one of many domestic and international efforts aimed at studying AMR and supporting innovation for diagnostics and mitigation.

A network of Antibiotic Resistance Laboratories, established in 2016, routinely tests and tracks emerging antibiotic resistance. When a germ of significance is identified, state and local health departments work with healthcare facilities to isolate patients and begin infection control procedures to reduce and stop further transmission.[4] In addition, a Global Antimicrobial Resistance Laboratory & Response Network was launched in 2021, which will span 50 countries and improve the detection of emerging AMR threats, as well as identify risk factors that drive the emergence and spread of AMR across healthcare, the community and the environment.

CDC and the U.S. Food and Drug Administration house an extensive isolate bank, providing samples at no cost (excluding shipping) to approved institutions for diagnostics and drug development, including validation of laboratory results and assays. As of February 2021, the isolate bank housed 29 panels and 952 isolates gathered from national reference labs and tracking activities, as well as from specimens in healthcare, food and the community.

Further spurring innovation is the Antimicrobial Resistance Diagnostic Challenge, a joint effort between the National Institutes of Health and the Health and Human Services Office of the Assistant Secretary for Preparedness and Response in support of the National Action Plan for Combating Antibiotic Resistant Bacteria. In 2021, the challenge awarded a $19 million federal innovation prize for rapid point-of-care laboratory diagnostic tests to combat the development and spread of drug-resistant bacteria. Funding for the prize was split between the National Institute of Allergy and Infectious Diseases and Biomedical Advanced Research and Development Authority. The winner was Visby Medical's single-use disposable rapid test for gonorrhea.[8]

The challenges of AMR are unrelenting, but so too are efforts to detect and combat it. Through prioritized global awareness and innovation in diagnostics, perhaps one day soon the etiology of its spread and identification of appropriate targeted interventions will provide for a better understanding and further development of a strong and meaningful intervention. ❖

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# Putting Patients First

Value-based healthcare prioritizes positive outcomes and positions patients at the center of future healthcare systems.

By Trudie Mitschang

**VALUE-BASED HEALTHCARE** is a model that essentially puts patient outcomes front and center, and it's an approach that has been gaining momentum for years. In fact, value-based care now accounts for approximately 50 percent of all healthcare payments. In simple terms, value-based healthcare rewards healthcare providers for providing quality care to patients that results in improved outcomes. Under this approach, providers seek to achieve the triple aim of providing better care for patients and better health for populations at a lower cost.

Value-based care focuses on care coordination that ensures patients are given the right care by the right provider at the right time. Using this approach, physicians are tasked with collaborating on care decisions, rather than operating in silos that lead to care gaps or redundancies. *The New England Journal of Medicine* (NEJM) defines value-based healthcare as a "delivery model in which providers, including hospitals and physicians, are paid based on patient health outcomes."[1] In other words, providers

should be rewarded for helping patients achieve the health outcomes that matter most to them.

In many ways, value-based care is at the forefront of future medical regulations and treatments. For example, the U.S. government is using this approach to transition toward medical activities that treat the overall health of a patient rather than reacting to symptoms once a person becomes sick.

"We will not achieve value-based care until we put the patient at the center of our healthcare system," said Seema Verma, the administrator of the U.S. Centers for Medicare and Medicaid Services (CMS).[2]

## The Essential Role of Primary Care

A value-based healthcare model incentivizes healthcare providers to get and keep their patients healthy, which can in turn lower healthcare costs. In many cases, this begins with the primary care physician. For many patients, the primary care physician is their first point of contact with the healthcare system. Research indicates that when incentives for primary care providers are structured to reward high-caliber care, the quality and cost effectiveness of patient care improves.[3]

In an effort to promote primary care as part of the national shift to value-based care, CMS launched payment models meant to shift more primary care providers to outcomes-based reimbursement. Dubbed the CMS Primary Cares Initiative, the program aims to reduce administrative burden for providers, while incentivizing clinicians to spend more time with patients and focus on preventive care. "As we seek to unleash innovation in our healthcare system, we recognize that the road to value must have as many lanes as possible," said Verma. "Our Primary Cares Initiative is designed to give clinicians different options that advance our goal to deliver better care at a lower cost, while allowing clinicians to focus on what they do best: treating patients."[3]

**Value-based care focuses on care coordination that ensures patients are given the right care by the right provider at the right time.**

While all the payment models are voluntary, the agency estimates the Primary Cares Initiative could shift nearly 11 million traditional Medicare beneficiaries into value-based payment relationships. The range of programs are meant to give clinicians an option for how much risk to assume over their Medicare population.

CMS officials say to help independent practices make the jump to value-based care, the organization is building improved reporting and feedback systems that can provide clinicians insight into their month-to-month performance. Using this model, doctors earning $200,000 could earn up to $300,000 if they effectively keep their patients healthy.

CMS is also developing a Direct Contracting payment model based on geography through which entities will bear 100 percent of total risk for beneficiaries in a target region. These entities will be selected through a competitive application process and are required to commit to provide CMS a specified discount amount off of the total cost of care. "CMS Primary Cares is a clear effort to shift one quarter of our Medicare population to outcomes-based payments," said Adam Bohler, the director of the CMS Innovation Institute. "It's time to dismantle the old broken fee-for-service system and replace it with one that is focused on outcomes and quality."[3]

Accountability is also a factor; value-based reimbursements are calculated by using numerous measures of quality and determining the overall health of populations. Unlike the traditional model, value-based care is driven by data because providers must report to payers on specific metrics and demonstrate improvement. For instance, providers may have to track and report on hospital readmissions, adverse events, population health, patient engagement and more.

When it comes to reimbursement, value-based care ties payments for care delivery to the quality of care provided and rewards providers for both efficiency and effectiveness. In this way, it may offer an alternative — and potential replacement — for fee-for-service reimbursement, which pays providers retrospectively for services delivered based on bill charges or annual fee schedules. Fee-for-service encourages many providers to order more tests and procedures, as well as manage more patients to get paid more.

Additionally, under fee-for-service models, cost variations for procedures and tests increased, and the healthcare industry was spending more to treat patients, even though patient outcomes were not necessarily improving. The model also challenged provider workflows because physicians were seeing more patients and each claim had to be processed in a fragmented network.

**Value-based payment models were not only good for business during the pandemic, but they also ushered in a wide acceptance of telemedicine.**

According to a State Health Care Cost Containment Committee report, "The opportunity exists to transform how healthcare is delivered. The goal is straightforward but ambitious: Replace the nation's reliance on fragmented, fee-for-service care with comprehensive, coordinated care using payment models that hold organizations accountable for cost control and quality gains."[4]

## The Influence of Emerging Technology

To bring value-based healthcare to life over the past few years, industry leaders have recognized the need for a "new generation of enabling information technology." A report by *NEJM Catalyst* notes, "New systems are needed to facilitate dramatic improvements in patient outcomes and efficiency and, importantly, to end an era in which health IT has entrenched the status quo, perpetuated silos and blocked reimbursement reform."[5]

Traditional healthcare technology systems evolved within a fee-for-service environment, which means tracking patient care and payments occur within specialty silos like anesthesiology, critical care and radiology. These systems were primarily designed to track meaningful use criteria — computerized order entry, electronic prescribing and electronic messaging with patients — and improve billing speed and accuracy for siloed services. The question then is: What would healthcare delivery look like if it applied customer experience data (similar to other industries like retail or banking)? In this case, patients and payers could expect:

- Records that are immediately updated and accessible across all system touchpoints
- Patient and family preferences that are a central part of the care planning process
- Stakeholders who are informed about each other's activities in real-time
- Prices and total costs visible to all participants
- Errors promptly identified and corrected
- Results routinely captured and analyzed for continuous improvement

A shift to value-based healthcare requires healthcare systems to create a patient-centered, condition-focused model of care that incorporates payment for a bundle of services resulting in improved health or a return to wellness. To be successful with this model, healthcare systems must follow patients from diagnosis to care outcomes, which should also be linked to cost.[6]

Of course, making a full transition to value-based healthcare will not be without hurdles. The current U.S. healthcare system structure is complex and inefficient when it comes to data sharing. In addition, the healthcare industry hasn't invested significantly in technology, partly because it hasn't been necessary to remain competitive. According to Harvard Business School Institute for Strategy and Competitiveness, "Per capita investment in health IT has lagged behind other industries. Although the recent emphasis on 'meaningful use' of IT has expanded the health IT industry, its functionality has been limited to being excellent revenue cycle tools in a fee-for-service-based delivery system. The transformation to a value-based system requires the support of condition-based care through data sharing, outcomes, cost measurement and reporting enabled by information technology, and technical support of new value-based payment methods."[7]

Despite the challenges, the evolution of value-based healthcare is likely to accelerate, given CMS's goal to advance the model to lower costs while improving care. Currently the federal government — acting as a single-payer — accounts for 25.9 percent of national health expenditures, making the federal government the largest single payer of healthcare in the U.S. With COVID-19-induced losses in the nation's hospitals and healthcare systems reaching $323 billion in 2020 alone, value-based healthcare's promise of lowering costs and improving care quality is well-positioned to accelerate change.[6]

"Standardized outcomes, transparently reported by condition, are essential for both care improvement and for making informed choices by patients, payers and other provider organizations. Outcomes represent the ultimate measure of quality," says Harvard Business School.[7]

## A Pandemic-Driven Shift

The COVID-19 pandemic undoubtedly put the healthcare system to the test, and it affected performance across the board. Inpatient numbers increased, quality of care declined, preventive care for children and adults lapsed, and people delayed cancer screenings. But it also catapulted the healthcare system forward with an ability to deliver on value-based care in several ways:

- Telemedicine became a permanent tool for many practices.
- Remote patient monitoring is more widely available and a part of care delivery.
- American Medical Association (AMA) medical updates for coding and documentation guidelines improved.

In addition, healthcare practitioners learned to be more flexible and perceived the need to create a quality dashboard that contains what the quality measure should be, how to adjust the measure for things like pandemics and how to make adjustments as needed.

The evolving changes driven by the pandemic may become the springboard to successfully handling healthcare issues stemming from recent (as of this writing) spikes in COVID-19 cases to handling the expected surge of patients who resume healthcare after putting it on hold. This may require healthcare delivery to evolve into a hybrid of different platforms such as home-based testing, point-of-care testing, more preventive care, more outbound mobile centers and community-based centers, and community health workers connecting with people who are hard to reach to bring them into the care system.

"When the world shut down in April and May of 2020, fee-for-service models ceased," says David Snow, chairman and CEO of Cedar Gate Technologies, a value-based healthcare information technology company. "However, providers in value-based care payment arrangements such as capitation continued forward — taking care of patients and generating revenue."

Value-based payment models were not only good for business during the pandemic, but they also ushered in a wide acceptance of telemedicine. Snow is also the chair of a telemedicine organization and recalls how difficult it was to drive adoption pre-pandemic. "Virtual care was deemed to be lower quality in comparison to an in-person visit," says Snow. "It took COVID to dispel this preconceived notion. It is clear now that telemedicine delivers enormous clinical quality, financial value and efficiencies. Sometimes it takes an earth-changing event to reorient things."

Preexisting conditions became newly challenging during the pandemic, as chronic diseases such as diabetes and hypertension risked being untreated. Many patients fell behind on care, which added significant risks to those with preexisting conditions. Thankfully, that trend has shifted. "Patient volumes dropped dramatically in the spring of 2020 but have come roaring back," adds Snow. "The challenge is that some people incurred harm and detrimental consequences from the disruption — particularly in the gap between the initial weeks of the pandemic and the full adoption of telemedicine. Motivated by patient outcomes, value-based providers were driven to quickly adapt to telemedicine to avoid disruptions to patient care."[8]

Snow noted that in value-based models, wellness and the avoidance of expensive and invasive treatments becomes the incentive, as opposed to the illness itself. These models offer improved analytics that are precise about performance improvement opportunities and reduced cost of care, giving practitioners the ability to use technology to solve issues as they arise.

## From Fringe Idea to a Mainstream Framework

Through adoption and integration of innovative solutions in care management, payers and providers can benefit from the explosive innovations driven by COVID-19 — many of which were already under development but are now being accelerated. In many ways, healthcare technology that offers multifaceted solutions to drive preventive and proactive patient care is actually within reach. "COVID's impact resulted in dramatic change and is now part of our healthcare framework. We're not going back to the old way," explains Snow. "It's a positive change. There's no doubt in my mind value-based care will be the dominant theme in the next 10 years for reimbursement — it's going mainstream."[8] ❖

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

# Weight Loss with Intermittent Fasting?

A growing trend for shedding unwanted pounds, this weight-loss technique may help many achieve their goals.

By Meredith Whitmore

**MANY HEALTHCARE** professionals have no doubt heard of intermittent fasting (IF) and its current popularity for weight loss, among other health benefits. Although fasting has been used for religious and health purposes throughout history, it has only recently become a "fad" of sorts, suddenly trendy and much-discussed. Fasting is attracting everyone from elite athletes to supermodels. These days, however, it's also of interest to physicians and other healthcare providers who see beyond the temptation to discount it as a dangerous and passing weight-loss craze. While there has been much controversy over this practice, many healthcare providers are beginning to have a new, more positive perspective on this ancient health practice and its past proponents. Hippocrates, for example, said, "To eat when you are sick is to feed your illness." Plutarch agreed, saying, "Instead of using medicine, better fast today." Beyond these two highly regarded historical figures, Plato and Aristotle were also enthusiastic devotees of fasting.[1]

Ancient Greeks believed in fasting largely because medical treatment could be observed through nature. For instance, most animals do not eat while ill, and humans typically do the same. These observations have led some to consider fasting the "physician within." For example, when ill with the flu, most people do not feel like eating. In fact, fasting is a universal mammalian instinct in response to many types of illnesses.[1]

Yet, apart from fasting for illness, one question remains: Does IF truly work for safe weight loss? Or, are athletes, models, ancients and millions of others wrong?

## What Is Intermittent Fasting?

Before delving into the research and anecdotal evidence, it's helpful to understand what IF is.

First, for most who practice it, IF is a lifestyle and not a diet. Many who practice IF want to make this distinction clear since more than a few see this lifestyle as a means to long-term good health, rather than merely weight loss. The benefits of IF, which include autophagy (cleaning out damaged cells), managing or reversing type 2 diabetes, reversing fatty liver, lowering blood pressure, and improving overall quality and length of life, are all reasons many practice it.

Simply put, IF is a regimen that focuses on periods of fasting, with either abstinence or significant calorie reduction, as well as periods of eating. Increasingly, researchers and healthcare providers view IF as alternating body composition through loss of fat mass and weight, without lowering metabolism that prevents fat loss. This is accomplished by cycling between reduced calories and normal eating during "feeding windows."[2]

Individuals adopt IF according to various fasting plans (see 7 Types of Intermittent Fasting), but following are

three of the main fasting schedules.

Alternate-day fasting: As the name implies, individuals fast every other day and, on alternate days, there is no food restriction. An example might be fasting Monday, Wednesday and Friday, with no food restrictions on Tuesday, Thursday, Saturday and Sunday.

Whole-day fasting: This plan involves complete fasting or eating only approximately 25 percent of daily caloric needs one or two days per week, with no food restrictions on alternate days. An example is the 5:2 diet approach, which involves windows of feeding times five days of the week, cycled with a zero or 400- to 500-calorie diet the other two days of the week.

Time-restricted feeding: With this plan, individuals follow a meal plan each day with a designated time frame for fasting. An example would be meals eaten between 8 a.m. and 3 p.m., with fasting during the remaining hours of the day.[2] Some fast for longer periods, but the most beneficial fasting time is generally three days.[3]

"[IF] makes intuitive sense," states Harvard University physician and writer Monique Tello, MD, MPH. "The food we eat is broken down by enzymes in our gut and eventually ends up as molecules in our bloodstream. Carbohydrates, particularly sugars and refined grains (think white flours and rice), are quickly broken down into sugar, which our cells use for energy. If our cells don't use it all, we store it in our fat cells as, well, fat. But sugar can only enter our cells with insulin, a hormone made in the pancreas. Insulin brings sugar into the fat cells and keeps it there.

"Between meals, as long as we don't snack, our insulin levels will go down and our fat cells can then release their stored sugar to be used as energy. We lose weight if we let our insulin levels go down. The entire idea of IF is to allow the insulin levels to go down far enough and for long enough that we burn off our fat."[3]

All of these regimens may sound drastic, and they could be for those who have not slowly prepared their bodies for such a lifestyle (e.g., fat adaptation). But, countless people who have prepared and tried this way of life have lost hundreds of pounds and benefited from a host of other health benefits.[2]

## Why the Calories-In, Calories-Out Model Does Not Work

Physician, author and researcher Jason Fung, MD, a nephrologist at the University of Toronto, is integrally responsible for the current interest in IF. Years ago in his practice, he learned the importance and efficacy of utilizing fasting and a low-carb lifestyle while treating kidney patients with type 2 diabetes. In his books *The Obesity Code* and *The Complete Guide to Fasting*, among others, Dr. Fung discusses the fact that obesity is not related to consuming too many calories or by not exercising enough. "Fundamentally, obesity is a hormonal problem," Dr. Fung writes in *The Complete Guide to Fasting*. "The underlying cause of obesity turns out to be hormonal, rather than a caloric imbalance. Insulin is fat-storage hormones. When we eat, insulin increases, signaling our body to store some of this food energy as fat for later use. It's a natural and essential process that has helped humans survive famine for thousands of years, but excessively and persistently high insulin levels result inexorably in obesity. Understanding this leads naturally to a solution: If excessive insulin is causing obesity, then clearly the answer lies in reducing insulin." Dr. Fung emphasizes that one way to reduce insulin is through IF. A simple illustration is to consider how insulin levels are elevated throughout the day when a person eats three meals and snacks throughout at least a 14-hour day. Insulin remains high. If a person has a time-restricted window for eating, however, insulin levels are not as elevated, causing the body to more efficiently use the body fat in storage.[2]

Anecdotal evidence, a glance at IF social media groups (including before-and-after photos of remarkable weight loss and improved health), YouTube videos, podcasts with IF experts, websites (e.g., dietdoctor.com; thefastingmethod.com) and books reveal IF is much more than a passing fad. The scientific evidence and

### 10 BENEFITS OF INTERMITTENT FASTING

1. PROTECTS AGAINST NEURODEGENERATIVE DISEASE
2. DECREASES INSULIN LEVELS AND INCREASES HUMAN GROWTH HORMONE
3. REDUCES INSULIN RESISTANCE AND LOWERS BLOOD SUGAR LEVELS
4. REDUCES RISK OF HEART DISEASE
5. REDUCES BLOOD PRESSURE AND CHOLESTEROL LEVELS
6. BOOSTS METABOLISM FOR FAT LOSS
7. EXTENDS LIFESPAN, HELPING PEOPLE LIVE LONGER
8. REDUCES OXIDATIVE DAMAGE AND INFLAMMATION IN THE BODY
9. REMOVES WASTE MATERIAL FROM CELLS
10. REDUCES LEPTIN LEVELS, INCREASING TESTOSTERONE

good results make IF worth a healthcare professional's time, let alone a patient's. *The New England Journal of Medicine's* 2019 study on IF's health benefits, including weight loss, also reveals an intriguing and effective "new" way that healthcare providers can help patients and themselves.[4]

In addition to his books and research, Dr. Fung cofounded the Intensive Dietary Management program and the health coaching program called The Fasting Method. *BioSupply Trends Quarterly* had a recent opportunity to interview Dr. Fung regarding his apparently controversial yet effective treatment methods.

## An Interview with Dr. Fung

**BSTQ:** You're a nephrologist and not a nutritionist. So, how did you learn about IF?

**Dr. Fung:** I work with kidney patients who often had type 2 diabetes. A main key to remedying that is to lose weight. So, I got really interested in weight loss and various weight-loss methods. Yet, a lot of what I initially read on weight loss was not very helpful or correct in the long run. The calories-in calories-out approach did not look like a good strategy to me. As I started to research fasting — because, honestly, you aren't taught much about fasting in medical school — I saw that there's quite a lot of good science surrounding it. So, after looking at the results, I began recommending fasting to patients. Fasting was a much better strategy. At least it was another weight-loss approach patients could use, and if it worked for them, great. If it didn't, they could try another method. But, they got some really fantastic results, including putting type 2 diabetes into remission. That's how it all began, and that's why I've wanted to talk and write about IF — to highlight some of the misconceptions surrounding it. So many people think it's unhelpful or dangerous such as that it will cause muscle loss, and there are other misunderstandings regarding what it is and how it works. I've tried to demystify it a bit. IF does not equate to starvation.

**BSTQ:** Beyond type 2 diabetes and obesity, what are the other common conditions that can be reversed if not cured with IF?

**Dr. Fung:** Fatty liver and polycystic ovarian syndrome, to name just two. Fatty liver is one of the leading causes of liver failure today, and it came out of nowhere. In the 1980s, for example, the disease barely existed. It went from being a rarity to becoming one of the most important liver diseases today, even while hepatitis B and C have been decreasing for decades. Fatty liver is reversible with fasting. Its origin has much to do with eating processed foods and frequent meals throughout the day. Those practices are

### 7 Types of Intermittent Fasting

1) 5:2 Fasting: One of the most popular IF methods made mainstream by the book *The FastDiet*, this approach allows individuals to eat normally for five days (without counting calories) and then eat 500 or 600 calories a day for women and men, respectively, on the other two days. The idea is that short bouts of fasting keep people compliant; if they are hungry on a fast day, they just have to look forward to tomorrow when they can "feast" again.

2) Time-Restricted Fasting: Using this approach, individuals choose an eating window every day, which should ideally leave a 14- to 16-hour fast. (Due to hormonal concerns, it is recommended women fast for no more than 14 hours daily.) For instance, the eating window might be from 9 a.m. to 5 p.m. Much of the time spent fasting is time spent sleeping.

3) Overnight Fasting: This approach is the simplest and involves fasting for a 12-hour period every day. For example, individuals can choose to stop eating after dinner by 7 p.m. and resume eating at 7 a.m. with breakfast the next morning. The benefit of this method is that it's easy to implement.

4) Eat Stop Eat: With this approach, individuals complete one or two 24-hour fasts per week and commit to a resistance-training program. This allows people to eat a slightly higher amount of calories on the other five or six nonfasting days.

5) Whole-Day Fasting: This approach allows individuals to eat once a day, so the fasting period is 24 hours (dinner to dinner or lunch to lunch). The advantage is that, if done for weight loss, it's really tough (though not impossible) to eat an entire day's worth of calories in one sitting. The disadvantage is that it's hard to obtain all the nutrients the body needs to function optimally with just one meal.

6) Alternate-Day Fasting: Using this approach, people might fast every other day, with a fast consisting of 25 percent of their calorie needs (about 500 calories) and nonfasting days being normal eating days.

7) Choose-Your-Day Fasting: With this approach, individuals might do the time-restricted fasting (fast for 16 hours, eat for eight, for instance) every other day or once or twice a week. For example, if Sunday is a normal day of eating, a person would stop eating by 8 p.m. and then resume eating again on Monday at noon. Essentially, it's like skipping breakfast a few days a week.

Source: Migala J. The 7 Types of Intermittent Fasting, and What to Know About Them. Everyday Health, April 20, 2020. Accessed at www.everydayhealth.com/diet-nutrition/diet/types-intermittent-fasting-which-best-you.

two of the reasons there is metabolic disease today.

**BSTQ:** Can you tell us about the other benefits of fasting that are so exciting?

**Dr. Fung:** I think one is from a weight-loss perspective, naturally. Weight loss was the goal for many of my patients. One of the things people have always talked about is calories in calories out, but then I looked at what that underlying process was and started asking questions. What is it that causes people to have problems such as hunger and a lower metabolic rate? What is causing people to eat more than they should in the first place? Why aren't more and more people losing weight and getting healthier using the food pyramid?

It's the same thing with metabolic rate. One of the things that was fairly obvious initially was that people's metabolic rate would go down as they started to lose weight on the calories-in calories-out approach and as they burned fewer calories. It would make their own weight loss less effective. That's a huge problem. But when people start fasting, which results in hormonal changes, their metabolic rate typically goes up. For obvious reasons, that's very beneficial.

**BSTQ:** If fasting is so healthy, why are so many healthcare professionals unaware of or opposed to it?

**Dr. Fung:** I think it's because they never learned about it. The strange part is fasting has been around for thousands of years, but no one at all has been talking about it, thinking about it or using it. It's actually the most obvious thing: If you don't eat, you'll probably lose weight. Fasting was the oldest thing, the most obvious thing, and nobody was using it. Also, when you introduce something new, there's this suspicion that it's faddish, or there's some sort of trick, or if you didn't learn it in medical or dietary school, there must be some hidden danger. But fasting is not new. Fasting was something that was forgotten over time and was lost in the notion that eating six times a day was the way to lose weight. There's actually no science that shows eating six times a day is good for you.

**BSTQ:** Does funding have anything to do with the lack of general fasting knowledge?

**Dr. Fung:** Drug companies tend to have a lot of money and great marketing, and their general advice is to eat less and move more. But these general platitudes don't really help much. Then, there are weight-loss drugs. A lot of the excitement within the medical community is driven by the hype of drug companies. But there's no one saying, "We've got to push fasting." Those who believe in IF are not going to invite these doctors to a free dinner, set up conferences or create educational materials. So it's comparable to a big Hollywood movie that has a huge marketing budget versus the independent movie that has no marketing budget. It's not that doctors are looking to make money; it's just what is marketed to them on a much larger scale. It's a public relations problem.

**BSTQ:** Even with good information, why do you think so many people are still skeptics?

**Dr. Fung:** It's great to see IF featured in more mainstream publications such as *The New England Journal of Medicine*, but if there's only a handful of scholarly articles each year about IF, versus hundreds of articles about medications for weight loss, it's still an uphill battle. At least, however, the information is now out there.

**BSTQ:** Do you have any other thoughts for healthcare providers regarding efficacy and general information?

**Dr. Fung:** Two things: The first is that fasting is not some weird thing. It's actually part of a balance. You have to balance feeding and fasting. Feeding means your body is going to store calories, and fasting means your body is going to use calories. That's the way it works. If the body didn't have a way to store calories, people would die in their sleep every single night. But obviously, we do store calories, and if we store them, we have to give our bodies time to use them. If we don't, we gain weight. The thing is it's not as if no one ever fasts. Everybody is supposed to fast every single day. That's why we have the word "breakfast." If you are balancing feeding and fasting, then you're going to succeed, and if you want to lose weight, you're going to need to increase the fast. So fasting is not unnatural. It's just part of a natural process and balance. Second, a lot of the science does support fasting. It's not like there's no science behind it.

## To Sum It Up

Dr. Fung and other scholars are great proponents of fasting. For example, Philip Paracelsus, the founder of toxicology and one of three fathers of modern Western medicine (along with Hippocrates and Galen) wrote, "Fasting is the greatest remedy — the physician within." With more research surrounding IF, its excellent results and the increasing scientific support of the practice, IF could very well be something to begin incorporating into healthcare professionals' general toolkits. At the very least, they can offer the information to patients to let them determine whether it's a lifestyle they would like to try. After all, there is little to lose beyond weight. ❖

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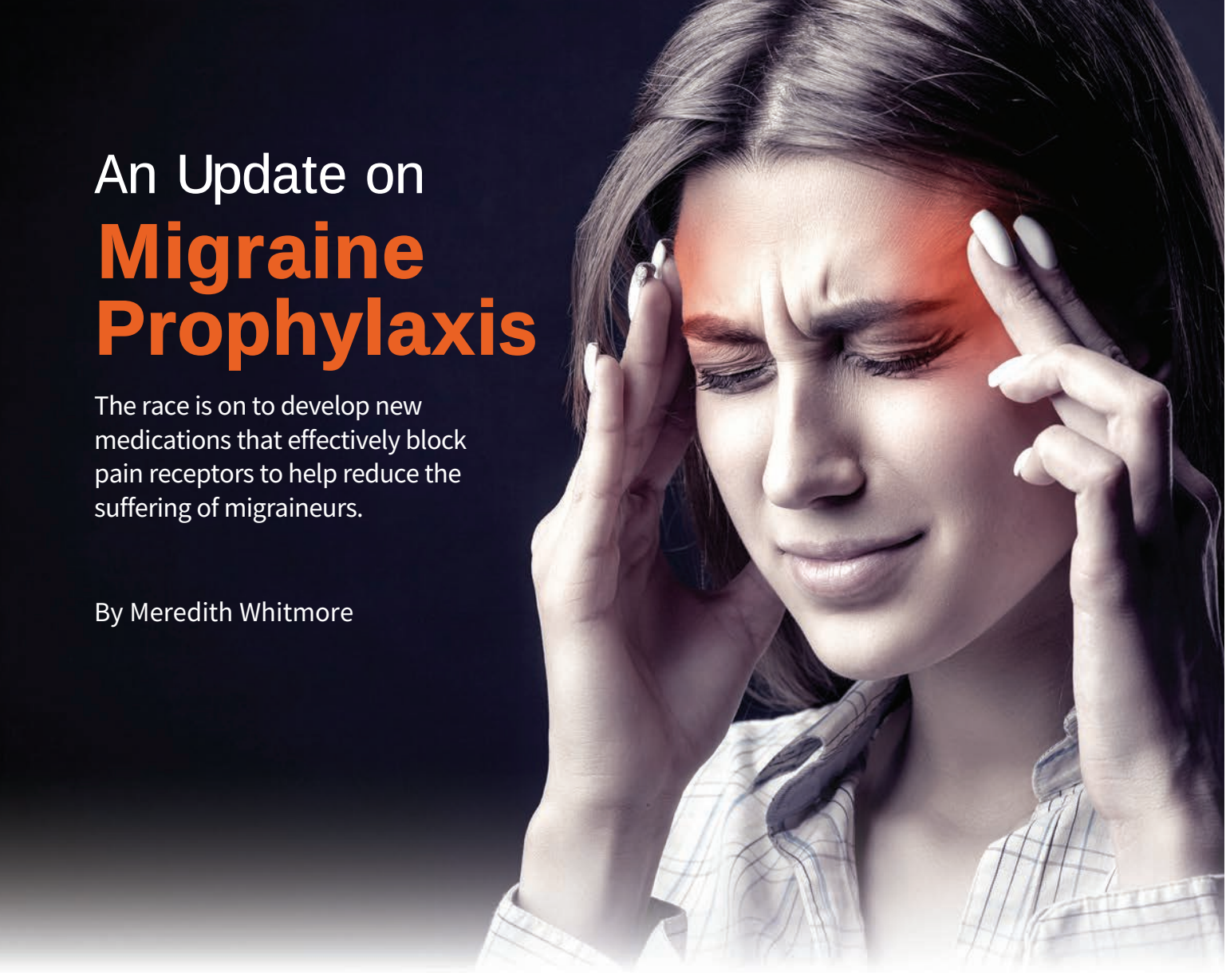
# An Update on Migraine Prophylaxis

The race is on to develop new medications that effectively block pain receptors to help reduce the suffering of migraineurs.

By Meredith Whitmore



**ROUGHLY 39 MILLION** Americans are affected by migraine, of whom more than 28 million are adult women. Due to nausea, light and sound sensitivity, throbbing pain and visual disturbances, among other symptoms, migraine attacks are usually debilitating and can last from four hours to 72 hours.[1] As a result, many migraineurs miss out on social opportunities and have much less time to perform daily tasks due to the illness.

Healthcare workers who do not suffer from migraine often misunderstand the condition and the suffering induced by the attacks. A migraine is not merely a bad headache; it is a primary headache and neurological disorder, which places it in a league of its own (Table).[2] Causes are not fully understood, but the illness can be linked to heredity, sex, hormonal changes, diet, weather, sleep changes and sensory stimuli.[2,3] The pain is so awful that one sufferer describes migraine as a "red-hot waffle iron stuck to the side of my head."[4] It's no wonder that migraine accounts for more than 800,000 emergency room visits in the U.S. annually.[5]

In addition to patients' misery, employers endure migraine consequences. More than 90 percent of migraine sufferers, for example, are unable to work or function normally at work while experiencing one. According to a 2020 analysis, the annual economic burden of migraine in the U.S. is approximately $78 billion.[1]

For decades, researchers have worked to understand migraine and to find new methods and medications to mitigate the excruciating pain and financial costs. Approximately 38 percent of patients with episodic migraine could benefit from preventive therapy, but surprisingly, less than 13 percent take prophylactic medications. Fortunately, this year looks brighter for migraineurs and employers with the efficacy of new drugs that promise to improve medication compliance and health.[6]

Yet, in today's rapidly changing pharmaceutical scene, healthcare workers may struggle to stay current regarding migraine medications. Following is a brief rundown of what's new and approved by the U.S. Food and Drug Administration (FDA).

## Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Migraine Prophylaxis

CGRP inhibitors are perhaps the most encouraging new prophylactics for migraine in decades. CGRP is a protein that, among other functionalities, carries pain signals along nerves. Its main role in migraine is to stimulate sensory nerves, causing inflammation, vasodilation throughout the meninges and inevitable pain. But it has been shown that by blocking CGRP or the receptor to which it links with an antibody, a very effective migraine treatment is possible.[7]

In fact, CGRP inhibitors demonstrate distinct advantages over more traditional migraine medications, including beta blockers, anti-seizure medications and antidepressants. What's more, CGRP inhibitors don't cause the same types of unpleasant side effects that can make other migraine medications hard or even impossible to take. Indeed, clinical trials have shown CGRP inhibitors have minimal side effects overall.[8]

There are two types of CGRP inhibitors: CGRP monoclonal antibody receptors and CGRP receptor antagonists, both of which work by interrupting the sequences that cause migraine pain, thereby relieving acute migraine in some cases and providing migraine prophylaxis in others.[8,9] Available in injectable and oral forms, most are approved for prevention alone, while others are approved for both prevention and treatment.[5]

While side effects of CGRP inhibitors are minimal for most people, the risk that a patient might react differently and more severely is still present. Common side effects include allergic reactions or hypersensitive skin; hives, rash, flushed skin; nausea, constipation or abdominal pain; fatigue; injection site reactions; weight loss; elevated liver enzyme blood tests; shortness of breath; soreness at injection site (for injectables); and muscle spasm.[6,9] Nevertheless, for many migraineurs, the minimal risk is very much worth the benefit of managing severe pain.

## FDA-Approved Monoclonal Antibody Receptors

Ajovy (fremanezumab-vfrm) from Teva Pharmaceutical Industries, administered through subcutaneous injection, is a fully humanized monoclonal antibody that targets the CGRP ligand. It has been shown to reduce migraine days with a 225 mg monthly injection or a 675 mg injection given every three months. Research shows Ajovy reduced migraine by five days a month in patients with chronic migraine, and it reduced migraine by an average of three-and-a-half days a month when taken quarterly or monthly over a 12-week period. Overall, 32 percent of patients with chronic migraine and 46 percent with episodic migraine had their monthly migraine days reduced by at least 50 percent over a 12-week period. However, those who are pregnant, breastfeeding or planning to become pregnant should not take this medication.

Emgality (galcanezumab-gnlm) from Eli Lilly, administered through subcutaneous

**Table. Headache or Migraine?**

| Headache (Can Be a Symptom of Illness) | Migraine (Is the Illness) |
|---|---|
| Pain around forehead | Pain on both sides of head |
| Mild dull pressure | Intense, pulsing or throbbing |
| Incidental, nonrecurring | Can last for days |
| Typically short-lived | Nausea and dizziness |
| Not usually accompanied by other symptoms | Flashing lights and blind spots |
| Treatable with medicine, rest and water | Commonly recurring |

injection once monthly, is also a fully humanized monoclonal antibody that targets the CGRP ligand. It is effective in preventing migraine, as well as cluster headaches. Emgality can be given as a single 300 mg injection to relieve an acute cluster headache episode and repeated monthly if needed. However, to prevent migraine effectively, it is given as a 240 mg loading dose the first month followed by 120 mg monthly injections. Research shows the drug can reduce the number of monthly migraine days by 50 percent or more for some patients. However, individuals younger than 18 years and anyone considering pregnancy, becoming pregnant or breastfeeding should not take this medication.

Vyepti (eptinezumab-jjmr) from Lundbeck, administered through intravenous infusion once every three months, is also a fully humanized monoclonal antibody that targets the CGRP ligand. While 100 mg is the recommended dose, some migraineurs benefit from the available and approved 300 mg dose. Research shows that after a single dose of 100 mg, patients who took Vyepti had fewer migraine days, on average, over three months.

Aimovig (erenumab-aooe) from Amgen, administered through subcutaneous injection once monthly, is yet another fully humanized monoclonal antibody that works by binding to the CGRP receptor. Research shows a monthly 140 mg injection of Aimovig has been shown to increase the chance of decreasing migraine frequency to at least 50 percent for one year.[10]

## FDA-Approved CGRP Receptor Antagonists

Qulipta (atogepant) from AbbVie, administered once daily in tablet form, is for migraine prevention only. Prescribed as a 10 mg, 30 mg or 60 mg daily dose, Qulipta has shown efficacy in reducing episodic migraine days at all doses. Clinical studies show it significantly reduced monthly migraine days across 12 weeks. However, individuals who have kidney or liver problems or who are pregnant, breastfeeding or planning to become pregnant should not take Qulipta.

Nurtec ODT (rimegepant) from Biohaven, administered in orally disintegrating tablet form every other day, has proven effective in increasing the chance of being pain-free within two hours of episodic migraine onset. Individuals take one 75 mg orally dissolved tablet at migraine onset and another if needed after at least two hours. Nurtec ODT can also be taken every other day for migraine prophylaxis, making it the only CGRP antagonist with FDA approval for both acute treatment and prevention of migraine. In a study of people who were prescribed either Nurtec ODT (669 people) or a placebo (682 people) to treat their migraine, more people taking Nurtec ODT experienced freedom from pain and other bothersome symptoms after two hours versus a placebo. And, those benefits were sustained through 48 hours for some people. In another study of people who were prescribed either Nurtec ODT (348 people) or a placebo (347 people) to prevent migraine, more people taking Nurtec ODT experienced reduced monthly migraine days. Again, those who have kidney or liver problems or who are pregnant, breastfeeding or planning to become pregnant should not take Nurtec ODT.[10]

Nurtec ODT is fast becoming the front-runner in migraine prophylaxis, possibly due to what *Forbes* calls "an all-out blitz advertising sales campaign," but more likely because it is effective in both preventing migraine, as well as treating acute migraine pain, which is a novelty in migraine medication.[5]

## A Boundless Contest

The rivalry among medications continues in the migraine prophylaxis contest. While it is a complex task for healthcare professionals to stay up to date about the new drugs that can best help individuals who suffer from this debilitating illness, it is also an exciting era for migraine prophylaxis developments and coming trends. The good news is future migraine treatment and prevention will likely greatly surpass the capabilities of current migraine prophylactics. But until then, healthcare providers have an excellent selection of medications that can help migraineurs end their suffering. ❖

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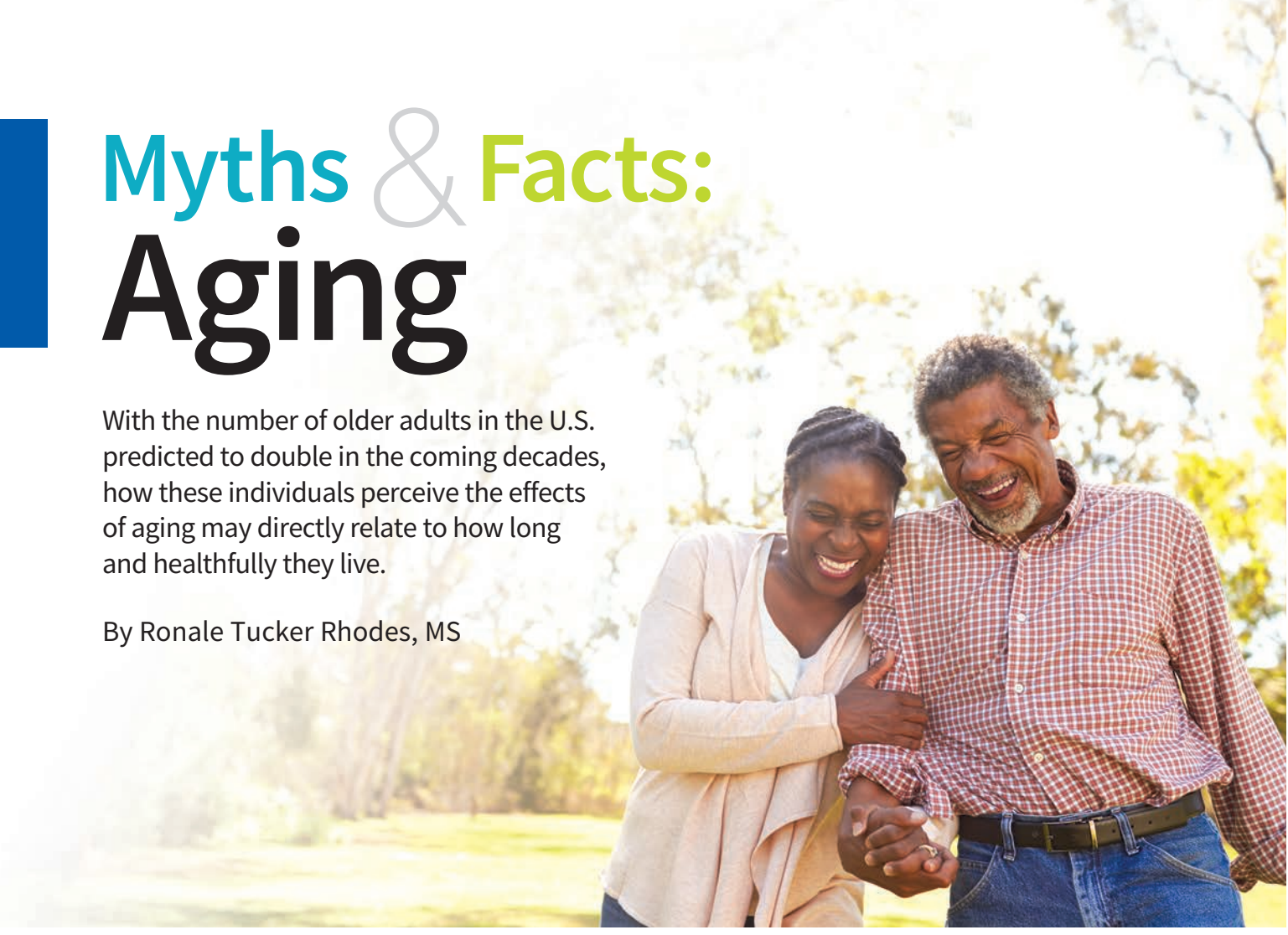
# Myths & Facts: Aging



With the number of older adults in the U.S. predicted to double in the coming decades, how these individuals perceive the effects of aging may directly relate to how long and healthfully they live.

By Ronale Tucker Rhodes, MS

**ACCORDING TO** estimates from the Census Bureau's National Demographic Analysis, the 2020 census highlights the sharp growth divide between the old and the young in America. Between 2010 and 2020, the number of people over age 55 grew by 27 percent, which is 20 times larger than the growth rate of the collective population under 55 (1.3 percent). And, the largest driver of this divide is the baby boomer generation that passed the age of 65 during the past decade, increasing the size of the 65- to 74-year-old age group by a half (Figure 1).[1] By 2060, the number of Americans aged 65 and older is projected to double to more than 987 million, and it will be the first time in history the number of older adults outnumbers children under age 5 years. What's more, older adults are expected to live longer than ever before, with one out of every four 65-year-olds today living past 90 years old.[2]

Interestingly, how healthfully people age depends a lot on how they perceive the effects of aging. Becca Levy, PhD, a public health and psychology researcher for more than 20 years, found that having positive perceptions about aging (e.g., wisdom, self-realization, satisfaction, generally being vital and robust) instead of negative perceptions (e.g., useless, helpless, devalued) is associated with a nearly eight-year increase in average lifespan. In her study, she analyzed longitudinal data from a group of 660 adults collected between 1975 and 1995 and mortality data obtained through 1998. At the beginning of the study, participants completed a survey designed to detect personally held stereotypes about aging, answering positively or negatively to statements such as "things keep getting worse as I get older" and "as you get older, you get less useful." Participants with positive scores outlived those with negative scores, and those with a positive bias were more likely to exercise, eat well, limit alcohol, be nonsmokers and have had preventive healthcare — all characteristics consistent with taking control of one's life.

Another of Dr. Levy's studies published in the *Journal of the American Medical Association* suggests seniors with positive age stereotypes are 44 percent more likely to fully recover from a severe disability.[3] So, with all the myths surrounding aging, it stands to reason that by dispelling them, people might have a more positive outlook about their expectations for growing old.

## Separating Myth from Fact

**Myth:** Physical deterioration is inevitable as individuals age.

**Fact:** While this isn't entirely untrue due to the wear and tear on bodies after decades of use, not all older adults' physical health is the same. In fact, many older adults are active and healthy, whereas others are frail with multiple health conditions.[4] Yes, stem cells do lose some of their potential and other cells weaken, but healthful habits can curb the physical aging process.[3] According to the World Health Organization, "increased physical activity and improving diet can effectively tackle many of the problems frequently associated with old age," including reduced strength, increased body fat, high blood pressure and reduced bone density.

Again, expectations play a role. Some studies show that merely expecting physical deterioration increases the likelihood that someone will physically deteriorate. In one study in which scientists surveyed 148 older adults about their aging, lifestyles and general health expectations, they found expectations regarding aging "play an important role in the adoption of physically active lifestyles in older adults and may influence health outcomes such as physical function." So, although some deterioration is likely, managing expectations will help individuals make better life choices to maintain physical health and fitness later in life.[4]

**Interestingly, how healthfully people age depends a lot on how they perceive the effects of aging.**

**Myth:** It's inevitable that older adults will experience cognitive decline.

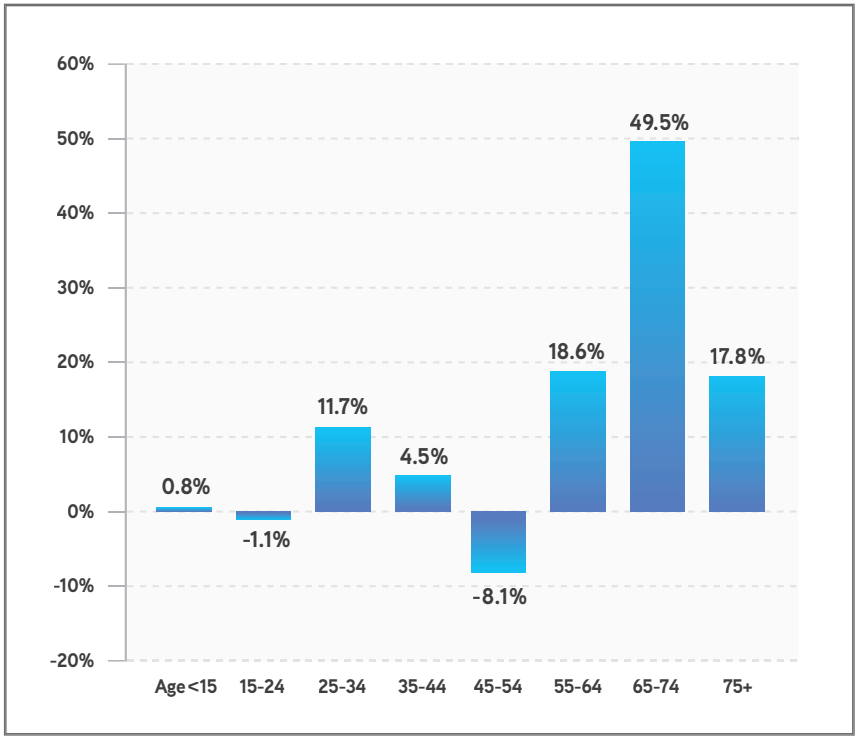
**Fact:** While some changes in cognition are normal with age such as slower reaction times, reduced problem-solving abilities, and a slower speed of processing information, many older adults outperform their younger counterparts on intelligence tests that draw on accumulated knowledge and experience.[2] And, it's known that cognitive development continues through life. According to a 2014 National Institutes of Health study, pursuing new interests that stimulate the brain help improve memory, and keeping the mind active and learning new skills help to build a cognitive reserve that allows the brain to become more adaptable and compensate for any age-related memory challenges.[4] What's more, wisdom and creativity often continue to the very end of life, and personality traits remain relatively stable over time.[2]

**Myth:** Cognitive decline leads to dementia.

**Fact:** While people who develop dementia tend to experience cognitive decline first, it does not necessarily signal the start of dementia. In fact, one study estimated 22.2 percent of people in the U.S. 71 years and older experience cognitive decline, of which only 11.7 percent to 20 percent develop dementia.

In 2015, the Alzheimer's Association evaluated the evidence of modifiable risk factors for both dementia and cognitive decline and found "there is sufficient evidence to support the link between several modifiable risk factors and a reduced risk of cognitive decline." These factors include maintaining regular physical activity; managing classic cardiovascular risk factors such as diabetes,

**Figure 1. Estimated U.S. Population Growth by Age, 2010-2020**




Source: William H Frey analysis of 2010 U.S. Census and 2020 Census Bureau demographic analysis estimates, released Dec. 15, 2020.

obesity, smoking and high blood pressure; a healthful diet; and lifelong learning.[5]

In addition, dementia is not a normal part of aging despite the growing risk of dementia as people age. Many people live into their 90s and beyond without significant declines in thinking and behavior that characterize dementia.[6]

**Myth:** Older adults need less (or more) sleep.

**Fact:** A common misconception is that a person's sleep needs increase or decline with age. An increase can often be attributed to older people enjoying a nap, whereas a decline is often attributed to rising earlier in the morning. The fact is older adults' sleep patterns are more fragmented because as the body changes with age, it can disrupt the circadian (daily) rhythms, which impacts sleep. There are also certain diseases that occur more commonly in older adults such as osteoarthritis and osteoporosis that can cause discomfort and influence an individual's ability to get to sleep or stay asleep.

But older adults still need between seven and nine hours of sleep per night, the same as all adults. In fact, the Centers for Disease Control and Prevention states adults aged 61 to 64 need seven to nine hours per night, whereas those aged 65 and older need seven to eight hours of sleep.

A silver lining to this sleep misconception is research suggests older adults handle sleep deprivation better than young adults, with older adults scoring better following a sleep-deprivation intervention in a range of measures, including negative affect, depression, confusion, tension, anger, fatigue and irritability.[5]

**Myth:** Older adults should not exercise to avoid injury.

**Fact:** It is often believed that exercise can do more harm than good for older adults, especially for those with a chronic condition. And, since bone density decreases with age, a fear of overexertion leading to injury is common. However, research proves there is a lot more to gain by being active and a lot to lose from being sedentary, which is more to blame than age when older adults lose their ability to do things on their own.[4,6]

Not only can exercise increase muscle strength and reduce fat, it can improve mental health. In one study, researchers put 142 adults aged 60 years to 80 years through a 42-week weight-lifting regimen and found it increased dynamic muscle strength, muscle size and functional capacity. Another study that involved 1,740 older adults found regular exercise was associated with a delay in onset of dementia and Alzheimer's disease.[5]

Most older adults can engage in some form of physical activity. Tai chi and similar mind and body movement practices have been shown to improve balance and stability to help maintain independence and prevent future falls. Other useful activities include walking, golfing, swimming and biking. However, it is recommended that those with certain conditions associated with age such as osteoporosis avoid high-impact exercise.[5,6]

**Myth:** Only older women get osteoporosis.

**Fact:** Both women and men are affected by osteoporosis, and by age 65 or 70, men and women lose bone mass at the same rate. While women naturally have smaller, thinner bones than men, putting them at higher risk of osteoporosis, 20 percent of those affected are men. One in every four men and one in every two women older than 50 will experience an osteoporosis-related fracture in their lifetime.[7] Causes of osteoporosis for both men and women include family history, a lack of calcium or vitamin D and too little exercise.[6]

**Myth:** Most older adults will have to give up driving.

**Fact:** Changes that occur with aging

can affect a person's ability to drive such as slower response speed, diminished vision or hearing, and reduced strength or mobility. However, it's not age that determines older adults' ability to drive but rather their ability to drive safely. Surprisingly, as the U.S. population ages, the number of licensed older adults continues to increase. According to the Federal Highway Administration, there were a record-high 221.7 million licensed drivers in the U.S. in 2016, including 41.7 million (almost one in five) who are 65 years and older.[6]

**Myth:** Older adults are often lonely and don't contribute much to society.

**Fact:** It is true that more older people live alone, but they are not necessarily lonely. In fact, their relationships may grow more intense in old age.[8] In addition, older adults are highly valued employees, colleagues and volunteers. According to researchers at the Stanford Graduate School of Education and the San Francisco-based nonprofit Encore.org, the majority of older adults want to contribute to society, and about a third actively do.[9] Also, a Pew Research Center study found 67 percent of seniors over age 65 use the Internet, and more than 100,000 individuals over age 50 participate in the nonprofit Road Scholar experiential learning program each year to better understand other cultures around the world.[10]

**Myth:** Older adults are not interested in sex.

**Fact:** A 2017 University of Michigan National Poll on Healthy Aging showed 65 percent of respondents aged 50 years to 80 years were interested in sex. Seventy-six percent agreed sex is an important part of a romantic relationship at any age, and 40 percent indicated they were still sexually active.[10]

While it's true that older age increases the risk of erectile dysfunction (ED) and vaginal dryness, these are not insurmountable issues for most people. An article in the *International Journal of Clinical Practice* indicates approximately 0.4 percent of men aged 18 years to 29 years experience ED compared with 11.5 percent of men aged 60 years to 69 years, which means nine out of 10 men in their 60s do not have ED. It's also true that as people grow older, some don't have the same sexual drive or desire, but this is not the case for everyone. In fact, researchers who conducted a study that involved 158 older adults wrote: "A remarkably robust sex life was evidenced by both the men and women, even until advanced old age."[5]

**Myth:** Most older adults live in nursing homes.

**Fact:** Actually, a very small percentage of older Americans resides in nursing homes, and only approximately 5 percent live in them at any given time. However, the percentage does increase with age, ranging from 1.1 percent for persons 65 years to 74 years to 3.5 percent for people 75 years to 84 years and 13.2 percent for people aged 85-plus.[2]

## Dispelling the Myths Now

The common theme to most myths surrounding growing old seems to center on inevitability or the perception that older age is associated with negative outcomes. But, as Dr. Levy stressed, being optimistic, diligent and having the will to live are important to living more healthfully as people age. While growing older does present challenges that differ for each person, aging by no means automatically results in a diminished quality of life, especially with today's scientific advances. The good news is getting to the truth surrounding these myths may help individuals make smart choices to keep their minds and bodies healthy. ❖

### Organizations with Information About Aging

- American Association of Retired Persons: www.aarp.org
- American Cancer Society: www.cancer.org
- Federal Highway Administration: www.safety.fhwa.dot.gov/older_users
- National Cancer Institute: www.cancer.gov
- National Center for Complementary and Integrative Health: www.nccih.nih.gov
- National Heart, Lung and Blood Institute: www.nhlbi.nih.gov
- National Institute of Arthritis and Musculoskeletal and Skin Diseases: www.niams.nih.gov
- National Institute of Mental Health: www.nimh.nih.gov
- National Suicide Prevention Lifeline: www.suicidepreventionlifeline.org

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*James serves as a role model for others with asthma through positive messaging in his Indy Lights motorsports campaign.*

# Asthma: *A Patient's Perspective*

By Trudie Mitschang

**BY ALL** accounts, James Roe lives life in the fast lane. An accomplished professional race car driver from Ireland, James is currently competing in Indy Lights presented by Cooper Tires, the third and top-level rung of racing in the Road to Indy ladder system. Diagnosed with asthma as a young child, James says he refuses to let his health limit him personally or professionally. Besides racing, his passion is to serve as a role model for young people and encourage others to always follow their dreams.

**BSTQ:** When were you diagnosed with asthma?

**James:** I was diagnosed when I was about 8 or 9 years of age. I had asthma quite severely growing up, especially in the winters in Ireland when the weather was cold. It hindered my sports activities because, when competing in athletics, I had to be very careful and always had to carry inhalers. Thankfully, after my diagnosis, I was able to work with my doctor to formulate a plan to manage it. I still use the same type of inhaler today that I used when I was 5 years old.

**BSTQ:** Is cold weather still a trigger for your asthma?

**James:** Cold weather is one of my main triggers, and I try to stay clear of it. I live in Indianapolis now, and the climate is a lot milder here. As a youth, I played a lot of sports, from football to rugby, and found that overexertion was an asthma trigger as well. I also have allergies to pollen and horsehair, both of which can cause symptoms.

**BSTQ:** How do you manage your asthma as a professional race car driver?

**James:** Being around idling cars and breathing in exhaust fumes is something I have to be mindful about, but it has never stopped me. In motorsports, there are many variables, and it's critically important for everyone on my race team to be on the same page. I have to let people around me know I have asthma. There's no shame in it. My race team knows where my inhaler is if I need it. Another thing I have to be mindful of is the pressure racing puts on my body. Drivers experience gravity forces (G-forces) when accelerating, braking or changing directions, which place a lot of strain on the lungs. In some cases, there are three to four G's pulling against my body, which is three to four times my body weight pulling me in a given direction.

> My goal is to put a positive spotlight on asthma to show it does not have to hold people back.

**BSTQ:** Do you have a specific training regimen that helps you prepare for that kind of stress?

**James:** I spend a lot of time working out to keep my lungs strong and healthy in order to compete. I focus a lot on opening up the chest or lungs with stretches that maximize lung capacity.

**BSTQ:** Having asthma can put you at higher risk for severe complications with COVID-19. How have you managed that risk?

**James:** I just follow the guidelines and keep a mask on in crowded areas. I also got vaccinated as soon as it was available.

**BSTQ:** Tell me about your advocacy work.

**James:** Currently, it is through positive messaging via my motorsports campaign in Indy Lights. We have more than 70 million avid fans throughout North America. My goal is to put a positive spotlight on asthma to show it does not have to hold people back. When I tell children I have asthma, many are surprised. Too many kids believe they can't do certain things because of their asthma. Then they meet me and see I'm in a high-adrenaline sport driving a race car 180 miles per hour, and they think, "He has asthma too, so why can't I follow my dreams?" It's a way to help people think differently about their asthma and their lives. I want them to believe their dreams are achievable. When they do, it's a win for me.

**BSTQ:** Do you have any other advice for asthma patients?

**James:** First, listen to your body. You can't turn a blind eye to symptoms. When asthma worsens, it becomes an issue you have to address. Next, find the right medication, and use it to your advantage so you can stop symptoms before they start. It sounds like such a simple thing, but it really is key. It's exactly what I did from an early age. I never want to have the mindset of "I have asthma, I can't do this." I believe there's nothing that can hold me back if I manage it successfully. ❖

*Dr. Marc Goldstein has been treating asthma patients for more than 30 years and is involved in asthma research and clinical trials.*

# Asthma: *A Physician's Perspective*

**MARC F. GOLDSTEIN**, MD, is a nationally recognized and awarded doctor, with extensive clinical and research experience. He is board-certified in allergy and immunology and has received the prestigious designations of fellow and diplomate at several of the nation's leading allergy, asthma and immunology organizations. Dr. Goldstein practices at The Asthma Center in Philadelphia, a comprehensive treatment center for adults and children, offering customized evaluations, diagnostics and treatment programs to manage each patient's specific allergy, asthma and sinus symptoms.

**BSTQ:** What is your background working with asthma patients?

**Dr. Goldstein:** I have been board-certified through the American Board of Allergy and Immunology since 1985, and I have more than 30 years of clinical experience treating asthma, allergy, immunology and sinus issues in both children and adults. I also have more than 20 years of research and clinical trial experience.

**BSTQ:** What are some common misperceptions about asthma?

**Dr. Goldstein:** Symptoms of asthma are commonly underreported. This is due to a poor perception of shortness of breath. When people experience shortness of breath for a long period of time, it becomes their "normal" way of breathing. As a result, it is more difficult for these individuals to recognize their breathing as abnormal. Additionally, people who have chest symptoms often attribute it to allergies. This is a fairly common occurrence. Similarly, people who get chest symptoms with a cold are often misdiagnosed with acute bronchitis. Lastly, it is not uncommon for individuals to think they have outgrown their childhood asthma. A person's symptoms may improve as they enter their teens and 20s, but asthma can reactivate in adults.

**BSTQ:** How do treatment protocols differ for children and adults?

**Dr. Goldstein:** Not all medications for adults work effectively or are approved for children of all ages. This is something that should be considered by physicians when prescribing. Additionally, there is a larger instance of exercise-induced asthma with children since they are more active in general. In regard to inhalers, children often have difficulty using asthma inhalers. One solution is the use of the holding chamber, which makes administering inhaler medications much easier. Another effective alternative is a nebulizer.

**BSTQ:** Are there lifestyle limitations (things they must avoid) for asthma patients?

**Dr. Goldstein:** Individuals with exercise-induced asthma may be advised to limit exercise activities. In addition, individuals with asthma should always have access to rescue emergency inhalers as a precautionary measure. Of course, those who have asthma should be regularly monitored by an asthma specialist due to the chronicity of their disease. Additionally, asthma is often triggered by animal dander, which means many people are not able to own pets and should limit their time around animals, in general.

**BSTQ:** How has asthma treatment evolved in recent years?

**Dr. Goldstein:** We now have once-a-day inhaler therapies that help immensely with patient compliance. A groundbreaking advance in the world of asthma is the development of biologic treatments. This is a common treatment that is utilized at The Asthma Center and has improved the quality of life for many patients.

**BSTQ:** Is patient compliance an issue among asthma patients?

**Dr. Goldstein:** Yes, especially among individuals with chronic asthma. These individuals need ongoing care, which means that they must dedicate a significant amount of time and energy to their lung health. There are also instances of forgetting to take medications. Oftentimes, those with asthma are advised to live in a pet-free environment because animal dander can negatively impact their breathing. This can be difficult for those who have bonded with a pet and are not willing to part ways.

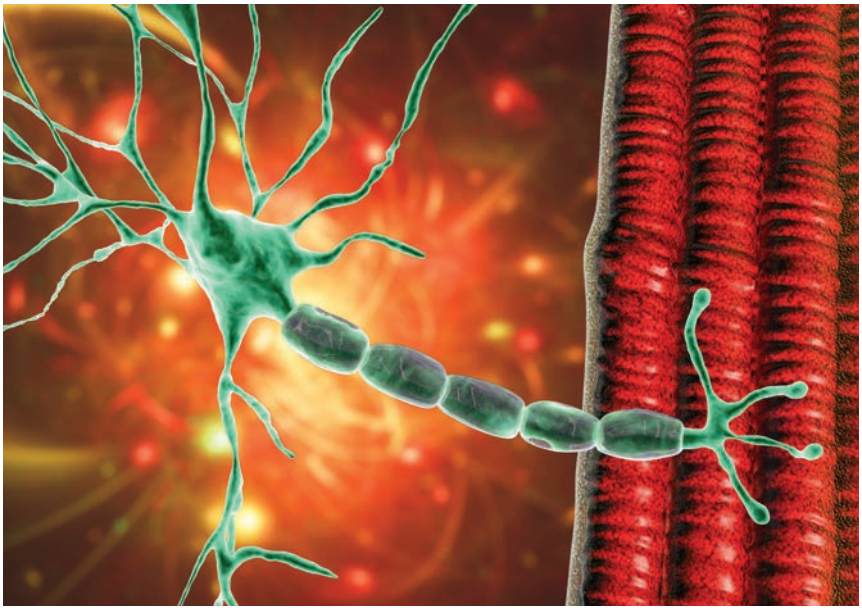
**BSTQ:** Any advice for newly diagnosed or long-time asthma patients?

**Dr. Goldstein:** My best advice for someone who is not feeling well or does not have well-controlled asthma is to see an expert as soon as possible to develop a treatment plan. Signs of poorly controlled asthma include difficulty breathing, interrupted sleep or trouble sleeping due to shortness of breath, and exercise-induced shortness of breath. Those newly diagnosed, as well as those with long-time asthma, should be monitored by an asthma specialist. ❖

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

# Neonatal Fc Receptor Blockers for Myasthenia Gravis: The Concept Is Now Reality

By Keith Berman, MPH, MBA



**WHILE THE** underlying cause of generalized myasthenia gravis (gMG) remains unclear, its pathogenesis is relatively straightforward: IgG autoantibodies target the nicotinic acetylcholine receptor (AChR) or other components of the postsynaptic motor end plate, breaking down motor nerve signaling to the muscle. MG can variously manifest as dyspnea, dysphagia, ptosis and fatigable muscle weakness affecting the neck and limbs. Bouts of severe muscular weakness can worsen to myasthenic crisis, with potentially life-threatening airway obstruction or respiratory failure.

In part because of the heterogeneous individual patient responses to available MG treatments, as well as a dearth of prospective clinical trials, there is no universally accepted MG management guideline. While acetylcholinesterase inhibitors, corticosteroids and thymectomy are generally considered first-line therapies for MG, many patients additionally require proven immunosuppressive therapies (ISTs) such as azathioprine, cyclosporine/tacrolimus or mycophenolate mofetil, or immunomodulatory therapies, including intravenous immune globulin (IVIG) or plasma exchange (PLEX).

In 2017, Soliris (emicizumab), Alexion Pharmaceuticals' complement inhibitor product, received its fourth approved indication for treatment of AChR-antibody positive (AChR-Ab+) MG. Prompted by this drug's exceedingly high annualized cost, a number of large U.S. health insurers have established restrictive coverage policies aligned with enrollment criteria for the pivotal study: failed treatment for at least one year with two or more ISTs (either in combination or as monotherapy), or failure on at least one IST and required chronic IVIG or therapeutic PLEX.[1,2] Other insurers have gone further, requiring the patient to have tried and failed from three to as many as six conventional MG treatment options before they will agree to cover Soliris.[2] Between these restrictive coverage policies and a boxed warning citing the risk of life-threatening or fatal meningococcal infections, adoption of this drug for the management of MG has been limited.

But four years later, in December 2021, a far more widely anticipated new MG immunotherapy arrived with the announcement by Dutch-Belgian biotechnology firm argenx that it received U.S. Food and Drug Administration (FDA) marketing approval for VYVGART (efgartigimod) for the treatment of the approximately 85 percent of MG patients who test positive for anti-AChR antibodies. VYVGART is the first of an entirely new drug category called neonatal Fc receptor (FcRn) blockers, which selectively reduce circulating levels of all four IgG subclasses, but have no effect on IgA, IgD, IgE or IgM levels.

VYVGART comprises a human immunoglobulin G1 (IgG1)-derived Fc fragment designed to avidly bind to endothelial cell FcRn. In doing so, VYVGART thwarts FcRn's physiologic function: to protect IgG from cellular digestion and "recycle" it back into the bloodstream, thereby extending the half-life of IgG to around 19 days to 23 days. As illustrated graphically in Figure 1, FcRn normally forms a complex with the constant Fc region of IgG taken up into endothelial cells from the circulation, and

internalizes that IgG into endosomes, which protects it from degradation by cellular lysosomes. The endosome migrates to the cellular surface, where by exocytosis, the intact IgG contained within it is released back into the circulation. By outcompeting IgG to bind to intracellular FcRn, the VYVGART IgG1-derived Fc fragment blocks the natural IgG recycling pathway, resulting in much-accelerated IgG degradation and a sharp decline in circulating IgG levels.

Guided by results from IgG pharmacokinetic studies (Figure 2), argenx settled on evaluating a dosing schedule of 10 mg/kg of VYVGART once weekly for four weeks, with a minimum 50-day cycle period before reevaluating whether and when to start the next four-dose VYVGART infusion series. The mechanism of action by which the drug acts to reduce MG-related weakness and disability is simplicity itself: By inducing a sharp, sustained reduction in total IgG, VYVGART equally reduces levels of anti-AChR IgG autoantibodies interfering with normal motor nerve conduction to affected muscles.

## Phase III ADAPT Trial Findings

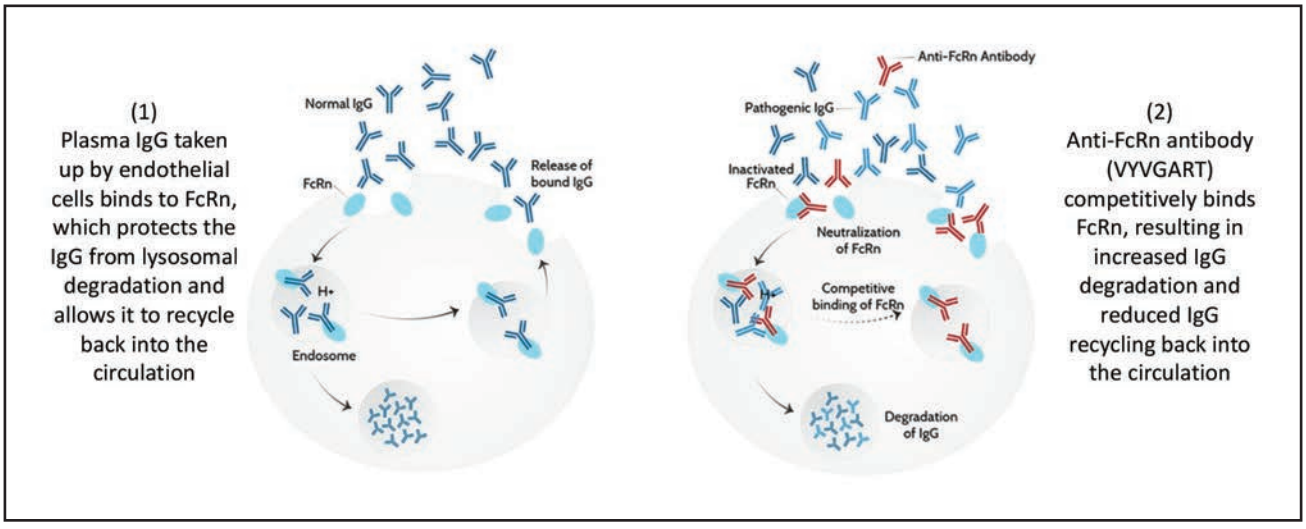
In mid-2021, findings from argenx's pivotal ADAPT study revealed just how effective this treatment strategy can be. A total of 167 gMG patients, 77 percent of whom who were AChR-Ab+, were randomized to receive four consecutive weekly infusions of 10 mg/kg of efgartigimod or placebo. To qualify for enrollment, at screening patients had to meet the following criteria:

- A Myasthenia Gravis Foundation of America (MGFA) clinical classification of class II (mild) to class IV (severe) weakness other than or in addition to ocular weakness;
- A Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥5 on an 8-point scale, where a higher score represents more severe disease;
- On a stable dose of MG therapy that included AChE inhibitors, steroids or nonsteroidal immunosuppressive therapies, either alone or in combination; and
- A baseline IgG level of at least 6 g/L.

The primary endpoint, assessed in the 129 study participants who were AChR-Ab+, was treatment response defined as a ≥2-point improvement from baseline for ≥4 consecutive weeks, with initial improvement by week 4 during the first treatment cycle. Each subsequent treatment cycle could begin only if 50 days or more had elapsed following initiation of the previous treatment cycle and 1) the total MG-ADL score was ≥5 points or 2) improvement in responders dropped to less than a 2-point reduction compared to the start of the cycle. The study's secondary endpoint was the Quantitative Myasthenia Gravis (QMG) score, a 13-item scale that measures ocular, bulbar, respiratory and limb function, where treatment response was defined as a minimum three-point improvement over baseline for four consecutive weeks.

After a single treatment cycle, 68 percent (44/65) of AChR-Ab+ patients in the VYVGART group were MG-ADL responders, compared to 30 percent (19/64) of control group patients (odds ratio, 4.95; 95% confidence interval, 2.21, 11.53; p<0.0001). The gap in response rate favoring VYVGART was even wider for QMG responders: 63

**Figure 1. (1) Physiologic FcRn-Mediated IgG Recycling (2) VYVGART Blockade of FcRn-Mediated IgG Recycling**



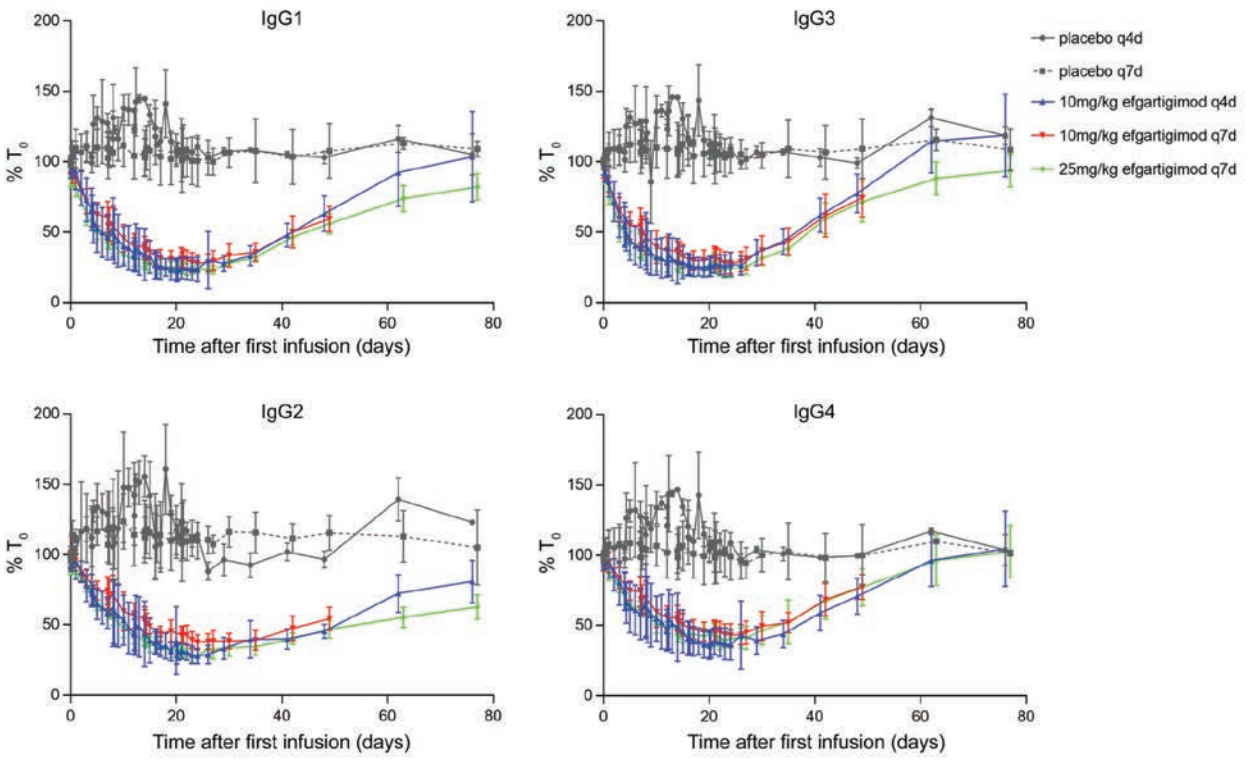
percent versus 14 percent ($p<0.0001$). After two treatment cycles, the response rate climbed to 79 percent, with nearly 90 percent of these responders experiencing a duration of response exceeding six weeks (Figure 3).

ADAPT study investigators also reported that 40 percent of AChR-Ab+ VYVGART group patients achieved minimal symptom expression at some point during their first treatment cycle, compared to just 11 percent in the placebo group. A further analysis revealed that about 45 percent of all VYVGART-treated MG patients, regardless of their AChR antibody status, were able to go eight or more weeks without retreatment following the last first cycle infusion.

While there are no specific contraindications for its use, the approved product labeling warns that VYVGART may increase the risk of infection. In the ADAPT study, 10 percent of VYVGART-treated patients developed urinary tract infections, versus 5 percent of placebo-treated patients. While not statistically significant, the respective rates of respiratory tract infection were 33 percent and 29 percent. Additionally, a higher frequency of patients who received VYVGART compared to placebo were observed to have below-normal levels of white blood cell counts (12 percent versus 5 percent), lymphocyte counts (28 percent versus 19 percent) and neutrophil counts (13 percent versus 6 percent). While the majority of infections and hematologic abnormalities were graded mild to moderate in severity, clinicians are advised to delay VYVGART administration in patients with an active infection until it is resolved, and to monitor patients on treatment for clinical signs and symptoms of infection.

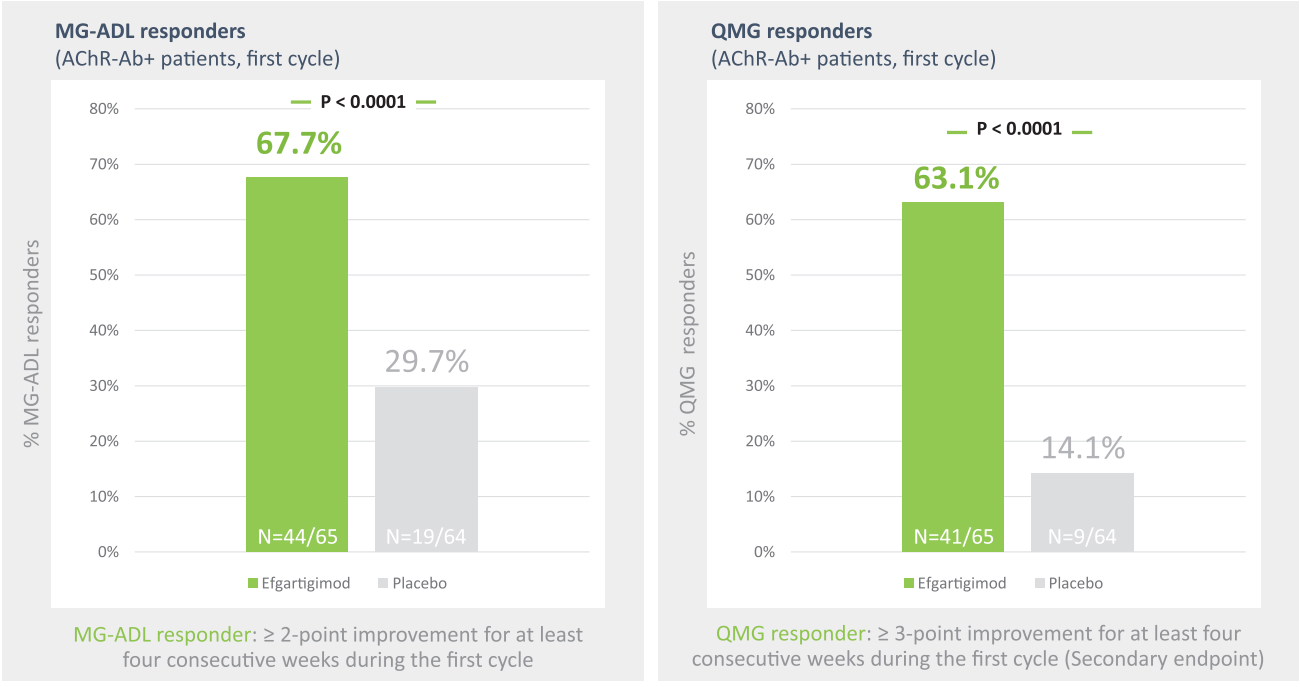
Nevertheless, argenx has reported no instances of dose-limiting toxicities in more than 600 healthy volunteers and patients treated across multiple clinical trials, including more than 125 patients who received VYVGART therapy longer than one year.

**Figure 2. Effect of Multiple Ascending Doses of Efgartigimod on Percentage Change in all Four IgG Subclasses Versus Baseline Over 80 Days from Initial Infusion**




Source: argenx investor presentation. ADAPT Phase 3 Topline Results, 26 May 2020 (pp. 9-10). Accessed at www.argenx.com/sites/default/files/event-attachment/Webcast_26052020_ADAPT_Ph3_Clinical_Results_FINAL.pdf.

**Figure 3. Phase III ADAPT Trial in AChR-Antibody Positive MG Patients: Response Rates Measured by MG-ADL and QMG**




Source: argenx investor presentation. ADAPT Phase 3 Topline Results, 26 May 2020 (pp. 9-10). Accessed at www.argenx.com/sites/default/files/event-attachment/Webcast_26052020_ADAPT_Ph3_Clinical_Results_FINAL.pdf.

## Where Will VYVGART Therapy Fit?

Now that it has secured marketing approval, the next question is obvious: For which MG patients is VYVGART an appropriate treatment option? The answer is far from straightforward, as physicians must weigh the merits and drawbacks of numerous available therapies and consider the highly individual patient response to these treatments, either alone or in combinations.

Because of its cost — about $225,000 per year for a typical MG patient, according to argenx CEO Tim Van Hauwermeiren[3] — it would not be unexpected if many health insurers choose to design coverage policies requiring patients to have failed to adequately respond to first-line MG treatments, and possibly one or more second-line immunosuppressive drug options as well. But beyond that, it remains to be seen which and how many established treatment options a patient candidate will need to give a fair trial and fail before any given insurer agrees to authorize VYVGART coverage.

Of particular interest will be how providers prioritize VYVGART in relation to two well-established immunomodulatory MG therapies: IVIG and PLEX. Both modalities are prescribed in a number of clinical circumstances, including:[4]

- Short-term treatment in MG patients with life-threatening signs such as respiratory insufficiency or dysphagia;
- When other treatments are insufficiently effective;
- Circumstances when a rapid response to treatment is needed; and
- Prior to initiating corticosteroids if deemed necessary to prevent or minimize exacerbations.

While IVIG and PLEX are considered to be similarly effective, expert consensus suggests PLEX is more effective and works more quickly in patients with impending or manifest myasthenic crisis.[4] Further, as PLEX works by physically removing plasma containing pathologic IgG autoantibodies against AChR or other motor end-plate receptors, which in essence is the same mechanism as VYVGART, both approaches act by reducing circulating levels of pathogenic anti-AChR antibodies.*

Yet between PLEX and IVIG, the latter treatment is used far more widely as maintenance therapy for refractory MG. While generally safe, PLEX exposes patients to significant risks of hemodynamic complications, infusion line-related infections and vascular access problems. Additionally, because the PLEX procedure requires highly trained apheresis nurses, it is

* One mechanism by which IVIG is thought to work against MG and certain other IgG antibody-mediated disorders is via saturation of FcRn receptors, reducing the recycling of endogenous anti-AChR antibodies and in turn lowering their circulating plasma levels.

**Table 1. Currently Active Clinical Trials Investigating IV or SC Efgartigimod**

| Indication | IV | SC | Trial | Primary Objective | Topline Data |
|---|---|---|---|---|---|
| Generalized myasthenia gravis | √ | | Phase IIIb ADAPT NXT | Efficacy, safety and tolerability of continuous dosing versus cyclic dosing | IQ 2023 |
| | | √ | Phase III ADAPT-SC | Safety, tolerability, efficacy, PK and QoL of SC efgartigimod | 1H 2022 |
| Immune thrombocytopenic purpura | √ | √ | Phase III ADVANCE (parallel trials) | Durable, sustained platelet count response (≥50 x $10^9$/L) | 2Q 2022 (IV)<br>1Q 2023 (SC) |
| Chronic inflammatory demyelinating polyneuropathy | | √ | Phase II/III ADHERE (stages A and B) | Safety and efficacy (relapse rate) | 1Q 2023 |
| Pemphigus vulgaris and foliaceus | | √ | Phase III ADDRESS | Achievement of clinical remission | 4Q 2022 |

*SC = Subcutaneous; IV = Intravenous; PK = Pharmacokinetics; QoL = Quality of Life*

not always readily accessible, particularly in smaller and more rural communities.

Where VYVGART ultimately fits into the MG treatment armamentarium in relation to IVIG and immunosuppressive drug options should become clearer with further clinical investigation and hands-on experience. But from the outset, VYVGART seems well-positioned to supplant PLEX for treatment of refractory MG, particularly for patients at increased risk for procedure-related complications or who live in communities without convenient access to PLEX services.

## SC Delivery and More Indications

On the heels of its pivotal study of IV-administered VYVGART, argenx's Phase III ADAPT-SC study is currently investigating a subcutaneous (SC) delivery form that can be self-administered by the patient at home. To facilitate SC administration of 1,000 mg of efgartigimod per weekly infusion session, argenx has in-licensed Halozyme Therapeutics' recombinant hyaluronidase, also called PH20.

As the IV formulation of VYVGART must be infused weekly, the convenience-based rationale for offering an SC efgartigimod formulation is compelling — more so even than the case for developing SC formulations of polyvalent human IG to relieve patients with primary immunodeficiency disorders of the inconvenience of clinic visits every three weeks to four weeks for their IVIG infusions.

With adjustments to the weekly SC dose to account for differences in pharmacokinetic parameters, there is every reason to expect argenx's investigational SC formulation of efgartigimod will achieve similar MG-ADL and QMG responder rates in AChR-Ab+ MG patients.

Both IV and SC efgartigimod formulations are now being evaluated in separate trials for the treatment of immune thrombocytopenic purpura (ITP). But in clinical trials currently investigating efgartigimod for chronic inflammatory demyelinating polyneuropathy (CIDP) and pemphigus vulgaris indications, argenx has elected to test only the SC version. Table 1 summarizes the current status and expected readout timing of topline results from these trials.

## A Promising Answer for a Clear Need

According to argenx's market research, the average person with MG is managed on more than two current treatments, yet 60 percent of patients report poor well-being due to debilitating muscle weakness and fatigue. Fully half are diagnosed with depression or anxiety in addition to MG, and half report they have completely stopped working due to the impact of their disease.[3]

The obvious unmet need for effective new MG treatment options, coupled with the evidence of VYVGART's effectiveness and its relatively benign adverse event profile, are encouraging signs for this novel therapy and its more convenient SC self-administered successor product, both for managing acute MG exacerbations and chronic weakness. Added to this are solid proof-of-concept data that argenx already has in hand for CIDP, pemphigus and ITP, and the company's announced ambition to develop and launch up to a dozen other autoimmune IgG-mediated indications by 2025. From all appearances, argenx and its unique FcRn blocker are just getting started. ❖

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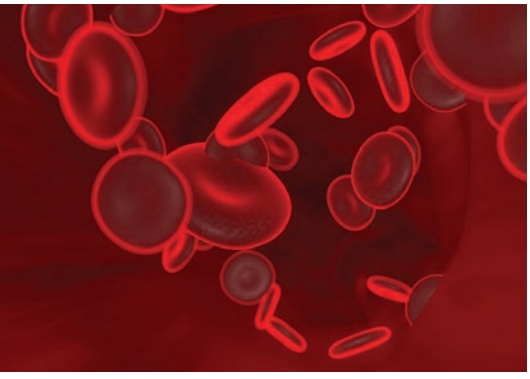
# Addition of Eltrombopag Improves Efficacy of Standard Therapy for Aplastic Anemia



A prospective, investigator-led, multicenter, open-label, randomized Phase III trial compared the efficacy and safety of standard immunosuppressive therapy comprising horse antithymocyte globulin [ATG] plus cyclosporine, with or without addition of Novartis' oral thrombopoietin receptor agonist Promacta (eltrombopag), as first-line therapy in 197 previously untreated patients with severe aplastic anemia. The primary endpoint was a hematologic complete response at three months.

A complete response at three months was documented in 10 percent of patients in Group A (standard treatment only) and 22 percent of patients in Group B (standard treatment plus eltrombopag); the odds ratio was 3.2 (95 percent confidence interval, 1.3 to 7.8; P = 0.01). At six months, the overall complete plus partial response rate was 41 percent in Group A and 68 percent in Group B. The median times to the first response were 8.8 months (Group A) and 3.0 months (Group B). The incidence of severe adverse events was similar in the two groups.

The investigators concluded that "the addition of eltrombopag to standard immunosuppressive therapy improved the rate, rapidity and strength of hematologic response among previously untreated patients with severe aplastic anemia, without additional toxic effects." ❖

Peffault de Latour R, Kulasekararaj A, Iacobelli S, et al. Eltombopag added to immunosuppression in severe aplastic anemia. *New Engl J Med* 2022 Jan 6;386(1):11-23.

# Many Clinically Stable CIDP Patients Can Safely Stop IVIG Maintenance Treatment

While intravenous immune globulin (IVIG) therapy is efficacious for patients with chronic inflammatory demyelinating polyneuropathy (CIDP), the lack of biomarkers for disease activity makes the need for ongoing treatment difficult to assess.

To determine whether IVIG withdrawal is noninferior to continuing IVIG treatment, a team of Dutch investigators performed a randomized, double-blind, IVIG-controlled noninferiority trial in 60 clinically stable adults with CIDP on IVIG maintenance therapy for at least six months. Patients either continued on IVIG treatment or received IVIG withdrawal as investigational treatment. The primary outcome measure was the mean change in logit scores from baseline to week 24 follow-up on the patient-reported Inflammatory Rasch-Overall Disability Scale (iRODS). The noninferiority margin was predefined as between-group difference in mean change scores of -0.65. Patients who deteriorated could reach a relapse endpoint according to predefined criteria; those in the IVIG withdrawal group entered a restabilization phase. All those in the withdrawal group who remained stable were included in a 52-week open-label extension phase.

The between-group difference in mean change iRODS scores was -0.47, with a 95 percent confidence interval from -1.24 to 0.31; noninferiority of IVIG withdrawal therefore could not be established. However, 41 percent of patients randomized to IVIG withdrawal remained stable for 24 weeks, compared to 58 percent in the IVIG continuation group. Of those in the IVIG withdrawal group, 28 percent remained stable at the end of the extension phase. Of those who relapsed and entered the restabilization phase, 94 percent restabilized within 12 weeks.

While acknowledging that it remains inconclusive whether IVIG withdrawal

is noninferior compared to continuing treatment, the investigators noted that "a considerable proportion of patients could stop treatment, and almost all patients who relapsed were restabilized quickly." They concluded that these findings "suggest that withdrawal attempts are safe and should be performed regularly in clinically stable patients." In addition, they noted that an unexpectedly high proportion of IVIG-treated patients experienced a relapse endpoint, emphasizing the need for more objective measures for disease activity in future trials. ❖

Adrichem ME, Lucke IM, Vrancken A, et al. Withdrawal of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. *Brain* 2022 Feb 8 [Online ahead of print].

## Medicare Immune Globulin Reimbursement Rates

Rates are effective April 1, 2022, through June 30, 2022

| | Product | Manufacturer | J Codes | ASP + 6% (before sequestration) | ASP + 4.3%* (after sequestration) |
|---|---|---|---|---|---|
| IVIG | ASCENIV | ADMA Biologics | J1554 | $963.54 | $948.09 |
| | BIVIGAM | ADMA Biologics | J1556 | $140.98 | $138.72 |
| | FLEBOGAMMA DIF | Grifols | J1572 | $77.43 | $76.19 |
| | GAMMAGARD SD | Takeda | J1566 | $139.85 | $137.61 |
| | GAMMAPLEX | BPL | J1557 | $101.47 | $99.84 |
| | OCTAGAM | Octapharma | J1568 | $83.64 | $82.30 |
| | PANZYGA | Octapharma/Pfizer | 90283/J1599 | $150.27 | $147.86 |
| | PRIVIGEN | CSL Behring | J1459 | $90.10 | $88.66 |
| IVIG/SCIG | GAMMAGARD LIQUID | Takeda | J1569 | $87.76 | $86.35 |
| | GAMMAKED | Kedrion | J1561 | $86.08 | $84.70 |
| | GAMUNEX-C | Grifols | J1561 | $86.08 | $84.70 |
| SCIG | CUTAQUIG | Octapharma | 90284/J3590 | $127.68 | $125.63 |
| | CUVITRU | Takeda | J1555 | $147.40 | $145.04 |
| | HIZENTRA | CSL Behring | J1559 | $117.87 | $115.98 |
| | HYQVIA | Takeda | J1575 | $152.47 | $150.02 |
| | XEMBIFY | Grifols | J1558 | $136.57 | $134.38 |

*ASP + 4.3% applies only after July 1, 2022. On April 1, 2022, a 1% reduction in payment will apply until July 1, 2022, unless further Congressional action is taken to extend the moratorium.

Calculate your reimbursement online at www.FFEnterprises.com.

## Immune Globulin Reference Table

| | Product | Manufacturer | Indication | Size |
|---|---|---|---|---|
| IVIG | ASCENIV LIQUID, 10% | ADMA Biologics | PI | 5 g |
| | BIVIGAM LIQUID, 10% | ADMA Biologics | PI | 5 g, 10 g |
| | FLEBOGAMMA 5% DIF Liquid | Grifols | PI | 0.5 g, 2.5 g, 5 g, 10 g, 20 g |
| | FLEBOGAMMA 10% DIF Liquid | Grifols | PI, ITP | 5 g, 10 g, 20 g |
| | GAMMAGARD S/D Lyophilized, 5% (Low IgA) | Takeda | PI, ITP, B-cell CLL, KD | 2.5 g, 5 g, 10 g |
| | GAMMAPLEX Liquid, 5% | BPL | PI, ITP | 2.5 g, 5 g, 10 g, 20 g |
| | GAMMAPLEX Liquid, 10% | BPL | PI, ITP | 5 g, 10 g, 20 g |
| | OCTAGAM Liquid, 5% | Octapharma | PI | 1 g, 2.5 g, 5 g, 10 g, 25 g |
| | OCTAGAM Liquid, 10% | Octapharma | ITP, DM | 2 g, 5 g, 10 g, 20 g, 30 g |
| | PANZYGA Liquid, 10% | Octapharma/Pfizer | PI, ITP, CIDP | 2.5 g, 5 g, 10 g, 20 g, 30 g |
| | PRIVIGEN Liquid, 10% | CSL Behring | PI, ITP, CIDP | 5 g, 10 g, 20 g, 40 g |
| IVIG/SCIG | GAMMAGARD Liquid, 10% | Takeda | IVIG: PI, MMN | 1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g |
| | | | SCIG: PI | |
| | GAMMAKED Liquid, 10% | Kedrion | IVIG: PI, ITP, CIDP | 1 g, 2.5 g, 5 g, 10 g, 20 g |
| | | | SCIG: PI | |
| | GAMUNEX-C Liquid, 10% | Grifols | IVIG: PI, ITP, CIDP | 1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g |
| | | | SCIG: PI | |
| SCIG | CUTAQUIG Liquid, 16.5% | Octapharma | PI | 1 g, 1.65 g, 2 g, 3.3 g, 4 g, 8 g |
| | CUVITRU Liquid, 20% | Takeda | PI | 1 g, 2 g, 4 g, 8 g, 10 g |
| | HIZENTRA Liquid, 20% | CSL Behring | PI, CIDP | 1 g, 2 g, 4 g, 10 g<br>1 g PFS, 2 g PFS, 4 g PFS |
| | HYQVIA Liquid, 10% | Takeda | PI | 2.5 g, 5 g, 10 g, 20 g, 30 g |
| | XEMBIFY Liquid, 20% | Grifols | PI | 1 g, 2 g, 4 g, 10 g |

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

# 2022-2023 Influenza Vaccine

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

| Product | Manufacturer | Presentation | Age Group | Code |
|---|---|---|---|---|
| **Quadrivalent** | | | | |
| AFLURIA (IIV4) | SEQIRUS | 0.5 mL PFS 10-BX | 3 years and older | 90688 |
| AFLURIA (IIV4) | SEQIRUS | 5 mL MDV | 6 months and older | 90687/90688 |
| FLUAD (IIV4) | SEQIRUS | 0.5 mL PFS 10-BX | 65 years and older | 90694 |
| FLUARIX (IIV4) | GSK | 0.5 mL PFS 10-BX | 6 months and older | 90686 |
| FLUBLOK (ccIIV4) | SANOFI PASTEUR | 0.5 mL PFS 10-BX | 18 years and older | 90682 |
| FLUCELVAX (ccIIV4) | SEQIRUS | 0.5 mL PFS 10-BX | 6 months and older | 90674 |
| FLUCELVAX (ccIIV4) | SEQIRUS | 5 mL MDV | 6 months and older | 90756* |
| FLULAVAL (IIV4) | GSK | 0.5 mL PFS 10-BX | 6 months and older | 90686 |
| FLUMIST (LAIV4) | ASTRAZENECA | 0.2 mL nasal spray 10-BX | 2-49 years | 90672 |
| FLUZONE (IIV4) | SANOFI PASTEUR | 0.5 mL PFS 10-BX | 6 months and older | 90686 |
| FLUZONE (IIV4) | SANOFI PASTEUR | 0.5 mL SDV 10-BX | 6 months and older | 90686 |
| FLUZONE (IIV4) | SANOFI PASTEUR | 5 mL MDV | 6 months and older | 90688 |
| FLUZONE HIGH-DOSE (IIV4) | SANOFI PASTEUR | 0.7 mL PFS 10-BX | 65 years and older | 90662 |

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

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

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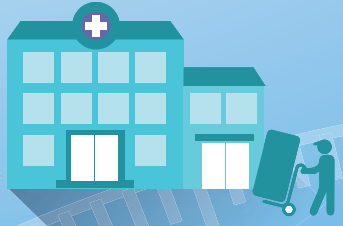

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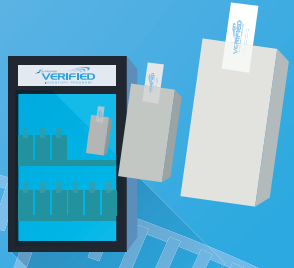


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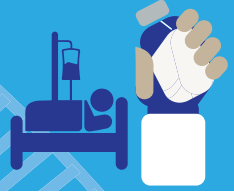

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