biosupplytrends
QUARTERLY
FALL 2022 INNOVATION

Virtual Care Solutions

Meeting Patient and Provider Needs

ADDRESSING THE
Healthcare Diversity Gap

TREATING GENETIC DISEASES
WITH Gene Therapy

UPDATE ON
Treating Alzheimer's

IMPROVING PATIENT ADHERENCE
Through Smart Packaging

MYTHS AND FACTS
ABOUT Depression

NOVEL IMMUNOTHERAPIES TARGETING RSV DISEASE | PAGE 48

Guaranteed Channel Integrity®
8 Critical Steps

STEP 1

Purchasing

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

STEP 2

Storage

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

STEP 3

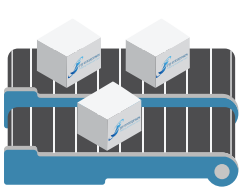
Specialty Packaging

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

STEP 4

Interactive Allocation

FFF's unique capability of interactive allocation allows us to do that through our field sales team's close relationship with our customers. Our team understands customers' ongoing requirements, responds to their immediate crises, and allocates product in real-time to meet patients' needs.



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

800.843.7477 | Emergency Ordering 24/7

STEP 5

Delivery

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

STEP 6

Methods of Delivery

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

STEP 7

Verification

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

STEP 8

Tracking

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

Up Front

Features

BioTrends Watch

BioFocus

BioSources

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

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

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

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

BioSupply Trends Quarterly accepts manuscript submissions in MS Word between 600 and 2,500 words in length. Email manuscripts to or request submission guidelines at editor@BSTQuarterly.com. *BioSupply Trends Quarterly* retains the right to edit submissions. The contents of each submission and their accuracy are the responsibility of the author(s) and must be original work that has not been, nor will be, published elsewhere, without the written permission of *BioSupply Trends Quarterly*. A copyright agreement attesting to this and transferring copyright to FFF Enterprises will be required.

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

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

nufactor®
A SPECIALTY INFUSION COMPANY

Making a difference one patient at a time

Immune Globulin • Factor • Infliximab

Scan code to visit us at nufactor.com

Nufactor Specialty Pharmacy has earned The Joint Commission Gold Seal of Approval

ACCREDITED
Specialty Pharmacy
Expires 03/01/2024

(800) 323-6832 | nufactor.com

Innovations for Improving Patient Treatment Outcomes

AS THE publisher of *BioSupply Trends Quarterly* magazine, our motto at FFF Enterprises for the past 34 years has been "Helping Healthcare Care." The reason: There is a patient at the center of everything we do. Catapulted by the COVID-19 pandemic, the world of medicine is changing fast, with innovations in telehealth, disease treatments and medication adherence. And, as we progress to meet the needs of a broadening patient population, we must expand our healthcare systems' diversity to also affect patient treatment outcomes.

Technology is expanding and improving to make it easier for patients and providers to connect, and telehealth is becoming the norm for many Americans. This comes after almost three years of dealing with the pandemic and with new viral threats looming, forcing the healthcare industry to adapt to meet the needs of both patients and providers. But, as we explain in our article "Pros and Cons of Virtual Care Solutions" (p.20), research has found that while the majority of Americans are willing to try video visits, most prefer visits in-person. And, even though most providers are struggling with virtual care demands due to investment and integration issues, it is clear that as it continues to grow, providers need to be on board with the necessary tools and training.

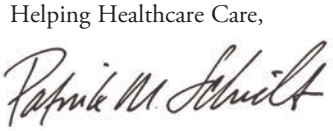
Solutions in disease treatment and management are also expanding. In our article "Breakthroughs in Gene Therapy" (p.23), we explore the advances in gene therapy and genome editing that show great promise for curing genetic diseases. Researchers are treating blindness, blood and immune disorders and sickle cell disease using CRISPR/Cas9 and CAR-T therapies. And, as major research institutions note, 2022 has built on the successes of gene therapies in 2021, proving to be a record year for approvals in this innovative area.

For those managing diseases with medications, nonadherence continues to plague patient outcomes, with only 50 percent of medications taken as prescribed. And, while packaging has historically helped in this arena, new smart packaging technologies are quickly improving adherence rates by up to 87 percent. We examine some of these new technologies in our article "Improving Patient Adherence with Smart Packaging" (p.28), including radio frequency identification systems, smart blister packs, smart inhalers and injectable pens, and bar code-enabled drug systems. But, as we note, with the newness of these technologies, security and safety concerns must be addressed.

One area affecting patient treatment outcomes that is gaining more attention is diversity, equity and inclusion. As we explain in our article "Addressing the Healthcare Diversity Gap" (p.32), minorities are underrepresented among physicians and in academic and clinical research, making it difficult for many to receive equitable care. And while the reasons are varied, the solution that is achieving success may lie in employing nonclinical professionals.

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

Helping Healthcare Care,



Patrick M. Schmidt
Publisher

biosupplytrends QUARTERLY

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

Publisher
Patrick M. Schmidt

Editor
Ronale Tucker Rhodes, MS

Associate Editor
Rachel Maier, MS

Art Director
Allan Bean

Contributing Writers
Keith Berman, MPH, MBA
Diane L.M. Cook
Bonnie Kirschenbaum, MS, FASHP, FCSHP
Trudie Mitschang
Amy Scanlin, MS
Jim Trageser
Meredith Whitmore

Please direct editorial, advertising and marketing communications to
44000 Winchester Road
Temecula, CA 92590
Ph: (800) 843-7477
Email: editor@BSTQuarterly.com

biosupply®

BioSupply® is the online product ordering platform by FFF Enterprises Inc., the largest and most trusted distributor of plasma products, vaccines, biosimilars and other specialty pharmaceuticals and biopharmaceuticals. Visit **fffenterprises.com** to learn more about us.

Point, Click, **Confidence.**

BioSupplyOnline.com

makes ordering your products easy, fast and convenient!

Available Products

Albumin/Plasma Protein Fraction
Ancillaries
Antithrombin
BioSurgical
Coagulation Factor
Essential Medicines
Hyperimmune Globulin
Immune Globulin
Influenza Vaccines
Oncology
Pediatric Vaccines
Pharmaceuticals

We are proud to be an accredited NABP® Verified-Accredited Wholesale Distributor for all authorized U.S. plasma products manufacturers.

BioSupply is a quick and easy-to-use platform offering instant access to the critical-care products you need when you need them. Our customer-driven online portal empowers you to order what you want, when you want it, with just one click so you can better manage your inventory. With over 33 counterfeit-free years, you know you are buying from a trusted leader in the industry. BioSupply offers:

- At-a-glance access to your account information
- Links to view open orders and ordering history
- Shortcuts to frequently purchased products
- FFF Sales Team contact information
- Detailed product pages
- Product alternatives if products are back-ordered or unavailable
- Convenience and accessibility to drop-ship products
- Shopping Cart feature displays account number and shipping address to minimize purchasing errors
- My Favorites feature for frequently ordered products
- BioVision reporting tool provides analysis of purchasing patterns

For ordering support, contact our Wow! Customer Care team:
P: (800) 843-7477 Emergency Ordering available 24/7/365
F: (800) 418-4333
E: customerservice@fffenterprises.com

FFF enterprises
Helping Healthcare Care®

HHS and ED Launch Joint-Department Effort to Expand School-Based Health Services

The U.S. Department of Health and Human Services (HHS) and U.S. Education Department (ED) have launched a joint-department effort to expand school-based health services, ensuring children have the health services and support necessary to build resilience and thrive. The joint effort will provide additional technical assistance, resources and support to schools that will provide guidance on the federal funding available for school-based physical and behavioral health services, including how Medicaid can support the delivery of these services; help reduce federal administrative burden for states and localities, including local educational agencies and barriers to the provision of school-based physical and behavioral health services; and improve and strengthen access to physical and behavioral health services.

"Our nation's children have been particularly impacted by the COVID-19 pandemic, including significant impacts on their mental health," said HHS Secretary Xavier Becerra and ED Secretary Miguel A. Cardona. "Youth reports of psychological distress have doubled since the pandemic began, with 25 percent reporting depressive symptoms and 20 percent reporting anxiety symptoms. Children and youth with intellectual or developmental disabilities and those with prior childhood trauma are at particular risk for pandemic-related mental health challenges, as are those who have faced previous discrimination in the healthcare system, including children and youth of color, immigrant children, children with disabilities and those who are LGBTQ+. While the pandemic's long-term impacts on children and youth are not fully understood, working together to build resilience in children, youth and families can promote equity and support recovery efforts. We will elevate opportunities under the American Rescue Plan funding along with existing federal resources to build a lasting and sustainable healthcare infrastructure for our children and youth." ❖

HHS Secretary Xavier Becerra, Education Secretary Miguel A. Cardona Announce a Joint Effort to Develop and Share Resources to Ensure Children Have Access to School-Based Health Services. U.S. Department of Health and Human Services press release, March 24, 2022. Accessed at www.hhs.gov/about/news/2022/03/24/hhs-secretary-xavier-becerra-education-secretary-miguel-a-cardona-announce-joint-effort-develop-share-resources-ensure-children-have-access-school-based-health-services.html.

NIH Establishes Antiviral Drug Discovery Centers

The National Institute of Allergy and Infectious Diseases (NIAID), a division of the National Institutes of Health (NIH), awarded approximately $577 million to establish nine Antiviral Drug Discovery (AViDD) Centers for Pathogens of Pandemic Concern. The AViDD award underscores NIAID's commitment to ongoing research into the cause, prevention, diagnosis and treatment of infectious diseases in the U.S. and worldwide.

"The COVID-19 pandemic has highlighted the need for new antiviral drugs, especially those that could easily be taken by patients at home while their symptoms are still mild," said NIAID Director Anthony S. Fauci, MD. Decades worth of research on the structure and vulnerabilities of coronaviruses prior to the COVID-19 pandemic informed and accelerated the response to COVID-19. "We hope that similar research focused on antivirals will better prepare us for the next pandemic."

The AViDD centers will conduct the groundbreaking, multidisciplinary research needed to develop candidate COVID-19 antivirals with an emphasis on those that can be taken in an outpatient setting, as well as enact a preemptive effort to develop antivirals targeting other viral families with high potential to cause a pandemic in the future. According to NIH, viral families to be studied include parayxoviruses, bunyaviruses, togaviruses, filoviruses (including Ebola viruses and Marburg virus), picornaviruses (including enteroviruses and other viruses that cause the common cold) and flaviviruses (including those that cause yellow fever, dengue and Zika).

Research will include early-stage identification and validation of novel viral targets, as well as identification of small molecules and biotherapeutics that directly block viral targets. After being evaluated for potency and breadth, the most promising drug candidates will move on to late-stage preclinical development. Collaboration among AViDD centers is encouraged. Research will be supported with and accelerated by access to and use of industry partner resources such as chemical libraries and expertise in product development pipeline. ❖

NIH Announces Antiviral Drug Development Awards. National Institutes of Health press release, May 18, 2022. Accessed at www.nih.gov/news-events/news-releases/nih-announces-antiviral-drug-development-awards.

HHS Launches the Inaugural PandemicX 2022 Cohort

The U.S. Department of Health and Human Services has launched the inaugural PandemicX 2022 cohort, a novel program to accelerate private-public collaboration comprised of 15 health technology startups. The PandemicX startups were selected through a rigorous process, 66 percent of which are both female-founded and minority-owned. The startup's proposed solutions align with federal health challenges and address health equity barriers and other disparities exacerbated by COVID-19 using data and innovation.

Through the six-month program, the startups had access to curriculum, mentorship, resources and other collaborations to scale their businesses and work toward creating actionable solutions to federal challenges, including health equity by design, national public health solutions, behavioral and mental health, socioeconomic outcome indicators and community resilience.

"The world needs technological and business innovation to increase equitable assets and to create a resilient society," said Micky Tripathi, U.S. National Coordinator for Health IT. "We know HealthTech startups are a force of good to help make wellness, health and wealth an accessible right, not a privilege. You cannot have health without resilience; you cannot have health without inclusion."

A list of all the startups, including specific details, can be viewed at masschallenge.org/announcement/mcht22cohort. ❖

Inaugural PandemicX Accelerator Graduates Cohort Creating a Model for Future Public-Private Collaboration. U.S. Department of Health and Human Services press release, Aug. 18, 2022. Accessed at www.hhs.gov/about/news/2022/08/18/inaugural-pandemicx-accelerator-graduates-cohort-creating-a-model-for-future-public-private-collaboration.html?utm_source=news-releases-email&utm_medium=email&utm_campaign=august-21-2022.

HHS Awards $1.5 Billion Grant to Combat Opioid Addiction

The U.S. Department of Health and Human Services (HHS), through the Substance Abuse and Mental Health Services Administration (SAMHSA), is announcing a State Opioid Response (SOR) grant funding opportunity that will provide nearly $1.5 billion to states and territories to help address the nation's opioid addiction and overdose epidemic. The SOR grant program provides formula funding to states and territories for increasing access to U.S. Food and Drug Administration-approved medications for the treatment of opioid use disorder (OUD) and for supporting prevention, harm reduction, treatment and recovery support services for OUD and other concurrent substance use disorders. It also supports care for stimulant misuse and use disorders, including for cocaine and methamphetamine. According to HHS, the program helps reduce overdose deaths and close the gap in treatment needs across America by giving states and territories flexibility in funding evidence-based practices and supports across different settings to meet local community needs.

"The State Opioid Response grant program delivers crucial aid to states and territories to help address in the crisis of overdose and death in our nation's communities," said HHS Secretary Xavier Becerra. "And, in line with HHS' Overdose Prevention Strategy, this funding helps facilitate state- and territory-level efforts to ensure the full continuum of prevention, harm reduction, treatment and long-term recovery supports are in place and accessible to all who need them."

Overdose deaths have accelerated during the COVID-19 pandemic, with data from the Centers for Disease Control and Prevention estimating that more than 105,000 people died from overdose in the 12 months ending in October 2021, the highest number ever recorded in a 12-month period. In addition to implementing service delivery models that enable the full spectrum of treatment and recovery support services, as well as prevention, education and harm reduction services, states and territories will be asked to develop naloxone distribution and saturation plans that will increase availability and accessibility of this lifesaving overdose-reversal medication.

The SOR grant will fund up to $1,439,500,000 to be awarded in fiscal year 2022 to 59 states and territories. This funding includes a set-aside for the states with the highest OUD-related mortality rates. ❖

Biden Administration Announces $1.5 Billion Funding Opportunity for State Opioid Response Grant Program. U.S. Department of Health and Human Services press release, May 19, 2022. Accessed at www.hhs.gov/about/news/2022/05/19/biden-administration-announces-15-billion-funding-opportunity-state-opioid-response-grant-program.html.

Proposed Payment Systems and Fee Schedules in 2023

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

PROPOSED RULES revising the Medicare Hospital Outpatient Prospective Payment System (OPPS) and the Medicare Ambulatory Surgical Center (ASC) services, along with new physician fee schedule (PFS) rule sets will significantly impact providers in 2023. Understanding new regulations, upgrading reimbursement skill sets and recognizing implications of billing decisions is crucial.

Key Pharmaceutical Focus Areas

Inpatient only (IPO) list. The IPO list delineates the services for which Medicare will pay only when performed in the inpatient setting. The Centers for Medicare and Medicaid Services (CMS) proposes removing 10 services from the IPO list, having determined that the procedures meet the current criteria for removal.

340B program. The proposed OPPS rule offers insight into how CMS may respond to a recent Supreme Court decision on 340B payment cuts and evaluates how to apply this to prior calendar years (2018-2022). CMS anticipates applying a payment rate of average sales price (ASP) +6% to certain drugs purchased through the program.

Nonopioid product payment. Section 6082 of the Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act requires payment review under OPPS/ASC for opioids and evidence-based, nonopioid alternatives for pain management to ensure no financial incentives to use opioids instead of nonopioids were offered. CMS proposes separate or modified payment for nonopioid pain management drugs and/or biologicals functioning as supplies in ASC settings when those products meet certain CMS criteria. Ensuring there are no financial incentives for the use of nonopioid pain management drugs is a key provision. Separate payment outside of the bundled procedure payment is proposed for four nonopioid drugs functioning as surgical supplies. Additional nonopioid products are also being considered.

Pass-through drugs. The concept of a unique payment category for pass-through drugs originated several years ago as prices began to rise for new breakthrough products used primarily in outpatient

2023 Proposed Payment Systems and Fee Schedules in 2023

New drugs not yet assigned unique HCPCS codes	New pass-through drugs	Non pass-through separately payable drugs costing >$135/day based on ASP	Policy packaged or lower-cost packaged products costing ≤$135/day based on ASP
	SI G	SI K	SI N
	On the bill as separate line items	On the bill as separate line items	Not on the bill as separate line items
See Addendum B for specific payment	ASP +6% Policy packaged offsets may apply	ASP +6% if not purchased under the 340B program	No change from 2022
		Payment based on wholesale acquisition cost (WAC) + 3% until enough ASP data is gathered	No separate reimbursement Drug costs are bundled into the procedure
		Formal proposed: ASP -22.5% if 340B purchased (some exceptions apply) WAC-priced drugs: WAC -22.5% Average wholesale price (AWP)-priced drugs: 69.46% of AWP Likely: ASP +6% based on court rulings	Due to threshold price of $135/day or statute Includes: -Diagnostic radiopharmaceuticals -Contrast agents -Anesthesia drugs -Implantable biologicals -Drugs, biologicals or radiopharmaceuticals used as supplies in a diagnostic test or procedure -Drugs, biologicals used as supplies or implantable devices in surgical procedures

settings. Remember that although under PFS, physician offices are paid at ASP +6% by statute. Under OPPS, payments can be variable at ASP plus a defined percentage that may be less than 6 percent.

The Medicare, Medicaid and State Children's Health Insurance Program Balanced Budget Refinement Act of 1999 includes a pass-through payment provision requiring additional payments to hospitals for current orphan drugs; current drugs, biologicals and brachytherapy sources used in cancer therapy; and current radiopharmaceutical drugs and biologicals. "Current" refers to those types of drugs or biologicals categorized above that are hospital outpatient services under Medicare Part B, for which transitional pass-through payment was made on the first date the hospital OPPS was implemented. Transitional pass-through payments also are provided for certain "new" drugs and biologicals not being paid for as a hospital-based outpatient department service as of Dec. 31, 1996, and whose cost is "not insignificant" in relation to OPPS payments for the procedures or services associated with the new drug or biological. For pass-through payment purposes, radiopharmaceuticals are included as "drugs." Products given pass-through status are assigned status indicator G (SI G) to differentiate them from SI K, outpatient products paid for separately, or SI N, products paid for as part of a bundle.

The statute requirement of ASP +6% was lengthened to three years after payment was first made for the product as a hospital outpatient service under Medicare Part B. Quarterly reviews with additions and deletions were implemented as well. During the COVID-19 public health emergency (PHE), several products were given extensions ranging from at least one quarter to several quarters. A table detailing these rules and expiration status is available on the Medicare website (cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Addendum-A-and-Addendum-B-Updates). Refer to Addendum B to determine SI G, SI K or SI N status. Payment amounts will be posted during the first quarter of 2023.

Rural emergency hospitals (REH). CMS will consider all covered outpatient REH services at a higher payment rate than the standard OPPS payment rate, plus 5 percent. In some cases, REHs may provide certain outpatient services beyond those paid under the OPPS and will be paid without an additional 5 percent. Sole rural community hospitals will be exempt from the site-neutral clinic visit cuts and will instead pay for clinic visits furnished in accepted off-campus provider-based departments of these hospitals at the full OPPS rate. REHs receive a monthly facility payment increased annually by the hospital market basket percentage.

Key Physician Focus Areas

Part B drug coverage. In physician office settings, Part B drug coverage remains at ASP +6% by statute. However, a $1.53 decrease in the Medicare PFS conversion factor to $3.08 will lead to significant cuts to physician reimbursement.

Access to care. Other policy changes increase access to care, including behavioral healthcare and accountable care organizations. Certain chronic pain management services are bundled into monthly payments to increase team-based care access with two new payment codes. Opioid treatment and recovery services furnished in mobile units to boost access for homeless and rural populations will be covered. A continued rollout of electronic prescribing of controlled substances under Part D continues with evaluating prescriber compliance and imposing steeper penalties by 2025.

Telehealth. A number of telehealth codes will remain available until 151 days after the end of the COVID-19 PHE. This allows CMS more time to determine whether codes should be made permanent. However, the temporary exception to allow direct supervision virtually for the provision of telehealth services by the clinical staff of physicians and other practitioners, including pharmacists, incident to their own professional services would no longer apply.

Vaccines and antibodies. Regular updates to the payment for preventive vaccines and clarification about payment policies for vaccines and monoclonal antibody products for COVID-19 will remain in effect until the emergency use authorization for drugs and biological products ends, regardless of when the larger COVID-19 PHE ends. Implementing requirements for manufacturers of certain single-dose container or single-use package drugs to provide refunds for discarded amounts applies to waste billing in this setting as well. (See Rules and Regulations Affecting Revenue on page 10 of the Spring 2022 issue of *BioSupply Trends Quarterly*, available at cloud.3dissue.com/2744/3598/8733/BSTQ_2022-04_Online-Issue/index.html.) ❖

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.

Telehealth: From Video Visits to Strategic Business

By Rachel Maier, MS

COVID-19 CATALYZED innovation in healthcare. When social-distancing protocols created an obstacle to providing in-person patient care, telehealth bridged the gap, and virtual video visits went from a rarely used alternative to common standard of care almost overnight. Demand for an interconnected, collaborative model of care that puts patient participation through technology at the forefront of health management is on the rise.

Early Forms of Telehealth

"Tele" simply means "at a distance."[1] People have been innovating ways to communicate vital health information from one geographic location to another for centuries, the earliest forms of which included smoke signals, communication drums and reflective devices — anything that could be used to transmit important information about a health situation.[2]

Today, telehealth involves "the use of telecommunications and information technology to provide access to health assessment, diagnosis, intervention, consultation, supervision and information across distance."[3] In broad terms, telehealth connects patients who need care with providers who deliver it from far away.

Modern Telehealth

Digital tools connected patients with providers long before COVID-19 necessitated virtual visits through online dashboards, email communication and automated prescription refills. These tools gave patients access to providers, as well as their personal health information, which enhanced overall quality of care.

But other forms of telehealth were not yet widely embraced. Asynchronous telehealth, often referred to as "store-and-forward" telehealth, was possible, but restricted. It allowed providers to collect patient data via virtual interviews, as well as compile and share patient information such as MRIs, X-rays and lab work among members of the care team. Evaluation could occur outside of real-time interactions from anywhere.

Further, technology for synchronous, face-to-face virtual video visits also existed before the pandemic, but it was not widely used either. Concerns about access to the technology necessary for video visits, cost for services rendered and quality of care gave patients and providers pause. Video visits were mostly reserved for rural patients without immediate access to healthcare professionals, but even rural usage was low.[4] Reimbursement restrictions and regulatory red tape made it difficult to implement telehealth technologies across the board.

The COVID-19 Catalyst

The COVID-19 public health emergency forced providers to embrace emerging telehealth technologies to stay afloat during an uncertain time. Video visits quickly went from rarely used to heavily relied upon. In addition to triaging suspected cases of SARS-CoV-2 infection, video visits were also used to perform routine primary care visits, monitor chronically ill patients and perform inpatient and outpatient support. Because patients could be "seen" by a medical provider at a distance, video visits protected both patients and providers from possible COVID-19 exposure regardless of the reason patients were seen.

When it became apparent that the situation warranted lifting regulations restricting the use of telehealth services, payers were quick to modify their existing rules to ensure services were available to meet patients' needs.[5] Eliminating restrictions on when and how providers could use telehealth according to Medicare's fee-for-service model made it accessible to a larger population of patients.

Virtual video visits are now widely accepted by patients as part of their providers' standard of care. In fact, more patients accept — and even expect — them now versus even just three years ago.

A study conducted by the National Center for Biotechnology Information assessed patient use of and satisfaction with telehealth services before and during the COVID-19 pandemic and found that both "patients and healthcare providers

have a high level of satisfaction with use of telehealth" and reported willingness to continue using video visits after the pandemic.[6]

Telehealth Tomorrow

The pandemic changed more than healthcare delivery; it also altered the way patients interact with their own health, a change that catalyzed innovation of tools to meet evolving expectations. Going forward, telehealth will be about more than providing virtual urgent care visits to mitigate the spread of COVID-19. It's increasingly about leveraging emerging technologies to improve access to, convenience of and collaboration with healthcare.

- *Access.* Telehealth expands access to specialty care by connecting patients to the healthcare professionals they need, particularly in rural areas where specialists may not be available. It helps offset provider shortages across the country by giving patients another option for receiving care. It also allows providers to consult with other more specialized providers on an as-needed basis.
- *Convenience.* Patients are increasingly behaving like consumers; they want quality service at a price they can afford. Emerging telehealth technologies give patients the power to get the care they need, when and where they need it, at a price they can more easily afford, without the hassle or headache of traditional office visits. Decreased wait time and increased access to specialists located far from home make telehealth desirable. Digital front doors streamline health management, making it easier and more convenient for patients to engage with their care team, schedule appointments, refill medications and more.[7] Decentralization of services allows for in-home data collection: patients to conduct tests from the comfort of their own home.
- *Collaboration.* Telehealth gives stakeholders tools to work together to improve the quality of patient outcomes. Providers are increasingly able to consult with each other across organizations through targeted collaborative agreements.[8] Patients want to play an active role in managing their own health, and telehealth tools are giving them a way to do so.

Moving Toward Mobile Health and Remote Patient Monitoring

Interconnected engagement is at the heart of the future of telehealth, particularly in terms of specialized medicine. Consumer-driven mobile health apps and patient monitoring equipment enable patients and providers to stay in sync as they partner to manage an array of conditions.

Mobile Health, or mHealth, refers to mobile app-based tools that give patients an active role in managing their care while communicating real-time data to healthcare professionals. AndHealth is one such app designed to help patients identify and address the root cause of chronic illnesses. It integrates action plans, behavior trackers, video chats, one-on-one health coaching, lab work and prescription management.[9]

Another example of mHealth is Healthy.io, an app that uses the power of the smartphone camera to increase access to medical testing. Currently used for kidney disease testing, Healthy.io's medical selfie technology shows promise for other chronic conditions as well by providing clinical results at crucial moments. It closes gaps in access and care, while increasing patient satisfaction and reducing costs. Patient data is digitized in a format that can be easily analyzed by artificial intelligence and shared across systems.[10]

Remote patient monitoring (RPM) uses technology to monitor and collect patient health data in real time, outside of a traditional clinical setting. It offers clinicians deeper insight to and tracking of symptoms needed to monitor a patient's condition remotely. One example is a continuous glucose monitor that reminds diabetics to take their insulin, allows clinicians to monitor disease and remotely sends blood pressure and blood oxygen levels. An estimated 70.6 million U.S. patients will use RPM tools by 2025.[11]

Toward a Connected Future

COVID-19 catalyzed development of technologies that are reimagining the way patients and providers communicate, gather and share information and participate in healthcare management. Expectations for convenient, connected care will continue to drive innovation for tools to meet specialized needs, enhance patient experience and improve overall health at lower costs. ❖

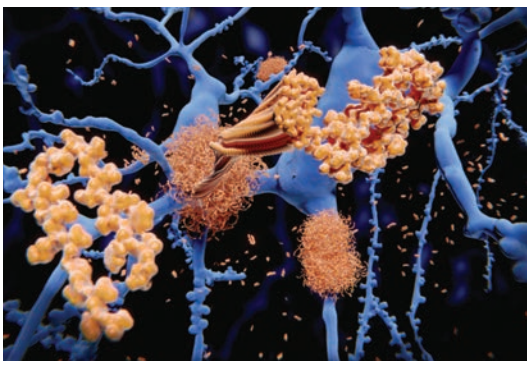
References

1. Merriam-Webster. Tele. Accessed at www.merriam-webster.com/dictionary/tele.
2. Sigmund Software. The History of Telehealth: Telemedicine Through the Years. Accessed at www.sigmundsoftware.com/blog/history-of-telehealth.
3. Medicaid.gov. Telemedicine. Accessed at www.medicaid.gov/medicaid/benefits/telemedicine/index.html.
4. Chu, C, Cram, P, and Sacha Bhatia, R. Rural Telemedicine Use Before and During the COVID-19 Pandemic: Repeated Cross-Sectional Study. *Journal of Medical Internet Resource*, 2021 Apr; 23(4): e269601. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC8023379.
5. HGA. The History of Telehealth, Feb. 8, 2021. Accessed at hga.com/the-history-of-telehealth .
6. Hays, RD, and Skootsky, SA. Patient Experience with In-Person and Telehealth Visits Before and During the COVID-19 Pandemic at a Large Integrated Health System in the United States. *Journal of General Intern Medicine*, Jan. 4, 2022. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC8725638 .
7. Patient Engagement HIT. Top Health IT Components of Medicine's Digital Front Door. Accessed at patientengagementhit.com/features/top-health-it-components-of-medicines-digital-front-door.
8. Howard, R, Leyden, T, and Englesbe, M. How Collaboration Can Drastically Improve U.S. Health Care. *Harvard Business Review*, March 16, 2022. Accessed at hbr.org/2022/03/how-collaboration-can-drastically-improve-u-s-health-care.
9. Allen, L. Matt Scantland Says His AndHealth App Can Reverse Migraine and Other Chronic Illnesses. *Columbus Monthly*, July 18, 2022. Accessed at www.columbusmonthly.com/story/lifestyle/around-town/2022/07/18/matt-scantland-startup-andhealth-targets-chronic-illness/10073758002.
10. Healthy.io. About Us. Accessed at healthy.io/about-us.
11. Dolan, S. The Technology, Devices, and Benefits of Remote Patient Monitoring in the Healthcare Industry. Insider Intelligence, Jan. 15, 2022. Accessed at www.insiderintelligence.com/insights/remote-patient-monitoring-industry-explained.

RACHEL MAIER, MS, is the associate editor of *BioSupply Trends Quarterly* magazine.

Diagnostics

New Test Detects and Measures Biomarkers in Blood Plasma to Earlier Diagnose Alzheimer's



The U.S. Food and Drug Administration has granted breakthrough device designation to Roche's Elecsys Amyloid Plasma Panel, a new solution to enable Alzheimer's disease to be detected earlier. The test detects and measures Alzheimer's disease biomarkers in blood plasma to indicate the need for further confirmatory testing for Alzheimer's disease. Roche is the first in-vitro diagnostics manufacturer to receive this designation for a blood-based biomarker test for Alzheimer's.

Currently, the diagnosis of Alzheimer's disease is largely based on clinical symptoms, including cognitive assessment, with a significant number of patients diagnosed when their disease has already advanced. The Elecsys Amyloid Plasma Panel is the first qualitative test that combines the result of the phosphorylated Tau (pTau) 181 protein assay and apolipoprotein (APOE) E4 assay in human plasma. Elevations in pTau occur in early stages of Alzheimer's, while the presence of APOE E4 constitutes the most common genetic risk factor for Alzheimer's disease. Patients testing negative with the Elecsys Amyloid Plasma Panel are unlikely to be amyloid positive and should be investigated for other causes of cognitive decline.

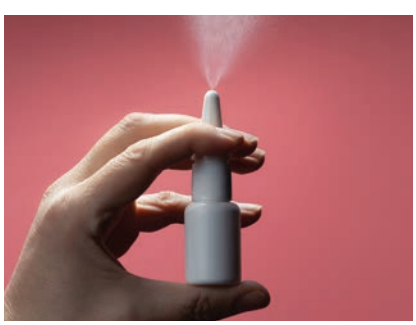
The test has the potential to ensure better identification of patients who require further confirmatory testing, which could be done via PET scan or cerebrospinal fluid (CSF) testing, supporting a more timely and accessible diagnosis. In conjunction with other diagnostic tools and the work Roche is doing in developing potential new treatments, this could be an important building-block toward improved care and outcomes for people with Alzheimer's disease.

Roche has also received a breakthrough device designation for the Elecsys ß-Amyloid (1-42) CSF and Elecsys Phospho-Tau (181P) CSF in vitro diagnostic immunoassays measuring ß-Amyloid (1-42) and Phospho-Tau concentrations in CSF in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease or other causes of dementia. ❖

F. Hoffman-La Roche Ltd. Roche's Elecsys Amyloid Plasma Panel Granted FDA Breakthrough Device Designation to Enable a Timely Diagnosis of Alzheimer's Disease. GlobalNewswire, July 19, 2022. Accessed at www.yahoo.com/now/roches-elecsys-amyloid-plasma-panel-050000470.html.

Research

Intranasal Flu Vaccine Developed with Nanoparticles



Researchers in a study funded by the National Institute of Allergy and Infectious Diseases and the National Institutes of Health have developed an influenza (flu) vaccine administered through the nose that has been constructed with nanoparticles and offers stronger protection. The vaccine, which led to robust cross-protection against flu in mice, consists of PEI-HA/CpG nanoparticles. PEI (polyethyleneimine), a robust and versatile delivery system, can simultaneously carry antigens (hemagglutinin [HA]) that induce an immune response in the body and adjuvants (CpG) that enhance the body's immune response to an antigen for optimum immunoenhancement. According to study results, the immune response and cross-protection exhibited defense against the flu virus more than six months after immunization.

"Our results revealed that the nanoparticles significantly enhanced HA immunogenicity, or the ability to provoke an immune response, providing cross-protection against different influenza strains," said Baozhong Wang, PhD, corresponding author of the study and a professor in the Institute for Biomedical Sciences at Georgia State University.

"Nanoparticle platforms have shown intriguing characteristics and great potential in the development of next-generation cross-protective influenza vaccines," adds Chunhong Dong, MD, PhD, the first author of the study and a postdoctoral fellow in the Institute for Biomedical Sciences. "However, challenges exist to the successful research and development of nanoparticle vaccines. Though no apparent adverse effects were observed in the study, a more comprehensive safety evaluation of the nanoparticle adjuvant system is needed before clinical trials." ❖

Study Develops Intranasal Flu Vaccine with Nano-Particles That Provides Robust Protection. ANI, Jan. 30, 2022. Accessed at www.aninews.in/news/science/study-develops-intranasal-flu-vaccine-with-nano-particles-that-provides-robust-protection20220130113220.

Research

New Program Launched to Identify Autoimmune Disease Therapies

A cross-disciplinary coalition of experts from academic centers across the United States is partnering with the National Institutes of Health (NIH), the U.S. Food and Drug Administration, pharmaceutical companies and nonprofit organizations to identify new targets for therapies for autoimmune-meditated diseases. The program, the Accelerating Medicine Partnership Autoimmune and Immune-Mediated Diseases (AMP AIM), launched in December 2021, is sponsored by NIH and supported by $58 million in public and private funding. The purpose of the initiative, according to NIH, is to "deepen our understanding of the cellular and molecular interactions that lead to inflammation and autoimmune disease."

AMP AIM is an expansion of a program launched in 2014 that focused on cellular and molecular pathways in rheumatoid arthritis (RA) and systemic lupus erythematosus. The expanded program will investigate psoriasis, psoriatic arthritis and Sjögren's syndrome, in addition to RA and lupus. ❖

Hurt, A. NIH Expands Autoimmune Research Program to Include More Rheumatic Diseases. Practical Pain Management, April 14, 2022. Accessed at www.practicalpainmanagement.com/news/nih-expands-autoimmune-research-program-to-include-more-rheumatic-diseases.

Medicines

FDA Approves New Gene Therapy Treatment for Rare Blood Disorder

The U.S. Food and Drug Administration (FDA) has given fast track approval through a pediatric disease voucher for Bluebird Bio's Zynteglo, a treatment designed to tackle the rare condition known as transfusion-dependent beta-thalassemia (TDBT), a blood disorder that reduces hemoglobin and red blood cell counts in the bloodstream, leading to reduced oxygen delivery. Each dose is tailored to an individual's genetic profile for maximum effectiveness.

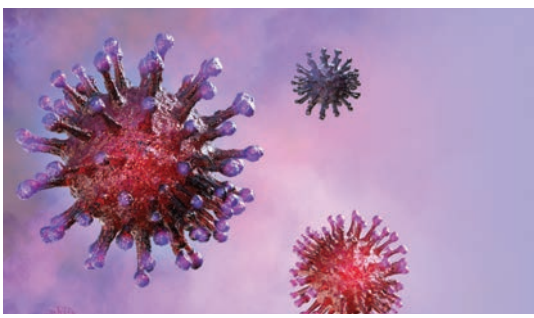
TDBT is an inherited disease that significantly lowers life expectancy, with the average U.S. patient suffering from the condition dying at age 37. Bluebird estimates between 1,300 and 1,500 people in the U.S. suffer from the disease. Transfusion-dependent patients have to undergo red blood cell transfusions as frequently as every two weeks. According to Bluebird, clinical trials of Zynteglo resulted in 89 percent of patients achieving "transfusion independence," defined as not needing a transfusion for at least 12 months.

But the price of Zynteglo, the most expensive drug in U.S. history, is $2.8 million. According to Bluebird, the price is a deal, since "the lifetime cost of medical care for a patient with transfusion-dependent beta-thalassemia can reach up to $6.4 million." ❖

$2.8m Gene Therapy Treatment Is America's Most Expensive Drug Ever. MSN, Aug. 19, 2022. Accessed at www.msn.com/en-us/health/medical/dollar28m-gene-therapy-treatment-is-americas-most-expensive-drug-ever/ar-AA10OQmw?li=BBnb7Kz.

Research

Flu Vaccines Poor Match to Influenza Strains This Season



According to the Centers for Disease Control and Prevention (CDC), this season's influenza (flu) vaccines offered meager protection against mild cases of influenza. Against the most common flu strain circulating this season, the flu vaccines reduced a person's chance of getting a mild case by 16 percent, which is "considered not statistically significant," although the vaccines should offer some protection against more severe illness. Put more bluntly, the flu vaccine was "essentially ineffective," said William Schaffner, MD, an infectious diseases expert at the Vanderbilt University Medical Center.

Research from earlier in the flu season found the vaccine was a poor match for the H3N2 strain of the virus, which CDC confirmed is the dominant strain detected this season. That flu strain, experts say, is particularly troublesome since it tends to mutate faster than other variants of influenza and traditionally leads to more hospitalizations and deaths.

These findings come amid the nation's second flu season in a row with low flu activity overall. Flu cases did start to rise in the fall, sparking fears of a "twindemic" of COVID-19 and the flu, but cases never took off like they do in typical flu seasons. ❖

Lovelace, B. This Season's Flu Vaccine Was a Poor Match for the Virus, CDC Reports. NBC News, March 10, 2022. Accessed at www.nbcnews.com/health/health-news/seasons-flu-vaccine-was-poor-match-virus-cdc-reports-rcna19485.

Research

First Human Clinical Trial of Cancer Killing Virus Has Begun

Researchers at California's City of Hope National Medical Center have begun the first clinical trials of a virus that kills cancer cells. The CF33-hNIS virus (referred to as Vaxinia) is an oncolytic virus, a genetically-engineered variety that habitually targets cancer cells while ignoring healthy cells. Vaxinia also works overtime by delivering specially-engineered white blood cells, known as CAR-T cells, to solid tumors. While CAR-T cells are vital to helping the body's immune system recognize cancer cells as a threat, solid tumors possess immunosuppressive microenvironments that act as barriers, preventing the CAR-T cells from entering and doing their job. By infecting solid tumors, Vaxinia can deliver the CAR-T cells to this environment and help the immune system tackle cancer the way it's supposed to — all while proactively killing off cancer cells along the way.

City of Hope has been working with biotechnology company Imugene Limited to develop Vaxinia since late 2020. The two organizations previously tested Vaxinia in mice, and the first human trial began in April and will last through the end of 2024.

In the Phase I trial, 100 participants will receive Vaxinia on the first and eighth days of the first portion of the trial, some of whom will receive it intravenously, while the rest will receive direct tumor injections. Additionally, some participants will undergo combined treatment using the drug pembrolizumab, which has historically been used to treat specific types of cancers. The trial is designed to help calibrate the ideal dosage for adult patients and determine whether Vaxinia is safe for human use. If the trial is successful, Vaxinia could be studied in larger participant groups — and even everyday healthcare settings — in the future. ❖

Nine, A. First Human Trial of Experimental Cancer-Killing Virus Underway. ExtremeTech, May 20, 2022. Accessed at www.extremetech.com/extreme/335945-first-human-trial-of-experimental-cancer-killing-virus-underway.

Research

NIH Launches Study to Evaluate Three mRNA Vaccines for HIV

The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), has launched a Phase I clinical trial evaluating three experimental HIV vaccines based on a messenger RNA (mRNA) platform — a technology used in several approved COVID-19 vaccines. NIAID is sponsoring the study, called HVTN 302, conducted by the NIAID-funded HIV Vaccine Trials Network (HVTN) based at Fred Hutchinson Cancer Research Center in Seattle.

The HVTN 302 study will examine whether the following three experimental HIV mRNA vaccines are safe and can induce an immune response: 1) BG505 MD39.3 mRNA, 2) BG505 MD39.3 gp151 mRNA and 3) BG505 MD39.3 gp151 CD4KO mRNA. Each investigational vaccine candidate is designed to present the spike protein found on the surface of HIV that facilitates entry into human cells. Each of the experimental vaccines encodes for different but highly related, stabilized proteins. None of the three vaccine candidates can cause HIV infection.

Led by principal investigators Jesse Clark, MD, of the University of California Los Angeles, and Sharon Riddler, MD, of the University of Pittsburgh, the HVTN 302 study will enroll up to 108 adults ages 18 years to 55 years at 11 sites in Birmingham, Ala., Boston, Los Angeles, New York City, Philadelphia, Pittsburgh, Rochester, N.Y., and Seattle. Each participant will be randomly assigned to one of six groups each receiving three vaccinations of one of the experimental vaccines. The first three groups (18 participants each), called Group A, will receive intramuscular injections of 100 micrograms (mcg) of their assigned vaccine candidate at the initial visit, at month two and again at month six. Participants in Group A will be evaluated two weeks after initial vaccination to ensure safety criteria have been met. If so, the remaining three groups of 18 participants each (Group B) will be vaccinated with 250 mcg of the assigned investigational vaccine, followed by injections two months and six months after the initial vaccination.

Safety and immune responses will be examined via blood and lymph node fine-needle aspiration samples taken at specified timepoints throughout the trial. Clinical staff will closely monitor participant safety throughout the study. The clinical trial is expected to be completed by July 2023.

More information about the HVTN 302 study is available on ClinicalTrials.gov using the identifier NCT05217641. ❖

NIH Launches Clinical Trial of Three mRNA HIV Vaccines. National Institutes of Health press release, March 14, 2022. Accessed at www.nih.gov/news-events/news-releases/nih-launches-clinical-trial-three-mrna-hiv-vaccines.

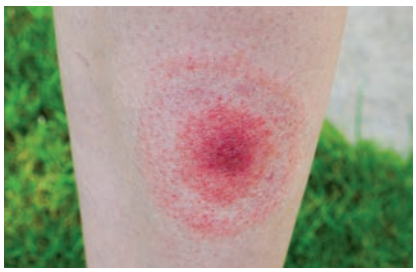
Research

Lyme Disease Vaccine Advances to Phase III Study

New data from a Phase II clinical trial of Valneva SE and Pfizer Inc.'s Lyme disease vaccine candidate, VLA15, shows it produced strong immune responses, prompting preparations for a Phase III study in the third quarter of 2022. In the trial, VLA15-221 produced stronger responses in adult participants between ages 18 years and 65 years after three priming doses compared to two priming doses. As a result, three-dose priming will be used for adults in the Phase III trial.

"Lyme disease is increasingly impacting people throughout the northern hemisphere, potentially due to environmental changes and more active outdoor lifestyles," said Kathrin Jansen, PhD, senior vice president and head of vaccine research and development at Pfizer. "The continued positive data from the VLA15-221 trial support the ongoing development of this vaccine candidate, and we look forward to continuing to work with Valneva to potentially help protect people against Lyme disease."

VLA15, currently the only Lyme disease vaccine candidate in clinical development, targets the outer surface protein A of Borrelia



burgdorferi, the bacteria that causes Lyme disease. Its data from the Phase II study supports strong immunogenicity and safety data already demonstrated in previous preclinical and clinical studies. Operating with fast track designation from the U.S. Food and Drug Administration, it has thus far shown an acceptable safety and tolerability profile in adults.

According to Valneva and Pfizer, a separate pediatric study should produce its initial data later this year. That trial is studying the safety and immunogenicity of VLA15 on patients between 5 years and 17 years of age. ❖

Valneva, GC. Pfizer Lyme Disease Vaccine Candidate to Enter Phase 3 Testing Following Positive Immune Showings. *Homeland Preparedness News,* Feb. 8, 2022. Accessed at homelandprepnews.com/stories/75852-valneva-pfizer-lyme-disease-vaccine-candidate-to-enter-phase-3-testing-following-positive-immune-showings.

Research

IVIG May Reverse Symptoms of Down Syndrome Regression Disorder

A new study shows treatment with intravenous immune globulin (IVIG) shows promise for children and young adults with Down syndrome regression disorder (DSRD), a condition in which functioning children and young adults with Down syndrome cease to eat, talk, exercise and perform normal daily functions such as getting dressed and going to the bathroom. According to Children's Hospital Los Angeles (CHLA) Director of Neuroimmunology Jonathan Santoro, MD, IVIG has not been used for DSRD in the past; however, IVIG in combination with psychotropic medication showed promising results in 80 percent of approximately 120 patients in the CHLA program, which is the largest of its kind in the country.

Dr. Santoro is the lead for a multicenter study on IVIG use in this patient population, which is expected to go to clinical trial in 2022, pending approval by the National Institutes of Health. ❖

IVIG Shows Potential to Reverse Symptoms of Down Syndrome Regression Disorder. *Pharmacy Times*, April 15, 2022. Accessed at www.pharmacytimes.com/view/ivig-shows-potential-to-reverse-symptoms-of-down-syndrome-regression-disorder.

Research

Combination COVID-19 and Influenza Vaccine Under Development

With predictions that COVID-19 boosters will be needed each year, some companies are working on combining those with the annual influenza (flu) vaccine in a single injection given each fall. Pharmaceutical companies Moderna and Novavax have already announced plans to work on a combination vaccine, but Moderna's CEO says it will not be ready until 2023.

However, there are technical challenges to creating a combination vaccine. One is that different scientific approaches have been used for the two types of vaccines. "Right now, the influenza vaccine is a different platform," said Anna Durbin, MD, director of the Center for Immunization Research at Johns Hopkins University. The most widely used flu vaccines in the U.S. contain inactivated (killed) or attenuated (weakened) virus to trigger an immune response in the body, which differ from mRNA (messenger RNA) vaccines that teach the body's cells how to make proteins that trigger immune responses.

In addition to differences in technology, another challenge is that the most common influenza vaccine in the U.S. is quadrivalent, meaning it is designed to protect against four different flu viruses. "This means the combined influenza/COVID vaccine would also likely need to be quadrivalent or at least trivalent. That makes the vaccine more complicated," said Dr. Durbin.

Similarly, the rise of new COVID variants may introduce challenges to vaccine development. ❖

Aboubakr, A. Scientists Are Working on Combo Flu and COVID-19 Shot, But Don't Expect One This Fall. ABC News, Feb. 26, 2022. Accessed at abcnews.go.com/Health/scientists-working-combo-flu-covid-19-shot-expect/story?id=83117084.

Research

NIAID Launches Study of Vaccine to Prevent EBV

The National Institute of Allergy and Infectious Diseases (NIAID) has launched an early-stage clinical trial to evaluate an investigational preventive vaccine for Epstein-Barr virus (EBV), the primary cause of infectious mononucleosis associated with certain cancers and autoimmune diseases. The Phase I study, which will be conducted at the National Institutes of Health Clinical Center in Bethesda, Md., is one of only two studies to test an investigational EBV vaccine in more than a decade.

Led by principal investigator Jessica Durkee-Shock, MD, of NIAID's Laboratory of Infectious Diseases, the study will evaluate the safety and immune response of an investigational EBV gp350-Ferritin nanoparticle vaccine with a saponin-based Matrix-M adjuvant. The experimental vaccine was developed by the Laboratory of Infectious Diseases in collaboration with NIAID's Vaccine Research Center. The Matrix-M adjuvant was developed by the biotechnology company Novavax, based in Gaithersburg, Md.

The vaccine works by targeting EBV glycoprotein gp350, which is found on the surface of the virus and virus-infected cells. EBV gp350 is also the primary target for neutralizing antibodies found in the blood of people naturally infected with EBV. Ferritin, a natural iron storage protein found in cells of all living species, is considered a promising vaccine platform because it can display proteins from the targeted virus in a dense array on its surface. The adjuvant is intended to enhance the immune response induced by the investigational vaccine.

The study will enroll 40 healthy volunteer adults ages 18 years to 29 years, half of whom have evidence of prior EBV infection and half of whom do not have evidence of prior EBV infection. Participants will be given a series of three 50-microgram injections of the experimental vaccine in the upper arm muscle, followed by 30 minutes to 60 minutes of observation after each dose. The second and third doses will be administered 30 days and 180 days after the initial dose, with follow-up visits between each vaccination and phone calls between visits. Participation is expected to be required for 18 months to 30 months, and the trial is expected to last four years. More information about the study is available on ClinicalTrials.gov using the identifier NCT04645147. ❖

NIH Launches Clinical Study to Evaluate an Investigational Preventative Vaccine for Epstein-Barr Virus. News Medical Life Sciences, May 6, 2022. Accessed at www.news-medical.net/news/20220506/NIH-launches-clinical-study-to-evaluate-an-investigational-preventative-vaccine-for-Epstein-Barr-virus.aspx.

Most Trusted

In Specialty Distribution *Since 1988*

At FFF Enterprises, we know that at the end of every transaction, there's a patient waiting for that product. That's why you can count on us to supply your patients with safe, reliable medications at the best prices available.

(800) 843-7477 | FFFENTERPRISES.COM

FFF enterprises
Helping Healthcare Care®

Pros and Cons of Virtual Care Solutions

Do the advantages of virtual care outweigh the drawbacks? Patients seem to think so.

By Meredith Whitmore

AS NEW HEALTH dangers and dilemmas emerge seemingly every year — if not every week — the healthcare industry continues to adapt to meet evolving demands via virtual care. Exploding in popularity out of necessity during the worst of the COVID-19 pandemic, virtual care bridged the gap between in-person office visits and restrictions prohibiting them. Fears of spreading and/or catching the SARS-CoV-2 virus during in-person medical visits led to a greater interest in and use of technology to provide and receive healthcare.[1]

In 2020 alone, video visits skyrocketed to 40,000 per day, which is 27 times as many as in 2019.[2] While that number has come down since offices have reopened, 76 percent of hospitals in the United States still use telehealth today, up from 35 percent a decade ago.[1] One in four Americans over age 50 said they'd had a virtual care visit during the first three months of the pandemic, up from just four percent of older adults who'd had a remote visit the previous year, and almost three-quarters of Americans surveyed said the pandemic made them more eager to try virtual care.[1]

Though various forms of virtual care have been in existence for some time, the pandemic normalized them. The process continues to be honed, and virtual visits can now be made as easily and frequently as most traditional office visits. In fact, at-home virtual visits were so convenient for patients during 2020, thanks to the decreased travel time, ease of availability, privacy of one's own home and lowered risk of possible exposure to disease, that virtual visits are here to stay. Patients and providers both now even expect it as standard practice.

Defining Virtual Care

But what is virtual care, exactly? It might seem like defining it should be easy, but the answer isn't exactly straightforward.

First, "virtual care" is an umbrella term that refers to all the ways patients and healthcare providers deliver care digitally. Second, while "telehealth" and "telemedicine" fall under the umbrella of virtual care, they are not synonymous terms. Telemedicine refers to the *practice* of medicine at a distance through the use of technology, including video visits to support diagnosis, treatment and prevention; post-op follow-up visits via text messaging, phone calls or video visits; and remote monitoring of patient conditions.[3] Telemedicine achieves everything a patient would accomplish during an in-person visit with a provider.[4] Telehealth refers to the *provision*

of medical services, both clinical and nonclinical, at a distance through the use of telecommunications technology. These technologies include the online platforms and digital tools themselves that facilitate care management, enable patient-provider communication, provide medical training and offer continuing medical education.[1,4]

The format of virtual visits bears little difference from traditional visits. The only major difference is location. Patients and providers discuss the same things they would during face-to-face encounters, but simply do so through a different medium, with vitals taken via mobile apps or digital devices and instructions offered through a screen. These media include video visits, phone appointments, email, virtual front doors, wellness apps, remote patient monitoring and online chat services for clinical advice. All forms of virtual care can be administered via a HIPAA-compliant program such as Zoom, Doxy.me or Microsoft Teams.

No matter how these resources are categorized, listed or distributed, healthcare professionals need to know what they are, how to use them and the pros and cons for both patients and providers.

Pros and Cons of Virtual Care

Virtual care offers many benefits, but there are some downsides to consider, too.

Convenience. Patients can access healthcare via a smart phone, tablet, desktop computer or laptop according to their own timetable. While not all conditions can be treated virtually, many can be addressed and monitored through mobile apps and take-home devices such as EKGs, remote blood pressure monitors, blood glucose monitors and other digital devices that make telemedicine feasible. These sophisticated devices save patients the stress of taking time off work, commuting and potential exposure to disease. In fact, nine out of 10 patients say they would cancel an appointment because of workplace stress or lack of sick time.[5] However, not every type of appointment can be conducted remotely. Patients and providers will always need to meet face-to-face for certain types of hands-on assessments such as reducing fractures or suturing skin lacerations; imaging and blood work must also currently be done on site. Still, in-person visits can be a waste of time and resources, making virtual care a more efficient mode of treatment.[6]

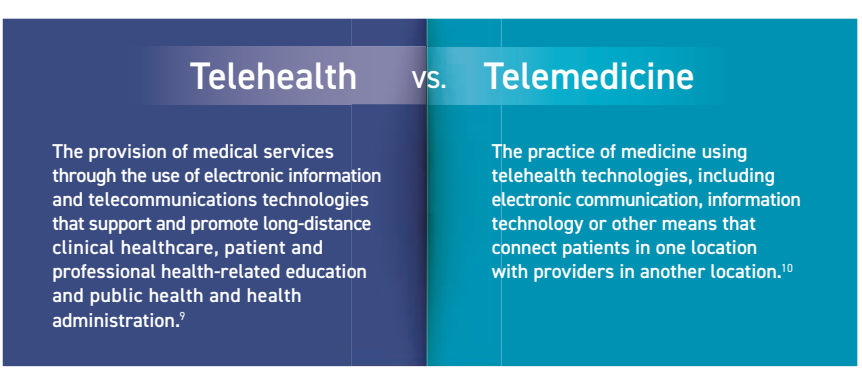
Context. Virtual visits give providers a window into a patient's home environment, which may help providers better understand patients' unique situations and implement an improved care plan. For example, during a video visit, an allergist might see triggers such as plants, pets and/or foods in a patient's home environment that could be causing symptoms; neurologists or physical and occupational therapists might see how well patients are able to navigate their homes by identifying stairs, ergonomic issues and fall risks; and psychiatrists might identify stressors in the home.[7] Visual clues provide context for patients' reported symptoms that providers wouldn't otherwise obtain.

Streamlined care management. Virtual care improves access to and interaction with patient information, which benefits patients and providers alike. Digital tools allow the care team to share and access patient information among themselves, improving communication among primary care providers (PCPs), specialists, nurses, pharmacists and anyone involved in the treatment plan. This includes test results, exam notes, email messages, text reminders and prescription information. By streamlining care management, healthcare providers have greater flexibility, all while lowering costs.[8] Also, virtual care gives providers the means to monitor patients who need more support, which helps give patients an active role in their own healthcare management, too. However, the security of electronic health records (EHR) is of concern since data breeches are possible.

Access. With virtual care, providers are accessible to rural patients who experience a dearth of healthcare resources. Statistics say there are fewer than 40 doctors for every 100,000 people in rural areas, whereas there are approximately 53 physicians per 100,000 people in urban areas. In rural areas, virtual care provides convenient, crucial access to providers that patients wouldn't otherwise have.

Beyond PCPs, virtual care also increases access to specialists who may be even further out of reach — not just for patients in rural areas, but even for those who live in small cities or suburbs. Virtual visits are usually available at a lower cost (just $40 or $50 per visit), which makes medical care more affordable.[6]

Provider burnout. Virtual care also helps combat clinician burnout. It increases schedule flexibility and allows providers to consult with each other more quickly



Virtual Care Pros and Cons

Pros	Cons
Increased access to providers	Concerns about privacy and cybersecurity
Cost-effective	Potential technical problems
Reduces spread of illness	Inability to conduct hands-on examinations
Flexible and time-saving	Increased and ongoing training needed
Convenient	Questions about regulation
Reduces cancellations/no-shows	Start-up costs for providers
Mitigates provider burnout	

regarding crucial situations such as life-and-death decisions. This can lead to timelier and more effective patient care. In addition, virtual care can cut the number of patient no-shows, which saves providers tremendous amounts of time and money.[6]

Cost. The United States spends more than $2.9 trillion on healthcare every year, more than any other developed nation. On top of that, an estimated $200 billion of those costs are avoidable, unnecessary spending. Virtual care has the power to cut healthcare spending by reducing problems such as medication nonadherence, unnecessary emergency department visits and time-consuming in-office visits.[6] While some virtual care services are not covered by insurance, telemedicine visits often cost less than in-office visits.

Naturally, every virtual care advantage has a drawback, and both patients and providers have their own perspectives regarding them.

Patient and Provider Preferences

So, who prefers virtual care: patients or providers? The answer isn't clear-cut.

According to a 2021 RAND Corp. survey, of the 2,080 adult patients surveyed, 66.5 percent indicated they were willing to have at least some video visits in the future. Fifty-three percent of that number preferred in-person visits; nearly 21 percent preferred video visits; and about 26 percent didn't have a preference or didn't know.[9] Forty-five percent of patients surveyed reported having had one or more video visits since March 2020. Of that number, approximately 31 percent preferred video visits, while nearly 44 percent still preferred in-person encounters. Only about two percent said they didn't want any more video visits in the future.[9]

While patients are at least somewhat willing to use video visits, providers aren't as eager. Even though patients prefer on-site visits, demand for virtual care continues to grow. Implementing telemedicine services increased provider workload, and they are struggling to keep up. The survey revealed only 45 percent of providers have been able to invest in telehealth technologies so far, and just 16 percent have invested in other digital tools. In addition, only 41 percent of providers believe that they can seamlessly integrate virtual care into their existing workflow because it often requires them to use disparate systems that do not integrate perfectly with EHRs, and other crucial technological errors often occur, including loss of audiovisuals during synchronous remote appointments.[2]

Further, providers are noticing that their relationships with patients are changing. Fifty-eight percent of providers surveyed reported they lost patients to other physicians or health systems since the beginning of the pandemic, possibly because patient-provider rapport is affected by screens or the fact that telehealth makes health data easier for patients to obtain, making it easier for them to switch healthcare providers.[2]

Perhaps not surprisingly, while two-thirds of providers and 60 percent of patients agreed that virtual health is more convenient than in-person care for patients, only 36 percent of providers find it more convenient.[2] Patients and providers clearly see the advantages and disadvantages to virtual care very differently.

Takeaways

Virtual care is almost certainly going to continue to grow and will likely become increasingly normalized as its technologies are fine-tuned and easier to use. While on-site visits will likely be preferred by patients and providers, both can also appreciate the convenience of virtual care while enduring the drawbacks that are inevitably present. Therefore, providers are wise to arm themselves with training and expertise, along with a warm onscreen manner, to be ready and willing to offer quality virtual care. ❖

References

1. Watson, S. Telehealth: The Advantages and Disadvantages. Harvard Women's Health. Oct. 12, 2020. Accessed at www.health.harvard.edu/staying-healthy/telehealth-the-advantages-and-disadvantages.
2. Cordina, J, Fowkes, J, Malani, R, and Medford-Davis, L. Patients Love Telehealth — Physicians Are Not So Sure. McKinsey and Company, Feb. 22, 2022. Accessed at www.mckinsey.com/industries/healthcare-systems-and-services/our-insights/patients-love-telehealth-physicians-are-not-so-sure.
3. Centers for Disease Control and Prevention. Telehealth and Telemedicine: A Research Anthology of Law and Policy Resources. Accessed at www.cdc.gov/phlp/publications/topic/anthologies/anthologies-telehealth.html#:~:text=Telemedicine%20is%20defined%20by%20the,provider.%E2%80%9D4%20The%20World%20Health.
4. Tiger Connect. Telehealth and Telemedicine Overview: What's the Difference? Jan. 3, 2020. Accessed at tigerconnect.com/blog/telehealth-vs-telemedicine-whats-difference.
5. Lee, E. How COVID-19 Accelerated the Push Toward Telehealth, July 28, 2020. Accessed at business.kaiserpermanente.org/insights/telehealth/covid-19-accelerated-telehealth.
6. Godman, H. Need an Appointment Right Away? Consider a Virtual Doctor Visit, Sept. 16, 2016. Accessed at www.health.harvard.edu/blog/need-an-appointment-pronto-consider-a-virtual-doctors-visit-2016091610206.
7. Care Innovations. Is Virtual Care Better? Accessed at news.careinnovations.com/blog/how-virtual-care-benefits-patients-clinicians-healthcare-organizations.
8. Hasselfeld, B. Hopkins Benefits of Virtual Medicine. Accessed at www.hopkinsmedicine.org/health/treatment-tests-and-therapies/benefits-of-telemedicine.
9. Terry, K. Majority of Patients Prefer In-Person Visits to Telehealth: Survey, Dec. 1, 2021. Accessed at www.webmd.com/lung/news/20211201/in-person-visits-vs-telehealth-survey.
10. U.S. Department of Health and Human Services. What Is Telehealth? Accessed at www.hhs.gov/hipaa/for-professionals/faq/3015/what-is-telehealth/index.html#:~:text=The%20Health%20Resources%20and%20Services,professional%20health%2Drelated%20education%2C%20and.

MEREDITH WHITMORE is a freelance writer and clinical mental health professional based in the Pacific Northwest.

BREAKTHROUGHS IN GENE THERAPY

Exciting new developments in gene therapy and genome editing show promise for treating a variety of genetic diseases.

By Diane L.M. Cook

RECENT BREAKTHROUGHS in gene therapy and genome editing are giving researchers and patients hope that cures are on the horizon for many genetic diseases, including blindness, blood and immune disorders and sickle cell disease.

According to the Alliance for Regenerative Medicine's (ARM) 2021 annual report, clinical advancements included the first proof of concept for an in vivo gene editing therapy, evidence that chimeric antigen receptor T-cell (CAR-T) therapies compare favorably with earlier-line treatments, and compelling early results that cell and gene therapies can treat complex, polygenic diseases. Results even suggest these therapies may be able to reverse damage that has already occurred.

Gene therapy continues to hold great promise for treating rare diseases with high unmet medical needs.

ARM's report notes that 2021 was the second best year for new product approvals, with six new regenerative medicines approved globally, and the best year for CAR-T products, with three new approvals. Nearly 60 percent of the 2,400 ongoing regenerative medicine trials at the end of 2021 targeted prevalent diseases. Further, gene editing continues to advance as a therapeutic modality. Forty-one trials in gene editing were ongoing at the end of 2021, about one-third of which were in the Phase I stage, with the remainder in the Phase II stage. The vast majority of these trials (80 percent) use clustered regularly interspaced short palindromic repeats (CRISPR), demonstrating the strong foothold this technology has established since the initiation of the first CRISPR gene editing trial in 2019.[1]

CRISPR is a customizable gene-editing tool that lets scientists cut and insert small pieces of DNA at precise areas along a DNA strand. An RNA-based system that can be easily modified to target multiple sites, it works by using a Cas9 enzyme to cut a DNA sequence at a specific genetic location, then deleting or inserting DNA sequences, which can change a single base pair of DNA, large pieces of chromosomes or regulation of gene expression levels.[2] This process is referred to as CRISPR/Cas9.

The results of recent clinical trials and the anticipated results of upcoming trials in regenerative medicine have shown or are expected to show positive results. Following is a look at the most promising breakthroughs for some of the most prevalent genetic diseases.

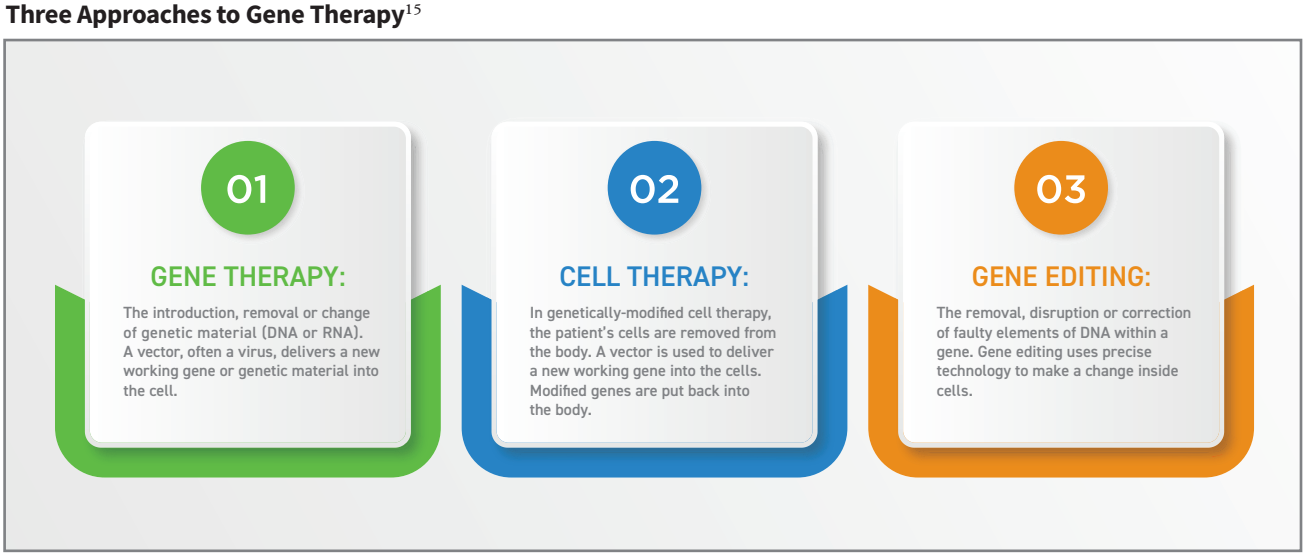
Blindness

The National Eye Institute (NEI), part of the National Institutes of Health, supports basic, translational and clinical research globally to help find therapies for blinding diseases such as genetic forms of retinal neurodegeneration that are largely untreatable today.

Loss of neurons in the retina constitutes the major cause of inherited blindness worldwide. To date, more than 250 genes have been identified as disease-causing for inherited retinal diseases (IRD), and most of these diseases are targets of gene replacement or gene-based therapies.

NEI-funded research has established that adeno-associated virus (AAV) vectors are among the most efficient gene delivery tools for modifying the function in retinal cells. A major breakthrough occurred a few years ago when several scientists used an AAV vector to deliver the RPE65 gene in retinal pigment epithelium cells of patients with a form of childhood blindness called leber congenital amaurosis (LCA). This treatment has now been approved by the U.S. Food and Drug Administration (FDA) and is available for patients. Gene therapy clinical trials using

Three Approaches to Gene Therapy[15]



AAV vectors are now being conducted for treatment of several IRDs and have shown promising results in patients.

In addition to funding extramural research in the United States and other countries, NEI has an intramural research program (IRP) located in Bethesda, Md., where several laboratories are involved in finding mechanisms of retinal diseases and developing treatments based on stem cells, small molecule drugs and knowledge of the gene defects. For example, the Neurobiology, Neurodegeneration & Repair Laboratory (NNRL), a division of the NEI-IRP, is working to understand biological pathways that lead to many different types of inherited blindness to design new treatments for several forms of IRDs.[2]

The NNRL and NEI's Gene Therapy Core scientists have collaborated on several projects, including preclinical gene replacement therapy for X-linked retinitis pigmentosa, in which long-term efficacy and preliminary safety studies of gene replacement therapy in Rpgr and Rp2 gene knock-out mouse models have paved the way for further clinical development.

For mechanism-based gene therapy for LCA due to CEP290 mutations, NEI is currently seeking mechanism-based gene therapy for the disease based on the existing knowledge of CEP290 protein structure and its interactome. Since CEP290 is a large gene for AAV delivery, NNRL scientists have been exploring the use of minigene and small molecule drugs for treatment of this devastating form of LCA. More recently, NNRL scientists have used retinas generated in a dish from patient stem cells to develop gene therapy for another autosomal dominant form of LCA caused by CRX mutations. Similar work is in progress for LCA caused by mutations in the NPHP5 gene.

Previously, NEI scientists had developed gene replacement therapy protocols for X-linked juvenile retinoschisis (XL-RS) by helping to design and develop the human retinoschisin AAV vector, which is currently being tested in Phase I clinical trials of XL-RS.[3]

For CRISPR/Cas9 mediated genome editing in postmitotic retinal neurons, NEI's initial effort will be focused on gene disruption mediated by nonhomologous end joining. This may lead to novel therapies for retinal degeneration caused by gain-of-function or dominant mutations.

CRISPR Gene Editing Market Growth Projection in the United States[15]

Global CRISPR gene editing market was valued at

$1.09 billion in 2021

Overall growth is projected to reach

$14.8 billion by 2030

(29.8% CAGR growth)

NEI is also supporting multiple basic and clinical research studies in IRDs. For example, researchers funded by NEI preserved vision in dogs with a disease similar to retinitis pigmentosa in humans using gene therapy for a blinding condition called autosomal dominant retinitis pigmentosa caused by a mutation in visual pigment rhodopsin. The researchers generated a gene therapy construct that knocks down the rod cells' ability to produce rhodopsin using a technology known as short-hairpin RNA (shRNA) interference. In dogs' retinas, the construct knocked down approximately 98 to 99 percent of rhodopsin (both mutated and normal). But because normal rhodopsin is required for the rods to detect light, the researchers added a "hardened" shRNA-resistant rhodopsin gene to the same vector. When treated with the combined vector, the dogs maintained healthy, functional photoreceptors, and because the vector was designed to produce human rhodopsin, it could potentially work in humans as well.[4]

In 2017, FDA approved Luxturna (voretigene neparvovec-rzyl), a new gene therapy to treat children and adult patients with an inherited form of vision loss that may result in blindness. Luxturna is the first directly administered gene therapy approved in the United States that targets confirmed biallelic RPE65 mutation-associated retinal dystrophy caused by mutations in a specific gene that leads to vision loss and may cause complete blindness in certain patients. It works by delivering a normal copy of the RPE65 gene directly to retinal cells, which then produce the normal protein that converts light to an electrical signal in the retina to restore patients' vision loss. Luxturna uses a naturally occurring AAV, which has been modified using recombinant DNA techniques, as a vehicle to deliver the normal human RPE65 gene to the retinal cells to restore vision.[5]

Blood and Immune Disorders

The California Institute for Regenerative Medicine (CIRM) has funded 76 clinical trials for gene-modified cell therapies with more than 3,200 patients enrolled, helping to cure more than 40 children of fatal immunological disorders. Highlights from three of these trials include:

X-linked severe combined immunodeficiency (XL-SCID). Also known as the "bubble boy" disease, XL-SCID is a rare immune disorder that is often fatal within two years of birth. In 2017, researchers took blood stem cells from a child, genetically reengineered them to correct the defective gene and then infused the reengineered cells back into the child. Over time, the cells multiplied and created a new blood supply free of the

How CRISPR/Cas9 Gene Editing Works

1) RNA identifies a specific portion of DNA
2) Cas9 enzyme cuts double-stranded DNA
3) Targeted piece of DNA is removed
4) New, reengineered sections of DNA are inserted
5) Reengineered genes are automatically incorporated when cells repair broken DNA
6) Disease is controlled going forward

How CAR-T Cell Therapy Works[17]

1) Apheresis: T cells are isolated and collected from the body
2) Reprogramming: T cells are sent to a lab where they are genetically modified with chimeric antigen receptors that recognize and kill diseased cells
3) Multiplication: Modified cells are multiplied until there are millions of new disease-attacking cells
4) Infusion: Modified cells are infused through an IV back into the patient's blood
5) Cell death: CAR-T cells track down and kill diseased cells

defect, which helped repair the immune system.[6] CIRM Director of Patient Advocacy Kevin McCormack says, "The child in this clinical trial is now almost 5 years old and is doing extremely well with no indication of any recurrence and is considered functionally cured because there have been no setbacks and his immune system appears to be functioning normally."

McCormack says approximately 50 more children have been treated with this same approach in a clinical trial that CIRM funded with Don Kohn, MD, of the University of California, Los Angeles. Last year, Dr. Kohn published a paper in the *New England Journal of Medicine* reporting that 95 percent of those children are now considered cured.

X-linked chronic granulomatous disease (XL-CGD). XL-CGD is a condition that affects the immune system's ability to fight off common germs, specifically bacteria and fungi, and can result in infections that would otherwise be mild in healthy people. In 2017, a patient received an infusion of his own blood stem cells that had been genetically modified to correct the X-CGD mutation.[7] "Five years posttreatment, this patient appears to be doing extremely well with no indication of any recurrence. He is considered functionally cured because there have been no setbacks, and his immune system appears to be functioning normally," says McCormack.

Cystinosis. Cystinosis is a rare, multisystem genetic disorder characterized by the accumulation of an amino acid called cystine in different body tissues and organs, including the kidneys, eyes, muscles, liver, pancreas and brain. It is caused by mutations of the cystinosin, lysosomal cystine transporter (CTNS) gene and is inherited as an autosomal recessive disease. This disease is classified as a lysosomal storage disorder.[8]

The Cystinosis Research Foundation (CRF) explains that the mutation in the CTNS gene is on the 17th chromosome that encodes a protein called cystinosin. This protein's function is to transport an amino acid called cystine out of an intracellular compartment called the lysosome. If the cystinosin protein is absent or dysfunctional, cystine accumulates within the lysosome and forms crystals, which kills the cells. Cystinosis slowly destroys organs of the body mentioned previously.[9]

According to CNF research, gene therapy for cystinosis has shown promising results in mice. In 2018, FDA approved a Phase I/II clinical trial for six adult patients to evaluate gene-corrected autologous stem cell transplant as a treatment. The first adult patient received the transplant in October 2019, the second and third patients were transplanted in 2020, the fourth patient was transplanted in November 2021 and the fifth patient received the transplant on March 29, 2022. All five patients are doing well and remain off oral cysteamine medication since their transplants. The sixth and final patient is expected to be transplanted by the end of 2022.

In the October 2019 transplant, the adult patient received an infusion of his own blood stem cells with a functional version of the defective CTNS gene, which reduced cystine buildup in affected tissues. The patient's gene-modified stem cells are expected to embed themselves in his bone marrow, where they should divide and differentiate into all types of blood cells. Those cells are then expected to circulate throughout his body and embed in his tissues and organs, where they should produce the normal cystinosin protein.[10] "The patient is showing signs of a strong response to the gene-modified hematopoietic stem cell gene therapy and is no longer taking the medication he used to rely on to keep him alive," says McCormack. "He has drastically cut his medications from 54 pills per day to around 20, and each year he is able to reduce those even more. The patient is not cured, but he is now able to do things that he was not able to do before and is able to imagine a normal life."

Sickle Cell Disease

In 2014, a team of scientists from the University of California, Los Angeles, the University of California, Berkeley and the University of California, San Francisco (UCSF) collaborated with Benioff Children's Hospital in Oakland on the first clinical trial to use CRISPR-based therapy on a patient's own blood stem cells to correct the mutated gene that causes sickle cell disease (SCD). The experimental four-step therapy involves collecting a patient's blood stem cells; using a brief electrical current to introduce CRISPR/Cas9 enzymes to the extracted stem cells along with a template for correcting the sickle mutation; using chemotherapy to make space in the bone marrow for the edited stem cells; and reintroducing the patient's own edited cells. This gene editing protocol is expected to correct the sickle mutation in approximately 30 percent of engrafting cells.[11]

A Phase I/II clinical trial will evaluate the transplantation of CRISPR/Cas9 corrected hematopoietic stem cells (CRISPR_SCD001) in nine patients between the ages of 12 years and 35 years old with severe SCD. The trial is expected to start on Dec. 1, 2022, with an estimated primary completion date of Dec. 1, 2024, and an estimated study completion date of Dec. 1, 2027. The primary endpoint of the trial will determine the safety of CRISPR_SCD001 through a 3+3 design with staggered enrollment and a pause in enrollment for a safety review after each of the first three patients is infused with the drug product. "After safety is assessed in the third patient, enrollment of the next three patients will not be staggered," say the researchers. "The first six subjects will be adults. If CRISPR_SCD001 is determined to be safe in the first six subjects, the trial will continue to enroll three adolescents between 12 years and 18 years of age to evaluate the safety in younger patients. The younger cohort also will follow staggered enrollment."[12]

This is the first time clinical researchers have attempted to correct a harmful beta-globin gene mutation in a patient's own cells with nonvirally delivered CRISPR gene-correction tools, according to Mark Walters, MD, a professor of pediatrics at UCSF and principal investigator of the clinical trial and gene editing project. "This therapy has the potential to transform sickle cell disease care by producing an accessible, curative treatment that is safer than the current therapy of stem cell transplant from a healthy bone marrow donor," says Dr. Walters. "If this is successfully applied in young patients, it has the potential to prevent irreversible complications of the disease."[13]

An Exciting Outlook

According to ARM, cell and gene therapy continues to hold great promise for treating rare diseases with high unmet medical needs. It believes 2022 is likely to be a record year for the approval of new gene therapies to treat rare diseases, with a total of four possible approvals in the United States and Europe. (Note: Since publication of ARM's 2021 annual report, one of the possible approvals was pushed back to 2023.) Two therapies to treat SCD could be available in the United States as soon as 2023 — a gene therapy and a first-ever CRISPR therapy.

"From the approval of CAR-T therapies treating blood cancers to gene therapies treating rare genetic diseases, 2022 is proving to be a strong year for the cell and gene therapy sector," says Stephen Majors, ARM director of public affairs. "And the strength of the late-stage pipeline bodes well for the next few years, with a variety of therapeutic approaches advancing to treat both rare and prevalent diseases." ❖

References

1. Alliance for Regenerative Medicine. Regenerative Medicine: Disrupting the Status Quo 2021. Accessed at alliancerm.org/wp-content/uploads/2022/03/ARM_AR2021_FINAL-singles.pdf.
2. National Institutes of Health. Gene Editing: Digital Media Kit. Accessed at www.nih.gov/news-events/gene-editing-digital-press-kit.
3. National Eye Institute. Neurobiology Neurodegeneration & Repair Laboratory, Nov. 29, 2021. Accessed at www.nei.nih.gov/research/research-labs-and-branches/neurobiology-neurodegeneration-repair-laboratory.
4. National Eye Institute. Ocular Gene Therapy Core, July 19, 2019. Accessed at www.nei.nih.gov/research/research-labs-and-branches/ocular-gene-therapy-core.
5. National Eye Institute. Researchers Find Potential New Gene Therapy for Blinding Disease, Aug. 20, 2018. Accessed at www.nei.nih.gov/about/news-and-events/news/researchers-find-potential-new-gene-therapy-blinding-disease.
6. FDA Approves Novel Gene Therapy to Treat Patients with a Rare Form of Inherited Vision Loss. U.S. Food and Drug Administration press release, Dec. 18, 2017. Accessed at www.fda.gov/news-events/press-announcements/fda-approves-novel-gene-therapy-treat-patients-rare-form-inherited-vision-loss.
7. Cortez, E. CIRM-Funded Stem Cell Clinical Trial Patients: Where Are They Now? California Institute for Regenerative Medicine, Jan. 19, 2022. Accessed at blog.cirm.ca.gov/tag/ronnie-kashyap.
8. Villa, Y. First Patient in CIRM Funded X-CGD Trial Gives Back by Working in Patient Care. California Institute for Regenerative Medicine, Oct. 7, 2020. Accessed at blog.cirm.ca.gov/2020/10/07/first-patient-in-cirm-funded-x-cgd-trial-gives-back-by-working-in-patient-care.
9. National Organization for Rare Disorders. Rare Disease Database — Cystinosis. Accessed at rarediseases.org/rare-diseases/cystinosis.
10. Cystinosis Research Foundation. What Is Cystinosis? Accessed at www.cystinosisresearch.org/what-is-cystinosis.
11. Villa, Y. CIRM-Funded Treatment for Cystinosis Receives Orphan Drug Designation. California Institute for Regenerative Medicine, March 10, 2020. Accessed at blog.cirm.ca.gov/2020/03/10/cirm-funded-treatment-for-cystinosis-receives-orphan-drug-designation.
12. Innovative Genomics Initiative. IGI Sickle Cell Initiatives: The IGI Is Working to Bring CRISPR-Based SCD Therapies to the World and Make Them Accessible. Accessed at innovativegenomics.org/sickle-cell-disease-crispr.
13. National Institutes of Health. U.S. National Library of Medicine. Transplantation of Clustered Regularly Interspaced Short Palindromic Repeats Modified Hematopoietic Progenitor Stem Cells (CRISPR_SCD001) in Patients with Severe Sickle Cell Disease, April 27, 2022. Accessed at clinicaltrials.gov/ct2/show/NCT04774536.
14. University of California, San Francisco, Benioff Children's Hospital. Sickle Cell Clinical Trial Aims to Cure Disease by Correcting Patient's Mutated Gene, Dec. 1, 2021. Accessed at www.ucsf.edu/news/2021/12/421901/sickle-cell-clinical-trial-aims-cure-disease-correcting-patients-mutated-gene#:~:text=Sickle%20Cell%20Clinical%20Trial%20Aims%20to%20Cure%20Disease%20by%20Correcting%20Patient's%20Mutated%20Gene,-UCSF%20Benioff%20Children's&text=UCSF%20Benioff%20Children's%20Hospital%20Oakland,to%20cure%20sickle%20cell%20disease.
15. American Society of Gene and Cell Therapy. Different Approaches, Nov. 5, 2021. Accessed at patienteducation.asgct.org/gene-therapy-101/different-approaches.
16. Straits Research. CRISPR Gene Editing Market Size Is Projected to Reach 14.80 Billion by 2030, Growing at a CAGR of 29.8%: Straits Research, Aug. 1, 2022. Accessed at www.globenewswire.com/news-release/2022/08/01/2489715/0/en/CRISPR-Gene-Editing-Market-Size-is-projected-to-reach-USD-14-80-Billion-by-2030-growing-at-a-CAGR-of-29-80-Straits-Research.html.
17. National Cancer Institute. CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers, March 10, 2022. Accessed at www.cancer.gov/about-cancer/treatment/research/car-t-cells.

DIANE L.M. COOK, B. Comm., is a Canadian freelance magazine writer with more than 330 articles published in several trade journals, including *Oilweek*, *Oilsands Review*, *Alberta Construction Magazine* and *Canadian Lawyer*.

Improving Patient Adherence Through Smart Packaging

Innovative drug packaging offers solutions to help patients who are struggling to take the right medication at the right time.

By Amy Scanlin, MS

AS MEDICATION adherence increasingly plays a major role in chronic disease management and increasing rates of drug resistance, the advent of smart packaging is a welcome addition to the pharmaceutical industry. Indeed, 25 percent of medications are never filled and another 20 percent are improperly taken, prompting the World Health Organization (WHO) to call the endemic of poor medication adherence a "worldwide problem of striking magnitude."[1]

Medication nonadherence poses significant challenges to understanding and tracking patient outcomes. The data necessary for making meaningful decisions are left incomplete: Providers are hampered in their ability to elicit the root cause of patients' complaints and must guess how self-reported medication adherence is helping or hurting patients' conditions. In fact, patients put themselves at a significant risk of adverse outcomes from nonadherence, whether they take medications in an incorrect amount or order, at an incorrect time or skip doses altogether. And, their perception about the value of prescribed drugs may be reduced because they don't fully experience the potential of the drugs' positive effects.

But barriers to adherence are multifaceted. Memory, lack of understanding of drug purpose or dosing, cost and other factors contribute to nonadherence. For instance, nonadherence can be either unintentional (when patients don't remember to take prescribed drugs or don't understand how to take them) or

intentional (when patients purposefully choose to take medications incorrectly or not at all). Regardless of the reason, these barriers are major roadblocks to improved health outcomes. While there isn't any one answer, smart packaging is a step in the right direction.

The Problem of Nonadherence

By some estimates, only 50 percent of medications are taken as prescribed. In a study aimed at understanding nonadherence, approximately 50 percent of all clinical trial participants admit to not following prescribed dosing regimens. And, 30 percent of those are noncompliant in just 100 days. The same study showed nonadherence costs the healthcare industry upwards of $100 billion annually — and that's just in the U.S. alone. In 2018, worldwide costs due to pharmaceutical nonadherence were estimated at $564 billion. It is thought that improving adherence rates — even by just 10 percent — could increase pharmaceutical revenues by $41 billion in the U.S. and $124 billion globally, not to mention improving mortality rates and health outcomes.[2]

Packaging Interventions — The Early Years

Packaging interventions have long been considered useful and, indeed, they have helped patients take medications as directed. Historically, blister packs listing days of the week have helped patients identify whether they have already taken the pill inside. Pill boxes prefilled by either patients or caregivers do the same thing and are particularly helpful when multiple medications are taken at once. Yet, although beneficial to a degree, these early interventions are limited in their effectiveness. Accuracy of medication monitoring is estimated to be just 70 percent when drug level markers are used, 60 percent when monitoring pill counts and 27 percent when relying on patient self-reporting.

Smart and Intuitive Packaging

Technology is bringing the next generation of packaging to the forefront. Electronic monitoring with time and day stamps, reminders to patients when medication is scheduled to be taken, and two-way communication between providers and patients all make improved medication adherence possible — and effective — to the tune of 87 percent when smart packaging is enabled. Smart packaging can even help monitor how medication has been stored such as confirming appropriate temperatures and alerting about degradation.

While certainly more costly than traditional packaging, these technologically advanced packages can provide numerous

benefits over traditional methods of monitoring for patients, their caregivers and the healthcare industry as a whole. Patient protocols and outcomes are more readily accessed using real-time data that is passively and seamlessly communicated to a cloud portal via Bluetooth and the Internet. From there, providers can use algorithms to get an accurate picture of how treatment is working, confirming whether it is even being used and, if so, how. That data gives a picture of any "drug holidays" and changes in dosage times or amounts, and it can determine whether the changes appear to be a one-off or part of a trend. The data also provides a starting point for discussions surrounding the treatment itself, an opportunity for further education and, when adherence is a challenge, plan revisions (if possible) to make course of treatment more suitable for patients.

It should be noted that in some surveys, the cost of smart packaging is a deterrent, particularly when it's not covered by insurance.[3] However, given the high cost of healthcare, particularly related to nonadherence, the benefits of smart packaging have the potential to offset expenditures.

New Technologies: Out of the Box

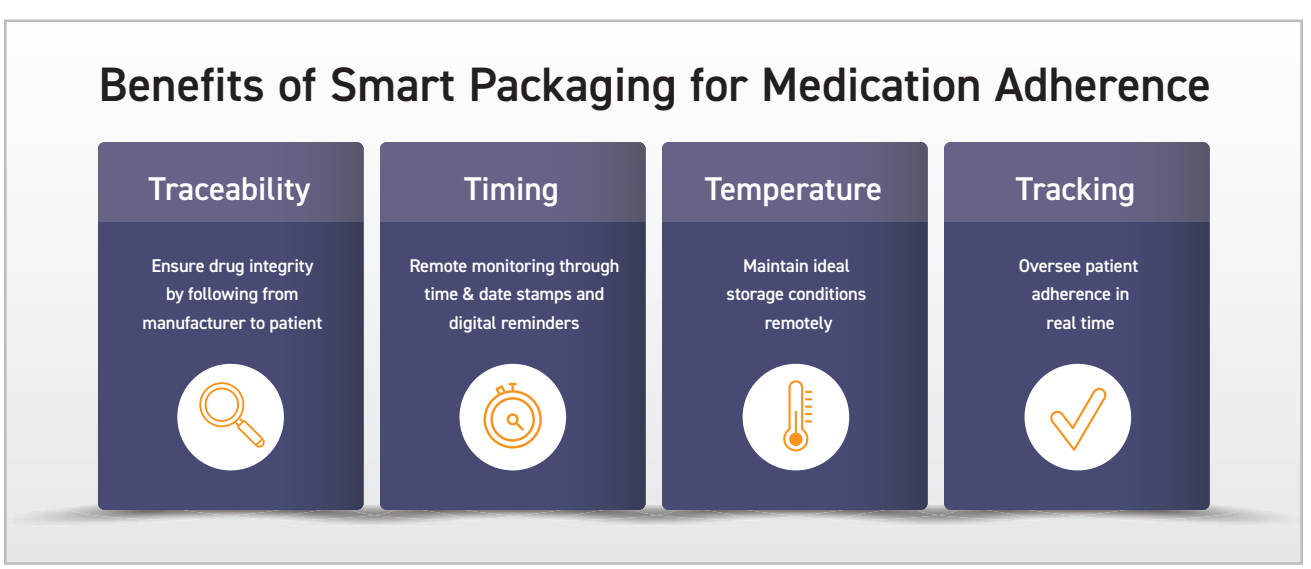
Medication adherence is a "modifiable risk factor," making smart packaging a potential game-changer in the efforts to increase patient adherence. Radio frequency identification systems (RFID), smart blister packs, smart inhalers and injectable pens, bar code-enabled drug systems and more are currently used to help improve medication adherence. Importantly, the U.S. Food and Drug Administration (FDA) confirmed the efficacy of these technologies.[4]

RFID. RFID tags are already widely used in hospital settings to confirm patient identity, deliver care instructions, track treatment and more. This technology, when used in smart packaging, also assists with pharmaceutical behavioral adherence. It sends reminders to patients to take their medications and includes dosing and product handling instructions that are easily scanned by compatible readers on smart phones or other connected devices. These tags can also be used in conjunction with facial recognition software to prevent misuse. Smart bandages with embedded RFID technology are similarly being used to monitor wound healing and deliver appropriate drug delivery.

All that is required for an RFID-enabled device is a microchip or transponder, an antennae and linkage to a software database. Then, data can be transmitted passively between the chip and monitoring device into a database where algorithms analyze medication use and outcomes from up to 1,000 meters away.[5]

An added benefit to RFID technology is the reduction of risk in the use of counterfeit drugs. Traceability throughout manufacturing, packaging and distribution can all be tracked. In combination with near field communication (NFC), the data are stored invisibly on the product and/or package, and codes can be scanned at any point during the process, including before secondary packaging. The same technology also enables faster and more coordinated recalls in the event of quality issues.[6]

Smart blister packaging. Smart blister packs enable monitoring through integrated circuits embedded in blister pack foil. Once the foil is broken, a time and day stamp is communicated via NFC-enabled smart phone applications to the cloud where, as with RFID, data



are collected, stored and analyzed by algorithms for providers' use.

As an added bonus for patients, smart blister packs also track whether they have ever been perforated. Reminders can be sent to patients, alerting them that it is time take a pill or that they are about to take a duplicate dose. Still another kind of blister pack blocks the ability to mix medications, helping patients keep their drug plans separate and straight.

What's more, this smart technology can be integrated into existing package designs so the patient notices little if any difference.

Smart inhalers and injectables. Inhalers with electronic monitoring capabilities have been available for more than 30 years, although it is only in the last 10 years that widespread use has come to the forefront thanks to advances in associated electronic technologies. Offering real-time reminders, smart inhalers release proper dosage amounts and communicate status to patients' providers. They also communicate the effectiveness of the users' technique through measurement of respiratory flow rate.[7]

Likewise, smart injectable pens also make self-administration of medicines more convenient. Smart pens can benefit diabetics, for instance, by calculating the appropriate insulin dosage based on patients' current blood sugar levels, activity level, carbohydrate consumption and other inputs. They can deliver accurate half-unit doses and alert patients to expired drugs or temperature fluctuations that render medications potentially unsafe.

Bar code-enabled dosage forms. Using a handheld device, patients can monitor intake of medications embedded with an FDA-approved edible bar code. Edible bar codes verify tablet or capsule authenticity and provide any related information from the package insert.

In solid dosage forms, the smart bar code is applied via an excipient either to an existing film coating or as an immediate-release outer coating. In capsule form, it is mixed into inks and directly applied to the outer coating. In addition to real-time monitoring of patient adherence and two-way communication between providers and patients, bar code-enabled dosage forms offer immediate and accurate adverse events reporting.

Medication adherence is a "modifiable risk factor," making smart packaging a potential game-changer in the efforts to increase patient adherence.

Security and Safety Concerns

Patients may have privacy concerns when smart packaging is introduced. While smart packaging poses the same inherent security risks as other wireless devices, great strides have been made to provide multi-layer security features such as user authentication that protects patient input and output. "Always on" connectivity, including Bluetooth, is required to communicate among many smart devices. In the event that wireless communications go down, a seamless switch to data communication must be made for continuity of monitoring and patient safety.

Health Outcome Goals and Medication Adherence

Employment of smart technologies offers a renewed opportunity for discussion between patients and providers to ensure medication goals are clearly articulated, understood and agreed upon. Think of medication adherence as a service enabling the entire care team to work together with the benefit of technology to determine reasons for medication nonadherence and to develop supportive solutions as needed. However, while smart packaging can make positive gains in medication adherence, the technology may go underutilized without patient buy-in.

As technological advances continue, the capabilities and usage of smart packaging will continue to grow with it, improving health outcomes and quality of life and reducing healthcare costs. Use of smart packaging in combination with a dedicated healthcare team can deliver a comprehensive solution to the costly problem of medication nonadherence. ❖

References

1. Conn, VS, Ruppar, TM, Chan, KC, et al. Packaging Interventions to Increase Medication Adherence: Systematic Review and Meta-Analysis. *Current Medical Research and Opinion*, Nov. 4, 2014. Accessed at www.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&retmode=ref&cmd=prlinks&id=25333709.
2. Vrijens, B. Smart Packaging in Clinical Trials: The Missing Piece in the Medication Adherence Puzzle. The Aardex Group, Feb. 14, 2022. Accessed at www.aardexgroup.com/2022/02/14/smart-packaging-the-missing-piece-in-the-medication-adherence-puzzle.
3. Smart Packaging Could Improve How Older Adults Take Medication. University of Waterloo, Canada press release, Feb. 24, 2022. Accessed at www.uwaterloo.ca/news/media/smart-packaging-could-improve-how-older-adults-take.
4. U.S. Food and Drug Administration. Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products. Guidance for Industry, March 2019. Accessed at www.fda.gov/media/121320/download.
5. Pal, P, Sambhakar, S, Dave, V, et al. A Review on Emerging Smart Technological Innovations in Healthcare Sector for Increasing Patient's Medication Adherence. *Global Health Journal*, December 2021. Accessed at www.doi.org/10.1016/j.glohj.2021.11.006.
6. Forcinio, H. Intelligent Packaging Promotes Interaction with Patients. Pharmaceutical Technology, June 1, 2020. Accessed at www.pharmtech.com/view/intelligent-packaging-promotes-interaction-patients.
7. Zabczyk, C, and Blakley, JD. The Effect of Connected "Smart" Inhalers on Medication Adherence. *Frontiers of Medical Technology*, Aug. 18, 2021. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC8757760.

AMY SCANLIN, MS, is a freelance writer and editor specializing in medical and fitness topics.

Addressing the Healthcare Diversity Gap

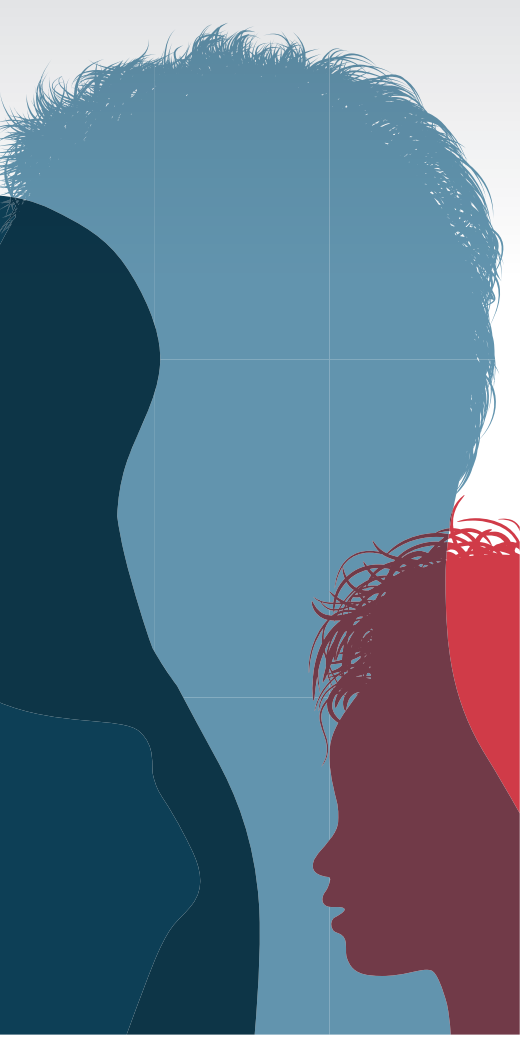
Diversity, equity and inclusion have been a recent focus for businesses and organizations across the world, but perhaps none stand to make a greater impact than the healthcare industry, where it directly affects individual health outcomes and quality of life.

By Trudie Mitschang

HEALTHCARE ORGANIZATIONS have a growing responsibility to improve diversity, equity and inclusion (DEI) efforts not only for their employees, but also to better serve the patients and families within their communities. While diversity is broadly defined as the inclusion of varied attributes or characteristics, within the medical community, diversity often refers to the inclusion of healthcare professionals, trainees, educators, researchers and patients of varied race, ethnicity, gender, disability, social class, socioeconomic status, sexual orientation, gender identity, primary spoken language and geographic region. As in other sectors, the root issues surrounding DEI in healthcare are multilayered and complex, and there is no one solution to the myriad challenges ahead for organizations hoping to grow and evolve.

Understanding the Demographics

According to the Association of Medical Colleges, only about 36 percent of active physicians are female; 5 percent of physicians identify as Black or African-American (despite making up 13 percent of the U.S. population) and fewer than 6 percent of physicians identify as Hispanic (even though Hispanics make up about 19 percent of the U.S. population). When



contrasting that with the fact that 28 percent of physicians and surgeons in the U.S. are immigrants, with doctors from India and China making up the largest groups, the key takeaway is that those from minority groups who have been historically oppressed in the U.S. have less representation in healthcare professions than immigrants of color.[1]

While discrimination, limited job offers and uneven promotion opportunities continue to be among the factors holding back DEI efforts in healthcare, four studies published within the first months of 2022 shed new light on some of the other leading factors. The first is a lack of diversity in academics. While the number of women represented in healthcare education has increased significantly over the past few years, the presence of Black men in the field has decreased dramatically, according to a finding from a recent study published in *The New England Journal of Medicine*.[2] "Even with advances, we are nowhere near representative parity," says Sophia Kamran, MD, a professor of medicine at Harvard Medical School.

To conduct her study, Dr. Kamran analyzed the gender, race and ethnicity of faculty at the nation's leading medical schools between 1977 and 2019. In an interview with the *Harvard Gazette*, Dr. Kamran noted that the findings from her study show the continued need for medical schools and medical programs to increase efforts to recruit underrepresented populations into the field and to help those students develop not just into doctors and researchers but also into academic leaders.[3] "This is an area in desperate need of study because we need to reverse these trends in order to address the lack of Black leadership at all levels of academic medicine," Dr. Kamran said. "I didn't have many mentors, teachers or role models in clinical medicine from a similar background as mine to help guide me. The U.S. population is going to continue getting more diverse as time goes on. We're sounding the alarm because we are clearly falling behind."

DEI Issues in Academic Research

Studies show that white men still tend to hold a majority of teaching roles in healthcare academics, and according to a study published in the *Journal of Racial and Ethnic Health Disparities*, many lead authors of medical studies published in two leading medical journals (*Journal of the American Medical Association* and *The New England Journal of Medicine*) were white men.[4]

The study also found that less than 7 percent of the primary authors leading the research in these premier medical journals were Black and less than 4 percent were Hispanic. It's important to note that this was the first study to provide concrete numbers for true representation among senior or primary authors on studies — the role normally filled by the person who serves as the figurehead for the research and who will benefit from it most in terms of publicity, academic tenure and leading industry job offers.

Assessing the Cost of Healthcare Education

The cost of healthcare education is another significant factor when it comes to racial inequities. According to a study published in *JAMA Network Open*, most students enrolling in medical schools, regardless of race, come from affluent backgrounds.[5] The study analyzed data from nearly 45,000 students who had recently enrolled in medical school and delved into the ethnicity of those

While the number of women represented in healthcare education has increased significantly over the past few years, the presence of Black men in the field has decreased dramatically, according to a finding from a recent study published in *The New England Journal of Medicine*.

candidates and the amount of money each student reported their parents earned annually. The findings show most of these students came from the nation's top 5 percent of wealthiest families.

When you consider that the Association of American Medical Colleges estimates that four years of medical school can cost between $250,000 and $330,000, it's easy to see how these types of wealth disparities can impact not just where these doctors choose to practice and in what they choose to specialize, but also the very way in which they interact with and relate to their patients.

In the effort to address the inequities in healthcare, community health workers have emerged as key players.

To begin addressing this issue, medical schools will need to consider outreach efforts in lower-income communities of color while also offering more scholarship programs to offset the prohibitive cost of a medical education.

Imbalances in Clinical Trials

Although not directly related to the gender, race or ethnicity of medical providers, clinical trials that are used to help observe risk factors for illness and are essential in the development of everything from pharmaceuticals to vaccines have also been a pain point when it comes to diversity and representation. Despite ongoing efforts at inclusion, people of color and ethnic populations are still poorly represented in these efforts, even though they are at a disproportionate risk for certain diseases. This disparity reduces the amount of data available and can limit physicians' knowledge of how to best treat diverse populations.

To address these concerns, the U.S. Food and Drug Administration (FDA) recently issued new guidelines that include increased public outreach campaigns, educational materials and new collaborations and partnerships — all designed to help enroll diverse populations within future studies, which could increase clinical trial diversity and broaden the type and amount of information healthcare providers will have for treating diverse populations. "The U.S. population has become increasingly diverse, and ensuring meaningful representation of racial and ethnic minorities in clinical trials for regulated medical products is fundamental to public health," said FDA Commissioner Robert M. Califf in a news release announcing the change in guidelines. "Going forward, achieving greater diversity will be a key focus throughout the FDA to facilitate the development of better treatments and better ways to fight diseases that often disproportionately impact diverse communities."[7]

Counting the Human Cost of Healthcare Inequity

People from underrepresented communities also face challenges in receiving equitable healthcare, often when it is needed most. The COVID-19 pandemic spotlighted these existing healthcare issues by disproportionally impacting communities of color. Pacific Islander, Latino, Indigenous and Black Americans all have a COVID-19 death rate of double or more than that of white and Asian Americans. And, these statistics create an urgent call to action for health administrators to prioritize cultural competency. "Our nation's health disparities increasingly fall along economic and racial lines," says Kysha Harriell, PhD, LAT, ATC, who co-teaches the Cultural Competence in Healthcare course at the University of St. Augustine for Health Sciences.[1] Dr. Harriell defines cultural competence in healthcare as "a set of behaviors, knowledge and skills that help administrators and practitioners respond to cultural issues relating to patients." She explains that "These skills will help create culturally competent administrators who are skilled at collaborating with a diverse team of colleagues and ensuring respectful and equal treatment of all patients."

A Look at Real World Examples

For many, the concept of healthcare inequity can still feel ambiguous until looking at actual case studies. Consider the case of Lamar Johnson, a 33-year-old African American patient deemed a "frequent flyer" (a term used to describe those who keep coming to the hospital for the same reason, often assumed to be drug seekers) by the nurses and doctors in the emergency department. Each time he came in complaining of extreme headaches, he was given pain medication and sent home. On his last admission, he was admitted to the ICU, where Courtney, a nurse, had just begun working. When she heard him described as a frequent flyer, she asked another nurse why he was thought to be a drug seeker. "He has nothing else better to do; I'm not sure why he thinks we can supply his drug habits," she was told. Although Courtney says her instincts told her something else was going on, she saw his

tattoos, observed his rough demeanor and went along with what everyone else was saying. While she was wheeling him to get a CT scan, Johnson herniated and died. It turned out that he had a rare form of meningitis. If the staff had not stereotyped him as a drug seeker, perhaps his life could have been saved.[9]

Also consider the case of Hilda Gomez, a Spanish-speaking patient who came into a clinic three days in a row to complain of abdominal pain. The first two times, the staff used her young, bilingual daughter to translate and treated her for the stomach ache she described. The staff didn't understand why she kept returning with the same problem until on her third visit, the nurse located a Spanish-speaking interpreter. It turned out that Gomez needed treatment for a sexually transmitted disease, but was too embarrassed to talk about her sexual activity with her daughter as interpreter.[9]

These cases help illustrate how much additional training is needed to address healthcare and nonhealthcare policies that have a disproportionate impact on the health of diverse communities. "When staff are in situations with people from different cultural backgrounds, they need to have the awareness and tools to respond and provide respectful, competent care," says Dr. Harriell.[1]

The Role of Community Health Partnerships

When it comes to building healthcare policies and processes, industry and organizational leaders are encouraged to put on what Julie Smithwick, the director for the Center for Community Health Alignment, calls health equity glasses. "It's like going to a 3D movie, and you have to proactively put on the glasses in order for the picture on the screen to come in with full effect," she explained. "When designing health systems and processes, leaders need their health equity glasses to see the full effect of how that policy will play out and affect traditionally marginalized communities."[10]

In the effort to address the inequities in healthcare, community health workers have emerged as key players. These nonclinical professionals are responsible for supporting patients, addressing patients' social needs and driving care coordination. By employing layperson community health workers for these duties, healthcare organizations can utilize their resources more efficiently while still ensuring patients receive comprehensive care. According to Anthony Davis, a veteran and community health worker at the Crescenz VA Medical Center, using his own experiences helps him relate to patients and support their individual needs.[11] "We do things that doctors, nurses and social workers don't," Davis said. "I noticed a lot of my patients had post traumatic stress disorder and were socially isolated. I took my time with them and got them to come out each week to social activities like movies or bowling. We even planted an urban garden. After these efforts, you can see the difference in their health."

Experts agree it is those shared experiences that make community health workers so successful. Separate research published by *JAMA Oncology* showed that nonclinical healthcare professionals are essential for filling in care gaps and can expand care to patients who otherwise would go without: "Unlike physicians and nursing staff, [community workers] are not limited by the traditional model of clinic-based care. They engage patients during clinical encounters with healthcare professionals and between appointments through frequent telephone communication."[12]

As healthcare continues to zero in on DEI issues, it's clear individuals and organizations will need to embrace those so-called "health equity glasses" and pursue a collaborative approach to achieve meaningful change. "We're only used to using the lenses that we're given, and we're not able to use an equity lens until we really understand it," Smithwick concluded. "In order to understand it, we have to partner with people who have been there, who have lived it and who have really delved into this stuff. You can find folks who are willing to partner with you in that way and help you see it through a different lens, and that's a really big step."[10] ❖

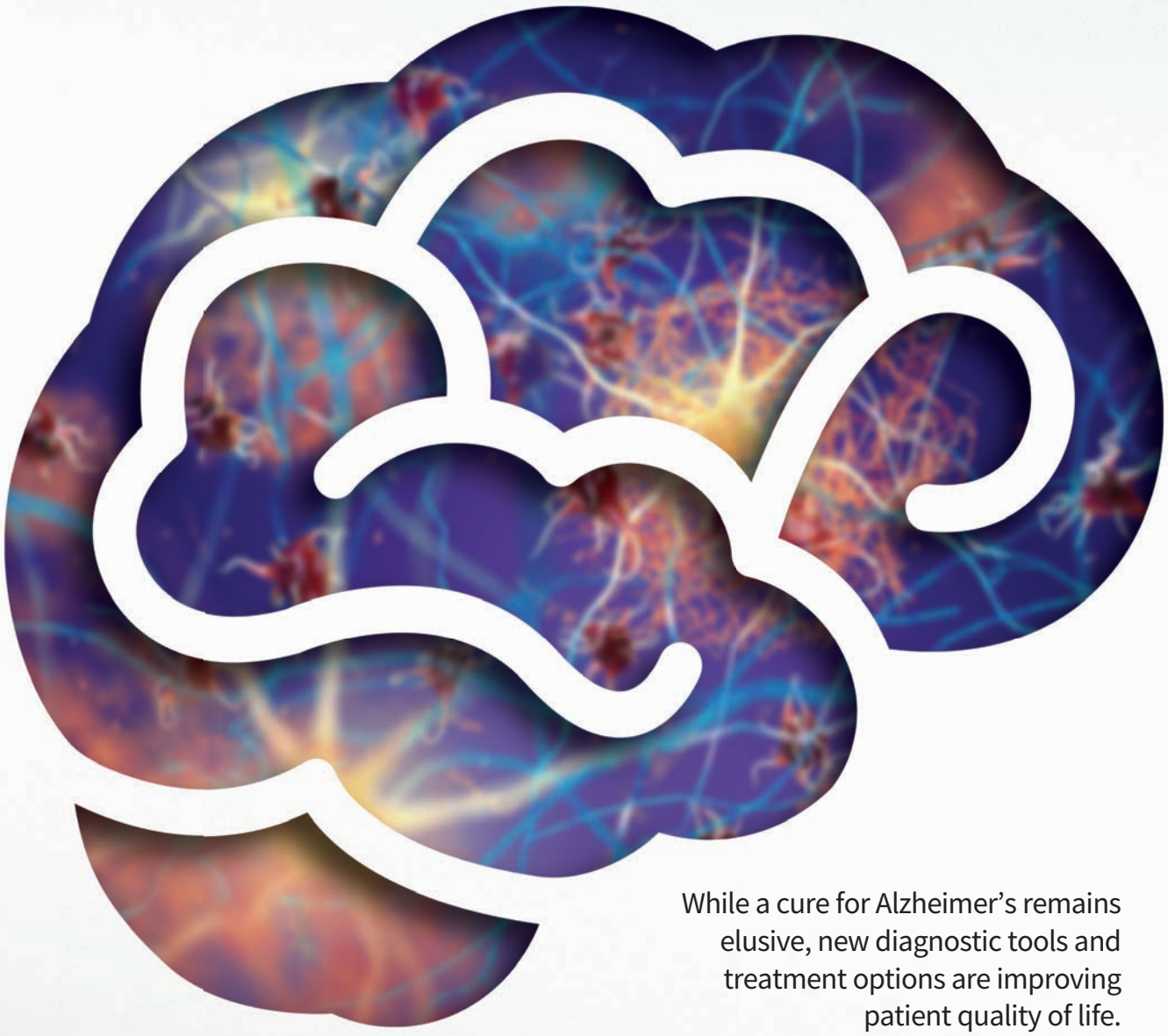
References

1. University of St. Augustine for Health Sciences. Diversity in Healthcare and the Importance of Representation, March 2021. Accessed at www.usa.edu/blog/diversity-in-healthcare.
2. Kamran, SC, Winkfield, KM, Reede, JY, and Vapiwala, N. Intersectional Analysis of U.S. Medical Faculty Diversity Over Four Decades. *The New England Journal of Medicine*, April 7, 2022; 386:1363-1371. Accessed at www.nejm.org/doi/full/10.1056/NEJMsr2114909.
3. The Troubling Decline of Black Men in Academic Medicine. *The Journal of Blacks in Higher Education*, May 2, 2022. Accessed at www.jbhe.com/2022/05/the-troubling-decline-of-black-men-in-academic-medicine.
4. Abdalla, M, Abdalla, M, Abdalla, S, et al. The Under-Representation and Stagnation of Female, Black, and Hispanic Authorship in the *Journal of the American Medical Association* and *The New England Journal of Medicine*. *Journal of Racial and Ethnic Health Disparities*, March 21, 2022; 21;1-10. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC8936038.
5. Shahriar, AA, Puram, VV, and Miller, JM. Socioeconomic Diversity of the Matriculating U.S. Medical Student Body by Race, Ethnicity, and Sex, 2017-2019. *JAMA Network Open*, 2022;5(3):e222621. Accessed at jamanetwork.com/journals/jamanetworkopen/fullarticle/2790107.
6. U.S. Food and Drug Administration. Clinical Trial Diversity. Accessed at www.fda.gov/consumers/minority-health-and-health-equity/clinical-trial-diversity.
7. FDA Takes Important Steps to Increase Racial and Ethnic Diversity in Clinical Trials. U.S. Food and Drug Administration press release, April 13, 2022. Accessed at www.fda.gov/news-events/press-announcements/fda-takes-important-steps-increase-racial-and-ethnic-diversity-clinical-trials.
8. Gawthrop, E. The Color of Coronavirus: COVID-19 Deaths by Race and Ethnicity in the U.S. APM Research Lab, Aug. 16, 2022. Accessed at www.apmresearchlab.org/covid/deaths-by-race.
9. Understanding Cultural Diversity in Healthcare. Case Studies. Accessed at www.ggalanti.org/case-studies-field-reports.
10. Heath, S. What Is Implicit Bias, How Does It Affect Healthcare? Patient Engagement HIT, Oct. 16, 2020. Accessed at patientengagementhit.com/news/what-is-implicit-bias-how-does-it-affect-healthcare.
11. Heath, S. Why Community Health Partnership Is Key to Drive Health Equity. Patient Engagement HIT, Aug. 3, 2020. Accessed at patientengagementhit.com/news/why-community-health-partnership-is-key-to-drive-health-equity.
12. Heath, S. Patient Care Navigators Increase Care Quality, Decrease Costs. Patient Engagement HIT. Accessed at patientengagementhit.com/news/patient-care-navigators-increase-care-quality-decrease-costs.

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

Update on Treatment Options for Alzheimer's

By Jim Trageser



While a cure for Alzheimer's remains elusive, new diagnostic tools and treatment options are improving patient quality of life.

IN A WORLD in which many deadly diseases have been defeated by the advent of modern medicine, perhaps no diagnosis is still so frightening as Alzheimer's disease.

A cancer diagnosis is certainly devastating, but many treatments offer realistic hope for beating the disease. Alzheimer's, on the other hand, is incurable. The diagnosis is an inevitable death sentence, and the unknown compounds fear. While most lay people understand the basics of cancer, even physicians struggle to understand Alzheimer's. We don't know the cause, there is no cure and available treatment options often feel inadequate for the task.

Alzheimer's inexorably steals that which most makes us who we are: our memory. It leaves families physically exhausted and emotionally hollowed. While a cure remains elusive for now, there are new drugs that can slow the progression of symptoms. In addition, researchers and caregivers learn more every day about how to provide care in ways that reduce stress for both patients and their families.

What Is Alzheimer's?

While the ancients wrote about dementia in both classical-era Egypt and Greece, Alzheimer's disease was first described in 1910 by German psychiatrist and neuropathologist Alois Alzheimer. One of Alzheimer's colleagues, Emil Kraepelin, is credited with naming the condition after his friend.[1]

During an autopsy of a woman who died of an unusual mental illness, Alzheimer noticed physical changes to her brain tissue, including clumps and bundles of fibers. More than a century later, researchers are still trying to determine exactly what causes the development of these clumps, now known as amyloid plaques, and fiber bundles, or tau tangles. We now know these result from abnormal concentrations of amyloid and tau proteins, but what is behind the abnormalities is not yet clear.[2] It is thought that the plaques and tangles cause neurons to lose connectivity with the rest of the brain, which leads to the observed memory and behavioral symptoms.[3]

Today, Alzheimer's is responsible for about 80 percent of all cases of dementia. Approximately 90 percent of people who develop Alzheimer's disease will first exhibit symptoms in their mid-60s or later, known as late-onset Alzheimer's. The 10 percent diagnosed in their early 60s or younger have early-onset Alzheimer's. The progression of the disease is the same for both populations.

Alzheimer's disease is the seventh-leading cause of death in the United States, taking about 134,000 American lives each year. Approximately six million Americans are suffering from Alzheimer's at any time.[4] Ten percent of Americans older than age 65 and about one-third of Americans older than age 85 have Alzheimer's. The life expectancy of someone diagnosed with Alzheimer's ranges from three to 11 years, although some live two decades or longer with the disease.[6]

Diagnosing Alzheimer's

Minor-to-moderate memory loss and decline in mental acuity is a normal part of aging. But Alzheimer's disease is marked by a decline so significant that it impacts a person's ability to function in everyday life.

Until recently, a definitive diagnosis could be made only after death when an autopsy could confirm the specific physical damage to the brain associated with Alzheimer's. While there is still no single test to diagnose the disease, doctors now have tools to confidently make a diagnosis through a combination of patient evaluation, family history and eliminating other possible causes of the reported or observed symptoms, as well as use of new imaging technology and tests that can detect biomarkers specific to Alzheimer's.

Memory loss is typically the first symptom patients and/or family members notice and report. In the earliest stages of Alzheimer's, patients may forget a recent conversation, not recognize familiar surroundings or put possessions in odd locations. Other symptoms that may accompany memory loss are changes in personality: becoming more irritable or aggressive; withdrawal from social situations; depression; or increased distrust or suspicion.

Memory loss is typically the first symptom patients and/or family members notice and report.

During an initial consultation, physicians should collect a family history, since Alzheimer's does seem to have a genetic component. A review of currently prescribed medications can identify other possible causes of memory loss. Physicians should also be sure to discuss patients' current emotional health. Stress, anxiety, depression and loss of sleep can also lead to memory loss, confusion and difficulty concentrating.[7]

Tools used to help diagnose Alzheimer's disease include:

• *Blood and urine tests.* These help identify other possible causes of the symptoms: vitamin B-12 deficiency, hypothyroidism and kidney or liver disease.

• *Magnetic resonance imaging (MRI).* MRI scans look for evidence of strokes, tumors, cranial fluid buildup or other conditions that can cause memory issues similar to those of Alzheimer's disease.

• *Mental tests.* These help physicians identify any issues with problem-solving, memory, counting and language skills that are consistent with Alzheimer's.

If a physician decides that the reported and/or observed decline in memory and other functioning is more severe than normal for a patient's age range, and no other potential cause is identified, then the following tests can be ordered to help confirm an Alzheimer's diagnosis:

• *Elecsys Amyloid Plasma Panel.* This newly approved blood scan tests for the presence of both tau proteins and the apolipoprotein E (APOE) genetic risk factor. A positive test will not be considered conclusive evidence of Alzheimer's but a trigger for further testing. (A negative result will indicate that symptoms are likely due to another cause.[8]) The panel was called a "breakthrough device" by the U.S. Food and Drug Administration (FDA) in July 2022, a designation that is speeding its progress toward release.

• *Spinal tap.* A spinal tap can detect abnormal levels of amyloid and tau proteins.

• *Computed tomography (CT) scan.* A CT scan can look for structural changes in the brain consistent with Alzheimer's.

• *Positron emission tomography (PET) scan.* A PET scan of the brain can detect accumulations of amyloid proteins, as well as locations where brain cells are inefficient in processing glucose, which is an important indication of Alzheimer's.[9]

Once other likely causes of the symptoms are eliminated and a diagnosis is made, it is important to begin treatment quickly.

Treating Alzheimer's

While a "whole patient" approach benefits prognosis in many cases, Alzheimer's treatment will generally require a "whole family" approach. Caring for a loved one with Alzheimer's takes both medical and

Alzheimer's Symptoms[16]

Early-Stage

- Memory loss
- Mood and/or personality changes
- Increased anxiety and/or aggression
- Poor judgment
- Loss of spontaneity
- Repeating questions
- Wandering or getting lost
- Misplacing items
- Increased time completing normal tasks
- Trouble handling money

Middle-Stage

- Increased memory loss and confusion
- Impulsive behavior and/or outbursts of anger
- Restlessness, agitation, anxiety, tearfulness
- Problems coping with new situations
- Problems recognizing family and friends
- Hallucinations, delusions and paranoia
- Wandering in the late afternoon or evening
- Difficulty with language and/or organizing thoughts
- Repetitive statements or movements
- Inability to learn new things
- Shortened attention span
- Difficulty carrying out multistep tasks
- Problems with reading, writing or working with numbers

Late-Stage

- Inability to communicate
- Difficulty swallowing
- Weight loss
- Groaning, moaning or grunting
- Increased sleeping
- Loss of bladder and bowel control
- Seizures
- Skin infections

Alzheimer's Risk Factors and Possible Prevention Measures[17]

Risk Factors

- Genetics
- Family history
- Advanced age
- Head trauma
- Hypertension
- Obesity
- Depression
- Poor sleep
- Smoking
- High cholesterol
- Type 2 diabetes

Prevention Measures

- Stay physically active
- Take care of your heart
- Follow a healthy diet
- Get enough vitamin D
- Enjoy social activities
- Challenge your brain

emotional preparation and support.

Treatment specifics will depend on what stage of disease progression the patient is in at diagnosis: early-stage, middle-stage or late-stage. While there is no cure for Alzheimer's, it is possible to slow the progression of symptoms and help preserve a higher quality of life.

During early- and middle-stage Alzheimer's, cholinesterase inhibitors can help slow progression of both memory loss and mood changes. These drugs work by helping to increase levels of acetylcholine, a chemical needed for neurons to communicate with one another that is typically decreased in Alzheimer's patients.[9] Popular drugs in this class include donepezil (Aricept), galantamine (Razadyne ER) and rivastigmine (Exelon). During middle- and late-stage Alzheimer's, memantine can be used to inhibit the effects of glutamate, which can overly excite neurons in Alzheimer's patients.[10] While both of these types of drugs can provide temporary relief from worsening symptoms for weeks — maybe even months — they eventually lose their efficacy.

Another option is aducanumab (Aduhelm), a recently approved drug found to help reduce amyloid plaque in Alzheimer's patients. FDA granted accelerated approval for aducanumab in June 2021, and it is still undergoing study, so approval could be rescinded if significant side effects are discovered.[11]

Antidepressants may also be used, by themselves or in conjunction with drugs listed above, to help treat behavioral issues associated with Alzheimer's.

There are currently no direct medical interventions available for treating Alzheimer's. Additional treatment options focus on keeping patients comfortable, doing as much as possible to lower stress-inducing events and ensuring patients' physical well-being.

In early-stage Alzheimer's, depending on the severity of the symptoms, patients often will be able to continue living at home as long as they have a strong support system. Modifications to living quarters and daily routines can help minimize stress.[12]

Modifications to living quarters include:

- Reducing clutter
- Removing throw rugs and other tripping hazards
- Keeping everyday items in the same place
- Removing as many mirrors as possible (Mirrors can confuse a patient with Alzheimer's.)
- Displaying photographs of loved ones and familiar keepsakes in visible areas
- Installing sturdy handrails on staircases and in bathrooms

Modifications to daily routines include:

- Making appointments consistent (scheduling them at the same time and on the same day of the week as much as possible)
- Using a large calendar or bulletin board to outline daily tasks and schedules and checking off items as completed
- Giving patients a mobile phone with the location finder enabled, and preprogramming family members' and other important phone numbers in the directory
- Ensuring patients carry their personal identification or wear a medical alert bracelet at all times
- Providing comfortable footwear that has good traction

While every case is unique, Alzheimer's generally progresses from mild symptoms (for instance, trouble completing familiar tasks such as operating a microwave or writing a list) to the point of severe mood swings and increasing confusion about basic information such as where they are or what day it is. Patients may be unable to decide on what clothes to wear or have a tendency to wander off. Another unfortunate side effect of middle- to late-stage Alzheimer's is incontinence.

Even in the middle stage, many normal

life activities can still be enjoyed with help from caregivers. The middle stage is usually the longest stage, often lasting years. However, noticeable declines are still likely to be apparent, and caregivers will likely need assistance, especially as the disease progresses.

During late-stage Alzheimer's, patients' ability to communicate becomes severely degraded. They may no longer be aware of their surroundings or be able to respond to normal stimuli. At some point, round-the-clock care will become necessary either at home or at a dedicated care facility. Many hospice programs will have an Alzheimer's care plan already in place to assist families in the final weeks or months.

The Other Patients

Caregivers need to be taken care of, too. Primary at-home caregivers — usually family members or close friends — benefit from routine medical care. They need to eat a healthy diet, get a good night's sleep, exercise regularly and find time to relax away from their caregiving duties. It is just as important for caregivers to receive care as it is for them to provide it.

Overwhelmed or depressed caregivers are not as effective as those who are taking care of their own health as well. Taking care of someone with Alzheimer's is emotionally taxing. Referring caregivers to a trusted therapist or suggesting a local support group can help ensure they have resources available to help them feel less isolated. Also, the Alzheimer's Association has a series of tools to help caregivers manage their own stress and understand when to seek help and how to process the grief that accompanies the progression of Alzheimer's disease. (See www.alz.org/help-support/caregiving/caregiver-health for details.)

Looking Ahead

One of the more intriguing areas of research lately has focused on prevention.

While the specific triggers that lead to Alzheimer's are unknown, there is quite a bit of evidence showing general rules of healthy living can significantly lower the risk of developing the disease. While no definitive link has been established (although active research continues), the National Institutes of Health suggests that individuals who control their blood pressure and weight; eat a healthy, balanced diet; and are physically active and socially engaged may be at a lower risk of developing Alzheimer's.

Given both the severity of the disease and the number of people it affects, research into Alzheimer's is a high priority. The government-run ClinicalTrials.gov site lists nearly 3,000 open or recent studies investigating the disease. Many of them are researching new methods of detecting Alzheimer's biomarkers or improving upon existing methods to allow for a quicker, more definitive diagnosis.

But other studies are searching for an actual cure for Alzheimer's. For instance, the University of Miami is studying patients who receive an injection of mesenchymal stem cells every 13 weeks for one year. Follow-up studies of cognitive function are due to be completed later this year, with results to follow.[13]

Other studies are researching both new and existing drugs, with many of them targeting the high concentrations of the amyloid and tau proteins causing the brain degeneration that leads to Alzheimer's.

Another noninvasive treatment is being studied at the Massachusetts Institute of Technology. This treatment uses a device that exposes patients to controlled, calibrated light and sound to stimulate the brain — hopefully countering the degenerative effects of Alzheimer's.[14]

Finally, a recent study looking at preventive measures found a strong correlation between those who receive an influenza vaccine and avoiding Alzheimer's later in life. Authors of the study completed at the University of Texas, Houston were unable to attribute the lower incidence of Alzheimer's to the vaccine itself, but noted that simply avoiding repeated influenza infections may have an impact. Other vaccinations have also shown a correlation with lower incidences of Alzheimer's.[15]

While progress continues to be made, both in our understanding of the underlying causes that lead to Alzheimer's and ways of treating it, a major breakthrough does not seem imminent. For the foreseeable future, gains in treatment are likely to be incremental, with families and physicians joining forces to provide as high a quality of life for patients as possible. ❖

References

1. Yang, HD, Kim, DH, Lee, SB, and Young, LD. History of Alzheimer's Disease. *Dementia and Neurocognitive Disorders*, December 2016, 15(4): 115–121. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC6428020.
2. National Institute on Aging. Alzheimer's Disease Fact Sheet. Accessed at www.nia.nih.gov/health/alzheimers-disease-fact-sheet.
3. National Institute on Aging. What Causes Alzheimer's Disease? Accessed at www.nia.nih.gov/health/what-causes-alzheimers-disease.
4. National Center for Health Statistics. Alzheimer Disease, Jan. 5, 2022. Accessed at www.cdc.gov/nchs/fastats/alzheimers.htm.
5. Mayo Clinic. Alzheimer's Stages: How the Disease Progresses, April 29, 2021. Accessed at www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers-stages/art-20048448.
6. Mayo Clinic. Memory Loss: When to Seek Help, May 7, 2022. Accessed at www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/memory-loss/art-20046326.
7. Shapiro, L. Blood Biomarker Test Designated a Breakthrough Device. *Alzheimer's News Today*, July 21, 2022. Accessed at alzheimersnewstoday.com/news/blood-test-earns-breakthrough-device-designation.
8. Cleveland Clinic. Alzheimer's Disease, March 18, 2019. Accessed at my.clevelandclinic.org/health/diseases/9164-alzheimers-disease.
9. Sing, R, and Sadiq, N. Cholinesterase Inhibitors. *StatPearls*, July 18, 2022. Accessed at www.ncbi.nlm.nih.gov/books/NBK544336.
10. National Library of Medicine. Memantine, Aug. 3, 2022. Accessed at www.ncbi.nlm.nih.gov/books/NBK500025.
11. FDA Grants Accelerated Approval for Alzheimer's Drug. U.S. Food and Drug Administration press release, June 7, 2021. Accessed at www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug.
12. Mayo Clinic. Alzheimer's Disease: Diagnosis & Treatment. Accessed at www.mayoclinic.org/diseases-conditions/alzheimers-disease/diagnosis-treatment/drc-20350453.
13. National Institute of Health. Alzheimer's Disease Stem Cells Multiple Infusions, July 31, 2019. Accessed at clinicaltrials.gov/ct2/show/NCT04040348.
14. National Institute of Health. High Frequency Light and Sound Stimulation to Improve Brain Functions in Alzheimer's Disease, Aug. 2, 2019. Accessed at clinicaltrials.gov/ct2/show/NCT04042922.
15. Bukhbinder, AS, Ling, Y, Hasan, O, et al. Risk of Alzheimer's Disease Following Influenza Vaccination: A Claims-Based Cohort Study Using Propensity Score Matching. *Journal of Alzheimer's Disease*, Aug. 2, 2022. Accessed at content.iospress.com/articles/journal-of-alzheimers-disease/jad220361.
16. National Institute on Aging. What Are the Signs of Alzheimer's Disease? May 16, 2017. Accessed at www.nia.nih.gov/health/what-are-signs-alzheimers-disease#:~:text=Memory%20problems%20are%20typically%20one,early%20stages%20of%20Alzheimer's%20disease.
17. Silva, MVF, Loures, CMG, Alves, LCV, et al. Alzheimer's Disease: Risk Factors and Potentially Protective Measures. *Journal of Biomedical Science*. May 26, 2019. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC6507104/#:~:text=However%2C%20acquired%20factors%20such%20as,the%20risk%20of%20AD%20development.

JIM TRAGESER is a freelance journalist in the San Diego, Calif., area.

Myths & Facts: Depression

The best way to help individuals suffering from depression is to spread awareness about the misconceptions surrounding this mood disorder.

By Ronale Tucker Rhodes, MS

DEPRESSION IS the leading cause of disability in the world. In October 2020, the World Health Organization (WHO) reported more than 264 million people suffer from depression worldwide.[1] Also in 2020, the National Institute of Mental Health reported an estimated 21 million adults (8.4 percent) in the United States had at least one major depressive episode, with episodes higher among adult females (10.5 percent) compared to males (6.2 percent). The prevalence of adults with a major depressive episode was highest among individuals 18 to 25 years old (17 percent). But, depression doesn't affect only adults. An estimated 2.9 million (12 percent) children and adolescents 12 to 17 years old in the United States have had at least one major depressive episode with severe impairment.[2]

One of the most common mental health disorders in the U.S., depression has affected some of the most noted people in history, including Abraham Lincoln, Stephen Hawking, Michelangelo and Winston Churchill.[3] Unfortunately, even for them, there were and continue to be countless stigmas and misconceptions about this serious mood disorder that need to be debunked to help heal those suffering from it.

Separating Myth from Fact

Myth: Depression is all in a person's head.

Fact: Depression is very real. It is a serious mood disorder caused by a combination of biological, environmental and social factors that impact a person's thoughts and emotions and how they handle daily activities such as sleeping, eating or working. Depression can also cause individuals to feel physically sick with fatigue, aches and pains.[4]

There are several types of depression, including major depression and persistent depressive disorder (the two most common forms), perinatal depression, seasonal affective disorder, depression with symptoms of psychosis and bipolar disorder. With major depression, symptoms that typically interfere with the ability to work, sleep, study and eat persist most of the time for at least two weeks. With persistent depressive disorder (dysthmia), the symptoms are less severe and last typically for at least two years. A couple of types of depression develop due to specific circumstances. For instance, perinatal depression is major depression either during pregnancy or after delivery, and seasonal affective disorder comes and goes with seasons. Depression with symptoms of psychosis is the most serious, causing individuals to experience delusions (disturbing, false fixed beliefs) or hallucinations (hearing or seeing things others don't see or hear). Bipolar disorder, previously referred to as manic depression, causes depressive episodes, as well as manic episodes that include elevated moods such as feeling happy, irritable or "up" with a marked increase in activity level.[5]

Myth: Depression is a normal part of life; everyone feels sad from time to time.

Fact: While depression can involve sadness, depressive symptoms go far beyond that. As mentioned, depressive symptoms can be emotional, cognitive, psychological or physical (see Signs and Symptoms of Depression). They can also vary in severity, duration and impact, and they can be unexplained, even when things in life seem to be going well.[6] For instance, feelings of sadness usually go away on their own, but depression can last from a few weeks to an entire year or longer.

Myth: Depression and anxiety are the same thing.

Fact: Anxiety and depression can be related, and they can cause similar symptoms, but they are two different conditions with their own causes. According to the Anxiety and Depression Association of America, many people diagnosed with depression have a history of anxiety; however, many also experience one without the other.[7]

Myth: Only adults are affected by depression.

Fact: Depression can develop at any age. While depression often occurs during adulthood, approximately three million children and adolescents suffer from it as well.

What's important to know is that depression isn't a one-size-fits-all condition. Symptoms differ depending on factors such as gender, life situation and age, and include:[8]

- *Young children*: being anxious or cranky, pretending to be sick, refusing to go to school, clinging to a parent or worrying a parent may die.
- *Older children and teens*: getting into trouble at school, sulking, being easily frustrated, feeling restless or having low self-esteem. This age is more likely to experience excessive sleepiness and increased appetite. Older children and teens may also have other disorders such as anxiety and eating disorders, attention-deficit hyperactivity disorder or substance use disorder.
- *Young adults*: being more likely to be irritable; complaining of weight gain and/or hypersomnia; and having a negative view of life and the future. They also often have other disorders such as generalized anxiety disorder, social phobia, panic disorder or substance use disorders.

Signs and Symptoms of Depression[8]

- Persistent sad, anxious or "empty" mood
- Feelings of hopelessness or pessimism
- Feelings of irritability, frustration or restlessness
- Feelings of guilt, worthlessness or helplessness
- Loss of interest or pleasure in hobbies or activities
- Decreased energy, fatigue or being "slowed down"
- Difficulty concentrating, remembering or making decisions
- Difficulty sleeping, early morning awakening or oversleeping
- Changes in appetite or unplanned weight changes
- Aches or pain, headaches, cramps or digestive problems without a clear physical cause and that do not ease even with treatment
- Suicide attempts or thoughts of death or suicide

• *Middle-aged adults*: having more depressive episodes, decreased libido, middle-of-the-night insomnia or early morning awakening. They may also experience gastrointestinal symptoms such as diarrhea or constipation.

• *Older adults*: symptoms that may be less obvious, but generally include sadness, grief or an overall lack of emotion. They are more likely to have other medical conditions or chronic pain that may cause or contribute to depression. Memory and thinking problems may also be prominent.

Myth: Only sensitive or emotional people are affected by depression.

Fact: People with specific personality types are not more likely to be affected by depression. And, while it is unknown what truly causes depression, whether it's genetics, behaviors, the environment, etc., it is known that chemical messengers in the brain regulate individuals' functions, including mood. Three transmitters are currently linked to mood: dopamine, serotonin and norepinephrine. When the brain produces too many or too few of these chemicals, their levels become unbalanced, which may lead to depression or other mental health disorders. And, since physical and emotional changes take place internally over time, depression can affect anyone, regardless of how sensitive they may be.[6]

Myth: Depression is caused by a traumatic event.

Fact: A traumatic event such as the loss of a loved one can trigger sadness and loneliness, but it doesn't cause depression. On the other hand, a traumatic event can heighten or intensify the symptoms of depression.[3]

Myth: Depression isn't genetic.

Fact: Research shows there is a 50/50 chance of someone developing depression if it runs in the family. However, it's a combination of genetic and external life experiences that determine whether depression surfaces.[3] In addition, other possible contributing factors of depression include certain medications, co-existing mental health conditions, substance use, chronic physical illness, gender identity, poor diet and nutrition, chronic stress and certain personality traits.[6]

The upside to a genetic link is that family members with depression may have a better understanding of the signs and symptoms, which can lead to a better chance of discovery and treatment. And, better medications to treat different kinds of depression could possibly be developed by current genome mapping research.[3]

Myth: Depression can't be diagnosed.

Fact: Depression can be diagnosed. The criteria for diagnosis is having five depression symptoms (see Signs and Symptoms of Depression) every day, nearly all day, for at least two weeks. One of those symptoms for adults must be a depressed mood or a loss of interest or pleasure in almost all activities. Children and adolescents, on the other hand, may be irritable rather than sad.

When being evaluated for depression, physicians will ask when symptoms began, how long they last, how often they occur and whether they keep the individual from going out or performing their usual activities. The physician will

The Connection Between Disease and Depression[13]

- Depression is experienced by:
  - -25 percent of cancer patients
  - -10-27 percent of post-stroke patients
  - -One in three heart attack survivors
  - -50 percent of Parkinson's disease patients
  - -One-third of persons with diabetes
  - -About 20 percent of women living with polycystic ovary syndrome
- Depression is the second-most common mental health condition among patients living with HIV
- Adults with a depressive disorder or symptoms have a 64 percent greater risk of developing coronary artery disease
- 33-50 percent of anorexia patients have a comorbid mood disorder such as depression
- More than 20 percent of Americans with an anxiety or mood disorder such as depression have an alcohol or other substance abuse disorder

Depression Statistics in the U.S.[13]

- Major depressive disorder is the leading cause of disability in the U.S.
- Major depressive disorder affects approximately 17.3 million (7.1 percent) of the U.S. population age 18 years and older in a given year.
- Major depressive disorder is almost twice as likely to affect women than men.
- 1.9 million children age 3 to 17 years have diagnosed depression.
- Seven million adults age 65 years and older are affected by depression.
- 40-70 percent of adult caregivers have clinically significant symptoms of depression.
- 17 percent of women with major depressive disorder have a high prevalence of low bone mass compared to 2 percent of women without major depressive disorder.
- Depression contributes to the estimated $100 billion annual cost of depression for employers, including $44 billion a year in lost productivity.
- Depression is the cause of more than two-thirds of suicides in the U.S. each year.

also rule out certain medications or medical conditions that can cause the same depression symptoms.[8]

Myth: Depression does not need to be treated.

Fact: People who are depressed can't just "shut it off." Treatment is necessary to address symptoms. Otherwise, without treatment, depression can worsen and lead to self-harming behaviors or suicide.[4]

Myth: Depression can be treated only with medication.

Fact: Treating depression usually involves medication, psychotherapy or both, and in some instances may require electroconvulsive therapy (ECT) or other brain stimulation therapies. Choosing the right treatment plan is based on each person's individual needs and medical situation, and it often takes trial and error to find the plan that works best.

When at least two antidepressants are tried, and they don't improve symptoms of depression, it is known as treatment-resistant depression.

Antidepressants are commonly used medications to treat depression, but they take time — usually four to eight weeks — to improve symptoms. These medicines help to improve the way the brain uses certain chemicals to control mood or stress, and several different types may need to be tried. Typically, a course of antidepressants will last between six and 12 months, and the medication will be tapered before being stopped.[5,8] It's important to note that while antidepressants impact the chemicals in a person's brain, they have no impact on personality, which is a common patient concern.[4] Currently, there are six different classes of medications approved to treat depression: selective serotonin reuptake inhibitors (the most commonly prescribed), serotonin and noradrenaline reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, norepinephrine and dopamine reuptake inhibitors, and noncompetitive N-methyl-D-aspartate receptor antagonists (see Antidepressant Medications and Common Side Effects).

When at least two antidepressants are tried, and they don't improve symptoms of depression, it is known as treatment-resistant depression. A newer U.S. Food and Drug Administration-approved medicine for treatment-resistant depression is esketamine (sold under the brand names Spravado, Ketanest and others), also known as ketamine or S-ketamine, a dissociative hallucinogen medication. Ketamine is delivered as a nasal spray and often acts rapidly, typically within a couple of hours. This medication is usually given in connection with an oral antidepressant. Another option for treatment-resistant depression is to add a different type of medicine that makes an antidepressant more effective such as an antipsychotic or anticonvulsant.[9]

Psychotherapy (talk therapy or counseling) can help by teaching new ways of thinking and behaving and ways to change habits that contribute to depression. Two effective psychotherapies are cognitive behavioral therapy (CBT) and interpersonal therapy (IPT). With CBT, individuals learn to challenge and change unhelpful thinking patterns and behavior using mindfulness principles and specialized forms of therapy targeting particular symptoms such as insomnia. The goal of IPT, which focuses on interpersonal and life events, is to help improve communication skills with relationships, establish social support networks and develop realistic expectations when crises or other issues arise.[5,8]

There are two common forms of brain stimulation therapy: electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS). ECT involves a brief electrical stimulation of the brain while the patient is under anesthesia, typically administered by a team of trained medical professionals that includes a psychiatrist, an anesthesiologist and a nurse or physician assistant. Extensive research has found ECT to be highly effective for the relief of major depression, with clinical evidence indicating that for individuals with uncomplicated, but severe major depression, ECT will produce substantial improvement in approximately 80 percent of patients.[10] rTMS uses painless, magnetic pulses to help lessen the symptoms of depression. Patients do not have to be hospitalized, and they don't need sedation or anesthesia. A course of rTMS is five times a week usually lasting four to six weeks.[11]

Myth: Depression is not a big deal.

Fact: Depression is a serious condition that can cause individuals to withdraw from loved ones, take dangerous risks or start conflicts with others. It can also lead to thoughts or actions of a suicidal nature, which makes it a very big deal.

Dispelling the Myths Now

More than 47,000 Americans died by suicide in 2017, according to the Centers for Disease Control and Prevention.

Antidepressant Medications and Common Side Effects[9]

Medication	Side Effects
Selective serotonin reuptake inhibitors	• Agitation • Nausea • Diarrhea • Sexual problems, including low sex drive or inability to have an orgasm • Dizziness • Headaches • Insomnia • Increased anxiety • Exhaustion • Dry mouth • Tremors
Serotonin and noradenaline reuptake inhibitors	• Headache • Dizziness • Nausea • Heavy sweating • Dry mouth • Constipation • Insomnia • Sexual problems, including low sex drive or inability to have an orgasm
Tricyclic antidepressants	• Dry mouth • Blurred vision • Increased fatigue and sleepiness • Weight gain • Tremors • Constipation • Bladder problems (retention of urine) • Dizziness • Increased heart rate
Monoamine oxidase inhibitors	• Drowsiness • Dry mouth • Dizziness • Headache • Nausea • Insomnia • Diarrhea or constipation • Weight gain • Low blood pressure • Tremors • Increased sweating • Sexual problems, including low sex drive or inability to have an orgasm • Bladder problems (difficulty starting urine flow)
Norepinephrine and dopamine reuptake inhibitors	• Headache • Insomnia • Dry mouth • Constipation • Nausea • Tiredness • Tremors • Increased sweating
Noncompetitive N-methyl-D-aspertate receptor antagonists	• Dizziness • Nausea • Sedation • Anxiety • Increased blood pressure • Dissociation (distortion of time, space, illusions) • Vomiting • Feeling drunk • Lack of energy

And, it is estimated that up to 60 percent of people who commit suicide have major depression. Thankfully, estimates suggest the suicide risk for the millions of individuals suffering from mental disorders, including depression, hovers around 5 percent to 8 percent.[12] While that's somewhat reassuring, depression is a serious illness, so it is imperative that health professionals help to dispel the myths surrounding it and the stigmas accompanying it.

While many wear pink ribbons in October in honor of breast cancer awareness month, there is another color to add to the mix in October: green. For millions of people, a green ribbon represents depression awareness month, and much like those who don pink in October, the green ribbon of depression awareness asks individuals to recognize signs and symptoms of the disease, promote funding in research and treatment and be aware of the importance of screening. ❖

References

1. Single Care Team. Depression Statistics 2022 (Updated Feb. 15, 2022). Accessed at www.singlecare.com/blog/news/depression-statistics.
2. National Institute of Mental Health. Major Depression. (Updated January 2022). Accessed at www.nimh.nih.gov/health/statistics/major-depression#part_155029.
3. Unity Point Health. 11 Common Myths & Misconceptions About Depression, April 15, 2022. Accessed at www.unitypoint.org/desmoines/article.aspx?id=a655c7e2-fe37-4817-887b-c762ff455b23.
4. The Recovery Village. 12 Common Myths About Depression, May 26, 2022. Accessed at www.therecoveryvillage.com/mental-health/depression/depression-myths.
5. National Institute of Mental Health. Depression Overview. (Revised July 2022). Accessed at www.nimh.nih.gov/health/topics/depression.
6. PsychCentral. Lingering Myths About Depression. Accessed at psychcentral.com/depression/what-depression-is-and-what-it-isnt.
7. UPMC Western Psychiatric Hospital. Myths and Facts About Depression, May 28, 2020. Accessed at share.upmc.com/2020/05/myths-and-facts-about-depression.
8. National Institute of Mental Health. Depression: Does Depression Look the Same for Everyone? Accessed at www.nimh.nih.gov/health/publications/depression.
9. Cleveland Clinic. Depression Medications. Accessed at my.clevelandclinic.org/health/treatments/9301-depression-medicines.
10. American Psychiatric Association. What Is Electroconvulsive Therapy (ECT)? July 2019. Accessed at www.psychiatry.org/patients-families/ect.
11. WebMD. What to Know About Repetitive Transcranial Magnetic Stimulation (rTMS), June 29, 2021. Accessed at www.webmd.com/depression/repetitive-transcranial-magnetic-stimulation.
12. Holmes, L. Rates and Statistics for Suicide in the United States. VeryWell Mind, June 24, 2021. Accessed at www.verywellmind.com/suicide-rates-overstated-in-people-with-depression-2330503.
13. Depression and Bipolar Support Alliance. Depression Statistics. Accessed at www.dbsalliance.org/education/depression/statistics.

Depression: *A Patient's Perspective*

By Trudie Mitschang

After battling depression for more than four decades, Debbie Dykes has found relief with an alternative therapy that was recently approved by the FDA for treatment-resistant depression.

BSTQ: When were your earliest symptoms of depression?

Debbie: I first noticed symptoms when I was 10 years old. I was already a studious kid, but depression kicked it into high gear. I studied, read and had little contact with other kids my age. I got good grades and never caused any trouble, so no adult ever questioned my withdrawal. But in high school, I had developed an eating disorder. Eating or not eating was the only thing I could control. My pediatrician diagnosed the anorexia but didn't recommend therapy.

BSTQ: Are there any details of your life that may have been triggering?

Debbie: The first five years of my life were idyllic. We had the perfect family. My parents were both gentle, soft-spoken and funny. When I was 6 years old, my dad was diagnosed with lymphoma, which was a death sentence in the 60s. He was gone in six months. When I was 8 years old, my mother married a charismatic Southern Baptist preacher with a big laugh, and life was a little brighter for about two years. It turned out he was just on his best behavior to win over the neighbors and our extended family. Then he began to beat us savagely; my brother Duane and I got beaten the worst because we protested or tried to protect each other. We were also molested over a 10-year period. I was always terrified and used to spend hours hiding in my closet with a book or a stuffed animal.

BSTQ: When were you diagnosed?

Debbie: When I was 25 years old, I was lying on my friend's bed waiting for her to change clothes so we could go to the lake. She pulled her belt out of her belt loops, and I had a full-blown panic attack. I started therapy shortly after that and was eventually diagnosed with depression.

BSTQ: What types of medications have you tried, and how did you respond?

Debbie: I refused to even consider taking medication until I was 40 years old. My wife, Sue, gave me an ultimatum to begin taking medication or she was going to leave. That started the never-ending search for the right prescription. I tried Effexor, Latuda, Lamictal, Pristiq, Trintellix, Wellbutrin, Abilify and various combinations from that list. Effexor worked the best, and the depression was bearable for almost 10 years, but it never fully went away.

BSTQ: Tell us about your experience with Ketamine.*

Debbie: Ketamine literally saved my life. In January 2020, I lost 25 pounds in six weeks. I was catatonic, playing word games for nine hours a day. Sue worked with my psychiatrist to find a doctor who provided me with ketamine as a last resort. I had six 40-minute intravenous infusions starting in February of that year. Sue said she could see a difference right away. After a few more treatments, I began to feel motivated again. I wrote a little, painted and resumed training for the Los Angeles Marathon. I felt more like my old self, a terminally positive introvert who just happens to have to take six pills a day. Ketamine is highly controlled and must be administered by a doctor who remains present and monitors vitals the entire session. It's expensive, but in the two years since my first treatment, my insurance company has agreed to pay for half.

BSTQ: What do you wish others understood about depression?

Debbie: I want people to know that depression is a disorder that can't be cured with positive affirmations, prayer, self-help books or thousands of dollars in therapy. Depression is a disease, like diabetes. You would never tell diabetics to just put a smile on their face or work on their attitude. You'd encourage them to take their meds and any available steps to minimize the risks associated with their disease.

BSTQ: Does depression run in your family?

Debbie: Yes. My great-grandmother and brother took their own lives. And my mother stayed in bed for 10 years.

BSTQ: How has this disease impacted your quality of life?

Debbie: Living with depression has instilled in me an urgent need to help as many people as I can. I also feel sorrow that I missed out on the life that I dreamed about as a child. I was supposed to be an accomplished writer, painter or sculptor. And after a successful career, I wanted to share my passion and knowledge with college kids like my father and my godfather did. All I ever wanted was to be extraordinary at one thing. Depression made me more practical, measured and ordinary. ❖

*Ketamine is a medication primarily used for induction and maintenance of anesthesia. It induces dissociative anesthesia, a trance-like state providing pain relief, sedation and amnesia. At lower, sub-anesthetic doses, ketamine is a promising agent for pain and treatment-resistant depression. In 2019, the FDA approved nonpsychedelic ketamine for use in clinical trials.[1]

Dr. Alexander Papp is a board-certified psychiatrist with more than 25 years of experience treating a wide range of mental health disorders. He uses an integrative approach when providing patient care and has a special interest in using alternative therapies, including ketamine.

Depression: *A Physician's Perspective*

ALEXANDER PAPP, MD, ABPN, is a diplomate of the American Board of Psychiatry and Neurology, an adjunct faculty member of Alliant International University and an assistant clinical professor at the University of California, San Diego. Dr. Papp has treated a wide range of mental health conditions in mental health clinics and private practice.

BSTQ: How prevalent is depression?

Dr. Papp: Fifteen to 20 million people are diagnosed with and treated for depression annually. Clinical depression is a serious condition that negatively affects how a person thinks, feels and behaves. It is persistent and often significantly interferes with normal functioning in daily life. When left untreated, symptoms can last for weeks, months or years.

BSTQ: Have you seen an increase in depression diagnoses since the pandemic?

Dr. Papp: Statistics show that both depression and anxiety have increased by as much as 25 percent worldwide. My practice saw a larger increase in new or worsening cases of anxiety than in new cases of depression.

BSTQ: How is depression typically diagnosed?

Dr. Papp: Diagnosis is based on patient-reported symptoms and observable patient behaviors. Patient-reported symptoms typically include complaints about mood dysfunction, decreased energy, persistent sadness, frequent crying and hopelessness. Patients often describe feelings of worthlessness and an overall inability to function in normal, day-to-day activities. Observable behaviors typically include visible signs of listlessness, neglected hygiene, profuse crying and changes in appetite and/or sleep habits. Patient intake questionnaires gather information about symptoms that are not easily observed.

BSTQ: Are certain demographics more at risk for depression?

Dr. Papp: Yes. Women are about twice as likely to become depressed than men, especially during the months after giving birth. Young adults are more likely to become depressed than any other age group. Multiracial people are more likely to suffer from depression than people from a singular race. However, white people are more likely to become depressed than people from other singular racial groups.

BSTQ: Is there any promising new research on effectively treating depression?

Dr. Papp: Researchers are exploring two new ways to treat depression. One avenue involves psychedelic drugs, primarily psilocybin (the active ingredient of the "magic mushroom"). Another avenue involves alternative medications to serotonin-based antidepressants.

BSTQ: What is treatment-resistant depression?

Dr. Papp: Treatment-resistant depression refers to cases of major depressive disorder that do not adequately respond to treatment from at least two different antidepressants from different classes. In this situation, "responding" to an antidepressant means more than just an improvement in mood, but also the resolution of most depressive symptoms and a return to normal functioning.

BSTQ: You've had success with ketamine. How does it work to reduce depression?

Dr. Papp: Ketamine works by quickly increasing the activity of the neurotransmitter glutamate in the frontal cortex of the brain, while also allowing new synapses to form in the same area. Ketamine bypasses the traditional serotonin route and directly activates glutamate. This is very different from traditional antidepressants, which first increase the activity of serotonin in multiple areas of the brain before affecting glutamate. Traditional antidepressants usually take two to four weeks to take effect, while ketamine yields an almost immediate effect.

BSTQ: Are there any adverse effects of ketamine as a treatment?

Dr. Papp: Ketamine has a few mild adverse effects, including a dream-like feeling, blurred or double vision, dizziness, nausea, vomiting and short-lived episodes of anxiety.

BSTQ: When should patients ask their doctor about trying ketamine as a treatment for depression?

Dr. Papp: Patients should speak to their doctor after they have tried several different antidepressant medications, or combinations of medications, at the highest dosage levels for at least two months without experiencing a return to normal functioning. ❖

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

Novel Immunotherapies Target RSV Disease at Both Ends of the Age Spectrum

By Keith Berman, MPH, MBA

THANKS TO recent improvements in disease surveillance, it is now appreciated that respiratory syncytial virus (RSV) infections account for a significant share of U.S. hospitalizations for lower respiratory tract disease, importantly including bronchiolitis and pneumonia. And like seasonal influenza, very young children, the elderly and others with compromised immunity account for nearly all of the annual serious disease burden associated with RSV.

Yet while influenza is a household word, RSV remains relatively little known to the general public. Why this dichotomy? In part it's because, each year, the general public is urged by providers and public health media campaigns to get immunized with a flu vaccine to prevent infection and illness. But at present, the converse is true for RSV: With the exception of one very narrowly indicated passive immunotherapy to protect very high-risk children,* there are no vaccines or other prophylactic immunotherapies to prevent serious RSV disease.

But with the anticipated approval of several highly promising RSV vaccines and passive prophylactic antibody therapies now in the development pipeline, RSV may transition from obscurity to broader public awareness as preventive treatment options become standard medical practice.

The U.S. RSV Disease Burden

Most children and adults infected during each typical five-month RSV season experience only minor cold-like upper respiratory symptoms, including rhinorrhea, coughing and sneezing, which generally resolve on their own within a week or two. However, infants in the first six months of life entering RSV season, premature infants born under 35 weeks of gestation, young children with congenital pulmonary or heart disease and adults over age 60 years with weakened immunity or chronic heart or lung disease are at much-increased risk of progressing to severe lower respiratory tract infection (LRTI).

* Synagis (palivizumab) injection, an anti-RSV monoclonal antibody indicated for the prevention of serious low respiratory tract disease in pediatric patients with 1) a history of prematurity (≤35 weeks of gestational age) and 6 months of age or younger at the beginning of RSV season, 2) bronchopulmonary dysplasia requiring medical treatment within the previous six months and who are 24 months of age or younger at the beginning of RSV season and 3) hemodynamically significant congenital heart disease and who are 24 months of age or younger at the beginning of RSV season.

Infants and at-risk young children. RSV is the most common cause of acute respiratory tract infections requiring medical intervention or hospital admission in infants and young children less than 2 years of age. While immaturity of immune defenses at this early age is clearly a contributor, another risk factor is a high surface-to-volume ratio of their still-developing airways. Because we are born with almost all of our airways and alveoli, the lumen size of bronchioles in infants is smaller relative to that of an adult and thus more prone to obstruction.[1] Not surprisingly, young children with a recent history of bronchopulmonary dysplasia are also at much increased risk of RSV bronchiolitis or pneumonia, as are those with congenital heart disease resulting in compromised pulmonary circulation.

RSV infections result in an estimated 500,000 emergency department visits and 1.5 million clinic visits each year in children under 5 years of age, according to the U.S. Centers for Disease Control and Prevention (CDC).[2] A large CDC surveillance study found RSV was associated with 20 percent of hospitalizations, 18 percent of emergency department visits and 15 percent of office visits for acute respiratory infections in children under 5 years of age.[3]

A subsequent CDC analysis of U.S. hospital discharges over a 10-year period found that the RSV-related LRTI disease burden falls most heavily on young infants, with 26 hospitalizations per 1,000 infants under age 1 year, dropping more than 10-fold to 1.8 per 1,000 children between ages 1 and 5 years. While estimates vary, RSV infection accounts for as few as 100 to several hundred deaths annually among infants younger than 1 year old.[4,5]

Older adults and those with chronic illnesses. The subgroups of adults at high risk of LRTI following RSV infection are in some respects the mirror image of infants and high-risk toddlers. CDC estimates that more than 177,000 adults, mostly older and nonelderly adults with chronic lung or heart disease or compromised immunity, are hospitalized, and 14,000 succumb to RSV infection each year.[6] The most serious complications potentially leading to death include:

- Pneumonia
- Exacerbation of chronic obstructive pulmonary disease (COPD) symptoms
- Exacerbation of asthma symptoms
- Congestive heart failure

A landmark study that prospectively followed separate cohorts of healthy elderly adults and high-risk adults living in Rochester, N.Y., found that, over the four-year surveillance period, RSV infection accounted for 10.6 percent of all hospitalizations for pneumonia, 11.4 percent for COPD, 5.4 percent for congestive heart failure and 7.2 percent for asthma.[7]

Just under one-fifth of healthy elderly patients who contracted RSV made a physician office visit, compared to nearly 30 percent of RSV-infected high-risk patients. But more tellingly, nine percent of high-risk RSV-infected patients visited the emergency room (ER) and 16 percent were hospitalized, while none of the RSV-infected healthy elderly patients required an ER visit or required hospitalization. Two RSV-related deaths occurred among 56 RSV-infected individuals in the high-risk cohort, and none among 46 RSV-infected individuals in the healthy elderly cohort. Nonetheless, RSV infection can infrequently result in serious LRTIs in generally healthy elderly adults.

RSV Vaccines Are Finally In Sight

A number of RSV vaccine development strategies have been pursued over the more than six decades since this enveloped virus was first identified in 1956 (Table). For older adults, three vaccination approaches that employ the RSV prefusion F (preF) protein — nucleic acid, subunit and vector-based vaccines — are currently being investigated in older adults. Stabilized preF subunit vaccines are also in late-phase development for maternal vaccination to passively transfer neutralizing anti-RSV antibodies across the placenta to the maturing fetus in the gestational third trimester.

CDC estimates that more than 177,000 adults, mostly older and nonelderly adults with chronic lung or heart disease or compromised immunity, are hospitalized, and 14,000 succumb to RSV infection each year.

But the first investigational RSV vaccine tested a half-century ago, a formalin-inactivated whole virus preparation (FI-RSV) with an alum adjuvant, foretold the development challenges that lay ahead. This vaccine not only failed to induce neutralizing antibodies or protect vaccinated infants,[8] but unexpectedly, vaccinated infants infected with RSV over the subsequent winter season experienced more pronounced disease than nonvaccinated infants. At one

Table. RSV Vaccine Types Currently in Clinical Development[23]

Type	Description	Development Stage
Subunit	Protein-based vaccine based on stabilized prefusion conformation of F fusion antigen (preF) or non-F viral antigens	Phase III Phase II
Nucleic acid	mRNA vaccines generally formulated with lipid nanoparticle, encoding stabilized preF antigen	Phase II/III
Recombinant vectors	Genes encoding RSV antigens of modified replication-defective virus delivered to induce humoral and cellular immunity	Phase III Phase II/IIb
Live attenuated	Deleted or modified proteins in the RSV genome that leads to restricted viral replication	Phase II Phase I
Particle-based	Synthetic virus-like particles that display multiple antigens via particle assembly	Phase I
Chimeric	Live attenuated replication-deficient or recombinant non-RSV viruses that express RSV proteins	Phase I

participating center, more than 80 percent of infected FI-RSV vaccine recipients required hospitalization, compared to just five percent of infected controls. A subsequent clinical trial using parenterally administered live RSV also failed to confer protection, but enhanced RSV disease did not occur.[9]

Most currently investigated vaccines are designed to induce humoral and T cell-mediated immunity against just one of the 11 proteins encoded by this single-stranded RNA virus: the F (fusion) transmembrane glycoprotein, which facilitates membrane fusion and viral penetration into the host cell. Unlike extensive antigenic variation seen in the G transmembrane glycoprotein, which is involved in viral attachment to the target cell, the F protein is highly conserved with respect to its amino acid sequence, making it an attractive target for vaccine development.

GlaxoSmithKline F glycoprotein antigen vaccine (RSVPreF3). With a focus on protecting adults aged 60 years and older at risk for serious RSV disease, GlaxoSmithKline (GSK) has developed a recombinant intramuscular (IM) subunit RSV preF glycoprotein antigen vaccine, called "RSVPreF3," that is combined with the company's proprietary AS-1 adjuvant now used in several licensed GSK vaccines.

In June 2022, GSK announced "positive headline results" from a prespecified interim analysis of its ongoing Phase III, multinational, observer-blind AReSVi 006 trial, with no unexpected safety concerns. Approximately 25,000 participants aged 60 years and older in the U.S., Canada and 15 other countries were randomized to receive a single dose of the RSVpreF3 vaccine or placebo.[10] Results from this trial investigating the immunogenicity, safety, reactogenicity and persistence of the vaccine candidate will be presented in a peer-reviewed journal and at an upcoming scientific meeting.[11]

RSVPreF3 is the first candidate RSV vaccine to show statistically significant and clinically meaningful efficacy in older adults. Further, the magnitude of its effect was consistent across both RSV A and B strains, and in individuals aged 70 years and older. "These [soon to be disclosed] data suggest our RSV vaccine candidate offers exceptional protection for older adults from the serious consequences of RSV infection," said Chief Scientific Officer and R&D President Hal Barron, MD. "Given the importance of these data, we plan to engage with regulators immediately and anticipate regulatory submissions in the second half of 2022."

GSK is additionally investigating a promising immunization strategy in expectant mothers to protect their young infants against serious RSV-mediated pulmonary disease. A recently completed Phase II trial randomized a total of 534 pregnant women to receive a single IM dose of an unadjuvanted form of RSVPreF3 or a saline placebo. Investigators examined titers of anti-RSV antibodies that crossed the placenta into the newborn, as well as percentages of infants with RSV-associated severe LRTI from birth to day 181 post-birth; their findings are expected to be presented shortly.[12]

Pfizer bivalent prefusion F vaccine (RSVpreF). Highly encouraging results have been reported from a Phase IIa study of Pfizer's RSVpreF vaccine candidate in 62 healthy adult volunteers 18 to 50 years of age, who were randomized to receive an IM injection of either the vaccine or placebo, followed 28 days later by intranasal inoculation with RSV A Memphis 37b challenge virus.[13] RSVpreF achieved protective efficacy of 86.7 percent (95 percent confidence interval 53.8 to 96.9 percent) for symptomatic RSV infection, confirmed by absence of any detectable viral RNA on at least two consecutive days. The median area under the curve for RSV viral load (expressed as hours x $\log_{10}$ copies per milliliter) was 0.0 in the vaccine group

and 96.7 in the placebo group. These findings coincided with a large increase in RSV group A-neutralizing titers 28 days after injection in vaccine group subjects, but not in placebo group subjects. No serious adverse events were observed in either group.

Moderna messenger RNA vaccine (mRNA-1345). The U.S. Food and Drug Administration (FDA) has granted this novel vaccine candidate a fast track designation for adults aged 60 years and older. Similar to its COVID-19 antigen vaccine, mRNA-1345 uses Moderna's messenger RNA delivery technology to direct production of the preF glycoprotein in cells of the vaccinated individual.

A Phase II/III trial of mRNA-1345 is now in progress. The Phase II segment is randomly assigning between 400 and 2,000 participants to receive a single injection of either mRNA-1345 or placebo. In the Phase III segment, between 32,000 and 34,000 participants aged 60 years and older will be randomized 1:1 to receive the vaccine or placebo, and followed for 12 months postinjection to assess the ability of mRNA-1345 to prevent a first episode of RSV-caused LRTI.[14]

Moderna is also conducting a trial involving co-administration of mRNA-1345 with a seasonal influenza vaccine (Afluria Quadrivalent), and separately with the company's SARS-CoV-2 vaccine, to evaluate the impact of co-administration on immune response to each of these vaccines.

CyanVac/Blue Lake PIV5-based vector vaccine encoding RSV-F protein. The clinical-stage vaccine developer Blue Lake Biotechnology and parent company CyanVac are developing a novel intranasally delivered RSV vaccine, named BLB-201, that uses a proprietary attenuated parainfluenza virus 5 (PIV5)-based vector to express the full-length RSV-F protein. BLB-201 is being developed for the prevention of RSV disease in adults over age 60 years and children under age 2 years. Administered for decades to dogs as part of combination distemper and kennel cough vaccines, this attenuated PIV5 vector is not known to cause disease in humans.

In July 2022, Blue Lake initiated a Phase I trial to assess the safety and immunogenicity of BLB-201 in 15 healthy young adult volunteers aged 18 to 59 years, and the same number of healthy older adults aged 60 to 75 years.[15,16] The trial is designed to assess the safety, tolerability and immunogenicity of a single dose of BLB-201. Based on preclinical studies showing that it is immunogenic and prevents RSV infection in animal challenge studies, BLB-201 has received fast track designation from FDA.

AstraZeneca/Sanofi long-acting monoclonal antibody. In collaboration with Sanofi, which will commercialize the product if approved, AstraZeneca is in late-stage development of nirsevimab, a single-dose, long-acting antibody intended to provide protection against RSV-caused LRTIs both for all infants experiencing their first RSV season, and for infants with pulmonary or cardiac conditions that place them at increased risk.

> A number of RSV vaccine development strategies have been pursued over the more than six decades since this enveloped virus was first identified in 1956.

Passive Immunotherapy for Healthy and High-Risk Infants

Because the relative immaturity of the immune systems of infants under age 2 years can limit the value of vaccination against RSV, most drug developers have settled on a passive immunotherapy strategy to prevent LRTI in this population. Since its approval in 1998, Sobi's Synagis (palivizumab) monoclonal antibody against the RSV F protein has been prescribed for the prevention of LRTI in premature infants (less than 35 weeks gestational age) aged 6 months or younger at the start of the RSV season, as well as children under age 24 months with significant congenital heart disease (CHD) or recently treated bronchopulmonary dysplasia (BPD). But Synagis' applicability beyond these narrow indications has been limited by the requirement to administer IM doses every month throughout the five-month RSV season.

In 2020, findings from a Phase IIb trial of nirsevimab in 1,453 healthy preterm infants (29 weeks to 34 weeks 6 days of gestation) showed a 70.1 percent lower incidence of medically attended LRTIs — mainly bronchiolitis and pneumonia — with a single prophylactic dose of nirsevimab than with placebo (2.6 percent versus 9.5 percent). The incidence of hospitalization for RSV-associated LRTI was 78.4 percent lower with nirsevimab than with placebo (0.8 percent versus 4.1 percent). Adverse events were similar in the two trial groups, with no notable

hypersensitivity reactions.[17] The Phase II/III MEDLEY trial documented a similar safety and tolerability profile for nirsevimab compared to palivizumab treatment when administered to preterm infants or those with chronic lung disease or congenital heart disease entering their first RSV season.[18]

Subsequently, the multinational Phase III MELODY study demonstrated that, compared to placebo injection, a single IM injection of nirsevimab achieved a 74.5 percent reduction in the incidence of LRTI caused by RSV in healthy preterm (≥35 week gestational age) and term infants entering their first RSV season (1.2 percent versus 5.0 percent; P<0.001).[19]

In a pooled post-hoc analysis, blood samples taken from infants dosed with nirsevimab exhibited RSV neutralizing antibodies roughly 50-fold higher than baseline at day 151 post-dose. RSV neutralizing antibody levels remained greater than 19-fold higher than levels in placebo recipients, with no known RSV infection through day 361, suggesting protection could extend beyond day 151.

Merck long-acting monoclonal antibody. MK-1654, Merck's anti-RSV antibody product, is also being investigated as a single-injection prophylactic treatment to prevent RSV-associated LRTI in 1) all infants entering their first RSV season and 2) young children in their second year of life who are at high risk of RSV disease. This IgG antibody binds to the highly conserved site IV of the F glycoprotein on RSV, and has increased potency compared to Synagis. MK-1654 attains its extended circulating half-life by means of three amino acid substitutions that augment recycling through the neonatal Fc receptor.

A Phase IIb/III randomized, placebo-controlled trial is now enrolling up to 3,300 healthy preterm and full-term infants to assess whether MK-1654 can significantly reduce the incidence of medically attended LRTIs over 150 days following injection with the vaccine. The study is expected to be completed in 2024.[20]

Findings from these trials have not yet been reported, but the company's model-based meta-analysis predicts a high probability that a single dose of ≥75 mg of MK-1654 will result in prophylactic efficacy in treated infants over the five-month RSV season.[21]

Meeting an Under-Recognized Need

Until recently, the morbidity and mortality burden associated with RSV infection had been underestimated at both ends of the age spectrum, infectious disease experts noted in a recent review. Perhaps most surprisingly, modeling studies now estimate that the overall RSV disease burden is similar to the burden of seasonal influenza in adults older than 65 years.[22]

No fewer than six vaccines and two monoclonal antibody products are now in Phase III clinical testing, with numerous others in Phase I or II development. Notably, AstraZeneca's nirsevimab is expected to be approved within the next year to two years;[23] the company's marketing authorization application was accepted for review earlier this year by the European Medicines Agency.

Thanks to the industry's efforts to advance an array of innovative new vaccines and antibody therapies that resolve the shortcomings of their predecessors, safe and effective prophylactic treatments for RSV may finally be close at hand. ❖

References

1. Griffiths C, Drews SJ, Marchant DJ. Respiratory syncytial virus: Infection, detection, and new options for prevention and treatment. *Clin Microbio Rev* 2017 Jan;30(1):277-319.
2. U.S. Centers for Disease Control and Prevention (CDC). Respiratory Syncytial Virus-Associated Mortality. Accessed at ndc.services.cdc.gov/case-definitions/respiratory-syncytial-virus-associated-mortality-2019.
3. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. *New Engl J Med* 2009;360:588-98.
4. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003;289:179-86.
5. Hansen CL, Chaves SS, Demont C, et al. Mortality associated with influenza and respiratory syncytial virus in the U.S., 1999-2018. *JAMA Netw Open* 2022 Feb 1;5(2):e220527.
6. U.S. Centers for Disease Control and Prevention (CDC). RSV in Older Adults and Adults with Chronic Medical Conditions. Accessed at www.cdc.gov/rsv/high-risk/older-adults.html.
7. Falsey AR, Hennessey PA, Formica MA, et al. Respiratory syncytial virus infection in elderly and high-risk adults. *New Engl J Med* 2005 Apr 28;352(17):1749-59.
8. Fulginiti VA, Eller JJ, Sieber OF, et al. Respiratory virus immunization: I. A field trial of two inactivated RSV vaccines; an aqueous trivalent parainfluenza virus vaccine and an alum-precipitated RSV vaccine. *Am J Epidemiol* 1969;89:435-48.
9. Belshe RB, Van Voris LP, Mufson MA. Parenteral administration of live respiratory syncytial virus vaccine: Results of a field trial. *J Infect Dis* 1982;145:311-19.
10. ClinicalTrials.gov. Efficacy Study of GSK's Investigational RSV Vaccine in Adults Aged 60 Years and Above (NCT04886596). Accessed at clinicaltrials.gov/ct2/show/NCT04886596?term=RSVPreF3&draw=1&rank=5.
11. GSK announces positive pivotal phase III data for its respiratory syncytial virus (RSV) vaccine candidate for older adults (June 10, 2022). Accessed at www.gsk.com/en-gb/media/press-releases/gsk-announces-positive-pivotal-phase-iii-data-for-its-respiratory-syncytial-virus-rsv-vaccine-candidate-for-older-adults.
12. ClinicalTrials.gov. Study of Safety, Reactogenicity and Immunogenicity of RSV Maternal Unadjuvanted Vaccine in Healthy Pregnant Women (Aged 18 to 40 Years) and Their Infants (NCT04126213). Accessed at clinicaltrials.gov/ct2/show/NCT04126213?term=Glaxosmithkline&cond=Respiratory+Syncytial+Virus+Infections&draw=2&rank=4.
13. Schmoele-Thoma B, Zareba AM, Jiang Q, et al. Vaccine efficacy in adults in a respiratory syncytial virus challenge study. *N Engl J Med* 2022 Jun 23;386(25):2377-86.
14. ClinicalTrials.gov. A Study to Evaluate the Safety and Efficacy of mRNA-1345 Vaccine Targeting RSV in Adults ≥60 Years of Age (NCT05127434). Accessed at clinicaltrials.gov/ct2/show/NCT05127434?term=Moderna+mRNA-1345&draw=2&rank=1.
15. ClinicalTrials.gov. Phase 1 Study of BLB-201 Vaccine in Healthy Young and Older Adults (NCT05281263). Accessed at clinicaltrials.gov/ct2/show/NCT05281263?term=BLB-201&draw=2&rank=1.
16. Blue Lake Biotechnology announced first participant dosed in a phase 1 clinical trial of its BLB-201 intranasal RSV vaccine (July 21, 2022). Accessed at www.prnewswire.com/news-releases/blue-lake-biotechnology-announces-first-participant-dosed-in-a-phase-1-clinical-trial-of-its-blb-201-intranasal-rsv-vaccine-301590734.html.
17. Griffin MP, Yuan Y, Takas T, et al. Single-dose nirsevimab for prevention of RSV in preterm infants. *New Engl J Med* 2020 Jul 30;383(5):415-25.
18. Sanofi. Nirsevimab shows positive topline results in RSV Phase 2/3 MEDLEY trial (June 28, 2021). Accessed at www.sanofi.com/en/media-room/press-releases/2021/2021-06-28-06-00-00-2253567.
19. Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. *New Engl J Med* 2022 Mar 3;386:837-46.
20. ClinicalTrials.gov. Efficacy and Safety of MK-1654 in Infants (NCT04767373). Accessed at clinicaltrials.gov/ct2/show/NCT04767373.
21. Maas BM, Lommerse J, Plock N, et al. Forward and reverse translational approaches to predict efficacy of neutralizing RSV antibody prophylaxis. *EBioMedicine* 2021 Nov;73:103651.
22. Mazur NI, Terstappen J, Baral R, et al. Respiratory syncytial virus prevention within reach: the vaccine and monoclonal antibody landscape. *Lancet Infect Dis* 2022 Aug 8;S1473-3099.

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

Going Beyond Distribution

FFF Enterprises is reinforcing the safety and efficacy of the pharmaceutical supply chain.

RESPONSIBLE DISTRIBUTION

Controlled Volume Measures™

Ensuring healthcare systems are prepared with adequate supplies of essential medications, especially during times of crisis or shortage.

FAIR PRICING

Costparency™

Our pledge to reject deceptive pricing tactics and provide the lowest cost available for products and services.

WORRY-FREE TECHNOLOGY

RightNow Inventory™

Inventory management system continuously monitors critical-care pharmaceuticals to minimize product waste and maximize patient safety.

Products You Need, When You Need Them

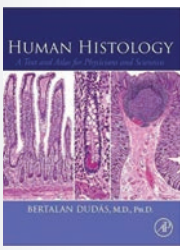
- Adult Vaccines
- Albumin
- Ancillaries
- Antithrombin
- Antivirals
- Biosurgicals
- Brand Pharmaceuticals
- Coagulation
- Controlled Substances
- Dermatology
- Generic Pharmaceuticals
- Hyperimmune Globulin
- Immune Globulin
- Influenza Vaccines
- Oncology
- Ophthalmology
- Orthopedic
- Pediatric Vaccines

FFF enterprises
Helping Healthcare Care®

Order Today

Biosupply.FFFenterprises.com | MyFluVaccine.com

(800) 843-7477 | FFFCUSTOMERCARE@FFFENTERPRISES.COM | FFFENTERPRISES.COM



Human Histology: A Text and Atlas for Physicians and Scientists, 1st Edition

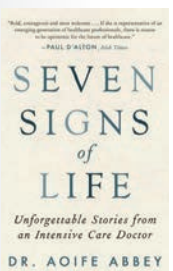
Author: Bertalan Dudas, MD, PhD

This text covers the normal histology of every organ in the human body, presenting full-page, low-magnification photomicrographs for organs and tissues that are surrounded by high-power images of the same sample. Each specimen is followed by a compact and simple-to-read description of the structures identified on the micrographs, offering a clear, visual understanding of this complex subject. With nearly 600 images, this reference is a resource for every clinical researcher and pathologist who needs easily accessible, relatively simple, detailed information on normal histology of different organs systems.

www.amazon.com/Human-Histology-Atlas-Physicians-Scientists/dp/0323918913

Seven Signs of Life: Unforgettable Stories from an Intensive Care Doctor

Author: Aoife Abbey, MRCP, FFICM

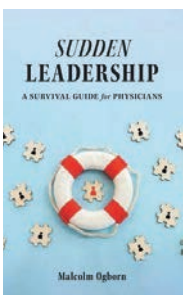


Dr. Aoife Abbey takes readers beyond the medical perspective to see the humanity at work inside hospitals through the eyes of doctors and nurses as they witness and experience the full spectrum of human emotion. It is their responsibility to mitigate the grief of a family in mourning, calm a patient about to die and confront their own fear of failure when lives are on the line. Whether they're providing hospice care or tending to victims of car accidents or violent attacks, determining the correct treatment for someone displaying signs of a heart attack, stroke or managing staff, stress is a doctor's No. 1 companion. Told using seven key emotions — fear, grief, joy, distraction, anger, disgust and hope — *Seven Signs of Life* opens the door, and heart, of the hectic life inside a hospital to reveal what it means to be alive and how it feels to care for others.

www.amazon.com/Seven-Signs-Life-Unforgettable-Intensive/dp/1951627482

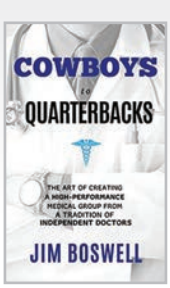
Sudden Leadership: A Survival Guide for Physicians

Author: Malcolm Ogborn, MBBS, FRCPC, COC, PCC



Sudden Leadership follows the early leadership journeys of two fictitious physicians. For each scenario in which the characters find themselves, Dr. Ogborn reviews relevant, evidence-based literature and offers pragmatic and field-tested approaches that allow new professional leaders to face their challenges with confidence. Topics include defining your leadership, attracting and engaging followers, motivating and managing others, running meetings, handling tough conversations, strong team leadership, mastering time allocation, successfully managing conflict, preventing burnout and leading change or system improvement.

www.amazon.com/Sudden-Leadership-Survival-Guide-Physicians/dp/1039132278



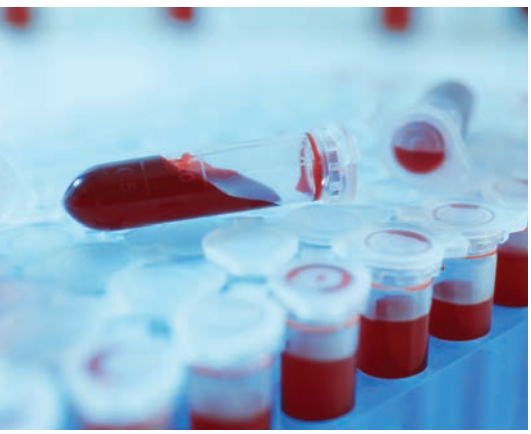
Cowboys to Quarterbacks: The Art of Creating a High-Performance Medical Group from a Tradition of Independent Doctors

Author: Jim Boswell

Jim Boswell, a well-known and recognized expert in creating high-performing, highly engaged physician partnerships, talks about how to create a culture that truly engages the physicians to contribute fully and become active leaders, fully aligned with the overall strategies of the health system. Drawing on more than three decades as a large group practice CEO, health system executive and physician alignment consultant, Boswell takes the reader through many real-life strategies and examples to engage their physicians and to create a collaborative environment based upon trust.

www.amazon.com/Cowboys-Quarterbacks-High-Performance-Tradition-Independent/dp/1950892476

Fitusiran Prophylaxis Reduces Bleeds Versus Prior Factor or Bypassing Agent Prophylaxis in Hemophilia A and B Patients



Prophylaxis with fitusiran, Sanofi's investigational small interference RNA (siRNA) therapeutic, significantly reduced bleeding in a Phase III multinational study in adults and adolescents with hemophilia A or B, with or without inhibitors, compared to their previous factor or bypassing agent (BPA) prophylaxis. Fitusiran targets antithrombin to rebalance hemostasis in people with hemophilia A or B, regardless of inhibitor status.

Of 65 study participants eligible for annualized bleeding rate (ABR) analyses, 50 had hemophilia A and 15 had hemophilia B; 19 participants had an inhibitor and 46 did not have an inhibitor. Median observed ABRs (interquartile range) were 4.4 (2.2; 10.9) with prior factor or BPA prophylaxis, and 0.0 (0.0; 2.3) with fitusiran prophylaxis. Fitusiran prophylaxis resulted in a 61.1 percent reduction in the estimated ABR versus factor or BPA prophylaxis

Forty-one of the 65 participants (63.1%) treated with 80 mg of subcutaneous fitusiran over a period of seven months experienced zero treated bleeds, compared to 11 (16.9%) of these participants on prior factor or BPA prophylaxis. Fitusiran also significantly improved health-related quality of life (HRQoL) in relation to prior factor or BPA, as measured by the Haem-A-QOL total score. Serious adverse events occurred in five of 65 participants (7.7%) during factor/BPA prophylaxis and nine of 67 (13.4%) during fitusiran prophylaxis. Two participants experienced suspected or confirmed thromboembolic events with fitusiran. ❖

Kenet G, Nolan B, Zulfikar B, et al. A Phase 3 study (ATLAX-PPX) to evaluate efficacy and safety of fitusiran, an siRNA therapeutic, in people with haemophilia A or B who have switched from prior factor or bypassing agent prophylaxis. International Society on Thrombosis and Haemostasis 2022 Congress (Abstract LB 01.1); 2022 July 9-13.

IVIG Improves Live Birth Rate in Women with Immune Conditions and Recurrent Pregnancy Loss: Review and Meta-Analysis

Encouraged by recent data suggesting intravenous immune globulin (IVIG) might be more effective in a subgroup of women with recurrent pregnancy loss (RPL) who additionally have an aberrant immunological profile, Dutch investigators conducted a systematic review and meta-analysis of studies on the effectiveness of IVIG treatment of this specific population.

Included among underlying immunological conditions in women with RPL were elevated NK cell percentage, elevated Th1/Th2 ratio and diagnosis with an autoimmune disorder. Eight nonrandomized controlled trials, including a total of 478 women (intervention: 248; control 194) met eligibility criteria.

A meta-analysis showed that treatment with IVIG was associated with a two-fold increase in the live birth rate (relative risk [RR] 1.98, 95% confidence interval [CI] 1.44-2.73, P < 0.0001). The effect of IVIG was particularly marked in the subgroup of studies including patients based on presence of elevated (greater than 12%) NK-cell percentage (RR 2.32, 95% CI 1.77-3.02, P < 0.0001), as well as in women who started IVIG therapy prior to or during the conception cycle (RR 4.47, 95% CI 1.53-13.05, P = 0.006).

The investigators noted, however, that "these results should be interpreted with caution as the studies are limited by low number[s] of participants and the nonrandomized design, which represent serious biases." They advocated for future randomized controlled trials in women with RPL and underlying immune conditions before using IVIG in a clinical setting. ❖

Habets DHJ, Pelzner K, Wieten L, et al. Intravenous immunoglobulins improve live birth rate among women with underlying immune conditions and recurrent pregnancy loss: a systematic review and meta-analysis. *Allergy Asthma Clin Immunol* 2022 Mar 11;18(1):23.

Medicare Immune Globulin Reimbursement Rates

Rates are effective Oct. 1, 2022, through Dec. 31, 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	$79.74	$78.46
	GAMMAGARD SD	Takeda	J1566	$148.00	$145.63
	GAMMAPLEX	BPL	J1557	$102.15	$100.51
	OCTAGAM	Octapharma	J1568	$84.20	$82.85
	PANZYGA	Octapharma/Pfizer	90283/J1599	$139.28	$137.04
	PRIVIGEN	CSL Behring	J1459	$93.40	$91.91
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$90.46	$89.01
	GAMMAKED	Kedrion	J1561	$89.34	$87.90
	GAMUNEX-C	Grifols	J1561	$89.34	$87.90
SCIG	CUTAQUIG	Octapharma	J1551	$127.21	$125.17
	CUVITRU	Takeda	J1555	$149.00	$146.61
	HIZENTRA	CSL Behring	J1559	$123.63	$121.65
	HYQVIA	Takeda	J1575	$158.85	$156.30
	XEMBIFY	Grifols	J1558	$137.79	$135.58

Calculate your reimbursement online at www.FFFenterprises.com.

Immune Globulin Reference Table

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

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

2022-2023 Influenza Vaccine

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

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

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

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

Don't *ah-choo* this season

Protect Patients From The Flu

MYFLUVACCINE.COM

YOU PICK THE PRODUCTS • YOU PICK THE QUANTITY • WE DELIVER

(800) 843-7477 | FFFenterprises.com

MyFluVaccine® Program Advantages

With MyFluVaccine® you can take control and manage your flu inventory with ease while meeting your flu clinic demands. Our revolutionary online vaccine ordering platform paves the way to help you improve your patients' care.

MyFluVaccine® (MFV) is a program of FFF Enterprises Inc., the nation's largest and most trusted distributor of flu vaccines and critical-care biopharmaceuticals.

myfluvaccine®

Benefits:

Choice
Multiple presentations from top manufacturers.

Commitment
Aligned with manufacturers' estimated shipping commitments.

Confidence
Dependable deliveries to meet your patients' needs.

Safety
Guaranteed Channel Integrity® ensures safe, reliable products for your patients.

BioSupply Trends Quarterly
44000 Winchester Road
Temecula, CA 92590-9760

PRSRT STD
US POSTAGE PAID
LEBANON JUNCION, KY
PERMIT NO. 714