FALL 2021

biosupply trends
QUARTERLY

SPECIAL FOCUS:
INNOVATION

Healthcare Delivery

Meeting the Needs of an Elderly Demographic

Primary Care Expansion
IN A POST-COVID-19 WORLD

The Future of Telehealth
OPTIONS AND REIMBURSEMENT

Predictive Medicine:
TRANSITIONING FROM 'SICK' CARE TO 'PREVENTIVE' CARE

Will Virtual Clinical Trials
EQUAL INCREASED DRUG APPROVALS?

MIS-C:
A COMPLICATION OF COVID-19

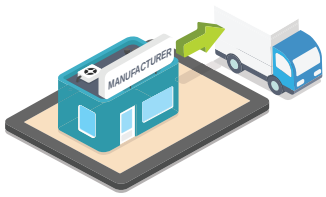
Hemophilia Gene Therapy Cures p.56

Guaranteed Channel Integrity®
8 Critical Steps

STEP 1

Purchasing

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



STEP 2

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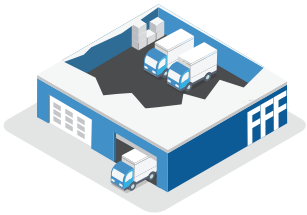
The healthcare products we store and transport are sensitive to temperature variations. Our state-of-the-art warehouse is temperature-controlled, monitored 24/7, and supported with backup generators in the event of power loss. In addition, we only stack products double-high to minimize pressure on fragile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



STEP 3

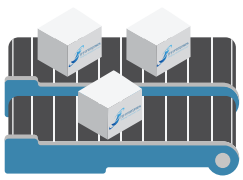
Specialty Packaging

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.

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About BioSupply Trends Quarterly

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

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The Future of Medicine: How Care Delivery Is Changing

THE HEALTHCARE system is poised to change more in the next decade than it has in the past 50 years. At the root of this dynamic is an aging population and a pandemic that is transforming the way healthcare is delivered. These are exciting times, but they will also likely be fraught with significant challenges.

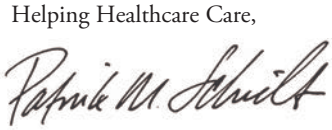
With one out of five Americans reaching retirement age by 2030 and elderly adults expected to outnumber children just five years later, the number of available healthcare workers to provide care will likely be insufficient to meet demand. But, as we discuss in our article "Impacts of an Aging Demographic on Healthcare" (p.16), the industry is eyeing alternatives to meet this demand, including technological innovation and preventive care. Digital health apps to monitor chronic conditions, telehealth appointments and Internet access to medical resources and information will help to potentially increase care access and minimize costs. In addition, many healthcare organizations and a growing number of start-ups are promoting preventive health services to help seniors live more independently and avoid the high cost of hospitalizations and long-term care.

Of course, the COVID-19 pandemic is also contributing to the healthcare shortage due to overburdened resources, logistical challenges and declining revenues. Recognizing this, primary care practices are adapting by expanding their services into the retail market. In our article "Expansion of Primary Care in a Post-COVID-19 World" (p.24), we delve into the many ways these facilities are increasing access to care through telemedicine, as well as providing services in big-box settings such as Walmart and CVS that offer wellness and prevention programs and upfront fee disclosures. Indeed, overcoming financial barriers to care is paramount to care access, which could be achieved by reimbursing pharmacists who provide healthcare services such as vaccination and counseling.

It is becoming increasingly clear that predictive medicine could be key to preventing the risk of disease. In our article "Predictive Medicine: How DNA Testing Is Influencing Healthcare" (p.28), Brandon Colby, MD, founder and CEO of Sequencing.com, the world's largest platform for DNA testing and analysis, gives readers a bird's-eye view of how genetic testing and whole genome sequencing can help predict what disease risk a person might face, as well as suggest ways to prevent it and devise a treatment plan. As Dr. Colby explains, it's about changing the paradigm of healthcare from a "sick care" model to one focused on personalized prevention of disease.

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

Helping Healthcare Care,



Patrick M. Schmidt
Publisher

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

Publisher
Patrick M. Schmidt

Editor
Ronale Tucker Rhodes, MS

Assistant Editor
Cheryl Brooks

Art Director
Allan Bean

Contributing Writers
Keith Berman, MPH, MBA
Bob Geng, MD, MA
Matthew Hansen, DPT, MPT, MBA
Bonnie Kirschenbaum, MS, FASHP, FCSHP
Trudie Mitschang
Amy Scanlin, MS
E. Richard Stiehm, MD
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

HHS Launches Reimbursement Program for COVID-19 Vaccine Administration Fees

The U.S. Department of Health and Human Services (HHS) has launched a new program that covers costs of administering COVID-19 vaccines to patients enrolled in health plans that either do not cover vaccination fees or cover them with patient cost-sharing. Since providers cannot bill patients for COVID-19 vaccination fees, this new program, the COVID-19 Coverage Assistance Fund (CAF), addresses a compensation need for providers on the frontlines vaccinating underinsured patients.

"After securing enough COVID-19 vaccines for all adults, the Biden-Harris Administration is elevating work to boost access to them," said HHS Secretary Xavier Becerra. "We listened to our healthcare providers on the frontlines of the pandemic. On top of increasing reimbursement rates tied to administering the shots, we are closing the final payment gap that resulted as vaccines were administered to underinsured individuals. No healthcare provider should hesitate to deliver these critical vaccines to patients over reimbursement cost concerns."

CAF is focusing on instances in which individuals have insurance, but vaccines are either not covered or are with patient cost-sharing. To address these gaps, CAF will compensate providers for eligible claims at national Medicare rates that increased in March to reflect newer information on the true costs associated with administering the vaccines. CAF also builds on the Health Resources and Services Administration's COVID-19 Uninsured Program, which has been reimbursing providers for vaccine administration fees associated with uninsured individuals. ❖

HHS Launches New Reimbursement Program for COVID-19 Vaccine Administration Fees Not Covered by Insurance. U.S. Department of Health and Human Services press release, May 3, 2021. Accessed at www.hhs.gov/about/news/2021/05/03/hhs-launches-new-reimbursement-program-for-covid19-vaccine-adminsitration-fees-not-covered-by-insurance.html?utm_source=news-releases-email&utm_medium=email&utm_campaign=may-9-2021.

New Rule Protects Consumers Against 'Surprise' Medical Bills

The U.S. Department of Health and Human Services (HHS) has issued "Requirements Related to Surprise Billing; Part I," an interim final rule that will restrict excessive out-of-pocket costs to consumers from surprise billing and balance billing. Surprise billing happens when people unknowingly get care from providers outside of their health plan's network for both emergency and nonemergency care. Balance billing, when a provider charges a patient the remainder of what insurance does not pay, is currently prohibited in both Medicare and Medicaid. This rule will extend similar protections to Americans insured through employer-sponsored and commercial health plans.

Among other provisions, today's interim final rule:

- Bans surprise billing for emergency services. Emergency services, regardless of where they are provided, must be treated on an in-network basis without requirements for prior authorization.
- Bans high out-of-network cost-sharing for emergency and nonemergency services. Patient cost-sharing, such as coinsurance or a deductible, cannot be higher than if such services were provided by an in-network doctor, and any coinsurance or deductible must be based on in-network provider rates.
- Bans out-of-network charges for ancillary care (like an anesthesiologist or assistant surgeon) at an in-network facility in all circumstances.
- Bans other out-of-network charges without advance notice. Healthcare providers and facilities must provide patients with a plain-language consumer notice explaining that patient consent is required to receive care on an out-of-network basis before that provider can bill at the higher out-of-network rate.

"No one should ever be threatened with financial ruin simply for seeking needed medical care," said U.S. Secretary of Labor Marty Walsh. "Today's interim final rule is a major step in implementing the bipartisan No Surprises Act that will protect Americans from exorbitant health costs for unknowingly receiving care from out-of-network providers."

The interim final rule will take effect for healthcare providers and facilities Jan. 1, 2022. For group health plans, health insurance issuers and Federal Employees Health Benefits Program carriers, the provisions will take effect for plan, policy or contract years beginning on or after Jan. 1, 2022. ❖

HHS Announces Rule to Protect Consumers from Surprise Medical Bills. U.S. Department of Health and Human Services press release, July 1, 2021. Accessed at www.hhs.gov/about/news/2021/07/01/hhs-announces-rule-to-protect-consumers-from-surprise-medical-bills.html?utm_source=news-releases-email&utm_medium=email&utm_campaign=july-4-2021.

HHS Issues '100-Day Report' to Strengthen Supply Chain Pharmaceutical Products

A report has been issued by the U.S. Department of Health and Human Services (HHS) with recommendations to strengthen the country's supply chain for key products, including pharmaceuticals, critical to the economic prosperity and national security of the U.S. The "100-day report" is a culmination of the analysis by various government departments of supply chain vulnerabilities. It specifically highlighted a shortage of essential medicine during the early stages of the COVID-19 pandemic that "wreaked havoc on the U.S. healthcare system."

The report identifies key vulnerabilities — mostly quality issues — in the current drug supply chain that contribute to drug shortages. Importantly, 503B outsourcing facilities are the only pharmaceutical compounders that must follow and comply with current good manufacturing practices to ensure quality. Outsourcing facilities have mitigated drug shortages before, during and will continue to do so after the COVID-19 pandemic.

To help healthcare providers connect with outsourcing facilities that are mitigating drug shortages, the Outsourcing Facilities Association released and maintains a database of outsourcing facilities and the drug shortage products they produce. A more robust and timely listing of drug shortages by the U.S. Food and Drug Administration (FDA) on FDA's drug shortage list will enable outsourcing facilities to respond to drug shortages in a more timely fashion while softening the impact of drug shortages on the uninterrupted provision of quality healthcare. ❖

Fact Sheet: Biden-Harris Administration Announces Supply Chain Disruptions Task Force to Address Short-Term Supply Chain Discontinuities. The White House press release, June 8, 2021. Accessed at www.whitehouse.gov/briefing-room/statements-releases/2021/06/08/fact-sheet-biden-harris-administration-announces-supply-chain-disruptions-task-force-to-address-short-term-supply-chain-discontinuities.

$2M NIH Grant Awarded to Study Alzheimer's

The National Institutes of Health (NIH) has awarded a $2 million grant for a preclinical study at The University of Texas Health Science Center at Houston (UTHealth) that will examine the role of infections in the development of Alzheimer's disease.

Specifically, the study will look at the role of sepsis and meningitis in the development of Alzheimer's and seek to identify the underlying molecular and cellular mechanisms. The hope is that doctors in the future will be able to identify patients who have an increased risk of developing Alzheimer's based on whether they previously had sepsis or meningitis.

According to Rodrigo Morales, PhD, associate professor in the department of neurology at the university's McGovern Medical School, the activation of the peripheral immune system, or the immune system outside the brain and spinal cord, could be a link between infections and the development of Alzheimer's. Immune responses in the brain or other peripheral locations could activate resident immune cells in the brain. The team's hypothesis is that "chronic immune activation or severe acute events may lead to different clinical conditions at short or long terms."

The researchers pointed out that a damaged blood-brain barrier could be another link between infections and an increased risk of developing Alzheimer's. "The blood-brain barrier acts as the defense mechanism for the brain allowing certain substances to enter the brain and keeping other substances out, but during an event like an injury or infection, that barrier is compromised, which allows those substances that might be harmful to the brain to enter it," said Dr. Morales. "These substances can lead to the buildup of inflammation in the brain, which in turn can lead to the development of Alzheimer's disease."

Transgenic mice and human samples will be used in the study, as well as a technology known as protein misfolding cyclic amplification, an in vitro technique that has previously shown to detect altered

proteins associated with Parkinson's and Creutzfeldt-Jakob disease.

"If we can prove the theory that infection is one of the factors that triggers Alzheimer's disease, and specifically sepsis and meningitis, we can pay more attention to these diseases and possibly be able to avoid the onset of dementia for people in the long term," added Tatiana Barichello, PhD, co-principal investigator of the study. ❖

Pinto V. $2M NIH Grant Goes to Study of Infection's Role in Alzheimer's. *Alzheimer's News Today*, July 26, 2021. Accessed at alzheimersnewstoday.com/2021/07/26/2m-nih-grant-uthealth-study-role-of-infection-alzheimers-development.

2022 Proposed OPPS/ASC and PFS Payment Rules: The Impact on Pharmacy

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

THE PROPOSED 2022 outpatient prospective payment system (OPPS)/ ambulatory surgery center (ASC) and physician fee schedule (PFS) rule sets impact all pharmacy practices. Continuing disruptions in healthcare involving multiple sites of care and new requirements necessitate new strategies that emphasize health equity and patient access to "create a healthcare system that results in better accessibility, quality, affordability, empowerment and innovation, touching on multiple facets of healthcare, from price transparency requirements to increased reimbursement rates for ASCs to a variety of health equity and patient safety efforts." The underlying message is that pharmaceutical practices must upgrade their reimbursement skill sets, become a player in sync with the directions being taken and recognize implications of their decisions, especially if made in a silo without knowledge of the payers.

2022 Proposed OPPS/ASC Key Areas

Transparency. Only 5.6 percent of U.S. hospitals are fully compliant with the Centers for Medicare and Medicaid's (CMS) price disclosure rule, according to a PatientRightsAdvocate.org study. New enforcement rules for hospital price transparency for standard charges continue to mandate hospitals publish payer-specific negotiated rates and other pricing information on their public websites, with failure-to-comply penalties increasing dramatically to as much as a minimum civil monetary penalty of $300 per day for smaller hospitals (bed count 30 or fewer), $10 per bed per day for hospitals with bed counts greater than 30, and up to $5,500 daily (maximum penalty per hospital increasing from $110,000 per year to more than $2 million per year). A ban on coding that hides prices is addressed in the clampdown on special coding that prevents search engines from displaying pricing in search results.

Inpatient-only (IPO) list changes. The 2021 OPPS rules began an IPO phase-out by removing nearly 300 of 1,700 services to improve restricted patient choice for surgery sites. The 2022 rules propose a halt to eliminating the IPO list that dictates services only payable by Medicare if performed in the inpatient setting. Both the proposed rollback of the IPO list and reversal of services removed in 2021 are based on stakeholder comments. Reinstated safety criteria for ASC services and removal of 267 procedures from the ASC-covered procedures list added in 2021 are also included. Pharmaceutical practices will be impacted by site changes, which equals loss of 340B pricing.

Other key areas focus on requests for information for rural emergency hospital providers outlined in the Consolidated Appropriations Act of 2021 and implementation of the radiation oncology model.

Nonopioid product payment (Section 6082 of the SUPPORT Act). This requires payment review under OPPS/ASC for opioids and evidence-based nonopioid alternatives for pain management to ensure there are no financial incentives to use opioids instead of nonopioids. In 2022, it is proposed to separate or modify payment for nonopioid pain management drugs/ biologicals functioning as supplies in ASC settings when those products meet certain CMS criteria (two products currently).

2022 Payment for Drugs and Biologicals (Based on 2019 vs. 2020 Claims Data)

CMS will continue to pay for Part B drugs divided into two categories:

separately payable with line-item reimbursement and not separately payable without line-item reimbursement since payment is part of a bundle/package. Billing for every drug is a CMS essential requirement regardless of which category covers the drug.

Separately payable with line-item reimbursement.

1) New drugs not yet assigned a unique HCPCS code will be paid at 95 percent of average wholesale price (AWP) when the NDC number is supplied and Medicare administrative contractor (MAC) requirements are met.

2) New pass-through drugs, biologicals and radiopharmaceuticals (status indicator [SI] G) remain at the 2021 reimbursement rate of average sales price (ASP) plus 6 percent. Policy packaged offsets may apply. Forty-six products keep pass-through status through 2022, with some expiration dates extended. Pass-through status expired for 25 products during 2021. All biosimilars are eligible for pass-through, not just the first one for each reference product. Details are available in Addendum B at www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Addendum-A-and-Addendum-B-Updates.

3) Specified covered outpatient drugs (SI K) retain the threshold of more than $130 per day based on ASP and are paid at ASP plus 6 percent if not purchased under the 340B program, or with payment based on wholesale acquisition cost (WAC) plus 3 percent until enough ASP data is gathered. Rates are ASP minus 22.5 percent if purchased under the 340B program (some exceptions apply) with WAC-priced drugs at WAC minus 22.5 percent and AWP-priced drugs at 69.46 percent of AWP.

Not separately payable without line-item reimbursement, paid as part of a bundle/package. These include lower-cost packaged products below the less than $130 per day threshold. Also included, regardless of cost, are products used in policy packaged services. Statute sets payment for these packaged drugs, biologicals and radiopharmaceuticals to be included in the services and procedures with which they are reported. Affected products are diagnostic radiopharmaceuticals; contrast agents; anesthesia drugs; implantable biologicals surgically inserted or implanted into the body through a surgical incision or natural orifice; drugs, biologicals and radiopharmaceuticals used as supplies in a diagnostic test or procedure; and drugs and biologicals used as supplies or implantable devices in a surgical procedure.

Note that pass-through expiration dates trigger a SI change from G to either K or N. This affects reimbursement rates and waste billing practices. Therefore, all drugs with SI of G, K and N must be billed for, regardless of whether they are separately payable. Unfortunately, it is common practice for some revenue cycle teams/billing services to put a hard stop on passing SI N-posted charges to the payer, which creates an inaccurate claims data file because the drug therapy and its costs are missing. It also prevents the payment of injectable drug administration charges because the administered drug isn't listed.

2022 PFS Key Areas

Incident-to-pharmacist-provided evaluation and management (E/M) services. There remain no changes in 2021. Reimbursement is limited to CPT code 99211. The changes to split-share billing apply only in institutional settings with no availability in outpatient settings since the "incident-to" regulations govern situations "where a nonphysician practitioner (NPP) works with a physician who bills for the visit, rather than billing under the NPP's own provider number."

Medicare Diabetes Prevention Program (MDPP). Provider enrollment application fees are waived for all organizations seeking to enroll in Medicare as an MDPP.

Vaccine provision/reimbursement. CMS is reviewing payments for COVID-19 and other preventive vaccines (e.g., influenza, shingles, pneumonia) and seeking feedback from vaccine providers regarding vaccine provision costs, including supplies and resources.

COVID-19. CMS is seeking provider input on what qualifies as the "home" in its preliminary policy to pay a $35 add-on for certain beneficiaries receiving COVID-19 vaccines at home, and whether COVID-19 monoclonal antibody products should be treated as other physician-administered drugs and biologics under Medicare Part B.

Electronic prescribing of controlled substances. The second phase of electronic prescribing for controlled substances for Medicare Part D drugs is being implemented with some exceptions: prescriber/dispensing pharmacy are the same entity; waivers will be provided for prescribers and prescribers in natural disaster areas/extraordinary circumstances; and compliance effective dates are extended by one year to Jan. 1, 2023 (Jan. 1, 2025 for long-term care Medicare Part D prescriptions).

Telehealth services.

1) Providers will be paid for certain mental/behavioral healthcare services provided via audio-only telehealth calls under certain services (opioid treatment counseling/therapy).

2) Geographic restrictions will be eliminated as barriers to telehealth services for mental health to allow for access to telehealth in the home.

3) Telehealth used for diagnosis, E/M and treatment of mental health disorders

will be covered. Physicians will be paid for mental health visits delivered via telehealth to rural and vulnerable patient populations.

4) Certain services will be added to the Medicare telehealth list to remain covered through the end of Dec. 31, 2023, so "there is a glide path to evaluate whether the services should be permanently added to the telehealth list following the COVID-19 public health emergency."

Other key issues are an appropriate use criteria penalty phase delay, quality payment program changes, physician assistant billing, Medicare Shared Savings program updates, treatment of critical care services and concurrent billing for chronic care management and transition care management services in rural healthcare centers and federally qualified healthcare centers. (Note: The final OPPS actual charge and PFS payment rule sets will be addressed in the Winter edition of *BioSupply Trends Quarterly*.)

2022 Medicare Inpatient Prospective Payment System/ Long-Term Care Final Rule

Inpatient rule sets in a variety of settings operate on a fiscal year beginning Oct. 1, while outpatient rule sets are on a calendar year beginning Jan. 1. After reviewing and considering facility submitted comments, CMS released multiple sets of final 2022 rules. Highlights include:

1) Add-on payment for COVID-19 treatment through the end of the fiscal year in which the public health emergency ends.

2) Most value-based payment program measures are suppressed during the public health emergency for COVID-19; hospitals will receive neutral payment adjustments in fiscal year 2022.

3) An approximate 2.5 percent rate increase is available to hospitals reporting quality data and that are meaningful electronic health record (EHR) users. Diagnosis-related group payments remain; however, clear, concise and accurate documentation is paramount.

4) Disproportionate shared hospital (DSH) uncompensated care payments will decrease by approximately $1.1 billion from fiscal year 2021.

5) CMS will implement its plan to remove median payer-specific negotiated rates by the Medicare Severity-Diagnosis-Related Groups (MSDRGs) with Medicare Advantage insurers, reducing administrative burdens.

6) The Inpatient Quality Reporting Program reduces payment to hospitals failing to meet defined requirements. CMS will add new measures to the program: COVID-19 vaccination rates among healthcare personnel, a metric targeting maternal morbidity, and two medication-related adverse event electronic clinical quality measures.

7) Changes to the Medicare Promoting Interoperability Program reduce the burden on eligible hospitals and critical access hospitals. Scoring thresholds considered to be meaningful EHR for the objectives and measures increases from 50 to 60 points, out of 100. Electronic clinical quality measures change with two new additions and three removals.

8) A new COVID-19 treatments add-on payment (NCTAP) is extended for certain eligible products through the end of the fiscal year in which the public health emergency ends. And, the NCTAP is discontinued for discharges on or after Oct. 1, 2021, for a product approved for NCTAP beginning in the fiscal year 2022.

Sequestration

Sequestration is derived from the Latin word sequestrare, which means something is locked away for safe keeping. When the ancient Romans couldn't agree who owned a piece of property, they gave it to a third party called the sequester who held onto it until the two sides resolved their differences. Currently, the budget limits Congress created in the 2011 Budget Control Act have been under threat of sequester to force legislators to reach deficit-limit agreements. Sadly, the threat didn't work; implementing the sequester, which cut spending from 2013 through 2021 with subsequent expiration dates extending into the future, the budget deficit looms larger.

This 2 percent reduction applies only to the 80 percent Medicare reimburses and not to the 20 percent patient copays. However, the COVID-19 pandemic brought a sequestration hold with the Coronavirus Aid, Relief and Economic Security Act, which suspended that cut to all Medicare fee-for-service claims from May 1 through Dec. 31, 2020. The Consolidated Appropriations Act of 2021 further extended the suspension to March 31, 2021. An act to prevent across-the-board direct spending cuts and for other purposes, signed into law April 14, 2021, extends the suspension period only to Dec. 31, 2021. And, the proposed infrastructure bill discussions maintain this date with no further extensions. ❖

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.

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Immune Discovery Could Prevent Hemophilia Treatment Failure

Researchers have made a key discovery that could prevent and eradicate immune responses that lead to treatment failure in approximately one-third of people with severe hemophilia A.

In the study, researchers used plasma samples from pediatric and adult hemophilia A patients and animal models to determine whether B-cell activating factor (BAFF) plays a role in the generation and maintenance of factor VIII (FVIII) inhibitors. They also looked at combining antibody to BAFF in an immune tolerance induction approach with a CD20 antibody (rituximab). Rituximab alone has shown mixed results in eradicating inhibitors when used alone in previous studies for hemophilia A.

Major findings from the study include:

• BAFF levels in plasma are higher in both pediatric and adult hemophilia A patients with persistent FVIII inhibitors,

and correlate with FVIII antibody titers, suggesting BAFF could be a potential harbinger for an ongoing humoral immune response to FVIII.

• An increase in BAFF levels after rituximab-based therapy precludes tolerance to FVIII.

• Blocking BAFF is effective in the prevention of FVIII inhibitors in an animal model of hemophilia A.

• Combination CD20/BAFF monoclonal antibody therapy induces tolerance in a hemophilia A animal model with established FVIII inhibitors. This is due to a concerted effect of the combination therapy on memory B cells and plasma cells.

Next, the researchers will perform in-depth mechanistic studies to identify additional BAFF modifiers, which may provide additional insight into the pathways that lead to BAFF elevation and inhibitor formation.

According to the researchers, these data also have important translational potential for inhibitors in hemophilia A, since there is a U.S. Food and Drug Administration-approved anti-BAFF antibody currently used as part of immunosuppressive regimens for autoimmune diseases. ❖

Immune Discovery Could Prevent Hemophilia Treatment Failure. Technology Networks, April 20, 2021. Accessed at www.technologynetworks.com/tn/news/immune-discovery-could-prevent-hemophilia-treatment-failure-347913.

Research

Methylprednisolone Added to IVIG May Cut Fever in MIS-C

Initial combination therapy of intravenous immune globulin (IVIG) plus methylprednisolone is associated with a better fever course than IVIG alone among patients hospitalized for multisystem inflammatory syndrome in children (MIS-C) associated with severe acute respiratory syndrome coronavirus 2 infection, according to a study published online in the *Journal of the American Medical Association*.

Naïm Ouldali, MD, PhD, from the Université de Paris, and colleagues compared the outcomes for IVIG plus methylprednisolone versus IVIG alone as initial therapy in 111 children with suspected MIS-C. Five children did not receive either treatment. They found three of 34 children in the IVIG and methylprednisolone group (9 percent) and 37 of 72 in the IVIG-alone group (51 percent) did not respond to treatment. The risk for treatment failure (persistence of fever two days after the introduction of initial therapy or recrudescence of fever within seven days) was lower in the IVIG and methylprednisolone group. The investigators also observed a significantly lower risk for use of second-line therapy in the IVIG and methylprednisolone group, along with a lower risk for hemodynamic support, lower risk for acute left ventricular dysfunction occurring after initial therapy, and shorter duration of stay in the pediatric intensive care unit (difference in days, –2.4).

"Combined treatment with methylprednisolone versus IVIG alone was associated with a better course of fever in MIS-C," the authors write. ❖

Ouldali N, Toubiana J, Antona D, et al. Association of Intravenous Immunoglobulins Plus Methylprednisolone vs Immunoglobulins Alone with Course of Fever in Multisystem Inflammatory Syndrome in Children. *JAMA*, Feb. 1, 2021 (published online). Accessed at jamanetwork.com/journals/jama/fullarticle/2776054.

Research

Elderly Patients of Women Doctors More Likely to Be Vaccinated Against the Flu

New research at the University of California, Los Angeles, suggests elderly patients of female physicians are more likely than those of male physicians in the same outpatient practice to be vaccinated against influenza (flu), a trend that is true for all racial and ethnic groups studied, which could provide insight into improving vaccination rates for flu, COVID-19 and other illnesses, according to the researchers.

The researchers examined Medicare claims data from 2006 through 2016 for both male and female beneficiaries age 65 years and older from four racial and ethnic groups: white, Black, Asian and Hispanic. The research sample included approximately 40 million patient visits to about 150,000 female physicians and 300,000 male physicians. They found patients of female physicians were vaccinated at higher rates than those of male physicians across the board:

- Among white men, the vaccination rate was 52.7 percent for those seen by female physicians, compared with 52.0 percent for male physicians. For white women, the rates were 54.6 percent (female physician) and 53.8 percent (male physician).
- Rates for Black men were 39.8 percent versus 38.1 percent, and for Black women, they were 41.6 percent versus 40.3 percent.
- Among Asian men, rates were 56.8 percent versus 54.7 percent, and for Asian women, they were 56.4 percent versus 55.7 percent.
- For Hispanic men, rates were 48.9 percent versus 47.3 percent, and for Hispanic women, they were 50.6 percent versus 49.1 percent.

The researchers also found female physicians were more likely than male physicians to get patients with more chronic conditions and co-morbidities vaccinated.

Overall, Black patients were about 14 percentage points less likely and Hispanics 5 percentage points less likely than whites to be vaccinated. Differences in vaccination

rates between patients of female and male physicians, says the researchers, represented 10 percent of the white-Black gap and about 30 percent of the white-Hispanic gap. Differences in communication style between female and male physicians, which have been documented in previous studies, may also contribute to the differences in vaccination rates. ❖

Rivero E. Patients of Women Doctors More Likely to Be Vaccinated Against the Flu. UCLA Newsroom, April 13, 2021. Accessed at newsroom.ucla.edu/releases/patients-of-female-doctors-more-likely-to-get-flu-vaccination.

Drug Labeling

FDA Amends Hydroxyethyl Starch Products Boxed Warning About the Risk of Mortality, Kidney Injury and Excess Bleeding

The U.S. Food and Drug Administration (FDA) is requiring safety labeling changes to the prescribing information for the class of hydroxyethyl starch (HES) products to amend the boxed warning to warn about the risk of mortality, kidney injury and excess bleeding. FDA is also requiring related changes to the indications and usage, contraindications, warnings and precautions, and adverse reactions sections.

Currently, there are three FDA-approved innovator HES products: HESPAN (6% hetastarch in 0.9% sodium chloride injection; B. Braun Medical Inc.), HEXTEND (6% hetastarch in lactated electrolyte injection; BioTime Inc.) and Voluven (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection; Fresenius Kabi). HESPAN and HEXTEND are indicated for "treatment of hypovolemia when plasma volume expansion is desired," and Voluven is indicated for "treatment and prophylaxis of hypovolemia in adults and children." There is also currently one approved generic version of HESPAN that is distributed in the U.S. (6% hetastarch in 0.9% sodium chloride injection; Hospira Inc.).

Data from a randomized controlled trial, a meta-analysis and observational studies collectively show an increased risk of mortality, acute kidney injury (AKI) and excess bleeding in surgical patients who are treated with HES products, as well as an increased risk of mortality and AKI in blunt trauma patients who are treated with HES products.

FDA has concluded that changes to the boxed warning are warranted to highlight the risk of mortality, AKI and excess bleeding, as well as to include a statement that HES products should not be used unless adequate alternative treatment is unavailable. ❖

Labeling Changes on Mortality, Kidney Injury, and Excess Bleeding with Hydroxyethyl Starch Products. U.S. Food and Drug Administration press release, July 7, 2021. Accessed at www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/labeling-changes-mortality-kidney-injury-and-excess-bleeding-hydroxyethyl-starch-products.

Medicines

15-Valent Pneumococcal Vaccine Approved by FDA

A pneumococcal 15-valent conjugate vaccine (VAXNEUVANCE, Merck) for the active-immunization prevention of invasive disease caused by Streptococcus pneumoniae (IPD) among adults 18 years and older has been approved by the U.S. Food and Drug Administration (FDA). The indication includes prevention of disease caused by serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F. The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) was anticipated to provide recommendations regarding the new vaccine in October.

Approval for the 15-valent vaccine was based on findings from seven randomized, double-blind, clinical trials showing its noninferior immune response to marketed 13-valent pneumococcal conjugate vaccine (PCV13) for the two vaccines' shared 13 serotypes, per opsonophagocytic activity (OPA) geometric mean titers (GMTs). Investigators from the clinical trials additionally reported superior immune response with the 15-valent vaccine versus PCV13 for shared serotype 3, plus 22F and 33F. The pivotal Phase III PNEU-AGE trial showed 15-valent vaccine's superiority to PCV13 based on statistically significantly greater OPA GMT ratios for serotypes 22F and 33F. The OPA GMT ratio for serotype 3, a key secondary objective for PNEU-AGE, also showed statistical significance for 15-valent vaccine. Comparative randomized controlled trials assessing the two vaccines' clinical efficacy have not been conducted.

In a statement accompanying the approval, PNEU-AGE coordinating investigator Jose Cardona, MD, of the Indago Research and Health Center, stressed the importance of bolstered protection for older adults at risk of life-threatening complications associated with IPD. "The FDA's approval of VAXNEUVANCE is based on robust Phase II and III studies assessing immune responses in a broad range of adult populations and provides an important new option in protection from invasive pneumococcal disease," said Dr. Cardona. ❖

Kunzmann K. FDA Approves Pneumococcal 15-Valent Conjugate Vaccine for US Adults. Contagion Live, July 16, 2021. Accessed at www.contagionlive.com/view/fda-approves-pneumococcal-15-valent-conjugate-vaccine-us-adults.

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Impacts of an Aging Demographic on Healthcare

Why healthcare needs to pivot to meet the demands of an aging population.

By Trudie Mitschang

2030 IS POISED to be an interesting year in the United States. As life expectancy continues to tick upward, rising from less than 70 years old in 1968 to almost 80 years old today, the U.S. Census Bureau confirms that in 2030, one out of every five Americans will reach retirement age.[1] In fact, the number of Americans over age 65 years is expected to double from roughly 50 million today to nearly 100 million by 2060. As we collectively age, these shifting demographics are poised to put undue pressure on an already challenged national healthcare system.[2] And, while the U.S. is currently ranked among the top countries in the world for the elderly, there are significant disparities across the country when it comes to healthcare access and quality of life. "The aging of baby boomers means that within just a couple of decades, older people are projected to outnumber children for the first time in U.S. history," said Jonathan Vespa, a demographer with the U.S. Census Bureau. "By 2035, there will be 78 million people 65 years and older compared to 76.7 million under the age of 18 (Figure 1)."[3]

This seismic demographic shift will impact everything from the availability of elder and long-term care to Social Security and public health services. According to Census Bureau projections:[2]

- The old-age dependency ratio (the ratio of older adults to working-age adults) will also shift. In 2020, there were 3.5 working-age adults for every retirement-age person, but by 2060, that ratio will drop to just 2.5.
- The U.S. home care market is expected to grow from $100 billion to $225 billion by 2024, driven by an expanding geriatric population.

The bottom line? There will be far more demand for healthcare, likely exceeding supply and taxing industries already struggling with a shortage of qualified caregivers. A study conducted by Mercer healthcare staffing agency predicts U.S. providers will face a collective shortage of approximately 500,000 home health aides, 100,000 nursing assistants and 29,000 nurse practitioners by the year 2025 (Figure 2).[4] "Few other industries are racing the clock to find a future-ready workforce like today's healthcare administrators," said Jason Narlock, senior consultant at Mercer.

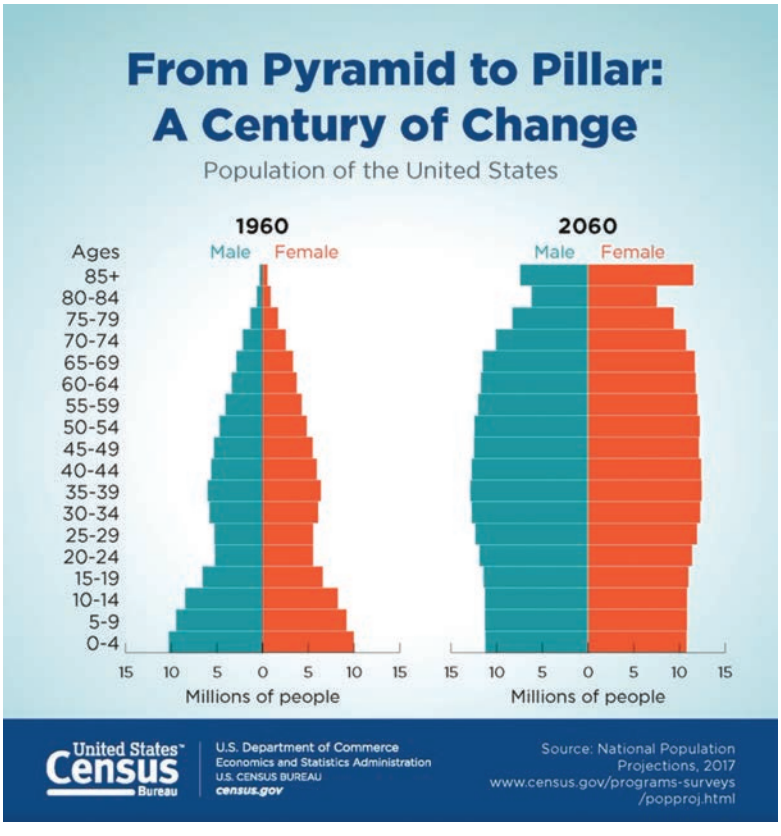
Healthcare Tech Trends for an Aging Population

Despite these dire predictions, the future healthcare prospects of an aging population are not all doom and gloom. Digital technology and trends within healthcare have already made tremendous strides, especially on the heels of the COVID-19 pandemic. By all accounts, digital tools, platforms and resources are expected to become more prevalent in the coming years — with the potential to help minimize healthcare costs, especially among older adults.

There will be far more demand for healthcare, likely exceeding supply and taxing industries already struggling with a shortage of qualified caregivers.

One of the factors positively influencing the use of technology to support healthcare demand is that the aging U.S. population is largely comprised of tech-savvy baby boomers. From online Google symptom searches to telehealth appointments, 78 percent of this demographic is

Figure 1.



actively using technology to access medical resources and information.[5]

Boomers are also highly likely to own and use smartphones and download and use apps. A 2019 Rock Health Consumer Adoption survey noted that smartphone and app use among people 55 years old to 65 years old is near that of their younger counterparts (generally within 10 percent).[6]

As millennials begin turning 40 in 2021, they are proving to present a number of healthcare challenges.

Technology may also help drive home healthcare costs down. According to the American Association of Retired Persons, 87 percent of adults age 65 and older want to stay in their current home and community as they age, a massive financial benefit compared to the cost of an assisted living facility or nursing home care. Thanks to telehealth technology that allows medical professionals to monitor patients outside of traditional clinical settings, many older adults can get the monitored care they need from the comfort and familiarity of their homes.

In a collaboration between Senior Whole Health of Massachusetts and Best Buy subsidiary GreatCall, a provider of smartphones and tech geared toward seniors, a new app called Care Team can monitor and support senior patients through GreatCall's Lively Home monitoring system. The system uses sensors to monitor daily activities — food intake, sleep patterns, physical activity, mobility — and apply predictive analytics to identify behavior trends and flag anomalies. A pilot study indicates that utilizing this kind of "passive monitoring" for proactive intervention can help trim healthcare costs by reducing the rate of unnecessary hospitalizations, while also helping seniors remain independent longer.[7]

Based on current doctor-to-patient ratios, the projected shortage in hospice and palliative medicine specialists could range from 10,640 to almost 24,000 by 2040, according to a report published in the *Journal of Pain and Symptom Management*.[8] Another innovative technology that supports the need for home care and hospice services has been developed by Intermountain Health Care. Named Intermountain at Home, the platform integrates remote monitoring and access to round-the-clock virtual urgent care and doctor appointments. By utilizing telemedicine with home care visits, it bridges potential shortages in palliative care.[9]

Finally, as of 2020, Medicare Advantage plans began including telemedicine within the standard benefits package, expanding access to telehealth services so patients can connect with their doctors by phone or video chat, regardless of where they live.[10]

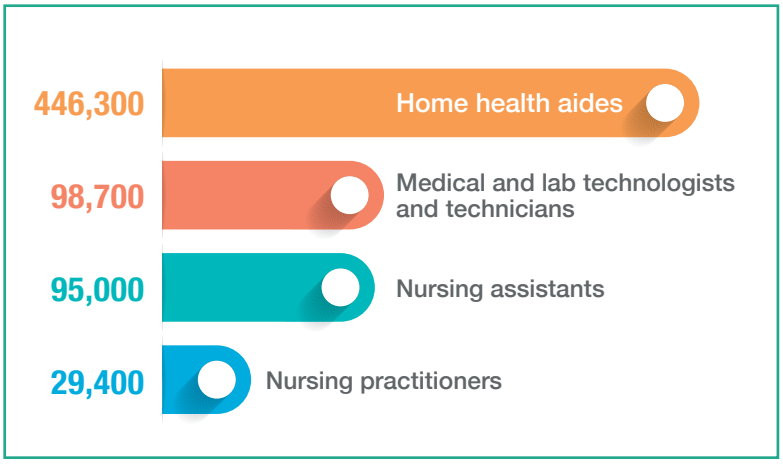
Facing the Challenge of Chronic Disease

According to a World Health Organization report, as life expectancy increases, the prevalence of disability will decrease thanks to numerous medical advances that have slowed disease progression. As a result, there will be a decrease in severe disability, but increased instances of chronic diseases and the resulting healthcare costs that go with them.

With an aging population, certain health conditions are statistically expected to increase as well, a prospect that will challenge the healthcare system based on the sheer volume of potential patients. Some of the diagnoses expected to increase include:[11]

- Cancer: The number of cancer cases is expected to surpass 27 million by 2030.
- Dementia: Alzheimer's Disease International projects there will be 115 million individuals living with Alzheimer's disease/dementia in the world by 2050.
- Obesity: Not only is obesity a risk factor for many health conditions, but it is very costly. Patients who are obese cost Medicare approximately 34 percent more compared with

Figure 2. By 2025, the US will likely face a shortage of...



Source: Mercer's U.S. Healthcare External Labor Market Analysis

patients of normal weight.

• Diabetes: The number of Americans with diabetes is expected to rise from 30 million today to 46 million by 2030, with one of every four boomers living with this chronic disease.

• Fall-related injuries: According to a report released by the American Hospital Association, more than one-third of adults 65 or older fall each year. Of those who fall, 30 percent suffer moderate to severe injuries (such as hip fractures) that decrease mobility and independence.

In the face of these concerns, specific challenges to the healthcare system include a shortage of healthcare professionals to meet the growing demands; the sustainability and structure of federal programs in relation to the increasing aging population; changing family structures possibly leading to fewer family caregivers; and ongoing adjustments needed to navigate the nuances of the Affordable Care Act.

Of course, the future economic demands on healthcare are not only driven by the baby boomer generation. As millennials begin turning 40 in 2021, they are proving to present a number of healthcare challenges. A Blue Cross Blue Shield (BCBS) report on the health of millennials indicates this population is less healthy than the previous Generation X and will likely contribute to greater demand for treatment and even higher healthcare costs in the years ahead.[12]

Millennials, most commonly defined as those born between 1981 and 1997, are the largest generation in the U.S. labor force — surpassing both baby boomers and Generation X — and still growing. The BCBS report findings indicate older millennials have higher prevalence rates for nearly all the top 10 health conditions than Gen X members when they were the same age. These conditions include depression, hypertension, high cholesterol and type II diabetes. Increases in substance abuse disorders, psychotic disorders and other behavioral health conditions within this population will also increase demand for behavioral health providers. The findings in the report highlight the need to consider how the evolving needs of millennials impact overall healthcare utilization — a demographic that historically was not a large driver of overall healthcare demand.[12] "There's no question that some emerging evidence shows many millennials are unhealthier than predicted," says Georges Benjamin, MD, executive director of the American Public Health Association. "Hypertension, diabetes and obesity drives a lot of that." Dr. Benjamin adds that the obesity epidemic may be one of the root causes of the rise in rates of hypertension, diabetes and even certain types of cancer.[13]

In part, the declining health of millennials may be due to their collective aversion to preventive care. Another study

found two-thirds of millennials only see a doctor when they are sick, and 68 percent don't have a primary care physician because they don't think they need one. Instead, they seek care only when a major problem develops. Without intervention to prevent or best manage the severity of disease, mortality rates could rise more than 40 percent compared to the previous generation at the same age.[14]

Counting the Cost of Care

While living healthier and longer is certainly everyone's goal, longer lifespans coupled with increased costs of living have skyrocketed end-of-life care, putting a very real strain on government resources and patient bank accounts.

In collaboration with Genworth Financial, a 2018 *Washington Post* report[15] estimates the annual median cost of a private nursing home room at $100,375, with the cost of an at-home health aide service averaging $50,336 a year. For many seniors and their families, the costs of long-term care are simply out of reach.

That leaves taxpayer-funded programs and government services to absorb the cost of long-term care. Medicaid covers long-term

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Important Safety Information

ALBUTEIN® 25% (albumin [human] U.S.P.) is indicated for: hypovolemia, cardiopulmonary bypass procedures, acute nephrosis, hypoalbuminemia, ovarian hyperstimulation syndrome, neonatal hyperbilirubinemia, adult respiratory distress syndrome (ARDS), and prevention of central volume depletion after paracentesis due to cirrhotic ascites.

ALBUTEIN® 5% (albumin [human] U.S.P.) is indicated for: hypovolemia, cardiopulmonary bypass procedures, hypoalbuminemia, and plasma exchange.

ALBUTEIN 5% and 25% are contraindicated in patients with a history of hypersensitivity to albumin preparations or to any of the excipients, and in patients with severe anemia or cardiac failure with normal or increased intravascular volume.

Allergic or anaphylactic reactions require immediate discontinuation of the infusion and implementation of appropriate medical treatment.

Hypervolemia may occur if the dosage and rate of infusion are not adjusted to the patient's volume status. At the first clinical signs of fluid overload, the infusion must be slowed or stopped immediately. Use albumin with caution in conditions where hypervolemia and its consequences or hemodilution could represent a special risk to the patient.

The colloid-osmotic effect of human albumin 25% is approximately five times that of blood plasma. Therefore, when concentrated albumin is administered, care must be taken to assure adequate hydration of the patient. Patients should be monitored carefully to guard against circulatory overload and hyperhydration. Patients with marked dehydration require administration of additional fluids.

Concentrated (20% - 25%) human albumin solutions are relatively low in electrolytes compared to 4% - 5% human albumin solutions. Regularly monitor the electrolyte status of the patient and take appropriate steps to restore or maintain the electrolyte balance when albumin is administered.

Regular monitoring of coagulation and hematology parameters is necessary if comparatively large volumes are to be replaced. Care must be taken to ensure adequate substitution of other blood constituents (coagulation factors, electrolytes, platelets and erythrocytes).

Regularly monitor hemodynamic parameters during administration of ALBUTEIN® 5% and 25% (albumin [human] U.S.P.).

ALBUTEIN 5% and 25% must not be diluted with sterile water for injection as this may cause hemolysis in recipients.

Albumin is a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for ALBUTEIN 5% or 25%.

The most serious adverse reactions with use of albumin are anaphylactic shock, heart failure and pulmonary edema. The most common adverse reactions are anaphylactoid type reactions. Adverse reactions to ALBUTEIN normally resolve when the infusion rate is slowed or the infusion is stopped. In case of severe reactions, the infusion should be stopped and appropriate treatment initiated.

Please see accompanying full Prescribing Information for ALBUTEIN 5% and 25%.

GRIFOLS

ALBUTEIN

FlexBag 5% (albumin [human] U.S.P.) 5% solution

These highlights do not include all the information needed to use ALBUTEIN FlexBag 5% safely and effectively. See full prescribing information for ALBUTEIN FlexBag 5%.

ALBUTEIN FlexBag 5% (albumin [human] U.S.P.)
5% solution
Initial U.S. Approval: 1978

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

ALBUTEIN 5% is an albumin solution indicated for:
- Hypovolemia.
- Cardiopulmonary bypass procedures.
- Hypoalbuminemia.
- Plasma exchange.

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

For Intravenous Use Only

Dosage and infusion rate should be adjusted to the patient's individual requirements.

Indication	Dose
Hypovolemia	Adults: Initial dose of 20 g (including renal dialysis). For acute liver failure: initial dose of 12 to 25 g.
Cardiopulmonary bypass procedures	Adults: Initial dose of 25 g.
Hypoalbuminemia	Adults: 50 to 75 g For pre- and post-operative hypoproteinemia: 50 to 75 g. For burn therapy after the first 24 h: initial dose of 25 g and dose adjustment to maintain plasma protein concentration of 2.5 g per 100 mL. Third space protein loss due to infection: initial dose of 50 to 100 g.
Plasma exchange	The dose required depends on the volume of plasma removed during the procedure.

Do not dilute with sterile water for injection as this may cause hemolysis in recipients.

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

ALBUTEIN 5% is a solution containing 50 g per L of total protein of which at least 95% is human albumin.

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

- Hypersensitivity to albumin preparations or to any of the excipients.
- Severe anemia or cardiac failure with normal or increased intravascular volume.

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

- Suspicion of allergic or anaphylactic reactions requires immediate discontinuation of the injection and implementation of appropriate medical treatment.
- Hypervolemia may occur if the dosage and rate of infusion are not adjusted to the patient's volume status. Use with caution in conditions where hypervolemia and its consequences or hemodilution could represent a special risk to the patient.
- Monitor electrolytes, coagulation and hematology parameters, and hemodynamic status when albumin is given.
- Do not dilute with sterile water for injection.
- This product is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.

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

The most common adverse reactions are anaphylactoid type reactions.
To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals LLC at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: No human or animal data. Use only if clearly needed.

Revised: 07/2021

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ALBUTEIN

FlexBag 25% (albumin [human] U.S.P.) 25% solution

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ALBUTEIN FlexBag 25% (albumin [human] U.S.P.)
25% solution
Initial U.S. Approval: 1978

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

ALBUTEIN 25% is an albumin solution indicated for:
- Hypovolemia.
- Cardiopulmonary bypass procedures.
- Acute nephrosis.
- Hypoalbuminemia.
- Ovarian hyperstimulation syndrome.
- Neonatal hyperbilirubinemia.
- Adult respiratory distress syndrome (ARDS).
- Prevention of central volume depletion after paracentesis due to cirrhotic ascites.

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

For Intravenous Use Only

Dosage and infusion rate should be adjusted to the patient's individual requirements.

Indication	Dose
Hypovolemia	Adults: Initial dose of 25 g (including renal dialysis). For acute liver failure: initial dose of 12 to 25 g.
Cardiopulmonary bypass procedures	Adults: Initial dose of 25 g.
Acute nephrosis	Adults: 25 g together with diuretic once a day for 7 - 10 days.
Hypoalbuminemia	Adults: 50 to 75 g For pre- and post-operative hypoproteinemia: 50 to 75 g. For burn therapy after the first 24 h: initial dose of 25 g and dose adjustment to maintain plasma protein concentration of 2.5 g per 100 mL. Third space protein loss due to infection: initial dose of 50 to 100 g.
Ovarian hyperstimulation syndrome	Adults: 50 g to 100 g over 4 hours and repeated at 4-12 hour intervals as necessary.
Neonatal hyperbilirubinemia	1 g per kilogram body weight prior to or during exchange transfusion.
Adult respiratory distress syndrome (ARDS)	Adults: 25 g over 30 minutes and repeated at 8 hours for 3 days, if necessary.
Prevention of central volume depletion after paracentesis due to cirrhotic ascites	Adults: 8 g for every 1000 mL of ascitic fluid removed.

Do not dilute with sterile water for injection as this may cause hemolysis in recipients.

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

ALBUTEIN 25% is a solution containing 250 g per L of total protein of which at least 95% is human albumin.

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

- Hypersensitivity to albumin preparations or to any of the excipients.
- Severe anemia or cardiac failure with normal or increased intravascular volume.

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

- Suspicion of allergic or anaphylactic reactions requires immediate discontinuation of the injection and implementation of appropriate medical treatment.
- Hypervolemia may occur if the dosage and rate of infusion are not adjusted to the patient's volume status. Use with caution in conditions where hypervolemia and its consequences or hemodilution could represent a special risk to the patient.
- When concentrated albumin is administered, care must be taken to assure adequate hydration of the patient.
- Monitor electrolytes, coagulation and hematology parameters, and hemodynamic status when albumin is administered.
- Do not dilute with sterile water for injection.
- This product is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.

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

The most common adverse reactions are anaphylactoid type reactions.
To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals LLC at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: No human or animal data. Use only if clearly needed.

Revised: 05/2019

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3055225

care needs, but typically only for seniors with limited financial resources and only for certain types of care facilities. That means for many seniors, a continuing-care community won't be a viable option, and traditional nursing homes that accept a limited number of Medicaid patients may be their only alternative.

While living healthier and longer is certainly everyone's goal, longer lifespans coupled with increased costs of living have skyrocketed end-of-life care, putting a very real strain on government resources and patient bank accounts.

One way to get ahead of these concerns is by putting renewed focus on preventive medicine. Many healthcare organizations proactively promote preventive services to improve patient health outcomes for older adults, with the goal of extending the ability of seniors to live independently and cut down on costly repeat hospital stays and long-term care.

Healthcare startup Landmark Health has created an in-home, risked-based medical group focused on the chronically ill and elderly population. The Huntington Beach, Calif.-based company boasts about 150,000 patients annually, and continues to expand its reach.[16] The company's healthcare model features a team of physicians who go into patients' homes and includes an interdisciplinary team of social workers, dietitians and pharmacists to meet patients' unique needs. The model allows physicians to see fewer patients so they are able to spend more time with each while developing their care plans. It also provides door-to-door transportation and virtual visits, hoping to reduce hospitalizations by getting patients access to care before an adverse health event.

Similarly structured Oak Street Health is a network of value-based primary care centers for adults on Medicare that recently announced the opening of its 100th center. The company serves nearly 110,000 patients across 15 states. With a mission of rebuilding healthcare, Oaktree's innovative model focuses on quality of care over volume of services and assumes the full financial risk of its patients. The company's primary care providers specialize in caring for Medicare patients and seniors with an emphasis on preventive care that strives to keep seniors healthy and out of the hospital. "We are more committed than ever to bringing our innovative care model and unmatched patient experience to more communities and improving health outcomes for our patients," said Mike Pykosz, chief executive officer.[17]

Is There a Silver Lining?

What has been dubbed the graying of America has put a spotlight on the need for more conversation and collaboration between all stakeholders in the healthcare industry and Washington D.C.-based policymakers. To address the tsunami of concerns, players in every field will need to work together to solve the coming challenges. Embracing technology, funding innovation and addressing access to care issues are imperative. By working together, the healthcare system — and the patients it supports — can age more gracefully and meet future demands ❖

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

Expansion of Primary Care in a Post-COVID-19 World

Expansion of sites of care may soon provide more options for patients and caregivers.

By Amy Scanlin, MS

IF THERE HAS ever been a time in history that highlights the enormity and burden of healthcare challenges, it is amid this COVID-19 pandemic. With provider resources stretched to the limits, logistical challenges halting delivery of some supplies and declining revenues leading to layoffs, the pandemic has become the perfect storm to showcase problems within the healthcare system. Indeed, the industry is now forced to rebuild, reconsider and recalculate quickly to keep pace with patient demands. And for primary care settings, this translates to expansion.

To overcome familiar stresses of complicated billing structures and provider shortages, the healthcare industry is looking for new options and opportunities that enhance capabilities and care offerings to reach a wider demographic. How? With 90 percent of Americans living within five miles of a pharmacy[1] and within 15 miles of a major big-box retailer, stores such as Walmart, Walgreens and CVS are expanding their scope beyond the pharmacy and into primary care services. Community-based and easily accessible, these retailers may be poised to assume a new role in the future of care, both in-person and via telemedicine.

Location, Location, Location

With the spread of COVID-19 and the need for increased physical distancing, the location to receive care has become a great concern, and now provides a great opportunity. Fairly quickly, the option of telemedicine services became the new normal, and may prevail, particularly for those with transportation, ambulatory and time challenges. Provided patients have access to a reliable Internet connection and mobile device, a primary care option could be right at their fingertips, either with their current trusted provider or via a new care team through one of the many telemedicine organizations.

Of course, not everyone is interested or able to take advantage of telehealth. Some prefer in-person consultations, even if they are outside of a traditional healthcare setting. For instance, a *Journal of the American Medical Association* study found patients actively access healthcare services twice as often in community pharmacies versus primary care facilities, particularly in smaller and isolated communities where hospitals and other primary

care settings are hard to reach. According to the study, pharmacists working as educators and coaches are efficacious in influencing community outcomes, including improved immunization rates, smoking cessation rates and lowered cardiovascular disease risks. Their care has also shown to positively influence improved lung function in patients with respiratory conditions and reduced hospital readmission rates in patients with heart failure.[2]

In the early days of the pandemic, the Centers for Disease Control and Prevention (CDC) urged retailers providing pharmacy services to do whatever was necessary to stay open and serve the public, and they did, providing medication counseling, addressing overall health concerns, supporting self-care and, importantly, offering a line of communication between patients and providers. Now, as COVID-19 vaccines are being administered, CDC estimates the vaccination timeline could improve by seven weeks and cover 80 percent of Americans with the inclusion of pharmacies as part of the distribution model.[1]

In a system where primary care resources are strained, expanding the model of healthcare into big box settings can help fill gaps and provide good options for helping patients seeking preventive services and chronic disease management. Particularly in rural settings and underserved communities, big-box stores with healthcare services and pharmacies may offer patients their only opportunity to have regular healthcare visits. By locating these services in a familiar location and one in which patients would be frequenting anyway, their chances of proactively seeking care and managing their health increases, potentially reducing the burden on the larger healthcare system.

In some big-box retailers, pharmacists already play the role of health and pharmacologic counselor, immunizer and educator, so an expansion of care seems a natural fit. With approximately 50 percent of U.S. adults having one or more chronic disease, 80 percent of whom are treated with prescription drugs, pharmacists are vital to long-term management of healthcare concerns.

As healthcare expands further into big box retailers, staffing will also expand to include primary care physicians, physician assistants and certified nurse practitioners, all of whom work collaboratively to diagnose, treat, prescribe and refer patients to specialty care as needed. Walmart Health is one example, with health centers expanding into communities with limited preventive care options. CVS HealthHUB is also expanding its pharmacy services with Minute Clinics and educational programming. In many cases, these retail healthcare settings offer both in-person and telemedicine options for a set fee that is disclosed to the patient up front, regardless of the patient's insurance, facilitating a transparent pricing model.

Overcoming Financial Barriers to Care

Pharmacies served communities faithfully with "lights on, doors open," according to National Association of Chain Drug Stores (NACDS) President and CEO Steven C. Anderson in the early days of the pandemic; however, their pharmacologic services still fight government bureaucracy that can hinder effective patient care.

As an example of bureaucratic roadblocks, the Centers for Medicare and Medicaid Services does not recognize pharmacists as healthcare providers, thus making them ineligible for merit incentive payment systems. Yet, the critical services pharmacists offer extend well beyond dispensing and inoculating since they can and do work as part of a multi- and interdisciplinary healthcare team in support of providers' and patients' goals. Even so, with few exceptions, thanks to a negotiated fee-for-service payment model, much of the support provided by pharmacists is not billable.

With the spread of COVID-19 and the need for increased physical distancing, the location to receive care has become a great concern, and now provides a great opportunity.

While providers are striving to serve patients against a sea of complicated and limited billing structures, one demonstration of the financial benefits of clinical pharmacology can be extrapolated to community pharmacies. For instance, the Veterans Administration reports a $4 cost benefit for every $1 in clinical pharmacology services invested.[3] Still, most insurance plans do not offer a designation code for billing many pharmacy services, even though Medicare Parts B and D allow for the administration of influenza and pneumococcal vaccines. These fee-for-service payments, which many argue prioritize volume over value, are in the early stages of change. Collaborative drug agreements that allow physicians to authorize pharmacists to oversee drug therapy for certain patients is one example that allows participation in a performance-based model of care that can be evaluated based on quality metrics.[4]

Patients are also concerned about rising costs and lack of predictability in pricing for their healthcare services, including reimbursements for prescription drug programs. One benefit for many in big-box healthcare settings is upfront fee disclosures, which patients can use to determine whether to pay for services out of pocket or go through their insurance provider.

As healthcare expands further into big-box retailers, staffing will also expand to include primary care physicians, physician assistants and certified nurse practitioners.

But, it's not just primary care being incorporated into big box healthcare models. Wellness and prevention programs offer expanded opportunities for health education, nutrition services and support groups. Increased educational opportunities could be the boon needed to encourage engagement in those with historically limited access or interest in health improvement programs. CVS HealthHUBs, for instance, advertise meeting space for community-based programs. "We have a sense of urgency about the need to bring real change to healthcare," says Kevin Hourican, executive vice president of CVS Health and president of CVS Pharmacy. "What's clear to us is that it will take more than incremental steps to fix what is broken in the healthcare system."[5]

Roadmap for the Future

Whether pharmacists work alongside providers as part of a comprehensive care team or providers practice under the shingle of big-box retailers or via telemedicine, patient care enhancement involves moving away from silos and toward accessibility, including enhanced data management.[6]

A Deloitte survey of U.S. physicians from Jan. 15, 2020, to Feb. 14, 2020, recommends shifting focus toward patient empathy, well-being and prevention services that support delaying and averting diseases and envisions a future in which a clinician's "training and culture-building department … is bigger than their coding department."

And, core educational competencies outlined in the Institute of Medicine's *Health Professions Education: A Bridge to Quality* stress the utilization of patient-centered care in which needs are addressed through interdisciplinary teams. According to the book, to better serve patients, improved sharing of pertinent information among patients and providers, and between care teams, is being discussed.

According to the Deloitte survey, the industry can accomplish these goals through greater use of data-driven technology and expanded capabilities that support a collaborative healthcare team approach. As an example, pharmacy information technology systems may limit capabilities and patient discussions due to lack of synergy with the larger electronic health record system. Additionally, patients are taking an increasingly active role in managing their own health data, so much so that 65 percent of physicians expect consumers will own and control their own data within five to 10 years and become a greater part of the equation.[6]

With the U.S. Bureau of Labor and Statistics anticipating an increase of 14 percent in the number of healthcare worker jobs,[7] now is the time to rethink how and where healthcare is being delivered. Meeting patients where they are, both literally and figuratively, ensuring a supportive structure of care that addresses the whole patient, and conveying information in such a way that patients are capable and motivated to take ownership of their own outcomes provide the best chances for success.

In the end, whether in a pharmacy, big-box or traditional healthcare setting, an ability to ask intuitive questions, hear the answers and integrate that information across data points ensures patients are the ultimate beneficiaries. As the U.S. healthcare system returns to normal, a new normal is on the horizon, one that expands options for patients, caregivers and the future of care. ❖

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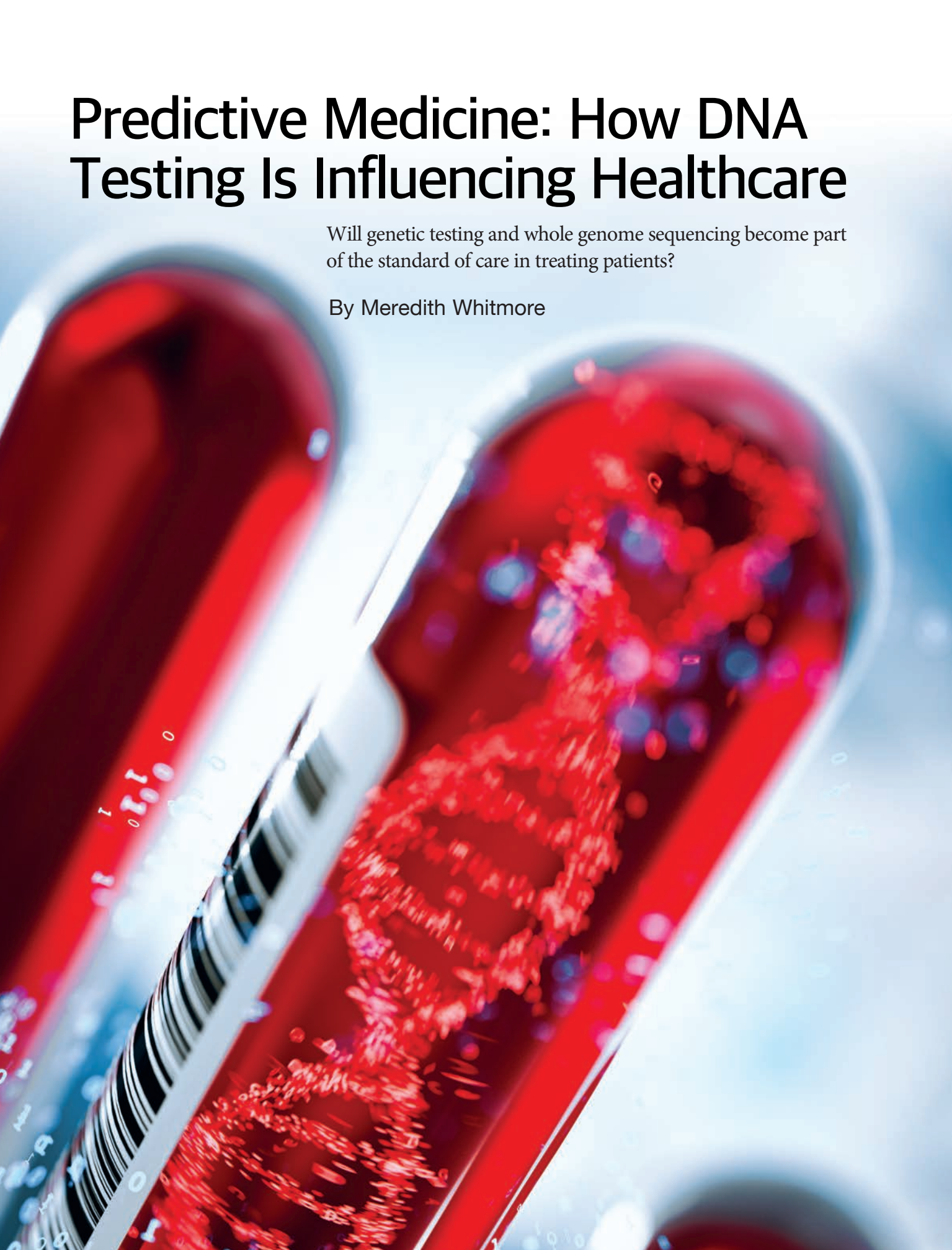
Predictive Medicine: How DNA Testing Is Influencing Healthcare

Will genetic testing and whole genome sequencing become part of the standard of care in treating patients?

By Meredith Whitmore



PREDICTIVE MEDICINE IS growing in its influence on healthcare in the United States and around the world. Yet few healthcare professionals can correctly articulate just what it is, its anticipated (and likely revolutionary) influence on how medical care functions, and how it will greatly benefit patients and professionals.

BioSupply Trends Quarterly recently conducted an interview with Brandon Colby, MD, founder and CEO of Sequencing.com, the world's largest platform for DNA testing and analysis. The Sequencing.com team consists of medical doctors, geneticists, bioinformatics experts and software developers who share a passion for helping patients live healthier, happier and longer through DNA analysis. Dr. Colby is trained in clinical genomics and internal medicine, and he has a bird's-eye view of predictive medicine that few can rival.

BSTQ: How would you best describe predictive medicine?

Dr. Colby: Predictive medicine uses patients' biomarkers and genetic information to understand what diseases they are at risk for throughout life. That information is also used to implement proactive, preventive measures that will help mitigate the risks of those diseases even before they arise.

BSTQ: How prevalent is predictive medicine today, and what is it anticipated to be in the future?

Dr. Colby: Today, predictive medicine is used in pieces by different physicians. For instance, oncologists may utilize genetic testing to look at people's risk for certain types of diseases. Internal medicine physicians and pharmacologists may use particle genomics, which is a way to look at people's genes to determine what medications may pose risk of an adverse reaction for them. Different specialties are using genetic testing in different ways to understand risk. Those are small pieces of predictive medicine: personalized proactive prevention put into place by predicting what a person is at risk for and using that information to steer some type of treatment plan or preventive plan. So, it is not very prevalent in terms of being its own specialty. Rather, it is about predictive medicine having more and more of an impact upon each individual specialty as healthcare providers become comfortable using genetic information and integrating it into their practice.

BSTQ: Can you provide a recent example of a case in which predictive medicine was used successfully?

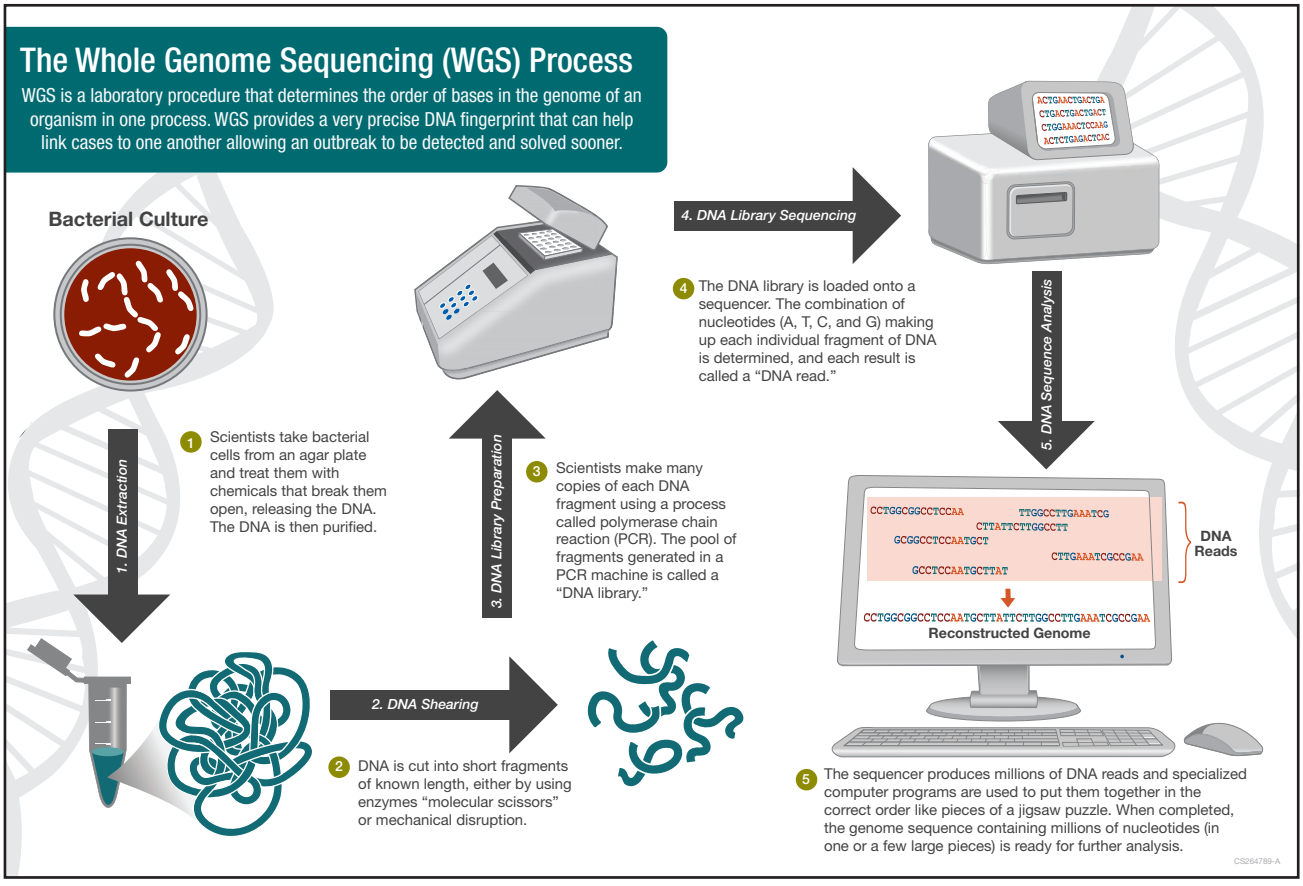
Dr. Colby: When it comes to the genes we're familiar with, such as the BRCA1 and BRCA2 genes that cause a very significant increased risk of breast cancer, there are many ways to implement personalized, preventive measures throughout a person's life, even early on for adolescents. A recent case was a young girl whose BRCA1 mutation was detected that had the potential to dramatically increase her risk of cancer. While there was no really drastic preventive measure at that point in her life, we were able to advise her parents of the importance of avoiding radiation exposure to their daughter's chest throughout her life. So, when she goes to the dentist, the importance of making sure the lead vest is covering her chest and her thyroid extremely well should be communicated. If she has a cough and goes to her pediatrician, that pediatrician should understand to hold off on a chest X-ray unless it is very urgent she have one. Any radiation exposure to her chest is like throwing gasoline on a fire, increasing the risk of breast cancer. So while there's no medication that can be given — and, of course, we're not going to perform surgery on someone so young — there are still steps we were able to provide to these parents. With this knowledge, there was a type of empowerment in that they understood the risks, and they understood that their daughter will likely have to deal with breast cancer down the line. But, at least today, they're able to take some steps that will help limit her overall risk throughout her life.

Predictive medicine uses patients' biomarkers and genetic information to understand what diseases they are at risk for throughout life.

BSTQ: Why is predictive medicine important in healthcare?

Dr. Colby: It's quintessential to the survival of healthcare. It helps to reformulate healthcare from being about "sick care," or focusing only on people who have already become sick. Healthcare providers know there's a losing battle in waiting for someone to get sick. Predictive medicine is changing the whole paradigm of healthcare from that "sick care" model to one that is truly healthcare focused on personalized prevention of disease. There is no other way to predict disease risk without predictive medicine that focuses on patients on a personal level, understanding their environmental risks, as well as their genetic risks, including what's already happening inside their bodies today. With predictive medicine, we can go beyond and focus on the personalized prevention of disease, which is really when we start to prevent disease from ever

Figure



Source: www.cdc.gov/pulsenet/pdf/Genome-Sequencing-508c.pdf

occurring. That way, we're getting ahead of the problem, and that's when our healthcare system is going to be able to survive, both in terms of bandwidth and cost. It is a lot more cost-effective to stop a disease from occurring than to treat it once it has arisen.

Oncologists are now experts at using BRCA1 and BRCA2 testing as part of their practices. For psychiatrists, pharmacogenomics continues to play an increasing role in their practices. The daily use of genetic information by physicians is also quickly moving into internal medicine to identify risk and prescribe optimal treatments for chronic diseases.

And, studies have shown that BRCA1 and 2 testing have very clear economic benefits for identifying those people who are at risk for breast cancer (including men), and then monitoring and preventing the cancer before it occurs. If we look at the cold numbers, predictive medicine offers a significant advantage to the medical system and the entire world in terms of detecting disease at its earliest stages when treatment is usually most effective, or preventing disease from occurring in the first place.

BSTQ: What are some of the complications of predictive medicine?

Dr. Colby: In terms of understanding the risk, we're not usually talking about absolutes. We're talking about risks such as odds ratios and relative risks for increasing or decreasing the risk of disease in individuals. So, it can be a little bit of a gray area, for instance, if a person may have an increased risk for liver cancer, but that increased risk in terms of absolute risk is not very significant. What is really needed is a guide to understanding these risks to help steer whether what has been detected on a genetic level is or is not important.

BSTQ: What are the tools used in predictive medicine?

Dr. Colby: The predictive tools I use daily are genetic testing results, which allow me to understand changes in genes and/or genetic variances a person has and conditions for which they are at risk. I also use biomarkers, which are usually blood tests

that will indicate serum levels of a substance. Even something as simple as vitamin D has a lot of predictive value in terms of risks for certain diseases, so that's another example of a simple biomarker I test for frequently when I treat patients. Genetic risk doesn't change from the day a person is conceived until the day he or she dies, and the risks are able to be identified for the long term. You can look at a baby and understand his or her risk of developing Alzheimer's disease 30, 40, 60 years into the future. Biomarkers, on the other hand, give us a much better idea of what's going on within that person's body today, as well as within the next six months to a year. So, genetic testing and biomarkers together provide a much clearer predictive picture than either alone — the biomarkers in terms of what's going on in the short term and the genetics for what's going on in the long term.

BSTQ: With regard to predictive tools, are false-positives and false-negatives a problem?

Dr. Colby: They are definitely a problem. Whenever we're looking at multivariant analysis, there are many different data points being obtained for a test. There are always going to be some that are lower quality, and there are always going to be some false-positives and false-negatives within that data set. For instance, for a data set in which we're simply looking at vitamin D levels, it is much easier to get the correct result. But when we start to look at genes using something like 23andMe or other such companies, they review about 600,000 data points. Genetic variances within a person's genome for whole genome sequencing is what I focus on — sequencing a person's entire genome — which includes more than three billion data points. So, when analyzing an entire genome, it is important to understand there are going to be false-positives and false-negatives and how to implement different quality controls to limit those false-positives and -negatives. If we come back to the BRCA1 and BRCA2 testing example, when that is detected, it's crucial to have a follow-up genetic test to confirm the results. That's part of the counseling a physician provides: making sure the initial test is correct when a result is going to potentially have a very profound impact. A follow-up test ensures that something like a false-positive is not guiding our approach so it first must be validated.

BSTQ: Are there any ethical objections to predictive medicine?

Dr. Colby: For those of us who employ predictive medicine, ethics are not as impactful when testing people who are not pregnant but may be thinking about getting pregnant. When it comes to genetic testing, usually the ethical debates are limited. Most physicians, patients and others are OK with people learning about their genes.

However, there is a different type of ethics surrounding predictive medicine when it comes to various companies that perform genetic testing such as 23andMe, Ancestry.com and other similar types of companies. One of the ethical debates surrounding this type of testing is what those companies do with the genetic data after they obtain it. For example, are they selling it? Or, what else might they be doing with it?

BSTQ: Is there anything else you would like to add regarding predictive medicine?

Dr. Colby: One of the most important things is there's a true revolution in the field of genetic testing, and that surrounds whole genome sequencing. As I mentioned, companies such as 23andMe and Ancestry.com look at around 600,000 genetic variants, but that is less than 0.1 percent of a person's genome. Whole genome sequencing (Figure) obtains data on all three billion genetic variants, which is 100 percent of a person's genome. While the cost of whole genome sequencing in a single person was more than $1 billion 20 years ago, the cost today is now less than $500 a person! Studies have projected that within the next several years, we're going to start to see hundreds of millions of people having their genome sequenced.

One of the most important things is there's a true revolution in the field of genetic testing, and that surrounds whole genome sequencing.

Governments around the world are already evaluating the recommendation that all newborns have their whole genome sequenced at the time of birth. In the United States, there's the All of Us Research Program from the National Institutes of Health, which has sequenced the genome of a million people. Similar programs exist in the United Kingdom, European Union and China. So, we're about to see this major influx of genetic information into the medical field, where everyone will start to have their genome sequenced and will want their medical providers to utilize the data as part of their care using predictive medicine. ❖

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

Telehealth Delivery Options and Reimbursement

While not all regulations and reimbursement models for telehealth post-COVID-19 are in place, some have become permanent and others may be extended.

By Matthew Hansen, DPT, MPT, MBA

MANY HEALTHCARE PROVIDERS and patients, eager for a way to connect without increasing risk of exposure to COVID-19, have learned telehealth options also present other benefits, including convenience, efficiency related to cost and time, and improved access to hard-to-reach and high-risk populations. Consequently, after years of slow growth as a primarily supplemental service, the COVID-19 public health emergency (PHE) quickly mainstreamed the use of telehealth services in a matter of weeks to months in early 2020.

The Centers for Medicare and Medicaid Services (CMS) reported 43.5 percent of Medicare beneficiaries' primary care visits were performed via telehealth in April 2020. And the number was even higher for beneficiaries living in metropolitan areas that were harder hit by the virus.[1] As reported by Inside Health Policy, a Medicare Payment Advisory Commission (MedPAC), there were 8.4 million telehealth services paid for under the physician fee schedule in April 2020, compared to just 102,000 in February 2020.[2] During 2020, 30 percent of Medicare beneficiaries nationwide had at least one telehealth visit, amounting to tens of millions of visits.[3]

Although virtual visit utilization has decreased significantly from its peak during last year's second quarter, it's become apparent that telehealth will remain a significant part of the healthcare system as the country emerges from the pandemic. How prominent its use will be depends in large part on the same factors that inhibited its growth during the preceding decade: regulation and reimbursement models.

Referencing a 2020 article in the *Journal of the American Medical Association*, *Modern Healthcare* reported that Medicare reimbursement for audio and video telehealth calls was just $15 prior to the COVID-19 PHE, "a rate that researchers said did not even cover the cost of submitting the insurance claim."[4] Additionally, very few Medicare services were approved for reimbursement in past years, although some private insurers and Medicare Accountable Care Organization (ACO) participants were reporting some early success with virtual wellness visits.

Telehealth Flexibilities During the COVID-19 PHE

Under certain circumstances, the secretary of the Department of Health and Human Services (HHS) may use section 1135 of the Social Security Act to temporarily modify or waive certain Medicare, Medicaid, Children's Health Insurance Program or Health Insurance Portability and Accountability Act (HIPAA) requirements. These waivers can be issued individually or as a blanket waiver for all providers to help beneficiaries continue to sufficiently access health services and supplies.

Various Section 1135 telehealth waivers have been issued during the COVID-19 PHE. In addition, CMS added more than 140 telehealth services to the physician fee schedule, including emergency department visits, initial nursing facility and discharge visits, home visits and therapy visits.[5,6,7] Some of these services will become permanent, while others are set to expire either by the end of 2021, unless extended, or at the end of the PHE.

According to Medicare, beneficiaries may currently use telehealth "for office, hospital visits and other services that generally occur in-person." Additionally, regardless of where someone lives,* established Medicare patients "may have a brief communication service with practitioners via a number of communication technology modalities, including synchronous discussion over a telephone or exchange of information through video or image," or have non-face-to-face patient-initiated communications with their doctors by using online patient portals.

Some telehealth services do not presently require both audio and video capabilities and can be conducted by phone only. Healthcare providers also currently have the option of supervising services through audio or video communication instead of in-person.[8,9]

When video or text capabilities are used, a notification of enforcement discretion[10] issued by the Office of Civil Rights (OCR) at HHS authorizes covered healthcare providers to use widely available, nonpublic-facing communication applications to deliver telehealth. Furthermore, OCR indicates it "will exercise its enforcement discretion and will not impose penalties for noncompliance with the regulatory requirements under HIPAA rules against covered healthcare providers in connection with the good faith provision of telehealth during the COVID-19 nationwide public health emergency."

Examples of public-facing applications, which are not permitted, include Facebook Live and Twitch. The following are video chat and text-based applications that are allowed during the PHE:

Video chat applications

- Apple FaceTime
- Facebook Messenger video chat
- Google Hangouts video
- Zoom
- Skype

Text-based applications

- Signal
- Jabber
- Facebook Messenger
- Google Hangouts
- WhatsApp
- iMessage

With few exceptions, any provider eligible to bill Medicare for professional services is eligible to bill for telehealth during the PHE, and telehealth visits billed to Medicare are paid at the same Medicare fee-for-service rate as an in-person visit. Providers should just make sure their billing departments use the correct telehealth modifier(s) with the billing code.

Although virtual visit utilization has decreased significantly from its peak during last year's second quarter, it's become apparent that telehealth will remain a significant part of the healthcare system as the country emerges from the pandemic.

Medicaid covers some telehealth services, and many states have secured special Section 1135 waivers for its expanded use, but coverage differs from state to state. Multiple commercial plans have also broadened their coverage of telehealth during the pandemic, with coverage likewise varying widely by provider.

** For the duration of the COVID-19 PHE, telehealth services may even be provided across state lines; however, the practice is subject to requirements set by the states involved: telehealth.hhs.gov/providers/policy-changes-during-the-covid-19-public-health-emergency/telehealth-licensing-requirements-and-interstate-compacts/ for state-level policies and interstate agreements.*

Telehealth Coverage After the COVID-19 PHE

The good news for telehealth fans is that several services have already been made permanent, and they are expected to continue and increase for better access and quality of care. These include 60 of the 144 telehealth services that had been temporarily approved by the end of President Trump's term, including services for cognitive assessment and care planning; group psychotherapy, psychological and neuropsychological testing; and domiciliary, rest home or custodial care for established patients. There is also a lot of discussion in Congress and at CMS about supporting the permanence — or at least the extended trial — of many more services.

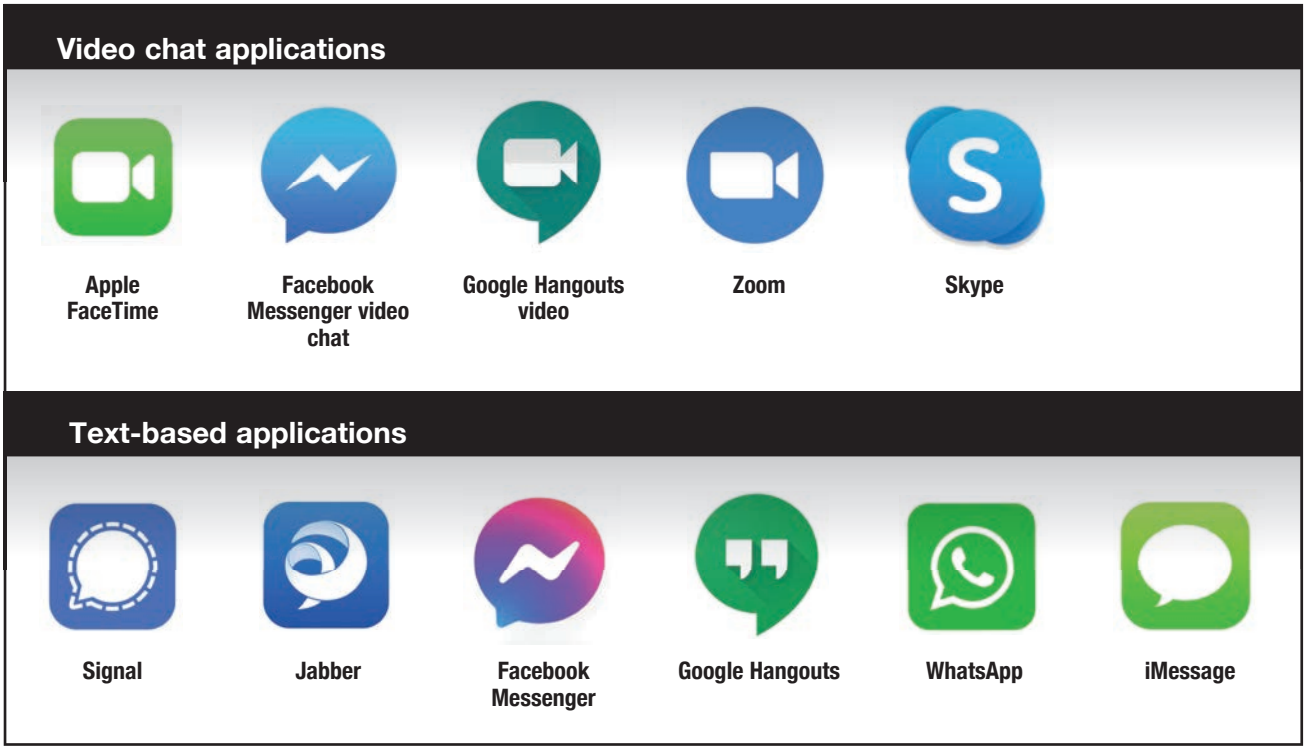
To support the advancement of telehealth, CMS has created a process for adding codes to the list of services eligible for reimbursement from Medicare that includes assigning requests to one of three categories. Category 1 is for services on the Medicare telehealth list similar to those already approved (e.g., professional consultations and office visits). Category 2 is for services not similar to current telehealth services on the Medicare list, but which pose a significant benefit for the patient. Category 3 services are those that were added during the pandemic that will remain covered until the end of the calendar year when the COVID-19 PHE is declared over, but for which there is not yet enough evidence available to consider the services permanent additions under Category 1 or 2.[11]

One of the persisting questions is how Medicare providers should be paid for telehealth services. Although reimbursement rates for telehealth and in-person services are currently the same, without further Congressional action, payment parity will expire at the end of the PHE.

Most providers prefer to see parity continue; however, some officials and payers are concerned that keeping telehealth rates the same as for in-person visits will result in its overutilization. Congress could pass legislation to expand telehealth services Medicare is allowed to cover, as well as direct CMS to create fair rates, but it is widely expected most of the details regarding payment will be left to CMS.

In mid-March 2021, MedPAC, an organization that advises Congress on Medicare policy, published recommendations to Congress regarding telehealth as part of the COVID-19 PHE response. MedPAC advised Congress to continue some telehealth coverage expansions for one to two years to allow more time for collecting data on the impact of services on access, quality and the cost of care before making any policies permanent, but to revert to lower payment rates.

Video Chat and Text-Based Applications Allowed During the Public Health Emergency:



MedPAC's argument for lower payment rates was based on its conclusion that "services delivered via telehealth likely do not require the same practice costs as services provided in a physical office."[12] However, opponents to this viewpoint argue that although overhead costs may eventually be less for certain providers if a significant portion of their services are provided via telehealth instead of in-person, those savings are still theoretical and would not been seen until much later. Furthermore, the hourly compensation for professionals providing telehealth services is no different than if they were providing the services in-person. Many parties also believe telehealth will result in cost savings to the healthcare system as a whole and believe sharing the benefits of savings with providers would encourage new innovation and the most efficient models of care to evolve.

In its report to Congress, MedPAC also recommends continuing to allow audio-only interactions for clinical assessments and other clinically beneficial visits (e.g., management visits with established patients). To help combat potential fraud, the group advises CMS to establish additional safeguards, including closer scrutiny of claims from outlier clinicians who bill significantly more telehealth services than others; prohibiting "incident-to" billing for telehealth services provided by clinicians who are able to bill Medicare directly; and requiring an in-person visit before clinicians can order costly lab tests or durable medical equipment for a beneficiary.

CMS and the House Committee on Ways and Means Committee, which has jurisdiction over Medicare financing, continue to take recommendations from MedPAC and others regarding what telehealth coverage should look like after the COVID-19 PHE. And, while it is not likely Congress will mandate parity in the commercial market, it's worth noting that history has shown private insurers often feel compelled to follow Medicare's lead.

Guidelines Will Ensure Quality Care

According to an article by McKinsey & Co., an organization that helps private, public and social sectors create change, "approximately $250 billion — or 20 percent of all Medicare, Medicaid and commercial outpatient, office and home health spend, could potentially be virtualized," a number that would reflect a diversion of approximately 20 percent of emergency department visits, 24 percent of outpatient office visits and 35 percent of home health services.[13]

Most would concede there are some healthcare services that simply can't be replaced — at least effectively — by a virtual alternative. Still, many services can, and they may even be more effective than an in-person visit for one reason or another.

For providers and healthcare consumers alike, it will be important to remain vigilant for both national and local telehealth updates, as well as to actively advocate for desired change. If they have not already taken the step, providers should proactively establish best-practice telehealth guidelines. Telehealth unavoidably changes the nature of the encounter between clinician and patient/client, and establishing guidelines and expectations will not only help ensure quality care, but it could also instill confidence in the future of telehealth with regulators and payers. ❖

One of the persisting questions is how Medicare providers should be paid for telehealth services.

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MATTHEW DAVID HANSEN, DPT, MPT, MBA, is a practicing physical therapist in Utah and president of an allied healthcare staffing and consulting agency named SOMA Health, LLC. He completed his formal education at the University of Utah, Salt Lake City, and has additional training in exercise and sports science, motor development and neurological and pediatric physical therapy.

Decentralized Clinical Trials: Coming Virtually to a Research Facility Near You

Virtual clinical trials may increasingly replace in-person trials due to their advantages in helping to bring drugs to market.

By Amy Scanlin, MS

AS THE PHARMACEUTICAL industry pivots and takes stock of a new post-COVID-19 normal, ensuring the safety of clinical trials is at the forefront of sponsors' and investigators' minds. Exploring the feasibility and utility of mobile technologies was already well underway prior to March 2020; however, a fresh look at their opportunities was captured in a paradigm shift when on Jan. 27, 2021, the U.S. Food and Drug Administration (FDA) released "FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency." In the guidance, the agency supported an expanded vision of clinical trials — one that includes alternative methods of safety assessments (e.g., phone contacts, virtual visits and alternative locations for assessments, including local labs or imaging centers) provided good clinical practices (GCPs) are assured and adhered to and risks to integrity are minimized.

Remote patient monitoring is nothing new. Considering the power of passive data capture of activity tracking through worn sensors, medication adherence through smart-cap bottles, data entry into mobile devices and telehealth services, and as innovative usage of technology progresses, the in-person model of healthcare may not be the gold standard in the future.

However, shifting to a virtual clinical trial as a natural extension of in-person trials is another story, particularly when the shift happens during a global pandemic. Virtual equals complexity, given the agency's willingness to consider remote monitoring. And, ensuring all modifications to ongoing or planned studies take into account the potential safety impacts became priority No. 1. FDA does not require investigators or subinvestigators to have direct face-to-face contact with patients. Also, there is no definition for the term "clinical trial site," so the decision to extend to a decentralized trial might be acceptable. In question, however, are potential limitations to a single investigator's ability to oversee a decentralized trial,[1] particularly when an opportunity to expand participants into multiple geographic regions is presented.

For trials already in process at the outbreak of COVID-19, sponsors in consultation with clinical investigators, institutional review boards and independent ethics committees were forced to determine whether participants' safety, welfare and rights were best served by continuing per the approved protocol, whether discontinuation of participation in the trial was most appropriate or whether another alternative method of safety assessment could reasonably be made. For instance, could phone contacts or virtual visits ensure trial participant safety, as well as in-person consultations? If trials can be expanded, what are the implications of licensing when trial participation crosses state lines?

Opportunities for Drug Development

It can take 10 years and tens of millions of dollars to bring a drug to market in the U.S. A large portion of that expense (9 percent to 14 percent) is paid to research clinics to which study participants must report on a regular basis. This means the pool of available participants must be located within easy travel proximity to the (typically urban) centers conducting the trials, resulting in fairly homogenous studies. Recruitment and retention are two additional challenges with nearly 40 percent of trials failing to meet initial recruitment targets, and 49 percent of participants dropping out prior to study completion.[2] A major reason for participant attrition is the time, inconvenience and effort of traveling to the clinical sites for monitoring. Yet, FDA has stated its intent for greater diversity in clinical trials, meaning an expanded pool of participants must be recruited.

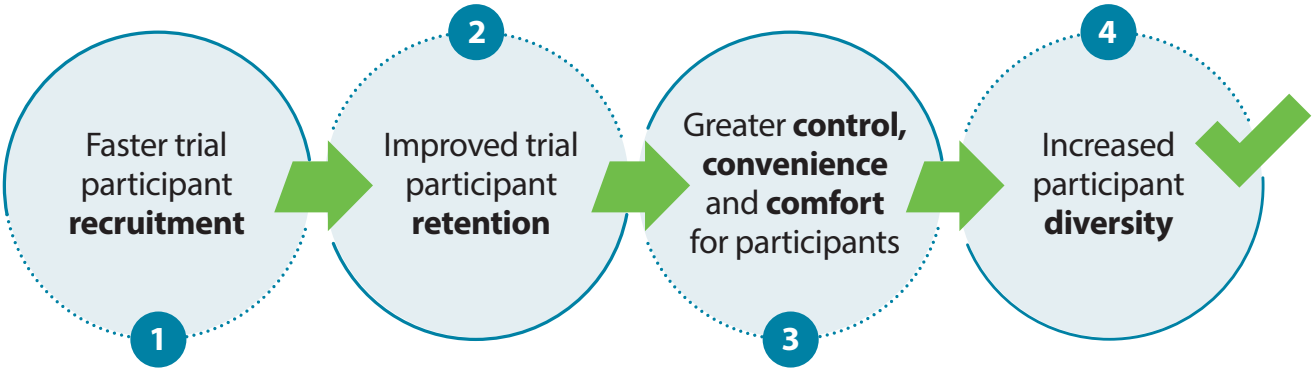
As such, decentralized trials offer an ability to recruit greater numbers of participants and retain them thanks to the convenience of remote data collection. Although occasional in-person monitoring may be required (a hybrid model), by largely removing geographic barriers, increased diversity will create new opportunities for drug development. And, while the first completely randomized virtual clinical trial for an investigational new drug was announced in 2011, the current state of the industry is similar to that of biomarkers in the early 2000s,[3] showing great potential.

It can take 10 years and tens of millions of dollars to bring a drug to market in the U.S.

Of course, not every clinical trial is appropriate to be held entirely virtual (for instance, those requiring imaging or drugs with uncertain safety profiles are two that would require a hybrid model at a minimum) because at the heart of any trial is safety. And, even though emphasis on patient safety is no different between decentralized and in-person clinical trials, an argument in support of a virtual component is the ability to continuously monitor through remote sensing, enabling faster response times in cases of adverse events.

However, there remain obstacles to virtual clinical trials, namely medical licensing and drug dispensing, particularly with a direct-to-patient investigational drug product. Appropriate state licenses are required, even when monitoring is remote, meaning

Potential Benefits of Using Decentralized Clinical Trials



an investigator is required in each state where participants will receive treatment. The Clinical Trials Transformation Initiative (CTTI) also recommends, in their 2018 document "CTTI Recommendations: Decentralized Clinical Trials," contracting with companies able to provide licensed mobile healthcare practitioner research services across states in which a trial is conducted. Additionally, due to changing state laws regarding licensing of telemedicine, enlisting legal expertise is recommended.[4] What's more, the integrity of the supply chain must be expressly spelled out and approved as part of the trial protocol design so that the process is clear to the investigator, internal review board and applicable regulatory agencies. All parties must understand and be capable of meeting their obligations.

Not every clinical trial is appropriate to be held entirely virtual because at the heart of any trial is safety.

Wearables

So, how can data be collected in a virtual clinical trial? The easy answer could be wearables. Their ability to capture vitals such as heart rate and blood pressure and their capability to track and record adverse events, sleep and movement makes them already useful tools in assessing diseases such as depression, progression of multiple sclerosis and heart disease. And, although there are noted differences in accuracy and fidelity between clinical and consumer-grade devices, gaps are closing rapidly.

The opportunities for data collection and their utility are seemingly endless. With appropriate consideration of fit-for-purpose and verification, wearables transmitting data both actively and passively can early identify safety issues that would affect dosing and/or discontinuation of drug candidates from certain trials. Wearables can also enable faster and more objective data collection.

Of course, like any technology, wearables are not infallible. Very real concerns are software and hardware failures, lapses in tracking due to Internet outages or just a simple loss of battery life. If not provided to trial participants, wearables may introduce economic bias. There may also be differences in Health Insurance Portability and Accountability Act (HIPAA) requirements depending on whether the technology is provided as part of the trial or if data is delivered from participant-owned technology.

Data Integrity, Sharing and Patient Protections

As with any clinical trial, patients' understanding of how their data will be collected, stored, used (and reused) and shared is paramount. And, that task becomes more complicated when the trial is conducted virtually. Investigators need to minimize the amount of data collected, limit who has access and develop accountability into the clinical trial design, all of which needs to be conveyed to participants. Open communication about what will happen to their data helps participants build trust in the process.

The term "data" includes all data, including what is captured in the background of another activity, termed paradata. Paradata may include time stamps, geolocation, digital health technology settings and other information having little to do with the clinical trial. Specific informed consent for paradata is necessary, as is ensuring all data, passive, para and otherwise is de-identified. New federal and industry policies for mixed uses and data sources, as well as participant informed consent on data collection, are recommended.[1]

The question of data accuracy is also paramount for investigators. For instance, by what mechanisms can investigators ensure the virtual data being collected is that which was intended? Are patients using the device correctly? Is the data really from the intended patient? How is this verified?

Source data, audit trails, the data originator and what constitutes a final result all are currently under debate. And this is compounded by differing rules regarding data consent, ownership, sharing, usage, privacy and security — particularly with varying laws by geography. In the U.S., HIPAA laws require consent for data collection and sharing, although data collected by personal devices, provided it is de-identified, can be shared in aggregate with less explicit information about who will ultimately have access. Of interesting note is that neither "clinical trial" nor "virtual clinical trial" is defined as part of HIPAA, although the act does discuss research requirements.[1] Ensuring data protection is further complemented by what is known as the Common Rule, the short name for the Federal Policy for the Protection of Human Subjects, which is a standard of ethics that governs biomedical behavioral research involving human subjects.

In the European Union (EU), the General Data Protection Regulation (GDPR) requires clear definitions of data use, consent and sharing regardless of how it is collected. Within the U.S., California's Consumer Privacy Act has a much stricter interpretation of data than HIPAA, aligned more closely to the EU's GDPR, including a higher bar for data de-identification.[1] While an internationally harmonized approach would seemingly be of great benefit, this is such a new area of study that any meaningful outcome is likely a long way into the future.

In terms of clinical trial data collection, protections under HIPAA are less clear when a commercial or personal mobile device is used for data collection; however, the Federal Trade Commission has authority to ensure vendors are held liable for data breaches. Devices given to study participants are more likely to be covered under HIPAA. The CTTI recommends understanding applicable privacy laws by state and other jurisdictions, including those outside of the U.S., in which data will be collected. Experienced IT vendors can provide insights into telemedicine best practices.

Decisions on data collection, mapping, storage and sharing need to be made early and discussed in clinical trial pre-meetings with FDA. In addition to data storage and consent, training and troubleshooting for all parties from participants to investigators must be articulated.

Adverse Events Reporting

An imperative consideration for virtual clinical trials is safety monitoring. Participants must be clear about steps that should be taken when an adverse event is suspected. Where do they go? Who do they contact? Likewise, guidelines for the appropriate response plans and monitoring must be established for investigators, including communication up the chain for other participants, personnel, third-party vendors and other applicable parties. Safety monitoring can be aided by digital technologies, but given the criticality of identifying an adverse event and the necessity of follow-on actions, remote monitoring should never be a sole substitute for human interaction and intervention. All parties must know what to do in the event technology goes down.

The question of data accuracy is also paramount for investigators.

Standard Operating Procedures

As always, all of this information should be mapped out in standard operating procedures. GCPs are the lifeblood of clinical trials and will be reviewed and assessed by FDA. It is critical for all accountable parties to be identified, to map out the supply chain, and to understand proper storage and handling of drug products. It also must be articulated how participants will take part, how their data will be collected, used and shared, and affirmed that they understand by giving informed consent.

Decentralized clinical trials have the potential to change our understanding of diseases and the way healthcare is practiced. But out of sight does not mean out of mind. Ensuring virtual clinical trials have the same diligent protocol design and monitoring as in-person clinical trials can literally open the world of possibilities. ❖

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

Multisystem Inflammatory Syndrome in Children: A Complication of COVID-19

Much remains to be learned about this new condition affecting a growing number of children. However, it is hoped with increased vaccination and fewer cases of the SARS-CoV-2 virus, case numbers of MIS-C will also go down.

By Jim Trageser

ONE OF THE ongoing challenges of a new infectious disease is deciphering the complications that can come with it. This is true with the rapid emergence of COVID-19, which now requires many researchers and physicians to determine which long-term health conditions COVID-19 patients develop in the ensuing weeks, months and years can be attributed to the virus. This is particularly necessary since all COVID-19 survivors will develop health issues over the course of their lives, and the vast majority of them will be seemingly due to another cause.

Many infections can lead to post-infection syndromes. For example, acquired immune deficiency syndrome, caused by the human immunodeficiency virus, is probably the best known. But toxic shock syndrome, Guillain-Barré syndrome, rheumatic fever, erythema multiforme, hemolytic uremic syndrome and post-streptococcal glomerulonephritis are also well-known and well-studied conditions that can be triggered by a viral or bacterial infection.

Now, with hundreds of millions of people around the world contracting COVID-19, and millions of them progressing to acute infections requiring hospitalization, medical researchers have a unique opportunity to mine data and watch for emerging conditions associated with COVID-19 and SARS-CoV-2, the virus that causes it — one of which is multisystem inflammatory syndrome in children (MIS-C).

What is MIS-C?

Also known as pediatric multisystem inflammatory syndrome,[1] MIS-C is marked by severe inflammation of organs and tissues, persistent fever and gastrointestinal (GI) distress,[2] and it appears to be an autoimmune response to a viral infection.

Since MIS-C has only recently been identified and is currently defined by its symptoms, a more detailed understanding of what constitutes MIS-C has not yet been determined. Research into the specific nature of the inflammation is still in its early stages. Therefore, for now, MIS-C is a term used to describe symptoms

in children who exhibit inflammation and fever after contracting COVID-19, with no other discernible cause. The Centers for Disease Control and Prevention (CDC) notes that 99 percent of patients diagnosed with MIS-C test positive for the SARS-CoV-2 virus, and the other 1 percent had close contact with someone diagnosed with COVID-19. As of late June, CDC was reporting more than 4,100 cases of MIS-C in the United States alone.[3]

In addition, physicians and researchers have noted that some adults are also exhibiting similar symptoms. This is now known as multisystem inflammatory syndrome in adults (MIS-A).[2] The diseases are otherwise identical, but when patients are 21 years and older, it is classified as MIS-A. For unknown reasons, MIS-C is far more prevalent than MIS-A even though children are statistically less likely to contract COVID-19 and typically have far less severe cases of the virus than adults.

Causes of MIS-C

While there is an overwhelming temporal association between COVID-19 and MIS-C, researchers have not yet identified any proof to definitively tie the condition to COVID-19.[2] Nevertheless, most research is progressing with the assumption that the SARS-CoV-2 virus is the triggering agent for a number of reasons.

For instance, researchers noted a spike in the number of patients with lingering fever, inflammation and GI symptoms at the same time hospitalizations due to COVID-19 were spiking. As such, it was theorized early that these symptoms could be tied to a recent SARS CoV-2 infection.[4] Further, the symptoms had no other discernable underlying cause, and the collection of symptoms had never been seen in these numbers.

Thus, it's not surprising that the sudden appearance of thousands of patients manifesting a distinct set of symptoms during a global pandemic certainly makes the SARS-CoV-2 connection a logical place to begin research.

Recently, researchers at Mt. Sinai Hospital announced they have discovered a possible clue as to the cause and trigger for MIS-C: Patients displaying symptoms also have two specific T cells in an "exhausted state" from overexposure to pathogens.[5]

Symptoms and Progression of MIS-C

Since symptoms of MIS-C may manifest weeks after COVID-19 and many pediatric cases of COVID-19 are so mild that they are never diagnosed, parents may not make the connection. Typically, symptoms will appear between three weeks and six weeks after COVID-19 infection.[6]

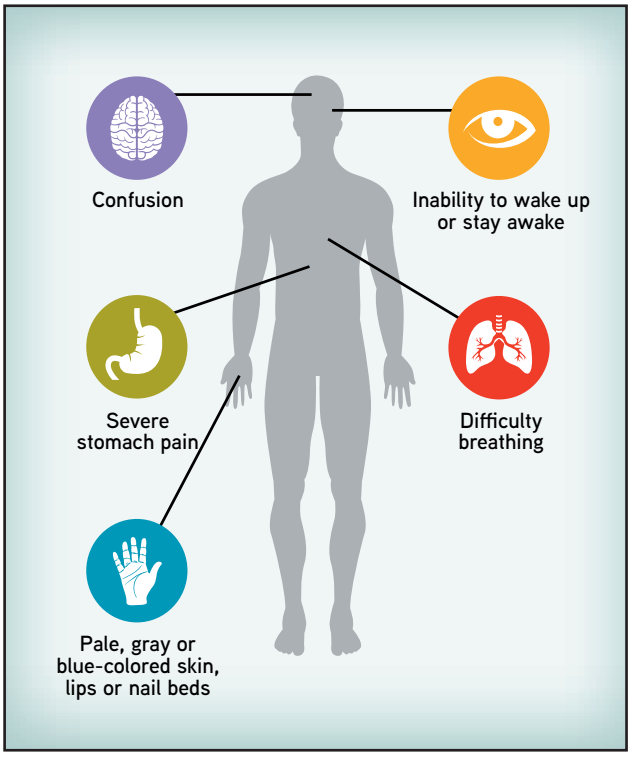
It should be noted that not every patient will exhibit the same symptoms; however, the Mayo Clinic identifies any combination of two or more simultaneous symptoms — with no other recognizable cause — to be of concern:

- Fever lasting more than 24 hours
- Vomiting
- Diarrhea
- Extreme fatigue
- Accelerated heartbeat
- Accelerated breathing
- Abdominal pain
- Rash
- Redness or swelling of the lips or tongue
- Redness or swelling of the hands or feet
- Enlarged lymph nodes
- Red eyes
- Headache, dizziness, light-headedness

Severe symptoms requiring emergency medical care include any of the following (Figure 1):

- Severe stomach pain
- Difficulty breathing
- Confusion
- Pale, gray or blue-colored skin, lips or nail beds
- Inability to wake up or stay awake

Figure 1. Severe Symptoms of MIS-C Requiring Emergency Treatment



If left untreated, the inflammation associated with MIS-C can damage the heart, lungs, blood vessels, kidneys, brain, eyes, digestive system and/or skin. And, the damage can become permanent and can lead to death.[2]

Diagnosing and Treating MIS-C

MIS-C was first described mere months after the COVID-19 outbreak began in the United States, when researchers first suspected there could be severe complications from the virus. In the year since MIS-C was first noted, public health officials have isolated a specific set of criteria to diagnosis the condition.

CDC has now issued a three-step diagnostic tool:[7]

- An individual under the age of 21 years presenting with fever over 100.4 degrees Fahrenheit for more than 24 hours, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)
- No alternative plausible diagnoses
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology or antigen test; or exposure to a suspected or confirmed COVID-19 case within the four weeks prior to the onset of symptoms

To determine if there is multi-organ involvement, CDC recommends — but does not limit physicians to — the following tests:

- Elevated C-reactive protein
- Erythrocyte sedimentation rate
- Fibrinogen, procalcitonin
- D-dimer
- Ferritin
- Lactic acid dehydrogenase
- Interleukin 6, elevated neutrophils, reduced lymphocytes and low albumin

While popular media accounts of MIS-C have associated the condition with serious cases of COVID-19, there have also been diagnosed cases in which patients were asymptomatic during COVID-19 infection. And, a small number of MIS-C patients apparently never developed COVID-19 but were exposed to those who did. So while parents may insist their child never had COVID-19, physicians need to run the full gamut of tests.

In fact, CDC recommends even suspected cases of Kawasaki syndrome be reported to public health authorities as a possible case of MIS-C. However, testing should obviously continue to make a definitive diagnosis. In addition, MIS-C can manifest with symptoms similar to those of sepsis or toxic shock syndrome, which also need to be ruled out before a final diagnosis is possible.[2]

Once MIS-C is diagnosed, patients should be admitted to the hospital as soon as possible if they are not already there so treatment can begin immediately to protect organs and other tissues from permanent damage due to inflammation.

According to the Mayo Clinic, specific treatment will depend on which organs are inflamed. Steroids may be used to reduce inflammation, while intravenous immune globulin can help repair the immune system. When the lungs are affected, oxygen or even a ventilator may be required to assist with breathing. In a few extreme cases, extracorporeal membranous oxygenation has been used. To prevent sepsis in the inflamed areas, antibiotics may be prescribed even before cultures are run.[7]

Fortunately, most patients recover quickly and completely with proper treatment. However, since MIS-C is a recently discovered condition, the long-term prognosis is not yet clear. Follow-up examinations are recommended until more is learned.[5]

Preventing MIS-C

Since infection by the SARS-CoV-2 virus is the suspected trigger, preventing infection is the only way to prevent MIS-C.

Children 12 years and older can now receive the Pfizer-BioNTech vaccine. But, children younger than 12 years should take normal precautions to try to prevent infection (Figure 2):

Figure 2. Preventing MIS-C

- Wash hands frequently
- Avoid touching the face
- Avoid those who are coughing, sneezing or otherwise appear ill
- Practice social distancing
- Wear a cloth mask
- Clean and disinfect surfaces in the home

Ongoing Research

MIS-C has been recognized only since 2020, and it is likely it has existed for less than two years, since the SARS-CoV-2 virus made the jump to humans.

While the speed of research to date has been impressive, much still needs to be learned, including the trigger that leads some patients with COVID-19 to develop MIS-C, the specific biological causes of the inflammation, and any new treatments to reduce the damage MIS-C can cause.

The National Institutes of Health (NIH) has launched the Collaboration to Assess Risk and Identify Long-Term Outcomes for children with COVID-19, and MIS-C is a major area of study for this new program. Because inflammation poses the greatest risk to patients with MIS-C, the new program is led by the National Heart, Lung and Blood Institute with assistance from the National Institute of Allergy and Infectious Diseases.

This effort has already approved and provided funding for three main areas of research:[8]

- Long-Term Outcomes after the Multisystem Inflammatory Syndrome In Children (MUSIC) will coordinate through the Pediatric Heart Network to focus on cardiovascular complications from MIS-C.
- Pharmacokinetics, Pharmacodynamics and Safety Profile of Understudied Drugs Administered to Children per Standard of Care (POPS) will be coordinated through the Pediatric Trials Network and will focus on the efficacy of treating children with medicines that have shown promise in treating COVID-19 in adults.
- Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISM) will study the immunological aspects of SARS-CoV-2 infection in children.

Other research already funded by NIH includes Predicting Viral-Associated Inflammatory Disease Severity in Children with Laboratory Diagnostics and Artificial Intelligence (PreVAIL kIds), which seeks ways to use artificial intelligence to identify patients most likely to develop MIS-C.

While clinicaltrials.gov lists only a handful of current studies being conducted for MIS-C, that number includes two trials studying the use of stem cells to fight the condition, one of which is being conducted at Duke University and the other at Singapore-based Mesoblast International Sàrl.

Another study, conducted by the Tuberculosis Research Centre in India in conjunction with NIH, is comparing different strains of the SARS-CoV-2 virus to determine if some are more likely to lead to the development of MIS-C.

And, a few other studies are following the long-term outcome of children diagnosed with MIS-C. But these studies will take years to determine outcomes and decades to come to a close.

Given how recently this condition was identified, it is likely numerous other studies in the pipeline have yet to receive U.S. Food and Drug Administration approval.

Looking Ahead

With COVID-19 increasingly appearing to be endemic and as new seasonal variants emerge, MIS-C is likely here to stay. Widespread inoculations and growing immunity among those who have contracted the disease should eventually drive case numbers of COVID-19 down, particularly with periodic vaccine boosters to address new variants. Reducing the number of COVID-19 cases will have the added benefit of reducing MIS-C cases, assuming the temporal associations eventually lead to a more tangible link between the virus and the syndrome. However, the unfortunate reality is pediatricians and emergency room physicians will likely have to add MIS-C to the list of conditions to diagnose and treat for the foreseeable future.

The good news is there is nothing to suggest MIS-C is going to become more common, unless new strains of the virus appear that affect the body differently. And, hopefully, with more and improved vaccines for the SARS-CoV-2 virus, it will become increasingly rare. ❖

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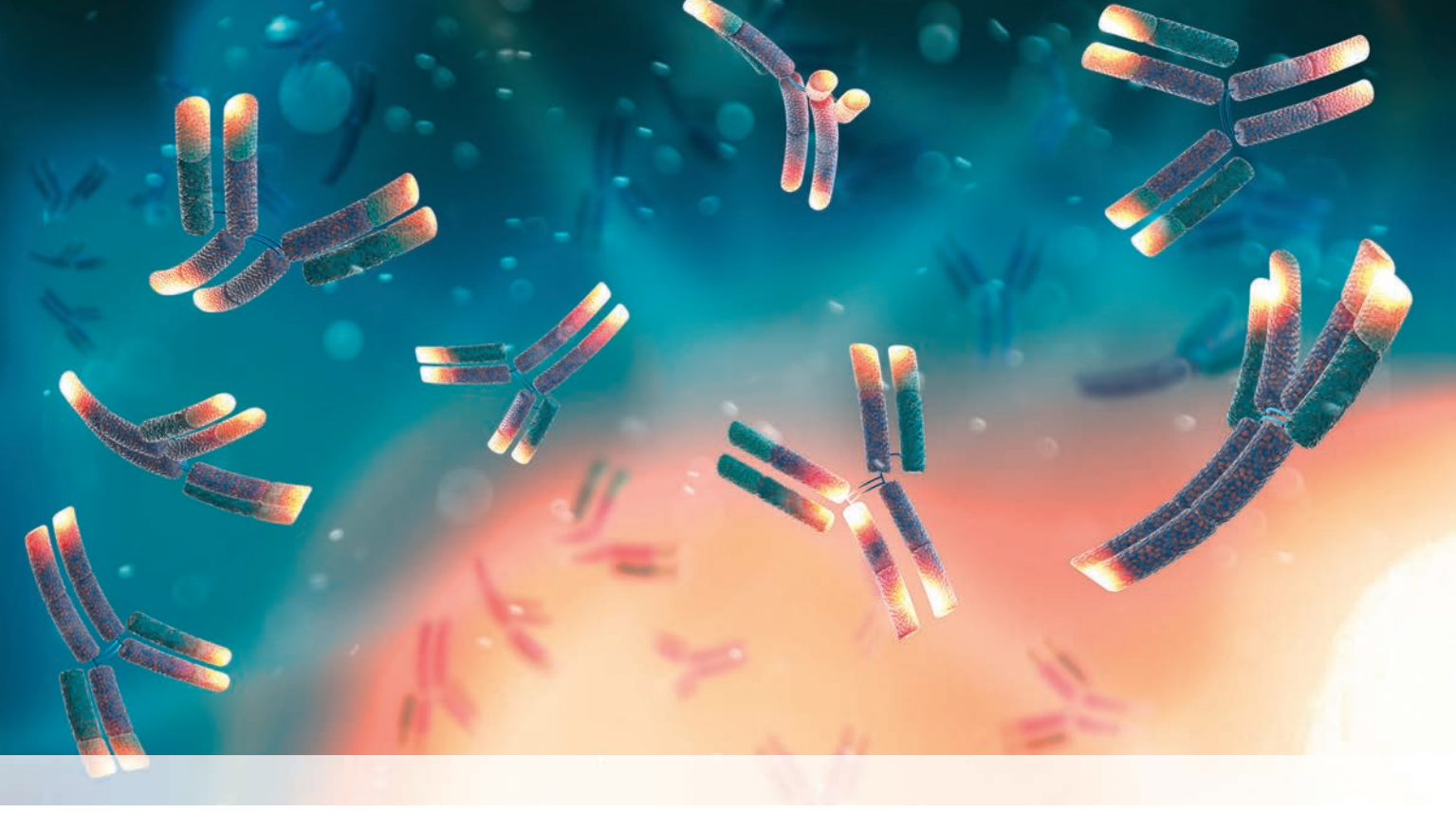
JIM TRAGESER is a freelance journalist in the San Diego area.



Anti-COVID Monoclonal Cocktails

Newly created treatments for high-risk COVID-19 patients have proved highly effective. Unfortunately, challenges with their distribution and administration have limited their use.

By Bob Geng, MD, MA

AS ATTENTION fixates on the development of vaccines against COVID-19, researchers have achieved another equally impressive yet less-celebrated victory: the creation of antiviral monoclonal cocktails. The concept of discovering and cloning antibodies against deadly viruses has been around for decades, but it only came to fruition during this pandemic. With Regeneron's casivirumab/indevimab cocktail and Lilly's bamlanivimab and recently approved etesevimab, there is now a range of precision medicine-targeted therapies against COVID-19. The speed of their development was nothing short of miraculous, and while efficacy/safety data are still limited to a handful of studies, observations thus far have convinced the U.S. Food and Drug Administration (FDA) to grant them emergency use authorization (EUA). Yet, while their development was an amazing example of the tremendous possibilities of collaboration between the public and private sectors, their distribution and administration have been met with myriad challenges.

All of these monoclonal antibodies are designed to neutralize the receptor binding domain of the spike protein of SARS-CoV-2 (the virus that causes COVID-19) to prevent it from binding onto the ACE2 receptor and enter the host cell. They were derived from evaluation of convalescent blood from recovered patients. Of all of the targeted antibodies produced by the B cells directed against SARS-CoV-2, the key was to find the ones with the best ability to bind to the spike protein to specifically target the virus's ability to infect the cell. State-of-the-art sequencing, bioinformatics and manufacturing technologies allowed for rapid identification, selection and production to initiate clinical studies. These monoclonal combinations target different regions of the receptor-binding domain and do not compete with each other for binding. By using more than one monoclonal to neutralize the spike protein, the chance of evolution of viral variants/mutations that could potentially elude neutralization in the future is decreased. In preclinical animal model studies, all of the monoclonals

demonstrated efficacy in neutralizing the virus to significantly decrease replication and viral load in the host.

Both Regeneron and Lilly monoclonal cocktails have similar eligibility criteria based on the EUA. They were created to treat ambulatory adolescent and adult patients who have mild-to-moderate COVID-19 and are at a high risk for hospitalization and serious complications but have not yet needed to be hospitalized. High risk is defined the same for both of the EUAs: over 65 years of age, immunocompromised state (either immunodeficiency or on immunosuppressive therapies), diabetes, chronic kidney disease or obese with a body mass index (BMI) greater than 35. Patients over 55 years of age may be eligible if they also have hypertension, chronic obstructive pulmonary disease or other forms of chronic lung disease or heart disease. For adolescents to be eligible, they must be either overweight with a BMI greater than the 85th percentile for age/gender, have heart disease, chronic respiratory disease (i.e., asthma), be dependent on a medical technology or device, have sickle cell disorder or have a developmental neurologic disorder. However, the complexity surrounding the full understanding of these eligibility criteria may be a challenge in the broad adoption of these therapies.

Lilly Monoclonals: Bamlanivimab and Etesevimab

The Lilly monoclonals have undergone a series of clinical trials, including the pivotal study BLAZE-1 in the ambulatory population that generated data for FDA to grant the EUA, as well as studies looking at lower-dose combinations, larger population sizes and postexposure prophylaxis. Because the study in hospitalized patients was stopped due to lack of efficacy, the therapies are indicated only for ambulatory use.

Initially, FDA approved the bamlanivimab monotherapy because it demonstrated significant efficacy and appeared to be safe and tolerable. However, FDA recently discontinued the EUA for bamlanivimab monotherapy due to the concern of developing treatment-emergent viral variants. The treatment-emergent variant rate for their placebo arm was 4.8 percent, but the rate for the bamlanivimab monotherapy was 9.4 percent. On the other hand, the treatment-emergent variant rate for the combination therapy group was only 1 percent, which was substantially lower than the placebo group. Therefore, this highlights the fact that combination therapy, which blocks multiple targets on the receptor-binding domain of the spike protein, decreases the likelihood of viral mutations.

The current EUA approval is for combination therapy of bamlanivimab 700 mg plus etesevimab 1,400 mg mixed together as an intravenous (IV) infusion given over at least one hour. This is based on efficacy and safety data from the combination therapy clinical trial. And, while the clinical trial used a higher dose of both monoclonals, it was determined a lower dose of each could achieve similar antiviral activity as the higher-dose formulation. Based on publicly available data, the safety and tolerability did not raise any significant concerns in the clinical trials. Treatment-emergent adverse events were not significantly different between the combination monoclonal group versus the bamlanivimab monotherapy or the placebo group. Adverse events were also determined to be mostly mild or moderate, although there was a case of anaphylaxis that resolved with epinephrine treatment. In the studies, around 1 percent to 2 percent of subjects who received the monoclonals developed some mild to moderate immediate hypersensitivity events that all resolved.

From an efficacy standpoint, the combination therapy group demonstrated a significant decrease in viral load compared to placebo from day three to day 11 post-administration. Patients with persistently higher viral load had worse clinical outcomes, and the percentage of those patients was much lower in the combination therapy group compared to the bamlanivimab monotherapy group or the placebo group. Clinical outcome measures also demonstrated efficacy. By the end of the 11 days of observation, the symptom score reduction was over eight points compared to placebo, and was statistically significant. The rate of hospitalization/emergency department (ED) visits for 28 days after therapy was 0.9 percent for the combination monoclonal group compared to 1.6 percent in the bamlanivimab monotherapy group and 5.8 percent in the placebo group. That is an 84 percent relative rate reduction in the hospitalization/ED visit rate when comparing the combination therapy versus placebo. Specifically, when the high-risk group of patients who were either older than 65 years or obese with a BMI greater than 35 was evaluated, reductions in hospitalization/ED visits was even more staggering: 0 percent in the combination monoclonal group and 13.5 percent in the placebo group.

Both Regeneron's and Lilly's monoclonal cocktails have similar eligibility criteria based on the EUA.

Regarding efficacy of neutralization of newly emerging viral variants, the FDA fact sheet on the EUA states the bamlanivimab and etesevimab combination therapy had no reduction in activity against the United Kingdom variant, but did demonstrate varying degrees of reduced ability to neutralize the South African, Brazil, California and New York variants.

Many physicians today are either uninformed or underinformed about the availability and efficacy/ safety data on these therapies.

Regeneron Monoclonals: Casirivimab and Imdevimab

The Regeneron monoclonals are approved for combination IV infusion therapy at 1,200 mg for each of the monoclonals (total 2,400 mg) administered over at least one hour. Multiple clinical trials were conducted, and more ongoing studies are evaluating the safety and efficacy of this combination therapy. The current EUA indication is for treatment of nonhospitalized high-risk patients, but additional studies are underway exploring its potential use for hospitalized patients, household contact prophylaxis and subcutaneous formulations. As of the end of January 2021, more than 12,000 patients have been enrolled in clinical trials for these therapies.

Combination therapy was able to significantly reduce the viral load compared to placebo at both the lower dose (approved total combination therapy of 2,400 mg) and higher dose (8,000 mg) with a similar degree of viral load reduction. Clinical outcome measures showed the combination monoclonal therapy group was able to reduce medically attended visits (combined number of ED visits, hospitalizations, urgent care visits, physician office visits and telemedicine visits) by 57 percent compared to placebo (from 6.5 percent in the placebo group to 2.8 percent in the 2,400 mg dose group). Looking only at ED visits or hospitalizations 28 days post-treatment, the rate was 4 percent for the placebo group and 2 percent for the 2,400 mg treatment group.

Overall, the combination therapy was well-tolerated, and there did not appear to be any significant safety concerns. The serious adverse event rate was 1.6 percent in the 2,400 mg treatment group and 2.3 percent in the placebo group, and none of these events was determined by investigators to be related to treatment. The high-dose (not approved dose) group had a 1.5 percent rate of infusion reactions compared to 0.4 percent in the placebo arm, but the 2,400 mg dose group (approved dose) had no observed infusion-related reactions reported in the study. There was one anaphylactic reaction following infusion of the combination therapy that resolved with epinephrine use.

The ability of casirivimab and imdevimab combination therapy to neutralize newly emergent variants was examined as well, and according to the FDA fact sheet, there was no significant reduction in neutralization activity against any of the characterized variants studied.

Challenges with Adoption

The hope for the development of these monoclonal therapies was that they would be widely distributed and utilized to prevent serious morbidity and mortality in symptomatic high-risk patients. However, while the government has been eager to fund the development, production and distribution of these therapies, the actual uptake has been underwhelming and slow due to a number of reasons.

First, since they are approved under the EUA and do not have full FDA approval, the manufacturers are not permitted to market them to clinicians or patients, which reduces the overall awareness of their existence. Many physicians today are either uninformed or underinformed about the availability and efficacy/ safety data on these therapies. A significant number of patients are also unaware of their existence. Even among patients who are aware of their existence, some believe they are difficult to obtain or available only to privileged groups.

Second, since these therapies are authorized only for nonhospitalized ambulatory patients, many of the typical COVID-19 frontline clinicians (hospitalists, ED physicians, pulmonologists and infectious disease specialists) who are predominantly hospital-based are not as significantly involved in the process of identifying eligible candidates and administering therapy. The EUA for these monoclonals shifts the focus to the community ambulatory providers such as primary care physicians who do not typically prescribe biologic therapies that require IV infusions. Many primary care providers are heavily reliant on telemedicine during the pandemic, and it may be difficult to assess degree of symptoms without physical exam or vitals to determine eligibility for the treatments.

Third, biologic therapies are usually distributed via specialty pharmacies or administered in infusion centers. But due to the pandemic, many infusion centers have limited capacity and may not allow patients with active infections to enter due to risk of

potential spread of infection to others. Special infusion centers had to be created specifically for the administration of these therapies with areas for monitoring after infusion.

Furthermore, healthcare is far more conservative than other technological fields, and adoption of change is much slower. Professional organizations, academic societies and specialist associations often take years to adopt new guidelines or incorporate new data into existing guidelines. What's more, the general adage of medicine is to do no harm, and many academics and specialists feel they still need larger study populations and longer observation periods to fully endorse novel therapy regimens.

There are multiple ways to overcome these challenges to help bring these lifesaving therapies to at-risk patients faster. For example, the government at all levels should increase the awareness campaign regarding the availability of these therapies. A significant amount of attention has been given to the vaccine rollout, but on state, local and federal government health-related agencies' websites, there should also be information regarding the monoclonal therapies. More attention should be placed on outpatient specialty societies that focus on respiratory disease and are comfortable with biologic therapies such as allergists/immunologists and ambulatory specialists who can evaluate for eligibility and potentially prescribe treatment. Networks of providers should be developed to facilitate the multidisciplinary care of COVID-19 patients before they reach the hospital. Lastly, more treatment centers should be established, and their locations should be publicized so all ambulatory providers in the region know where they can send their patients. A concerted collaborative effort of clinicians, hospitals, infusion centers and medical societies will help raise awareness and lead to better outcomes for these patients. ❖

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BOB GENG, MD, MA, studied medicine at Washington University School of Medicine in St. Louis, where he also completed his residency training in internal medicine. He is currently an assistant professor in allergy and immunology at the University of California, San Diego. Dr. Geng received his bachelor's and Master of Arts degrees in Georgetown University's School of Foreign Service.

A Brief History of Immunity and Immunoglobulins

Discoveries about the types of immunity eventually led to the use of human antibodies to treat disease.

By E. Richard Stiehm, MD

ABOUT THREE THOUSAND years ago, Mesopotamians believed disease was attributed to the celestial cycles of the planets, stars and moon (astrology). Astrologists posited these movements affected every aspect of life, including the weather, natural disasters and even human disease. In fact, astrology remained a legitimate scholarly subject pertaining to medicine until the study of medicine began in the 17th century.

One thousand years later, miasma was thought to be the likely cause of disease. According to the miasma theory, disease is caused by poisonous vapors or mists arising from decaying organic matter, contaminated water, foul air or sick patients. These vapors could affect individual patients or even whole communities, thus explaining disease among close contacts and entire communities.

Another early theory known as theurgy suggested disease is caused by angry gods punishing individuals or communities because of their bad behavior. The severe punishment inflicted by these gods led to suffering, disease and even death.

Greek philosopher Aelius Galen (129-219 A.D.), often considered "The Father of Medicine," believed disease was due to an imbalance of the four vital humors — blood, phlegm, yellow bile and black bile — leading to the temperaments sanguine, phlegmatic, choluric and melancholic, a set of genetically determined psychic qualities a person possesses. Treatments for these temperaments included cupping, bleeding, leeches, purgatives and expectorants to restore humoral balance.

Yet, most of these theories were abandoned when the germ theory of disease became established in the 17th century.[1]

Early Theories About Immunity and Contagion

It was long known, as recorded by the Athenian historian Thucydides (460-400 B.C.), that persons who survived bubonic plague would not get a second attack. Thus, survivors were able to care for plague patients without becoming ill. This concept of immunity was substantiated by Persian physician Rhazes who in 900 A.D. recorded that survivors of smallpox were immune to a second attack.[1]

But, acquired immunity was not limited to disease. In 100 B.C., Mithridates, the King of Pontus (a small kingdom on the Black Sea), was concerned about attempts on his life by poisoning. So he made a concoction of the 12 known poisons (called mithridaticum) and took small and increasing doses of the mixture so he could survive deliberate poisoning. It worked so well that when he tried to commit suicide by self-poisoning, he was unable to do so!

In 60 A.D., the Roman statesman and poet Marcus Lucanus (39-65 A.D.) described the resistance to lethal snake bites developed by the snake charmers of the Psylli tribes of North Africa, for which Lucanus coined the Latin term "immunis evasi."

During the periodic epidemics of smallpox and bubonic plague, it was realized that some illnesses were contagious. In 1546 A.D., Italian Girolamo Fracastoro suggested contagion was caused by invisible seeds (seminaria) in the air, earth or water, arising from an infected person or decaying organic matter. Seminaria had an affinity for certain organs or tissues or for one of the four humors proposed by Galen. It was believed when all of the seeds were expelled, recovery ensued, and the patient was resistant to a second attack.[1]

Smallpox Immunity: The Royal Experiment of 1717

When Mary Wortley Montagu, the wife of the British ambassador to Constantinople, was concerned her young children would get smallpox[2] (variola), she heard inoculation (aka variolation, the method of inoculation first used to immunize individuals against smallpox) would protect against the dread disease. Variolation involved taking the powdered crusts of the sores of a patient recovering from smallpox and placing them under the skin of a second person, resulting in a mild case of smallpox, rendering the recipient immune. Its slight mortality, less than 2 percent, was much lower than the 30 percent to 50 percent mortality or the scarring and blindness of surviving patients.

After having the procedure performed on several prisoners and orphans, subsequently exposing them to smallpox and finding they were protected, Lady Mary had her children variolated. When she returned to London, she convinced the leaders of the British army to variolate all its soldiers. She also told the firebrand American preacher Cotton Mather about variolation, who brought it to Boston to halt the smallpox epidemic of 1771. It was then that George Washington had his surgeon general, Benjamin Rush, inoculate the entire Continental Army, preventing the inoculated British army from gaining a biological advantage.

Edward Jenner and Vaccination

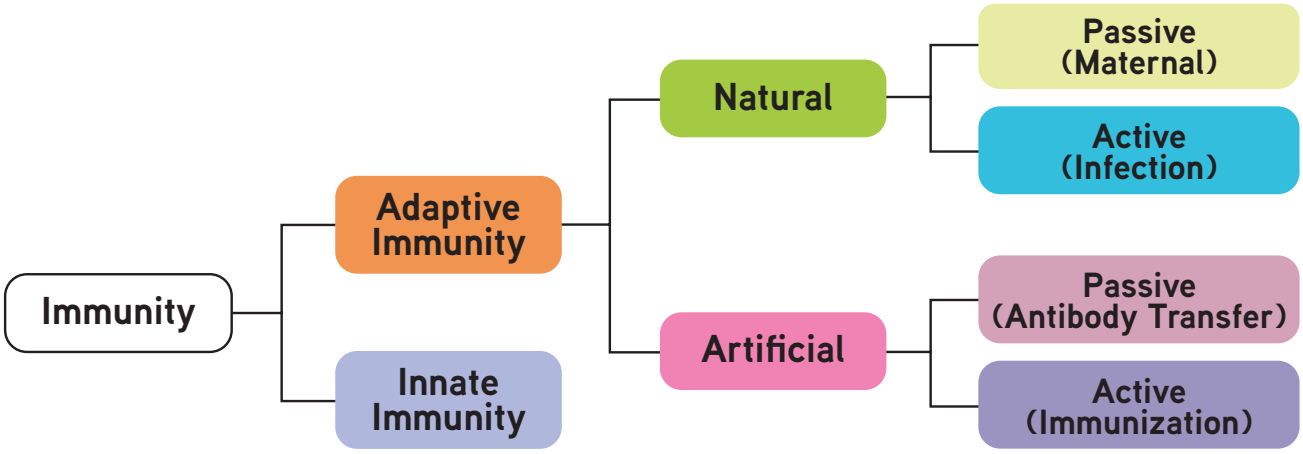
According to legend in 1776, English physician Edward Jenner (1746-1823) heard a Bristol milkmaid exclaim, "I shall never have smallpox for I have had cowpox; I shall never have an ugly pockmarked face." After confirming this observation, Dr. Jenner took material from the cowpox sore of the finger of milkmaid Sarah Nelmes and inoculated it into both arms of 8-year-old James Phipps, the son of his gardener. James developed a slight fever but quickly recovered. He was then challenged with an exposure to smallpox, and he indeed was immune. (But the causative agent of smallpox remained a mystery.)

Dr. Jenner's friend, Richard Dunning, coined this procedure "vaccination," which was quickly adopted. Indeed, Dr. Jenner was awarded a medal by Napoleon Bonaparte, a French statesman and military leader, and at Jenner's request, Bonaparte released two British prisoners after the war of 1812. After that, vaccination spread worldwide, leading to the complete eradication of smallpox from the world in 1980.[1,2]

During the periodic epidemics of smallpox and bubonic plague, it was realized that some illnesses were contagious.

The Germ Theory of Disease

Bacteria's role in disease was first suggested in 1656 A.D. by German Jesuit priest and scholar Athanasius Kircher who observed tiny worms in the blood of plague patients during a Rome epidemic. More well-known are the 1670 studies of Dutch microscopist Anton van Leeuwenhoek who observed multi-shaped motile particles in swamp water that he called animalcules (microbes), which were spherical, rod-shaped and spiral-shaped, all of which were renamed bacteria.



Using the new microscope, English Catholic priest John Tuberville Needham (1713-1781) noted that freshly boiled mutton gravy when placed in a corked bottle was soon swarming with live animalcules. He attributed this to a result of spontaneous generation, or a "vegetative force." But an Italian priest from Modena, Italy, Lazzaro Spallanzani (1729-1799) was skeptical. He placed boiled mutton gravy in a sealed glass flask that, unlike the corked flask, was airtight, and its gravy remained free of animalcules. He also observed that a cultured single animalcule transformed from a spherical shape to that of a dumbbell before dividing into two identical spherical animalcules. Spallanzani concluded life only arises from other life, whether bacteria, plants or animals, thus disproving spontaneous generation.[3]

In 1847, Hungarian physician Ignaz Semmelweis noted a high incidence of puerperal (postpartum) fever in women whose deliveries were assisted by doctors returning from the autopsy room. He instituted handwashing with chlorinated lime, reducing the incidence of puerperal fever from 18 percent to 2 percent.

In 1855, London physician John Snow witnessed an epidemic of cholera in a district of London using water pumped from the lower Thames River next to a sewage outlet. However, cholera was not occurring in districts using water from upstream Thames River. So, he recommended boiling the water and later removed the pump handle, thus interrupting the epidemic. This is regarded as the first epidemiologic study!

In 1860, French microbiologist Louis Pasteur (1822-1895) was able to culture bacteria from several patients with severe infections, including puerperal fever. In 1861, he proposed the germ theory of disease,[4] a theory that was supported by German scientist Robert Koch (1843-1910) who proposed his four Koch postulates that must be met before a specific bacterium is proven to cause a specific disease:

1) The bacterium must be present in every case of the disease.

2) The bacterium causing the disease must be grown in a pure culture.

3) The disease must be reproduced by the cultured bacterium in a previously healthy host (e.g., an animal).

4) The bacterium must be recoverable from the experimentally infected animal.

These conditions are not always possible when the bacteria cannot be cultured (e.g., leprosy) or if there is no animal model (e.g., smallpox).

Pasteur is regarded as the Father of Microbiology. Born to humble parents in rural France, he was an average student, more interested in fishing and sketching. He failed his first college exam but was eventually admitted to the École Normale Superiérure of Paris, graduating in 1846. After several appointments in various French institutions, he became the director of his own laboratory in Paris, the future Pasteur Institute.

Pasteur is best known for heating milk and wine to inhibit bacterial contamination (pasteurization), but that was just one of his multiple accomplishments. He saved the French silk industry by developing a method to screen silkworm eggs for those not infected (a method still used today), and using killed bacteria from pure cultures, he developed vaccines for chicken cholera, cattle anthrax and swine erysipelas.

Rabies and the Rabies Vaccine

Pasteur's most innovative accomplishment was the development of a rabies vaccine, despite its unknown cause and the inability to see it or grow the rabies virus.

Indeed, viruses had not been discovered until German agriculturist Adolf Mayer (1843-1942) in 1876 showed tobacco mosaic disease was contagious by making an extract of the affected tobacco leaves and using it to transfer the disease to healthy tobacco plants. In 1892, Russian biologist Dmitry Ivanovsky (1984-1920) showed that these extracts were still contagious when passed through a bacterial filter, thus free of bacteria, but when the filtrate was boiled, it was no longer infectious! In 1935, virologist Wendell Meredith Stanley (1904-1971) of the University of California, Berkeley, crystallized the tobacco mosaic virus, an RNA virus with a molecular weight of 18,000. He was awarded a Nobel Prize for this in1946.

Rabies is usually acquired by the bite of a rabid animal, typically a dog or bat, and is almost always fatal. Pasteur's rabies vaccine was derived from the dried nerve tissue of rabies-infected rabbits. His first patient was 9-year-old Joseph Meister who, on July 6, 1885, was badly mauled by a rabid dog. Pasteur gave the boy 13 injections of the vaccine over 11 days, at some personal risk since he was not a licensed physician. And, the boy did not get rabies. Pasteur tested his vaccine in 350 bitten patients with only one failure. The Pasteur Institute in Paris was then established to produce the vaccine.

Pasteur died in 1894 without ever knowing the cause of rabies. He achieved worldwide acclaim, resulting in multiple statues, streets and buildings in his honor. After a funeral service in Notre Dame Cathedral, his body was interred in a vault at the Pasteur Institute, covered with Byzantine mosaics depicting his many achievements.

Bacterial Toxins and Antitoxins

Pasteur's liquid broth cultures were a mixture of many bacteria. In 1881, Koch added gelatin to a broth culture and poured it on a glass plate with the intent to grow colonies of a single bacterium. This effort was greatly improved when the wife of his assistant suggested adding agar to the broth instead of gelatin. When poured on the glass plate, the cooled agar broth adhered to the glass as a gel and promoted the growth of a pure bacterial colony. The isolated bacteria could then be transferred to liquid broth to grow large amounts of a single bacterium used to isolate its toxin and develop a vaccine.

In 1884, German bacteriologist Fredrich Loeffler (1852-1915) identified and cultured Corynebacterium diphtheriae that causes diphtheria (known as "The Strangling Angel of Children" since it killed thousands of kids every year). In 1888, Pierre Roux (1853-1933) and Alexandre Yersin (1863-1943) isolated and concentrated the diphtheria toxin while working in Pasteur's laboratory.

In 1890, Kitasato Shibasaburo and Emil von Behring gave small heat-weakened injections of diphtheria toxin to guinea pigs and then used their serum to protect other guinea pigs from lethal injections of the toxin. They called this "antitoxin activity." Von Behring then used horse (equine) diphtheria antitoxin to successfully treat patients dying of diphtheria. This treatment was widely adopted, earning him the first Nobel Prize in Medicine in 1901.

German immunologist Paul Ehrlich (1854-1915) subsequently called antitoxin an "antikorper" (antibody), a term now used to depict all types of antibodies (e.g., antitoxins, agglutinins, precipitins, bacteriolysins, opsonins, neutralizing antibodies, etc.).

Von Behring's work soon led to the development of tetanus antitoxin in horses, since they are large, calm and plentiful. Other animal antibodies for specific diseases were also developed, including those to Haemophilus influenzae, pneumococci and snake venoms.[5] These animal antibodies are antigenic, so they must be used with caution since they sometimes cause anaphylaxis.

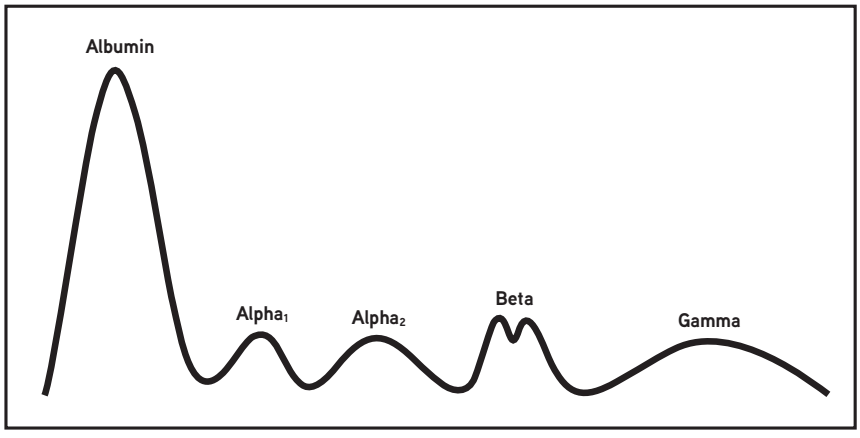
In 1914, von Behring used a mixture of toxin and antitoxin to minimize the toxic effect of immunizing animals for antitoxin production. In the 1920s, French veterinarian Gaston Ramon (1886-1963) made vaccines even safer by treating toxins with heat and formaldehyde, rendering the toxin nonreactive but maintaining its ability to provoke protective antibodies. These altered vaccines are termed "toxoids" and are still in use today.

Isolation of Human Immunoglobulin

Charles F. McKhann, MD, and Fu Tang Chu, MD, in 1933 noted that serum from the placental blood of newborn infants had the same antibodies as those of their mother's blood, indicating the placental transfer of maternal antibodies. Using ammonium sulfate precipitation, they showed these antibodies were in the globulin fraction of the serum. These placental antibodies were first used in children to prevent or modify measles.

In 1937, Arne Tiselius, PhD, of Sweden, using a new optical instrument termed electrophoresis, showed serum contains five distinct fractions, based on their mobility in an electric field. These include albumin, alpha-1 globulin, alpha-2 globulin, beta globulin and gamma globulin. The gamma globulin fraction contains most of the antibodies of the serum (Figure).

Figure. Electrophoretic Profile of Serum Proteins



In 1942, at the beginning of World War II, the U.S. Army commissioned Edwin Cohn, PhD, at Harvard to isolate human albumin from blood donors to treat shock in soldiers wounded on the battlefield. Dr. Cohn and his team developed a plasma fractionation procedure using cold ethanol at different concentrations and acidity (pH) to isolate several plasma fractions, including albumin (fraction 5) and gamma globulin (fraction 2), also known as immune globulin (IG).

Therapeutic Human Immunoglobulins

These days, plasma from several thousand adults are pooled and fractionated to obtain Cohn fraction 2, the material used to manufacture IG preparations in use today. This fraction is treated with stabilizers, filtered to remove large complexes, tested for sterility and assayed for antibody content.[5] These IG products contain antibodies to multiple bacteria and viruses.

Some IG products are derived from individuals with high levels of antibodies against specific pathogens. These high-titer products include cytomegalovirus IG, tetanus IG, hepatitis B IG, hepatitis C IG, varicella-zoster IG, rabies IG, botulism IG and Rh IG, the latter of which is given to Rh-negative pregnant mothers to prevent Rh hemolytic disease in their newborns. COVID-19 IG is now being used to treat the current SARS-CoV-2 infection.

Monoclonal Antibodies

In 1975, Georges Kohler and Cesar Milstein of the University of Cambridge described a method to obtain large amounts of pure antibody of known specificity (a monoclonal antibody).[6] They first isolated a single B cell making a single type of antibody from the spleen of an immunized mouse. This B cell was expanded to produce a short-lived cell line, which they fused with a malignant B cell line that was not secreting antibody. The resulting cell, termed a hybridoma, combined the specific antibody of the mouse B cell with the immortality of the cancer cell line. These hybridomas can be grown in large quantities to produce an unlimited supply of one specific antibody. Kohler and Milstein received the 1984 Nobel Prize for this discovery.

Most monoclonal antibodies are used in the laboratory to identify different types of normal and abnormal cells in the blood or tissues. Today, several hundred monoclonal antibodies are also used in the practice of medicine.[4] Four are directed against microbes, including respiratory syncytial virus, the anthrax bacterium, the C. difficile bacterium and the HIV gp120 receptor on CD4 T cells. Most recently, antiviral monoclonal cocktails have been developed to treat SARS-CoV-2 infection (see p.44). Many more are in the pipeline for therapeutic use.

A Long Line of Medical Discoveries

Early theories about disease and immunity led to our current understanding of how human antibodies can treat disease. It began as early as 3000 B.C., when the ancient Babylonians believed disease was caused by the movement of the planets and stars (astrology). One thousand years later, miasma theory suggested disease was caused by poisonous mists or vapor. Other cultures attributed disease to angry gods. And in 500 B.C., Galen believed disease was due to an imbalance of the four humors: blood, phlegm, yellow bile and black bile.

Recurrent epidemics such as the bubonic plague and smallpox led to the realization that some illnesses are contagious, and some survivors developed immunity to a second case of the disease.

The discovery of bacteria by the Dutch microscopist van Leewenhoek prompted Pasteur and Ehrlich to culture bacteria and thus develop the germ theory of disease. Bacterial cultures were used to develop vaccines against an organism or its toxin. Von Behring first used horse antitoxin to save a child with diphtheria, earning him the first Nobel Prize in Medicine. About the same time, Pasteur developed a vaccine to rabies, although he could not see or culture the rabies virus.

In the early years of the 20th century, antibody activity was shown to be present in the gamma globulin fraction of serum. This fraction, termed Cohn fraction 2 or IG, was first isolated in the 1940s and used to prevent hepatitis, poliomyelitis and measles. In 1954, IG was first used to treat a boy with agammaglobulinemia. High-titered IGs were also developed using donors with elevated levels of antibody to a specific pathogen.

In 1975, Kohler and Milstein isolated, cultured and immortalized a B cell making a single antibody and then fusing it with a malignant B cell line. This created an immortal cell, called a hybridoma, which can be expanded and cultured indefinitely to provide an unlimited supply of a specific antibody.[4] There are now more than 600 monoclonal antibodies used in the diagnosis and treatment of human disease.[5] ❖

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E. RICHARD STIEHM, MD, is professor of pediatrics at the David Geffen School of Medicine at the University of California, Los Angeles.


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After meeting a classmate with kidney disease, Eldonna Edwards was determined to donate a kidney to someone in need, which she finally did after a four-year search.

Live Donor Organ Transplant: *A Patient's Perspective*

By Trudie Mitschang

WHEN ELDONNA Edwards went back to college at age 48, she never expected her biggest lesson would be one that couldn't be learned in a classroom. A chance meeting with a classmate suffering from kidney disease started a chain of events that set Eldonna on her path to become a living organ donor.

It started out as a simple lunch with a fellow student, a chance to compare class notes and simply get to know each other. When the conversation turned personal and the classmate confided she had kidney disease, Eldonna's curiosity was piqued. "She was a beautiful, intelligent person who contributed a lot in class," says Eldonna. "After several days of reflection, I decided I wanted to offer my kidney to the student."

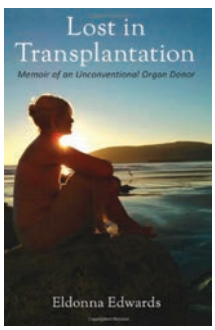
While the woman declined, partly because she wasn't ready for surgery and partly due to outdated rules at the time that disallowed nonrelated donors at most hospitals, the experience inspired Eldonna to learn more. "Knowing people were dying due to these prohibitive policies prompted me to write a class paper arguing for obvious changes that needed to be made in a broken system," she recalls. "The more research I did, the more determined I became to be part of the solution — to put my kidney where my mouth was, so to speak. I love this quote from Jane Goodall: 'You cannot get through a single day without having an impact on the world around you. What you do makes a difference, and you have to decide what kind of difference you want to make.' I realized that maybe I couldn't change the world, but I could change one person's world."

While writing her research paper, Eldonna stumbled upon a website featuring profiles of patients needing donors. She felt a special connection with one of those people — a hospice nurse and new grandmother — and offered to be tested as her living donor. It wasn't a match, but Eldonna was undeterred. As she continued her search for a compatible kidney recipient, her story took a series of unexpected turns, and four years later her kidney finally went to a man in his 50s who lived in New Jersey. "In the beginning, I didn't speak of my kidney donation except to close friends and family because I worried it would move the focus onto me and not on the people on the organ donation waiting list. Eventually, I realized my discomfort was nothing compared to the suffering kidney patients and their families experience on a daily basis. To me, these were the real heroes. By not sharing my story, I'd lose a huge opportunity to educate people about the tragic shortage of organs. In doing so, I'd hopefully inspire altruism in others."

Eldonna ended up writing a book about her experience titled *Lost in Transplantation: Memoir of an Unconventional Organ Donor*, and her story was also featured in the documentary "Perfect Strangers" directed by Jan Krawitz. Today, Eldonna travels the country speaking about the importance of living donation. "I'm honored to be a Donate Life Ambassador and to participate on the advisory board for the American Living Organ Donor Fund." An in-demand keynote speaker, Eldonna also helps moderate Kidney Transplant Donors & Recipients, a thriving Facebook community with more than 11,000 members seeking support and advice, and volunteers to mentor potential donors referred to her by transplant hospitals and other organizations.

For those considering living organ donation, Eldonna advises: "Choose your hospital wisely. You need to feel comfortable with the transplant coordinator. You should feel valued. And make sure they are good communicators who care about you, the donor."

For the patients on the receiving end, Eldonna says: "Be an extraordinary steward of your new kidney so you can become a light on the path of those still waiting. Remember, you don't owe your donor anything. I thought I was going to change someone's life, but I ended up changing my own. In other words, what started out as a compassionate response to a single individual has blossomed into a far-reaching connection with a multitude of wonderful people who I now call my friends. I have been blessed with deeper meaning and greater purpose in my life. People often thank me for what I did, but in my mind, the gifts I received were much greater than the one I gave." ❖



Eldonna authored a book about her transplant experience, and her story was also featured in a documentary titled "Perfect Strangers."

Live Donor Organ Transplant: *A Physician's Perspective*

Dr. Nancy Ascher, who has devoted her life to organ transplanation, hopes more people will decide to donate a portion of their liver or one of their kidneys while they are still living.

NANCY ASCHER, MD, PhD, has devoted her career to organ transplantation and transplant surgery. The first woman to have performed a liver transplant, she has inspired many women in the medical field, especially in transplantation. She has served on the Presidential Task Force on Organ Transplantation, Surgeon General's Task Force on Increasing Donor Organs and Secretary of Health and Human Services Advisory Committee on Organ Transplantation. Dr. Ascher has been the chair of the University of California San Francisco Department of Surgery for 17 years, greatly increasing gender diversity among faculty and residents. And, in a unique collaboration, she partners with her husband, John Roberts, MD, on a number of transplant surgeries; she removes the donated organ, and her husband transplants it into the recipient.

BSTQ: Why did you choose this area of medical specialty?

Dr. Ascher: I was interested in a field that would keep me stimulated and engaged for many years. I also wanted a career that would provide me with an opportunity to perform research relevant to the clinical work I was doing. I was fortunate to pick transplantation because it fulfills the conditions I have described. In addition, bringing health to sick patients is incredibly gratifying. We also care for patients over many years so we get a glimpse into our patients' lives in the long run.

BSTQ: You and your husband have a unique surgical relationship. Tell our readers about that.

Dr. Ascher: One of the programs at our institution is live donor liver transplant, where we take a portion of a liver from a healthy person and transplant it into someone with liver disease. The liver grows back in the donor and grows in the recipient as well. In this surgery, I do the donor hepatectomy (partial liver removal), and my husband transplants the liver into the ill recipient.

BSTQ: What are some common misperceptions about live-donor transplants, and how do you address them?

Dr. Ascher: People don't realize that the liver can regenerate. So, while the donor surgery is dangerous at the front end, the liver grows back to almost normal size. Nonetheless, the donor needs to be screened extensively; it is a complex and taxing operation. In the case of live kidney donation, we are born with two kidneys and can live normally with one, so most of us can donate a kidney if we have normal kidney function. Unfortunately, many patients who need kidney or liver transplants will never get them when they are on the waiting lists. There are simply not enough cadaveric donors to meet the needs. We need live donors to make up the difference.

BSTQ: To your point, in the U.S., there is a disproportionately low number of organ donors compared to those in need of transplant. How can we increase these numbers?

Dr. Ascher: For those who have signed their donor card, I think it's fantastic. I think it would be even better if donors decided he or she wanted to donate a kidney while alive so that, during their lifetime, they can enjoy knowing the gift that they've provided for someone else may have saved a life. I'm advocating for both deceased donation and live donation as an option for people who might want to give a portion of their liver or one of their two kidneys.

BSTQ: What future innovations in the field of organ transplantation excite you?

Dr. Ascher: The use of stem cells to help regenerate the liver could be a reality within the five-year time frame. There are also exciting things related to how the body adapts to the liver and how our patients can get by with less and less immunosuppression over time. Of course, the fact that we are already using live donors is a major advance in the field of liver transplantation because it means someone doesn't have to die for a patient to recover from liver disease. Another exciting advance in liver surgery is that we can cut the liver into two segments for two different recipients. In the near future, we will have machines that will allow us to keep the (deceased donation) liver out of the body for a period of time after donation to have it recover if it's somewhat diseased, until it can be successfully transplanted. The direction we're headed is really exciting! ❖

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

Hemophilia Gene Therapy: Cures May Finally Be at Hand

By Keith Berman, MPH, MBA

THE CONCEPT of gene therapy can be traced back at least 80 years, but its real genesis began with Professor William Szybalski, who in 1962 performed the first virus-mediated gene transfer to mammalian cells to correct a genetic defect. Two decades later, scientists fully characterized the normal amino acid sequences of factor VIII (FVIII) and factor IX (FIX), and successfully induced immortalized hamster ovary or kidney cells to express them in large-scale cell culture for purification into concentrates for the treatment of hemophilia A and B. If mammalian cells could be coaxed to produce large quantities of functional clotting factor, it was not a major conceptual leap to imagine targeted cells in the hemophilia patient himself could do so as well. And thus was born the dream of exploiting gene therapy to essentially cure hemophilia.

Where Clotting Factor Therapy Falls Short

Administered prophylactically, either recombinant or plasma-derived factor concentrates can sharply reduce the risk of spontaneous hemorrhage, limit the severity of traumatic bleeds and protect joints from chronic bleeding-related arthropathy. For people living with severe hemophilia, in whom less than 1 percent FVIII or FIX activity results in frequent spontaneous bleeding episodes, sustained maintenance of just 5 percent of the normal endogenous level of FVIII or FIX can improve the disease to a mild phenotype, sharply reducing the risk of frequent or serious bleeding events.

But as transformational as factor concentrates have been for persons with hemophilia, they are still well short of a functional cure.

Most obviously, there is the requirement for frequent self-injections and the ever-present potential for breakthrough

Table. Hemophilia A and B Gene Therapies Currently in Clinical Development

Hemophilia A

Company	Product	Clinical Developjment Status
BioMarin Pharmaceutical	valoctocogene roxaparvovec	Phase III
Spark Therapeutics/Pfizer	SPK-8011	Phase I/II→III
Pfizer	giroctocogene fitelparvovec (SB-525)	Phase III

Hemophilia B

Company	Product	Development Status
uniQure	etranacogene dezaparvovec (AMT-061)	Phase III
Pfizer	fidanacogene elaparvovec (PF-06838435)	Phase III
Freeline Therapeutics	FLT180a	Phase I/II→III
Belief Biomed	BBM-H901	Phase I

bleeds, particularly if a dose is missed. Additionally, because hemophilia patients don't naturally produce normal clotting factor, their immune system can "see" the exogenous FVIII or FIX protein as a foreign antigen and generate inhibitor antibodies that block its critical function in the coagulation cascade. Inhibitors occur in an estimated 25 percent to 30 percent of persons with hemophilia A and about one in 20 persons with hemophilia B, but generally with higher severity.

Thus, the decades-old dream is to correct the factor deficiency through a single infusion of a hemophilia gene therapy that produces steady high protective levels of FVIII or FIX. Ideally, a single injection of viral vectors carrying the normal gene would result in a permanent functional cure, freeing patients with severe or moderately severe disease from the lifelong need to regularly self-administer factor concentrates* and the residual risk of serious or potentially life-threatening bleeding events.

In addition, a bonus for the healthcare system is the potential for hemophilia gene therapy to dramatically reduce the lifetime cost of managing severe hemophilia, now estimated to well exceed $20 million with both prophylaxis and on-demand treatment strategies.[1]

Hurdles That Must Be Crossed

At least six companies currently have prospective hemophilia A and B gene therapies in various stages of clinical testing (Table). The prospect of eventual regulatory approvals of these treatments got a significant boost with the U.S. Food and Drug Administration's (FDA) 2017 marketing clearance of the first gene therapy: Kymriah (tisagenlecleucel), a genetically modified autologous T-cell immunotherapy for the treatment of a form of acute lymphoblastic leukemia in children and young adults.[2] But unlike in vivo hemophilia gene therapies, nearly all of which are given intravenously, Kymriah is the first of a class of chimeric antigen receptor T-cell (CAR-T) gene therapies wherein large numbers of patient T lymphocytes are collected by apheresis and modified ex vivo to incorporate a gene coding for a specific protein that directs the T cell to target and kill leukemia cells.

More akin to hemophilia are a number of investigational gene therapies that similarly target serious or life-threatening genetic disorders, notably including sickle cell disease (SCD), beta thalassemia and severe combined immunodeficiency. These treatments similarly involve the infusion of many copies of a gene-carrying adeno-associated virus (AAV) or lentiviral vector designed to target and transduce liver or other cells to express the critical missing enzyme or other functional protein.

But there are two fundamental hurdles that any hemophilia or other investigational gene therapy must address:

- Clinical trial results must demonstrate there are no serious safety concerns associated with infusing the viral vector. Specifically, patient studies need to show the gene therapy does not induce a serious immune response or cause hematological malignancies through insertional mutagenesis. While leukemias that plagued early human gene therapy experiments have not been identified in subjects receiving newer AAV or lentiviral vectors, in August 2021, a case of myelodysplastic syndrome prompted FDA to place a clinical hold on bluebird bio's cerebral adrenoleukodystrophy (CALD) gene therapy program.[3]
- Transduced cells must express therapeutic levels of the fully functional

** or emicizumab-kxwh (Hemlibra)*

clotting protein on a sustained basis. Simply put, the agency wants to see robust documentation of gene therapy durability, which can only come from extended follow-up of numbers of treated study participants.

These issues came into sharp focus with FDA's recent response to BioMarin Pharmaceutical's biologics license application (BLA) for its hemophilia A gene therapy, valoctocogene roxaparvovec in December 2019 — the first-ever U.S. filing for approval of any hemophilia gene therapy. The BLA was based on three years of clinical data from Phase I/II trials, as well as interim Phase III trial results. An approval announcement by the following August was widely anticipated in the hemophilia community. Instead, in August 2020, FDA issued a complete response letter, indicating the submission did not provide adequate assurance of safety or efficacy. The agency cited inconsistencies between Phase I/II and pivotal studies, and asked BioMarin to provide an additional two years of data from its ongoing Phase III trial, whose last-enrolled participant will complete two years of follow-up in November 2021.

This unexpected rejection of BioMarin's approval submission sent shock waves through the hemophilia research and patient communities. But perhaps it shouldn't have. Available treatments for genetic disorders such as SCD, beta thalassemia or CALD are accompanied by serious adverse effects, or are risky or challenging to perform. Patients with severe SCD, for example, require frequent transfusions that result in iron overload that in turn can damage vital organs; treatment of the iron overload requires iron chelating agents that have their own toxicities. Even with regular transfusions to keep circulating red blood cells with the HbS mutation below the target level, most patients with the severe phenotype experience hospitalizations for sickle cell crises and much-shortened lifespans.[4] Assuming a well-matched donor can be found, the only available treatment option for CALD is hematopoietic stem cell transplant (HSCT), which is associated with a risk of infection, graft-versus-host disease, engraftment failure and death; five-year survival following HSCT for treatment of CALD is less than 80 percent.[5]

At least six companies currently have prospective hemophilia A and B gene therapies in various stages of clinical testing.

Severe hemophilia presents a much different scenario. The available treatments for hemophilia — highly concentrated factor concentrates or emicizumab — are very safe and highly effective in reducing bleeding risk when self-administered prophylactically under the guidance of a trained specialist. Treatment-compliant individuals can live relatively normal lives, with a low risk of premature death. Even instances of severe inhibitors can be managed or eradicated with early, aggressive immune tolerance induction supported with bypassing agents.[6]

Thus, from a regulatory perspective, investigational gene therapies for hemophilia A and B might need to meet an incrementally higher standard for approval than other gene therapies that target severe genetically based diseases for which available treatment options are problematic or offer only limited benefits.

Hemophilia A Gene Therapies in the Pipeline

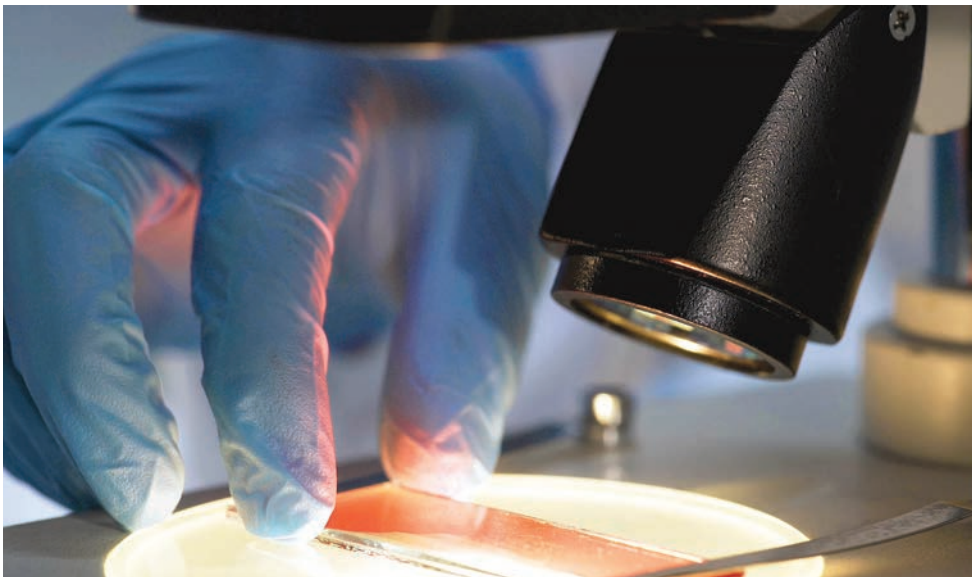
The simpler structure and much smaller number of amino acids that comprise the FIX molecule helped to give investigational hemophilia B gene therapies a substantial head start in their early development. But after years of lagging behind, hemophilia A gene therapies have caught up, with three prospective treatments now in Phase II or Phase III clinical testing.

BioMarin Pharmaceuticals (valoctocogene roxaparvovec). In early 2020, a United Kingdom research team reported that all 13 adult subjects with severe hemophilia A who received the two highest doses of valoctocogene roxaparvovec (also called AAV5-hFVIII-SQ) had complete resolution of bleeding in all previously affected target joints, no bleeding events and complete cessation of prophylactic FVIII use over two to three years of follow-up. Study participants who received the two highest doses — 4×10^{13} or 6×10^{13} vector genomes per kilogram of body weight (4e13 or 6e13 vg/kg) — had a median FVIII expression of 13 percent and 20 percent of normal — well above the protective FVIII threshold level.[7]

Subsequently, BioMarin presented detailed findings from its Phase III GENEr8-1 study, whose 134 enrolled

participants make it the largest global pivotal trial to date to evaluate any hemophilia gene therapy. At the end of the first post-infusion year, the mean endogenous FVIII expression level climbed from a baseline of 1 IU/dL to 42.9 IU/dL (median 23.9), and remained steady in a subset of 17 patients who were out at least two years from their single dose of valoctocogene roxaparvovec. In a prespecified subset of 112 patients with a mean follow-up of 72 weeks, the annualized FVIII utilization rate was reduced by 99 percent, from a mean of 3,961 IU/kg/year (median 3,754) to just 57 IU/kg/year (median 0). The mean annualized infusion rate (AIR) was correspondingly reduced by 99 percent from 136 (median 129) to 2.0 (median 0) infusions per year. The annualized bleeding rate (ABR) fell by 84 percent from 2.8 (median 2.8) bleeding episodes at baseline to 0.8 (median 0.0) episodes per year following valoctocogene roxaparvovec gene therapy ($p < 0.001$).

Elevated alanine aminotransferase (ALT), an enzyme whose increased blood level is generally indicative of liver cell damage, was the most common adverse event identified in study participants, about three-quarters of whom were treated with corticosteroids. The average duration on corticosteroids was 33 weeks; predictably, its use was associated with side effects that included insomnia, cushingoid changes and increased weight. But importantly, no Grade 4 ALT elevations occurred, and no participants met Hy's law criteria for drug-induced liver injury. "The demonstrated bleed control at 52 weeks and beyond in this pivotal study supports our thesis that gene therapy can play an important role in the treatment of severe hemophilia," said lead principal investigator Margareth C. Ozelo, MD, PhD.



BioMarin plans to resubmit a BLA for valoctocogene roxaparvovec in the second quarter of 2022, which will include FDA's requested two-year follow-up data for all 134 subjects in the 4e13 vg/kg and 6e13 vg/kg dosage cohorts of the company's Phase III GENEr8-1 study.

Spark Therapeutics/Roche (SPK-8011). Spark's SPK-8011 comprises a bioengineered AAV vector containing a codon-optimized FVIII gene under the control of a liver-specific promoter. To date, Spark has enrolled fewer study participants than BioMarin, but has reported on patients who have been followed for as long as four years following vector administration. A total of 18 Phase I/II study participants have received SPK-8011 in four dose cohorts, ranging from 5×10^{11} vg/kg to 2×10^{12} vg/kg. In the 16 patients with sustained FVIII expression, the ABR and annualized FVIII infusion rates were reduced by 91 percent and 97 percent, respectively.

Interim data indicate SPK-8011 has "an acceptable safety profile," according to the company, with no deaths and no FVIII inhibitor development with up to four years of follow-up. Two of 17 participants with more than one year of data lost FVIII expression as the result of a presumptive immune response to the AAV capsid that was unresponsive to immunosuppression. Seven participants experienced transient, asymptomatic liver function test elevations, all of which were mild or moderate and have resolved; one experienced a grade 2 transaminitis, which resolved after intravenous steroid treatment.

Earlier this year, Spark also reported stable and durable FVIII activity at more than 52 weeks of follow-up in all four adult Phase I/II study subjects with severe hemophilia and no history of inhibitors treated with a different investigational hemophilia A gene therapy — SPK-8016 — at a comparatively low vector dose of 5×10^{11} vg/kg.

One of the four subjects who did not require immunomodulatory agents had the highest level of FVIII activity (21.8 percent of normal), while the others received tapering doses of oral corticosteroids and steroid-sparing

immunomodulatory co-therapies and maintained FVIII levels of 5.9 percent of normal or higher. Collectively, they experienced a 98 percent reduction in the AIR and an 85 percent reduction in the ABR after a follow-up of 15 months to 18 months.

Pfizer (giroctocogene fitelparvovec; SB-525). Initially developed by Sangamo Therapeutics, this recombinant AAV serotype 6 vector (AAV6) carries DNA-encoding B domain-deleted human FVIII, with an expression cassette designed for optimal liver-specific expression of the protein.

The five participants in the high-dose 3 x 10^{13} vg/kg cohort of the Phase I/II Alta study had sustained very high, steady-state FVIII activity levels, with a group median FVIII activity of 56.9 percent of normal from week 9 to week 52. Beyond week 3 following infusion of SB-525, none experienced any bleeding events or required prophylactic factor within the first year. One patient had one target joint bleed requiring FVIII therapy after week 52. Four of the five participants in the high-dose cohort received oral corticosteroids for ALT elevations, all of which fully resolved.

Over the next year, a total of 63 participants with severe or moderately severe hemophilia A will be enrolled in the AFFINE Phase III open-label registrational trial to evaluate the efficacy and safety of a single infusion of SB-525; they will be followed over a five-year study period after the single infusion to further assess the ABR relative to previous FVIII prophylaxis, as well as the magnitude and durability of the FVIII activity level.

"Given the Phase I/II study findings to date, we believe that [SB-525] has the potential to sustain factor levels and reduce annual bleed rates, suggesting this one-time gene therapy could potentially transform the standard of care for eligible patients worldwide," said Pfizer's rare disease chief development officer Brenda Cooperstone.

A fourth company, privately held Expression Therapeutics based in Atlanta, has developed a novel ex vivo hemophilia A gene therapy that involves harvesting autologous hematopoietic stem cells from the patient, selecting for CD34+ cells, genetically modifying them using its proprietary lentivirus-FVIII vector and, following a conditioning regimen, reinfusing the transduced CD34+ cells so they can engraft in the stem cell compartment within the bone marrow. A Phase I clinical trial in seven patients with severe hemophilia A is expected to start enrollment early in 2022.[8]

Hemophilia B Gene Therapies in the Pipeline

The competitive field working to introduce a hemophilia B gene therapy has recently been pared back with the discontinuation of programs sponsored by Sangamo Therapeutics (SB-FIX) and Takeda (TAK-748), leaving at least four companies with promising candidate products in the race: Pfizer, Netherlands/U.S.-based uniQure, U.K.-based Freeline and Shanghai-based Belief Biomed.

uniQure (etranacogene dezaparvovec; AMT-061). AMT-061, an enhanced construct of uniQure's original AMT-060 gene therapy candidate, comprises an AAV5 viral vector carrying a gene cassette with the high-functioning Padua variant of FIX. uniQure and CSL Behring have entered into a commercialization and license agreement providing CSL Behring exclusive global commercialization rights to AMT-061.

Interim clinical data from all 54 hemophilia B patients enrolled in the company's pivotal Phase III HOPE-B trial have demonstrated durable, sustained increases in FIX activity at 52 weeks following infusion of a single dose of AMT-061, with a mean of 41.5 percent of normal, compared to a mean of 39.0 percent of normal at 26 weeks of follow-up.

The ABR during the 52-week follow-up period was reduced by 80 percent to 0.68 bleeding episodes per year, from the pre-treatment baseline of 3.39 episodes per year ($p < 0.0001$). The annualized rate of spontaneous bleeding requiring treatment dropped by 85 percent from 1.16 at baseline to 0.18 bleeds per year during the 52-week follow-up period. FIX replacement therapy in all patients declined by 96 percent, with 52 of 54 patients successfully discontinuing their prophylactic infusions.**

"The 52-week data show mean FIX activity in the normal range and increases our confidence in the potential durability and long-term benefits of [AMT-061], bringing us one step closer to our goal of delivering this groundbreaking therapy," said uniQure R&D president Ricardo Dolmetsch, PhD.

Pfizer (fidanacogene elaparvovec). Fidanacogene elaparvovec is a bioengineered AAV vector utilizing a high-activity FIX transgene. In 2018, Spark Therapeutics transferred responsibility for all clinical development, regulatory and manufacturing activities to Pfizer.

*** One nonresponder received less than 10 percent of the AMT-061 dosage due to an infusion reaction, while the second nonresponder had an unusually high preexisting neutralizing antibody titer against AAV5 that is expected in less than 1 percent of the general population.*

Now dubbed "PF-06838435," this gene therapy is currently in a Phase III trial enrolling 55 adult hemophilia B patients with severe or moderately severe disease (residual FIX activity less than or equal to 2 percent).

At 52 weeks following vector infusion, 15 adult hemophilia B patients in an earlier Phase I/II study experienced a mean steady-state FIX level of 22.9 percent (± 9.9 percent), with a drop in the ABR from 8.9 ± 14.0 bleeds prior to treatment to 0.4 ± 1.1 bleeds. Twelve of 15 patients reported zero bleeds over the 52 weeks following fidanacogene elaparvovec infusion. Five patients required a total of 20 factor infusions. There were no reported serious adverse events, and all hepatic transaminase elevations responded to treatment with corticosteroids.

Thus far, with up to five years of follow-up in 14 participants, fidanacogene elaparvovec appears to be generally well tolerated, according to a very recent report by the Phase I/II clinical study team. Mild sustained elevations of uncertain etiology in some study subjects continue to be monitored.

Freeline Therapeutics (FLT180a). Another AAV-based gene therapy, FLT180a has been administered to 10 patients with severe hemophilia B in four dosage cohorts. With follow-up periods ranging from 26 weeks to 104 weeks, durable, long-term elevation in FIX activity was observed for up to two years in the two patients enrolled in the lowest dose cohort (4.5e11 vg/kg); both had levels of 38 percent of normal, with no evidence of transaminitis.

Remarkably, three patients who received a dose of 9.75e11 vg/kg had week 3 FIX activity levels of 136 percent, 82 percent and 105 percent of normal; a fourth patient had a FIX expression of just 3 percent of normal, preceded by an increase in ALT. Average FIX expression in two patients who received a dose of 1.5e12 vg/kg averaged 160 percent of normal, which was deemed to be higher than required for the potential treatment of hemophilia B.

The competitive field working to introduce a hemophilia B gene therapy has recently been pared back.

"These data suggest that FLT180a has the potential, using relatively low doses, to create durable FIX activity levels in the normal range … and provide functional cures," said Freeline CEO Theresa Heggie. Freeline is currently screening potential participants for enrollment in a planned Phase III clinical trial.

Belief Biomed (BBM-H901). Specific findings have not yet been released for Belief's bioengineered AAV containing a codon-optimized human FIX gene under the control of a liver-specific promoter, which is currently in Phase I clinical development. But the company reports an investigator-initiated trial of BBM-H901 has already demonstrated "high efficacy and safety," with stable FIX activity, a significant decline in ABR and no evidence of serious adverse events.

Not If But When

Available data suggest that several hemophilia A and B gene therapy candidates have acceptable safety profiles, consistently and durably induce protective clotting factor levels, essentially end the need for prophylactic factor replacement therapy, and dramatically reduce the risk of bleeds requiring treatment.

While the excellent effectiveness and safety of current prophylaxis therapies make it incumbent for gene therapies to demonstrate long-term safety and efficacy, all indications are that the dream of a functional cure for severe hemophilia will soon become reality for thousands of affected individuals in the U.S. and throughout the world. ❖

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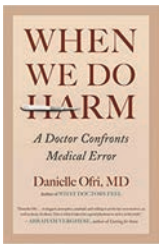
KEITH BERMAN, MPH, MBA, is the founder of Health Research Associates, providing reimbursement consulting, business development and market research services to biopharmaceutical, blood product and medical device manufacturers and suppliers. He also serves as editor of *International Blood/Plasma News*,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

Current Procedural Coding Expert 2022 (Spiral), 1st Edition

Author: Optum360

This book contains the entire 2022 current procedural terminology (CPT) code set and includes and excludes notes for coding guidance and Medicare icons for speedy coding, billing and reimbursement. Also included is a comprehensive listing of annual code additions, revisions, deletions and reinstatements in the appendix; new code icons and notes; reimbursement information; and mid-year changes not found in the American Medical Association's CPT codebook. This easy-to-navigate resource is intended to benefit physician practices, outpatient hospitals and ambulatory surgery centers.

www.amazon.com/Current-Procedural-Coding-Expert-Spiral/dp/1622547446



When We Do Harm: A Doctor Confronts Medical Error

Author: Danielle Ofri, MD

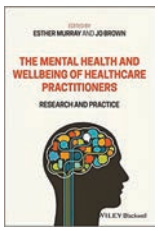
Medical science has made enormous strides in decreasing mortality and suffering, but treatment can also cause harm, a significant portion of which is preventable. In *When We Do Harm*, practicing physician and author Danielle Ofri places the issues of medical error and patient safety front and center. Drawing on current research, professional experience and extensive interviews with nurses, physicians, administrators, researchers, patients and families, Dr. Ofri explores the diagnostic, systemic and cognitive causes of medical error. She advocates for strategic use of concrete safety interventions such as checklists and improvements to the electronic medical record, but focuses on the full-scale cultural and cognitive shifts required to make a meaningful dent in medical error. Woven throughout the book are powerfully human stories.

www.amazon.com/When-We-Do-Harm-Confronts/dp/0807003042

The Mental Health and Wellbeing of Healthcare Practitioners: Research and Practice, 1st Edition

Authors: Esther Murray and Jo Brown

In *The Mental Health and Wellbeing of Healthcare Practitioners,* accomplished researchers and authors Esther Murray and Jo Brown deliver an insightful exploration of the theoretical and practical aspects of implementing mental health improvement within the healthcare system through a range of practical examples and cases. The book also explores the possibilities available to professionals to talk about their mental health using "borrowed" words and concepts, and uncovers structural and social concerns that prevent practitioners from accessing the time and space they need to address their mental health concerns.



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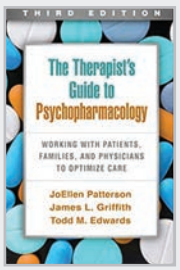

The Therapist's Guide to Psychopharmacology: Working with Patients, Families, and Physicians to Optimize Care, Third Edition

Authors: JoEllen Patterson, PhD, LMFT, James L. Griffith, MD, and Todd M. Edwards, PhD, LMFT

Now in a revised and updated third edition, this practitioner guide and text incorporates the latest knowledge about psychopharmacology and collaborative care. Therapists and counselors will learn when and how to make medication referrals and how to address patients' questions about drug benefits, side effects, safety and more. Organized around frequently encountered mental health disorders, the book explains how medications work, including what they can and cannot accomplish. Strategies for collaborating successfully with patients, family members and prescribers are discussed in detail. The text features case examples, sample referral letters, checklists and a glossary. New to this edition are chapters on the therapeutic relationship and bipolar disorder; expanded discussions of distinguishing psychiatric illness from normal distress, optimizing collaboration with psychiatrists, how medications work in the brain, treatment of chronic pain and more; and additional case vignettes and psychopharmacology "rules of thumb."

www.amazon.com/Therapists-Guide-Psychopharmacology-Third-Physicians/dp/1462547664

First-Line Intravenous Immune Globulin Monotherapy Evaluated in Idiopathic Inflammatory Myopathy

Dutch investigators conducted a Phase II open-label clinical study to evaluate the efficacy and safety of intravenous immune globulin (IVIG) as first-line treatment in a consecutive series of patients with newly diagnosed, biopsy-proved idiopathic inflammatory myopathy (IIM) of less than nine-month duration. Included were nine patients with dermatomyositis, six with immune-mediated necrotizing myopathy, four with nonspecific myositis/overlap myositis and one with anti-synthetase syndrome. Patients with inclusion-body myositis and prior use of immunosuppressants were excluded from the study.

The treatment regimen consisted of IVIG (Privigen) monotherapy for a total of nine weeks, including a 2 g/kg body weight loading dose and two subsequent maintenance doses of 1 g/kg administered at three-week intervals. The primary outcome measure was the number of patients with at least moderate improvement on the 2016 ACR-EULAR Total Improvement Score.

Eight patients (8/19, 42 percent; Clopper-Pearson confidence interval 19.6, 64.6 percent) experienced at least moderate improvement by nine weeks. Of these responders, six patients demonstrated improvement by three weeks. Seven of the 19 evaluable patients required rescue medication due to insufficient efficacy and were prematurely withdrawn from the study. Three serious adverse events occurred, including a life-threatening pulmonary embolism in a study participant diagnosed with ovarian cancer during the study.

The investigators concluded first-line IVIG monotherapy led to clinically relevant improvement in nearly one-half of IIM patients, the majority of whom experienced a rapid clinical response. While advising caution about its use in patients with concomitant malignancy or other factors placing them at increased risk of thrombosis, the study authors recommended further studies to assess the efficacy of add-on IVIG treatment in combination with glucocorticoids.

Lim J, Eftimov F, Verhamme C, et al. Intravenous immunoglobulins as first-line treatment in idiopathic inflammatory myopathies: a pilot study. Rheumatology *(Oxford) 2021 Apr;60(4):1784-92.*

High Oncotic Pressure Cardiopulmonary Bypass Priming with Human Albumin Improves Outcomes in Pediatric Open-Heart Surgery

Noting a paucity of literature regarding the association of high-oncotic priming solutions for pediatric cardiopulmonary bypass (CPB) and clinical outcomes, specialists at India's Sir Ganga Ram Hospital conducted a double-blinded, randomized controlled study to examine the impact of high oncotic pressure priming by the addition of 20 percent human albumin prior to the initiation of CPB.

Consecutive children with congenital heart diseases admitted for open-heart surgery were randomized to the conventional prime group (n = 37) or the high oncotic prime group (n = 39). In the first 24-hour postoperative period, children in the albumin group had a significantly lower occurrence rate of hypotension (28.2 vs. 54 percent, P = 0.02), a lower requirement for fluid boluses (25.6 vs. 54 percent, P = 0.006) and a shorter lactate clearance time (6 vs. 9 hours, P < 0.001). Platelet count was also significantly higher in the albumin group at 24 hours (112 vs. 91 x 103/μL, P = 0.02).

There was no significant difference between groups in intra-CPB hemodynamic parameters or incidence of acute kidney injury. In a risk-stratified subgroup analysis, both a reduced intensive care unit stay (4 days vs. 5 days, P = 0.04) and hospital stay (5 days vs. 7 days, P = 0.002) were documented in the albumin prime group. The investigators concluded high oncotic pressure addition of concentrated albumin to the CPB prime might be beneficial over conventional blood prime, and that further studies are warranted.

Rauf A, Joshi RK, Aggarwal N, et al. Effect of albumin addition to cardiopulmonary bypass prime on outcomes in children undergoing open-heart surgery (EACPO Study) — a randomized controlled trial. World J Pediatr Congenit Heart Surg *2021 Jan;12(1):61-9.*

Medicare Immune Globulin Reimbursement Rates

Rates are effective Oct. 1, 2021, through Dec. 31, 2021

	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	$140.89	$138.72
	FLEBOGAMMA DIF	Grifols	J1572	$73.61	$72.43
	GAMMAGARD SD	Takeda	J1566	$130.98	$128.88
	GAMMAPLEX	BPL	J1557	$97.06	$95.50
	OCTAGAM	Octapharma	J1568	$83.26	$81.92
	PANZYGA	Octapharma/Pfizer	90283/J1599	**	**
	PRIVIGEN	CSL Behring	J1459	$88.96	$87.53
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$88.98	$87.55
	GAMMAKED	Kedrion	J1561	$96.44	$94.89
	GAMUNEX-C	Grifols	J1561	$96.44	$94.89
SCIG	CUTAQUIG	Octapharma	90284/J3590	**	**
	CUVITRU	Takeda	J1555	$144.96	$142.64
	HIZENTRA	CSL Behring	J1559	$115.82	$113.96
	HYQVIA	Takeda	J1575	$151.55	$149.12
	XEMBIFY	Grifols	J1558	$136.05	$133.87

* ASP + 4.3% applies only after Jan. 1, 2022, unless the Medicare Fee-for-Service sequestration payment adjustment suspension is ended.

Calculate your reimbursement online at www.FFEnterprises.com.

** ASP-based Medicare payment rate not yet available; payment rate assigned by your Medicare Administrative Contractor.

Immune Globulin Reference Table

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

2021-2022 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	90688
AFLURIA PEDIATRIC (IIV4)	SEQIRUS	0.25 mL PFS 10-BX	6-35 months	90685/90687
FLUAD (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90694/90654
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	2 years and older	90674
FLUCELVAX (ccIIV4)	SEQIRUS	5 mL MDV	2 years and older	90756*
FLULAVAL (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUMIST (LAIV4)	ASTRAZENECA	0.2 mL nasal spray 10-BX	2-49 years	90672
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL SDV 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	5 mL MDV	6 months and older	90688
FLUZONE HIGH-DOSE (IIV4)	SANOFI PASTEUR	0.7 mL PFS 10-BX	65 years and older	90662

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

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

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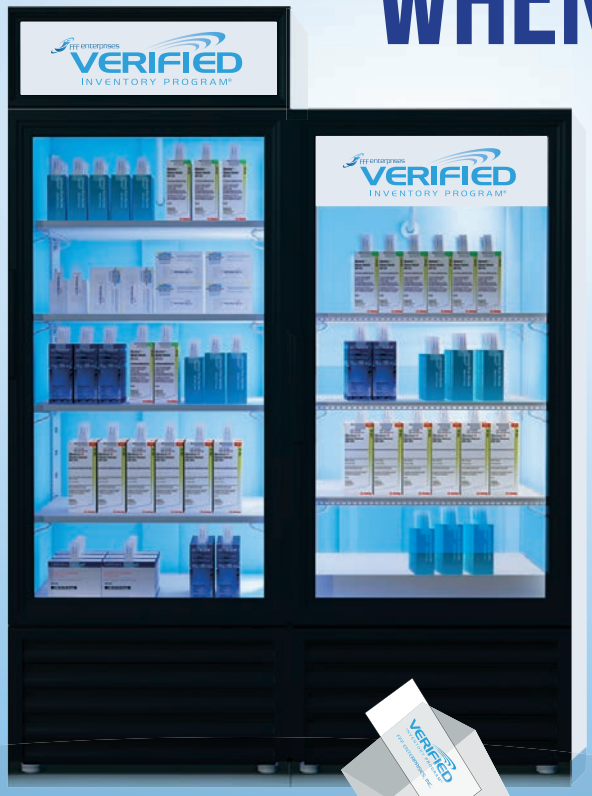

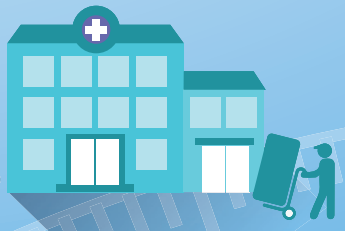

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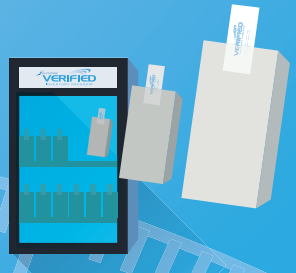

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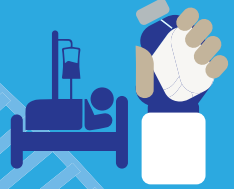

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