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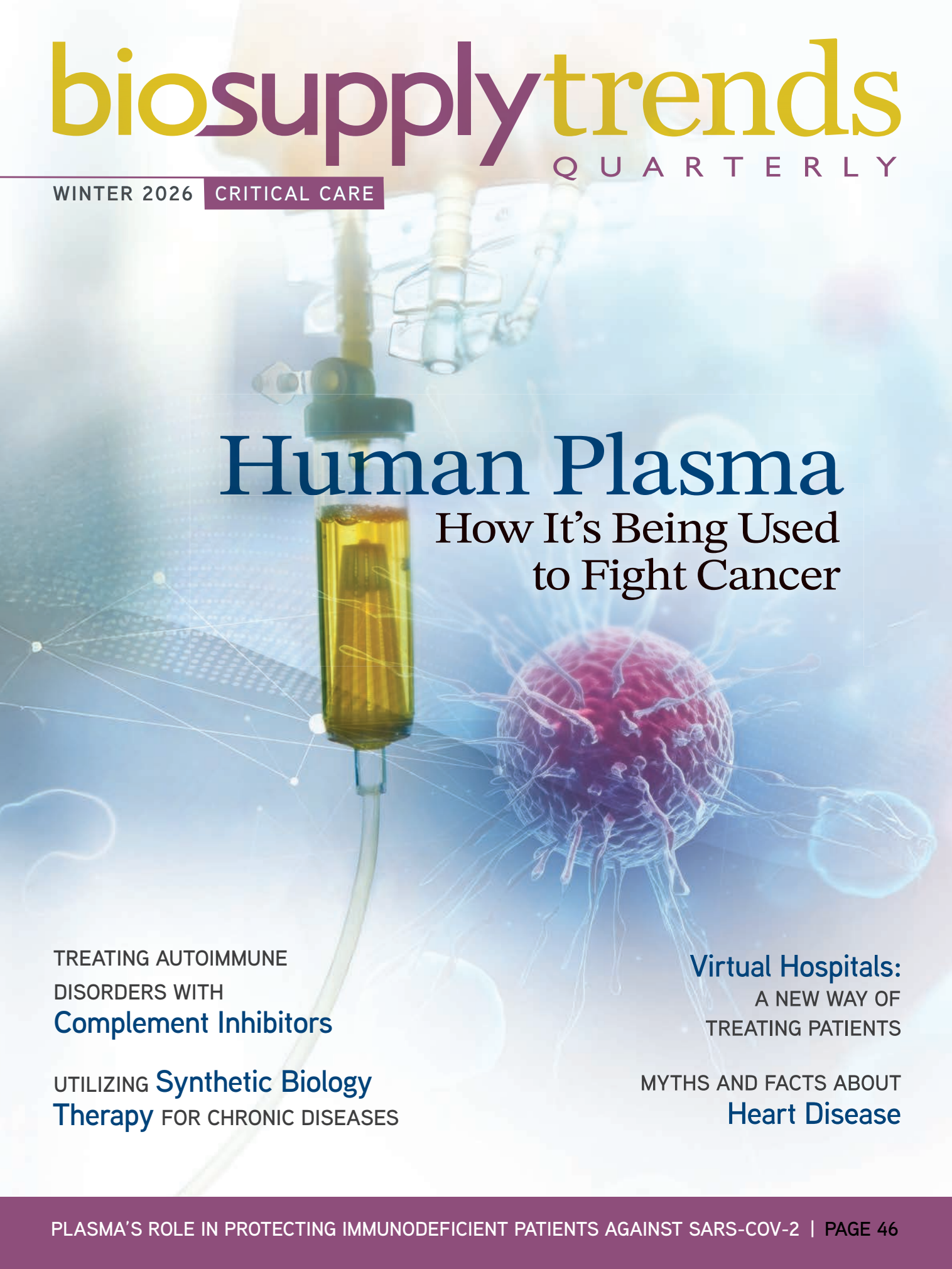
QUARTERLY
WINTER 2026 CRITICAL CARE



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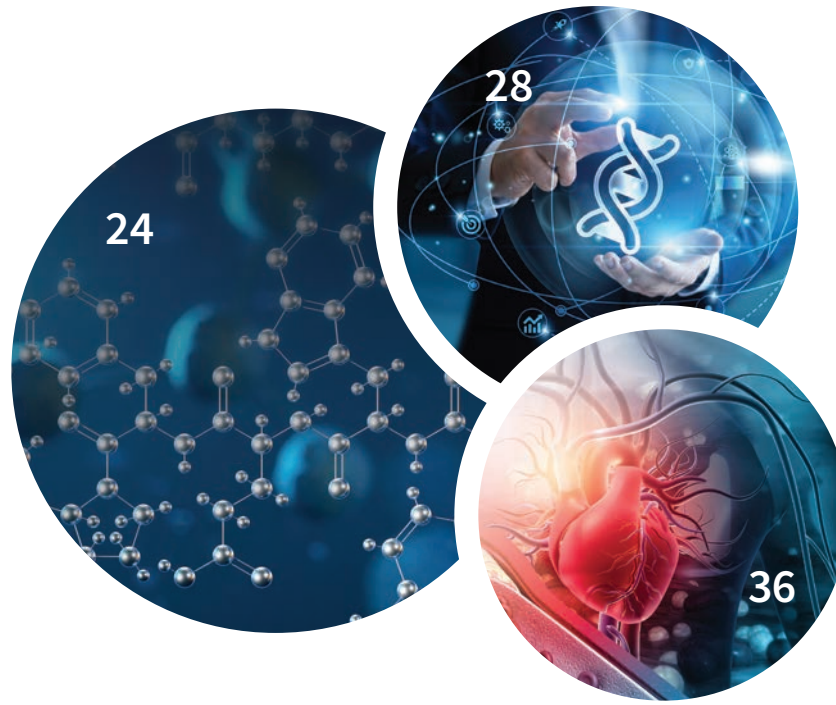

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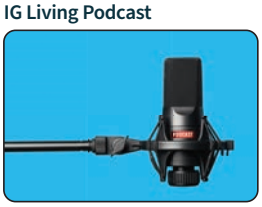

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New Therapies Show Promise for Treating Critical Illnesses

IN THIS ISSUE of *BioSupply Trends Quarterly*, we take an in-depth look at burgeoning therapeutic methods poised to change the way physicians treat key critical illnesses.

For example, cancer treatments typically consist of surgery, chemotherapy and radiation, but innovative approaches are being added to the oncology toolbox. One such therapy is plasma therapy. While plasma therapy itself is not new, we are just beginning to explore its potential for use in cancer patients. As we discuss in our article "Plasma's Pivotal Role in Cancer Therapy" (p.20), plasma contains lifesaving properties; it shows potential to filter out harmful antibodies that build up in cancer patients and kill cancer cells. More research is needed, but plasma therapy may soon be considered part of routine cancer treatment.

Another example: autoimmune disease. Autoimmune disease in the United States is approaching epidemic levels, with some studies projecting an increase of three to 12 percent every year. More alarmingly, we still don't really know why. "The reasons behind the increasing prevalence of autoimmune diseases are not fully understood," said Molly Murray, president and chief executive officer of the Autoimmune Association. Research continues to race toward answers, and we're learning more about immune conditions all the time. One potentially revolutionary approach: complement inhibitors, which suppress the immune system and prevent the complement system from damaging the body's own tissues. Our article "Complement Inhibitors as Therapeutic Agents for Autoimmune Disease" (p.24) explores the potential for complement inhibitors to bring hope to patients with lupus, rheumatoid arthritis and other autoimmune diseases.

Using the body's natural defenses to combat critical illness is one thing; but using synthetically made cells is another. We explore this new approach to therapeutics in our article "Using Synthetic Biology to Create Therapeutic Solutions" (p.28). Some experts say synthetic biology has advantages over traditional cellular therapies because it can be designed to focus on singular targets with unparalleled precision and seamlessly integrates with natural immunity. Despite its promise, synthetic biology remains controversial, and questions about ethics and access are important to consider.

One thing is certain: Chronic disease, unexpected health events and the natural aging process all require medical care. The gap between the millions of Americans who need care and the workers who provide it continues to widen. We look at a growing strategy that successfully closes the gap in our article "Virtual Hospitals: A New Era of Care" (p.32). Virtual hospitals deliver a wide range of medical services to patients who receive care in the convenient, familiar comfort of their own homes.

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

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

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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.

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HHS Doubles AI-Backed Cancer Research Funding

The U.S. Department of Health and Human Services (HHS) has doubled funding for its Childhood Cancer Data Initiative (CCDI) at the National Institutes of Health (NIH). Designed to accelerate the development of improved diagnostics, treatments and prevention strategies, the increase changes the current funding from $50 million established in 2019 to $100 million. The initiative will also bring in private-sector partners to apply advanced artificial intelligence (AI) to speed up cures for pediatric cancer.

HHS will use AI to maximize the potential for electronic health record and claims data to inform research and clinical trial design. Parents will remain in control of their child's health information as the data is used to benefit patients and researchers.

"We are dedicated to using every innovative method and technology at our disposal in our fight against childhood cancer," said NIH Director Jay Bhattacharya, MD, PhD. "By doubling down on this mission with AI, we are ensuring that state-of-the-art science is being leveraged to provide answers about these diseases that would otherwise be out of reach." ❖

HHS Doubles AI-Backed Childhood Cancer Research Funding. National Institutes of Health news release, Sept. 30, 2025. Accessed at www.nih.gov/news-events/news-releases/hhs-doubles-ai-backed-childhood-cancer-research-funding.

NIH Launches $50 Million Autism Data Science Initiative

The National Institutes of Health (NIH) has launched the Autism Data Science Initiative (ADSI), a research effort to harness large-scale data resources to explore contributors to the causes and rising prevalence of autism spectrum disorder. More than $50 million in awards will support 13 pioneering projects that draw on genomic, epigenomic, metabolomic, proteomic, clinical, behavioral and autism services data. These projects will integrate, aggregate and analyze existing data resources, generate targeted new data and validate findings through independent replication hubs.

A key feature of ADSI is the use of exposomics — the comprehensive study of environmental, medical and lifestyle factors in combination with genetics and biology. Projects will investigate a wide range of influences, including environmental contaminants such as pesticides and air pollutants, maternal nutrition and diet, perinatal complications, psychosocial stress and immune responses during pregnancy and early development.

Examples of funded efforts include examining how prenatal exposures interact with genetic risk in large autism cohorts, how causal inference methods can clarify contributors to rising prevalence and how adult outcomes such as community participation and mental health can be improved through service innovations. Independent replication and validation centers will test models across diverse populations, ensuring findings are transparent, reproducible and useful for real-world application.

Each ADSI research team will work in partnership with the autism community to help shape the direction of the research and ensure the perspectives of autistic individuals, caregivers and service providers inform the initiative. ❖

NIH Launches $50M Autism Data Science Initiative to Unlock Causes and Improve Outcomes. National Institutes of Health news release, Sept. 22, 2025. Accessed at www.nih.gov/news-events/news-releases/nih-launches-fifty-million-autism-data-science-initiative-unlock-causes-improve-outcomes.

$3.4 Million Grant Awarded to Study Treatments for CCHFV

Scott Pegan, PhD, a professor of biomedical sciences at the University of California, Riverside School of Medicine, has been awarded a grant from the National Institutes of Health of approximately $3.4 million over five years to lead an international study focused on developing protective antibodies against Crimean-Congo hemorrhagic fever virus (CCHFV), a biosafety level 4 pathogen and a category A bioterrorism agent causing severe viral hemorrhagic fever with mortality rates reaching up to 40 percent, for which there is currently no approved vaccine or specific antiviral therapy.

Designated a priority pathogen by the World Health Organization and the National Institute of Allergy and Infectious

Diseases, CCHFV is considered the reference virus for the nairovirus genus, which includes emerging pathogens such as Benji, Songling, Wetland, Yezo and the Pacific Coast tick nairovirus.

The project will study survivors of CCHFV in Kazakhstan, Turkey and Uganda to find antibodies that protect against the virus. Dr. Pegan's research team will also explore how the immune system fights the virus and work to develop monoclonal antibody treatments that are effective against different strains for future testing. A monoclonal antibody is a type of lab-made protein that mimics the immune system's ability to fight harmful viruses or bacteria.

"By focusing on non-traditional viral targets, our approach could lead to new, lifesaving therapeutics and help establish a framework for addressing future nairovirus outbreaks," Dr. Pegan said. ❖

Pittalwala, I. NIH Grant Supports Research on Dangerous Emerging Virus. UC Riverside News, Sept. 23, 2025. Accessed at news.ucr.edu/articles/2025/09/23/nih-grant-supports-research-dangerous-emerging-virus.

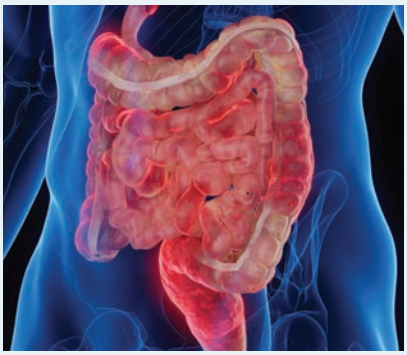
NIH Grant Awarded to Study Treatment for Crohn's Disease

Trethera Corp., a clinical stage biopharmaceutical company developing first-in-class therapies for cancer and autoimmune diseases, has been awarded a $1.8 million National Institutes of Health (NIH) grant for preclinical studies of TRE-515 as a Crohn's disease treatment. TRE-515 is a once-daily oral therapy that inhibits deoxycytidine kinase (dCK), an enzyme critical to the deoxyribonucleoside salvage pathway driving abnormal cell proliferation in autoimmune diseases such as Crohn's.

The award follows Trethera's prior $400,000 NIH Crohn's research grant and builds on the encouraging findings presented at the 2025 Crohn's & Colitis Congress that highlighted compelling preclinical data demonstrating that TRE-515 outperformed Johnson & Johnson's market-leading drug, Stelara. TRE-515 blocked inflammatory bowel disease symptoms in mice by selectively limiting activated CD4 T-cell proliferation.

"This continued NIH funding validates Trethera's innovative approach of targeting dCK, a key metabolic vulnerability in autoreactive immune cells causing Crohn's disease," said Ken Schultz, MD, chairman and CEO of Trethera. "We are accelerating TRE-515 development as a first-in-class therapy for Crohn's patients with high unmet medical needs."

In its written summary, the NIH peer review panel said, "TRE-515 is the only dCK inhibitor in development, so this approach is highly innovative… supported by strong preliminary data that TRE-515 is noninferior to current standard of care therapies… TRE-515 is not strongly immunosuppressive and has a favorable safety profile… oral administration will make it especially



attractive… exciting potential and the commercialization plan is exceptional."

Beyond Crohn's disease, TRE-515 is also being evaluated in Phase I clinical trials for solid tumors and ALS (Lou Gehrig's disease). With dual potential across cancer and inflammatory diseases, the TRE-515 development program represents a broad platform to transform patient outcomes. ❖

Trethera Receives $1.8 Million NIH Grant to Advance TRE-515 Development for Crohn's Disease. Trethera Corp. press release, Sept. 23, 2025. Accessed at firstwordpharma.com/story/6095134.

Payment in 2026 Necessitates Being Proactive

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

HEALTHCARE FACILITIES are facing multiple financial challenges with changes, including regulatory mandates, margin erosion and compression in payer rates. Optimizing payment will depend on data and revenue integrity, as well as understanding the three pillars of payment: payer requirements, health system adherence/governance and infrastructure data and support.

At a time when this scenario is squeezing healthcare revenue, are you in one of the many systems relying on reactive reimbursement strategies or leaving millions on the table because you are not proactive in seeking out leaks? Here's where you can find some meaningful remedies for 2026.

Capturing Revenue: Codes Submitted on the Claim

Capturing revenue begins with the charge description master (CDM) and its link to the pharmacy drug master (PDM). If a product is being used in the facility, it must have an assigned CDM number and be linked to its PDM description to be entered into the electronic health record (EHR) and subsequently sent to the payer. Make it your goal to add a drug before the first dose is administered.

- *What is included in the CDM description?* At a minimum: either the long or short description of drug name and strength (dependent on system number of characters) from the healthcare common procedure coding system (HCPCS) tables, HCPCS code, billing unit, natinoal drug code (NDC) number, dosage form and perhaps other terms depending on system space limitations.
- *Why is this important?* Because it is the only information on the electronic claim sent to the payer to describe the drug and amount administered to the patient! A mismatch in any of the components of the CDM description or billing unit calculation results in payment denial or payment inaccuracy.
- *Where can I start looking for issues?* Although your CDM is likely thousands of lines long, use a data sorting tool even as simple as Excel to sort on the HCPCS code. Hone in on J9999, C9399, J3490 and J3590: These codes may have been used while awaiting a permanent HCPCS code. Payment is denied if one has been assigned and you are still using these codes.[1]

However, if there is an actual need for use, you must identify the drug by including its NDC code and dose administered, as it is the only way the payer will be able to reimburse for the cost of the product rather than a standard reimbursement amount that is usually less than $50.

Billing Unit Assignment and Calculation

Years ago, the Centers for Medicare and Medicaid Services (CMS) ceased paying for entire vials, amps or containers of injectable products and instituted payment only for the actual dose of the drug administered. Since doses vary due to weight, illness, severity, etc., each HCPCS code has its own assigned billing unit to calculate the appropriate reimbursed payment. Although a commercially available crosswalk usually determines this entry into your system, errors associated with new or facility-built entities are often the culprits. Billing unit assignment could change, or the original entry could be incorrect with a decimal place error.

Current Procedural Terminology (CPT)

The American Medical Association released 2026 changes, including 288 new codes, 84 deletions and 46 revisions. New codes are those for shorter duration remote patient monitoring, augmentative and assistive AI services, hearing device services, as well as revision for leg revascularization. Updated appendices P and T list services provided via audio-video or audio-only technologies recognized by the CPT Editorial Panel as correlating to in-person services. These additions increase flexibility in how behavioral health services are delivered, helping to overcome access barriers, especially in rural, underserved and vulnerable communities. As you develop and expand the clinical services your facility will be offering in the new payment year, connecting them to the appropriate CPT codes is the backbone of payment. Additionally, three new codes cover immunization counseling when an immunization is not administered to the patient on the same date.[2]

The Rural Health Transformation Fund

The Rural Health Transformation Fund is a $50 billion funding pool set aside in the new tax law that was designed to help rural providers weather healthcare cuts. The fund is divided into two parts:

$25 billion will be evenly distributed to states with approved plans, and $25 million will be awarded "based on individual state metrics and applications that reflect the greatest potential for and scale of impact on the health of rural communities," according to CMS. Rural hospitals, critical access hospitals, safety-net hospitals, sole community hospitals, Medicare-dependent hospitals and low-volume hospitals are eligible to receive funding support, as well as federally qualified health centers, rural health clinics and community mental health centers.

Specifics apply to how states can use the funding: at least three of a prescribed set of activities, such as recruiting staff, setting up new technologies, paying providers, developing value-based care initiatives and supporting access to substance use disorder treatments, among others. Not more than 10 percent of funds can be used for state administrative expenses.[3]

NCD and ICD-10 Revisions

Both international classification of disease (ICD)-10 code sets and national coverage determinations (NCDs) also can change. Your financial team receives automatic downloads of these, but those affecting your practice may not reach the pharmacy department. A simple Internet search of any NCD will provide the details of what it entails, which gives you the basics of what documentation must be in the EHR to substantiate payment.

Evaluation and Management (E/M) Services Coding

In September 2025, CMS published a revised 35-page Medicare Learning Network (MLN) booklet that clinical staff should use to learn details of billing for clinical services. Highlights relevant to your practice include general principles of E/M documentation, and common sets of codes used to bill for E/M services, chronic pain management and telehealth services.[4]

Internet-Only Manual (IOM) Update: Addition of Section 70.2 to Publication 100-04, Chapter 17 – Billing Zero Charges for Drug Line Items Provided at No Cost

CMS updated the IOM to provide billing instructions for the submission of zero-charge line items for drugs provided at no cost. "According to the Social Security Act (SSA) Section 1861(v)(1)(A), the reasonable cost of any service is the cost actually incurred, excluding any part of an incurred cost found to be unnecessary in the efficient delivery of needed health services. If a provider does not purchase a drug, but provides the administration service, the physician cannot bill Medicare for the drug. However, the administration of the drug, regardless of the source, is a service that represents an expense to the physician. Therefore, administration of the drug is payable if the drug would have been covered when purchased by the physician. Under such circumstances, to avoid drug administration code denials, a drug code must be present on the same or prior claim and $0 should be entered for the billed amount of the drug."[5]

From the perspective of the provider, there are at least three opportunities for using "$0 priced drugs": white bagging, patient assistance drugs and sample drugs, as well as study drugs. As healthcare is on the cusp of dramatic change with many new regulations dictating eligibility, coverage and payments, it behooves providers to establish a mechanism for efficiently and effectively handling these. Basically, all require the same steps: knowing the payer requirements, establishing procedures for handling and storage, and adjusting the PDM/CDM to accommodate EHR records/claims submission for a $0 priced drug.

Be Proactive to Stay Financially Sound

Understand that payer-mandated acquisition in some format is here to stay. Can you afford to ignore it and do your own thing? ❖

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Revisiting HIPAA: Updates to Know

By Lee Warren

THE HEALTH INSURANCE Portability and Accountability Act (HIPAA), enacted in 1996, is the cornerstone of patient privacy and data security in the U.S. healthcare system. It established national standards for the privacy and security of patients' health information, defining how protected health information (PHI) can be used, shared and stored by healthcare providers and health plans.

HIPAA gives patients the right to access and control their healthcare records, while requiring covered entities to protect patients' data. Enforcement is overseen by the Health and Human Services (HHS) Office for Civil Rights, with penalties for violations ranging from fines to criminal charges.

> Recent updates in 2024 and proposed changes for 2025 reflect evolving healthcare practices, technological advances and societal considerations.

Recent updates in 2024 and proposed changes for 2025 reflect evolving healthcare practices, technological advances and societal considerations. In 2024, HHS updated HIPAA rules regarding reproductive health records and substance use disorder (SUD) records, both of which took effect that year, while proposals for 2025 address care coordination, administrative procedures and enhanced cybersecurity safeguards for electronic health information. Together, these updates and proposals represented HHS's ongoing efforts to adapt HIPAA regulations to a changing legal, technological and healthcare environment.

Reproductive Health Privacy

In 2024, HHS issued a final rule titled "HIPAA Privacy Rule to Support Reproductive Health Care Privacy," which clarified how reproductive health records must be handled. The rule addressed disclosure requirements, including restrictions on sharing reproductive health information with law enforcement or other third parties, and updated the notice of privacy practices to reflect patients' rights regarding this sensitive information.[1]

In 2025, a federal court vacated the attestation requirement, which would have required entities requesting reproductive health information to formally state that the request complied with HIPAA. Other parts of the 2024 rule, such as the disclosure restrictions, remain in effect.[1]

In practice, when a patient checks in at a clinic, her reproductive health information (for example, abortion or miscarriage care) cannot be shared for investigations unless required by law. If another provider, insurer or government agency later requests those records, the clinic must follow standard HIPAA Privacy Rule procedures for disclosure. While a signed attestation from the requester is no longer required, covered entities must still ensure that any sharing of reproductive health information complies with HIPAA and applicable federal or state laws.

Substance Use Disorder Records

Major updates were issued by HHS in 2024 regarding the confidentiality of SUD treatment records, updating 42 CFR Part 2 (a set of federal regulations that governs the confidentiality of SUD patients) to bring consent, disclosure and breach notification requirements into closer alignment with HIPAA, as required by the Coronavirus Aid, Relief and Economic Security (CARES) Act.

Patients may now give a single consent for their records to be used and disclosed for treatment, payment and healthcare operations, with recipients permitted to redisclose information under HIPAA rules. The changes also applied HIPAA's breach notification standards to SUD programs, expanded patients' rights to receive an accounting of disclosures and updated notice requirements to mirror HIPAA's Notice of Privacy Practices. Enforcement was strengthened through new noncriminal fines, and programs gained flexibility by no longer being required to segregate SUD records when shared under broad consent.[2]

In practice, when patients enter a primary care clinic and disclose they are receiving treatment for SUD at a specialty program, they can now sign one broad consent, allowing their SUD records to be shared with the clinic, their insurance company and other treating providers for care coordination and billing. The clinic no longer needs to maintain separate files for those records since redisclosure rules

now align with HIPAA. If there's ever a breach of those records, such as a stolen laptop containing PHI, the SUD program must notify the patient promptly, and regulators need to be informed if the breach meets reporting thresholds.

Additional 2024 Rule Proposals

In addition to the two rules finalized in 2024, HHS issued several proposed updates and guidance that remain under review and have not yet taken effect. These proposals primarily affect covered entities, which include healthcare providers, health plans and healthcare clearinghouses that create, receive or transmit PHI. They also indirectly affect business associates, such as IT vendors, billing companies and cloud service providers, that handle PHI on behalf of covered entities. While not finalized, these proposals provide insight into the future direction of HIPAA regulations.

One major proposal seeks to modernize the HIPAA Security Rule. It would strengthen administrative, technical and physical safeguards for electronic PHI, including more detailed risk analyses, mandatory encryption of data, improved breach response plans and requirements for annual compliance audits.[3]

Another proposal focuses on revising the Notice of Privacy Practices, the document that informs patients about how their health information may be used and shared, as well as their rights under HIPAA. The revisions aim to make patient rights and data-use policies clearer and more transparent.[4]

HHS also released updated guidance to help covered entities and business associates address ongoing cybersecurity risks.[3] This guidance emphasizes practices such as regular risk analyses, employee training, incident response planning and stronger technical safeguards, but it remains advisory rather than regulatory.

In addition, the agency issued fact sheets and educational materials to raise awareness about phishing, ransomware and other common threats to PHI.[5] While these resources do not have the force of law, they indicate HHS's ongoing concern about cyber threats and encourage healthcare organizations to prepare for stricter requirements that may result from the pending Security Rule changes.

Proposed 2025 HIPAA Security Rule Changes

The following highlights summarize the key elements of the proposed 2025 Security Rule changes healthcare organizations would need to prepare for if the rule is finalized.[3,6]

- All safeguards required: The long-standing distinction between "required" and "addressable" standards would be removed. Every safeguard would become mandatory, with only narrow exceptions.
- Stronger risk management: Covered entities would have to maintain a written, detailed risk assessment, including an up-to-date inventory of all technology assets and a network map showing how electronic PHI flows through their systems.
- Incident response upgrades: Organizations would need written response plans capable of restoring critical systems and data within 72 hours. These plans would also be tested and revised on a regular basis.
- Technical protections: Encryption of electronic PHI would become mandatory, alongside multifactor authentication, anti-malware protections, consistent system configurations (the standardization of computers, servers and devices) and network segmentation (the division of an organization's computer network into separate sections to limit sensitive data).
- Ongoing oversight: Entities would have to conduct a compliance audit at least once every 12 months, perform vulnerability scans every six months and run penetration tests annually to prove security measures are effective.
- Faster notifications: Access changes (such as when an employee leaves) and activation of contingency plans would have to be reported to the appropriate parties within 24 hours.

An Evolving Landscape

The evolving landscape of HIPAA regulations underscores the need for proactive healthcare management. As privacy concerns grow and technology advances, healthcare leaders must stay informed. The 2024 updates and 2025 proposals represent a pivotal moment in HIPAA's history — one that demands renewed attention to compliance, patient rights and data security. ❖

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4. U.S. Department of Health and Human Services. Model Notices of Privacy Practice. Accessed at www.hhs.gov/hipaa/for-professionals/privacy/guidance/model-notices-privacy-practices/index.html.
5. U.S. Department of Health and Human Services. Cyber Security Guidance Material. Accessed at www.hhs.gov/hipaa/for-professionals/security/guidance/cybersecurity/index.html.
6. The Center for Excellence for Protected Information. HHS HIPAA Security Rule NPRM Fact Sheet. Accessed at coephi.org/resource/hipaa-security-rule-nprm-fact-sheet.

LEE WARREN is a freelance journalist and author from Omaha, Neb. When he's not writing, he's a fan of sports, books, movies and coffee shops.

Research

Study Shows Hormone Therapy Is Linked to Autoimmune Disease

In a retrospective cohort study, the use of hormone therapy in postmenopausal women was associated with a significantly higher incidence and risk of autoimmune diseases.

For the study, the researchers used data from the U.S. Collaborative Network within the TriNetX Global Health Research Network, which allowed for real-time access to de-identified patient data. Postmenopausal women were identified with ICD-10 codes indicating menopause. Women with records of estrogen use on or after menopause diagnosis were assigned to the hormone therapy cohort, and those without such records were assigned to the non-hormone therapy cohort.

The research team used propensity score matching to balance baseline characteristics, such as age, ethnicity and comorbidities, including obesity, type 2 diabetes, essential hypertension and major depressive disorder. After matching, each cohort included 907,911 postmenopausal women. Mean age was 60.5, 77.6 percent were white, 7.6 percent were Black and about six percent were Hispanic or Latino.

When evaluating individual autoimmune conditions over the full postmenopausal period, there were statistically significant increases in risk for all conditions, except for Graves' disease and autoimmune hepatitis. Risk ratios ranged from 1.03 for psoriasis to 2.90 for lichen sclerosus. The hazard of developing any autoimmune disease over the full period was higher among hormone therapy users.

"Hormone therapy remains a safe and important option for many women when used appropriately but, like any treatment, it should be individualized while we await more research on its possible links to autoimmune disease," said Xuezhi (Daniel) Jiang, MD, PhD, of Drexel University College of Medicine in Philadelphia. "Because this was a retrospective database study, more research is needed before drawing firm conclusions." ❖

Henderson, J. Hormone Therapy Linked to Autoimmune Disease in Women. MedPage Today, Oct. 27, 2025. Accessed at www.medpagetoday.com/meetingcoverage/tms/118155.

Research

COVID mRNA Vaccine Induces Immune Response Against Cancer

New research at the University of Florida (UF) and the University of Texas MD Anderson Cancer Center has found that patients with advanced lung or skin cancer who received a COVID-19 mRNA vaccine within 100 days of starting immunotherapy drugs lived significantly longer than those who did not get the vaccine.

The study involved records of 180 advanced lung cancer patients who received a COVID vaccine within a 100-day period before or after starting immunotherapy drugs and 704 treated with the same drugs who did not receive the vaccine. Getting the vaccine was associated with a near doubling of median survival, from 20.6 months to 37.3 months.

Of the metastatic melanoma patients, 43 received a vaccine within 100 days of initiating immunotherapy, while 167 patients did not receive a vaccine. With the vaccine, median survival increased from 26.7 months to a range of 30 to 40 months; at the time the data were collected, some patients were still alive, meaning the vaccine effect could be even stronger.

Receiving non-mRNA pneumonia or flu vaccines resulted in no changes in longevity.

To back their findings, UF researchers then used mouse models to pair immunotherapy drugs with an mRNA vaccine targeted specifically at the COVID spike protein. Those experiments showed they could turn unresponsive cancers into responsive ones, thwarting tumor growth. "One of the mechanisms for how this works is when you give an mRNA vaccine, that acts as a flare that starts moving all of these immune cells from bad areas like the tumor to good areas like the lymph nodes," said Elias Sayour, MD, PhD, a UF Health pediatric oncologist and the Stop Children's Cancer/Bonnie R. Freeman Professor for Pediatric Oncology Research.

The next step is to launch a large clinical trial through the UF-led OneFlorida+ Clinical Research Network, a consortium of hospitals, health centers and clinics in Florida, Alabama, Georgia, Arkansas, California and Minnesota. "One of our key motivations at OneFlorida is to move discoveries from academic settings out into the real world and the places where patients get care," said Betsy Shenkman, PhD, who leads the consortium.

If confirmed, the new findings unlock numerous possibilities, and the researchers said an even better nonspecific universal vaccine could be designed. For patients with advanced cancers, the increased survival from such a universal vaccine could provide a priceless benefit: more time. "If this can double what we're achieving currently, or even incrementally — five percent, 10 percent — that means a lot to those patients, especially if this can be leveraged across different cancers for different patients," said Dr. Sayour, an investigator with UF's McKnight Brain Institute. ❖

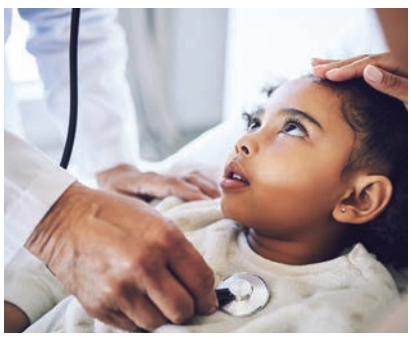
Jaffee, M. Study Finds COVID-19 mRNA Vaccine Sparks Immune Response to Fight Cancer. University of Florida news release, Oct. 20, 2025. Accessed at news.ufl.edu/2025/10/covid-vaccine-cancer.

Medicines

FDA Accepts NDA for Leniolisib to Treat Children with APDS

The U.S. Food and Drug Administration (FDA) has accepted Pharming Group's supplemental new drug application (NDA) for leniolisib to treat activated phosphoinositide 3-kinase delta syndrome, or APDS, in children aged 4 to 11 years. There are no approved treatments in this age group for APDS, a rare primary immunodeficiency caused by variants in PIK3CD or PIK3R1, which is vital to immune cell development and function.

Leniolisib (Joenja) is an oral, selective phosphoinositide 3-kinase delta inhibitor that inhibits the production of phosphatidylinositol-3-4-5-trisphosphate, an important cellular messenger that regulates cell proliferation and differentiation, cytokine production, cell survival, angiogenesis and metabolism.



The supplemental NDA is based on data from a multinational, single-arm Phase III trial in children aged 4 to 11 years who experienced measurable reductions in lymphadenopathy and a statistically significant increase in naïve B cells over 12 weeks, indicating the underlying immune defect was being corrected. Also, the application included safety data from eight months of treatment. "The study demonstrated clinically meaningful results in both efficacy endpoints and was generally safe and well-tolerated by the 21 patients," said Anurag Relan, MD, chief medical officer at Pharming Group.

Patients experienced these improvements across all four dose levels in the study, Dr. Relan noted, adding that these findings were consistent with benefits seen in adolescent and adult patients as well. FDA approved leniolisib for patients aged 12 years and older in March 2023.

A Prescription Drug User Fee Act date was set for Jan. 31, 2026. ❖

Gawel, R. FDA Accepts Supplemental New Drug Application for Leniolisib for Children with APDS. Healio, Oct. 20, 2025. Accessed at www.healio.com/news/allergy-asthma/20251019/fda-accepts-supplemental-new-drug-application-for-leniolisib-for-children-with-apds.

Research

Study Finds Possible Link Between Chronic Pain and Eosinophilia

A small study of medical records led by Julie Pilitsis, MD, PhD, professor and chair of the department of neurosurgery at the University of Arizona College of Medicine in Tucson, unexpectedly found that 12 percent of chronic pain patients who were treated with spinal cord stimulation or an implanted pain medicine pump had a white blood cell condition called eosinophilia. The condition is often a result of something gone awry with the immune system and is typically seen in less than one percent of the general population. While patients with eosinophilia didn't appear to fare any worse in their treatment, the findings suggest a possible link between chronic pain and the immune system.

A spinal cord stimulator is an implanted device that sends low levels of electricity directly into the spinal cord to relieve pain. An intrathecal pain pump is surgically implanted and delivers pain medication directly into the fluid surrounding the spinal cord.

Dr. Pilitsis and her co-workers reviewed the medical records of 212 patients who underwent spinal cord stimulation or intrathecal drug pump implantation for high-impact chronic pain. They evaluated data from 114 patients who had routine blood tests done within the month prior to treatment to determine the incidence and clinical relevance of eosinophilia.

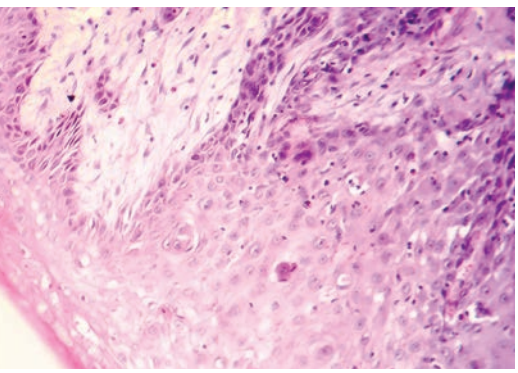
"The condition typically affects fewer than one in 100 people, and we found 14 of 114, or roughly 12 percent, in this group had eosinophilia before treatment," Dr. Pilitsis said. "Now we're asking what is it about eosinophilia that might predispose someone to chronic pain? Should we be looking at this as a biomarker before and after treatment to see if the latter reduces the eosinophilia?"

Roughly 70 percent of spinal cord stimulation patients see some reduction in pain. "We don't know if this could be a marker to help identify patients who might do better or worse with treatment, and if inflammation plays a role," Dr. Pilitsis said. "Could spinal cord stimulation reduce inflammation at some point? It's just speculation, but for those who don't do well, we could think of adding an anti-inflammatory to the chronic pain treatment. We still have many questions." ❖

Benowitz, S. Researchers Find Potential Link Between Chronic Pain, Immune Condition. The University of Arizona Research & Partnerships. Accessed at research.arizona.edu/news/researchers-find-potential-link-between-chronic-pain-immune-condition.

Medicines

FDA Approves Libtayo for Cutaneous Squamous Cell Carcinoma



The U.S. Food and Drug Administration (FDA) has approved Libtayo (cemiplimab-rwlc) for the adjuvant, or postsurgical, treatment of adults with cutaneous squamous cell carcinoma (CSCC) at high risk of recurrence after surgery and radiation.

Approval of the drug was based on results of the C-POST randomized, double-blind, multicenter, placebo-controlled trial of 415 patients with CSCC who were at a high risk of recurrence following surgery and radiation. In the trial, patients were required to complete postsurgical radiation therapy within two to 10 weeks of randomization, and the study excluded patients with autoimmune disease who required systemic immunosuppressant agents within five years, a history of solid organ transplant, prior allogenic or autologous stem cell transplantation, uncontrolled HIV, hepatitis B or C infection or an ECOG performance status of two or higher. Patients in the trial were evenly randomized to receive Libtayo or placebo.

Results showed median disease-free survival, or the time from randomization until the first documented disease recurrence or death due to any cause, was not reached in the Libtayo arm and 49.4 months in the placebo arm. The prescribing information of Libtayo includes warnings and precautions for immune-mediated side effects, infusion-related reactions, complications of allogenic hematopoietic stem cell transplantation and embryo-fetal toxicity.

"When we looked at the C-POST study, we actually discovered that those patients who, for example, got anti-PD-1 therapy — in the case of the C-POST study, it was Libtayo — and they also compared it to an arm of patients who got placebo, they actually found statistical significance in terms of disease recurrence," explained Vincent Ma, MD, a faculty member in the Division of Hematology, Medical Oncology and Palliative Care at the University of Wisconsin. "Overall, I think the conclusion from the study is that because we saw a disease-free survival benefit from patients who received adjuvant Libtayo for one year in the C-POST study, it is likely to eventually become standard of care in the future for patients who have high-risk squamous cell carcinoma of the skin following surgery and radiation." ❖

Biese, A. FDA Approves Libtayo for Cutaneous Squamous Cell Carcinoma Treatment. Cure Today, Oct. 8, 2025. Accessed at www.curetoday.com/view/fda-approves-libtayo-for-cutaneous-squamous-cell-carcinoma-treatment.

Research

FDA Expands Approval for Recombinant VWF

The U.S. Food and Drug Administration (FDA) has expanded the approval of recombinant von Willebrand factor (VWF), marketed as Vonvendi, to include routine preventive use in adults with all types of von Willebrand disease (VWD) and on-demand treatment of bleeding episodes and perioperative use in children with VWD.

The approval makes recombinant VWF the first non-plasma-derived VWF product available for pediatric populations and expands the previous indications for recombinant VWF, which were for on-demand treatment of bleeding episodes and perioperative use in adults and preventive use only in adults with type 3 VWD. According to FDA, the therapy is the only non-plasma-derived VWF product approved for VWD in the U.S.

Approval is supported by data from a trio of clinical trials, including a Phase III study in children with VWD and a Phase IIIb continuation trial in adults and children with VWD, in addition to supportive real-world data. The company pointed out recombinant VWF has a uniquely long half-life of 22.6 hours for adults and 14.3 hours for children, with most nonsurgical bleeds in clinical trials treated with a single infusion in children and adults.

Prior to this expanded approval, Takeda's Vovendi had received three prior approvals in the past decade. The initial approval for recombinant VWF occurred in December 2015, when FDA approved the therapy for treatment of bleeding episodes in patients with VWD based on a pair of clinical trials, including 69 adult participants. ❖

Campbell, P. FDA Expands Approval for Recombinant VWF, Includes Pediatric Patients. HCP Live, Sept. 5, 2025. Accessed at www.hcplive.com/view/fda-expands-approval-for-recombinant-vwf-includes-pediatric-patients.

Research

Study Shows ALS May Be an Autoimmune Disorder

Researchers at La Jolla Institute for Immunology (LJI) and Columbia University Irving Medical Center have discovered that amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, may be an autoimmune disorder. The researchers found that inflammatory immune cells, called CD4+ T cells, mistakenly target certain proteins that are part of the nervous system in people with ALS.

"This is the first study to clearly demonstrate that in people with ALS, there is an autoimmune reaction that targets specific proteins associated with the disease," says LJI Professor Alessandro Sette, PhD, who co-led the study with Professor David Sulzer, PhD, of the Columbia University Irving Medical Center.

In the study, the researchers examined T cell responses in ALS patients and found two distinct patient groups: one that had shorter predicted survival times with inflammatory CD4+ T cells quick to release inflammatory mediators when they recognized C9orf72 proteins, and a second group that also had harmful inflammatory CD4+ T cells, but also had higher numbers of anti-inflammatory CD4+ T cells. This second group also had significantly longer projected survival times.

Anti-inflammatory CD4+ T cells are important because they can regulate disease. For example, when the immune system fights a viral infection, it produces inflammatory T cells to eliminate the infected cells. Once the immune system clears the virus, anti-inflammatory CD4+ T cells prevent overzealous T cells from damaging healthy tissues. The researchers weren't expecting to observe this same process in ALS patients, which suggests CD4+ T cells may reduce harmful autoimmune responses and slow the progression of ALS. "This protective T-cell response is strongest in people with a longer predicted survival time," says Emil Johansson, PhD, a visiting scientist in the Sette Lab.

According to LJI Research Technician Tanner Michaelis, who served as the study's first author, future ALS therapies might boost protective CD4+ T cell responses and dial back harmful inflammation. "Hopefully, now that we know the specific target for these immune cells, we can make more effective therapies for ALS," says Michaelis. "This approach may be applicable for additional disorders such as Parkinson's, Huntington's and Alzheimer's," adds Dr. Sette. ❖

McCury-Schmidt, M. ALS Appears to Be an Autoimmune Disease. La Jolla Institute for Immunology, Oct. 1, 2025. Accessed at www.lji.org/news-events/news/post/als-appears-to-be-an-autoimmune-disease.

Research

Merck's Pneumococcal Vaccine Elicits Immune Responses to 21 Serotypes in Children with One or More Health Conditions

Positive results from Merck's Phase III STRIDE-13 trial for its Capvaxive vaccine, a pneumococcal 21-valent conjugate vaccine, show it has the potential to provide additional protection in individuals 2 through 17 years old.

The study examined the safety, tolerability and immunogenicity of Capvaxive compared to PPSV23 in 882 children and adolescents aged 2 to 17 years who have completed a primary pediatric pneumococcal vaccination regimen and have one or more chronic medical conditions that put them at an increased risk of pneumococcal disease. Conditions included diabetes, chronic compensated liver disease, chronic lung disease, chronic heart disease or chronic kidney disease. In the study, participants were randomized 3:2 to receive a single dose of Capvaxive or PPSV23. Results showed the vaccine covered approximately 78 percent of invasive pneumococcal disease (IPD) cases, with 11 unique serotypes that account for approximately 34 percent of IPD cases. According to the company, the vaccine was found to be superior to the PPSV23 vaccine for each of the nine serotypes unique to Capvaxive, as measured by serotype-specific OPA GMTs at 30 days post-vaccination, which was the primary immunogenicity endpoint.

Although the vaccine was designed for adults and is currently approved for individuals 18 years of age and older, the pediatric population can benefit from this vaccine. "While Capvaxive was designed to specifically cover the serotypes that cause the majority of invasive pneumococcal disease (IPD) cases in adults, findings from STRIDE-13 underscore its added potential to help protect children and adolescents who are at an increased risk," said Paula Annunziato, MD, senior vice president of infectious diseases and vaccines in Global Clinical Development at Merck Research Laboratories. ❖

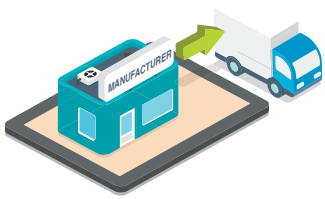
Parkinson, J. Pneumococcal Vaccine Elicits Immune Responses to 21 Serotypes in Children with 1 or More Health Conditions. Contagion Live, Sept. 12, 2025. Accessed at www.contagionlive.com/view/pneumococcal-vaccine-elicits-immune-responses-to-21-serotypes-in-children-with-1-or-more-health-conditions.

Guaranteed Channel Integrity®
8 Critical Steps

STEP 1

Purchasing

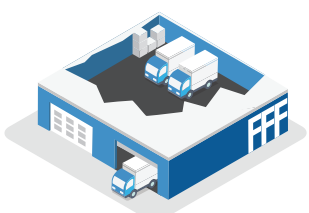
At FFF, we only purchase product from the manufacturer–never from another distributor or source–so the integrity of our products is never in question.



STEP 2

Storage

The healthcare products we store and transport are sensitive to temperature variations. Our state-of-the-art warehouse is temperature-controlled, monitored 24/7, and supported with backup generators in the event of power loss.



STEP 3

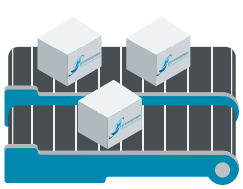
Specialty Packaging

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.

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STEP 5

Delivery

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

STEP 6

Methods of Delivery

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

STEP 7

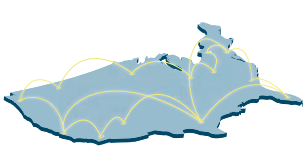
Verification

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

STEP 8

Tracking

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



Plasma's Pivotal Role in Cancer Therapy

Known as liquid gold, human plasma is proving to be a valuable ally in the fight against cancer.

By Diane L.M. Cook

PLASMA THERAPY is a promising new treatment for cancer. While plasma therapy itself is not new, its potential to cure myriad cancers is just beginning to be explored.

What makes plasma therapy a viable treatment option for cancer? According to Toby Simon, MD, a medical consultant at the Plasma Protein Therapeutics Association, plasma contains lifesaving properties that, when harnessed through fractionation, produce therapies that are viable options for fighting cancer. "Plasma therapies result from fractionation of the plasma based on changes in temperature, ethanol content, pH and other steps that include chromatography for purification and pathogen reduction for safety," Dr. Simon explained. "These therapies result in safe and effective parenteral medications with unique properties useful in saving and sustaining lives for many patients."

A Brief History of Plasma Therapy

Plasma contains antibodies helpful for fighting infections and has been used in some therapeutic capacity for more than a century. According to Plasma Heroes, an educational initiative of the Immune Deficiency Foundation designed to support plasma donation and the patients who rely on plasma-based products, using plasma for therapeutic purposes dates back to 1913 when plasmapheresis (separating the plasma from blood cells) in animal models was originally described, but it was not yet used in humans. However, plasma was given to patients via whole blood transfusions (as in the Spanish influenza pandemic of 1918) until 1938, when researchers discovered how to separate plasma from whole blood in humans.

Not long after that, World War II broke out, greatly increasing the demand for blood and plasma to treat wounded soldiers. During that time, Edwin Cohn, PhD, developed a process called cold ethanol fractionation that separated the proteins in the plasma (albumin, fibrinogen, globulins). Plasma went on to be used to make immune globulin (IG) treatments for primary immunodeficiency diseases in 1952 via intramuscular injection. By 1959, plasmapheresis was used to save the life of an adolescent boy with thrombotic thrombocytopenic purpura (TTP).

The modern plasmapheresis process originated at the U.S. National Cancer Institute between 1963 and 1968. By the 1970s, intravenous IG (IVIG) was introduced. Later, the first studies that demonstrated the anti-cancer effect of gas plasma on tumor cells in rodent models were published in 2010. By 2013, research into plasma oncology was gaining momentum, with studies exploring the effects of cold atmospheric plasma (CAP) on various cancer cells.[1,2,3] To date, there have been many successful examples of using direct plasma therapy for certain types of cancers.

Direct Plasma Therapies

Four types of direct plasma therapies are used to treat different types of cancers:

1) *Therapeutic plasma exchange (TPE)*. TPE is similar to plasmapheresis. However, in TPE, the plasma is discarded completely and is substituted with a replacement fluid, either donor plasma or albumin solution. According to Plasma Heroes, "TPE involves removing some of a patient's blood. The plasma is separated out from the rest of the blood components, and then the remaining blood cells are put back along with healthy plasma from a plasma donor."[4]

TPE shows therapeutic value in patients with cancers such as lymphoma, thymoma and multiple myeloma. Harmful antibodies build up in the plasma of patients with these cancers. The antibodies that attack healthy parts of the body are called autoantibodies, and studies show replacing these antibodies has a positive impact on patients. For example, "[Thymoma] cancer causes a person's immune system to destroy acetylcholine receptors. These receptors are proteins that bind nerves and muscles. In the absence of these receptors, individuals experience muscle weakness and fatigue. TPE can reduce these symptoms by filtering out the autoantibodies that damage these receptors."[4]

A thymoma is a tumor on the thymus, a small organ that plays a role in the immune system. A common complication of thymoma is the autoimmune disease myasthenia gravis (MG). In MG, the destruction of acetylcholine receptors at the junction of nerves and muscles results in muscle weakness and fatigue. TPE can reduce the symptoms of MG by filtering out the autoantibodies that damage these receptors.[5]

TPE shows therapeutic value in patients with cancers such as lymphoma, thymoma and multiple myeloma.

Multiple myeloma involves abnormal cells in the plasma and excess proteins called free light chains (FLCs), which can cause kidney damage by creating casts (obstructions) in the small tubules of the kidneys. TPE can filter out FLCs and prevent kidney damage in multiple myeloma patients.[5]

2) *Cold atmospheric plasma (CAP)*. CAP is a non-thermal plasma that can be applied directly to tumors or used to create plasma-activated media (PAM), which can then be used to treat cancer cells. CAP is an ionized gas made through gases such as helium, argon and nitrogen and applied at less than 104 degrees Fahrenheit.[6] Although CAP is a newer treatment currently being tested in U.S. Food and Drug Administration (FDA)-approved clinical trials,[7] it has shown promise in killing cancer cells, particularly in in vitro and in vivo studies, and is being explored as a potential treatment for various cancers.[7]

CAP contains toxic molecules called reactive oxygen species which target cancerous tissue cells, inducing oxidative stress and damaging the cells in the process. Thus, the cancer cells are no longer able to grow and multiply.[7] One benefit of CAP is it can identify and destroy cancer cells without harming healthy cells: It can remove very small cancerous tumors that surgeons might have missed, and it does it without causing damage to other parts of the body.[7]

In 2019, FDA approved CAP technology, currently the only way to remove microscopic cancer tumors remaining from surgery, for first-ever use in a clinical trial. According to FDA, "[CAP] technology selectively kills tumors through toxic molecules called reactive oxygen species, which damage targeted cancerous tissue but do not affect normal biological tissue. Lasers could also kill tissue, but the high heat would also bring permanent damage to

Plasma Resources

American Association for Cancer Research (AACR). AACR is a leading organization for cancer research, providing a platform and resources for researchers working on a wide array of cancer treatments, including advancements in plasma-based therapies. Visit www.aacr.org.

International Plasma Awareness Week (IPAW). IPAW, a joint effort of PPTA and its member companies, is the premiere awareness opportunity for plasma donation and the plasma medicines it helps create. IPAW was launched in 2013 to raise greater awareness about the importance of donating plasma. Visit www.plasmaweek.org.

Plasma Heroes. An initiative of the Immune Deficiency Foundation, Plasma Heroes is a resource designed to guide individuals through the journey of plasma donation, encourage others to donate, and better support those who rely on plasma-based products. Visit www.plasmahero.org.

Plasma Protein Therapeutics Association (PPTA). PPTA represents the biologics and biotechnology industries, including more than 1,000 human plasma collection centers in North America and Europe, as well as the manufacturers of plasma protein therapies. Members of PPTA produce approximately 80 percent of the plasma protein therapies in the United States and 60 percent of those manufactured in Europe. PPTA advocates for patient access to plasma-derived medicines, improved the availability of plasma and advances the understanding of the plasma ecosystem. Visit www.pptaglobal.org.

PlasMACT (Plasma against Actinic Keratosis). PlasmACT's primary objective is to leverage state-of-the-art plasma multijet technology to advance the understanding and application of medical gas plasma therapy for actinic keratosis. This involves interdisciplinary collaboration between experts in physics, chemistry, biology and medicine who are committed to bridging the gap between academic research and practical healthcare solutions. Visit plasmact.eu.

surrounding tissue."[8]

Further, a recent study led by Professor Han Wei at the Hefei Institutes of Physical Science of the Chinese Academy of Sciences showed that low-dose CAP treatment could effectively slow down tumor growth: "CAP damages the mitochondria, which are the powerhouses of the cell. This damage messes up the cell's energy production and causes oxidative stress. The lack of energy and stress on the cells prevents them from dividing properly. This leads to a form of cell death called 'mitotic catastrophe,' which stops the tumor from growing."[9]

CAP has shown to be effective in skin, breast and lung cancers, and, so far, does not seem to be limited to any one type of tumor, so it can potentially work on many other types of cancer as well.

3) *Plasma-activated medium (PAM)*. PAM is a culture medium or liquid that has been treated with a non-thermal atmospheric plasma to create a stable solution of reactive oxygen and nitrogen species (RONS). These RONS give PAM anti-tumor properties by promoting cell death in cancer cells. PAM is used to treat tumors without direct contact with the plasma source. It has shown promising anti-tumor effects, leading to cell death and hindering proliferation in various cancers. It can also enhance the effectiveness of conventional chemotherapies.

PAM has also been found to inhibit the growth and viability of various cancer cells, including glioblastoma, ovarian and gastric cancers. Studies have shown PAM can inhibit the metastasis of ovarian cancer cells and enhance the efficacy of chemotherapy treatments such as carboplatin and cisplatin. PAM treatment has also been shown to reduce endometrial cancer cell viability by inducing autophagic cell death.[10,11] The following studies highlight PAM's potential as an effective treatment for other cancers:

- A study conducted at the University of Bari Aldo Moro in Bari, Italy, showed how a sealed dielectric-barrier discharge was used to disentangle the effect of reactive nitrogen species (RNS) from that of reactive oxygen species (ROS) on cancer cells. The study investigated metastatic melanoma and pancreatic cancer, two cancers with poor prognoses. According to the study, "Both tumor models exposed to [plasma-activated liquid media] PALM rich in H_2O_2 showed a reduction in proliferation and an increase in calreticulin exposure and ATP release, suggesting the potential use of activated media as an inducer of immunogenic cell death via activation of the innate immune system."[12]
- A study conducted at the Islamic Azad University in Tehran, Iran,

investigated PAM in an effort to develop more effective treatments for breast cancer. The study investigated the impact of PAM in the presence of doxorubicin (DOX), a chemotherapy drug that has been used to treat various cancers of the breast, head and neck, lung, liver and ovaries. The study investigated the impacts of prepared PAM combined with DOX on the viability of MCF-7 breast cancer cells and showed that "low doses of DOX plus 3-min PAM could be a promising strategy for cancer therapy."[13]

• Researchers at the Dong-A University in Busan, South Korea, conducted a study on the involvement of ferroptosis, another cell death pathway that is involved in PAM-induced cell death. The study reported, "PAM promotes cell death via ferroptosis in human lung cancer cells, and PAM increases intracellular and lipid ROS, thereby resulting in mitochondrial dysfunction. The treatment of cells with N-acetylcysteine, an ROS scavenging agent, or ferrostatin-1, a ferroptosis inhibitor, protects cells against PAM-induced cell death." The study demonstrates that "PAM inhibits tumor growth in a xenograft model with an increase in 4-hydroxynoneal and PTGS2, a byproduct of lipid peroxidation, and a decrease in FSP1 expression."[14]

4) *Fresh frozen plasma (FFP)*. FFP is comprised of the liquid component of blood that has been separated from donated whole blood and then frozen within six to eight hours after collection. It contains clotting factors, antibodies and other proteins. FFP is thawed before transfusion, and its administration is indicated for patients with coagulation factor deficiencies, abnormal coagulation test results and active bleeding.

Although FFP is not used as a direct cancer treatment, it can be used as part of a patient's treatment plan. The main purpose of using FFP in cancer treatment is to help replenish important substances the patient's body needs that are impacted negatively, not only by the disease itself, but also by other treatments such as chemotherapy. FFP can also enhance the effectiveness of other therapies such as chemotherapy or targeted drugs.

A major component of using FFP is to replace a person's clotting factors. Cancer treatments such as chemotherapy can lower blood cell counts, which directly affects the body's ability to make clotting factors. FFP is also used to treat disseminated intravascular coagulation, as well as TTP.[15]

Phase II of a clinical trial conducted in 2021 at the University of California, Davis, studied the use of ofatumumab and FFP in patients with relapsed or refractory chronic lymphocytic leukemia (CLL). The researchers explained that many patients with CLL have low levels of complement and that, even though FDA has approved several drugs for use in this cancer, these drugs are often used as combination therapies, and many people, especially elderly patients, cannot tolerate the use of multiple drugs because of the side effects. Therefore, the researchers wanted to investigate a less toxic and more effective treatment option such as FFP therapy.

The main purpose of this study was to see if patients responded to FFP therapy and ofatumumab. Another purpose of the study was to learn if this therapy would increase the chances of curing patients of leukemia. The study also looked at the levels of complement in the participants' blood, as the levels of complement might allow for a better understanding of whether increasing the levels of complement by giving FFP might help control leukemia.[16]

More Research Is Needed

While more research and clinical trials are needed before this up-and-coming therapy can be considered a routine cancer treatment, some plasma therapies are clearly already being used to treat many cancers with great success. ❖

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Complement Inhibitors as Therapeutic Agents for Autoimmune Disease

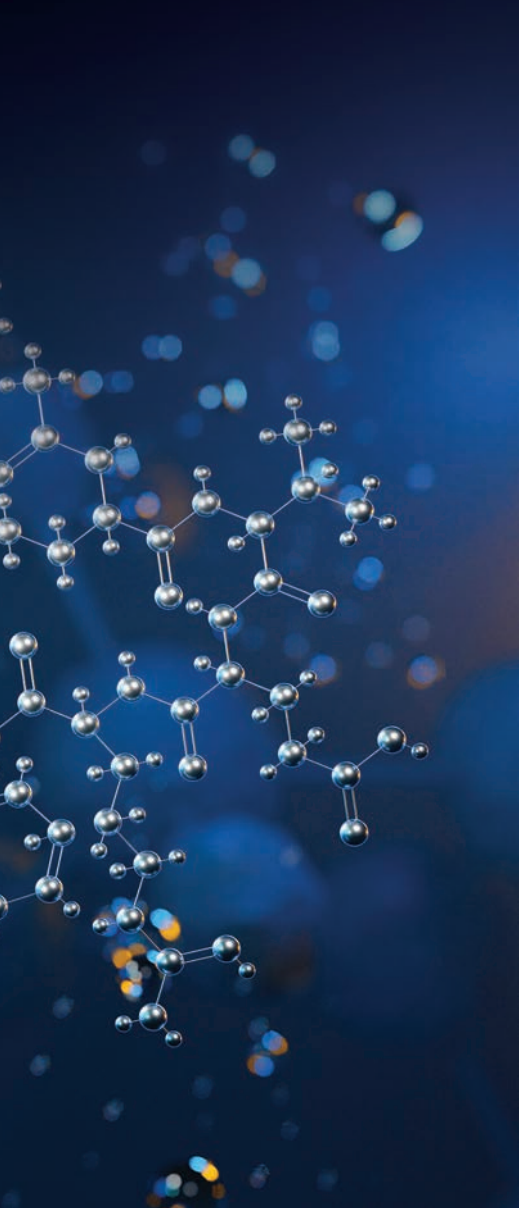
While still in their early stages of research, FDA has approved more than a dozen complement inhibitors to treat various conditions, and there is hope that more will be on the horizon to treat others.

By Jim Trageser

THE TREMENDOUS complexity of the immune system is, perhaps ironically, providing new avenues for treating diseases of and caused by the immune system. Many of these are rare conditions for which only palliative care was previously available. While the "complement revolution" that brought new treatments to market only began with the 2007 release of the C5 inhibitor eculizumab (Soliris),[1] the road to this point began some 130 years ago.

Growing scientific curiosity about how the human body defended itself against disease led to increased research into the immune system in the late 1800s.[2] Belgian physician Jules Bordet, who was studying cholera under Louis Pasteur at the time, discovered that the immune system includes a heat-sensitive component (the innate immune response) and a parallel ability to customize a response to the presence of specific bacteria (the adaptive immune system). This 1896 discovery of the duality of the immune system would eventually result in Bordet being awarded the 1919 Nobel Prize in Physiology or Medicine.[3] Three years after Bordet's 1896 discovery of the heat-sensitive bacteria-destroying substance, fellow future Nobel winner Paul Ehrlich, MD, termed this substance "complement" to emphasize what he saw as its role assisting antibodies in destroying invasive bacteria.[4]

Although our understanding of the specifics of the complement system has grown dramatically in the century since (for instance, what Dr. Bordet thought was a plasma is in fact a series of proteins), Bordet's basic model of the first-line innate response and Dr. Ehrlich's name for it remain. And while research continues into the immune system, we now know that when the



complement system is malfunctioning, it can cause serious health complications. This can include conditions arising from an overactive complement system (atypical hemolytic uremic syndrome and C3 glomerulopathy) or an underperforming complement system (hereditary angioedema).

With dozens of complement proteins now identified, researchers have successfully developed a new class of immunosuppressive drugs known as complement inhibitors. Although those that are on the market have successfully passed clinical trials with the United States Food and Drug Administration (FDA), their use still requires close monitoring due to the dangerous, often life-threatening side effects associated with suppressing the immune system.

What Is the Complement System?

The complement system is part of the innate immune system, which also includes the skin and mucous membranes as a physical barrier; stomach acids to protect us when we eat; and phagocytes to attack bacteria in the bloodstream.

Following up on Dr. Bordet and Dr. Ehrlich's work, in 1907 Adolfo Ferrata, MD, and Erwin Brand, MD, discovered that two separate substances were present in the complement system, and a third substance was added by the 1920s. The next four decades brought improved lab equipment that allowed researchers to discover that Dr. Bordet's substance or serum was in fact a series of more than 40 proteins.[2]

Today, it is understood that the complement system has three pathways of activation: classical, alternative and lectin. They are defined by the specific protein that is first activated in response to infection. Once one of these proteins is cleaved from its zymogens precursor (which are spread throughout the body), it then causes other enzymes to cleave, and they do the same to a third class, which activates a fourth, etc. — very quickly unleashing a cascade of bacteria-fighting proteins.[4]

The proteins are designed to latch on to bacteria cell membranes, either tearing the membranes open and killing the bacteria (lysis), or by marking it for destruction by a phagocyte (opsonization). Other proteins in the complement cascade are anaphylatoxins, which initiate inflammation by attracting immune cells to the area of infection or injury.

Once an infection is waning, the complement system also helps clear the body of dead cells, is involved in the growth of new cells and helps regulate the overall immune system.[7]

How Do Complement Inhibitors Work?

There are more than a dozen complement inhibitors currently approved by FDA, and dozens more in clinical trials.[6]

One of the byproducts of an immune response is inflammation — the body's call to arms to deal with infection or injury and to promote healing afterward. The C3a and C5a complement proteins in particular stimulate other immune cells to migrate to an area of injury or infection, a precursor to inflammation.[7] But if acute inflammation is literally a lifesaver, when something goes wrong and chronic inflammation sets in, it often causes significant damage to the body. Specific conditions associated with complement dysregulation and chronic inflammation include rheumatoid arthritis, systemic lupus erythematosus, ANCA-associated

Complement inhibitors are designed to stop chronic inflammation and its harm to the body by ending a wayward immune response.

vasculitis and autoimmune bullous dermatoses.[7]

Complement inhibitors are designed to stop chronic inflammation and its harm to the body by ending a wayward immune response. As the complement cascade process is hierarchical, the earlier up the chain the process is inhibited, the more effective at suppressing inflammation it is likely to be. But the obverse fact is that the more effective at suppressing inflammation a treatment is, the more likely it is to allow for unwanted secondary infections.[6]

There are more than a dozen complement inhibitors currently approved by FDA, and dozens more in clinical trials.

Complement proteins are named roughly in the order of their activation during a cascade (although the initial order varies depending on whether the activation pathway is classical, lectin or alternative). In the classical pathway, the C1 protein is activated first; in the alternative pathway, it is the C3 protein; and in the lectin pathway, the C2 and C4 proteins. All three pathways quickly arrive at a common cascade point with the C5 protein.[5] By targeting one of these complement proteins and effectively deactivating it, complement inhibitors can stop a complement cascade from proceeding further.

The first complement inhibitor, eculizumab (Soliris, Bkemv, Epysqli), works by binding to the C5 protein, preventing it from cleaving into C5a and C5b, thus interrupting the normal cascade after the first couple rounds of reactions.[8] It was originally approved in 2007 to treat paroxysmal nocturnal haemoglobinuria (PNH), a genetic condition in which one of the naturally occurring proteins that normally regulates the complement cascade is missing, leading to the complement system running unchecked and destroying red blood cells and, if left untreated, the marrow as well.[9]

Eculizumab has subsequently also been approved by FDA to treat:

• *Atypical hemolytic uremic syndrome (aHUS)*, an extremely rare genetic condition in which red blood cells are destroyed, platelet counts are low and the kidneys are unable to properly cleanse the blood.[10]

• *Generalized myasthenia gravis (gMG).* For patients of this rare neuromuscular disease who test positive for the antiacetylcholine receptor (AchR) antibody, eculizumab has shown to be effective[11] as has a subsequent FDA-approved drug, zilucoplan (Zilbrysq), a macrocyclic peptide that targets the C5 protein.[6]

• *Neuromyelitis optica spectrum disorder (NMOSD)*, an autoimmune disease in which the immune system attacks optical nerves, as well as the brainstem and spinal cord. Eculizumab use resulted in statistically relevant reduction in relapse episodes.[12]

What Other Conditions Can Be Treated with Complement Inhibitors?

While there are more than a dozen complement inhibitors presently approved by FDA, many target the same disease or condition, so there are fewer than a dozen diseases that can currently be treated with these drugs.

In addition to the above four conditions, others that have a complement inhibitor available include:

• *Paroxysmal nocturnal haemoglobinuria (PNH).* Physicians now have alternatives to eculizumab for treating PNH. These include iptacopan (Fabhalta), a small-molecule factor B inhibitor. This complement inhibitor has also shown promise in off-label treatment of C3 glomerulopathy (C3G),[13] a complement-mediated kidney disease caused by uncontrolled activation of the alternative pathway of the complement cascade.[14] Pegcetacoplan (Empaveli, Syfovre) is a C3 inhibitor now approved for treating PNH,[15] as well as geographic atrophy.[6] Another option, approved in 2018, is ravulizumab (Ultomiris), a monoclonal antibody that suppresses the C5 protein. It was also approved for treating aHUS and MG.[6]

• *Hereditary angioedema.* This is a rare genetic condition that causes swelling of various body parts due to a mutation in the SERPING1 gene, which contains instructions for building the C1 inhibitor protein. These mutations can lead to having too few C1 proteins, malformed C1 proteins or other abnormalities.[16] Treatment consists of either extracted or synthesized C1 inhibitor to replace the missing or malformed proteins, and it is sold under the brand names Berinert, Cinryze, Haegarda and Ruconest.[6]

• *Cold agglutinin disease.* This is a disorder in which the immune system tags red blood cells as invaders, leading to their destruction. The cause is not yet understood, but sutimlimab (Enjaymo) — a monoclonal antibody that targets the C1s protein — has been shown to halt the anemia caused by the condition.[17]

• *Geographic atrophy.* This late stage of age-related macular degeneration not only responds to treatment with pegcetacoplan, but also avacincaptad pegol (Izervay), a C5 inhibitor.[6]

• *CD55-deficient protein-losing enteropathy (CHAPLE disease).* This ultra-rate condition (fewer than 100 diagnosed cases around the world) is a genetic disease that results in an overactive complement system. It can now be treated with pozelimab-bbfg (Veopoz), a monoclonal antibody that targets the C5 protein.[18]

• *Antineutrophil cytoplasmic antibody-associated vasculitis (ANCA-associated vasculitis).* This is a family of autoimmune conditions leading to inflammation of blood vessels. One of the more effective treatments has been rituximab (typically used in treating certain cancers), and recent studies show that including the C5aR inhibitor avacopan (Tavneos) improved patient outcomes.[19]

What Are the Drawbacks?

Immunosuppressants in general carry the risk of secondary infections, and complement inhibitors share that common danger.

With eculizumab, for instance, it is recommended patients be vaccinated for Neisseria meningitidis before treatment begins since patients on eculizumab are at heightened risk of infection.[8] Also, since young children do not yet have fully developed adaptive immune systems, their bodies rely more heavily on innate immunity. The use of complement inhibition in children may thus involve a higher risk of infection than with adults.[6]

Every complement inhibitor will have detailed instructions, including any recommended prerequisite inoculations and warnings of certain secondary conditions that may preclude use of that specific treatment.

What Treatments Are in the Pipeline?

Complement inhibitors are an outlier in treating rare or orphan diseases because there is a substantial body of active research and clinical trials into these treatments. Admittedly, many of those trials are taking existing complement inhibitors and trying them on different autoimmune diseases to see if they are effective there as well — a relatively low-overhead endeavor.

For instance, at FDA's clinicaltrials.gov website, there are more than 100 current or recent clinical trials into the already-approved eculizumab — applying it to different diseases and conditions, ranging from transplant patients to CD59 deficiency.

Other studies are looking at sutimlimab (approved for treating cold agglutinin disease) to see if it is effective at treating other complement-mediated disorders.[20]

And new complement inhibitors are in the pipeline: One potential C1s inhibitor, RAY121, is under study by a Japanese pharmaceutical firm to gauge its safety.[21]

But complement inhibitors are also being looked at for conditions other than immunological disorders: One study in the Netherlands seeks to find out whether complement inhibitors can be used to reduce inflammation in patients with traumatic brain injury.[22]

Looking Ahead

With research into the complement system truly still in its beginning stages, and with technology now allowing for the relatively quick (compared to previous decades) and inexpensive development of tailored drugs, there is hope other complement-related conditions such as lupus and rheumatoid arthritis will also have treatments available to provide relief to those suffering from them. ❖

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Using Synthetic Biology to Create Therapeutic Solutions

This revolutionary technology shows promise for addressing a myriad of challenges in medicine, but ethical dilemmas remain.

By Amy Scanlin, MS

THE SYNTHETIC biology industry is in a heyday of medical and pharmaceutical innovation, bringing new hope for chronic diseases. The ability to create living cells from nonliving components, to reprogram cellular functions and design new biological pathways, to create therapeutic interventions that may one day mitigate complex immune diseases and metabolic disorders, provide cures for cancers and infectious diseases and positively affect a myriad of health disorders is an exciting field of study. Synthetic biology is also changing approaches to personalized drugs and drug delivery systems. Together, this rapidly expanding industry is expected to reach $37 billion by 2026[1] and by some estimates $100 billion by 2030.[2]

The field of synthetic biology began growing rapidly in the 1990s when ex vivo genetically corrected lymphocytes were used to treat two patients with severe combined immunodeficiency caused by adenosine deaminase deficiency. Since then, next-generation DNA sequencing and progress in engineering biology have birthed overlapping fields of research that will one day enable treating, replacing and repairing malfunctioning cells and genes for the benefit of diseases difficult to treat by traditional means.[3]

In fact, synthetic biology is at the crossroads of biology, engineering and artificial intelligence (AI). Faster and more sophisticated data analysis and predicted effects may one day limit the need for lengthy laboratory tests to gain approvals from the United States Food and Drug Administration, as was seen with the design and emergency use authorization of the COVID-19 vaccines.

At its core, one of the many challenges of synthetic biology is creating an artificial cell that bypasses protein synthesis as it transcripts/translates genetic information. But, as researchers combine, reengineer and equip organisms to create artificial biological smart cell networks, the benefits could be endless.

Today, synthetic immune cells already have the ability to sense, detect and treat some diseases the natural immune system has difficulty coping with, sending engineered proteins to their target cells and triggering desired changes in gene expression. For instance, engineered human kidney cells are showing promise for maintaining glucose homeostasis and correcting diabetic hyperglycemia in mice; they are also changing fibroblasts into cells similar to stem cells that can be used therapeutically, all without using human embryos.[1] New innovations and uses for synthetic biology continue to be uncovered, each moving one step closer to targeting diseased cells without impacting healthy cells.

But, synthetic biology is not without

controversy, including the ethical questions of genetic engineering, equity and access. Still, the power of this incredible field of study is promising to bring the reality of comprehensive personalized medicine one step closer.

Synthetic Immunity

The immune system is a delicate balance, with cells continuously detecting and responding to disease and imbalances. Sometimes that response is targeted, such as killing invader cells, and sometimes the response is more subtle, such as with the secretion of cytokines and chemokines that recruit cells to target the problem. But, with the advent of synthetic biology, immune cells can be removed, modified, reprogrammed and reinserted into the patient when their natural immunity cannot cope with existing threats. This approach creates a new, long-term protective memory against the disease, thereby reducing the risk of relapse.[4]

The idea of improving one's immune system via the introduction of synthetic cells is an innovative approach, one that some believe has advantages over traditional cellular therapies because of synthetic's ability to be designed with molecular-level precision and focus on singular targets in a way that mirrors and integrates with one's systemic natural immunity[5] with a lower risk of harming healthy cells.

In controlling things like T-cell activation and elimination of bacteria, desirable phenotypes may be brought online more effectively.[5] Today, modification of the patient's own cells is most common, though in the future, creating engineered nonhuman cells may be a more cost effective, normal practice.

Metabolic Diseases

Metabolic diseases are often chronic and genetically influenced, and frequently involve complex metabolic imbalances. Traditionally, therapies used to treat metabolic diseases manage symptoms rather than cure the underlying cause. However, synthetic biology enables the development of tailored solutions such as reprogramming cellular functions and creating new biological pathways that can address these disorders at their roots.

For example, engineered bacteria offers an opportunity to positively influence a number of metabolic diseases. In laboratory mice on a high-fat diet, engineered gut bacteria are successfully delivering the incretin hormone GLP-1 to stimulate B-cell insulin secretions and lower glucose concentrations. Researchers are also examining the use of engineered E. coli gut microbes to treat obesity by synthesizing anorexigenic lipid precursors.[1]

Additionally, modified Escherichia coli Nissle 1917 (EcN-GM) inserted into mice is showing the potential to positively affect obesity and the associated health risks, including food intake and hepatic weight.[6] And, the treatment of diabetes may be revolutionized with the study of light-controlled optogenetics, where light is directed to activate desired cells or genes, reducing the risk of cross-reactivity that can be found with chemical inducers. Opto-human embryonic kidney (opto-HEK) cell studies in mice with experimental type II diabetes showed blue-light-sensitive proteins produced an insulinogenic hormone that improved blood glucose levels. Another kind of therapy, LightOn, is a photo-switchable system that enables expression of insulin and improves blood glucose. Far-red-light controllable designer cells are also being studied for their ability to express GLP1.[7]

Drug Innovations and Vaccine Development

Synthetic biology's use in reverse vaccinology is well-recognized as a scalable and sustainable approach to drug development — particularly after a fully synthetic mRNA vaccine for the COVID-19 virus was in design within days of the virus's genome release, and emergency use authorization was granted just 11 months later.

Synthetic biology and reverse vaccinology are also being used in the development of personalized cancer vaccines and treatments thanks to proprietary immunogenic neoantigens and sequencing algorithms that define genomic mutations in sequenced tumors when compared to reference genomes. In particular, this technology is showing promise in pancreatic and melanoma cancers.[8]

Synthetic biology is at the crossroads of biology, engineering and artificial intelligence.

Emerging innovations in cell-free protein systems may provide for rapid vaccine production at a fraction of the cost of traditional vaccines. With cell-free protein synthesis, transcriptional and translational cell information allows for protein production without the need for living cells, eliminating many challenges of traditional vaccine development.[9]

Therapeutic genetically engineered bacteria may also become a cutting-edge new treatment as biomarkers sense their control over the timing, localization and dosage. In mice studies, gene circuits are proving flexible, sustainable and

predictable as candidates for treating some cancers, particularly when combined with synthetic surface adhesions targeted to bind to cancer-specific molecules.[1]

Artificial Intelligence and the Future of Synthetic Biology

The addition of artificial intelligence (AI) to the field of synthetic biology exponentially expands opportunities for medical innovation to seemingly endless possibilities. Moving from the early days of predictive protein structure from amino acid sequences to today's use with predictive physical outcomes of nucleic acid sequences, development times have shortened and complexity of achievable biodesign has expanded. AI's ability to process large and precise datasets enables it to quickly identify research candidates, design laboratory studies for those candidates, uncover hidden patterns and regulatory elements, and model and predict behaviors all while analyzing results. Because AI is so powerful, it can not only decrease the length of time required for research, but its predictive abilities help reduce laboratory testing time requirements and thus innovation costs.[10] It can also improve scalability.

However, use of AI is not without risk, particularly the risk for engineering a harmful sequence that spreads uncontrollably. This dual-use dilemma poses a very real biosecurity risk. Whether that threat is an undetected flaw in data algorithms or the intentional misuse of that data by nefarious persons who aim to exploit and harm, audits, transparency and accountability will help filter potentially dangerous risks.

Proactive awareness of risk is especially important in these early days as an industry-wide regulatory policy framework lags innovation, creating incomplete oversight.

AI's immense power must never take the place of ethical judgment and human stakeholder intervention at every level to ensure responsibility, transparency and regulatory conformance, all without stifling scientific breakthroughs. Differentiating AI's routine tasks from nonroutine decision-making is key.

Ethical Considerations

As synthetic biology capabilities grow, so too do ethical questions, particularly as desired outcomes vary across communities and countries. This synthetic life created for therapeutic purposes is so new, so rapidly evolving, that it has become entangled with broader societal questions and concerns.

Is gene optimization preferable to natural order? What do we know of patient safety in a field where long-term outcomes are yet unknown? Can this technology be used equitably across the healthcare system? How should the dual-use dilemma be addressed? All are difficult challenges, particularly as technology advances more quickly than policy debates and decisions.

Unintended consequences and unpredictability of synthetic biology is a real concern, and despite science's best efforts to study and predict, there are questions as to whether harmful side effects or worse might affect patients. In the excitement of a new experimental treatment, even with informed consent, sometimes decisions are made before all of the facts are at hand.

Equity and access to care are always concerns in the innovation space as well. However, as synthetic biology is further studied and understood as it comes online and becomes mainstream, the expectation is a lowering of costs and speeding up of production. Even the fact that synthetic cells may not need the refrigeration like human-derived products do is a potential win for production and delivery. In the short term, like any new healthcare innovation, the risk of global disparities is real. In the long run, however, there is real and positive potential for a cost-effective, scalable solution for many of today's challenges.

The dual-use dilemma of a technology created for good, but one that could also cause harm, is a grave concern, so much so that the World Health Organization and other nongovernmental organizations have highlighted these issues and called for regulatory policy and oversight, particularly for AI in the bioengineering space.[10]

Even so, the possibilities for synthetic biology are exciting, and much work continues to improve methods and technologies that will one day enable engineered cells to advance into viable therapeutic treatments. ❖

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Virtual Hospitals:
A New Era of Care

From reduced wait times to greater care access, virtual hospitals bring hospital-level care directly to patients' homes. While obstacles exist, potential benefits represent a transformative step in healthcare delivery.

By Trudie Mitschang

HEALTHCARE SYSTEMS around the world are under growing pressure driven by shifting demographics, social changes and evolving health needs. Among the biggest challenges are aging populations and the rise in chronic conditions; the number of people over 60 will skyrocket to approximately 2.1 billion by 2050.[1] At the same time, chronic noncommunicable diseases are anticipated to consume nearly 80 percent of healthcare resources worldwide.[2]

On top of aging populations and rising demands for care, the healthcare industry is also facing a workforce shortage. Even before the pandemic, projections suggested a gap of up to 10 million workers worldwide by 2030, a shortfall that has only added to the heavy workloads already driving burnout and high turnover among clinicians.[3] Add to that the escalating costs associated with every sector of healthcare, and it's easy to understand why confidence in traditional care models is diminishing. Enter the "virtual hospital."

A More Personalized Approach

By definition, a virtual hospital is essentially a healthcare facility without walls. By using technology, it delivers a wide range of medical services directly to patients in their own homes. Rather than being confined to a hospital bed, patients can access high-quality care from a team of healthcare professionals while remaining in familiar surroundings and close to loved ones.

Although the idea of virtual hospitals is not new, the COVID-19 pandemic accelerated their adoption. During lockdowns, they proved especially effective in managing patients remotely, often through simple tools such as pulse oximeters combined with secondary care monitoring. These early successes showcased the model's potential and spurred significant investment,

particularly in programs designed for vulnerable or frail patients. The aim was not only to reduce pressure on overcrowded facilities but also to deliver outcomes that equaled or even surpassed traditional care by blending proactive medicine with greater convenience for patients.

Daniel Varga, MD, chief physician at Hackensack Meridian Health, describes the "hospital at home" model as an innovative way to provide hospital-level care without requiring patients to check into a facility. "This model uses a combination of in-person visits from caregivers and remote monitoring by physicians and nurses," Dr. Varga explains. "Vital signs, blood pressure and oxygen saturation levels are continuously monitored, ensuring that patients receive the same quality of care as they would in a hospital setting. This approach not only frees up hospital beds for urgent surgical patients but also creates capacity for more patients to be served."[4]

One of the greatest benefits of virtual hospitals is continuous monitoring. Whether caring for a newborn at home, a patient recovering from surgery or an elderly resident in a nursing facility, virtual hospitals provide constant oversight that makes early intervention possible when needed. The model also contributes to greater hospital efficiency. By shifting certain services such as physiotherapy, mental health support and chronic disease management into a virtual setting, hospitals can streamline workflows and reduce the strain on departments that do not require urgent, in-person care. This approach helps distribute the workload more evenly, shortens wait times and allows healthcare providers to treat more patients at the same time. Moving consultations and follow-up visits online adds another layer of efficiency, while virtual care platforms make it easier for doctors and specialists to collaborate remotely, share expertise and coordinate patient care without needing to be physically present.

Another important advantage is the reduction in healthcare costs. Patients who do not need to be hospitalized can remain at home under virtual hospital care, lowering expenses tied to examinations, treatments and unnecessary emergency room visits. Remote triage, such as video consultations with a primary care physician, makes healthcare more accessible while helping avoid the high cost of urgent care. Providers benefit as well, since virtual hospitals reduce overhead costs by limiting reliance on physical infrastructure, from building maintenance to medical supplies. The result is a more affordable model for both patients and healthcare systems.[5]

Virtual hospitals provide constant oversight that makes early intervention possible when needed.

Telemedicine vs. Virtual Hospitals: Understanding the Difference

Telemedicine has been around for many years, giving doctors the ability to connect with patients through phone calls or video chats. This model is primarily designed for individual consultations: answering questions, diagnosing conditions or managing follow-up appointments. Virtual hospitals take things a step further by delivering a more complete model of care. Instead of a single doctor-patient interaction, they rely on teams of specialists working together to provide care around the clock. These professionals operate from a centralized hub, supported by advanced digital systems, which allows them to treat and monitor patients no matter where they are located. In this setup, patients receive the same ongoing oversight they would in a physical hospital, but without the need to be admitted in person.

The success of virtual hospitals depends on multiple technologies, including:

- *Telemedicine*: platforms that allow patients and providers to interact in real time through video, reducing the need for in-person visits while maintaining high-quality care.
- *Internet of things devices*: wearable tools such as glucose meters, heart monitors or blood pressure cuffs that transmit continuous health data back to clinicians.
- *Artificial intelligence and machine learning*: systems that analyze large volumes of patient information, spotting patterns and irregularities to guide clinical decisions.
- *Electronic health records*: digital files that make it easy for healthcare teams to share information, coordinate care and track patient history across settings.
- *Cloud computing*: secure, scalable platforms that store and manage extensive medical data, ensuring healthcare teams can access records and applications anytime, anywhere.

The role of the provider must also evolve to meet the demands of a virtual hospital model. In telemedicine, the physician's role is primarily focused on individual, episodic encounters. This model mirrors the traditional office

visit but removes geographic barriers, expanding access while maintaining the one-to-one relationship at the center of clinical decision-making. Clinical responsibility lies almost exclusively with the treating physician, who must rely on the patient's account of symptoms and whatever limited home-monitoring data is available.

By contrast, a virtual hospital represents a system-level model in which the physician becomes one member of a multidisciplinary team providing continuous, hospital-grade oversight. Physicians in a virtual hospital are not isolated in their clinical decision-making but collaborate in real time with nurses, pharmacists and specialists, often supported by advanced monitoring technologies. Rather than simply consulting, physicians in this model are responsible for synthesizing continuous streams of physiologic data, prioritizing interventions and coordinating care across multiple providers and settings. The scope of responsibility extends from individual clinical judgment to team-based management of acuity and workflow.[6]

These distinctions change not only the practice environment but also the physician's competencies. Telemedicine requires strong diagnostic acumen in the absence of physical exam tools, efficient patient communication and adherence to regulatory frameworks. Virtual hospital practice, on the other hand, demands fluency in remote monitoring platforms, comfort with data-driven triage and skill in interprofessional collaboration. For physicians, telemedicine expands access to individual encounters, while virtual hospitals redefine inpatient-level care delivery, requiring doctors to operate more as clinical leaders within an integrated digital system.

Clinicians must adapt to new modes of practice that shift their role from bedside care to remote, team-based monitoring — often requiring new skill sets and trust in technology.

Addressing Adoption Barriers

While virtual hospitals hold promise for expanding access and reducing the strain on physical facilities, there are significant barriers to widespread adoption. One of the most pressing challenges is technological infrastructure. Effective virtual hospitals rely on continuous remote monitoring, seamless integration of electronic health records and reliable connectivity across diverse geographic regions. Variability in broadband access, hardware compatibility and the sophistication of data platforms can undermine reliability. For physicians, inconsistent or incomplete data streams raise the risk of delayed interventions or clinical errors, which in turn can erode trust in the model.[7]

Equally pressing are regulatory and reimbursement frameworks. While telemedicine has made gains in coverage and billing clarity, the virtual hospital model straddles inpatient and outpatient domains, creating ambiguity around licensure, liability and compensation.[8] In addition, physicians often face unclear rules across state lines and payment models that do not reflect the demands of hospital-level oversight. These gaps create hesitation for both hospitals and providers, limiting investment and slowing adoption.

Cultural and workflow concerns further complicate implementation. Clinicians must adapt to new modes of practice that shift their role from bedside care to remote, team-based monitoring — often requiring new skill sets and trust in technology. Patients, too, may perceive a diminished personal connection in this model, especially in high-acuity or end-of-life care.[8]

These combined challenges align with findings from a Deloitte survey of healthcare executives, in which two-thirds of participants identified regulatory barriers and payment reform as the top roadblocks to virtual care adoption. Nearly one-third also pointed to the need for stronger technological infrastructure, including 5G connectivity and advanced AI capabilities. Importantly, many executives underscored that a move toward value-based care, rather than fee-for-service (FFF), will be critical for virtual hospitals to achieve sustainability, as FFS incentives remain misaligned with preventive, digitally enabled models.[9]

According to the report, "With the wider healthcare ecosystem transforming around them, hospitals and health systems should prioritize a system that can enable all caregivers to practice at the top of their license and affirms physicians as partners in care rather than employees to be managed."

It goes on to stress that physicians and clinicians within an organization are the drivers of change. When developing criteria for specific technology investments, organizations should include physician time and workflow in addition to business value, while organization leaders should consider investing in training tools that can help clinicians feel confident about their changing roles.

What the Future Holds

The inherent promises of virtual hospitals extend far beyond making healthcare easier to access. They represent an opportunity to fundamentally reshape how care is delivered and experienced, with the potential to reduce wait times, eliminate the burden of long-distance travel and overcome geographic and logistical barriers to care. Instead of patients waiting weeks for appointments or spending hours in hospital waiting rooms, care can be brought directly to them — wherever they are. This shift expands the reach of medicine, allowing patients to receive primary care, specialist consultations, mental health support and chronic disease management in the comfort of their own homes.

At their best, virtual hospitals have the potential to not only transcend geography but also optimize the use of scarce healthcare resources. By integrating advanced monitoring tools, data analytics and coordinated team-based care, they give physicians the ability to intervene earlier, manage higher volumes of patients more efficiently and improve overall outcomes. This reallocation of time and expertise allows health systems to extend high-quality services to more people without requiring equivalent expansions in physical infrastructure.

Ultimately, the evolution of virtual hospitals underscores the broader transformation underway in healthcare. By leveraging telehealth, remote monitoring and digital technologies, virtual hospitals make care more accessible, convenient and responsive to patient needs. In a rapidly changing healthcare environment, they are poised to become a cornerstone of future health systems — helping providers deliver safe, high-quality and patient-centered care on a scale that traditional models alone could not achieve. ❖

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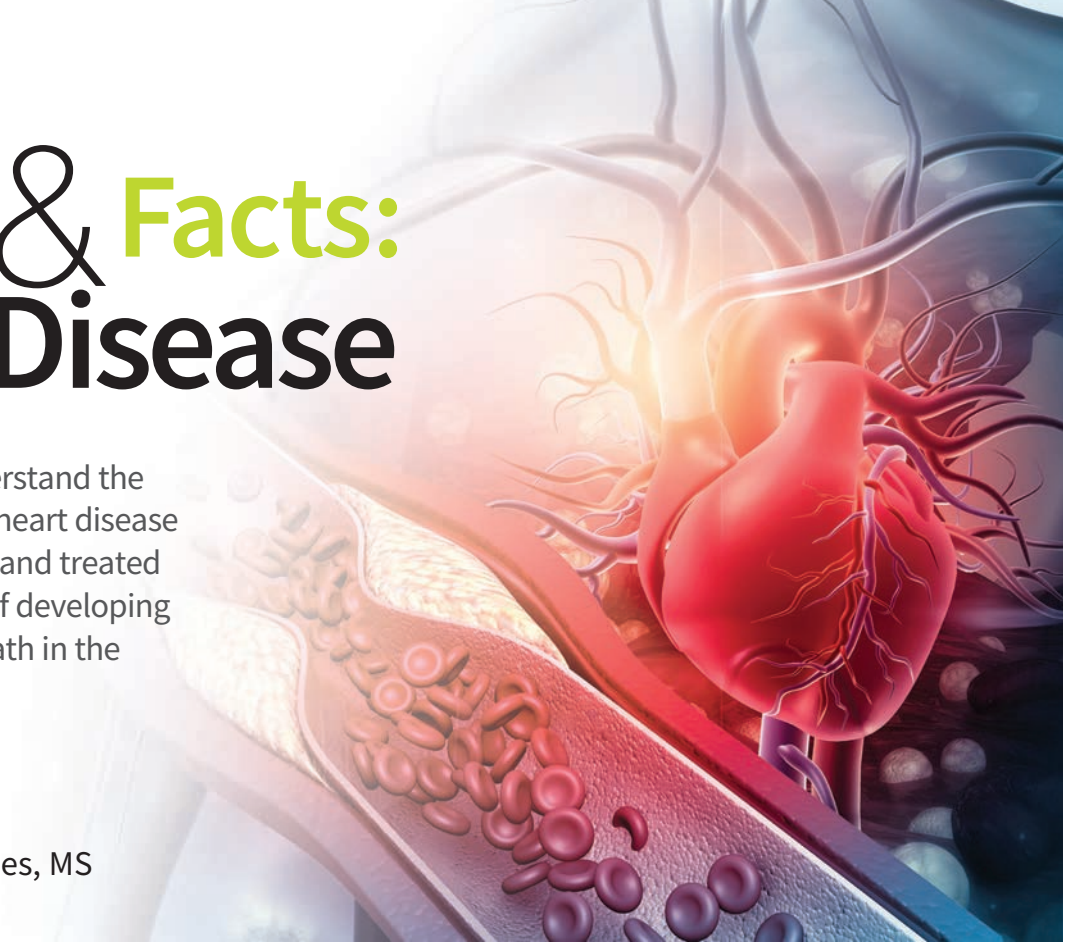
Myths & Facts: Heart Disease



Americans need to understand the realities of what causes heart disease and how it is diagnosed and treated so they take their risks of developing this leading cause of death in the U.S. more seriously.

By Ronale Tucker Rhodes, MS

HEART DISEASE is the leading cause of death for men, women and people of most racial and ethnic groups, killing one person every 34 seconds.[1] Astonishingly, heart disease claims more lives in the U.S. than all forms of cancer and accidental deaths — the number two and three causes of death — combined.[2] In 2023, 919,032 people died from heart disease, equivalent to one in every three deaths. It is an expensive disease that cost the U.S. about $417.9 billion from 2020 to 2021, including the cost of healthcare services, medicines and lost productivity due to death.[1]

Heart disease can be traced back to Egyptian mummies, some 3,500 years old, that had evidence of cardiovascular disease — specifically coronary artery disease (CAD), also known as atherosclerosis (narrowing of the arteries) in different arteries of the body. When exactly civilization first became aware of CAD is difficult to determine; however, it's known that Leonardo da Vinci (1452-1519) investigated coronary arteries. But, it wasn't until the 1900s that there was an increased interest, study and understanding of heart disease. Specifically, in 1915, a group of physicians and social workers formed an organization called the Association for the Prevention and Relief of Heart Disease in New York City. Then, in 1924, multiple heart association groups became the American Heart Association Trusted Source, consisting of doctors concerned about the disease because they knew little about it, and patients had little hope for treatment or a fulfilling life. In the late 1940s and early 1950s, researchers began to understand the causes of heart disease and its relationship to diet. In the 1960s and 1970s, the first treatments, including bypass surgery and balloon angioplasty, were used to help treat heart disease. In the 1980s, stents were used to open narrowed arteries. And, in 2014, the Scripps Research Institute developed a new blood test that is able to predict who is at high risk for the occurrence of a heart attack.[3]

While heart disease was an uncommon cause of death in the U.S. at the beginning of the 20th century, by mid-century, it had become the most common cause of death due to an increase in the prevalence of coronary atherosclerosis with resultant coronary heart disease, as documented by autopsy studies. The number of deaths peaked in the mid-1960s, and has been declining to the present day.[4] Yet, it continues to kill more people in the U.S. than any other cause, according to the American Heart Association's 2025 Heart Disease and Stroke Statistics Update, due to ongoing increases in high blood pressure, obesity and other major risk factors.[2]

Unfortunately, many people underestimate their risk of contracting heart disease and delay seeking care, mainly due to the many myths and misconceptions circulating, creating a false sense of security. As such, much more needs to be done to spread awareness about heart disease and to separate myth from fact.

Separating Myth from Fact

Myth: Heart disease is an old person's disease.

Fact: While age *is* the most important determinant of cardiovascular health, heart disease affects people of all ages. From 2009 to 2018, the respondent-reported prevalence of heart disease decreased in adults aged 55 to 64 and 65 to 74, but remained stable in adults aged 18 to 44, 45 to 54 and 75 and over. In 2019, the prevalence of heart disease increased with age, reported by one percent of adults aged 18 to 44, 3.6 percent of adults aged 45 to 54, 9.0 percent of adults aged 55 to 64, 14.3 percent of adults aged 65 to 74 and 24.2 percent of adults aged 75 and over.[5]

The main reason older adults are more susceptible to heart disease is due to age-related changes like artery stiffening, valve wear and tear, and thickening of the heart muscle.[6] But, as early as childhood and adolescence, plaque can start building up in the arteries and later lead to clogged arteries. In fact, almost one in two U.S. adults (age 20 and older) has heart disease.[7] The main risk factors other than age for why heart disease can strike before age 50 include smoking; pregnancy issues such as preeclampsia, gestational diabetes and preterm labor; familial hypercholesterolemia (high cholesterol); race; and depression.[8]

"Heart disease starts basically when we are born," says Tansel Turgut, MD, a Michigan City interventional cardiologist with Franciscan Physician Network. "Aortic disease, atherosclerosis or heart disease doesn't start when we're like 40, 50, 60. It starts at ages like 3, 4, 5. Weight, obesity, diabetes, high blood pressure, unhealthy eating habits and smoking directly affect us starting at a very, very young age, contrary to what we have been thinking for many years, that it starts in the elderly. Heart disease doesn't check our ID."[9]

Myth: Heart disease is a man's disease.

Fact: Just like age, heart disease *does* affect more men than women, but most people (only about half or 56 percent) in the U.S. don't realize that heart disease is also the leading cause of death among females. More than 60 million women (44 percent) in the U.S. are living with some form of heart disease, and it affects women of all ages. In 2023, 304,970 women — or about one in every five — died from heart disease.[10]

Myth: Heart disease affects all races and people of socioeconomic status equally.

Fact: Unfortunately, this is far from true. According to a 2015 literature review on the current science and evidence of population-level differences in risk factors for heart disease among different racial and ethnic populations in the U.S., heart disease disproportionately affects Black/African Americans. More Asian Americans are likely to contract coronary artery disease earlier in life than other races. And, non-White Hispanics have lower cases of cardiovascular disease than Black and Asian Americans, with White Americans having the lowest cases.[11]

Why are Blacks and Hispanics more susceptible to heart disease? According to Annapoorna Kini, MD, professor of medicine and cardiology at the Icahn School of Medicine at Mount Sinai, "the prevalence of high blood pressure in African-Americans is the highest in the world. Research suggests African-Americans may carry a gene that makes them more salt-sensitive, increasing the risk of high blood pressure and heart disease. African-Americans are disproportionately affected by obesity. Among non-Hispanic Blacks 20 and older, 63 percent of men and 77 percent of women are overweight or obese. African-Americans are [also] more likely to have diabetes than non-Hispanic Whites."[12] For Hispanic individuals, recent studies have shown high rates of traditional heart disease risk factors such as obesity, hypertension, diabetes, hyperlipidemia and emerging cardiovascular disease risk factors like hypertensive disorders of pregnancy, psychological stress and occupational exposures.[13]

Myth: A "small" heart attack is no big deal.

Fact: Even a mild heart attack is a big deal. According to the Cleveland Clinic, a "mild heart attack" is a term physicians use to describe heart attacks that only partially block blood flow to the heart — unlike the full-blown variety, which happens when a blood vessel is completely blocked. Mild heart attacks are still major medical emergencies that limit the supply of oxygen-rich blood to the heart muscle, causing damage. But they may affect a smaller portion of the heart — or cause less damage — than a "major" heart attack. Nevertheless, having a heart attack of any kind raises the risk for future cardiac events.[14]

Myth: There are obvious signs of heart disease.

Fact: The signs of heart disease depend on what type of heart disease it is. And for most types of heart disease, there may

While age is the most important determinant of cardiovascular health, heart disease affects people of all ages.

be no obvious signs. Following are the different types of heart disease (Figure):[15]

• Coronary artery disease (CAD) is a common heart condition that affects the major blood vessels that supply the heart muscle. It is usually caused by a buildup of fats, cholesterol and other substances in and on the artery walls. This buildup of what is called plaque in the arteries is called atherosclerosis, which reduces blood flow to the heart and other parts of the body and can lead to a heart attack, chest pain or a stroke. Symptoms typically include chest pain, chest tightness, chest pressure and chest discomfort, called angina; shortness of breath; pain in the neck, jaw, throat, upper belly or back; and pain, numbness, weakness or coldness in the legs or arms if the blood vessels in those body areas are narrowed. However, an individual may never know if he or she has CAD until a heart attack, angina, a stroke or heart failure occurs.

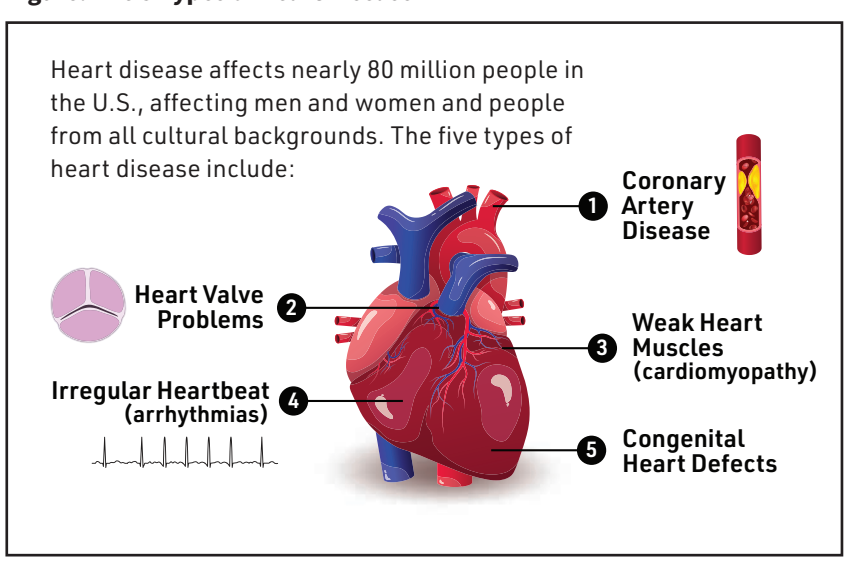
• Heart valve disease can either be called a stenosis if a heart valve is narrowed, or a regurgitation if a heart valve lets blood flow backward. Symptoms depend on which valve isn't working right, and may include chest pain, fainting or almost fainting, fatigue, irregular heartbeats, shortness of breath and swollen feet or ankles.

• Disease of the heart muscle, called cardiomyopathy, may not cause any symptoms, but as the condition gets worse, symptoms may include dizziness, lightheadedness and fainting; fatigue; feeling short of breath during activity or at rest; feeling short of breath at night when trying to sleep, or waking up short of breath; rapid, pounding or fluttering heartbeats; and swollen legs, ankles or feet.

• Irregular heartbeats, called arrhythmias, can cause the heart to beat too quickly, too slowly or irregularly. Heart arrhythmia symptoms can include chest pain or discomfort, dizziness, fainting or almost fainting, fluttering in the chest, lightheadedness, racing heartbeat, shortness of breath and slow heartbeat.

• Congenital heart defects, heart conditions a person is born with, are typically noticed soon after birth. Congenital heart defect symptoms in children could include blue or gray skin (depending on skin color, these changes may be easier or harder to see); swelling in the legs, belly area or areas around the eyes; and shortness of breath during feedings, leading to poor weight gain. However, some congenital heart defects may not be found until later in childhood or during adulthood, with symptoms including getting very short of breath during exercise or activity, easily tiring during exercise or activity, and swelling of the hands, ankles or feet.

Figure. The 5 Types of Heart Disease



Myth: Heart disease symptoms are identical for men and women.

Fact: This is perhaps the biggest misconception of all. In fact, heart disease can develop and present in dramatically different ways across the sexes due to a variety of reasons:[16]

1) Much like men and women display differences in their anatomy and physiology, they also have differences in their cardiovascular systems. Compared to men, women have smaller hearts and narrower blood vessels.

2) While a heart attack occurs when cholesterol plaque builds up inside the walls of arteries and causes damage in the major blood vessels, men typically develop this plaque buildup in the largest arteries that supply blood to the heart, whereas women are more likely to develop this buildup in the heart's smallest blood vessels, known as the microvasculature.

3) Men and women experience different symptoms during a heart attack, with men and women typically presenting with chest pain, but women also more likely than men to experience nausea, sweating, vomiting and pain in the neck, jaw, throat, abdomen or back.

4) Women are more likely than men to suffer from diseases that mimic a heart attack such as a coronary spasm that occurs when a blood vessel clamps down and mimics a heart attack, a coronary dissection that occurs when the wall of a blood vessel tears, or broken heart syndrome, which is a chemical heart attack where enzymes in the blood and

changes in the heart muscles resemble a heart attack, but there are no blocked arteries like you see in CAD.

5) Men and women may have different risk factors for heart disease. Risk factors for heart disease in women include reproductive history and certain pregnancy conditions, such as preeclampsia and gestational diabetes, which may be powerful predictors of future risk of heart disease.

Research also shows an increase in cardiac events among women approximately 10 years after menopause. Although the exact reasons remain unclear, decreased estrogen can affect cholesterol balance and artery health, increasing the risk of heart disease.[17]

Myth: If you have heart disease, it's best to take it easy.

Fact: Actually, the opposite is true. According to cardiologist Richard T. Lee, MD, co-editor in chief of the *Harvard Heart Letter*, physical activity helps strengthen the heart muscle, improves blood flow to the brain and internal organs, and improves overall health and well-being. "For the vast majority of people with heart disease, being sedentary is a bad idea. It can lead to blood clots in the legs and a decline in overall physical condition," says Dr. Lee.[18]

When performed regularly, moderate- and vigorous-intensity aerobic activity can lower the risk for coronary heart disease. But for those who already have been diagnosed with heart disease, the heart works better with regular aerobic activity. What's more, physical activity can reduce the risk of a second heart attack in people who already have had heart attacks. But, vigorous aerobic activity may not be safe for people who have heart disease.[19]

Studies have shown heart attack survivors who are regularly physically active and make other heart-healthy changes live longer than those who don't. "We want activity after a heart attack. Very soon, we want them out of bed, we want them walking," says Dr. Turgut. "We want them as active as possible, and we send them to cardiac rehab. That's another thing, cardiac rehab decreases deaths actually 25 to 30 percent in the hospitalizations, but only 20 to 30 percent of our patients go to cardiac rehab."[9]

Heart disease does affect more men than women, but most people (only about half or 56 percent) in the U.S. don't realize that heart disease is also the leading cause of death among females.

Myth: Diabetes and high blood pressure won't cause heart disease if you take medication.

Fact: According to the American Heart Association, "Treating diabetes can help reduce your risk for or delay cardiovascular diseases. But even when blood sugar levels are under control, you're still at increased risk for heart disease and stroke. That's because the risk factors that contribute to diabetes onset also make you more likely to develop cardiovascular disease. These overlapping risk factors include high blood pressure, overweight and obesity, physical inactivity and smoking.[7]

Myth: You can lower your risk of heart disease with vitamins and supplements.

Fact: Researchers at Johns Hopkins Medicine say vitamins and supplements don't protect people from heart disease. After reviewing randomized clinical trials involving hundreds of thousands of subjects, in which some were given vitamins and others a placebo, they found "no evidence of benefits to cardiovascular disease," says Johns Hopkins physician Edgar R. Miller III, MD, PhD, whose research review on the topic has been published in the *Annals of Internal Medicine*. "Supplements were ineffective and unnecessary. The bottom line is, we don't recommend supplements to treat or to prevent cardiovascular disease. The good news is, you don't have to spend any money on supplements."

However, they do say that one possible exception is omega-3 or fish oil capsules, which is a type of fatty acid found in fish and marine algae that helps the heart. But patients should be cautioned that consuming too much of certain vitamins can be harmful. For example, too much calcium and vitamin D are associated with an increased risk of cardiovascular disease, Dr. Miller says.

Another concern is that what is on a supplement label isn't always what is in it. Investigations have shown that too often pills said to contain medicinal herbs are actually full of fillers like powdered rice or even dangerous substances. Some don't even contain any of the herbs on the labels. "Supplement production is not regulated by the FDA, nor does the industry need to prove health benefits, so they can use vague language like 'good for heart health' — but they can't say 'will lower blood pressure,'" Dr. Miller adds.[20]

Myth: If you have smoked for years, you can't reduce your risk of heart disease by quitting smoking.

Fact: Only good comes from quitting smoking. In fact, the benefits of quitting

smoking start the minute a person quits, no matter their age, how long they have smoked or how many cigarettes a day they smoked. Heart attack risk drops by 50 percent only one year after quitting. And in 10 years, it will be the same as if that person had never smoked.[18]

Myth: People with a family history of heart problems have no way of preventing them.

Researchers at Johns Hopkins Medicine say vitamins and supplements don't protect people from heart disease.

Fact: There is no question that genetics play a role in the risk for heart disease depending on the number and age of affected first-degree relatives. Many cardiac disorders can be inherited, including arrhythmias, congenital heart disease, cardiomyopathy and high blood cholesterol. Just one genetic variation (mutation) in a single gene can affect the likelihood of developing heart disease. A study that examined 2,302 male and female offspring participants with a parental history of premature cardiovascular disease (fathers younger than 55 years and mothers younger than 65 years) who were analyzed for cardiovascular disease risk found that after eight years of follow-up, cardiovascular disease risk increased 75 percent with a paternal and about 60 percent with a maternal history of premature cardiovascular disease. It also found that cardiovascular disease risk increased about 40 percent in those whose siblings had cardiovascular disease.

Yet, the study authors pointed out that while "unlucky genes can double or triple the risk of heart disease … genes do not act alone — lifestyle, diet and exercise modify the risk of [cardiovascular disease]. These factors are more important than simply having a genetic makeup that predisposes one to heart disease."[21]

Myth: There are no tests to detect heart disease.

Fact: Multiple tests can detect heart disease:[22]

- A routine annual physical can reveal critical risk factors such as high blood pressure, high cholesterol, type 2 diabetes, smoking and family history. If heart disease runs in the family, a person may be asked to undergo a radiologic test that detects calcium in the arteries surrounding the heart.
- Blood tests can be conducted to check for certain heart proteins that slowly leak into the blood after heart damage from a heart attack. For example, a high-sensitivity C-reactive protein test checks for a protein linked to inflammation of the arteries. Other blood tests check cholesterol and blood sugar levels.
- A chest X-ray will show the condition of the lungs and if the heart is enlarged.
- An electrocardiogram (ECG or EKG), a test that records the electrical signals in the heart, can tell if the heart is beating too fast or too slow.
- A Holter monitor, a portable ECG device that's worn for a day or more to record the heart's activity during daily activities, can detect irregular heartbeats that aren't found during a regular ECG exam.
- An echocardiogram, which uses sound waves to create detailed images of the heart in motion to show how blood moves through the heart and heart valves, can help determine if a valve is narrowed or leaking.
- Exercise tests or stress tests, which often involve walking on a treadmill or riding a stationary bike while the heart is checked, help reveal how the heart responds to physical activity and whether heart disease symptoms occur during exercise.
- A cardiac catheterization test, which uses a long, thin flexible tube called a catheter that is inserted in a blood vessel (usually in the groin or wrist) and guided to the heart assisted by a dye that helps the arteries show up more clearly on X-ray images, can show blockages in the heart arteries.
- A heart CT scan, also called a cardiac CT scan, and a heart magnetic resonance imaging scan, can collect images of the heart and chest.

Other tests may include a transesophageal echocardiography to assess the function of heart valves, follow heart valve disease and look for blood clots inside the heart; a pharmacologic stress test to determine the cause of chest pain, shortness of breath and weakness;[23] a coronary artery calcium score test to measure the amount of calcium buildup in the coronary arteries[24]; among others.

Myth: Diagnosing and treating heart disease are the same for men and women.

Fact: Actually, men and women require different diagnostic heart care. For instance, if a heart attack is suspected, both men and women receive a cardiac troponin (cTn) test that measures circulating levels of troponin, a protein released in the blood when a heart attack has damaged heart muscle. If there are higher levels of troponin, there is more heart damage. But the clinical threshold that signals a heart attack may differ across the sexes. "Some women may be having a heart attack but are falling below the level of detection. Providers are only starting to apply sex-specific thresholds for certain diagnostic tests," says Michelle O'Donoghue, MD, a Mass

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Another diagnostic test, cardiac catheterization, long considered the gold standard for diagnosing a heart attack, looks for blockages in large arteries. But, since women are more likely than men to experience more plaque buildup in the smallest arteries, this test may not be the most appropriate to diagnose heart disease in women. Instead, a cardiac MRI to look for inflammation of the heart, or intracoronary imaging to look at the inside of blood vessel walls within the heart, may be more appropriate.

The same is true for treatment. Medical providers treat the typical cholesterol plaque buildup in the largest blood vessels of the heart, whereas there is not a great understanding of how to treat plaque in the microvasculature, or inflammation of the heart. As such, more clinicians are approaching treatment decisions with the knowledge that women may benefit from treatments that are different from those used in men, from subtle calibrations in pacemakers to variations on angioplasty.[16]

Myth: Angioplasty and stenting, or bypass surgery, can fix a person's heart.

Fact: While angioplasty and bypass surgery can relieve chest pain (angina) and improve quality of life, they don't stop the underlying disease, which is atherosclerosis.[18]

In fact, National Institutes of Health-funded studies have found that invasive procedures such as bypass surgery and stenting are no better at reducing the risk for heart attack and death in patients with stable ischemic heart disease than medication and lifestyle changes alone. The studies, the official outcomes of the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA), the largest and one of the most consequential studies of its kind, were designed to settle a decades-old controversy in cardiology.

The ISCHEMIA trial followed more than 5,000 patients with stable heart disease and moderate to severe heart disease for a median of 3.2 years. It compared an initial conservative treatment strategy to an invasive treatment strategy. The conservative treatment strategy involved medications to control blood pressure, cholesterol and angina (chest discomfort caused by inadequate blood to the heart), along with counseling about diet and exercise. The invasive treatment strategy involved medications and counseling, as well as coronary procedures performed soon after patients recorded an abnormal stress test. The trial allowed tests that assess coronary blood flow restriction, called ischemia, to determine who could participate in the study.

"Previous studies have reached similar conclusions as ISCHEMIA, but they were criticized for not including patients who had severe enough disease to benefit from the procedures. ISCHEMIA studied only patients with the most abnormal stress tests," said Yves Rosenberg, MD, study co-author and chief of the National Heart, Lung, and Blood Institute's Atherothrombosis and Coronary Artery Disease Branch. "These findings should be applied in the context of careful attention to lifestyle behaviors and guideline-based adherence to medical therapy, and will likely change clinical guidelines and influence clinical practice."[25]

Dispelling the Myths Now

Heart disease remains the leading cause of disease globally. But extensive research is ongoing to advance innovative therapeutics and novel diagnostics for prevention and treatment. And, while heart disease is a serious challenge, knowledge about the disease and encouraging healthy habits allow for early intervention, which can prevent serious health events such as heart attack and stroke. ❖

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Heart Disease: *A Patient's Perspective*

By Trudie Mitschang

THE FIRST twinge of chest pain struck Heather Bardeleben late one night as she pored over a spreadsheet at her suburban Chicago home. When her husband, Bill, suggested she lie down, she brushed him off. "I'll be fine," she insisted.

But the pain didn't go away. Her arms grew heavy, dizziness crept in and her home pulse oximeter showed dropping oxygen levels. By morning, Heather instinctively knew it had to be her heart.

Heather saw her cardiologist who ran an EKG, but it came back normal. Anxiety or acid reflux, she was told. Her primary care physician echoed the same theory, though he ordered a cardiac MRI just in case. When she couldn't get the MRI scheduled and her pain intensified, Heather went to the ER. Again, tests looked normal, but because of her continuing chest pain, Heather was admitted to the hospital. Nitroglycerine pills helped, but the pain did not go away. Even so, a hospital cardiologist told her to go home, again saying she merely had anxiety or reflux. "There's nothing wrong with your heart," he told her. "I don't know why you're here."

At that point Heather asked for an angiogram; both of her parents had received stents after X-rays had revealed blockages in their arteries, so she understood her risk factors. Unfortunately, the hospital doctor disagreed and sent her home, saying her symptoms didn't warrant one.

A week later, Heather bent to sit on the couch and felt a sharp snap in her chest — like a twig breaking. She immediately knew something was terribly wrong. A portable device she'd purchased to monitor her father after his bypass surgery showed atrial fibrillation. "I'm in trouble," she thought, moments before collapsing.

Paramedics revived her after her heart stopped that day, and by the time she got to the hospital, an angiogram revealed what she had feared: Plaque had ruptured, causing a clot, a heart attack and cardiac arrest. A stent was placed in her right coronary artery, though a 70 percent blockage remained in her left anterior descending (LAD) artery. Within two weeks, she had chest pain again, but doctors reassured her it was just her body adjusting to the stent. Days later, she suffered another heart attack, this time caused by artery spasms.

In late 2020, during the height of the COVID-19 pandemic, Heather received a pacemaker and implantable defibrillator to regulate her heart rhythm. She was sent home the same day but soon returned to the hospital with severe chest pain and was admitted for observation. Heather's heart stopped five times that night, and doctors attempted to save her by inserting a stent in her LAD. Unfortunately, due to the CPR and stent procedure, she went into critical takotsubo cardiomyopathy (temporary heart failure). Yet another procedure was performed to place an Impella heart pump to give her time to potentially recover. It saved her life.

Five years later, Heather is alive and thriving. She has lost 65 pounds, keeps tabs on her heart rate and ends her workday around 5:30 p.m. to limit stress. She also urges friends and family members to advocate for themselves in medical situations — to seek additional testing or a second opinion when they don't get answers. If they are refused a test, she advises them to ask that the denial be recorded in their chart. She's learned, she says, that doctors can make mistakes.

"Not advocating strongly enough nearly cost me my life. In total, I suffered from two heart attacks, six cardiac arrests and critical takotsubo cardiomyopathy. Before each event, I sought medical help for symptoms that indicated a potential heart-related event. If I had received an angiogram when I first presented with symptoms, it is likely that the blockage would have been discovered and stented prior to rupture — potentially preventing the chain of events that nearly killed me."

She also speaks candidly about what she sees as gender bias in cardiac care, noting that when her husband Bill later sought care for chest pain, he received an angiogram immediately, while Heather's concerns were dismissed: "I was told repeatedly I had reflux or anxiety, that it was anything but my heart."

Heather's story is a reminder that symptoms don't always fit neat textbook definitions and that patient voices matter. For Heather, survival has become more than a personal victory — it's become a mission to help others recognize the importance of self-advocacy and to challenge assumptions that can cost lives.

With her miraculous story of perseverance and survival, Heather notes she gets a very different response today if she complains of any abnormal feelings in her chest: "Now they take me seriously." ❖

Heart Disease: *A Physician's Perspective*

NANCY SWEITZER, MD, PhD, is an internationally recognized cardiologist, physician-scientist and clinical researcher specializing in heart failure and transplant cardiology. Currently serving as associate director of the Institute for Clinical and Translational Science and vice chair of clinical research in the department of medicine at Washington University in St. Louis, she has previously led major academic programs as chief of cardiology and director of the Sarver Heart Center at the University of Arizona. A fellow of the American Heart Association, American College of Cardiology and Heart Failure Society of America, Dr. Sweitzer's research centers on understanding and advancing therapies for heart failure with preserved ejection fraction (HFpEF).

BSTQ: What initially drew you to the specialty of heart disease?

Dr. Sweitzer: I've been in the field for a long time. What first drew me to cardiology, and then to heart failure, was the ability to treat people and make them feel better. I've now been involved in trials for 25 years; watching new therapies improve both the quality and duration of life has been incredibly gratifying. I always say I have the best job in the world. We care for people in shock, people who are dying, people who are critically ill, and we have tools that can save lives. But we also build long-term relationships with patients over years, even decades, helping them to feel better, stabilize their disease and achieve their goals.

BSTQ: How can we improve cardiovascular care for women?

Dr. Sweitzer: I would love to see more women in trials. Companies sometimes say, "We provide childcare," but women in their 70s with heart failure don't need childcare, they need husband care. Many are caregivers not just for children, but for spouses and family. That burden makes trial participation difficult, especially with heart failure. We need innovative ways to lower those burdens while still learning what we need to know. It's also important to talk about awareness. When women are diagnosed with heart disease, they're often shocked to learn it's the number one killer of women. That's because women don't talk about it. Women with breast cancer share their diagnosis, but women with heart failure keep it quiet. Part of that is the stigma that heart disease is the result of bad habits. However, age is the biggest risk factor, and none of us can avoid aging. I hope we can relieve some of the shame and encourage women to talk about heart disease, thereby raising awareness and increasing research participation.

BSTQ: How does socioeconomic status influence trial design and outcomes?

Dr. Sweitzer: Socioeconomic status affects everything. If you have food or housing insecurity, the last thing you can do is participate in voluntary research. Yet cardiovascular risk disproportionately affects people with socioeconomic disadvantages, and we need more resources devoted to that problem. I practice in St. Louis, Mo., a city with a troubled history around race and inequity. We've done well enrolling minority and some disadvantaged patients in trials, but the truly disadvantaged, those facing multiple insecurities, can't participate. They simply don't have the capacity.

BSTQ: How is digital health influencing cardiovascular care?

Dr. Sweitzer: Digital health is very exciting. People are collecting more health data than ever, though right now it tends to be healthy people. It will be interesting when patients with chronic diseases start generating that data, which we can then interrogate and learn from. I recently uploaded an app that can estimate my risk of systolic dysfunction with an Apple Watch ECG. With AI, wearables and apps, we'll have enormous opportunities for earlier and easier diagnosis. But again, it comes back to socioeconomic disparities. These tools tend to reach higher socioeconomic groups. The challenge is making sure digital strategies reach the populations who need them most. That's a big societal issue we still need to solve.

BSTQ: What advice would you give to those entering the cardiology field?

Dr. Sweitzer: At this stage, my greatest satisfaction comes from helping young cardiologists and physicians build careers in clinical research. Those of us in clinical practice see unmet needs most clearly. We're well-positioned to ask the right questions, then develop the skills and tools to design studies, gather data and move the field forward. For me, I've always kept both parts of my career alive: patient care and research. I love medicine and I love my patients, but I'm never happier than when I'm diving into new data and seeing what clues they hold. That's the excitement I try to pass on to young people: Stay curious, ask great questions and keep both the science and the patient at the center of it all. ❖

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

SARS-CoV-2 and COVID-19: Plasma Supply and IG Replacement Therapy to Protect Immunodeficient Patients

Can anti-SARS-CoV-2 antibodies in the plasma supply protect against COVID infection in immunodeficient patients? Research suggests otherwise.

By Terry O. Harville, MD, PhD

THE GLOBAL PANDEMIC beginning in late 2019 and early 2020 caught nearly everyone off guard and was a wake-up call for developing preparations to protect us all. Since this was the result of a novel zoonotic virus common in bats and now infecting humans, for which humans had not developed immune protection, and since there had not been prior evolutionary exposure to the virus, there was concern about how well the human immune system could respond. Hope was expressed by many that as soon as vaccinations became available and there were survivors of infection, antibodies would become present in donor plasma supply to provide protection for immunodeficient patients. However, I was concerned that this may not be correct.

Anti-ACE2, Anti-Idiotypic Antibodies

SARS-CoV-2 infects cells via binding to ACE2 on the surface of cells via the receptor-binding domain (RBD) region of the spike protein of the virus. Accordingly, we were the first to hypothesize that making antibodies to the RBD region (via vaccination or by infection) would, in turn, result in anti-idiotypic antibodies that would bind to ACE2.[1] Further, we were concerned these antibodies could disrupt ACE2 function (regulation of inflammation and blood pressure), which could result in increased inflammation in patients and dysautonomia (dysregulation of blood pressure). We studied this and demonstrated it to be true: People infected with SARS-CoV-2 do make anti-ACE2 antibodies, and these disrupt ACE2 function.[2]

Subsequently, researchers reported that microvascular clots could be found throughout the tissues in persons infected with SARS-CoV-2. They noted that the anti-ACE2 antibodies could be involved by binding to endothelial cells of the blood vessels, which then would initiate the complement cascade, resulting in damage, which subsequently would initiate the clotting cascade and thereby result in microclotting throughout the body, causing organ dysfunction.[3] Other researchers also found anti-ACE2 antibodies, which correlated with neurologic symptoms in post-COVID-19 patients, as well as in some patients after vaccination.[4]

It is known that the neutralizing antibodies (directed to the RBD region) generated by infection or by vaccination last only a few months, at least in persons with normal functioning immunity. While this may not seem to have a "most direct" effect on the anti-ACE2 antibodies via normal immune system function, the production of anti-ACE2 antibodies could directly affect the presence of the neutralizing anti-RBD antibodies. Figure 1 demonstrates this process: An antibody made to the SARS-CoV-2 spike protein RBD region becomes a new antigen for the immune system to generate an antibody against it. This initial antibody is known as an "idiotype," and the antibody directed against it is an "anti-idiotype."

Therefore, an antibody that can bind to the RBD region (idiotype) will "look like" the ACE2 protein (the binding target of the RBD region). So, an antibody to the RBD region-antibody (anti-idiotype) will be capable of binding to ACE2. Under normal immunologic control, this is perceived as "autoantibody production," which in turn shuts off the antibody production, and antibodies are then lost with a typical half-life of three to four weeks, and expectedly becoming very low after five to six months. Since this is not synchronized across all plasma donors, there is concern that significant amounts of anti-ACE2 antibodies could be in the donor plasma supply at any time.

Autoimmune Antibodies After COVID-19

A group of scientists who were among the first to study and report the presence of autoimmune antibodies in patients after COVID-19 found most people produce more than 1,000 autoantibodies.[5] Subsequently, numerous other studies demonstrated a myriad of autoantibodies persisting in people after COVID-19 infection.[6,7] Indeed, we have data demonstrating specific autoimmune antibodies directed to central nervous

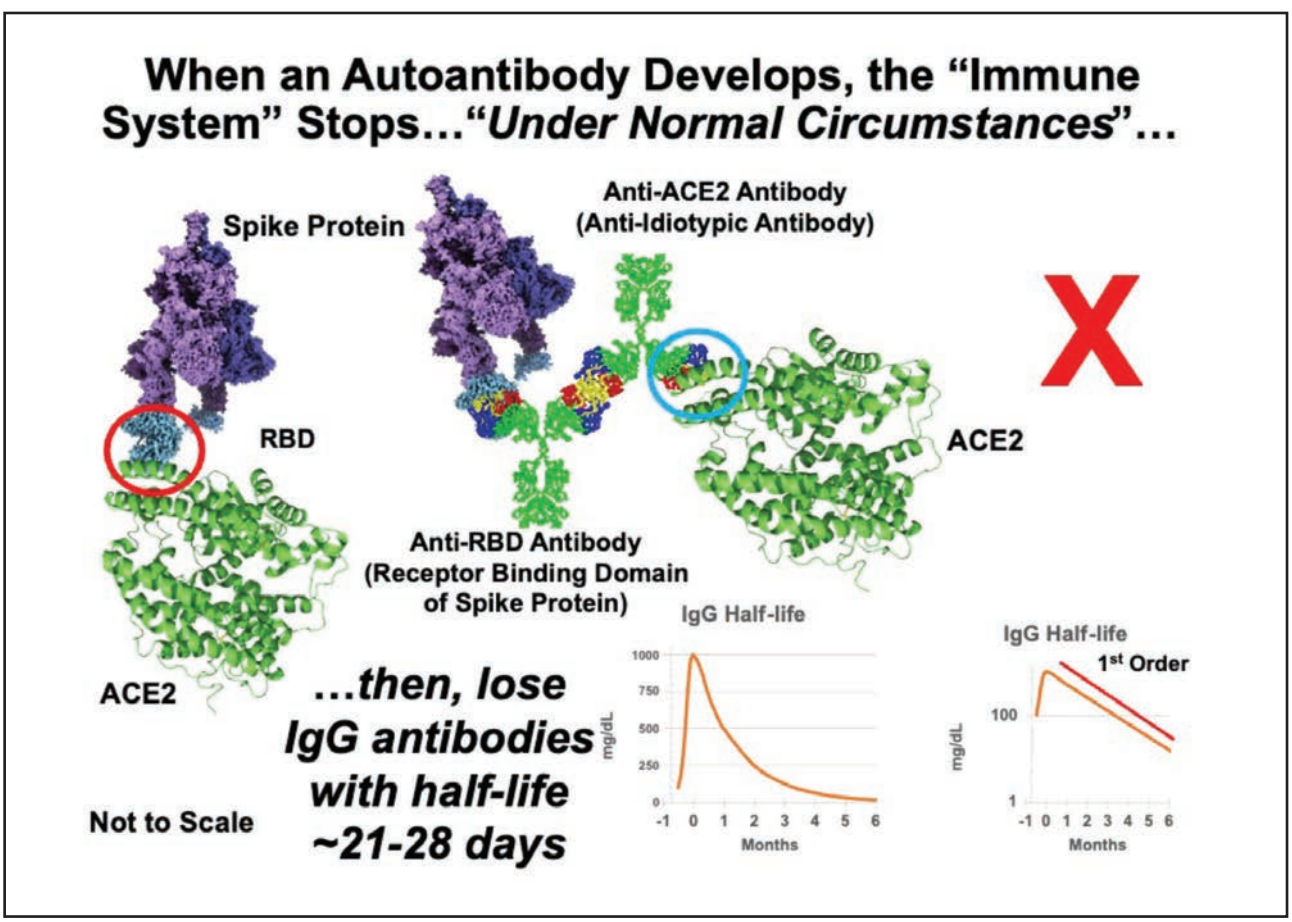
system proteins in patients exhibiting long COVID. Thus, the immune system, not knowing how to correctly respond to this zoonotic virus, ends up generating substantial numbers of autoimmune antibodies. It is of concern that these will become prominent in the donor plasma supply, as more people have survived the infection and donate.

There may be some good news, though. Vaccination has been demonstrated to prevent or reduce the symptoms of long COVID.[8] We believe vaccination with an mRNA vaccine guides the immune system in such a strong manner to help redirect it away from autoantibody production, since it is focused on anti-RBD antibody production. As such, this could help reduce the extent of autoantibodies present over time, but we need frequent and ongoing vaccinations to accomplish this! Therefore, if we could prevent natural infections through extensive vaccination, we could effectively reduce the level of autoantibodies in donor plasma. Unfortunately, though, there could still be issues with anti-ACE2 antibodies generated by vaccination.

Post-Infection Convalescent Plasma for Treating COVID-19

Early in the pandemic, there were no vaccines and no antiviral medications for treatment. So, just like the late 1800s concept, "anti-serum" from a prior infected animal or person could be used to treat the current infection in someone. In fact, this has been quite successful, winning the Nobel Prize for Emil von Behring in 1901.[9] As early survivors of COVID-19 became available, "convalescent plasma" was obtained for treating patients who were ill with COVID-19. But, early attempts

Figure 1.



The RBD (receptor-binding domain) region of the SARS-CoV-2 spike protein binds to ACE2 on cell surfaces for entry of the virus into cells (left side of figure). Antibodies generated against the RBD region will look like ACE2 at the binding position (upper middle of the figure). This antibody, as a "new protein" to the immune system, will result in a new antibody directed to this region. This "new" antibody will bind to ACE2 (upper middle right of figure). The initial antibody is known as an "idiotype," and the secondarily developed antibody is known as an "anti-idiotype." Since anti-ACE2 is an autoantibody that disrupts ACE2 function, the immune system somehow detects this aberration. This then "shuts off" antibody production (upper right of figure), with antibodies lost with a half-life of approximately 21 to 28 days, so that the levels fall to very low after five to six months (lower middle to lower right of figure). This is a reason we need frequent revaccination for COVID-19. Further, since the mRNA vaccines produce such a "robust" response, they may be capable of actually reducing the extent of generation of autoantibodies by focusing on the RBD antibody production, but anti-ACE2 antibodies could still be produced.

were not very successful.[10] It was thought that the anti-viral titer (the amount of anti-SARS-CoV-2 antibodies present) was too low in the convalescent donor plasma, but the reality was that even higher titers of post-COVID-19 convalescent plasma were not that useful. Indeed, there have been meta-analyses demonstrating no overall significant benefit from the use of convalescent plasma to treat COVID-19.[11]

Further, we know vaccination does not prevent infection from occurring, but reduces the chance of dying.[12] This is based on the fact that T lymphocyte immunity from vaccination is quite robust and long-lived, helping to prevent death, whereas antibody production does not seem to provide as much relevant benefit.[13] Considering the lack of benefit from convalescent plasma and the fact that vaccine-induced antibodies or prior infection-induced antibodies do not prevent infection, it is not clear whether anti-SARS-CoV-2 antibodies in immune globulin (IG) replacement therapy actually provide the typically expected benefit of antibodies to patients.

Replacement IG Recalls

Anti-SARS-CoV-2 antibodies were reported to be detected in the donor plasma for intravenous IG (IVIG) and subcutaneous IG (SCIG) production late in 2020.[14] Since 2022, there have been at least 12 recalls of IVIG and SCIG due to unexpected reactions.[15] While these recalls have not directly been reported to be due to antibodies related to COVID-19, the timing is highly suggestive that plasma donors who had prior COVID-19 infection have become significant plasma donors, with the implication that their autoimmune antibodies are in the donor plasma supply. As such, adverse reactions may be expected to occur.

Anti-SARS-CoV-2 antibodies were reported to be detected in the donor plasma for intravenous IG and subcutaneous IG production late in 2020.

Discussion

SARS-CoV-2 presented as a novel zoonotic virus for which our immune system had no prior knowledge or recourse. As a consequence of how the virus infects cells, anti-ACE2 antibodies are generated. Additionally, after COVID-19 infection, patients may develop more than 1,000 autoantibodies. Microclotting is a severe consequence of having anti-ACE2 antibodies and autoantibodies, with studies suggesting these can result in multiple tissue and organ dysfunction and, importantly, brain injury.

Anti-SARS-CoV-2 antibodies do not prevent infections from occurring, and data presented have not demonstrated benefit against COVID-19 infection, but vaccination (and natural infection) do result in T lymphocyte anti-SARS-CoV-2 function, which can prevent death. Recurrent vaccination with mRNA vaccines may be helpful for reducing the amount of autoantibodies by focusing the immune system on anti-RBD antibody production and redirecting it from autoantibody production, but at the risk of production of anti-ACE2 antibodies.

Therefore, while many have been hoping for anti-SARS-CoV-2 antibodies to become prominent in the plasma supply for protecting immunodeficient patients, I have remained concerned that the co-occurring autoimmune antibodies may actually be detrimental. And now, the reduction in access to COVID-19 mRNA vaccines may exacerbate the situation. ❖

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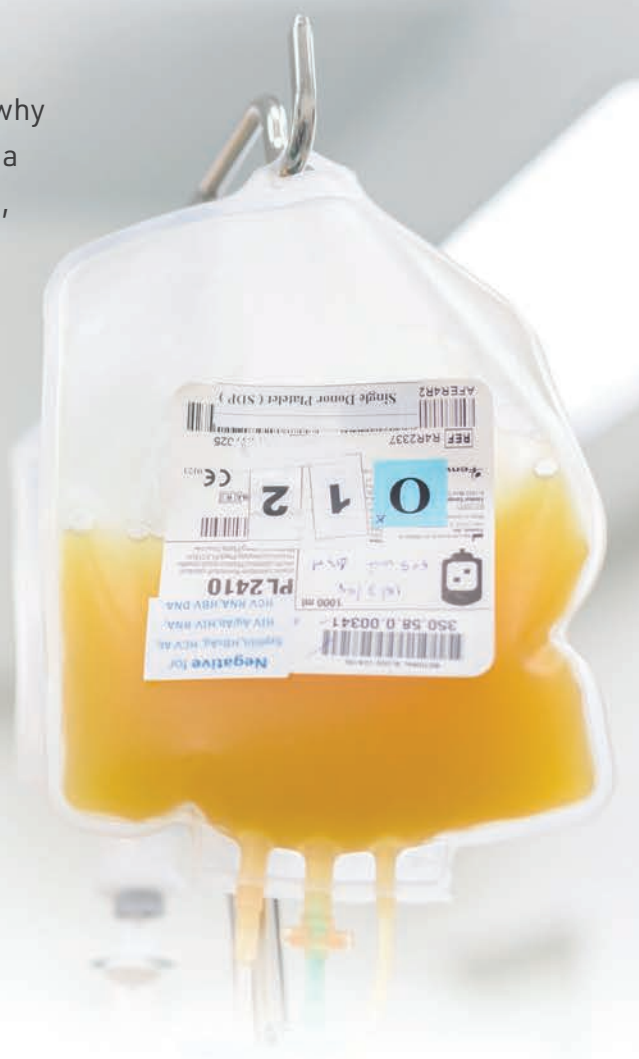

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Virtual Reality in Healthcare

VIRTUAL REALITY (VF) is a three-dimensional, computer-generated environment that can be explored by and interacted with by a person,[1] and it is quickly emerging as a resource to support hospital inpatient healing. How? Through an immersive, therapeutic digital experience tailored to a patient's individual needs. VR shows promise in many applications, including helping patients regain control of their bodies after neurological impairment and managing pain and anxiety related to medical procedures.

• Neurorehabilitation: Brain injuries such as stroke or traumatic brain injuries disrupt normal brain function, often causing cognitive, neurological and psychological problems. VR has been shown to help patients with these injuries regain function and control.[2] According to a 2021 European study investigating VR for neurorehabilitation and cognitive enhancement, "VR provides a safe, controlled environment for performing customizable, engaging rehabilitation activities that promote learning of motor skills."[2]

• Pain management and mental health: The same study showed VR as an effective intervention in pain management and reduction of stress and anxiety.[2] Pain is the most common reason people seek medical care, and anxiety is prevalent among hospital inpatients.[3,4] VR can be used as a form of "distraction analgesia"[2] alone, or it may be combined with prescription pain medications. It can also be used for "environmental enrichment to trigger the neural mechanisms of recovery."[2] VR is especially useful for reducing stress in inpatient pediatric patients.[5]

Here are three VR solutions making a name for themselves in the world of hospital-grade VR therapeutics:

MindMotion PRO

MindMotion PRO is an immersive VR specially designed for acute neuro-rehabilitation in hospitals. Approved by the U.S. Food and Drug Administration (FDA), this tool offers repetitive, task-specific training ideally suited for delivering therapy to patients recovering from upper-limb hemiparesis. Its engaging, entertaining interface features 17 games to promote embodiment and agency over upper-limb control; proprietary tracking technology uses a custom-built camera system; and optical markers and inertial measurement units capture subtle intended movements and amplify them for gameplay. For more information, visit *mindmaze.com/digital-therapies-for-neurorehabilitation/#mindmotion-pro*.

XRHealth VR CBT

XRHealth's VR CBT device is an FDA-registered VR multi-tool used for at-home patient pain management; mental health and stress relief; and physical therapy. The platform integrates artificial intelligence, VR and extended reality (XR) for rehabilitation, offering immersive environments that boost patient engagement and therapeutic success in three distinct therapeutic areas:[2] Physio space for physical rehab of extremities, neck mobility, balance motor skills, fatigue and post-COVID respiratory care; Cogni space for cognitive training, occupational rehabilitation and cognitive behavioral therapy; and Reliever space XR for alleviating chronic and acute pain during daily activities and medical procedures. For more information, visit *www.xr.health/us/dme*.

Kind VR

KindVR's VR therapies are designed to help pediatric patients lower pain and alleviate stress due to medical procedures. Designed with child life specialists, hospital staff and patients in mind, KindVR's HIPAA-compliant clinically validated software, hospital-ready VR equipment and comprehensive training program is easy to implement and safe to use. KindVR systems are currently used at more than 70 hospitals and clinics. For more information, visit *www.kindvr.com/hospital-programs*.

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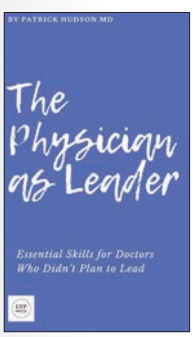
The Physician as Leader: Essential Skills for Doctors Who Didn't Plan to Lead (Coaching for Physicians Series)

Author: Patrick Hudson, MD

The Physician as Leader is not a management manual. It's a practical, personal guide for doctors who find themselves leading — teams, decisions, conversations — whether they meant to or not. Drawing on decades of experience as a surgeon, coach and ethics consultant, Patrick Hudson, MD, offers a different kind of leadership training: one rooted in emotional intelligence, clinical presence and the realities of modern medical life, with a tone that's warm, wry and unscripted.



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Communication in Healthcare: Charting the Course to Better Outcomes with Trust, Respect, and Teamwork

Author: Anne Marie Morse, DO, FAASM

Using a simple metaphor of a vehicle on a road for the wellness journey, Anne Marie Morse, DO, FAASM, explains how to put the patient at the wheel, with the healthcare partner as the car's GPS: Guiding Partner Specialist. Rather than patient-centered care, Dr. Morse advocates for patient-directed care, informed by mutual respect, accountability and awareness of all parties involved in the wellness journey. Each chapter addresses a different stage in the wellness journey, from preparing for a first appointment to handling the outcomes of test results.

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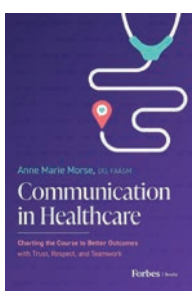

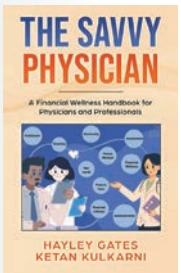

The Savvy Physician: A Financial Wellness Handbook for Physicians and Professionals

Authors: Hayley Gates and Ketan Kulkarni, MD

Written by a medical student and physician, this book is a nationally collaborative, evidence-based, unbiased educational resource for physicians and professionals from all fields. Every chapter includes exercises and questions for review and reflection, as well as expert comments. The information is relevant regardless of geographic location and to all fields of work.

www.amazon.com/Savvy-Physician-Financial-Physicians-Professionals/dp/B0FLVPZY95

A Prescription for Caring in Healthcare Leadership: Building a Culture of Compassion and Excellence

Author: Joshua D. Hartzell, MD

Joshua D. Hartzell, MD, shares more than 20 years of leadership experience and insights from 17 leaders to show how caring-inspired leadership can improve well-being, morale and patient outcomes. Readers will discover how to lead with caring and reconnect healthcare providers to their purpose, prioritize self-care and team well-being, set high standards and give compassionate feedback, delegate effectively to foster professional growth, invest in the careers and lives of those they lead and recognize their team to boost morale and create a positive culture.

www.amazon.com/Prescription-Caring-Healthcare-Leadership-Compassion/dp/B0DSQ4276K

Medicare Immune Globulin Reimbursement Rates

Rates are effective Jan. 1, 2026, through March 31, 2026

	Product	Manufacturer	J Codes	ASP + 6% (before sequestration)	ASP + 4.3% (after sequestration)
IVIG	ALYGLO™	GC Biopharma	J1552	$247.69	$243.71
IVIG	ASCENIV™	ADMA Biologics	J1554	$980.91	$965.18
IVIG	BIVIGAM®	ADMA Biologics	J1556	$159.29	$156.74
IVIG	GAMMAGARD® SD	Takeda	J1566	$157.78	$155.25
IVIG	GAMMAPLEX®	BPL/Kedrion	J1557	$127.86	$126.05
IVIG	OCTAGAM®	Octapharma	J1568	$94.77	$93.43
IVIG	PANZYGA®	Octapharma/Pfizer	J1576	$142.44	$140.43
IVIG	PRIVIGEN®	CSL Behring	J1459	$100.56	$99.14
IVIG	YIMMUGO®	Kedrion	C9399**	•	*
IVIG/SCIG	GAMMAGARD LIQUID®	Takeda	J1569	$94.58	$93.24
IVIG/SCIG	GAMMAKED™	Kedrion	J1561	$98.15	$96.76
IVIG/SCIG	GAMUNEX®-C	Grifols	J1561	$98.15	$96.76
SCIG	CUTAQUIG®	Octapharma	J1551	$148.23	$146.13
SCIG	CUVITRU®	Takeda	J1555	$172.62	$170.18
SCIG	HIZENTRA®	CSL Behring	J1559	$145.43	$143.37
SCIG	HYQVIA®	Takeda	J1575	$183.25	$180.66
SCIG	XEMBIFY®	Grifols	J1558	$150.56	$148.43

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

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** For other payers, bill YIMMUGO® with a HCPCS code or codes as instructed by each payer.

Immune Globulin Reference Table

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

2025-2026 Influenza Vaccines

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

Product	Manufacturer	Presentation	Age Group	Code
Trivalent				
AFLURIA® (IIV4)	CSL Seqirus	0.5 mL PFS 10-bx	6 months and older	90685
FLUAD® (IIV4)	CSL Seqirus	0.5 mL PFS 10-bx	65 years and older	90694
FLUARIX® (IIV4)	GSK	0.5 mL PFS 10-bx	6 months and older	90686
FLUBLOK® (ccIIV4)	Sanofi	0.5 mL PFS 10-bx	9 years and older	90682
FLUCELVAX® (ccIIV4)	CSL Seqirus	0.5 mL PFS 10-bx	6 months and older	90674
FLULAVA®L (IIV4)	GSK	0.5 mL PFS 10-bx	6 months and older	90686
FLUMIST® (LAIV4)	AstraZeneca	0.2 mL nasal spray 10-bx	2-49 years	90672
FLUZONE® (IIV4)	Sanofi	0.5 mL PFS 10-bx	6 months and older	90686
FLUZONE® (IIV4)	Sanofi	5 mL MDV	6 months and older	90657/90658
FLUZONE® HIGH-DOSE (IIV4)	Sanofi	0.5 mL PFS 10-bx	65 years and older	90662

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

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

2025-2026 COVID-19 Vaccines

Product	Manufacturer	Presentation	Age Group	Code
SPIKEVAX® (COVID-19 Vaccine, mRNA)	Moderna US, Inc.	0.5 mL PFS 2-ctn and 10-ctn	12 years and older	91321
mNEXSPIKE® (COVID-19 Vaccine, mRNA)	Moderna US, Inc.	0.2 mL PFS 10-bx	65 years and older 12-64 years with one underlying high-risk condition	91323
SPIKEVAX® (COVID-19 Vaccine, mRNA)	Moderna US, Inc.	0.25 mL PFS 10-ctn	6 months to 11 years	91322
NUVAXOVID™ (COVID-19 Vaccine, Adjuvanted)	Sanofi	0.5 mL PFS 10-ctn	12 years and older	91304
COMIRNATY® (COVID-19 Vaccine, mRNA)	Pfizer-BioNTech	0.3 mL PFS 10-ctn	12 years and older	91320

2025-2026 Respiratory Syncytical Virus (RSV) Products

Product	Manufacturer	Presentation	Age Group	Code
ABRYSVO™	Pfizer	0.5 mL Kit 1-ctn	pregnant individuals 32-34 weeks gestation; 60 years and older; 18-59 years with increased risk for LRTD caused by RSV	90678
ABRYSVO™	Pfizer	0.5 mL Kit 5-ctn		90678
ABRYSVO™	Pfizer	0.5 mL PFS and Act-O vials 10-ctn		90678
AREXVY	Pfizer	0.5 mL SDV 10-bx	60 years and older; 50-59 years with increased risk for LRTD caused by RSV	90679
BEYFORTUS®	Sanofi	0.5 mL PFS 5-bx	neonates and infants born during or entering their first RSV season; children up to 24 months	90380
BEYFORTUS®	Sanofi	1 mL PFS 5-bx	neonates and infants born during or entering their first RSV season; children up to 24 months	90380
ENFLONSIA™	Merck	0.7 mL PFS 10-pk	neonates and infants born during or entering their first RSV season	90382
mRESVIA®	Moderna	0.5 mL PFS 10-bx	60 years and older; 18-59 years with increased rick for LRTD caused by RSV	90683

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