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WINTER 2025 CRITICAL CARE

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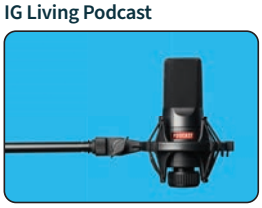

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Demand for Quality Care Fuels Healthcare Delivery Advances

HEALTHCARE DELIVERY continues to evolve as demand for care quality grows. For instance, gone are the days when patients unquestioningly follow their doctors' care instructions, as "healthcare consumers" instead seek out the best treatment options catered to their individual needs; no longer are hospitals the only choice for acute care, with more patients opting for at-home treatment; and the challenges of caring for loved ones who live long distances away are not as formidable due to an expanding number of tools, services and resources.

Personalized care is being driven by healthcare consumerism, a movement that began in the 1930s and 1940s with a demand for universal healthcare coverage, but that has now transformed into a demand for a higher caliber of care. As we explain in our article "Meeting the Demand for Personalized Care" (p.22), this trend is being fueled by technology, genomics and tailored care plans known as "precision care" rather than a one-size-fits-all treatment. We provide some specific examples of how the healthcare industry is evolving to meet the demand for personalized care, as well as discuss the benefits for patients and the healthcare industry in terms of better outcomes and lowered costs.

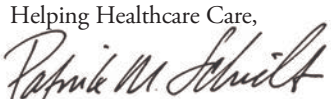
While house calls were once a thing of the past, receiving care in the home is on the rise. In-home doctor visits are expected to quadruple by 2050 due to an aging population, but another trend being spurred by the older adult patient population is a model of home care known as hospital at home, or HaH. In our article "Hospital at Home: The Future of Care?" (p.26), we explain how acute care at home started as a small pilot program in 1996 and then continued into a demonstration model in 2002, neither of which gave much steam to the HaH model. But, when the pandemic hit in 2020, the HaH model suddenly became necessary, made possible by telehealth and remote patient monitoring that allowed providers to manage patient care from a distance. We discuss how HaH works and its pros and cons. With so many people preferring to be treated at home versus in the hospital, as well as the fact that the home is a safer environment for most patients, HaH is likely here to stay.

Technology has also led to the ability to manage the care of aging family members who are often choosing to age at home rather than in assisted care facilities. Our article "Managing Care from Afar: The Challenges and Solutions of Long-Distance Health Management" (p.30) looks at the unique challenges faced by long-distance caregivers and the many solutions now available, including assistive technologies, coordinated care networks and professional care managers — all of which help to keep families' loved ones safe in the comfort of their own home.

On a final note, we are debuting a new column in this issue titled BioTech on p.56, which will feature technological tools to help you manage your healthcare facilities. We hope you will find it beneficial to your business endeavors.

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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Guidance for Second Medicare Drug Price Negotiation Released

The U.S. Department of Health and Human Services, through the Centers for Medicare and Medicaid Services (CMS), has released final guidance outlining the process for the second cycle of negotiations under the Medicare Drug Price Negotiation Program. The guidance also explains how CMS will help ensure people with Medicare can access drugs at the negotiated prices from the first and second cycles when those prices become effective beginning in 2026 and 2027.

CMS will announce the selection of up to 15 additional drugs covered by Part D for the second cycle of negotiations by Feb. 1, 2025. This second cycle of negotiations with participating drug companies will occur during 2025, and any negotiated prices for this second set of drugs will be effective starting Jan. 1, 2027.

This final guidance incorporates lessons learned from the first cycle of negotiations, and outlines requirements

and parameters for how participating drug companies must ensure eligible people with Medicare prescription drug coverage will have access to the negotiated prices for 2026 and 2027, including procedures that apply to participating drug companies, Medicare Part D plans, pharmacies, mail order services and other entities that dispense drugs covered under Medicare Part D. Notably, the final guidance states that CMS will engage with a Medicare Transaction Facilitator that will serve as the infrastructure in the exchange of data and the optional facilitation of payments to ensure eligible individuals with Medicare and the pharmacies that serve them have access to the maximum fair prices.

"We are continuing to implement the prescription drug law thoughtfully, prioritizing engagement with all interested parties, and ensuring the process is as transparent and inclusive as possible," said Meena Seshamani, MD, PhD, CMS deputy administrator and director of the Center for Medicare. "As we approach the second cycle of negotiations, we continue to focus on ensuring people with Medicare prescription drug coverage have access to the innovative cures and therapies they need at prices they can afford." ❖

HHS Releases Final Guidance for Second Cycle of Historic Medicare Drug Price Negotiation Program. U.S. Department of Health and Human Services press release, Oct. 2, 2024. Accessed at www.hhs.gov/about/news/2024/10/02/hhs-releases-final-guidance-second-cycle-historic-medicare-drug-price-negotiation-program.html.

Multi-Million Dollar Grant Awarded for Organ Transplantation Research

Researchers at the Terasaki Institute for Biomedical Innovation have been awarded a multi-million dollar grant from the National Institutes of Health (NIH) to advance research in organ transplantation and antibody-mediated rejection. The research will focus on creating a state-of-the-art multi-organs-on-a-chip platform comprised of a vascularized liver-on-a-chip and heart-on-a-chip, with a fully integrated biosensor system to study the underlying mechanisms of antibody-mediated rejection and liver-mediated cardiac allograft tolerance. This cutting-edge model will simulate the complex physiological functions and microvasculature of liver and heart allografts to explore mechanisms of antibody-mediated rejection and tolerance with unprecedented precision.

"We hope that our proposed model will provide critical insights that can lead to improved treatment strategies and outcomes for transplant patients," said Vadim Jucaud, PhD, assistant professor and principal investigator of the project. "It is great to see the NIH invest in developing next-generation in vitro models for organ transplantation research. This novel multi-organ-on-a-chip platform will allow us to continue the pioneering work of my early career mentor, Dr. Paul I. Terasaki." ❖

NIH Awards Multi-Million Grant for Groundbreaking Organ Transplantation Research. News Medical Life Sciences, Sept. 6, 2024. Accessed at www.news-medical.net/news/20240906/NIH-awards-multi-million-grant-for-groundbreaking-organ-transplantation-research.aspx.

HHS Proposes Rule to Advance Health Equity

A rule has been proposed by the U.S. Department of Health and Human Services (HHS) to advance health equity and support whole-person care. The proposed rule would also strengthen primary care, expand access to behavioral health, oral health and caregiver training services, maintain telehealth flexibilities and expand access to screening for colorectal cancer and vaccinations for hepatitis B.

"This proposed rule strengthens the care people with Medicare receive, advancing HHS's goal of a healthcare system that not only treats those who are sick but also keeps people well," said HHS Secretary Xavier Becerra. "The law lowers costs for seniors and people with disabilities and uses rebates from drug manufacturers to strengthen Medicare. It also increases access to behavioral and dental care, expands access to cancer screenings and supports caregivers."

"Whole-person care means moving toward a healthcare system that recognizes each unique aspect of a person and their well-being, including physical health, behavioral health, oral health, social determinants of health and caregiving supports, and it all starts first with a foundation of primary care that can integrate these components," said Meena Seshamani, MD, PhD, deputy administrator of the Centers for Medicare and Medicaid Services (CMS) and director of the Center for Medicare. "We are taking lessons learned from numerous CMS Innovation Center models to strengthen primary care teams and accountable care organizations, allowing them to better meet the unique needs of every person with Medicare." ❖

HHS Proposes Physician Payment Rule to Drive Whole-Person Care and Improve Health Quality for All Individuals with Medicare. U.S. Department of Health and Human Services news release, July 10, 2024. Accessed at www.hhs.gov/about/news/2024/07/10/hhs-proposes-physician-payment-rule-drive-whole-person-care-improve-health-quality-all-individuals-medicare.html.

CMS Issues Final Rule on 2025 Home Health Prospective Payment Systems

The Centers for Medicare and Medicaid Services (CMS) issued a final rule on its 2025 home health prospective payment system, which updates Medicare payment policies and rates for home health agencies. This rule will also provide updates to the intravenous immune globulin (IVIG) items and services' payment rates for durable medical equipment suppliers.

With this final rule, CMS finalized a permanent prospective adjustment of -1.975 percent (half of the calculated permanent adjustment of -3.95 percent) to the 2025 home health payment rate, which seeks to clarify the impact of implementing patient-driven grouping models. CMS said this adjustment aims to account for differences between assumed and actual behavior changes on estimated aggregate expenditures. Additionally, CMS applied a 3.925 percent reduction for 2023 and a 2.890 percent reduction for 2024, which were half of the estimated required permanent adjustments.

As part of this final rule, CMS is deciding upon a crosswalk for mapping responses on the current outcome and assessment information set (OASIS), OASIS-E — in response to the prior OASIS set, OASIS-D — with the intention of analyzing the difference between assumed and actual behavior changes on estimated aggregate expenditures, recalibrated patient-driven grouping model case-mix weights and updated low-utilization payment adjustment (LUPA) thresholds, functional impairment levels and comorbidity adjustment subgroups. Additionally, CMS intends to finalize and adopt the most recent office of management and budget core-based statistical area delineations for home health wage indexes; an occupational therapy low-utilization payment adjustment add-on factor and updated physical therapy, speech-language pathology and skilled nursing low-utilization payment adjustment add-on factors; and an updated 2025 fixed-dollar loss ratio for outlier payments.

This final rule settles the rate update for the 2025 IVIG items and services' payment under the IVIG benefit. Additionally, CMS is finalizing updates to the home health agency conditions of participation, which aim to reduce avoidable care delays by helping ensure that referring entities and prospective patients can select the most appropriate home health agency based on their care needs. ❖

CMS Releases Final Rule on 2025 Home Health Prospective Payment Systems. HomeCare, Nov. 4, 2024. Accessed at www.homecaremag.com/news/cms-releases-final-rule-2025-home-health-prospective-payment-systems.

Understanding Drugs and Money in 2025

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

SPECIALTY MEDICATIONS have dramatically improved the lives of so many both in terms of quality and longevity. They're an integral part of the first approach to treatment in an ever-increasing number of disease states. However, the cost of the ever-expanding portfolio of these products has ballooned to an astronomical number.

Many years ago, the approval of using generic pharmaceutical products upon patent expiration brought financial relief. In a similar manner, the use of biosimilar products upon patent expiration of biologics was predicted to have a tremendous impact on costs as well when the first biosimilar was released in 2015. The U.S. Food and Drug Administration (FDA) published its Biosimilars Action Plan (BAP) in 2018; it was updated in April 2024 to reinforce its strategy to further expand biosimilar product availability and use, marking the 50th biosimilar agent release. According to Sarah Yim, MD, director of FDA's Office of Therapeutic Biologics and Biosimilars, "The [updated] BAP describes the agency's high-level vision to encourage innovation and competition for biologics and to facilitate the development of safe and effective biosimilar and interchangeable biosimilar products at potentially lower costs for patients."

This article focuses on four goals that are designed to increase biosimilar uptake: improving efficiency of the biosimilar development and approval process; maximizing scientific and regulatory clarity surrounding biosimilars; developing communication strategies to improve patient, clinician and payer understanding of biosimilars; and supporting market competition, as well as identifying misinformation.

The Inflation Reduction Act (IRA): Continued Implementation

Although many aspects of the IRA are designed to drive down costs that cover a multitude of areas outside of the healthcare environment, three primary components are related to prescription drugs: the Drug Price Negotiation Program, Medicare Part B and Part D inflation rebates and the Medicare Part D redesign.

In early October 2024, the Centers for Medicare and Medicaid Services (CMS) released final guidance outlining the process for the second cycle of drug price negotiations under the Medicare Drug Price Negotiation Program. It also explains how CMS will help ensure Medicare beneficiaries access the first and second wave of negotiated prices (first 10 drugs, Jan. 1, 2026; next 15 drugs, Jan. 1, 2027). Implementation will be supported by a Medicare transaction facilitator to ensure Medicare beneficiaries and pharmacies have access to maximum fair prices, as well as CMS-hosted monthly technical calls for pharmacies and a series of patient-focused roundtable events.

As part of the IRA Rebate Program, some Medicare beneficiaries paid less for coinsurance for 54 Part B drugs through the end of 2024. The law includes a rebate program that reduces their financial responsibility for co-pays for medications that increase in price by more than the rate of inflation. Collectively, more than 100 drugs have sustained the co-pay price reductions through the program since April 1, 2023. This will continue on a quarterly basis through 2025. For more information, see the quarterly average sales price (ASP) pricing file at www.cms.gov/medicare/payment/part-b-drugs/asp-pricing-files. Qualifying products are indicated with "inflation-adjusted coinsurance" in the notes column.

Rebate implementation proposals will:

- Codify policies related to rebates drug manufacturers must pay when the price of their product increases more rapidly than inflation
- Remove 340B Drug Pricing Program claims using national provider identities and/or Medicare provider numbers from all claims used to determine rebate amounts
- Establish a process for reconciling rebate amounts for Parts B and D drugs
- Clarify rebate amounts in specific circumstances such as when drugs are subject to wastage refunds

Biosimilar reimbursement is enhanced to encourage use. IRA establishes a payment rate for biosimilars under Part B during the initial period:

- Initial period payment rate is the lesser of the biosimilar's wholesale acquisition cost (WAC) +3%, or 106% of the reference product's ASP for biosimilars furnished on or after July 1, 2024.
- Increased Part B add-on payment for qualifying biosimilars from 6% to 8% of the reference product's ASP for a five-year period. During this period, the payment for such biosimilars would be the biosimilar's ASP +8% of the ASP of

the reference biological.

The accuracy and completeness of claims data drives rebates calculated by CMS and paid by the manufacturer.[1,2,3]

The ABCs and Ds of Medicare

- Part A covers the inpatient environment with the inpatient prospective payment system rules following a fiscal year calendar effective Oct. 1; 340B program pricing does not apply.
- Part B covers the outpatient environment with the outpatient prospective payment system (OPPS) rules and the physician office setting with the physician fee service (PFS) rules following a calendar year effective Jan. 1. Drugs are covered as incident to both OPPS and PFS. Some sites will be eligible for the 340B pricing program.
- Part C Medicare Advantage (MA) may include drugs controlled by pharmacy benefit managers (PBMs). Each eligible Medicare beneficiary has the option of remaining a traditional Medicare patient or becoming a Medicare Advantage patient (Part C) instead. This means leaving "fee-for-service" and moving to managed care provided by the private sector. Greater than 50 percent of Medicare recipients have moved to the MA option. (The beneficiary could change on an annual basis, although it's difficult to switch to once again become a traditional Medicare patient.) Medicare Advantage is operated by commercial/private insurance plans. Medicare pays these plans a fixed fee per patient for taking these beneficiaries into their managed care plans. These companies profit if the expenses for these patients are less than the flat fee they receive, hence PBMs, prior authorizations, site-of-care, treatment ladders, formularies, etc., are used to reduce costs.
- Part D provides prescription drug coverage for home/ambulatory use. Medication therapy management is available; applicable sites are eligible for the 340B pricing program.

PrEP for HIV and Related Preventive Services

In a somewhat surprising move, CMS Medicare moved oral pre-exposure prophylaxis (PrEP) dosage forms out of Part D and into Part B effective Sept. 1, 2024. This means they will cover oral and injectable forms of PrEP and other related services to prevent HIV without cost-sharing (i.e., deductibles or co-pays) under Medicare Part B. CMS posted a final national coverage determination (NCD) for PrEP using antiretroviral drugs to prevent HIV infection. NCDs are made through an evidence-based process and are posted on the CMS Medicare Coverage Center website to provide stakeholders with the Medicare coverage criteria for each technology, a summary of the evidence considered and CMS' rationale for the decision. See www.cms.gov/medicare/coverage/prep for more information.

Despite concerns raised by the pharmacy and patient community, CMS recently confirmed that with this transition, HIV PrEP prescribed by a pharmacist will not be covered by Medicare Part B. Although pharmacists have expanded authority to prescribe HIV PrEP in many states with many HIV PrEP clinics by pharmacists, there is the possibility that this unintended consequence of the NCD may impact many Medicare beneficiaries and pharmacists. Additionally, people can access PrEP medications only from a pharmacy that is enrolled in Medicare Part B. Medicare Advantage plans must follow this NCD, including providing PrEP drugs for HIV with no cost sharing at in-network providers beginning Sept. 30, 2024.

CMS determined that PrEP using antiretroviral drugs to prevent HIV is covered as an additional preventive service for individuals at increased risk of HIV acquisition. CMS found that PrEP using antiretroviral drugs to prevent HIV is reasonable and necessary for the prevention of an illness or disability; recommended with a grade of A by the United States Preventive Services Task Force (USPSTF); and appropriate for individuals entitled to Medicare benefits under Part A or enrolled under Part B.

The physician or other healthcare practitioner who assesses the individual's history will also make the determination of whether the individual is at increased risk for HIV. CMS covers furnishing HIV PrEP using antiretroviral drugs, including the supplying or dispensing of these drugs and the administration of injectable PrEP.

For individuals being assessed for or using PrEP to prevent HIV, CMS covers all the following as an additional preventive service: up to eight individual counseling visits with a physician or other healthcare practitioner every 12 months, which include HIV risk assessment (initial or continued assessment of risk); HIV risk reduction and medication adherence; up to eight HIV screening tests every 12 months; and a single screening for hepatitis B virus.[4] ❖

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

Improving Care and Service by Capturing Patients' Voices

Listening to patients' experiences about their care can improve their care quality and overall health.

By Amy Scanlin, MS

COUNTLESS PAPERS have touted the importance of returning to a patient-first care approach that prioritizes effectiveness, efficiency and value-based care. But, what does having a patient-centered care approach mean when viewed through the lens of an industry beholden to data-driven metrics and often-hindered siloed processes and technologies?

Patient-centered care is a patient-first focus. It means putting oneself in the patients' shoes and viewing care from their viewpoint. One important way of doing this is by capturing patient voices in their own words and using their perceptions of care to help improve delivery. When patients' perceptions are measured by more than the numerical rating scales, their substantive feedback can provide opportunities for care improvements.

What Are Patient Voices?

Patient voices are firsthand accounts of patients' experiences and can include any number of variables such as how easy the appointment process was, their perceptions of the clinic or office, how well they were kept informed about their health, the support received when making important decisions and how well they understood provider instructions after returning home. All of these experiences and perceptions can provide valuable information that elucidates where improvements in the care journey may be needed and do so by eliminating unconscious bias.

But, patient voices are subjective and influenced by numerous social determinants of health. Patients' perspective can also be affected by how vulnerable they feel, data literacy, communication styles and language. In one example, after an oncologist shared with a patient a detailed and lengthy diagnosis, he learned that the patient had heard nothing beyond the word "cancer." For him, this revelation informed how he would deliver information in the future. Allowing a few minutes for patients to absorb what they have heard is equally important to the information they hear.[1]

So, how can healthcare organizations actively listen, prioritize and involve patients in their healthcare decisions, while soliciting feedback that can turn their experiences into meaningful and useful change?

Patient-Centered Approach to Care

The question of how to most effectively and meaningfully capture patient voices that support clinical decision-making can be a challenge. After all, patients are already sharing their experiences on social media and ratings websites, but soliciting feedback through validated open-ended questions that are balanced, complete and meaningful has the potential to significantly increase the number and quality of comments at point of care.[1] These narrative surveys provide a starting point to return to a patient-centered approach to care.

For more than two decades, the Consumer Assessment of Healthcare Providers and Systems initiative has developed surveys that help providers understand the patient experience. Supported by the Assessment for Healthcare Research and Quality (AHRQ) and downloadable from the AHRQ website, these surveys can be adjusted and administered in a variety of formats that eliminate the "one-size-fits-all" approach.[2]

As more patient data is gathered, stakeholders must devote time and attention to building an infrastructure that enables measurement tools for continuous improvement across multiple stakeholders. In fact, Congress mandated outpatient surveys for ambulatory care as part of reimbursement payments, and a growing number of hospitals and clinics

have added senior level staff who oversee patient experiences to ensure satisfaction.[3]

With buy-in from the top, transparency in communication identifies patterns of mistakes and where improvements can be made while removing barriers to change.

Patient-Reported Outcomes

Patients should be at the center of every discussion, so capturing patient-reported outcomes (PROs) in patients' own voices is an important standardized assessment. How well patients understand their own health, factors that influence their health, desires and expectations for health outcomes, how well they comply with treatment protocols, and whether they feel they are getting the care they are seeking are all factored into PROs. Soliciting this information can help to inform clinical and quality-of-care outcomes and improve patient satisfaction. It also ensures patients' voices are central to care delivery.

But scaling PRO assessments so they influence higher quality care at a lower cost across an organization can be challenging. In part, the rigorousness of information collected, the diversity of that information and how best to leverage the information are three persistent challenges. For example, depression, a common measure in health assessments, may be viewed and treated differently depending on the context of where the information was collected. Preventive care, specialty care and interventional care each view depression as an important measure of health, but treatments differ across the spectrum of care.[4] Patient workflows and reporting requirements must be addressed in each case.

Because patients may not always be able to make reliable attributions of their experiences, learning from patient feedback requires interpretive skills and analysis of patterns in patient narratives.[3] Data in the healthcare industry is growing exponentially, so capturing and distilling all of that data is as big a challenge as understanding how to respond to data trends that inform necessary improvements. Machine learning is one option that supports aggregation of patient responses; however, the costs may be prohibitive.

Quality Across the Spectrum

PROs can be collected through mailed surveys, electronic health records, survey apps and other means to ensure useful capturing and scoring of data that supports downstream quality improvements.

As the healthcare industry strives for continual improvement, vigilance in quality of care across the economic spectrum must be included. That includes capturing patient voices in ways that meet patients where they are, not necessarily where it may be most convenient for data capture. Surveys sent through the mail in patients' native languages with return postage paid is one way to encourage responsiveness without relying on technology that may not be available to them.

A Commitment to Improvement

Gathering patient voices and turning those narratives into meaningful data has the potential to improve patient and provider learning experiences, as well as actionability where changes could lead to both improved quality of care and overall patient health.

But the commitment to most effectively gather and use this data takes top-down directed time and resources. Providers should take care when speaking with patients directly about their experiences, as well as when developing or choosing patient surveys so the data gathered is meaningful and complete. Then, they should look for response trends, both positive and negative, that can influence future decisions in care delivery. Patient voices are strong indicators of organizational health, and those voices should be heard. ❖

> When patients' perceptions are measured by more than the numerical rating scales, their substantive feedback can provide opportunities for care improvements.

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

Research

mRNA Cancer Vaccine Begins Trials for Non-Small Cell Lung Cancer

An mRNA vaccine has entered human trials as a treatment for lung cancer. Unlike traditional cancer vaccines such as the HPV vaccine, BNT116 is a therapeutic cancer vaccine designed to reduce tumor growth in patients with cancer or prevent its recurrence. BNT116 contains the genetic code for six molecules frequently seen in non-small cell lung cancers, which make up 80 to 85 percent of lung cancer diagnoses. Exposure to these six molecules primes immune cells to recognize these molecules on cancer cells and eliminate them.

Intended for use in advanced non-small cell lung cancer, BNT116 is being studied in the clinical trial to assess its safety and preliminary efficacy on a small group of patients, with a target enrollment size of 130 across seven countries. Beyond confirming patient safety, the Phase I trial is intended to determine the optimal dose of the drug before initiating larger Phase II and III trials. "You have to start somewhere, and just to get to a Phase I trial, many drugs fall by the wayside. And if patients respond to this, they're actually going to benefit; it can be lifesaving, even in a Phase I trial," said Stuart Edmonds, executive vice president of mission, research and advocacy at the Canadian Cancer Society.

Traditionally, cancer treatment has been comprised of three pillars: chemotherapy, radiation and surgery. Poisoning, zapping and shaving off cancer cells were the only available options to eliminate tumors, often sacrificing healthy cells in the process. But, now, oncologists consider immunotherapy to be a fourth pillar of cancer treatment. Immunotherapy not only includes cancer vaccines but represents a broader category of treatment, including tools such as immune checkpoint inhibitors, which reinvigorate immune cells to become better killers of cancer cells. The common thread among these treatments is the use of the human immune system's ability to kill cancer cells in a more targeted way. This works because of a key vulnerability of cancer cells, which express antigens not normally seen on healthy cells, allowing them to be identified and targeted by the immune system.

BNT116 is also being studied in different combinations with more conventional treatments, cemiplimab and docetaxel. Cemiplimab is an immune checkpoint inhibitor, under the same umbrella of immunotherapy as cancer vaccines. Docetaxel, on the other hand, is a standard chemotherapy drug. A separate Phase II trial is also under way to compare how effective BNT116 is in combination with cemiplimab versus cemiplimab alone. ❖

Ryu Won Kang, J. New Lung Cancer Vaccine Is a Cousin of the mRNA Vaccine That Starred During COVID. National Post, Oct. 26, 2024. Accessed at nationalpost.com/news/new-lung-cancer-vaccine-is-a-cousin-of-the-mnra-vaccine-that-starred-during-covid.

Medicines

Pfizer's RSV Vaccine ABRYSVO Approved by FDA

The U.S. Food and Drug Administration (FDA) has approved ABRYSVO (respiratory syncytial virus vaccine [RSV]), a bivalent RSV prefusion F (RSVpreF) vaccine, for the prevention of lower respiratory tract disease (LRTD) caused by RSV in individuals 18 through 59 years of age who are at increased risk for LRTD caused by RSV. ABRYSVO now offers the broadest RSV vaccine indication for adults, which previously included those 60 years and older. Additionally, it remains the only RSV immunization approved for pregnant individuals at 32 through 36 weeks of gestation to protect infants from birth up to 6 months of age.

Approval was based on inferred efficacy from the Phase III clinical trial MONeT (RSV iMmunizatiON Study for AdulTs at Higher Risk of Severe Illness), which investigated the safety, tolerability and immunogenicity of ABRYSVO in adults at risk of RSV-associated disease due to certain chronic medical conditions.

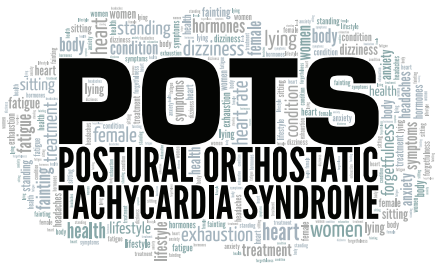
Among U.S. adults 18 to 49 years of age, 9.5 percent have an underlying chronic condition, such as obesity, diabetes, chronic obstructive pulmonary disease (COPD), heart failure, chronic kidney disease and asthma, that puts them at increased risk of developing and being hospitalized for RSV-associated LRTD, and this rises to 24.3 percent among those 50 to 64 years of age.

"RSV represents a significant threat to younger adults with certain chronic conditions. After decades of vaccine research by the scientific community and Pfizer, we now have the opportunity to help alleviate the burden of RSV in this high-risk adult population," said Aamir Malik, chief U.S. commercial officer and executive vice president at Pfizer. "With this approval, we are proud that ABRYSVO is now the only RSV vaccine indicated for adults aged 18 to 49 at increased risk for the disease, expanding on its existing indications for older adults and pregnant women." ❖

U.S. FDA Approves Pfizer's RSV Vaccine ABRYSVO® for Adults Aged 18 to 59 at Increased Risk for Disease. Pfizer press release, Oct. 22, 2024. Accessed at www.pfizer.com/news/press-release/press-release-detail/us-fda-approves-pfizers-rsv-vaccine-abrysvor-adults-aged-18.

Research

CSL Begins Enrollment for Hizentra Study for POTS



CSL Ltd. has begun enrolling U.S. patients in a Phase III late-stage randomized control trial to assess whether Hizentra subcutaneous immune globulin (SCIG) can alleviate symptoms of postural orthostatic tachycardia syndrome (POTS) — a blood circulation disorder that is one of the most common and disabling symptoms of long COVID with no approved therapies. The U.S. Food and Drug Administration granted the trial a fast track designation, recognizing its potential to address a significant unmet need. One hundred seventy seven participants in the study will be randomized to receive infusions of Hizentra or a placebo for 24 weeks, followed by an open-label treatment phase. The primary goal is to measure the proportion of participants who no longer meet the diagnostic criteria for post-COVID POTS. The study is slated to conclude in September 2027.

POTS is marked by sudden increases in heart rate, dizziness, fatigue and other symptoms when moving from a seated or lying position to standing. As of the end of 2023, more than 400 million people globally are estimated to have developed long COVID, with studies indicating around two to 14 percent of COVID survivors develop POTS, and another nine to 61 percent experience POTS-like symptoms within six to eight months.

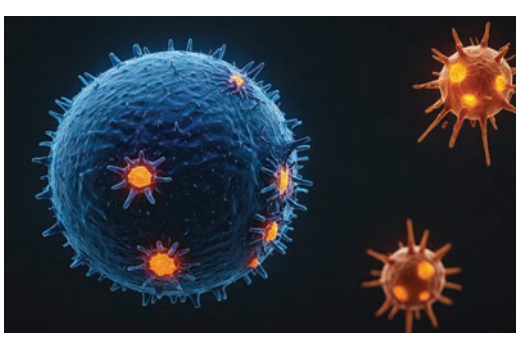
"Subcutaneous immune globulin is particularly interesting," said Akiko Iwasaki, PhD, director of Yale's Center for Infection and Immunity. Previous studies with intravenous IG have raised concerns that symptom improvements might be due to large saline infusions in the placebo group, but SCIG bypasses this issue. The CSL-sponsored trial also uses a control injection of the same volume to ensure accuracy.

Animal studies from Dr. Iwasaki's lab have shown that IG from long COVID patients reporting new pain symptoms following infection can transfer that pain to recipient mice, suggesting that certain autoantibodies may target pain neurons. If true, healthy human IG could potentially block the receptors responsible for this pain. ❖

Gale, J. CSL Enrolls Long Covid Patients in Study of Immunoglobulin Therapy for POTS. BNN Bloomberg, Oct. 25, 2024. Accessed at www.bnnbloomberg.ca/business/international/2024/10/25/csl-enrolls-long-covid-patients-in-study-of-immunoglobulin-therapy-for-pots.

Research

Changes in Immune Cell Gene Activity May Indicate Probability of Developing MS



Individuals with multiple sclerosis (MS) have high levels of immune cells called cytotoxic T cells, which normally help kill cancer and cells infected by germs. In MS, these cells accumulate in areas with visible myelin damage, but until recent study results, the role the cells play in the disease had remained unknown.

In a study published in the journal *Science Immunology*, researchers studied the T cells of 12 pairs of identical twins, one of whom had MS and the other did not. Specifically, they looked at genes that were switched on in the twins' T cells by measuring RNA, a molecule that helps cells make proteins from DNA's blueprints. This revealed that the T cells of people with either MS or central nervous system (CNS) inflammation were more active and triggered more immune signaling than those in people with neither condition. The researchers also found more activation in genes that help keep T cells switched on.

By categorizing the hyperactive genes by disease stage, the researchers showed that the genes involved in T cell activation were most prominent in people who had CNS inflammation, but not full-blown MS. People with MS had more gene activity tied to helping T cells survive, move around the body and call on other parts of the immune system to attack. Overall, the more advanced a person's disease stage, the more T cells they had that showed these genetic changes, which lends weight to the hypothesis that these T cells drive inflammation in MS.

Being able to detect the earliest indicators of MS may help to make a diagnosis and initiate therapy before any significant neurologic damage can occur. ❖

Kavaka, V, Mutschler, L, De La Rosa, C, and Beltran, E. Twin Study Identifies Early Immunological and Metabolic Dysregulation of CD8+ T Cells in Multiple Sclerosis.. *Science Immunology*, Sept. 27, 2024. Accessed at www.science.org/doi/10.1126/sciimmunol.adj8094.

Research

Study Finds Repeat Dosing of IVIG and PLEX Common in GBS, Resulting in Harm to Nonresponders

According to randomized controlled trials, repeat intravenous immune globulin (IVIG) dosing and plasma exchange (PLEX) followed by IVIG (combination therapy) have no additional therapeutic benefit in Guillain-Barré syndrome (GBS) nonresponders. Furthermore, the delineation between GBS and acute onset chronic inflammatory demyelinating polyneuropathy (A-CIDP) can be particularly challenging and carries therapeutic implications.

In the retrospective study of a large healthcare database for patients with GBS in the U.S. from 2001 to 2018, the researchers identified individuals initially diagnosed with GBS and later reclassified as CIDP. Multivariable logistic regression models were developed to determine associations between patient factors and repeat IVIG dosing, combination therapy and diagnostic reclassification from GBS to CIDP.

They identified 2,325 patients with GBS, of whom a total of 39.7percent received repeat IVIG and 6.1 percent received combination therapy. The proportion of individuals initially diagnosed with GBS and then reclassified as CIDP was 32.0 percent. Repeat IVIG, combination therapy and diagnostic reclassification remained stable over time. Female sex and medium-high net worth were associated with repeat IVIG therapy, while Asian ethnicity was associated with diagnostic reclassification from GBS to CIDP.

The researchers found repeat IVIG dosing was quite common in GBS before newer trials suggesting harm in nonresponders, and IVIG/PLEX combination therapy continues to persist despite strong evidence against use in nonresponders. Further, nearly one in three patients initially diagnosed with GBS is subsequently diagnosed with CIDP, but the reasons are unclear. ❖

Stino, AM, Reynolds, EL, Watanabe, M, and Callaghan, BC. Intravenous Immunoglobulin and Plasma Exchange Prescribing Patterns for Guillain-Barre Syndrome in the United States—2001 to 2018. *Muscle and Nerve,* Sept. 26, 2024. Accessed at onlinelibrary.wiley.com/doi/full/10.1002/mus.28265.

Research

New Type of Blood Test Can Identify Kids at Risk of Diabetes

Scientists at Kings College London have discovered a novel link between lipids and disorders affecting children's metabolism that may provide an early warning system for obesity-related problems such as type 2 diabetes and liver and heart disease. The researchers say this could assist medical professionals in identifying early disease indicators in children more quickly and facilitating their access to the appropriate treatment by using blood plasma testing machines already in use in hospitals. The findings also contest the common idea that cholesterol is a leading cause of complications stemming from obesity in children, identifying new lipid molecules that contribute to health risks such as blood pressure but are not only correlated with a child's weight.

In the study, the researchers took a control sample of 1,300 children with obesity and assessed their lipids in blood. Afterward, 200 of them were placed on

the HOLBAEK model for a year, a lifestyle intervention for people with obesity that is popular in Denmark. Subsequent readings showed that among the intervention group, counts of lipids tied to diabetes risk, insulin resistance and blood pressure decreased, despite limited improvements in some children's body mass index.

According to Cristina Legido-Quigley, PhD, a group leader in Systems Medicine at Kings College London, head of Systems Medicine at the Steno Diabetes Centre Copenhagen and principal author of the study, "For decades, scientists have relied on a classification system for lipids that have split them into good and bad cholesterol, but now with a simple blood test, we can assess a much broader range of lipid molecules that could serve as vital early warning signs for illness. In the future, this has the potential to be an entirely new way to evaluate someone's personal risk of disease, and by studying how to change lipid molecules in the body, we could even prevent metabolic diseases like diabetes altogether."

The next step for the researchers is to help understand how genetics affects lipids and what this means for metabolic diseases, as well as how these lipids can be changed to improve health. ❖

Study Finds How New Type of Blood Test Could Identify Children at Risk of Diabetes. Healthworld.com, Sept. 21, 2024. Accessed at health.economictimes.indiatimes.com/news/industry/study-finds-how-new-type-of-blood-test-could-identify-children-at-risk-of-diabetes/113539021.

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Medicines

FDA Approves Dupixent for Chronic Obstructive Pulmonary Disease

The U.S. Food and Drug Administration (FDA) has expanded its approval of Dupixent to chronic obstructive pulmonary disease (COPD). This permits Dupixent's use as an add-on maintenance treatment of adults whose COPD is inadequately controlled by available therapies. The every-other-week injectable drug is now the first biologic therapy approved by FDA for treating COPD, and is the sixth FDA-approved indication for the drug.

Dupixent is an antibody designed to block IL-13 and IL-4, two signaling pathways that drive inflammation. In COPD, the drug is intended to specifically address type 2 inflammation, an excessive immune response characterized by accumulation of certain immune cells in tissue. Dupixent's FDA approval in COPD covers the drug's use to treat patients whose disease is driven by immune cells called eosinophils.

Approval is based on results from two Phase III studies that compared the drug to a placebo in adults who were currently receiving standard-of-care inhaled therapy. Results for both studies showed statistically significant reductions in the annualized rate of moderate or severe COPD exacerbations measured over one year. ❖

Vinluan, F. Sanofi and Regeneron Biologic Drug Dupixent Notches a New FDA Approval in COPD. MedCityNews, Sept. 29, 2024. Accessed at medcitynews.com/2024/09/sanofi-regeneron-copd-dupixent-fda-approval-biologic-drug.

Research

Scientists Develop $25 Nasal Spray That Is 99% Effective Against Colds, Flu and COVID-19

Scientists at Harvard Medical School have developed a simple nasal spray, made of harmless ingredients, that can protect people against flu, colds and COVID-19 with near-100 percent success, and it costs just $25.

The new spray is called the Pathogen Capture and Neutralizing Spray, or PCANS, though they are marketing it under the name Profi. Its ingredients are pectin, gellan, polysorbate 80, benzalkonium chloride and phenethyl alcohol, all of which were drawn from the U.S. Food and Drug Administration's (FDA) inactive-ingredients database and "generally recognized as safe" list. "We performed rigorous screening of ingredients that have been used in approved nasal formulations or have been widely recognized for their safety, and identified combinations and concentrations that maximize effectiveness and safety," says Nitin Joshi, PhD, an assistant professor at Harvard.

According to the researchers, the spray "coats the nasal cavity, capturing large respiratory droplets from the air and serving as a physical barrier against a broad spectrum of viruses and bacteria, while rapidly neutralizing them with over 99.99 percent effectiveness." In other words, it catches the viruses and bacteria at the typical point of entry into the body — the nose — and stops them there.

In the study, mice were exposed to a severe flu virus. All of the mice who were given the new spray survived. Among mice who were not given the spray, none survived.

The researchers used a 3D-printed replica of a human nose to test the nasal spray's efficacy. "In ... research in our labs, the nasal spray reduced the load of viruses and bacteria — including influenza A and B, SARS-CoV-2, RSV, adenovirus and a bacterial form of pneumonia — by over 99.99 percent and persisted in the nose for eight hours," says Jeffrey Karp, PhD, distinguished chair at Brigham and Women's Hospital and professor at Harvard Medical School and MIT in Boston.

However, these results came from a study involving mice, not people, and the study was conducted in a laboratory, not the outside world. In addition, the spray

has not gone through the process of getting regulated as a medical treatment by FDA. The researchers decided against getting FDA approval due to the cumbersome federal regulatory structure, which can take years, to market the spray as a medical product. Instead they are selling it as a personal-care product. "Because of the nature of the ingredients ... we do not need clinical trials (and we don't make any medical claims — as this is regulated as a personal care product/cosmetic)," they say. This means that even though research published in a peer-reviewed journal points toward 99.99 percent effectiveness, they can't make these claims in their marketing materials. ❖

Dow Jones. Harvard Scientists Say This $25 Nasal Spray Beats Flu, Colds and COVID-19 with 99% Success. Morning Star, Sept. 28, 2024. Accessed at www.morningstar.com/news/marketwatch/20240928268/harvard-scientists-say-this-25-nasal-spray-beats-flu-colds-and-covid-19-with-99-success.

Research

HIV Vaccine Elicits Potent Response in Nonhuman Primates

A study conducted by researchers at Weill Cornell Medicine has demonstrated that a series of six vaccinations containing a modified protein from the surface of HIV particles stimulated initial steps of a potent immune response in young nonhuman primates. According to the researchers, this difficult-to-achieve response represents an important step toward providing full and potentially lifelong protection against the virus, suggesting childhood immunization against HIV could one day provide protection before risk of contracting this potentially fatal infection dramatically increases in adolescence.

In the study, the researchers started with an experimental vaccine developed previously from spike proteins on the envelope of HIV particles. The modified vaccine was administered to five young primates in three priming doses, starting less than a week after birth. This was followed up with three doses of the vaccine matching the original HIV envelope protein, with the last dose given when the animals reached 78 weeks old, roughly equivalent to 4 or 5 years old for a human. As a control, five animals received all six doses of the original envelope protein vaccine.

Three of the five animals who received the modified version of the priming vaccine developed antibodies that appeared to be precursors to the sought-after broadly neutralizing response. Tests suggested these antibodies attacked the site the virus uses to invade CD4 T cells. However, they were not yet fully effective against the same breadth of HIV strains as mature broadly neutralizing antibodies. One of the three animals also showed signs of developing the mature, broadly neutralizing response.

According to Ashley Nelson, PhD, an assistant professor of immunology research

in pediatrics at Weill Cornell Medicine, the next step is figuring out how to reliably elicit a full-on broadly neutralizing response: "We still need to identify the right combination of viral proteins to get us further down that path, starting from the earliest stages in life when multi-dose vaccines are commonly given." ❖

New Study Highlights Potential of Childhood Immunization. News Medical Life Sciences, Aug. 30, 2024. Accessed at www.news-medical.net/news/20240830/New-study-highlights-potential-of-childhood-immunization-against-HIV.aspx.

Medicines

First Nasal Self-Administered Flu Vaccine Approved by FDA

The first influenza nasal spray vaccine that can be self-administered has been approved by the U.S. Food and Drug Administration (FDA). FluMist, manufactured by MedImmune, which was acquired by AstraZeneca in 2007, was first approved by FDA in 2003 for individuals between 5 and 49 years of age. Its approval has since been expanded to include children as young as 2 years old.

FluMist is the first flu vaccine that can be administered without a healthcare provider's involvement. The spray contains a weakened form of flu virus

strains and still requires a prescription. However, it can be administered by "the vaccine recipient or a caregiver who is 18 years of age or older."

"Today's approval of the first influenza vaccine for self- or caregiver-administration provides a new option for receiving a safe and effective seasonal influenza vaccine potentially with greater convenience, flexibility and accessibility for individuals and families," said Peter Marks, director of FDA's Center for Biologics Evaluation and Research.

According to FDA, AstraZeneca plans to make FluMist available through a third-party online pharmacy. ❖

Choi, J. FDA Approves First Self-Administered Flu Vaccine. The Hill, Sept. 20, 2024. Accessed at thehill.com/policy/healthcare/4891060-fda-approves-first-self-administered-flu-vaccine.

Research

Lab Value Predictive of COVID-19 Disease Severity in Children

A study has found measurements of C-reactive protein (CRP), lactate dehydrogenase (LDH) and albumin are potentially predictive markers for disease severity in children hospitalized with COVID-19.

The multicenter retrospective cohort study at four pediatric referral hospitals in Iran between April 2020 and March 2021 assessed the discriminative ability of laboratory and clinical parameters to pinpoint predictors of disease severity and mortality among children hospitalized with COVID-19. Patients aged 18 and younger who were admitted to the hospital and tested positive for SARS-CoV-2 via reverse transcriptase-polymerase chain reaction (RT-PCR) were eligible for inclusion. COVID-19 severity was classified as either severe/critical or mild/moderate, depending on respiratory failure, shock, organ failure, severe pneumonia, hypoxia, elevated respiratory rate and abnormal blood gas analysis results. Using demographic, clinical and laboratory data, a predictive model was developed, the performance of which was evaluated using metrics such as sensitivity, specificity, positive predictive value rates and receiver operating characteristics. Logistic regression models were used in statistical analyses.

A total of 468 patients (median age, 4.2; boys, 52.9 percent; median duration of hospital stay, six days) were included in the study, 67 (14.3 percent) of whom had severe/critical disease and 401 (85.7 percent) of whom had mild/moderate disease. The median hospitalization stay was 12 days and 15 days among those in the severe/critical and deceased groups, respectively. Of the 23 (4.9 percent) patients who died, 19 (86.2 percent) had underlying conditions. Fever (64.5 percent) and cough (41.5 percent) were the two most frequently reported symptoms among all patients.

Overall, 36.5 percent of patients had underlying conditions. Underlying conditions were more prevalent among patients with severe/critical disease versus those with mild/moderate disease (80 percent versus 36.5 percent). The prevalence of abnormal chest computed tomography findings was not significantly different between the two groups.

Although median white blood cell count (WBC) and polymorphonuclear leukocyte count did not differ between the two groups, several other laboratory markers did differ. Patients with severe/critical versus mild/moderate disease had significantly higher neutrophil-to-lymphocyte ratios and LDH levels. In contrast, patients with mild/moderate versus severe/critical disease had higher median lymphocyte count and serum albumin levels. Significant differences in the presence of underlying conditions, WBC count, albumin levels, LDH levels and CRP levels were also found between patients who died versus those who recovered.

Respiratory distress, tachypnea, hypotension, acute kidney damage, intubation requirement and oxygen requirement were significantly more prevalent in the severe/critical versus mild/moderate disease group and were associated with higher mortality rate. Edema of the hands and feet was also significantly associated with mortality and disease severity.

The area under the curve for disease severity and death was 0.818 and 0.873, respectively. Specifically, a strong predictive ability was demonstrated by albumin, CRP and LDH.

"By understanding factors that influence disease progression and severity in pediatric cases, healthcare providers can better tailor treatment strategies, allocate resources effectively and improve outcomes for children affected by the virus," the researchers concluded. ❖

Basilio, P. COVID-19 in Children: Laboratory Values Are Predictive of Disease Severity. Pulmonary Adviser, Sept. 4, 2024. Accessed at www.pulmonologyadvisor.com/news/covid19-in-children-laboratory-parameters-are-predictive-of-disease-severity-2.

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Meeting the Demand for PERSONALIZED CARE

As a patient-driven priority, personalized healthcare is poised to become a permanent fixture in the public health landscape. But challenges remain.

By Trudie Mitschang

THE CONCEPT OF healthcare consumerism is not new, but it has definitely evolved. As healthcare costs continue to rise, patients are looking for healthcare experiences that mirror those they have in other service sectors, with an increasing expectation that interactions with providers and payers be as frictionless as those in the hospitality, airline or e-commerce industries.

Armed with an arsenal of Internet-based research, today's patients are technologically savvy and personally empowered to expect a higher caliber of care that factors in their unique health profiles and lifestyles. No longer content to passively accept treatment plans, this new-breed patient expects and even demands solutions that cater to their needs and preferences. They also want care that is backed by data — not just physician opinions.

One recent survey conducted by Abbott found that while 79 percent of patients have confidence in physicians' decision-making ability, they believe technology is needed to deliver more personalized care.[1] Another survey by Accenture found that 88 percent of healthcare consumers expect their care to be as personalized as their experiences during online shopping or vacation planning. The survey identified four essential components that define human-centric, personalized healthcare, including the need for empathetic emotional support, ease of access to care through technology, a desire for increased trust in the physician/patient relationship and an emphasis on equitable care.[2]

In a 2022 Healthcare Insights Study conducted by CVS Health, 1,000 U.S. consumers and 400 healthcare providers were asked what kind of healthcare experience they would like and what kinds of barriers hinder their ability to receive optimal health outcomes. The survey stated, "Providers and consumers agree that increasing engagement and communication improves health outcomes. Whether their goal is decreasing daily stress levels or increasing overall well-being, 81 percent of consumers say it is very important their primary care provider is "aware of their overall happiness and life satisfaction levels and aware of how they deal with difficult emotions and stress."[3]

Additional highlights from the CVS survey include:

- Ninety-two percent of consumer respondents said that convenience is an important factor when choosing a primary care provider; 33 percent of those respondents scheduled a virtual visit to save money and/or time.
- Fifty-three percent of healthcare provider respondents said that adding virtual care options resulted in more visits.
- The majority of healthcare provider respondents — 94 percent — said that interventions such as text message reminders or phone follow-ups assist patients in following their prescribed care plan.

Genomics as a Key Driver of Personalized Care

Genomic medicine, which involves understanding how a person's genetic makeup influences their health, has become a cornerstone of personalized care. With the Human Genome Project's completion in 2003 and subsequent breakthroughs in genomic-based research, healthcare providers can now analyze a patient's genetic information to predict, diagnose and treat diseases more precisely and personally than ever.[4]

"The Holy Grail in healthcare has long been personalized medicine, or what is now called precision medicine," says Kemal Malik, member of the Bayer board of management responsible for innovation. "But getting to the level of precision we wanted wasn't possible until now. What's changed is our ability to sequence the human genome."[4]

Many diseases, including cancers, are caused by alterations in our genes. Genomics can detect a disease long before symptoms present themselves, allowing for early diagnosis and more successful treatment outcomes. For instance, genetic testing for BRCA1 and BRCA2 mutations has become common in assessing breast cancer risk, allowing for proactive measures in prevention and early detection.

"Healthcare will move more toward prevention rather than cure," Malik says. "To date, genomics has had the most impact on cancer, because we can get tissue, sequence it and identify the alterations." In the United States, the Cancer Genome Atlas has mapped the key genomic changes in more than 30 types of cancer. Such databases could deliver a definitive diagnosis in seconds, and even recommend targeted treatments based on the DNA of both the patient and the disease.[4]

The Human Genome Project has fueled the discovery of nearly 2,000 disease genes, and these are proving highly effective at providing fast and accurate analysis. As genomics and biotechnology continue to evolve, the demand for tailored treatments is expected to rise as well.

The Influence of AI

The integration of artificial intelligence (AI) and machine learning into healthcare has also enhanced personalized care by enabling data analysis on a large scale. AI can process vast amounts of patient data and provide recommendations based on patterns that human clinicians might not easily recognize.

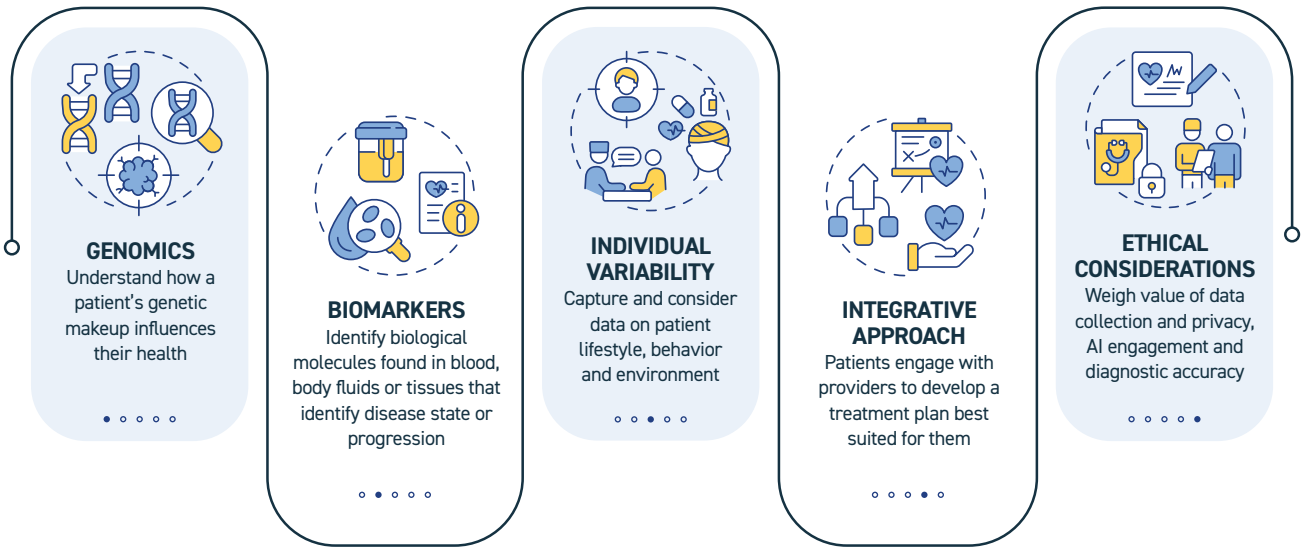
AI can be used to diagnose diseases, develop personalized treatment plans and assist clinicians with decision-making.

In the clinical setting, particularly in oncology, AI tools have the potential to personalize diagnosis and treatment for patients by drawing on a variety of data types, from genomics and electronic health records to environmental factors.

AI algorithms fall into three broad categories: machine learning, language processing and computer vision. Among them, computer vision has been one of the fastest-moving areas of AI development. In recent years, a multitude of new programs and commercial partnerships have cropped up around algorithms that read images, such as radiology scans or histology slides, and detect markers indicative of disease presence or progression with equal or greater precision than human experts.[5]

For example, digital pathology firm PathAI boasts a long list of biotech and pharma partnerships, including one with Roche Tissue Diagnostics to develop AI-driven companion diagnostics for

THE VALUE OF AI IN PERSONALIZED HEALTHCARE



identifying subsets of patients most likely to benefit from various treatments. Other companies developing AI-based digital pathology tools for precision medicine include firms such as Paige and Tempus.[5]

In 2021, Paige became the first company to have an AI-based cancer diagnostic tool approved by the U.S. Food and Drug Administration. The tool, Paige Prostate, analyzes biopsied prostate tissue and identifies areas likely to contain cancer cells, which a human pathologist evaluates and confirms.

"When you're talking about precision medicine, it's about sub-segmenting the population into strata and trying to find the solutions that work for those specific segments of populations," says Nimita Limaye, research vice president with IDC Health Insights.[6]

AI can be used to diagnose diseases, develop personalized treatment plans and assist clinicians with decision-making. Rather than simply automating tasks, AI is about developing technologies that can enhance patient care across healthcare settings. However, challenges related to data privacy, bias and the need for human expertise must be addressed for the responsible and effective implementation of AI in healthcare.

Precision Care for Chronic Disease

As chronic conditions such as diabetes, hypertension and obesity continue to rise globally, there is increasing recognition for the need to pursue personalized care plans. Since chronic diseases often require ongoing, complex management strategies that vary from patient to patient, personalized care approaches, including tailored dietary recommendations, medication regimens and lifestyle changes, have been shown to significantly improve patient outcomes.

One example is in the treatment of type 2 diabetes. Genetic research has identified several gene variants that influence the risk of developing this disease along with a patient's response to specific drugs, such as metformin, a common treatment for managing blood glucose levels. According to a study in *Diabetes Care*, a variant of the SLC2A2 gene affects how efficiently the body absorbs glucose from the blood. Understanding this variation helps doctors select the most effective drug and dosage for individuals with specific genetic profiles.[7]

Cardiovascular disease, including conditions such as hypertension, coronary artery disease and heart failure, is another area where precision medicine is making an impact. One-size-fits-all treatment approaches may not always provide the best outcomes due to variations in how patients respond to medications such as statins or anticoagulants. Through genetic testing, precision medicine can identify patients with specific genetic variants that may influence their risk of adverse effects from statins (used to lower cholesterol) or help determine which patients will benefit most from anticoagulant therapies to prevent strokes or heart attacks. A well-known example is the CYP2C19 gene, which affects how patients metabolize clopidogrel, a blood thinner used to prevent blood clots in people with heart disease. Individuals with certain variants of this gene are

less likely to benefit from clopidogrel, and precision medicine can help guide alternative treatment strategies.[8]

Asthma, a chronic respiratory condition characterized by airway inflammation and breathing difficulties, affects individuals differently, with some experiencing mild symptoms and others dealing with severe, life-threatening episodes. Precision medicine has revealed that asthma is not a single disease but a collection of subtypes, each with different underlying mechanisms. One of the key breakthroughs in asthma management has been the identification of specific biomarkers that allow for targeted therapies. For example, patients with high levels of a specific inflammatory marker, known as eosinophils, may benefit from biologic therapies, such as monoclonal antibodies targeting interleukin-5 (IL-5), which reduces the number of eosinophils and helps control severe asthma symptoms. Treatments such as mepolizumab and benralizumab are more effective for patients with eosinophilic asthma than traditional inhaled corticosteroids, which are often the default treatment plan.[9]

Implications for Healthcare Providers and Systems

The growing demand for personalized care presents both opportunities and challenges for healthcare providers and systems. On the positive side, personalized care has the potential to improve patient outcomes, reduce hospital readmissions and enhance the overall patient experience. Patients receiving care tailored to their unique characteristics are more likely to adhere to treatment plans, leading to better health outcomes and cost savings in the long run.

A report from Harvard Business Review Analytic Services, an independent commercial research unit within *Harvard Business Review*, analyzed how expanding precision medicine offers healthcare providers new opportunities to provide high-value care and concluded that the expansion of precision medicine could have a major impact on outcomes and costs.[10]

"While precision medicine can be seen by some people as genomics-guided treatment, I think this definition is too limiting," says Larry Chu, MD, MS, a Stanford professor who advised President Barack Obama on the 2015 Precision Medicine Initiative. "I think precision medicine means precisely diagnosing conditions, then integrating all relevant patient data and insights to guide care to the best outcomes. It is about providing the right treatment to the right patient at the right time."[10]

The report argued that the practice of precision medicine will grow, thanks to the promise of benefits to healthcare organizations, providers and patients in the form of better outcomes and reduced costs. Research suggests that eliminating unwarranted variations in medical care can reduce the cost of patient management by at least 35 percent.[10]

However, the implementation of personalized care requires significant investments in technology, data management and clinician training. Healthcare providers must be able to access and analyze large amounts of patient data, including genetic information, to deliver personalized treatments. This requires advanced infrastructure and robust data-sharing mechanisms to ensure patient information is securely stored and shared across different healthcare providers.

In addition, personalized care raises ethical concerns related to data privacy and equity in access. As healthcare becomes more tailored to individual needs, it is crucial to ensure all patients, regardless of socioeconomic status, have access to these advanced care models. Addressing these concerns will be essential for ensuring the equitable and effective delivery of personalized care.

The Road Ahead

Advances in genomics, patient expectations, technological innovation and the need for more effective chronic disease management all factor into the rising demand for personalized medicine. As healthcare systems continue to evolve, personalized care promises a more patient-centered experience. However, realizing the full potential of this trend will require a commitment to clinician training, investments in systems and technology integration and big-picture thinking when it comes to ensuring equitable access for all patient populations. ❖

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Hospital at Home: *The Future of Care?*

With its lower costs and patient preference, HaH is poised to alleviate some of the problems hospitals face, but there are obstacles to overcome before it becomes a mainstay program.

By Rachel Maier, MS

HOUSE CALLS were the norm not 100 years ago. When someone got sick, doctors provided dependable, personalized care in the comfort of patients' own homes, and it cultivated a system of two-way trust. Patients knew their doctors, and doctors knew their patients. It wasn't about meeting quotas or hedging lawsuits. Doctors treated their patients as people first, sick people second.

Times changed, and a confluence of factors shifted medical visits away from patients' homes and toward centralized clinics and hospitals: Technology. Transportation. Education. Efficiency. And of course, healthcare reform. The Hill-Burton Act (also known as the Hospital Survey and Construction Act) of 1946 gave grants and loans to healthcare facilities for construction and modernization; Title XVIII and Title XIX of the Social Security Act established Medicare and Medicaid in 1965, which standardized care and gave birth to the fee-for-service model healthcare still uses today.[1] The result? Acute care hospitals became the new normal, offering patients a place to seek urgent medical care.

But the elephant in the room remains: Patients don't really like going to the hospital, let alone staying there for an indeterminate amount of time. The food. The beds. The bureaucracy. Patients spend a lot of time waiting to see the doctor or get updates about the treatment plan, and often experience uncoordinated, fragmented care that makes them feel lost in the shuffle. And, hospital stays are riddled with risk, from misdiagnoses and medical mix-ups to hospital-acquired infections and depression. Hospital stays are stressful, and the hospital is not always the ideal place for healing to happen. Hospital at home (HaH) is a recent twist on a traditional practice that's gaining steam as a viable alternative to brick-and-mortar inpatient settings, but the future of HaH remains uncertain.

A New Spin on an Old Practice

Even as hospitals became the norm, some experts still saw the value and potential of providing acute-level care to patients in the comfort of their own home and developed their idea into the precursor of today's HaH model. The brainchild of John Burton, MD, of the Johns Hopkins School of Medicine and Donna Regenstreif, PhD, of the John A. Hartford Foundation, the HaH model was designed to provide safe, effective care to aging patients with common conditions that didn't really need the intensive care hospitals provided. The idea was to equip patients to receive treatment from a physician who would oversee their care while they recovered at home. It wasn't about turning patients away; it was about setting them up for success in the comfort of their own home. Bruce Leff, MD, developed eligibility criteria for patients and a clinical model for the program, and then designed a national study to investigate whether the idea could work.[2] A 17-patient pilot trial was conducted between 1996 and 1998 that showed the program was feasible, safe and cost-effective.[3]

Then, between 2000 and 2002, a National Demonstration and Evaluation Study was conducted in three Medicare managed care organizations and one Veterans Affair medical center. The study showed that compared to traditional inpatient hospital care, the HaH model had better clinical outcomes; a shorter average length of stay; higher patient and family satisfaction; fewer lab and diagnostic tests; fewer complications such as delirium, infections, need for sedatives or physical restraints; and lower care costs by up to 30 percent.[2] However, the hospitals received limited reimbursement, and the HaH model did not gain much steam.[4]

Then, COVID-19 hit in 2020. The public health emergency (PHE) overwhelmed the healthcare system with sick patients and caused a shortage of hospital beds. Treating sick patients at home became a solution to an acute problem. Many healthcare facilities were equipped with the technology to leverage telehealth and remote patient monitoring to manage patient care from a distance. The Centers for Medicare and Medicaid Services (CMS) quickly launched the Acute Hospital Care at Home program in November 2020; under its provisions, certain Medicare-certified hospitals were allowed to provide acute-level care to patients at home rather than in the hospital, providing 1) they had the equipment and infrastructure to do so and 2) patients were stable enough and willing to receive care at home. To participate in HaH, hospitals must submit a waiver request to CMS; the request specifically asks CMS to waive §422.23(b) and (b)(1) of the Medicare Conditions of Participation, which require 24/7, immediate availability of registered nursing services on the hospital premises to patients.[5]

The program was a success. In fact, once the PHE ended, the HaH initiative continued under the Consolidated Appropriations Act of 2023, which extended the waiver until Dec. 31, 2024.[6] As of this writing, 331 hospitals provide HaH services, including flagship Johns Hopkins and three other highly influential hospitals in the United States: Mass General Brigham, Mayo Clinic and Mount Sinai Health System.[7]

But the waiver is set to expire — and soon. In fact, congressional action is needed and indeed is in progress as of this writing. Introduced in the House by Representatives Brad Wenstrup, R-Ohio, and Earl Blumenaur, D-Ore., and in the Senate by Senators Tom Carper, D-Del., and Tim Scott, R-S.C., the Hospital Inpatient Services Modernization Act seeks to extend the waiver for five more years, through the end of 2029. The American Hospital Association (AHA) supports extending the HaH program, describing it as "a safe and innovative way to care for patients in the comfort of their homes. This kind of care is well suited for medium acuity patients who need hospital-level care but are considered stable enough to be safely monitored from home."[8]

Even as hospitals became the norm, some experts still saw the value and potential of providing acute-level care to patients in the comfort of their own home and developed their idea into the precursor of today's HaH model.

How HaH Works

Each participating healthcare system may have their own process and procedure, but Johns Hopkins Medicine published the following steps a typical HaH program will follow:[9,10]

1) *Assessment*. A patient who would typically be admitted to the hospital who is diagnosed with one of the valid HaH conditions is identified in the emergency department or ambulatory site. Staff

assess if the patient is a good candidate for the program using validated criteria. Those best suited to HaH services include patients with community-acquired pneumonia, congestive heart failure, chronic obstructive pulmonary disease (emphysema), cellulitis, volume depletions/dehydration, urinary tract infection/urosepsis, deep venous thrombosis or pulmonary embolism, among others. Patients with these conditions who are otherwise stable can be treated outside of the hospital.

2) *Admission*. If a patient fits eligibility criteria and is willing to participate, the HaH team meets with the patient and caregiver to discuss the HaH program and assess the suitability of the patient's home for HaH. For example, the patient must have electricity and running water. If the home is suitable, the patient is admitted to and treated by HaH until he or she is stable enough for discharge.

3) *Equipment*. A care team member brings medical equipment and communication devices to the patient's home, sets them up and teaches the patient and his or her caregivers how to use the devices. The patient's diagnosis, prognosis and treatment plans are also discussed.

4) *Monitoring*. The patient's vital signs are monitored electronically by the care team via remote patient monitoring; the patient is evaluated daily by the HaH physician who completes an assessment and continues to implement appropriate diagnostic and therapeutic measures. The physician makes one or more home visits per day and is available 24 hours a day/7 days a week for any urgent or emergent situation. The patient also receives daily nursing visits according to the patient's clinical need. Nurses are available 24 hours a day/7 days a week for any urgent or emergent situation.

5) *Diagnostic studies and treatments*. The patient can receive diagnostic studies such as electrocardiograms, echocardiograms and X-rays at home, as well as treatments, including oxygen therapy, intravenous fluids, intravenous antibiotics and other medicines, respiratory therapy, pharmacy services and skilled nursing services. Diagnostic studies and therapeutics that cannot be provided at home (such as computerized tomography, magnetic resonance imaging or endoscopy) are available via brief visits to the acute hospital.

6) *Evaluation*. The clinicians use care pathways, including illness-specific care maps, clinical outcome evaluations and specific discharge criteria.

7) *Discharge*. When the patient is discharged by the HaH physician, care reverts to the patient's primary care physician.

Praise for HaH

Johns Hopkins says its HaH program costs less than brick-and-mortar hospital stays, and the length of stays are shorter. It also reports that cases of delirium were "dramatically lower" in HaH patients.[11]

A 2019 study found that care for HaH patients cost 38 percent less than those receiving in-hospital care. HaH patients had fewer laboratory or imaging studies and fewer specialty consultations. They spent more time up and around and less time sedentary or lying down. HaH patients had better outcomes and fewer readmissions than those who received in-hospital care.[12]

But perhaps the best indication that HaH is a net gain for the healthcare industry is this: Patients like it. According to a survey conducted by Vivalink in June 2024, 84 percent of respondents reported they would participate in a HaH program if it meant they could go home sooner. Seventy seven percent said if their doctor recommended HaH monitoring, they would trust that opinion. Of those who have experienced HaH, 84 percent reported a positive experience.[4] Most patients reported the ease and comfort of receiving medical care at home were important. "It's clear that patients value receiving care in familiar environments, as survey results show strong support for HaH programs," said Jiang Li, PhD, and CEO of Vivalink. "Policymakers should recognize the value of at-home care and seek to ensure its continuation, meeting the clear demands and needs of patients."[13]

Pushback

And yet, not everyone in the industry is so sure HaH programs are a smart move.

Some nurses are pushing back, saying it comes down to patient safety. Patients who qualify for HaH programs are too sick to be left alone, they say, and waiving the requirement of on-site, 24/7 access to nursing care puts acutely ill patients in jeopardy. "Acute care means that your condition is likely to change and you are likely to experience, or at high risk to experience, complications. So even if you're feeling well, that could change quickly," said Michelle Mahon, RN, assistant director of nursing practice for National Nurses United.[11] For nurses like Mahon, 24/7 remote monitoring isn't good enough.

Critics cite other concerns, too, including, but not limited to:[11,14]

- Fears of hedge funds and private equity firms investing in the program without regulations
- Differing state rules regarding paramedics' ability to provide acute hospital care in homes
- Difficulty recruiting nurses who are willing to go into patients' homes in urban areas
- Physician reluctance to refer patients due to uncertainty of care quality and fear of malpractice
- Complexity of integrating medical equipment with electronic health records

• Lack of streamlined standards, logistics and regulation

A New Way Forward?

There are still plenty of kinks to work out when it comes to creating a viable HaH program that works for patients and providers alike. Providing acute care outside a brick-and-mortar hospital setting carries some inherent risk, and building a successful HaH system involves investment in infrastructure and personnel. But proponents of HaH say the risk is small and the investment is worth it because hospitals are often at-capacity and short-staffed, and are treating conditions that don't require intensive inpatient care, not to mention that many patients would rather be at home. "In most cases, if you do a good evaluation of appropriateness, the home is a safer place for most patients, so they also tell us that's where they want to be," explained Colleen Hole, BSN, MHA, FACHE, and vice president of clinical integration and population health at Atrium Health. With the way technology is advancing, better connectivity and increasing convenience may very well continue to make HaH a viable option for hospitals to ease the burden of balancing capacity with patient care. ❖

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Managing Care from Afar:
The Challenges and Solutions of Long-Distance Health Management

Overseeing a loved one's healthcare is stressful, especially when at a distance. These innovative strategies can help.

By Lee Warren

MANAGING care from a distance has become an increasingly common challenge for families in the United States. As of the 2020 United States Census, 55.8 million people are age 65 or older — that's 16.8 percent of the population — and many of them are choosing to "age in place," or grow old in their own home rather than in an assisted living community.[1] And as people age, they increasingly need help managing their care from family. However, as many as 11 percent of caregivers live more than two hours away from their loved ones and conduct caregiving tasks from far away,[2] spending $7,242 annually (about a quarter of their annual income) on out-of-pocket costs on caregiving expenses,[3] as well as enduring emotional strain from juggling responsibilities remotely. Even so, long-distance caregivers are finding ways to manage their loved ones' care, and they have more tools and options than ever before.

Unique Challenges of Geographical Separation

Long-distance caregivers face all the same challenges as local caregivers, including balancing caregiving responsibilities with work, family and personal life; bearing financial costs associated with caregiving; navigating the healthcare system; managing conflicts or unequal distribution of caregiving duties among family members; handling legal documents; ensuring a care recipient's home is safe and accessible; finding respite care or support; discussing and planning end-of-life wishes and decisions; and figuring out how to handle grief and other emotions associated with caregiving.

But long-distance caregivers also face a unique set of challenges above and beyond those faced by local caregivers — challenges that stem from geographical separation from the care recipient. These include difficulty assessing the person's condition accurately, coordinating care with local providers and managing emergencies remotely. Long-distance caregivers often struggle with feelings of guilt and inadequacy due to their absence, while also dealing with the financial and time burdens of travel. Reliance on technology for communication and monitoring is crucial, yet it can be challenging when not proficient.

Long-distance caregivers must navigate unfamiliar healthcare systems from afar, manage finances and legal documents remotely and find ways to maintain emotional connections despite the distance. They also face hurdles in arranging in-home services, participating in medical decisions and balancing their caregiving duties with local responsibilities. The stress of not being immediately available, coupled with the difficulty of providing hands-on care, can lead to burnout, especially without readily accessible local support systems.

A Case Study

Tom Bryant, a 58-year-old man who lives in Omaha, Neb., is currently a long-distance caregiver for his parents who live in Kingman, Ariz. (1,400 miles away) — both of whom have varying stages of dementia. He describes his father, who has been battling the disease for 10 years, as being in the late stages of dementia. His mother, who is more functional, has "holes" in her memory, often filling in the gaps with information that isn't true as her mind races to make sense of her life.

Working with local healthcare providers and case managers who can be the eyes and ears for distant family members helps ensure continuous care.

Both parents are now living in the memory care wing of an assisted living facility, but they still need someone to make caregiving decisions for them. Bryant makes several trips per year to Arizona to care for his parents. In 2021, he spent the summer there taking care of his parents' affairs and getting to know their bankers and healthcare facility workers. His sister, Teresa, who lives on the east coast, has also been able to travel to Arizona to care for their parents whenever they needed special attention and Bryant wasn't available.

"We're caring for them long distance as best we can with phone calls," Bryant said. "We're very intimately involved long distance with the staff. I'm on a first-name basis with the directors of all these places. When I call, I can tell the person who answers my name and ask for a staff member by name. And that's been helpful."

Bryant often coordinates care over the phone. When his father developed a tendency to turn violent when a facility staff member "ruffles his feathers," the assisted living facility evicted him after one such incident, which meant Bryant was on the phone right away, trying to get his father into an Alzheimer's facility that could handle him.

But some incidents require in-person attention: Before his mother was moved to the memory care wing, she wandered outside one night barefoot in the winter, believing she was looking for a swimming pool that didn't exist. She ended up losing eight toes due to frostbite. Bryant traveled to Arizona to care for her.

One tool that helps Bryant stay connected from afar is an electronic device called a GrandPad — a simplified tablet for seniors that has phone capabilities. Bryant calls his mother every Tuesday and Friday on it. "I talk her down from the ledge on a pretty regular basis," Bryant said. "I have a tendency to be able to cool her out a little bit — measurably, not completely."

Bryant and his sister work well as a team, but not all long-distance caregivers have the support of a sibling, and they can't always travel as often as Bryant and his sister can. But there are some practical things long-distance caregivers can do to get organized, stay connected and manage care from afar.

Staying Connected

The National Institute on Aging offers the following ideas for caregivers to stay connected and handle the affairs of care recipients from a distance:[4]

- Create a list of important phone numbers and email addresses. Keep it in a shared document or spreadsheet online and update it regularly.
- Set up a shared calendar online or in a smartphone app to coordinate with other caregivers.
- With permission, attend the care recipient's telehealth visits.
- Participate remotely in conference calls or video meetings with healthcare staff.
- Help the care recipient learn about texting or video call features on his or her smart phone.
- If the care recipient is comfortable using a computer or tablet, set up an email account for him or her.

Innovative Assistive Technologies

Long-distance caregivers can also take advantage of many other technological tools to help them stay updated and informed about the care recipient's day-to-day activities. Some devices even allow caregivers to control care recipient's home environments from afar:

- Wearable monitors and apps for medication and glucose tracking are great for long-distance monitoring.
- For patients with Alzheimer's disease or dementia, GPS tracking insoles can be placed inside their shoes and monitored from a distance.
- Smart watches can be set up to send real-time alerts in case of a fall. They can also monitor heart rates and changes in weight, track sleeping patterns and more.
- Smart stove sensors such as Ome Kitchen can be installed in the care recipient's home for caregivers to monitor a stove remotely, with the ability to turn it off from afar.
- Smart door locks can be installed on standard doors. These require a pin code to unlock and can be shared with family members and caregivers.
- Smart cameras can be useful to monitor falls or other emergencies and allow caregivers to have instant access to their care patient.
- Smart assistants (such as Alexa or Google Home) can be used to set up reminders to take medications or for upcoming healthcare appointments.
- Smart pill dispensers such as Hero Health offer an automated, one-button press to sort and dispense doses and is linked with an app that helps manage and track medications and adherence.
- Rx text alerts can be set up to send automated refill or prescription pick-up notifications to a caregiver's phone; some pharmacies even offer free delivery.
- Websites such as Lotsa Helping Hands, Meal Train and Care Calendar can help caregivers coordinate meals and more for the care patient.
- Health update blogs can be set up to keep family and friends in the loop. One example is CaringBridge, which sends email notifications to friends and family so they can stay updated, allowing the caregiver to provide the information just one time rather than sending out the same information via text or email over and over.

To Learn More About Innovative Assistive Technologies, visit:

Ome Kitchen Smart Knob:
www.omekitchen.com

Hero Health Smart Pill Dispenser:
www.herohealth.com

Lotsa Helping Hands:
www.lotsahelpinghands.com

Meal Train:
www.mealtrain.com

Care Calendar:
www.carecalendar.org

CaringBridge:
www.caringbridge.org

Coordinated Care Networks

Volunteer and low-cost organizations and agencies also avail themselves to caregivers to help with transportation to medical appointments, meal delivery and social visits. The National Association of Area Agencies on Aging provides a list of these types of organizations. The Family Caregiver Alliance also has listings of state-by-state resources where caregivers can get information specific to where their loved one resides.

Working with local healthcare providers and case managers who can be the eyes and ears for distant family members helps ensure continuous care. This team-based approach can alleviate some burdens.

Use of Professional Care Managers

For caregivers who are dealing with difficult or extreme circumstances, hiring a professional care manager (also known as geriatric care managers or aging life care professionals) can help families coordinate care; make informed decisions; identify social services and programs; make referrals to financial, legal or medical professionals; create short- and long-term care plans; act as a liaison to family members; arrange respite care; and more to help caregivers stay updated on their loved one's condition without being physically present.

Caregivers can find directories for professional care managers through websites such as AgingCare, AgingLifeCare Association, Caring and others (Table).

Table. Free and Low-Cost Caregiving Resources

Agencies and Programs	Website
AARP	www.aarp.org www.aarp.org/caregiving/prepare-to-care-planning-guide www.aarp.org/legal-counsel-for-elderly/what-we-do/info-2017/pro-bono-project.html
AgingCare	www.agingcare.com www.agingcare.com/local/geriatric-care-managers
Aging Life Care Association	www.aginglifecare.org www.aginglifecare.org/ALCAWEB/Shared_Content/ALCA_Directory/ALCA_Find_an_Expert.aspx
American Bar Association	www.americanbar.org/groups/legal_services/flh-home/flh-free-legal-help
Caring	www.caring.com www.caring.com/senior-care/geriatric-care-managers
Family Caregiver Alliance	www.caregiver.org
Legal Services Corp.	www.lsc.gov www.lsc.gov/about-lsc/what-legal-aid/i-need-legal-help
National Association of Area Agencies on Aging	www.healthinaging.org www.healthinaging.org/tools-and-tips
National Disability Rights Network	www.ndrn.org www.ndrn.org/about/ndrn-member-agencies
U.S. Department of Veteran Affairs	www.caregiver.va.gov www.caregiver.va.gov/support/Legal_Financial_Planning.asp

The AgingCare website recommends that professional care managers be certified by the National Association of Social Workers, the Commission for Case Manager Certification or the National Academy of Certified Care Managers and be a member of the Aging Life Care Association. And, its website offers a list of interview questions a caregiver might want to ask potential candidates.

Legal Considerations

Like other caregivers, those who are doing so long distance need to consider securing power of attorney or guardianship, advanced directives and estate management documents. This can feel overwhelming from afar, but many free or low-cost resources are available, including from the AARP (that offers family caregiving guides for free, as well as some pro bono services), American Bar Association (which offers pro bono programs for low-income clients), U.S. Department of Veterans Affairs, Legal Services Corporation (a nonprofit organization that provides free legal services to low-income Americans), National Disability Rights Network (which provides legally based advocacy services to people with disabilities) and more.

Innovation Eases the Burden

As our population ages and families become more geographically dispersed, the need for effective long-distance caregiving strategies will only grow. By leveraging technology, professional services and community resources, caregivers can bridge the physical gap and provide meaningful support to their loved ones. The future of long-distance caregiving lies in the continued development of user-friendly technologies, the expansion of telehealth services and the strengthening of support networks.

Healthcare professionals will need to recognize the evolving landscape of caregiving and work to support both care recipients and their distant caregivers. By doing so, distance will not compromise the quality of care and connection that every individual deserves. Continuous education, open communication and a willingness to adapt will be the key to navigate the complex landscape of long-distance caregiving in the years to come. ❖

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The Expanding Role of Immune Globulin Treatment in Diseases: Utilization and Growth

New research showing the therapeutic benefit of immune globulin for treating a variety of autoimmune diseases is contributing to market growth of this essential medicine.

By Diane L.M. Cook

SALES OF immune globulin (IG) are up. According to the Marketing Research Bureau (MRB), manufacturer-level sales of intravenous IG (IVIG) in grams grew more than 10 percent in 2023 compared to 2022.[1] Matthew Hotchko, president of MRB, explained that the various disruptions related to the COVID-19 pandemic caused IG demand to drop in 2021 and recover in 2022 and 2023. "The particularly high 10 percent-plus growth rate in IG demand that we saw in 2023 may partly reflect a catch-up effect, as undiagnosed patients whose access to specialist care was delayed by the pandemic finally received their diagnoses and prescriptions for IG therapy," he says.

Hogan Lovells, a global law firm specializing in commercial, regulatory and legal issues, conducted a roundtable discussion focused on access to and use of

IG therapies and published its conclusions in the Hogan Lovells Roundtable Report in May 2022. The report found that each year in the United States, approximately 275,000 patients are treated with IVIG and subcutaneous IG (SCIG) therapies for a variety of conditions. "In 2020, roughly 110 million grams of IG were used to treat patients," according to the report. "These patients have conditions in more than eight medical specialties and receive treatment for hundreds of indications."[2] Categories of conditions treated with IG therapy include primary immune deficiency (PI) — 30 percent or about 400 conditions; secondary immune deficiency (SID) — 17.5 percent or about 200 conditions; neurology — 40 percent or about 50 conditions; and all others — 12.5 percent or about 300 conditions.[2]

IG therapy is a medicine made from human blood plasma. The plasma is processed from donated human blood and contains antibodies that protect the body against diseases. Recently, the role of IG has expanded both in its utilization and growth, meaning more patients can benefit from IG therapy, which is often the only treatment for many rare, life-threatening chronic diseases and genetic conditions. IG therapy increases the chances of regular access to plasma medicines, which contributes to the improvement of health outcomes for patients.

Indications

According to Terry Harville, MD, PhD, a professor of pathology and laboratory services and internal medicine at the University of Arkansas for Medical Sciences, IG therapy can be used as either 1) replacement therapy for people who are deficient in immunoglobulin (antibodies) or 2) immune modulation. "The initial intended use of IG therapy was for patients with antibody deficiencies to replace [the antibodies] they were missing," he explained. "The earliest documented use was in patients with X-linked agammaglobulinemia, a [PI] affecting males who are unable to produce B lymphocytes and are thereby unable to make antibodies. Yet, this is considered a rare disorder, perhaps one in one million live births. More commonly, IG replacement is used for patients diagnosed with CVID [common variable immune deficiency], of which some registries may have as many as one in 3,000 people, although most textbooks suggest one in 10,000 to 50,000 people.

IG therapy increases the chances of regular access to plasma medicines, which contributes to the improvement of health outcomes for patients.

"As with many new medications, for example, when cortisol became available, it was tried in many conditions which did not have better treatment options. One of the earliest was Kawasaki disease, where a total dose of two grams per kilogram of body weight infused over two to five days demonstrated benefit. From there, similar dosing has been used to treat thrombocytopenia and other hematologic cytopenias. Subsequently, it was tried for Guillain-Barré syndrome, where it was found to be as efficacious as undergoing plasmapheresis. Subsequently still, a variety of neurologic disorders, which for the most part can be considered some form of autoimmune encephalopathy, have had beneficial results. Related conditions such as PANDAS/PANS have benefit. We recently reported the use in patients with catatonia, which may be one of the rarest usages."

Utilization

The Hogan Lovells Roundtable Report showed that approximately 65 percent of IG use in the United States is on-label use, meaning it is prescribed to treat conditions for which the U.S. Food and Drug Administration (FDA) has granted approval. The other 35 percent is prescribed for off-label use to treat conditions for which it is medically acceptable according to existing treatment guidelines and evidence-based, real-world use.[2]

A study that described U.S. IG utilization patterns from 2009 to 2019 showed growth in both commercial and Medicare populations. Respectively, IG administrations per 100,000 person-years increased by 120 percent and 144 percent; IG recipients per 100,000 enrollees grew by 71 percent and 102 percent; average annual administrations per recipient rose by 28 percent and 19 percent; and average annual dose (grams) per recipient increased by 29 percent and 34 percent.[3] The study also showed that IG administrations associated with immune deficiency per 100,000 person-years increased by 154 percent and 176 percent. Autoimmune and neurologic conditions were associated with higher annual average administrations and doses than other conditions.[3]

In contrast to the Hogan Lovells Roundtable Report, there is a consistent increase of non-specific IG use in Québec, Canada, according to Héma-Québec, a nonprofit organization that supplies blood and other human

biological products to local hospitals. Québec's Ministry of Health's data for the use of IG reports that more than two million grams were administered at an average of 349.6 grams per user, or 232.4 grams per 1,000 people. The rate of Quebecers who have received IG is 67 recipients per 100,000 people. Nearly half of the IG used was administered for a neurological indication; nearly a third was administered for an immunological indication; and just under 10 percent was administered for hematological indications. PI was the medical condition for which IG was administered to the largest number of users (20.1 percent); chronic inflammatory demyelinating polyneuropathy (CIDP) was the medical condition for which the highest amount of IG was administered (21.6 percent or an average of 671.1 grams per patient); and in nearly 20 percent of users, IG was either administered for an unclear indication at 14.3 percent or absent at 4.7 percent. In total, this represents 15 percent of the quantities of IG.[4]

Keith Berman, MPH, MBA, founder of Health Research Associates and plasma industry consultant, says there are currently 12 unique licensed IVIG products, three of which are approved for SC administration. Three of the 12 IVIG products are available in both 5 percent and 10 percent IgG concentrations. There are also five unique licensed SCIG products, including HYQVIA, which is co-administered with a special agent that facilitates SC delivery of substantially increased doses of IG into the infusion site, thereby reducing infusion frequency.

Over the last year, two new 10 percent IVIG products have received FDA marketing approval — Yimmugo and ALYGLO. Manufactured by Grifols' Biotest subsidiary, Yimmugo is expected to be available through Kedrion Biopharma in the first quarter of 2025. The Korean plasma products manufacturer GC Biopharma initiated its first shipments of ALYGLO in July 2024.

"Like other licensed IG preparations, these new IVIG products will likely be used as well for a wide range of off-label uses, including treatment of SIDs, as well as numerous immune-mediated hematological, neurological, neuromuscular, rheumatologic and other disorders," says Berman.

Berman also notes that government health authorities in other countries — notably Australia and the United Kingdom — have published guidance for the clinical use of IG products based on the robustness of the evidence for effectiveness and safety. "The Australian national guidance indicates that IG has an established therapeutic role for the treatment of immune thrombocytopenic purpura in adults. In the example of bullous pemphigoid, IG has an emerging therapeutic role, indicating that there's already some available evidence of benefit. But for other disorders, such as relapsing-remitting multiple sclerosis (RRMS), the guidance says IG use should be reserved for exceptional circumstances only," said Berman.

The types of disease states that are seeing the most growth in IG treatment use include neurological disorders.

Growth

Dr. Harville says the growth of IG treatment for different disease states can be attributed to solving the challenge of not suppressing the immune system: "An ideal IG therapy would provide only benefit and create no harm. With autoimmune disorders, the typical approach is to suppress the immune system. Therefore, the patient becomes susceptible to infections and can even be at risk for developing malignancies. Immune modulation via infusion of IG does not suppress immunity, taking away these risks. Furthermore, providing a large antibody experience from the donors can enhance the immune protection of the patient. Therefore, we can achieve benefit with low risk for harm to the patient."

Dr. Harville also says the types of disease states that are seeing the most growth in IG treatment use include neurological disorders: "Initially used for demyelinating conditions with benefit, IG is now used for other autoimmune encephalopathies. As we obtain more information and gain a better understanding, we have found a large variety of autoimmune antibodies in the central nervous system. Therefore, modulation of these autoimmune antibodies can and do provide benefit to patients with neurological disorders."

The most growth seen in IG treatment, he says, is in the subcutaneous infusion of replacement IG because it can reduce infusion-related side effects: "High-dose IG treatment is impractical subcutaneously because too much volume needs to be infused. Although, for some neurologic conditions such as CIDP, lower dosing and subcutaneous infusions

work. Similarly, treatment of pemphigus may need doses less than used for IG replacement and may be amenable for SCIG infusion. Anti-phospholipid disease may also require lower dosing amenable for SCIG infusion.

"Continued studies are needed to determine which disorders require the high pulse serum level of IG for efficacy, which could only be provided by intravenous infusion, versus those whereby other mechanisms of IG are helpful, such as the presence of anti-cytokine antibodies or anti-idiotypic antibodies, which are modulating immune function. In the latter, perhaps the slower introduction of IG via SC infusion may actually be of more benefit. Which poses the question: Is this why SCIG works well for CIDP treatment?"

Berman added that, both in the United States and abroad, growth in utilization of IG continues to be driven by the publication of new research documenting its therapeutic benefit in an ever-widening range of autoimmune, and in the case of transplantation alloimmune, disease states, as well as by growing numbers of patients diagnosed with secondary humoral immunodeficiency resulting from the growing use of B cell-depleting drugs that induce hypogammaglobulinemia (low IgG level).

"Over the last five years, the average annual growth rate in IG demand has exceeded seven percent, continuing nearly uninterrupted year-over-year growth that extends all the way back to the mid-1980s," Berman explained. "The explanation for this remarkable growth begins with the fact that IG is the purified concentrate of many thousands of immunoregulatory and anti-infectious IgG antibodies, which makes it a vastly different kind of product than any drug or single-molecule biotherapeutic agent."

Challenges to Utilization and Growth

According to Dr. Harville, broad use of IG therapy still has not been achieved because it has only a small number of FDA-approved indications, and IG therapy is expensive.

"When an autoimmune process is present, which could have theoretic benefit from IG infusion, it would be nice for third-party payers to allow a test usage. However, this raises a conflict if an infant with XLA may need five grams of IVIG a month whereas an adult with a neurological disease may need 200 grams of IVIG infusion several times," Dr. Harville explained. "Therefore, one adult treatment could use an amount of IG which could treat 16 infants with XLA for a year. While all patients deserve the best treatment available, the high amounts used in adults with neurological diseases could result in less availability for ongoing treatment of patients with PI, especially if a manufacturing shortage was to occur."

Advances Contributing to the Growing Need of IG Treatment

Representing more than 1,000 human plasma collection centers in North America and Europe, as well as the manufacturers of plasma protein therapies, the Plasma Protein Therapeutics Association (PPTA) says its members produce approximately 80 percent of the plasma protein therapies in the United States and 60 percent of those manufactured in Europe.

The PPTA's "Statement on Immunoglobulin Use to Meet Clinical Need" reports several advances are contributing to the growing clinical need of IG therapy: "Advances in the diagnosis, treatment and identification of many diseases has led to an increase in the number of patients treated with IG and other plasma-derived medicinal products (PDMP) in the past several years, particularly in Europe. These diseases include immune deficiencies, immune-mediated peripheral neuropathies, hereditary angioedema, alpha 1-antitrypsin deficiency, hemophilia and other bleeding disorders. In many cases, PDMPs are the only treatment option for these rare and serious diseases. Without these treatments, many patients might not survive or would have a substantially diminished quality of life.

"Improved diagnostic techniques, better awareness among physicians and greater use in emerging markets are further contributing to the growing clinical need for PDMPs. IGs have been proven to prevent or delay the development of comorbidities, positively affect a range of physician- and patient-reported outcomes, including improved quality of life, and are even cost-saving for certain conditions.

"Focused on addressing the growing clinical need for PDMPs, the growth in plasma collection over the past 10 years has mainly come from the private sector and its efficient plasmapheresis programs."[5] ❖

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Diagnosing and Treating Lyme Disease

While rare, Lyme disease can be debilitating and cause long-term damage due in part to delayed and missed diagnoses. However, there is hope of a vaccine in the future.

By Jim Trageser

LYME DISEASE HAS been with us for centuries, if not longer. While today it is the most prevalent vector-borne disease in the United States (with 25,000 to 30,000 cases reported per year[1]), it was only identified as a specific infection in 1975. That year, doctors noticed a surge in reported cases of juvenile rheumatoid arthritis near the town of Lyme, Conn. Many of the patients also exhibited a distinctive rash that looked like a bulls-eye target, along with swollen lymph nodes, extreme fatigue and headaches. But it wasn't until 1981 that researchers discovered the bacteria Borrelia burgdorferi living in the gut of deer ticks (Ixodes scapularis) and were able to tie that to the Lyme disease outbreak in Connecticut six years earlier.

In the half-century since Lyme disease was first identified, researchers have gained tremendous knowledge of its progression and its long-term effects on patients. They've identified additional tick species that can serve as vectors, and they've expanded the known species of Borrelia bacteria that can cause Lyme disease.

After geneticists at Yale outlined the full genome of the bacteria that causes Lyme disease in 2017, they were able to infer that it has existed in North America for more than 60,000 years.[2] An earlier study at the University of Bath found that the bacteria likely dates back to the most recent Ice Age in Europe.[3] With this knowledge, other medical researchers found references to the symptoms of Lyme disease going back to the earliest European immigrants to North America. European researchers have found descriptions of those same symptoms on the continent as far back as the late 19th century.

Fortunately, the development of effective antibiotics has allowed physicians to treat Lyme disease, although long-term symptoms are not yet fully understood, nor do they always respond to treatment. And while the only approved vaccine was withdrawn from market due to disappointing sales over two decades ago, research on new vaccines continues.

What Is Lyme Disease?

Lyme disease is an infectious disease that can cause debilitating pain and result in significant tissue damage, but is rarely fatal. It can be caused by any one of 18 different species of Borrelia bacteria.[4] The species found in Europe are distinct from those found in North

America. In the eastern United States, the main vector is the deer tick, while a relative found on the west coast, the western black-legged-tick, Ixodes pacificus, can also transmit the disease.

There are two distinct life cycles at work in Lyme disease: the bacteria itself and the ticks that carry the bacteria from one warm-blooded host to another. Most species of Borrelia will reproduce in a small mammal or bird. Larger hosts, such as deer or humans, do not appear to be viable hosts for Borrelia to reproduce in.[5] If an Ixodes tick feeds on a host, the bacteria can live in the tick but will not reproduce in the host due to the radically different biological environment. They do, however, move from the tick's stomach to the salivary glands using a flagellum, where they are now ready to be transmitted to a new warm-blooded host to reproduce.[6]

The ticks go through a four-part reproductive cycle: eggs, larvae, nymph, adult. The larvae and nymphs both feed on a warm-blooded host to help them develop to the next stage. When an infected nymph or adult feeds again, it can pass the Borrelia bacteria to the next host. (Adult females that are infected will not pass the bacteria to their offspring.[7])

While, as mentioned, about 25,000 to 30,000 cases are reported per year in the United States, it is not a mandatory reportable disease in most jurisdictions, so the true number is likely higher. It is more common in children whose play will take them into tall grasslands and wooded areas where ticks live. But hikers, farm workers, ranchers and other adults who spend time in areas of brush in the Midwest or northern reaches of the East Coast and West Coast are also at higher risk. The ticks that carry the bacteria that causes Lyme disease are at their most active in late spring, summer and early fall.

Symptoms and Progression of Lyme Disease

The first symptom of Lyme disease is a tick bite. But if it was a larvae or nymph, the bite may be too small to be noticed. A circular rash may spread from the point of the bite, but not all Lyme disease patients will develop the rash.

Other preliminary symptoms may include:[8]

- Headache
- Muscle pain
- Joint stiffness
- Fever
- Fatigue
- Swollen lymph nodes

This first round of symptoms is known as the early localized Lyme disease stage, and it generally lasts until three to four weeks after the tick bite.[9] If untreated, the disease will progress to what is known as early disseminated Lyme disease, which can last up to three months. This stage may be marked by some or all of these symptoms:

- Rashes on different parts of the body
- Muscle weakness on the face
- Irregular heartbeat
- Pain and/or weakness in the hands or feet
- Eye pain or vision loss
- Back, hip or neck pain

The final stage can last for decades, and is known as late disseminated Lyme disease. Any of the previous stage symptoms may manifest, and they may dissipate and return. Arthritis may develop in the knees or other large joints.

If a person contracts Lyme disease in Europe, he or she may also exhibit swollen, discolored skin on the back of the hands or top of the feet, which may not manifest for many years after the initial infection.

Frustratingly, even those who have been successfully treated with antibiotics and have no active infection can develop symptoms similar to those of late disseminated Lyme disease. This is known as posttreatment Lyme disease syndrome (PTLDS).[10]

Serious cases can cause damage to joints or other internal tissues, including the brain, leading to conditions known as chronic neurologic Lyme disease and neuropsychiatric Lyme disease. In more serious cases, this can lead to meningitis, encephalopathy, encephalitis and/or encephalomyelitis, all of which can lead to significant cognitive impairment or even psychosis.[10] Less severe symptoms may include trouble remembering, numbness in the feet or hands, chronic fatigue and depression.

While about 25,000 to 30,000 cases of Lyme disease are reported per year in the United States, it is not a mandatory reportable disease in most jurisdictions, so the true number is likely higher.

Diagnosing Lyme Disease

The Centers for Disease Control and Prevention (CDC) recommends a two-part blood test for Borrelia burgdorferi antibodies (both tests can be performed on a single sample).[11] The first test is the enzyme-linked immunosorbent assay (ELISA). If the first test result is positive (abnormal), a second test (Western blot) should be run.[12]

CDC urges physicians not to request an assay unless the symptoms are consistent with Lyme disease and the individual

would have had the opportunity to be bitten by a tick. The agency also cautions that a blood test can return a false negative if the blood is drawn within the first four to six weeks of infection, and it can also indicate a false positive if the patient has Epstein-Barr virus, syphilis, rheumatoid arthritis or relapsing fever.

Unfortunately, Lyme disease can be difficult to diagnose for several reasons. First, its symptoms mimic a number of other diseases. Second, the circular red rash, known as erythema migrans, fails to appear in at least one-quarter of people who are actually infected with Lyme bacteria. Third, current diagnostic tests do not always detect early Lyme disease since antibodies take time to rise to detectable levels.[13]

A study published in *Healthcare* in 2018 that analyzed 3,903 individuals registered with MyLymeData found that "more than half (51 percent) reported that it took them more than three years to be diagnosed and roughly the same proportion (54 percent) saw five or more clinicians before diagnosis." What's more, the study found there was a delay in diagnosis even when patients had an early onset of symptoms: "Diagnostic delays occurred despite the fact that 45 percent of participants reported early symptoms of Lyme disease within days to weeks of [tick] exposure." Findings showed the reasons for such delays included false negative lab tests (37 percent) or positive test results "that were dismissed as 'false-positives' (13 percent)." In addition, "the majority of patients (72 percent) reported being misdiagnosed with another condition prior to their Lyme diagnosis."[14] (See "Lyme Disease: A Patient's Perspective" and "Lyme Disease: A Physician's Perspective" on pages 48 and 49.)

Treating Lyme Disease

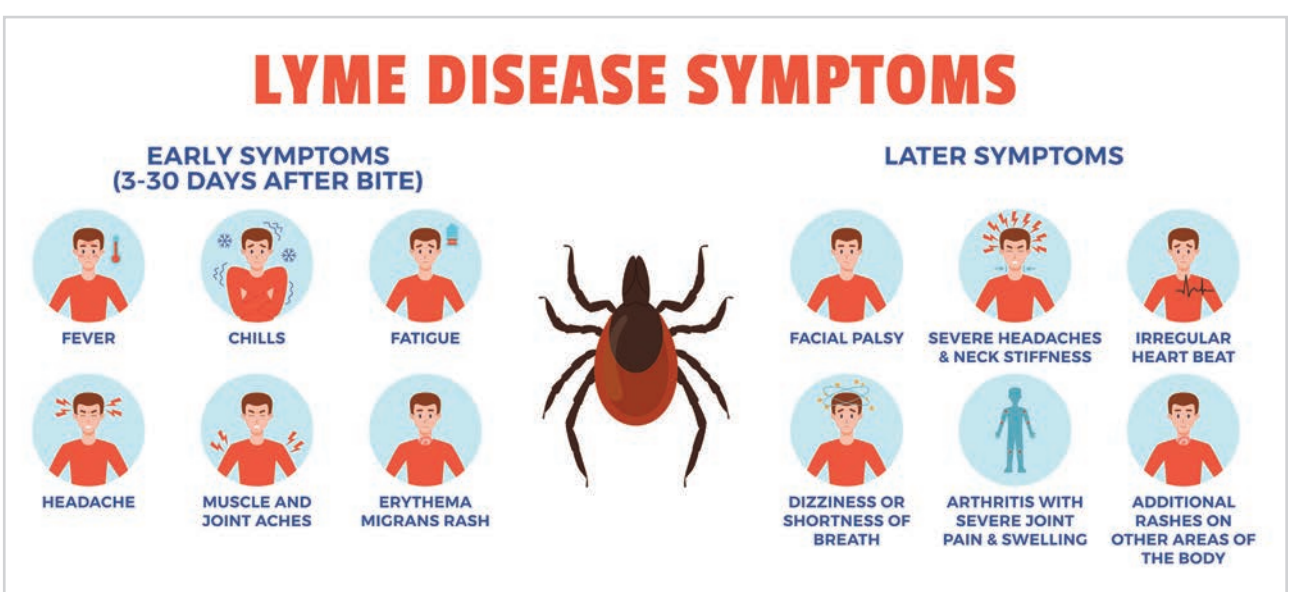
Even before Lyme disease was identified, physicians had noted that the symptoms later associated with the disease were eased by the use of penicillin. Cases that are caught early can be effectively treated with antibiotics to stop the bacterial infection before it spreads throughout the body. Doxycycline and amoxicillin are the most common treatments for early stages of Lyme disease, and they will address the rash in addition to the bacterial infection.[9]

If Lyme disease is not diagnosed until later stages, then symptoms may also need to be addressed, as well as the underlying bacterial infection. In later stages, the antibiotics may need to be administered intravenously to help them spread throughout the body. Whether oral or intravenous, the antibiotics may need to be taken for several weeks or even a month. For patients with joint or muscular pain, the pain can be treated with nonsteroidal anti-inflammatory drugs.

Patients who suffer from an irregular heartbeat as a result of Lyme disease may need a temporary pacemaker until the antibiotics decrease the infection.[15]

Severe or advanced cases may call for a stronger antibiotic such as ceftriaxone.

There is some indication that intravenous immune globulin (IVIG) can be effective in treating PTLDS since there seems to be an immunological component to the condition.[16] Researchers write that while there is enough clinical evidence to warrant further study, the overall effectiveness and the actual mechanism of how IVIG works are not yet known.[17]



Preventing Lyme Disease

The best treatment for Lyme disease is to not contract it in the first place. Patients in high-risk areas should be advised to wear long sleeves and pants, with cuffs than can be sealed, or to tuck pant legs into socks. Insect repellent should also be applied to both exposed skin and all external clothing. When returning from the outdoors in high-risk areas, all clothing should be immediately removed, and the skin should be inspected for ticks, removing any that are found.[18]

To date, there has only been one vaccine for Lyme disease — LYMERix— that was discontinued in 2002 due to low sales.[19] But, even that inoculation lost effectiveness over time, so anyone who received LYMERix before it was removed from market is no longer protected against Lyme disease.

Ongoing Research

Physicians and researchers still do not understand why some patients who have received antibiotics and show no signs of an active infection go on to develop PTLDS.

One new treatment that has been granted a patent (but has not yet entered clinical trials) would not only detect an active infection, but offers the promise of being able to determine when the infection has resolved. (Current tests often return a false positive even after the infection has ended since the body is still producing antibodies against the Borrelia burgdorferi bacteria.)

Case Integrative Health's patent uses a different method of checking for infection by measuring the immune response to Borrelia burgdorferi antigens.[20] Researchers at the company believe this method will provide a clearer picture of the state of infection, potentially preventing more patients from unknowingly progressing to late-stage Lyme disease if the initial round of antibiotics doesn't quell the infection.

Among the roughly 100 clinical trials into Lyme disease listed on the U.S. Food and Drug Administration's (FDA) clinicaltrials.gov website is a new recombinant vaccine candidate, VLA15.[21] Two randomized, observer-blind, placebo-controlled, multicenter Phase II studies of VLA15 were conducted. Both studies included participants aged 18 to 65 years without recent history of Lyme borreliosis or tick bites. Participants were randomly assigned to receive 90 µg (study one only), 135 µg or 180 µg VLA15 or placebo by intramuscular injection at months zero, one and two (study one) or zero, two and six (study two). The primary endpoint for both studies was OspA-specific IgG geometric mean titres (GMTs) at one month after the third vaccination and was evaluated in the per-protocol population. Study findings showed the vaccine was safe, well-tolerated and elicited robust antibody responses, with no related serious adverse events or deaths.[22] As of this writing, the vaccine is now in a Phase III trial titled VALOR (Vaccine Against Lyme for Outdoor Recreationists) that is evaluating it in individuals who have completed the primary vaccination series (three doses) of the vaccine. In this study, participants are being monitored for the occurrence of Lyme disease cases until the end of the Lyme disease season in 2024. Subject to positive Phase III data, Pfizer/Valneva aim to submit a biologic license application to FDA in 2026.[23]

Other clinical trials are looking into new blood tests to more accurately test for Lyme disease, as well as several novel approaches to the use of physical therapy to help patients recover from joint damage arising from late-stage Lyme disease.

Looking Ahead

While VLA15 shows promise as a potential vaccine, patients will continue to contract Lyme disease in the immediate future. Early detection and effective treatment are the best courses for keeping Lyme disease from progressing to a stage that inflicts significant damage. Educating patients in high-risk areas about how to protect themselves while outdoors remains the best preventive measure at this time. ❖

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Myths & Facts: Kawasaki Disease

Educating physicians about this not-so-rare disease can curtail lifelong consequences that can occur if not diagnosed and treated early.

By Ronale Tucker Rhodes, MS

NAMED AFTER Japanese pediatrician Tomisaku Kawasaki, Kawasaki disease (KD) is a rash/fever illness of early childhood in which coronary artery aneurysms (CAAs), sometimes fatal, may develop in up to 25 percent of untreated children. KD is a type of vasculitis, meaning it causes inflammation of the blood vessels. In 1967, Dr. Kawasaki first described 50 cases of KD in infants with persistent fever, accompanied by rash, lymphadenopathy, edema, conjunctival injection, redness and cracking of the lips, "strawberry tongue" and convalescent desquamation. However, during the 1960s, a significant controversy in Japan was whether the rash and fever sign/symptom complex was connected to subsequent cardiac complications in a number of cases. That connection was established in 1970 when the first Japanese nationwide survey of KD documented 10 autopsy cases of sudden cardiac death after KD. In 1974, the first English-language report of these KD patients was published by Dr. Kawasaki. The disease was independently recognized as a new and distinct condition in the early 1970s by pediatricians Marian Melish and Raquel Hicks at the University of Hawaii. Since that time, KD has become the leading cause of acquired heart disease among children in North America and Japan.[1,2]

The incidence of KD is highest in Japan with an annual rate of 130 to 140 per 100,000 children under 5 years of age. In comparison, the incidence of KD in the continental U.S. varies between nine and 20 per 100,000 children under 5 years of age, and for Japanese Americans living in Hawaii, the incidence is between 120 and 130 per 100,000 in children under 5 years of age.[1]

While an infectious agent is suspected, the actual cause of KD remains unknown. However, there has been significant progress toward understanding the natural history of the disease, and therapeutic interventions have been developed that halt the immune-mediated destruction of the arterial wall.[1] Unfortunately, despite more than a half century of treating KD patients, a great deal of myths continue to circulate, resulting in delayed treatment that can prove fatal.

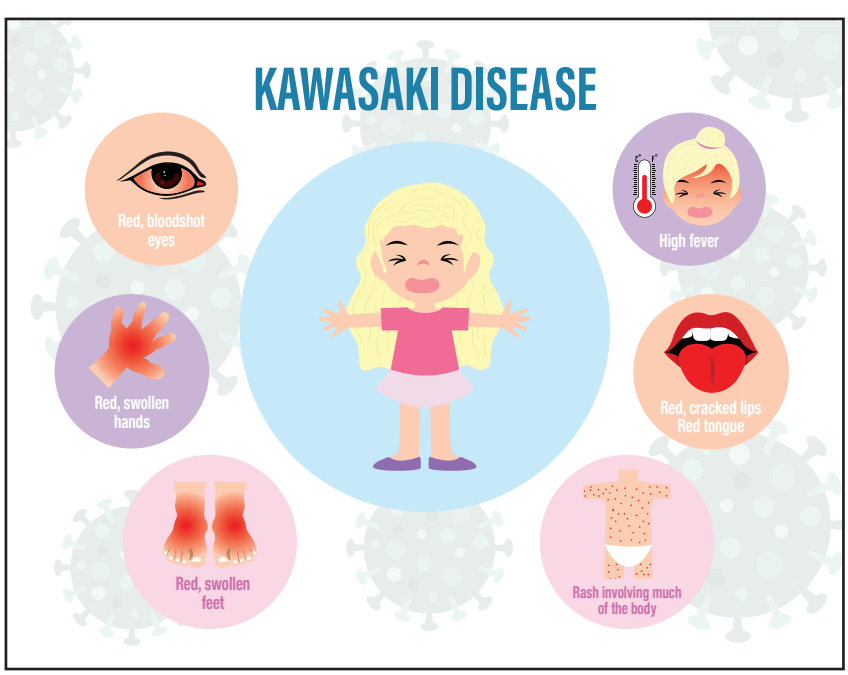
Separating Myth from Fact

Myth: Only Asian children are susceptible to KD.

Fact: While children of Asian or Pacific Islander descent have higher rates of KD, it can affect children of any race. In fact, KD has been diagnosed in more than 60 countries, including those in Asia, the Middle East, Latin America and Africa, as well as in North America and Europe.[3]

Myth: KD only occurs in children between the ages of 1 and 5 years.

Fact: KD more commonly affects children younger than 5 years old, and the majority of those are less than 2 years old. But, KD can be most severe in children



under 1 year of age. In addition, KD can affect older children.[4] In 2016, out of 5,440 KD-related hospitalizations in children under 18 years old, 3,935 involved children younger than 5 years old.[1]

KD also occurs more often among boys.[4]

Myth: KD is caused by a single biological factor that causes or contributes to the development of a disease or condition.

Fact: KD has been linked to a broad range of infectious agents, as well as environmental exposures, including carpet shampoo, genetic variants and meteorological patterns[5] (it is more commonly seen in the winter and spring months[4]). However, the etiology of KD remains unknown, and it is believed that KD likely results from the interaction of one or more infectious agents and genetic factors. What is known is that KD is not contagious.

Because KD occurs when children are most at risk of infection (6 months to 5 years) and in winter months, when most childhood infections occur, epidemiological evidence strongly suggests an infectious trigger.[5] Infections may cause the immune system to attack the blood vessel walls by mistake and cause inflammation. It is also suspected that KD might be the result of changes to certain genes or related to viral or bacterial infections.[6]

Myth: There is a link between KD and COVID-19.

Fact: No studies have found a link between KD and COVID-19. In fact, in Japan, a KD Surveillance Team reported that no association was observed between KD and COVID-19 during 2020.[7] Rather, COVID-19 may cause a condition known as multisystem inflammatory syndrome (MIS-C)-19 with symptoms that resemble KD in some children.[8]

Myth: If a child presents with a viral infection, a diagnosis of KD is unlikely.

Fact: In a study published in the journal *Pediatrics*, a positive respiratory viral PCR, including for SARS-CoV-2, or presence of viral symptoms at the time of symptom presentation does not exclude a diagnosis of KD. In the study of 192 children with KD, 93 (41.9 percent) had a positive respiratory viral PCR, which did not correlate with gastrointestinal or respiratory symptoms. The researchers noted that a positive PCR for respiratory viruses, such as adenovirus, may represent asymptomatic shedding or latency in the upper airway.[5]

Myth: Children with KD always display all of the known symptoms.

Fact: Actually, children with KD do *not* all experience the same or all of the symptoms of KD. To diagnose KD, a child will present with a fever greater than 101 degrees Fahrenheit for five or more days, as well as with at least four of the following symptoms:

- A rash on the main part of the body or in the genital area
- An enlarged lymph node in the neck
- Very red eyes without a thick discharge
- Red, dry, cracked lips and a red, swollen tongue (strawberry tongue)
- Swollen, red skin on the palms of the hands and the soles of the feet

And, while KD occurs suddenly, its symptoms often occur in phases. The above are known as Phase 1 symptoms. Phase 2 symptoms include:

- Skin peeling on the tips of the fingers and toes
- Diarrhea
- Abdominal pain
- Joint pain
- Vomiting

During the third phase, the signs and symptoms will go away slowly, sometimes taking up to eight weeks. In addition, children may show symptoms of tiredness, irritability and low energy.[5,9]

Long-term complications include coronary artery lesions that can cause heart disease, meningitis and arthritis.

Some children may develop what is known as incomplete KD that happens if they experience a high fever for five or more days but have fewer than four of the symptoms needed for a KD diagnosis. However, it's important to note that even children with incomplete KD are at risk of damage to their heart arteries.

There are no tests available to diagnose KD; it is diagnosed based on symptoms.[9] However, doctors may order blood tests and a urine sample to rule out other diseases and common viruses that present with the same symptoms such as a recent strep or viral infection. Other diseases that should also be ruled out include scarlet fever, juvenile rheumatoid arthritis, Stevens-Johnson syndrome (a disorder of the mucous membranes), toxic shock syndrome, measles and some illnesses caused by ticks such as Rocky Mountain spotted fever.[10]

If a child meets the criteria for a KD diagnosis, a cardiology team will need to be consulted to perform a history, physical exam, an electrocardiogram to assess the electrical system of the heart and an echocardiogram (an ultrasound of the heart). Even if these studies are normal, the child will receive treatment based on clinical symptoms and lab work.[4]

Myth: The treatment window for intravenous immune globulin (IVIG), first-line treatment for KD, is 10 days.

Fact: Timely treatment of KD is imperative to reduce the risk of complications. The goal of treatment is to lower fever, reduce swelling and prevent heart damage. Treatment includes moderate to high-dose aspirin until fever subsides for up to eight weeks and IVIG, which contains antibodies to stop the immune system from attacking the blood vessels. IVIG is the most effective treatment for KD. Children should be treated with IVIG preferably

Kawasaki Disease Facts

- There is no known cause, but it is thought to start from an infection or from exposure to some toxin.
- There is no firm evidence that the disease can spread from one person to another.
- It primarily affects children under the age of 5, with most cases occurring in 1- to 2-year-old children.
- Asian children are more prone to get the disease than non-Asian children.
- The disease is seen more often in the winter and spring seasons.
- There is no one test that can confirm this disease; a doctor makes the diagnosis from the symptoms and a few characteristic laboratory findings such as high platelet counts in the blood.
- It is treated in the hospital with medications that reduce inflammation, including intravenous immune globulin and aspirin.
- The treatment works best when it is started early, within 10 days of when symptoms begin.
- Twenty to 25 percent of children may develop swelling of the arteries in the heart if they are not treated.
- Early treatment can reduce the risk of heart complications. Other complications include arthritis, meningitis and, rarely, death.

Adapted from the Kawasaki Disease Fact Sheet accessed at health.maryland.gov/phpa/IDEHASharedDocuments/Kawasaki.pdf.

within 10 days of the onset of symptoms, and the American Heart Association and American Academy of Pediatrics recommend starting IVIG ideally within seven days. However, even if the 10-day window has passed, children should still be treated if they have a fever or other signs of inflammation.[11]

For children who don't respond to IVIG, corticosteroids may be an option.[4] More recently, a study has shown that adding glucocorticoids to the initial high-dose IVIG and aspirin regimen effectively reduced fever duration, length of hospital stay and incidence of coronary artery lesions (CALs) in children with KD who exhibited three or more risk factors for IVIG resistance. In that study, 236 IVIG-sensitive cases and 38 IVIG-resistant cases were gathered, with 26 cases in the observation cohort. Following treatment, those resistant to IVIG indicated higher rates of CALs compared with the IVIG-sensitive group at all post-treatment intervals. Prior to treatment, the observation group had higher CAL incidence than the IVIG-sensitive group.

In addition, patients with three or more high-risk factors in the IVIG-resistance group were deemed to be much higher than that of the IVIG-sensitive group. This was also the case in the observation group. In both the IVIG-sensitive and observational study groups, fever resolution times and duration of hospital stays were significantly reduced. According to the researchers, "this is especially notable given the more severe inflammatory reaction present in patients with KD who are IVIG-resistant than those who are IVIG-sensitive. Importantly, the treatment combination led to clinical improvement and CAL reduction in patients with KD without adverse effects related to glucocorticoids, a positive indication of safety."[12]

Myth: All children should receive high-dose aspirin in addition to IVIG.

Fact: While aspirin has been used as a concomitant drug in the treatment of KD, in recent years, the role and optimal dose of aspirin remain controversial. In 2020, results were published of a study conducted to identify if the dose of aspirin in the acute phase of KD will facilitate development of a more appropriate treatment strategy in improving the outcome of KD. In the study, a total of 2,369 patients with KD were retrospectively analyzed and divided into three groups according to the aspirin dose: 510 in group 1 (20 to 29 mg/kg/day), 1,487 in group 2 (30 to 39 mg/kg/day) and 372 in group 3 (40 to 50 mg/kg/day). The differences in laboratory data, rate of IVIG resistance and coronary artery damage were compared among the groups.

Results showed there was no difference in the incidence of CAAs in group 1 compared with groups 2 and 3 (two weeks of illness: 2.94 percent vs. 1.90 percent vs. 3.36 percent; three to four weeks of illness: 1.94 percent vs. 2.32 percent vs. 2.65 percent). The risk for developing CAA was not reduced at two weeks of illness onset in groups 2 and 3 compared with group 1. Furthermore, the risk for developing CAA was not reduced at three to four weeks of illness onset in groups 2 and 3. There was no significant difference in the rate of IVIG resistance among the groups. Platelet levels after IVIG treatment in group 1 were significantly lower than those in groups 2 and 3. C reactive protein of the 30 to 40 mg/kg day group was slightly higher than the other two groups. The researchers concluded that aspirin at the lower dose of 20 to 29 mg/kg/day dose not increase the risk of coronary artery damage and IVIG resistance compared with the high dose of 30 to 50 mg/kg/day. In addition, the low dose may have a lower risk for a potential effect on liver function.[13]

Myth: Once KD is resolved with treatment, there is no longer a risk of cardiovascular disease.

Fact: While IVIG treatment can decrease the risk of cardiovascular disease, it does not eliminate the risk of developing CAAs. However, if IVIG

is given within the first 10 days of the illness, it can decrease the risk of developing coronary changes from 25 percent to less than five percent.[4]

Even so, children who have had heart complications as a result of KD have an increased risk of developing cardiovascular complications later in life, including conditions such as heart attacks and heart disease.[14] New research shows that children with KD remain at an increased risk for cardiovascular events more than 10 years after hospitalization for their condition, highlighting the need for long-term heart disease surveillance and risk reduction strategies.

One study in Ontario, Canada, was conducted to determine the risk and timing of long-term cardiovascular events and death among KD survivors. In the study, the researchers identified all children up to 18 years of age who survived hospitalization for KD in Ontario between 1995 and 2018 using health administrative databases. They included only the first eligible hospitalization, excluding children who were previously diagnosed with KD, as well as non-residents of Ontario. They matched each KD case to 100 non-exposed control cases by age, sex and year. After following these patients until death or March 2019, or up to 24 years old, they determined the rates of cardiovascular events, major adverse cardiac events (such as heart attack or stroke) and death, comparing children who had KD with those who were not exposed to the disease. Specifically, they looked at four time periods after hospital discharge: zero to one year, one to five years, five to 10 years and more than 10 years.

The researchers found that, among 4,597 KD survivors, 746 or 16.2 percent experienced cardiovascular events compared with 5.2 percent of children without the disease. They also found that 79 or 1.7 percent experienced major adverse cardiac events compared to 0.7 percent of children without the disease, and nine died during the median 11-year follow-up period. The most frequent cardiovascular events experienced by KD survivors were ischemic heart disease, arrhythmias, high blood pressure and peripheral vascular disease. KD survivors were at higher risk of heart problems compared to patients who did not have the disease, and they experienced cardiovascular events sooner. Their risk was highest in the first year after they were discharged from the hospital. They were also at higher risk of heart surgery like coronary artery bypass grafting. However, their risk of death during follow-up was lower than non-exposed patients.[15]

Dispelling the Myths Now

Research continues in an effort to uncover the causes of KD. According to a paper published in *Clinical and Experimental Pediatrics* in 2022, "the leading theory for KD's pathogenesis is that an unknown infectious agent activates the immune system of a genetically susceptible child." According to the paper's author, several findings support this theory, including that KD occurs most commonly in the cold winter season when an unknown infectious agent activates the immune system of a genetically susceptible child; the significant overlap of clinical symptoms of KD and other infectious substances, particularly scarlet fever, newly described MIS-C and adenovirus; and reports that demonstrated the incidence of KD significantly decreased during the COVID-19 pandemic with the implementation of mask wearing and social distancing measures.[16]

In a 2024 paper published in *The Journal of Clinical Investigation*, the author notes that model predictions indicate that by 2030, one in every 1,600 adults will have experienced KD in the United States. He also points out that "once the etiology is solved, specific diagnostic tests will follow and epidemiology based on confirmed diagnoses will be possible."[17] In the meantime, with a better awareness of what is believed to be a rare disease but in fact is not, as well as dispelling the many myths concerning it, it is hoped that diagnoses of KD will be swifter to curtail the development of acute KD in children that leads to long-term health consequences. ❖

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Lyme Disease: *A Patient's Perspective*

By Trudie Mitschang

ARIZONA RESIDENT Joleen Larsen's life was upended when she learned her dad was diagnosed with a terminal illness in 2010. The single mom, who is known by family and friends as Jojo, relocated to Arkansas to spend time with her parents, a decision she is grateful for. Little did she know that a tick bite would soon permanently impact her health and alter the course of her life.

BSTQ: How were you exposed to Lyme disease?

Jojo: I started gaining weight and I would sleep easily 16 hours a day and still feel tired. I would call my friends back home in Arizona and cry for help; then, the pain began. I had been in a car accident back in 2009 and initially suspected that those injuries were the source of my pain. Now I know that was only part of my problem. I was in and out of doctor offices, constantly complaining about pain from head to toe, and eventually put on pain management, but I felt nobody was listening to me.

BSTQ: Can you describe your pain?

Jojo: My neck hurt every day for about 10 years. I had back spasms and any movement would cause them to ignite. It felt as if I was being shocked with electricity. My knees were in such pain, and then I got neuropathy so bad I couldn't walk. To this day, they still hurt. Over the years, I've had everything from ear ringing, restless leg syndrome and anxiety/depression, to hair loss, heart palpitations and rashes that itched and burned. My list of complaints became so long doctors wouldn't even look at me. I spent many years suffering, just hoping someone would listen.

BSTQ: What types of medication did you try?

Jojo: I have been on gabapentin and hydrocodone for pain relief. I was viewed as a pill seeker and hypochondriac, and I was never taken seriously.

BSTQ: When was your diagnosis confirmed?

Jojo: Things changed in the summer of 2023 when my mom found an article about alpha-gal syndrome, an allergic condition associated with tick bites. This illness triggers a severe allergy to beef, something I consumed three to four times a week. This explained at least some of my symptoms. When I realized alpha-gal's connection to Lyme disease, I called the Centers for Disease Control and Prevention (CDC) and was advised to go to the emergency room for testing. Although I initially tested negative, I did not give up. I started researching where to get treatment for Lyme disease and the options were very confusing, expensive and overwhelming. Eventually, I started looking locally in Arizona, and I found a naturopathic doctor, Jason Porter, NMD, DCN, who specializes in Lyme disease. Right away, based on my symptoms, he confirmed my suspicions and tested me for the common infections that come with it. I tested positive for Lyme disease and bartonella, also known as cat scratch fever. He also tested me for parasites and many other possible contaminants.

BSTQ: What was your treatment plan?

Jojo: I stopped eating sugar and carbohydrates because Lyme disease feeds off those things. I took parasite medication and herbs on a daily basis. I lost 50 pounds as my body healed, and my friends and family were terrified I was just ruining my life because nobody believed I had Lyme disease. I'm so very thankful to Dr. Porter for saving my life. I'm not saying this approach is the only way to get healed, but I feel pretty lucky. I still have struggles, but they are nothing like before.

BSTQ: How do you spread awareness about Lyme disease?

Jojo: During my research, I read a book by Ally Hilfiger called *Bite Me*. This is the best book to give to friends and family who don't understand what this disease is like. There is also a documentary called "The Quiet Epidemic." I highly suggest both to people who want to know how to support a loved one who has been diagnosed with Lyme disease. I also started my Facebook page called Ticked Off to get the word out on the dangers of being around ticks and how to protect yourself.

BSTQ: What has this experience taught you?

Jojo: I have discovered I am self-reliant and strong; no matter how many tears and fits of rage I've had, I survived. Lyme disease creates a very lonely world, and it all starts with a tick. I lost many years of my life, and I especially missed being an active mom for my kids. I hope sharing my story will help others find healing. ❖

Lyme Disease: *A Physician's Perspective*

KRISTOPHER PAOLINO, MD, is an assistant professor of medicine and assistant professor of microbiology and immunology at Upstate University Hospital in Syracuse, N.Y. He previously worked for the Walter Reed Army Medical Center and the Walter Reed Army Institute of Research in Washington, D.C. His research interests include vaccine development, Lyme disease, neglected tropical diseases and malaria.

BSTQ: What has driven your interest in diagnosing and treating Lyme disease?

Dr. Paolino: My clinical training included a master's degree in tropical medicine and hygiene as part of my third year of infectious disease fellowship, which included extensive time spent learning about various vector-borne diseases. When I moved back to New York, I was struck by the number of Lyme disease cases in the region and decided to focus more of my efforts on working with these patients. Lyme is fascinating given the different clinical presentations, as well as the potential for long-term symptoms due to reasons we do not completely understand.

BSTQ: Tell us about your role in studies to develop a test for Lyme disease.

Dr. Paolino: I have a long history of working in the clinical trial world, dating back to my days at the Walter Reed Army Institute of Research. Our team in the Upstate Global Health Institute at SUNY Upstate has attempted to enroll patients for a few different Lyme diagnostic studies over the past several years. These diagnostic assays have focused on increasing the sensitivity of the testing early in the course of infection. Surprisingly, despite the number of cases of Lyme in our region, recruitment has been difficult. Identifying patients in the early part of Lyme infection, to include those with the classic erythema migrans rash (bull's eye rash), that have not been on antibiotics for more than five days has proven difficult.

BSTQ: Are there a core set of symptoms with Lyme disease?

Dr. Paolino: Lyme is caused by the spirochete bacteria Borrelia burgdorferi. It can have a variety of signs and symptoms oftentimes associated with the stage of illness. Early localized is associated with the rash, which is not always present and does not always look like a classic bull's eye, presents with flu-like symptoms such as fevers, headaches and aches/pains. Early disseminated is associated with heart or nervous system involvement. Lyme carditis can result in a problem with the electrical activity of the heart, leading to heart block and slowed heart rate. Patients can present with fatigue or dizziness with any exertion, and may describe loss of consciousness. Lyme meningitis can present with headache, neck stiffness and sensitivity to bright lights. Other nerves can also be affected in the arms and legs, leading to weakness, nerve pain and neuropathy with numbness in the hands and feet. Late disseminated Lyme typically presents with arthritis symptoms, most commonly in the knees, but most joints can potentially be involved. Pain can potentially migrate from one joint to another.

BSTQ: What are some of the psychological impacts on patients with chronic Lyme?

Dr. Paolino: Psychologic impacts of Lyme disease have ranged from new-onset depression, anxiety, panic attacks, PTSD and delusional thoughts. The vast majority of these psychiatric symptoms do not respond to antibiotic treatment and require the care of a mental health professional. These symptoms can be severe and can lead to suicidal thoughts in some cases.

BSTQ: Tell us about the Upstate Medical University's Lyme and tick-borne disease treatment center.

Dr. Paolino: The tentative date of a "soft" opening will be in May 2025. We look to develop relationships with others in the university system to provide a multidisciplinary approach to care to include psychiatry/clinical psychology, neurology, rheumatology, physical therapy, occupational therapy, as well as a trained herbalist. We also plan on tying in our Global Health Institute research team to continue to try to bring new clinical trial opportunities to the region for Lyme and other tick-borne diseases.

BSTQ: What's promising on the treatment horizon?

Dr. Paolino: We have been participating in one of the sub-studies for the Pfizer/Valneva Lyme vaccine, and I am excited about what the results of the larger study will show. Providing a safe vaccine to be combined with preventive efforts (education, topical repellents, clothing treatments, tick checks and post-activity showers) will be useful in decreasing risk of acquiring the infection even further. I am also hopeful that efforts to understand post-infectious syndromes such as Long COVID will help us find better approaches for treating patients who suffer with long-term symptoms after Lyme treatment. ❖

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

In the R&D Pipeline: New Agents to Prevent and Treat Hereditary Angioedema Attacks

By Keith Berman, MPH, MBA

TISSUE EDEMA is a normal component of the acute inflammatory response to localized injury caused by invading pathogens, trauma, toxins, heat or other causes. This protective tissue swelling phenomenon is regulated in part by a protease inhibitor called complement 1 esterase inhibitor (C1-INH).

But individuals affected with hereditary angioedema (HAE) experience recurrent attacks of localized subcutaneous and mucosal swelling, the results of a deficient level of functional C1-INH (type I disease), or a normal level of a dysfunctional C1-INH protein (type II disease).* Roughly one in 50,000 people are living with this rare autosomal dominant disorder, which results from more than 200 known mutations affecting the SERPING1 gene that encodes C1-INH.

These acute and often painful attacks of soft tissue swelling typically involve the face, mouth, tongue, oropharynx, hands, feet, genitals or intestinal tract. While the frequency, severity and localization of these angioedema attacks varies widely from one individual to the next, at least 50 percent of untreated patients eventually experience laryngeal attacks, the worst of which can obstruct the upper airway and result in fatal asphyxiation.

Through multiple complex pathways (Figure), C1-INH works to modulate the extent of increased microvascular permeability and edema that naturally occurs during an inflammatory reaction (Figure). Specifically, C1-INH is the only known inhibitor that acts to regulate the conversion of prekallikrein to kallikrein. In persons with HAE, C1-INH deficiency or dysfunction leads to excessive kallikrein production, which in turn causes uncontrolled cleavage of high-molecular-weight kininogen (HMWK) to yield supra-normal levels of the potent vasodilator bradykinin. This excessive bradykinin binds to the bradykinin B2 receptor on vascular endothelial cells, further increasing vascular permeability that results in excessive localized swelling, inflammation and pain associated with HAE attacks.

* A third category of HAE is characterized by normal C1-INH levels and function, but with angioedema symptoms similar to those affecting people with types I and II HAE.

Today's Options to Treat and Prevent HAE Attacks

The management of HAE attacks is addressed therapeutically in two ways: 1) prophylaxis with medications to prevent HAE attacks from happening in the first place, or at least reduce their number and severity, and 2) treatment of HAE attacks, including breakthrough attacks in patients on drug prophylaxis, with medications that can limit their severity and shorten the time to symptomatic relief and resolution.

Approved Prophylaxis Options

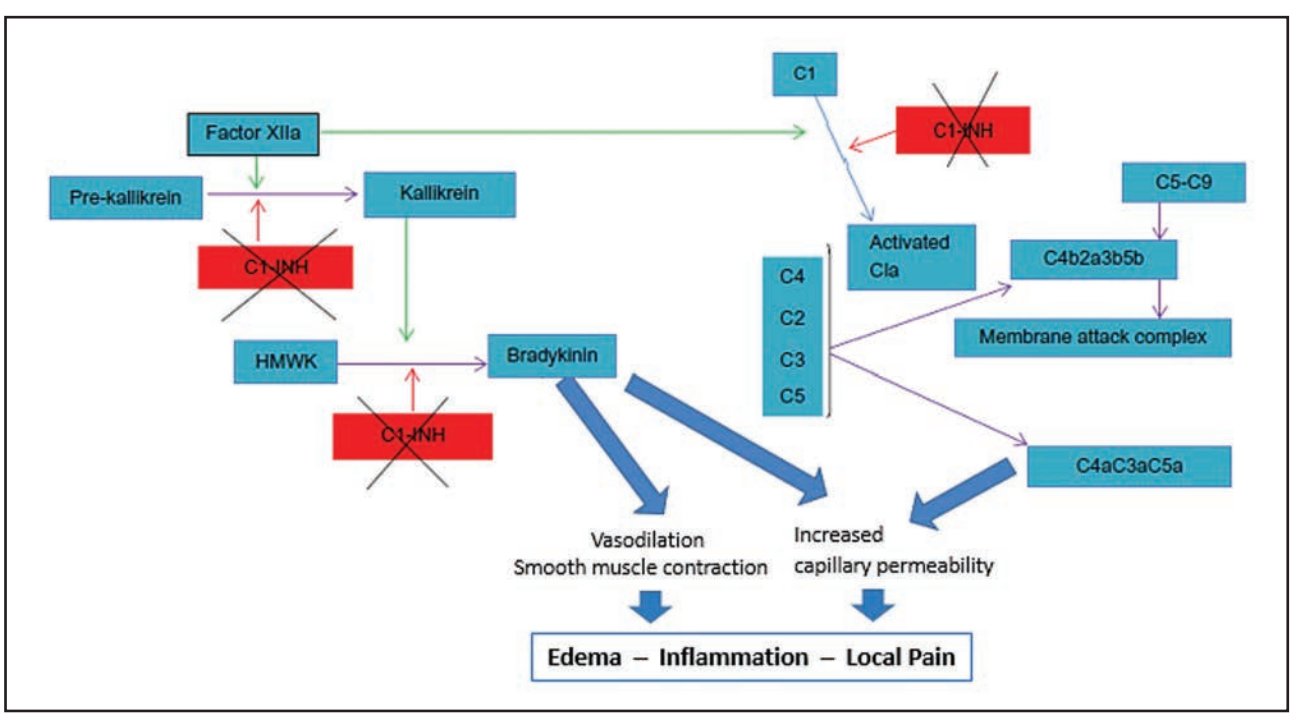
Prior to the approval of the first human C1-INH concentrates 15 years ago, HAE therapy was largely limited to long-term prophylaxis with antifibrinolytics, which were not reliably effective,[1] and with attenuated androgens, whose chronic administration was frequently associated with hepatotoxicity, virilization and other intolerable side effects.[2]

But the approvals of eight new HAE treatments over the last 15 years have transformed the management of adults and children with HAE. Very broadly, these agents can be classified in two ways: 1) replacement C1-INH therapies versus synthetic inhibitors that interfere with the kallikrein-kinin pathway, and 2) approved use for prophylaxis to prevent HAE attacks versus treatment of acute HAE attacks (Tables 1 and 2).

CINRYZE (C1 esterase inhibitor [human]). In 2008, Takeda's CINRYZE became the first human C1-INH product approved by the U.S. Food and Drug Administration (FDA) for routine prophylaxis to prevent HAE attacks. Approval was based on results from a study in 22 subjects randomly assigned to receive intravenous (IV) injections of saline placebo or 1,000 units of CINRYZE every three to four days for 12 weeks, then crossed over to the alternative treatment for a second 12-week evaluation period.[3] Mean attack rates during the two 12-week crossover periods were 6.26 and 12.73 for the C1-INH and placebo treatments, respectively. The differences in mean attack severity on C1-INH prophylaxis versus placebo (1.3 versus 1.9 on a 3-point scale) and total duration of attacks (2.1 versus 3.4 days) were also highly significant.

While all these outcomes are clinically important and clearly justify the use of C1-INH, the substantial frequency of breakthrough HAE attacks reveals that simply replacing C1-INH does not provide complete protection. Further boosting the

Figure. Hereditary Angioedema: Kallikrein-Kinin Pathway and Complement Cascade Dysregulation Resulting from Deficit of Normal C1-INH Production



Adapted from Ghazi A, Grant JA. Hereditary angioedema: epidemiology, management, and role of icatibant. *Biologics* 2013;7:103-13.

Table 1. Medications Approved for Prophylaxis to Prevent Hereditary Angioedema Attacks

Trade name (generic name)	Manufacturer	Mechanism of action	Delivery route
HAEGARDA (C1 Esterase Inhibitor Subcutaneous [Human])	CSL Behring	Inhibits plasma kallikrein, factors XIIa, C1, others	SC
CINRYZE (C1 Esterase Inhibitor [Human])	Takeda	Inhibits plasma kallikrein, factors XIIa, C1, others	IV
ORLADEYO (berotralstat)	BioCryst	Inhibits plasma kallikrein	Oral
TAKHZYRO (lanadelumab-flyo)	Takeda	Inhibits plasma kallikrein	SC

dose to try to reduce breakthrough attacks is also problematic, as IV-administered C1-INH has been associated with reports of serious arterial and venous thromboembolic events (TEEs).

HAEGARDA (C1 esterase inhibitor [human]). Almost a decade later in 2017, CSL Behring introduced HAEGARDA, its own human plasma-derived C1-INH product for routine prophylaxis to prevent HAE attacks in patients 6 years of age and older. But unlike delivery of CINRYZE by IV infusion, HAEGARDA is administered subcutaneously (SC). Because C1-INH has a half-life of just 20 hours, twice-weekly SC delivery of a much higher dose results in a smoothing of the pronounced "saw-tooth" pharmacokinetic profile, with higher and better sustained trough levels than occurs with twice-weekly IV administration of CINRYZE.[4] Not surprisingly, a recent study showed that, in patients who received twice-weekly intravenous C1-INH prophylaxis, breakthrough angioedema attacks tended to occur shortly before the next scheduled infusion, when the circulating level of infused C1-INH reaches very low nadir. This problem is essentially eliminated with higher-dose SC administration of HAEGARDA.[5]

A prospective, randomized, double-blind, crossover, placebo-controlled Phase III trial of self-administered SC HAEGARDA yielded unprecedented positive results: At a 60 IU/kg dose, the time-normalized median number of attacks was reduced by 87 percent versus placebo (0.52 versus 4.03 attacks per month).[6] Moreover, the average severity of HAE attacks was far milder in HAEGARDA-treated patients than those randomized to placebo; just nine percent of attacks were graded as "severe," compared to 69 percent of attacks in the placebo group. Fully 40 percent of study subjects did not experience any attacks over the 16-week treatment period, as compared with no attack-free subjects in the placebo group.[7]

This improved protection of HAEGARDA against HAE attacks relative to IV-administered CINRYZE is largely attributable to the ability of its twice-weekly SC dosing with 60 IU/kg to restore and maintain the circulating level of C1-INH above 40 percent of normal, which has shown to be associated with reduced risk of HAE attacks.

On the strength of its superior performance, a more convenient SC administration route and lack of evidence of any causal association with TEEs, HAEGARDA has largely supplanted CINRYZE as the preferred plasma-derived C1-INH product for use as prophylactic therapy in HAE patients.[8]

TAKHZYRO (lanadelumab-flyo). For patients prescribed routine prophylaxis to prevent attacks, HAEGARDA now mainly competes with two recently licensed non-plasma-based therapies (Table 1). Approved in 2018 for prevention of HAE attacks in adult and pediatric patients ages 2 years and older, Takeda's TAKHZYRO is a fully human monoclonal antibody that binds plasma kallikrein, inhibiting its ability to cleave HMWK and generate bradykinin.

Adult clinical trial subjects who self-administered a 300 mg SC dose of TAKHZYRO on a biweekly basis experienced 83 percent fewer moderate to severe HAE attacks, and 87 percent fewer attacks requiring on-demand treatment, than placebo group subjects. Also generally similar to Phase III study results with HAEGARDA, 77 percent of these subjects were attack-free during their steady-state day 70-182 treatment period, compared to just three percent of placebo group subjects.[9]

ORLADEYO (berotralstat). Approved in late 2020, BioCryst Pharmaceuticals' ORLADEYO is the first and currently the only once-daily oral therapy indicated for prophylaxis to prevent HAE attacks in adult and adolescent patients. Like TAKHZYRO, ORLADEYO binds to plasma kallikrein, inhibiting its bradykinin-generating activity.

In a Phase III trial, the recommended 150 mg dose of berotralstat achieved a 44 percent mean reduction in the monthly HAE attack rate, somewhat lower than that attained with HAEGARDA or TAKHZYRO. No difference between groups was observed in the proportion of attack-free patients. Adverse reactions occurring at a notably higher rate in

Table 2. Medications Approved for Prophylaxis to Prevent Hereditary Angioedema Attacks

Trade name (generic name)	Manufacturer	Mechanism of action	Delivery route
RUCONEST (C1 Esterase Inhibitor [Recombinant])	Pharming	Inhibits plasma kallikrein, factors XIIa, C1, others	IV
BERINERT (C1 Esterase Inhibitor [Human])	CSL Behring	Inhibits plasma kallikrein, factors XIIa, C1, others	IV
KALBITOR (ecallantide)	Takeda	Inhibits plasma kallikrein	SC
FIRAZYR (icatibant)	Takeda	Inhibits bradykinin from binding its target B2 receptor	SC

Table 3. Investigational Therapies to Prevent or Treat Hereditary Angioedema Attacks

Prophylaxis	Developer	Mechanism of action	Delivery route
Donidalorsen	Ionis	Targets prekallikrein production	SC
Garadacimab	CSL Behring	Inhibits activated factor XIIa	SC
Deucrictibant	Pharvaris	Inhibits bradykinin from binding its target B2 receptor	Oral
Attack treatment	**Developer**	**Mechanism of action**	**Delivery route**
Sebetralstat	KalVista	Inhibits plasma kallikrein	Oral
Deucrictibant	Pharvaris	Inhibits bradykinin from binding its target B2 receptor	Oral
Gene editing	**Developer**	**Mechanism of action**	**Delivery route**
NTLA-2002	Intellia	Disables gene encoding prekallikrein	Single IV

berotralstat group patients than in placebo group patients included abdominal pain, vomiting, diarrhea and back pain, but typically self-resolved and became less frequent over time.[10]

Approved On-Demand Treatment Options

More than a decade ago, two other C1-INH products also received FDA approval specifically for the treatment of acute HAE attacks: one purified from human donor plasma (CSL Behring's BERINERT) and one produced through recombinant DNA technology and purified from the milk of transgenic rabbits (Pharming's RUCONEST).

Also approved are two SC-administered, non-plasma-based drugs (Table 2) designed to treat HAE attacks by interfering with the kallikrein-bradykinin pathway: Takeda's plasma kallikrein inhibitor KALBITOR (ecallantide) and its bradykinin B2 receptor antagonist FIRAZYR (icatibant). While FIRAZYR can be self-administered by the patient upon recognition of an HAE attack, KALBITOR must be administered by a healthcare professional because of a very small risk (<2 percent) of allergic or anaphylactic reaction, effectively prolonging the time to treatment.

Two key treatment goals with all of these agents are to 1) reduce the time elapsed to achieve a specified reduction from baseline symptoms (or attain greater reduction of symptoms at a specified post-treatment time point), and 2) reduce the time to complete resolution of symptoms. An additional endpoint of interest is the usage of additional rescue medication; less frequent need for rescue medication is another important indicator of the product's effectiveness in shortening the time to symptom relief.

In 2021, the Hereditary Angioedema Association's (HAEA) Medical Advisory Board updated its published guidelines that cite key HAE management principles and product-specific efficacy and safety information to help clinicians choose from the various on-demand and prophylaxis treatment options. The 11 specialists who authored these guidelines emphasize that much of the decision-making process should reflect the reality that "HAE has a highly variable clinical course with numerous presentations and symptoms."[11]

HAE Therapies in the R&D Pipeline

The fact that clinicians now have an impressive armamentarium of HAE management options has not dissuaded a number of companies from developing entirely new potential therapies to treat or prevent HAE attacks (Table 3), in the hope

of pushing the envelope to demonstrate enhanced efficacy, tolerability and/or patient usage convenience.

Investigational Prophylaxis Therapies

Donidalorsen (Ionis Pharmaceuticals). This RNA ligand-conjugated antisense (LICA) agent is designed to precisely target and silence the production of prekallikrein, thereby interrupting the pathway that leads to HAE attacks. Ionis' recently completed Phase III OASIS-HAE trial randomized subjects with HAE to a SC 80 mg dose of donidalorsen or placebo every four weeks (Q4W) or every eight weeks (Q8W), and found that the mean attack rate from week five to week 25 was 87 percent lower in the Q4W group and 60 percent lower in the Q8W group than in the placebo group.[12]

In a separate Phase II open-label extension study evaluating flexible dosing of donidalorsen over two years, five of the eight subjects who received a single SC injection every eight weeks remained attack-free, while the other three subjects were switched to receive the drug every four weeks.[13] The mean monthly attack rate across all eight subjects declined from 0.28 attacks in year one to 0.04 attacks in year two. "At year two, donidalorsen Q8 was well-tolerated, had plasma prekallikrein levels similar to Q4W, and showed durable efficacy in HAE attack reduction, supporting the continued study of Q8W dosing," the study investigators concluded.

These findings suggest that the dosing frequency of donidalorsen could potentially be individualized based on the requirement to achieve protective efficacy against HAE attacks. A significant subset of fortunate HAE patients could require a single SC injection as infrequently as every eight weeks to remain attack-free.

Garadacimab (CSL Behring). Also identified as CSL312, this novel, fully-human monoclonal antibody interferes with the cascade of events leading to edema formation by inhibiting activated factor XII (FXIIa). Subcutaneous dosing of garadacimab starts with a 400 mg loading dose, followed by monthly self-administered doses.

> A number of promising new agents in the R&D pipeline are likely to be approved in the very near future, expanding an already impressive range of treatment options.

According to Phase III VANGUARD study findings reported last year, the mean number of HAE attacks in adult and adolescent participants randomized to receive garadacimab for six months was 87 percent lower than in the placebo group.[14] Both safety and tolerability appeared favorable, and FXIIa inhibition was not associated with an increased risk of bleeding or thromboembolic events. "These results underscore our belief that garadacimab has the potential to become a transformative first-in-class therapy for people living with HAE," said CSL's head of R&D and chief medical officer Bill Mezzanotte, MD, MPH.

Very encouragingly, garadacimab prophylaxis yielded greater than a 94 percent reduction in the number of attacks compared to the run-in period over a median exposure period of nearly 14 months. A remarkable 88 percent of patients were attack-free at the end of the 13- to 15-month open-label observation period. A biologics license application has been submitted to FDA, and CSL anticipates marketing approval sometime in the first half of 2025.[15]

Investigational On-Demand Treatment Therapies

Sebetralstat (KalVista Pharmaceuticals). Results from the placebo-controlled Phase III KONFIDENT trial involving 136 participants experiencing HAE attacks demonstrate sharp improvements in multiple outcome parameters for both those who received a single oral dose of this investigational plasma kallikrein inhibitor.[16] The median time to the start of symptom relief was significantly faster with the 300 mg (1.61 hours) and 600 mg doses (1.79 hours) than placebo (6.72 hours), as was the time to reduction in attack severity (9.27, 7.75 and >12 hours, respectively). The percentage of attacks with complete resolution within 24 hours was also higher with sebetralstat treatment (42.5 percent, 49.5 percent and 27.4 percent, respectively).

If approved, sebetralstat would become the first orally self-administered treatment for HAE attacks. "Having a safe and effective oral, on-demand treatment for HAE attacks could be immensely valuable in addressing unmet needs and reducing the treatment burden associated with current injectable treatments," said KONFIDENT trial

lead investigator Marc Riedl, MD.

Deucrictibant (Pharvaris). This Dutch R&D-stage company has developed an oral small-molecule bradykinin B2 receptor antagonist that has generated positive data in both Phase II on-demand and prophylaxis studies in patients with HAE. A multinational Phase II on-demand treatment trial involving 34 participants demonstrated an 84.5 percent reduction in the overall monthly attack rate with a daily 40 mg dose.[17] Even more impressive, the frequency of moderate and severe attacks was reduced by 92 percent; relative to 0.45 severe monthly attacks in the placebo group, there were no attacks in a total of 23 subjects who received either the 40 mg or a smaller 20 mg daily dose.

Earlier this year, Pharvaris initiated its Phase III, placebo-controlled cross-over RAPIDe-3 study to evaluate the efficacy and safety of an immediate-release capsule form of deucrictibant for the on-demand treatment of HAE attacks, including non-severe laryngeal attacks, in patients both using and not using long-term prophylactic medications.

Potentially Curative Gene Editing Therapy

Massachusetts-based Intellia Therapeutics has developed an investigational in vivo CRISPR-based gene editing therapy, dubbed NTLA-2002, that in an ongoing Phase II study has achieved what the company describes as "durable elimination" of HAE attacks in HAE patients. NTLA-2002 is designed to disable the prekallikrein-encoding KLKB1 gene in liver cells to prevent the downstream production of kallikrein, in turn "rebalancing" the HAE patient's kallikrein-kinin pathway and reducing excessive bradykinin production.

At both 25 mg and 50 mg doses, a single infusion of NTLA-2002 in a total of 21 study subjects resulted in an 80 percent reduction in monthly angioedema attacks relative to six risk-matched placebo group subjects. Even more promising, four of 10 subjects dosed with 25 mg and eight of 11 subjects dosed with 50 mg have remained completely attack-free over the 16-week observation period — a complete response with no requirement for any subsequent treatment.[18]

"Phase II data continue to reinforce the potential of a single dose of NTLA-2002 to be a functional cure for patients with HAE," investigators said in a presentation at this year's American College of Allergy, Asthma & Immunology Annual Scientific Meeting in Boston.

Normalizing Life with HAE

HAEA's Medical Advisory Board points out that "HAE is a chronic condition with tremendous variability in symptom quality, frequency and severity," necessitating that "HAE management plans be individualized with treatment tailored to each patient's medical needs, life circumstances and preferences, as well as tolerance of and response to specific medications."[11] This individualized approach, even for individuals with the most severe HAE clinical manifestations, has already allowed many to lead a normal life.

A number of promising new agents in the R&D pipeline are likely to be approved in the very near future, expanding an already impressive range of treatment options — while further increasing the complexity of the HAE management decision process.

But with each unique new therapy will also come the opportunity for clinicians to help more people living with HAE to finally free themselves from this frightening and disabling disease. ❖

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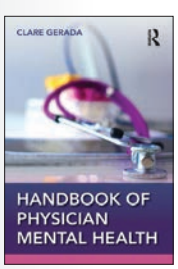

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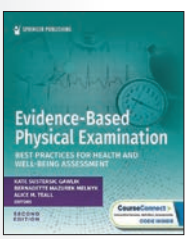

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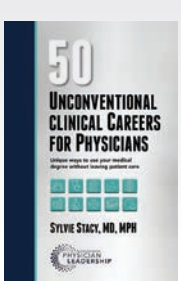
50 Unconventional Clinical Careers for Physicians: Unique Ways to Use Your Medical Degree Without Leaving Patient Care

Author: Sylvie Stacy, MD, MPH



This book is for physicians who are looking to move away from traditional clinical practice and explore new avenues in medicine. Each chapter includes general information about the career area, what physicians do in this type of work and what makes it unconventional. Chapters also cover options for employers or practice types and how to get into this type of career. Each section also includes an interview with a physician who practices in that area, providing readers with a real-world perspective on these careers. As a bonus, part 3 of the book covers how to transition to an unconventional clinical practice. www.amazon.com/50-Unconventional-Clinical-Careers-Physicians-ebook/dp/B0CY39YD4Y

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Medicare Immune Globulin Reimbursement Rates

Rates are effective Jan. 1, 2025, through March 31, 2025

	Product	Manufacturer	J Codes	ASP + 6% (before sequestration)	ASP + 4.3% (after sequestration)
IVIG	ALYGLO	GC Biopharma	J1599	$293.78	$289.07
	ASCENIV	ADMA Biologics	J1554	$989.94	$974.06
	BIVIGAM	ADMA Biologics	J1556	$153.26	$150.81
	GAMMAGARD SD	Takeda	J1566	$162.86	$160.25
	GAMMAPLEX	BPL	J1557	$113.53	$111.71
	OCTAGAM	Octapharma	J1568	$98.60	$97.02
	PANZYGA	Octapharma/Pfizer	J1576	$138.20	$135.98
	PRIVIGEN	CSL Behring	J1459	$98.57	$96.99
	YUMMIGO	Kedrion	J1599	*	*
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$92.92	$91.43
	GAMMAKED	Kedrion	J1561	$98.02	$96.45
	GAMUNEX-C	Grifols	J1561	$98.02	$96.45
SCIG	CUTAQUIG	Octapharma	J1551	$145.12	$142.79
	CUVITRU	Takeda	J1555	$166.11	$163.45
	HIZENTRA	CSL Behring	J1559	$136.37	$134.18
	HYQVIA	Takeda	J1575	$176.87	$174.03
	XEMBIFY	Grifols	J1558	$142.55	$140.26

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

Calculate your reimbursement online at www.FFFenterprises.com.

Immune Globulin Reference Table

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

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

2024-2025 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	3 years and older	90685
AFLURIA (IIV4)	CSL Seqirus	5 mL MDV	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	18 years and older	90682
FLUCELVAX (ccIIV4)	CSL Seqirus	0.5 mL PFS 10-bx	6 months and older	90674
FLUCELVAX (ccIIV4)	CSL Seqirus	5 mL MDV	6 months and older	90756*
FLULAVAL (IIV4)	GSK	0.5 mL PFS 10-bx	6 months and older	90686
FLUMIST (LAIV4)	Astrazeneca	0.2 mL nasal spray 10-bx	2-49 years	90672
FLUZONE (IIV4)	Sanofi	0.5 mL PFS 10-bx	6 months and older	90686
FLUZONE (IIV4)	Sanofi	5 mL MDV	6 months and older	90685
FLUZONE HIGH-DOSE (IIV4)	Sanofi	0.7 mL PFS 10-bx	65 years and older	90662

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

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

2024-2025 COVID-19 Vaccines

Product	Manufacturer	Presentation	Age Group	Code
SPIKEVAX COVID-19 Vaccine, mRNA	Moderna	0.5 mL SDV 10-pk	12 years and older	91322
MODERNA COVID-19 Vaccine, mRNA	Moderna	0.25 mL SDV 10-pk	6 months to 11 years	91321
NOVAVAX COVID-19 Vaccine, Adjuvanted	Novavax	0.5 mL SDV 10-pk	12 years and older	TBD
COMIRNATY COVID-19 Vaccine, mRNA	Pfizer-BioNTech	0.3 mL PFS 10-bx	12 years and older	91320

2024-2025 Respiratory Syncytical Virus (RSV) Vaccines

Product	Manufacturer	Presentation	Age Group	Code
ABRYSVO	Pfizer	0.5 mL Kit 1-ctn	60 years and older	90678
ABRYSVO	Pfizer	0.5 mL Kit 5-ctn	60 years and older	90678
ABRYSVO	Pfizer	0.5 mL PFS and Act-O vials 10-ctn	60 years and older pregnant individuals 32-34 weeks gestation	90678
AREXVY	Pfizer	0.5 mL SDV 10-bx	60 years and older	90679
BEYFORTUS	Sanofi	0.5 mL PFS 5-bx	children up to 24 months	90380
BEYFORTUS	Sanofi	1 mL PFS 5-bx	children up to 24 months	90381
mRESVIA	Moderna	0.5 mL PFS 10-bx	60 years and older	90683

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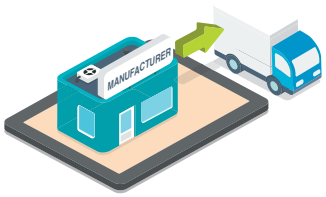
8 Critical Steps

STEP 1

Purchasing

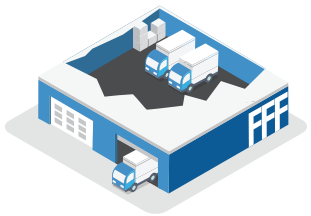
At FFF, we only purchase product from the manufacturer–never from another distributor or source–so the integrity of our products is never in question.



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

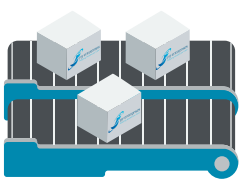
Specialty Packaging

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.

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