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QUARTERLY
FALL 2024 INNOVATION

ChatGPT

How It Is Optimizing Patient Care

Next Generation PCP:
AN EVOLVING CARE MODEL

HOW Gene Therapy
IS CURING DISEASES

ADVANCES IN TREATING
Menopause

INNOVATIONS IN
Bioidentical Hormone
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MYTHS AND FACTS ABOUT
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BioSupply Trends Quarterly is the definitive source for industry trends, news and information for healthcare professionals in the biopharmaceuticals marketplace.

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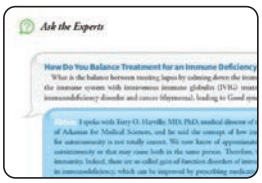

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Innovations Continue to Optimize Patient Care

MUCH HAS BEEN said about provider burnout in recent years. Too many patients; too little time; too few resources. Physicians are burned out, and patients are too. But healthcare continues to evolve and adapt, increasingly using artificial intelligence (AI) to do so.

Tired of long waits for short encounters in which they feel rushed, dismissed or both, patients are taking healthcare into their own hands. But, as we discuss in our article "ChatGPT: Optimizing Patient Care" (p.18), AI is changing how physicians deliver care. They are increasingly turning to AI tools to help them make patient care more efficient, accurate and understandable, freeing them up to focus on the patient instead of the many administrative tasks that impede upon their time.

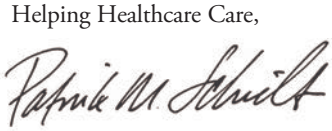
AI is changing the way patients receive care, too. As we discuss in our article "Next-Generation Primary Care: How 'Going to the Doctor' Is Changing" (p.22), patients are learning how both their genetics and their choices affect their health, and they are using AI and other technological tools to help inform their day-to-day decisions. Physicians are using AI and other technologies to stay connected with patients, better understand patient health data and enhance their own medical knowledge.

Interest in the interplay between genetics and health continues to rise, both in terms of preventive medicine and precision medicine. As our article "How Gene Therapy Is Curing Diseases" (p.26) observes, the dream of developing therapies to treat patients with otherwise incurable genetic diseases is becoming a reality: As of this writing, there are 38 gene therapies approved by the United States Food and Drug Administration (FDA) and many more in the pipeline. While the challenges of cost and delivery remain, this article highlights four newly FDA-approved treatments that illustrate the promise gene therapies hold for this patient population.

Several new FDA approvals are cause for celebration in women's health, too. Menopause is a perennial source of discomfort and declining quality of life for many women, but today more than ever, women have many therapeutic options that may help ease its symptoms. Our article "Innovations in Bioidentical Hormone Replacement Therapy" (p.36) takes a closer look at this equivocal therapy and the growing interest in it. And, our article "Advances in Treating Menopause" (p.30) lays out many other viable therapeutic options and emphasizes the importance of medical oversight during each phase of menopause, particularly during postmenopause when womens' risk for osteoporosis and cardiovascular disease goes up.

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

Helping Healthcare Care,



Patrick M. Schmidt
Publisher

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

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HHS Announces Price Cuts for 10 Medicare Drugs

The U.S. Department of Health and Human Services (HHS) has negotiated lower prices for 10 of the most expensive and widely used drugs covered under Medicare, which is expected to save the Medicare program $6 billion in the first year and reduce out-of-pocket costs for beneficiaries by $1.5 billion.

The 10 drugs selected for price reductions in 2026, along with their Medicare costs and the percentage discount from the 2023 list price, are as follows:

1) Eliquis: A blood thinner used to reduce the risk of stroke, costing Medicare $16.5 billion, to be 56 percent cheaper

2) Jardiance: A diabetes and heart failure medication, costing $7 billion, to be 66 percent cheaper

3) Xarelto: Another blood thinner, costing $6 billion, to be 62 percent cheaper

4) Januvia: A diabetes drug, costing $4.1 billion, to be 79 percent cheaper

5) Farxiga: Used for diabetes, heart failure and chronic kidney disease, costing

$3.3 billion, to be 68 percent cheaper

6) Entresto: A heart failure drug, costing $2.9 billion, to be 53 percent cheaper

7) Enbrel: An autoimmune condition treatment, costing $2.8 billion, to be 67 percent cheaper

8) Imbruvica: A leukemia treatment, costing $2.7 billion, to be 38 percent cheaper

9) Stelara: An autoimmune disease treatment, costing $2.6 billion, to be 66 percent cheaper

10) NovoLog, Fiasp (insulin aspart): Insulin products, costing $2.6 billion, to be 76 percent cheaper

The selected drugs accounted for $56.2 billion in Medicare spending in 2023 alone. Nearly nine million Medicare Part D beneficiaries were dispensed these drugs, making them the primary beneficiaries of the price reductions. Before the drug prices were finalized, the Congressional Budget Office estimated drug price negotiations could save the federal government $25 billion by 2031.

The Centers for Medicare and Medicaid Services (CMS) has announced plans to select another batch of drugs for price negotiations next year, with the goal of negotiating prices for up to 15 selected drugs. This process will continue in subsequent years, with CMS selecting up to 20 drugs each year for negotiation. ❖

Health and Human Services Announces Price Cuts for 10 Medicare Drugs, Saving Beneficiaries $1.5 Billion. Global Village Space, Aug. 15, 2024. Accessed at www.globalvillagespace.com/GVS-US/health-and-human-services-announces-price-cuts-for-10-medicare-drugs-saving-beneficiaries-1-5-billion.

CMS Proposes Payment Cut for Physicians

In July, the Centers for Medicare and Medicaid Services (CMS) issued a proposed rule that announces and solicits public comments on proposed policy changes for Medicare payments under the Physician Fee Schedule (PFS) and other Medicare Part B issues effective on or after Jan. 1, 2025. According to CMS, the proposed rule is one of several to create a more equitable healthcare system that results in better accessibility, quality, affordability, empowerment and innovation for Medicare beneficiaries.

By factors specified in law, average payment rates under the PFS are proposed to be reduced by 2.93 percent in 2025 compared to the average amount these services are being paid for most of 2024. The change to the PFS conversion factor incorporates the 0.00 percent overall update required by statute, the expiration of the 2.93 percent increase in payment for 2024 required by statute, and a relatively small estimated 0.05 percent adjustment necessary to account for changes in work relative value units for some services. This amounts to a proposed estimated 2025 PFS conversion factor of $32.36, a decrease of $0.93 (or 2.80 percent) from the current 2024 conversion factor of $33.29. ❖

Calendar Year (CY) 2025 Medicare Physician Fee Schedule Proposed Rule. CMS.gov news release, July 10, 2024. Accessed at www.cms.gov/newsroom/fact-sheets/calendar-year-cy-2025-medicare-physician-fee-schedule-proposed-rule.

SAMHSA Releases Annual National Survey on Drug Use and Health

The U.S. Department of Health and Human Services' (HHS) Substance Abuse and Mental Health Services Administration (SAMHSA) released the results of the 2023 National Survey on Drug Use and Health (NSDUH), which shows how people living in the United States reported their experience with mental health conditions, substance use and pursuit of treatment. The 2023 NSDUH report includes selected estimates by race, ethnicity and age group, and is accompanied by two infographics offering visually packaged highlight data, as well as visual data by race and ethnicity.

"Each year, data from the annual NSDUH provides an opportunity to identify and address unmet healthcare needs across America. We're pleased to see that more people received mental health treatment in 2023 than the previous year," said Miriam E. Delphin-Rittmon, PhD, HHS assistant secretary for mental health and substance use and the leader of SAMHSA.

Highlights of the report can be read at www.hhs.gov/about/news/2024/07/30/samhsa-releases-annual-national-survey-drug-use-and-health.html. ❖

SAMHSA Releases Annual National Survey on Drug Use and Health. U.S. Department of Health and Human Services news release, July 30, 2024. Accessed at www.hhs.gov/about/news/2024/07/30/samhsa-releases-annual-national-survey-drug-use-and-health.html.

FDA Modernizes Informed Consent Guidance, Aligning with Common Rule Changes

The U.S. Food and Drug Administration (FDA) has published new draft guidance on informed consent that lines up with revisions to the Common Rule made in 2017, offering up-to-date recommendations on starting the process with the sharing of essential clinical trial information in ways that patients can understand.

The 16-page guidance, which stresses flexibility in presenting information and encourages sponsors to "develop innovative ways and utilize available technologies to provide key information that will help prospective subjects better understand the reasons why one might or might not want to participate," includes sections on key information and facilitating understanding of that information. For example, FDA believes sponsors should think about using alternative methods for presenting core information in an understandable way such as by consulting with patient advocacy groups and/or potential patients to gather their perspectives. "The key information section could also be presented using alternative media such as illustrations, video and electronic tablets to meet the goals of improving clarity and increasing prospective subjects' understanding of consent information," the guidance adds.

The guidance delves into key elements of informed consent and how to best present them to potential participants:

- Voluntary participation and the right to discontinue participation
- The trial's purpose, expected duration and procedures
- Reasonably foreseeable risks and discomforts
- Reasonably expected benefits
- Appropriate alternative procedures
- Compensation and medical treatments for trial-related injuries
- Participation-related costs

On facilitating understanding, the guidance recommends taking a simple, concise approach by placing information in rounded boxes — "bubbles" — or another format that makes the information easy to read and understand. A two-column text approach, bullet points and "ample white space or empty space around discrete bubbles" can also suffice. The section also includes recommendations on the organization and presentation of the consent form, stressing the use of plain language that combines text with visuals.

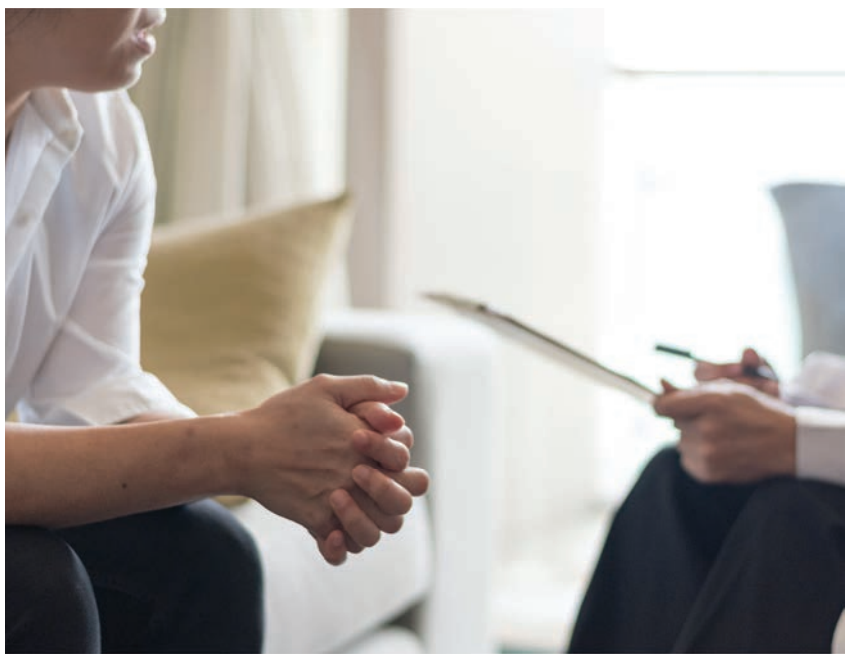
FDA also finalized its guidance on pharmacology considerations for antibody-drug conjugates. Changes from draft to final include:

- Terminology updates and editorial changes for better clarity
- Additional references to FDA guidances
- Additional considerations for dosing strategies ❖

Miessler, J. FDA Modernizes Informed Consent Guidance, Aligning with Common Rule Changes. Center Watch, March 4, 2024. Accessed at www.centerwatch.com/articles/26838-fda-modernizes-informed-consent-guidance-aligning-with-common-rule-changes?

CMS Proposed Payment Rules for 2025

By Bonnie Kirschenbaum, MS, FASHP, FCSHP



HEALTHCARE can be delivered in myriad different sites of care, and each of these has a Centers for Medicare and Medicaid Services (CMS) rule set that governs conditions of participation and the payment for goods and services. These rules and rates are updated and amended every year.

In addition to proposed payment rate changes, this year's proposed rules also include implementing policies that address health disparities, expand access to behavioral healthcare, improve transparency and promote safe, effective, patient-centered care.[1] Here are key highlights of proposed changes for the upcoming year.

New Rules for Inpatient and Long-Term Care Hospitals

Effective Oct. 1, 2024:

- 2.9 percent payment rate increase for hospitals that are meaningful users of electronic health records and submit quality measure data
- Separate inpatient prospective payment system payment for small, independent hospitals to establish and maintain access to essential medicines
- An initiative to address homelessness, which may lead to higher payouts for hospitals treating patients with housing needs
- Requirement for long-term care hospitals to report social needs such as housing and food insecurity

Further, the mandatory Transforming Episode Accountability Model (TEAM) will be implemented on Jan. 1, 2026. TEAM is a five-year demonstration model that will determine whether bundling all costs of care for an episode into an episodic-based payment for several common, high-cost procedures will reduce costs while maintaining quality.

Proposed Changes to Outpatient and Ambulatory Sites of Care

The proposed 2025 outpatient prospective payment system (OPPS), ambulatory surgery center and physician fee schedule (PFS) payment rule sets are being finalized and will begin Jan. 1, 2025. The scope is broad, covering healthcare in all outpatient settings to allow for shifts between various sites of care. Several other pieces of legislation being debated will significantly impact pharmacy practices, from revenue streams, operations and clinical services standpoints and reflect a deeper dive into prior authorizations, pharmacy benefit managers, transparency and site-of-care changes, as well as the 340B program.

Under OPPS, the 2025 drug packaging threshold is proposed to be $140 average sales price (ASP) for all drugs, biologicals and therapeutic radiopharmaceuticals with a proposed separate payment for diagnostic radiopharmaceuticals when their per-day cost exceeds the proposed threshold of $630. OPPS rates have a variable mark-up determined each year, and are remaining at ASP+6%, with the exception of those covered by the Inflation Reducation Act (IRA) at ASP+8%. PFS rates are covered by statute and remain at ASP+6%. Drugs and biologicals are paid for in one of four ways (Table).

Pass-Through Payment Provisions

These require additional payment under Medicare Part B for current orphan

drugs; current drugs and biologicals and brachytherapy sources used in cancer therapy; and current radiopharmaceutical drugs and biologicals. For at least two and up to three years, they also are provided for certain "new" drugs and biologicals whose cost is "not insignificant" in relation to OPPS payments for the procedures or services associated with the new drug or biological. For pass-through payment purposes, radiopharmaceuticals are included as "drugs."

Provisions of the Inflation Reduction Act of 2022

Some provisions of the IRA of 2022, including the Medicare Drug Price Negotiation Program, Medicare Prescription Drug Inflation Rebate Program and the Medicare Part D Redesign Program, are underway and melded into the 2025 rule sets. This can be confusing, especially with regard to biosimilars. Here's an example of how they apply:

• IRA establishes a payment rate for biosimilars under Medicare Part B during the initial period: For biosimilars furnished on or after July 1, 2024, the initial period payment rate is the lesser of the biosimilar's wholesale acquisition cost (WAC) plus 3 percent or 106 percent of the reference product's ASP. Subsequently this increased the Medicare Part B add-on payment for qualifying biosimilars from 6 percent to 8 percent 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.

• Under the OPPS threshold packaging policy, biosimilars are excepted when their reference biologicals are separately paid. (The goal is to promote use as a lower-cost alternative.) If the reference product cost per day falls below threshold, all biosimilars related to it would be similarly packaged regardless of whether their costs per day are above it.

Other Key Revisions and Requirements to Watch

• New status indicators (H1 for non-opioid medical devices for postsurgical pain relief and K1 for non-opioid drugs and biologicals for postsurgical pain relief) to identify products qualifying for separate payment under the new payment policy for non-opioid postsurgical pain management drugs, biologicals and devices to provide additional payments for access to non-opioid pain relief treatments until 2027

• Expanded coverage of hepatitis B vaccinations to beneficiaries who have not been previously vaccinated or whose vaccination status is unknown

• A new payment methodology for supplying and administering dependent care assistance programs such as pre-exposure prophylaxis (PrEP) for HIV consistent with ASP methodology (i.e., ASP+6%) (Use this PrEP payment methodology as it finalizes its national coverage determination moving PrEP coverage from Part D to Part B.)

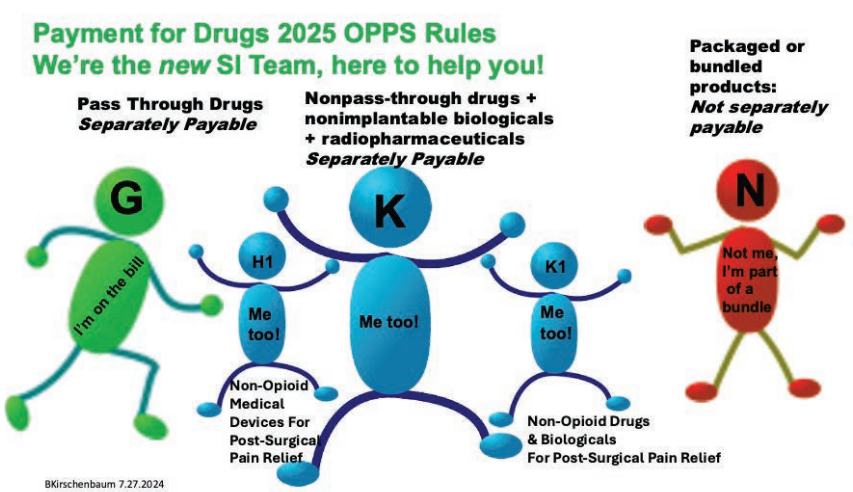
• Revised eligibility requirements in the special enrollment period (SEP) for formerly incarcerated individuals (released on or after Jan. 1, 2025) to tie the eligibility for this SEP to the Social Security Administration's determination that they are no longer incarcerated

• Codified requirement in the Consolidated Appropriations Act, 2023, to provide 12 months of continuous eligibility to children under the age of 19 in Medicaid and CHIP, with limited exceptions

• Updates to the conditions of participation (CoPs) for hospitals and critical access hospitals in an effort to advance the health and safety of pregnant, birthing and postpartum patients

• Separate payments to Indian Health Service (IHS) and tribal hospitals for high-cost drugs furnished in hospital-based outpatient departments through an add-on payment, in addition to the all-inclusive rate (AIR) under the authorities used to calculate the AIR starting Jan. 1, 2025

• Exceptions to the Medicaid clinic services benefit four-walls requirement for



How Drugs and Biologicals Are Paid

New Drugs Not Yet Assigned Unique HCPCS Codes	New Pass-Through Drugs	Non Pass-Through Separately Payable Drugs >$140/Day Based on ASP	Policy Packaged or Lower-Cost Packaged Products Costing ≤$140/Day Based on ASP
	SI G	SI K, K1, H1	SI N
95% of AWP may apply	Appears on the bill as separate line items	Appears on the bill as separate line items	Not on the bill as separate line items; paid as part of the service bundle
See Addendum B for specific payment	ASP+6% Policy packaged offsets may apply	ASP+6%	No change from 2023
	Payment based on WAC+3% until enough ASP data is gathered	Payment based on WAC+3% until enough ASP data is gathered	No separate reimbursement; drug costs are bundled into the procedure
	57 products keep/gain pass-through status Expirations: 25 drugs in 2024, 28 drugs in 2025	AWP-priced drugs: 69.46% AWP JG, TB modifiers remain NEW: radiopharmaceuticals greater than $630 ASP paid separately	1) Due to threshold price of $140/day or 2) Due to statute -Contrast agents -Anesthesia drugs -Implantable biologicals -Diagnostic radiopharmaceuticals -Drugs, biologicals, radiopharmaceuticals used as supplies in a diagnostic test or procedure -Diagnostic drugs, biologicals used as supplies or implantable devices in surgical procedures
	All biosimilars eligible for pass-through, not just the first one for each reference product	Biosimilars excepted from the OPPS threshold packaging policy when their reference biologicals are separately paid Pay separately for biosimilars even if per-day cost is less than the threshold packaging policy	

IHS and tribal clinics, and, at state option, for behavioral health clinics and rural clinics

- Electronic prescribing for controlled substances
- Additional proposed provisions that will impact clinical and distributive services, some of which may be in an incident to arrangement depending on a state's scope-of-practice limitations; payment for remote services that align OPPS payment for services furnished remotely to patients in their homes with payment under PFS includes payment for diabetes self-management training, remote nutrition therapy and mental health services
- New flexibilities for opioid treatment programs (OTPs), including permanently allowing audio-only periodic assessments and allowing the OTP intake add-on code to be furnished via two-way audio-video communications technology when billed for the initiation of treatment with methadone when clinically appropriate; payment increases apply to OTPs, as well as add-on codes for new U.S. Food and Drug Administration-approved opioid agonist and antagonist medications ❖

Reference

1. CY 2025 Medicare Hospital Outpatient Prospective Payment System and Ambulatory Surgical Center Payment System Proposed Rule (CMS 1809-P). CMS news release, July 10, 2024. Accessed at www.cms.gov/newsroom/fact-sheets/cy-2025-medicare-hospital-outpatient-prospective-payment-system-and-ambulatory-surgical-center.

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Going Green in Healthcare

By Rachel Maier, MS

SUSTAINABILITY. Eco-friendly. Going green. When it comes to healthcare, what is the industry imperative behind these buzzwords?

"Going green" in healthcare refers to incorporating environmentally friendly practices into healthcare delivery, according to the Institute of Medicine (IOM).[1] While there isn't a universal dictate for the healthcare industry to go green, many hospitals, clinics and other healthcare facilities are doing so anyway, taking the responsibility to "first, do no harm" one step further by identifying areas outside the scope of direct patient care that negatively affect public health and implementing strategies to promote healthier communities.

After all, the environmental impact of the healthcare industry is staggering. Perhaps it's not surprising since healthcare is always "on," and serving patients around the clock demands constant, concentrated energy use, generates an immense amount of waste and pours pollution into the community — all of which both paradoxically and negatively affects the health of those who work and live near the hospitals and clinics all over the world. According to Global Green and Healthy Hospitals (GGHH), an international network of hospitals and healthcare facilities dedicated to improving healthcare's impact on the environment, the healthcare industry — ironically and unintentionally — contributes to poorer health everywhere, from metropolitan cities to rural villages: "Through the products and technologies it deploys, the resources it consumes, the waste it generates and the buildings it constructs and operates, the health sector is a significant source of pollution around the world, and therefore an unintentional contributor to trends that undermine public health."[2]

The predicament is as much a local issue as a global issue: In the United States, hospitals collectively consume 10 percent of the total energy used by commercial buildings; account for seven percent of commercial and institutional water use; and generate more than five million tons of waste every year, according to Practice Greenhealth, the leading sustainable healthcare organization in North America.[3,4] It's an expensive problem, both in terms of money spent and lives affected. However, identifying ways to implement cleaner, more sustainable practices can save the healthcare industry money and improve the health of the planet and the people who inhabit it.

The Triple Bottom Line

The benefits of going green in healthcare are three-fold: It creates a "triple bottom line" — that is, improved social, environmental and economic outcomes.[1] According to IOM, "A hospital with a successful triple bottom line would boast positive impacts on the health and well-being of its patients, staff and visitors; efficient use of energy and natural resources, with minimal waste and pollution generated; and healthy financial performance."[1] In short, a triple bottom line benefits people, planet and profit:[1]

- *People*. Going green is about improving the health in the local community and communities around the world, ultimately lessening the healthcare industry's contribution to the burden of disease. As GGHH explains, "A green and healthy hospital recognizes the connection between human health and the environment and demonstrates that understanding through its governance, strategy and operations. It connects local needs with environmental action and practices primary prevention by actively engaging in efforts to foster community environmental health, health equity and a green economy."[2] When the environment is cleaner, people are healthier.
- *Planet*. The healthcare industry produces eight percent of total U.S. emissions, and one hospital patient in the U.S. generates about 33.8 pounds of waste every day, which adds up to about six million tons of waste every year.[5] Adopting sustainable practices such as using renewable energy sources and

recyclable or reusable medical equipment can help clean up the air and reduce the volume of waste sent to landfills, conserve and steward scarce resources and ultimately help clean up the environment, making the surrounding community healthier.[6]

• *Profit*. The U.S. healthcare industry comprises one-sixth of the American economy and spends $8 billion on energy every year, but implementing energy-saving practices could significantly lower that figure, which experts say would, in turn, yield more profit.[3] According to Energy Star, an agency administered by the U.S. Environmental Protection Agency that helps consumers identify and implement energy-efficient best practices, the savings of switching to clean, efficient energy sources in healthcare is comparable to generating new revenue. "Every $1 a nonprofit healthcare organization saves on energy is equivalent to generating $20 in new revenues for hospitals or $10 for medical offices."[7] Switching to renewable energy can reduce a healthcare facility's carbon footprint and bolster its bottom line.

Seven Simple Steps to a Greener Facility

Implementing a green strategy in healthcare facilities boils down to assessing and addressing eight essential areas of operations: buildings, chemicals, energy, food, sustainable procurement, transportation, waste and water. With so many pieces of this clean and green puzzle to fit together efficiently, you may wonder where to start or whether it's possible for your practice or facility to make a meaningful difference. It may be helpful to remember that at its heart, going green is about doing the best you can with what you have and stewarding resources to yield the best possible outcomes for your organization and local community. Taking stock of your buildings, policies, practices and people and identifying how to take better care of them is the best first step to take.

Here are seven simple steps to get you started:[7,8]

1) Identify areas for improvement. Measure and track current energy performance; ensure all equipment is functioning as specified and designed; and make a strategy for how to implement improvements over time.

2) Make simple changes. Retrofit inefficient lighting; install variable frequency drives and energy-efficient motors; balance air and water systems; and adjust thermostats for seasonal changes and occupancy.

3) Improve waste production and management. Move away from single-use, disposable items such as meal trays, utensils and medical gowns and use their reusable or compostable counterparts instead. Ensure effective waste separation and recycling methods are in place and being used properly.

4) Switch to safer cleaning supplies made without harsh chemicals. Use biodegradable, nontoxic, plant-based cleaners and disinfectants to lower the volatile organic compounds released by conventional cleaners.

5) Invest in energy-saving equipment. Install efficient heating, ventilation and air conditioning systems. Replace office, electronic and commercial cooking equipment with energy-efficient models.

6) Buy local, sustainable products whenever possible. Also referred to as "environmentally preferable purchasing," sustainable procurement prioritizes purchasing sustainable equipment and supplies to reduce exposure to toxins and minimize waste production. Purchase from local and/or fair trade suppliers whenever possible.

7) Educate staff and patients about how their behaviors affect energy consumption and waste production.

An Ongoing Effort

Going green is not an overnight exercise. Instead, it is an ongoing effort that requires vision, collaboration, strategy and funding. If your organization needs help identifying and implementing a greener strategy, consider working with a sustainability consulting firm that specializes in the healthcare industry. (Try an Internet search for "sustainable healthcare consulting firms" to get started.) These groups work with healthcare organizations to develop realistic, actionable plans to make their facilities and practices cleaner, greener and healthier for everyone. It is a tall order, but one well worth the investment, as it demonstrates leadership in the community, cleans up the environment, saves money and — perhaps most importantly — protects and promotes health.[1] ❖

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Medicines

FDA Approves Epinephrine Nasal Spray

The U.S. Food and Drug Administration (FDA) has approved the first needle-free alternative to the EpiPen. ARS Pharmaceuticals' Neffy is a single-use epinephrine nasal spray for the emergency treatment of allergic reactions, including anaphylaxis, in adult and pediatric patients who weigh at least 30 kilograms (about 66 pounds).

Approval comes after FDA declined to approve Neffy in 2023, asking the manufacturer to complete a study comparing repeat doses of Neffy to repeat doses of epinephrine injection. Neffy is a single-dose nasal spray administered into one nostril. A second dose (using a new nasal spray in the same nostril) may be given if there is no improvement in symptoms or if symptoms worsen.

The approval represents the first significant change in epinephrine delivery in more than 35 years. "This approval marks a watershed moment in addressing an unmet medical need for people with type 1 allergies — a treatment alternative that avoids the need to inject epinephrine with a needle, which can be fraught with anxiety and fear for many," said Richard Lowenthal, MS, MSEL, ARS co-founder, president and CEO. ❖

Weixel, N. FDA Approves Epinephrine Nasal Spray, a Needle-Free Alternative to EpiPen. The Hill, Aug. 9, 2024. Accessed at thehill.com/policy/healthcare/4820727-fda-approves-epinephrine-nasal-spray.

Medicines

Updated COVID Vaccines Approved by FDA

The U.S. Food and Drug Administration (FDA) has approved and granted emergency use authorization for updated mRNA COVID-19 vaccines (2024-2025 formula) to include a monovalent (single) component that corresponds to the Omicron variant KP.2 strain of SARS-CoV-2. The mRNA COVID-19 vaccines have been updated with this formula to more closely target currently circulating variants and provide better protection against serious consequences of COVID-19, including hospitalization and death. Today's actions relate to updated mRNA COVID-19 vaccines manufactured by ModernaTX Inc. and Pfizer Inc.

The updated mRNA COVID-19 vaccines include Comirnaty and Spikevax, both of which are approved for individuals 12 years of age and older, and the Moderna COVID-19 and Pfizer-BioNTech COVID-19 vaccines, both of which are authorized for emergency use for individuals 6 months through 11 years of age.

Unvaccinated individuals 6 months through 4 years of age are eligible to receive

three doses of the updated, authorized Pfizer-BioNTech COVID-19 vaccine or two doses of the updated, authorized Moderna COVID-19 vaccine. Individuals 6 months through 4 years of age who have previously been vaccinated against COVID-19 are eligible to receive one or two doses of the updated, authorized Moderna or Pfizer-BioNTech COVID-19 vaccines (timing and number of doses to administer depends on the previous COVID-19 vaccine received).

Individuals 5 years through 11 years of age regardless of previous vaccination are eligible to receive a single dose of the updated, authorized Moderna or Pfizer-BioNTech COVID-19 vaccines; if previously vaccinated, the dose is administered at least two months after the last dose of any COVID-19 vaccine. Individuals 12 years of age and older are eligible to receive a single dose of the updated, approved Comirnaty or the updated, approved Spikevax; if previously vaccinated, the dose is administered at least two months since the last dose of any COVID-19 vaccine.

Additional doses are authorized for certain immunocompromised individuals ages 6 months through 11 years of age as described in the Moderna COVID-19 and Pfizer-BioNTech COVID-19 vaccine fact sheets.

For approvals and authorizations of the mRNA COVID-19 vaccines, FDA assessed manufacturing and nonclinical data to support the change to include the 2024-2025 formula. The updated mRNA vaccines are manufactured using a similar process as previous formulas of these vaccines. ❖

FDA Approves and Authorizes Updated mRNA COVID-19 Vaccines to Better Protect Against Currently Circulating Variants. U.S. Food and Drug Administration news release, Aug. 22, 2024. Accessed at www.fda.gov/news-events/press-announcements/fda-approves-and-authorizes-updated-mrna-covid-19-vaccines-better-protect-against-currently.

Research

mRNA Cancer Therapy Boosts Immune Response

An investigational, individualized neoantigen therapy, with personalized encoded mRNA, has demonstrated potential to enable patients' immune systems to target cells that cause cancer.

The Phase I study evaluated the novel therapy mRNA-4157 (V940) in 16 patients, four of whom had resected non-small cell lung cancer and 12 of whom had resected cutaneous melanoma. The researchers encoded the patients' top neoantigens into each mRNA therapy. Melanoma patients were treated with both mRNA-4157 (V940) and the immune checkpoint inhibitor pembrolizumab.

Analysis from the study revealed mRNA-4157 (V940) "induced multiple forms of T cell proliferation, both alone and in conjunction with pembrolizumab." mRNA-4157 (V940) treatment was not associated with dose-limiting toxicity. The findings point to the long-term potential of the mRNA therapy. T-cell response to neoantigens was found to remain 30 weeks posttreatment, according to study data. The low toxicity of mRNA-4157 (V940) could help simplify "combining individualized neoantigen therapies and other immunotherapies," explained the researchers.

"We are entering an era in which we have the tools to make cancer therapies more precise and more personalized," said corresponding author Justin Gainor, MD, program director of the Center for Thoracic Cancers at Massachusetts General Hospital. "We've shown that we can develop an individualized neoantigen therapy by leveraging the specific characteristics of a given patient's tumor and cell type. This therapy was both safe and immunogenic, meaning that we were able to amplify existing responses and induce brand-new, long-lasting immune responses." ❖

Eckford, C. Personalised mRNA Cancer Therapy Shown to Boost Immune Response. *European Pharmaceutical Review*, Aug. 8, 2024. Accessed at www.europeanpharmaceuticalreview.com/news/232296/personalised-mrna-cancer-therapy-shown-to-boost-immune-response.

Medicines

FDA Approves Additional Indication for Fibryga

Octapharma USA's Fibryga (fibrinogen [human] lyophilized powder for reconstitution) has received U.S. Food and Drug Administration (FDA) approval for an additional indication: fibrinogen replacement in bleeding patients with acquired fibrinogen deficiency (AFD). As the first and only on-demand, virus-inactivated, human plasma-derived fibrinogen concentrate option with this approval, Fibryga represents a rapid and more precise option for severe bleeding scenarios than the current standard of care (cryoprecipitate).

The expanded FDA approval of Fibryga was based on the FIBRES [FIBrinogen REplenishment in Surgery] study published in *JAMA*, which was a head-to-head, multicenter, randomized clinical trial of 735 patients, demonstrating that fibrinogen concentrate was noninferior to cryoprecipitate and may be used instead of cryoprecipitate for the treatment of bleeding related to AFD. Fibryga had already received regulatory approval for the treatment of AFD in both the European Union in 2019 and Canada in 2020.

"In the surgical theater, time matters. And confidence matters. This expanded FDA approval of Fibryga represents a major step forward in our commitment to redefining the standard of care for patients experiencing major bleeding. It provides an important option for providers who must act urgently," said Flemming Nielsen, president of Octapharma USA. "We are proud to be the first to offer this therapeutic advancement — and a new standard of care — to hospitals, anesthesiologists, surgeons, OB/GYNs and patients across the United States."

This approval marks the third FDA approval received to date for Fibryga. In 2017, FDA granted an approval for acute bleeding episodes in adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. A second was received in 2020 for pediatric patients under 12 years for treatment of acute bleeding episodes in congenital fibrinogen deficiency. ❖

FDA Approves Additional Indication for Fibryga® for Fibrinogen Supplementation in Bleeding Patients with Acquired Fibrinogen Deficiency, Potentially Ushering in a New Standard of Care. Octapharma USA press release, Aug. 1, 2024 Accessed at www.prnewswire.com/news-releases/fda-approves-additional-indication-for-fibryga-for-fibrinogen-supplementation-in-bleeding-patients-with-acquired-fibrinogen-deficiency-potentially-ushering-in-a-new-standard-of-care-302213110.html.

ChatGPT

Optimizing Patient Care

The accomplishments of AI in the healthcare sector are impressive, but as AI continues to improve patient care and enhance provider skills, addressing its challenges will be critical.

By Lee Warren

ARTIFICIAL INTELLIGENCE (AI) in healthcare is growing at an unprecedented rate (Figure 1). Since OpenAI's ChatGPT (generative pre-trained transformer) was introduced to the world in November 2022, it has accomplished some amazing feats, including passing law exams at the University of Minnesota and the University of Pennsylvania's Wharton School of Business,[1] acing standardized tests and even helping to diagnose diseases that have sometimes baffled medical professionals.

One such medical case occurred when a woman's nanny told her that her 4-year-old son, Alex, needed Motrin every day before he could play, otherwise he had a meltdown. Over the next three years, Alex's mom, Courtney, took him to a dentist and 17 different doctors to try to determine the cause of his pain but had no success. Frustrated, Courtney opened ChatGPT one night after an emergency room (ER) visit and fed the AI opensource platform everything she knew about her son's symptoms, using data from her son's medical charts. ChatGPT suggested her son had tethered cord syndrome. Courtney scheduled an appointment with a neurosurgeon and told her what she suspected. The neurosurgeon ordered an MRI, then confirmed the diagnosis, allowing Alex to undergo surgery to correct the condition.[2]

While impressive, ChatGPT has some limitations. Researchers from the Innovation in Operations Research Center at Mass General Brigham (MGB) trained ChatGPT on all 36 published clinical vignettes from the Merck Sharpe and Dohme clinical manual and compared its accuracy on differential diagnoses, diagnostic testing, final diagnosis and management based on patient age, gender and case acuity. They concluded that ChatGPT achieved a diagnostic accuracy rate of 71.7 percent, comparable to human doctors in some scenarios. ChatGPT not only came up with possible diagnoses, but also made final diagnoses and care management decisions.[3] It demonstrated the highest performance in making a final diagnosis with an accuracy of 76.9

percent and the lowest performance in generating an initial differential diagnosis with an accuracy of 60.3 percent.[4] As such, physicians will continue to play a critical role in interpreting ChatGPT data as they seek the best possible care for their patients.

"ChatGPT struggled with differential diagnosis, which is the meat and potatoes of medicine when a physician has to figure out what to do," said Marc Succi, MD, associate chair of innovation and commercialization and strategic innovation leader at Mass General Brigham and executive director of its MESH Incubator's Innovation in Operations Research Group, in a statement. "That is important because it tells us where physicians are truly experts and adding the most value — in the early stages of patient care with little presenting information, when a list of possible diagnoses is needed."[3]

How Is AI Trained?

AI systems work by using algorithms and data. Data is collected and applied to mathematical models, or algorithms, which then use the information to recognize patterns and make predictions. Once algorithms have been trained, they are deployed within various applications where they continuously learn from and adapt to new data. This allows AI systems to perform complex tasks such as image recognition, language processing and data analysis with greater accuracy and efficiency over time.[5]

Beyond assisting with diagnoses, there are many more ways ChatGPT can benefit everyone involved in the healthcare process.

Minimizes Wait Times

Humber River Hospital in Toronto was the first in Canada to use AI to track and control patient flow. It is also being used there to analyze medical images to expedite pathology assessments, and it is being used to assist with making faster and more accurate diagnoses. What's more, AI is allowing doctors to obtain a more comprehensive understanding of patients' mental health by gathering feedback and following trends.[6]

In one study, ChatGPT-4 provided imaging recommendations and generated radiology referrals using clinical notes from ER cases. After evaluation by experts based on clarity, clinical relevance and differential diagnosis, the chatbot responded in approximately 95 percent of the cases, using the American College of Radiology Appropriateness Criteria (ACR AC) as the reference standard. More specifically, two radiologists compared ChatGPT's responses to the ACR AC, giving the chatbot mean scores of 4.6 and 4.8 (out of 5.0) for clarity, 4.5 and 4.4 for clinical relevance and 4.9 (from both readers) for differential diagnosis.[7] This reduces the likelihood of unnecessary or incorrect imaging, helps radiologists understand the clinical context better and can expedite diagnosis and treatment for patients.

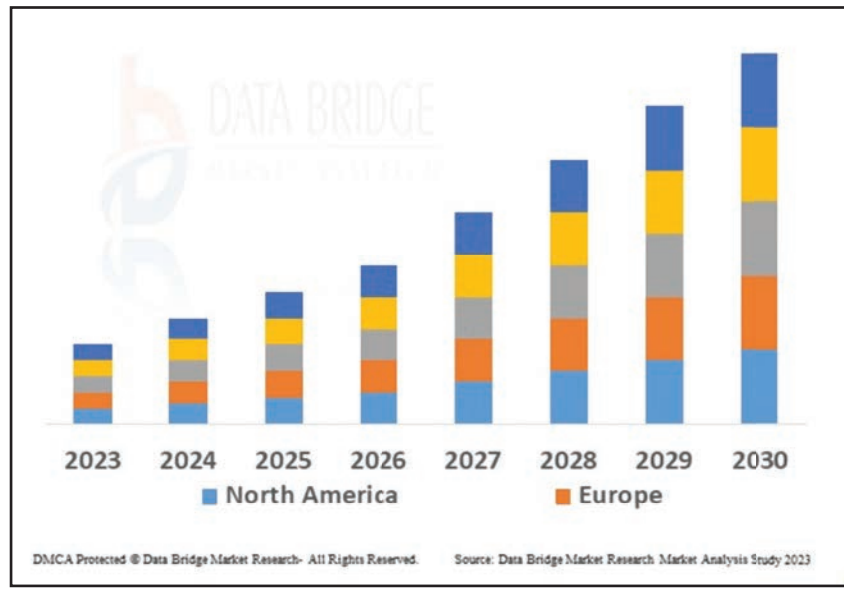
Assists Patient Understanding

The 21st Century Cures Act requires all providers to release medical notes to patients, but sometimes the clinical notes provided by doctors can be confusing. Health tech company Vital launched an AI-powered doctor-to-patient translator that turns medical terminology into plain language at a fifth-grade reading level, according to Aaron Patzer, co-founder and CEO at Vital.[8] This not only benefits patients, but clinicians as well, since they will have fewer patients confused by their notes.

Patients can also use other large language models (LLMs) such as ChatGPT to find clarity in the notes provided by their physicians. In a Yale University study involving 750 radiology reports, four different LLMs were tested — including ChatGPT, Bard and Bing — and found that all four were able to

Figure 1. Global AI Healthcare Market

Experts predict the global AI in healthcare market value will reach $272.91 billion by 2030.



Source: AI in Healthcare – Statistics and Trends. FreeAgent, March 15, 2023. Accessed at resources.freeagentcrm.com/ai-in-healthcare-statistics.

significantly simplify report impressions for patients with simple prompts such as, "I am a patient. Simplify this radiology report" and "Simplify this radiology report at the seventh grade level."[9]

In another study, 15 radiologists were tasked with rating the quality of simplified radiology reports by ChatGPT with respect to their factual correctness, completeness and potential harm for patients. The Likert scale analysis and inductive free-text categorization were used to assess the quality of the simplified reports. Most of the 15 radiologists agreed that the simplified reports were factually correct, complete and not potentially harmful to patients. One of the study's concluding points was that LLMs such as ChatGPT have vast potential to enhance patient-centered care in radiology and other medical domains, while still needing supervision by medical experts.[10]

Improves Efficiency

Improved efficiency is especially true as it relates to telehealth where it can provide preliminary consultations, gather patient history, schedule virtual appointments, transcribe patient conversations and general visit summaries, and offer initial medical advice, improving access to healthcare and reducing the burden on healthcare professionals. ChatGPT can also analyze vast amounts of medical literature and patient data to assist medical professionals in interpreting test results.[11]

Patients can use ChatGPT for real-time information about drugs, including side effects, proper dosage, administration, storage of medication, interactions and potential contraindications. The AI tool also provides potential alternatives for patients who are allergic or intolerant to specific prescriptions, and healthcare providers can use it to stay informed about new medications, drug recalls and other important updates in the pharmaceutical industry.[12]

ChatGPT may also offer nurses on-demand access to recent research and recommendations for remote patient monitoring, as well as offer support and guidance in real-time during physical checkups of patients. This may allow nurses to make better judgments and offer better care.[13]

Useful for Medical Training

Medical students at NYU Grossman School of Medicine are using ChatGPT to curate educational resources based on the diagnoses of patients being treated. This AI-driven system links patient data with relevant learning materials such as infographics and the latest medical literature, delivering customized educational content to students. ChatGPT is also being used to create virtual patients for training purposes, allowing students to practice interviewing patients and diagnosing conditions with feedback provided by AI.[14]

"I think in the future, we're going to see medical education models that have AI as a copilot sitting next to the student, sitting next to their faculty and coaches, providing guidance and advice along the way, curating curricula and assessments, and [...] at the level of that individual student, tailoring what they learn and how they learn so that they make the absolute best use of their time," said Marc Triola, MD, associate dean of education informatics and director of the Institute for Innovations in Medical Education at NYU Grossman School of Medicine.[14]

The benefit of ChatGPT goes beyond medical students: It can help provide additional training to doctors, too. Richmond University Medical Center conducted a proof-of-concept study that demonstrated how ChatGPT could teach physicians how to break bad news to patients. The study found that using the AI tool to role-play can be beneficial in improving communication skills in high-stress situations.[15] The process uses a standardized framework for breaking bad news known as SPIKES (Setting up, Perception, Invitation, Knowledge, Emotions with Empathy, and Strategy or Summary), and then the chatbot grades physicians on how well they did.

Drawbacks and Concerns

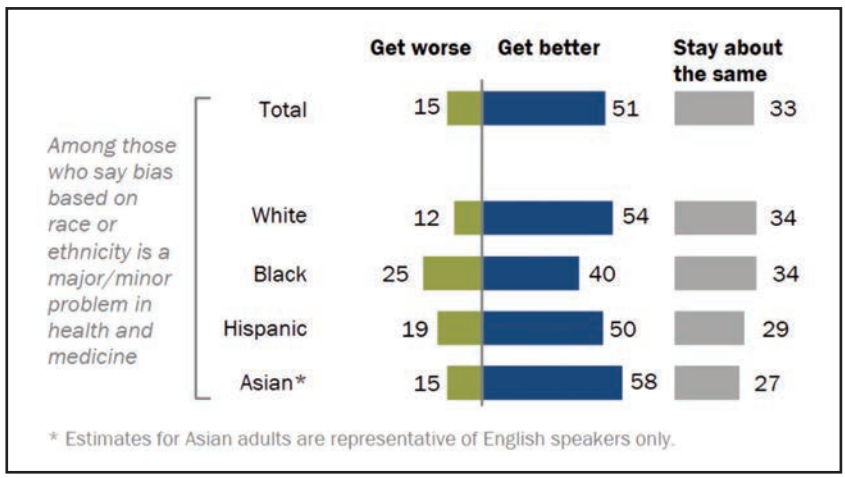
As mentioned, ChatGPT won't replace medical professionals. Instead, it will assist them in offering the highest quality of care possible. The use of AI technology in healthcare does come with some concerns, though.

"Hallucinations" are near the top of the list. IBM defines hallucinations this way: "AI hallucination is a phenomenon wherein a large language model (LLM) — often a generative AI chatbot or computer vision tool — perceives patterns or objects that are nonexistent or imperceptible to human observers, creating outputs that are nonsensical or altogether inaccurate."[16] ChatGPT comes with a disclaimer for every user: "ChatGPT can make mistakes. Check important info." As such, even though the AI tool has proven to be effective when it comes to diagnoses, medical education, streamlining the healthcare process and patient understanding, it is not a substitute for proper medical oversight.

Privacy is also a concern. Healthcare institutions manage these concerns through rigorous data privacy measures and compliance with legal standards such as Health Insurance Portability and Accountability Act in the United States and General Data Protection Regulation in the European Union. They do so by using encryption and anonymization to protect patient data during collection,

Figure 2. Ethnic Biases in Healthcare

Fifty-one percent of U.S. adults who say ethnic biases in healthcare are a problem believe AI will reduce bias.



Source: AI in Healthcare – Statistics and Trends. FreeAgent, March 15, 2023. Accessed at resources.freeagentcrm.com/ai-in-healthcare-statistics.

transmission and storage. They also implement robust access controls such as role-based permissions and two-factor authentication to ensure only authorized personnel can access sensitive information. Stanford Medicine uses a framework called ACCEPT-AI (Age, Communication, Consent and assent, Equity, Protection of data, and Technological considerations) to handle sensitive data, especially pediatric data, ethically. This framework guides researchers and clinicians in addressing consent and data protection issues.[17]

Finally, biases and fairness are a concern. AI models can inherit biases present in the training data, leading to unequal treatment of patients based on race, gender, socioeconomic status or other factors, which can exacerbate existing health disparities (Figure 2). In 2023, the Agency for Healthcare Research and Quality and the National Institute on Minority Health and Health Disparities convened a panel to examine and address the impact of healthcare algorithms on racial and ethnic disparities in healthcare. This resulted in five guiding principles for mitigating and preventing racial and ethnic bias in healthcare algorithms.[18] And, the Cleveland Clinic has an AI task force that evaluates algorithms for quality, ethics and bias to mitigate health disparities and ensure responsible AI use.[19] These types of guidelines and oversights of AI models will be crucial moving forward to ensure equitable output.

The Future of AI

As ChatGPT and other LLM technologies advance, they are expected to significantly enhance diagnostic accuracy and support personalized medicine by analyzing extensive patient data more effectively. Advancements in AI-driven medical training and virtual simulations will continue to refine the skills of healthcare professionals.

However, addressing ethical and regulatory challenges will be crucial. Ensuring data privacy, minimizing biases and maintaining the integral role of human expertise in patient care will need to remain key priorities. As AI tools evolve, ongoing collaboration between technologists, healthcare providers and policymakers will be essential to fully realize their benefits while mitigating risks. But with proper oversight, it can be used as a tool of great significance in facilitating better health. ❖

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Next-Generation Primary Care:
How "Going to the Doctor" Is Changing

The future of healthcare is being driven by digital transformations and emerging technology that provide preventive, personalized and predictive medicine.

By Amy Scanlin, MS

AS THE HEALTHCARE industry continues to suffer from provider shortages and increasing costs, the opportunity to rethink how patients receive care is leading to a collaborative and cohesive provider/patient approach. Supported by an acceleration in technological innovations, soon "going to the doctor" will encompass data as a decision-making tool like never before.

Today's patients are seeking a proactive approach to their healthcare journey. As wearables and software as service devices are providing increasingly complex information and suggesting clear linkages between choices, genetics and their direct impacts on health quality and longevity, interest in biometric feedback is gaining speed.

The expectation in today's connected world is for providers to be able to use patient-generated data and make informed decisions from it. The challenge for many providers, however, is the amount and speed in which data pours into the healthcare system, limiting an ability to use it to its fullest potential. By current estimates, 97 percent of data in hospitals already goes unused,[1] and the exponential growth of medical knowledge continues to double every 72 days.[2] This immense overload of information, coupled with the challenge of parsing out which data is most beneficial for the creation of a personalized care approach, can place roadblocks between providers and patients.

In some cases, data overload is prompting calls for specializations within healthcare fields that include data architecture and analysis that support subspecializations to aggressively target patients' specific disease states.

To that end, research and development funding in support of enhanced digital tools for the benefit of preventive, personalized and predictive medicine is increasing, as is support for AI-supported decision-making, diagnostics and specialty medicine programs. All of this data requires an analytical assessment to most effectively interpret and provide meaningful information that providers can use in determining patient care.

Productivity

In an industry in which an increasing patient load is leading to reduced time spent with each individual, AI tools, when properly integrated and interconnected, may be able to offer a solution to an overscheduled, overburdened workforce. Automating routine paperwork, billing, insurance and scheduling are some key areas where AI-enabled tools are already offering time-saving assistance. AI is also being studied and strengthened to support decision-making. Even newer AI technologies, known as ambient intelligence, are coming into the marketplace. Ambient intelligence listens and transcribes patient-provider conversations so that it can analyze the type of visit, input that information into electronic medical records (EMRs) and assign CPT billing codes. Providers need

never turn away from their patients to add notes into an EMR.[2]

Smart technologies are helping to improve the healthcare experience for both patients and clinicians. Patients appreciate that smart technologies allow their provider to better focus on their needs, and physicians may find use of AI means less time required for administrative duties. Work-life balance is a significant frustration for healthcare professionals as cited in a GE HealthCare study titled "Reimagining Better Health,"[3] and the administrative duties related to patient care is one such cause prompting some clinicians to leave the industry. If things do not improve, there may be a projected 12.9 million worldwide shortage of healthcare professionals by 2035.[4]

Though touted by some and distrusted by others, AI language learning models are here to stay and will continue to improve. By 2030, use of AI natural language processing is not only expected to be widespread, but predictive analytics is expected to be functional by 2035.[5]

Proactivity

Today's connected patients are interested in and well-informed about their healthcare risks, using data to inform behaviors as they take greater control of their healthcare journey. This proactive interest is leading to a greater emphasis on design of preventive care plans tailored to patients' needs as opposed to treating conditions once they arise.

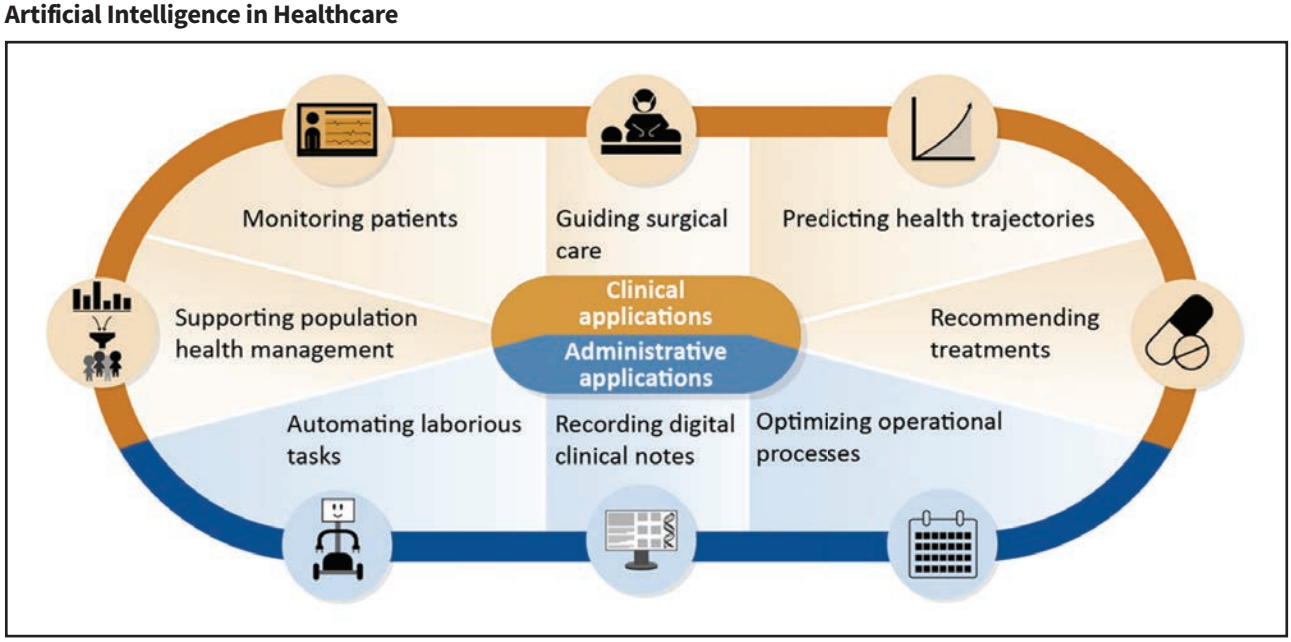
In the current healthcare model that favors treatment over prevention, 80 percent of health dollars are spent on 20 percent of patients. This trend is expected to continue with expenditures reaching $7 trillion by 2030 and $11.8 trillion by 2040. However, at the same time, expenditures on health promotion services are also expected to grow to approximately $8.3 trillion by 2040.[6] Spending on wellness devices and software apps, in particular, is growing as interest in innovation, accelerated technologies, data interoperability, architecture and analysis is helping to positively influence disease prevention by reducing health risks and delaying disease onset thanks to earlier diagnoses.

By some estimates, 16 percent of global consumers surveyed own a wearable device that tracks or monitors their health, and in the U.S., 14 percent of those surveyed had been prescribed a mobile health app by a healthcare provider. With an interest in health technologies comes an opportunity for providers to help patients understand the data their devices provide and to make informed choices based on this data. And while data delivered by mobile devices rarely makes its way into patients' EMRs today, it can still be integrated into traditional healthcare.[5]

Greater Specialization

As the pace of research and available data grow, some have questioned whether there is too much new healthcare information for generalists to stay on top of. Aging baby boomers (almost one-third of the world's population will

Artificial Intelligence in Healthcare



Source: Artificial Intelligence in Health Care: Benefits and Challenges of Technnologies to Augment Patient Care. U.S. Government Accountability Office, Nov. 30, 2020. Accessed at www.gao.gov/products/gao-21-7sp.

be 65 and older by 2025),[5] companion diagnostics, personalized care and an ever-increasing detailed knowledge of every known and emerging health condition are prompting the need for specialized care with subspecialty groups emerging.

Although consumers are collecting and using data specific to their own health, the prevalence of chronic conditions and our understanding of them continues to grow. Some specializations are specific to diagnoses, treatment and care management. Still other specializations focus on how to set up and use AI technologies to benefit healthcare systems and workplaces. Subspecialties are laser focused on the intricacies of specific diseases or treatments, and how to parse big data to generate personalized, meaningful data. As AI technologies continue to evolve, being able to identify pertinent information from it will evolve, too, causing data to become more broad but also more laser-focused. Medical specialists and subspecialists will rely on data specialists to support their analysis and decision-making tools for the benefit of patients.

Using Data to Support Telehealth Systems

Virtual care is a familiar solution that continues to ease scheduling burdens while improving access to care. As technology advances and remote monitoring of portable data becomes better integrated with standard healthcare metrics, consumers may one day be able to bypass routine telehealth appointments in favor of addressing many of their own healthcare needs at home.

In some cases, providers assign patients responsibility for monitoring their own "always-on" health data and basic diagnostic testing so they can report updates through patient portals. In other cases, wearables report this data directly back to healthcare providers or software as service providers with data directly ported into patients' EMRs. Virtual real-time monitoring and reporting is helping to improve patient outcomes since it can eliminate or reduce the costs required for routine office visits.

Combining virtual and in-person care is another approach that is easing bedside staffing burdens. For example, in-person physical examinations remain a cornerstone of patient care, but administrative tasks such as discharge paperwork, care instructions and follow-up appointment scheduling can be handled by a remote provider."[7]

The Way Ahead

Providers should think about preparing for a future of connected and integrated healthcare by taking a hard look at their current capability gaps and budgeting needs to fill them. Examples include replacing outdated software to capture always-on patient data, improving high-speed connectivity and developing staff and patient buy-in of new systems that include training on how to use them most effectively. Hesitation in a new and disruptive digital world can be eased by thoughtfully approaching the problem. Think about what kind of data should be collected and how it will be used and secured. Include whether new data and analytics specialties will need to be brought online to analyze and interpret.

Maintaining a personal connection between providers and patients is imperative, particularly in a digital, virtual world. In fact, strengthening these relationship practices and bringing digital tools online may be more critical to long-term success than ever. Equally important to communicating how to use these new technologies is why they have been incorporated into the care environment and how they will benefit the processes currently in place.

Consider new technology plans, particularly from patients' points of view with a special eye toward those who may be technology disadvantaged. Some, hopefully most, patients will be excited by the updates and enthusiastic for the increased participation and collaboration in their own care. But others may feel confusion and frustration, particularly those who value human interaction over technology.

Special attention must be given during any transitions to ensure no patients, regardless of their interest in and aptitude for technology, feel left behind. While digital technology is certainly not expected to replace in-person care, patients who are engaged in a digital future could replace their providers if they do not integrate into the digital world.[8] Even so, these tech-inclined patients are not the only individuals who must be considered.

In the rapidly changing healthcare industry, fueled in large part by digital transformations and emerging technology, the evolving healthcare model is likely to look quite different from today's. Use of wearables and analysis of patient data generated from them are driving a future of precision patient care and enabling rapid interventions for the benefit of all.[6] ❖

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How Gene Therapy Is Curing Diseases

For patients with genetic disease, recent evolution of and FDA approval for gene therapies are transforming care and turning an ambitious dream into a life-changing reality. But getting affordable treatments to patients safely and efficiently remains a challenge.

By Diane L.M. Cook

GENE THERAPY was first conceptualized in the 1960s but got its official start in 1972 when Theodore Friedmann and Richard Roblin published a paper in *Science* titled, "Gene therapy for human genetic disease?" which cited Stanfield Roger's proposal in 1970 that exogenous good DNA could be used to replace defective DNA in people with genetic disorders.[1]

The 1980s mostly consisted of research, and in the 1990s, the first clinical trials were conducted. But the death of three patients in 1999, 2003 and 2007 put a damper on gene therapy research. However, since the 2010s, research has been moving forward again with promising results.

The U.S. Food and Drug Administration (FDA) describes gene therapy as a technique that modifies a person's genes to treat or cure disease. Gene therapies can work either by replacing a disease-causing gene with a healthy copy of the gene; inactivating a disease-causing gene that is not functioning properly; or introducing a new or modified gene into cells to help treat a disease.[2]

Pfizer Inc.

On April 26, 2024, FDA approved Pfizer Inc.'s BEQVEZ to treat adults with moderate to severe hemophilia B who currently use factor IX (FIX) prophylaxis therapy; have current or historical life-threatening hemorrhage; or have repeated, serious spontaneous bleeding episodes, and do not have neutralizing antibodies to adeno-associated virus (AAV) serotype Rh74var (AAVRh74var) capsid, as detected by an FDA-approved test.

BEQVEZ is a one-time gene therapy with the potential to transform care for appropriate patients by reducing both the medical and treatment burden over the long term compared to factor replacement prophylaxis.

BEQVEZ is an AAV-based gene therapy designed to introduce in the transduced cells a functional copy of the FIX gene, encoding a high-activity FIX variant. For eligible patients living with hemophilia B, the goal of this gene therapy is to enable them to produce FIX themselves via this one-time treatment rather than having to receive frequent infusions of FIX, which is the current standard of care.

BEQVEZ is now available by prescription to eligible patients. "As we focus our attention on ensuring access and operational readiness, we have proactively worked with payers and treatment centers to help ensure healthcare systems are appropriately prepared to deliver BEQVEZ. We are also launching a warranty program based on durability of response for patients, with the goal of providing greater certainty to payers, maximizing access for eligible patients who receive BEQVEZ and offering financial protection by insuring against the risk of efficacy failure," says Sonal Bhatia, MD, senior vice president and head of U.S. specialty care medical affairs at Pfizer.

BEQVEZ will be administered via a one-time single-dose intravenous infusion in U.S. hospitals and other clinical centers, under the supervision of a physician experienced in the treatment of hemophilia. Many hemophilia patients receive care from designated hemophilia treatment centers, which play an important role in educating and caring for patients considering gene therapy. Due to the special handling requirements for gene therapies, Pfizer has established a process to evaluate the facilities and gene therapy capabilities of potential infusion sites, which has been initiated with several hemophilia treatment centers. Pfizer is committed to ensuring eligible patients who are prescribed BEQVEZ have access to it.

The standard of care for hemophilia B treatment is regular prophylactic intravenous infusions of FIX replacement therapy, often administered multiple times a week or multiple times a month, to control and prevent bleeding episodes.

With the approval of BEQVEZ,

physicians and patients now have another choice in the treatment of hemophilia B. A one-time dose of BEQVEZ has provided sustained bleed protection relative to standard of care in a pivotal clinical trial and may allow patients to avoid years of medical burden associated with prophylaxis. For healthcare systems, this could also reduce and offset the ongoing costs of hemophilia B disease management, lowering resource utilization compared with the current standard of care.

According to Dr. Bhatia, "Our hope is that BEQVEZ could allow people living with hemophilia more time for the things they love and support their ability to engage in the workforce, school and society. For context, research has shown that nearly 40 percent of employed patients with severe hemophilia reported experiencing restrictions in performing their job due to their disease, and a wide range of at least 13 percent of people living with hemophilia have faced unemployment due to disease-related complications."

Krystal Biotech Inc.

In May 2023, Krystal Biotech Inc.'s VYJUVEK was approved by FDA. VYJUVEK is the first and only redosable gene therapy for the treatment of dystrophic epidermolysis bullosa (DEB). VYJUVEK addresses the genetic cause of DEB to provide wound healing in a topical gel indicated for the treatment of wounds.

VYJUVEK is a herpes-simplex virus type 1 (HSV-1) vector-based gene therapy indicated for the treatment of wounds in patients 6 months of age and older who have DEB with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene.

DEB is a type of epidermolysis bullosa that is a serious genetic disease. It is caused by mutations in the COL7A1 gene, resulting in the lack of functional type VII collagen, which disrupts the formation of anchoring fibrils in the skin and prevents adhesion of the epidermis to the dermis. There are two types of DEBs based on inheritance patterns: dominant (DDEB) and recessive (RDEB).

DEB can lead to serious symptoms and complications. Symptoms primarily include skin fragility, blistering and wounds, and it can also result in damage to the mucosa and epithelial lining of organs. Some complications include infection of open wounds, esophageal stricture, gastrointestinal and genitourinary issues and cutaneous squamous cell carcinoma (SCC). DEB wounds can increase the risk of developing cutaneous SCC regardless of genetic subtype — RDEB or DDEB — size or chronicity.

VYJUVEK delivers two functional copies of the COL7A1 gene directly into keratinocyte and fibroblast cells of open wounds. (VYJUVEK does not replicate in the patient's cells nor does it integrate into the patient's cells' native genetic material.) The functional genes allow the body to produce type VII collagen protein, which is used to create and assemble anchoring fibrils. Anchoring fibrils help bind the epidermis and dermis together to promote wound closure. Results of GEM-3, the Phase III confirmatory study, showed that 66.7 percent of wounds that were closed at three months were also closed at six months. The primary endpoint of the study showed that primary wounds with complete wound healing was 100 percent closure at six months, and the key secondary endpoint of the study showed that primary wounds with complete wound healing was 100 percent at three months.

CRISPR Therapeutics

Founded in 2013, CRISPR Therapeutics was one of the first companies formed to utilize the CRISPR gene editing platform to develop medicine for the treatment of rare and common diseases. Emmanuelle Charpentier, PhD, CRISPR Therapeutics co-founder, and Jennifer Doudna, PhD, co-discovered CRISPR-Cas9, a gene therapy tool that edits genes by precisely cutting DNA and then harnessing natural DNA repair processes to modify the gene in the desired manner. The tool can disrupt (inactivate), delete (remove) or correct or insert genes, and it can edit cells in vivo or ex vivo.

CRISPR Therapeutics has a dedicated team called CRISPR-X that focuses on innovative research to develop next-generation editing and delivery modalities, such as all-RNA gene correction, whole gene insertion and non-viral delivery of DNA. The company says these cutting-edge technologies could underlie the next wave of gene-editing therapies.

American Society of Gene and Cell Therapy (ASGCT):

The "Hot Topics in Clinical Development: Risk-Benefit Analysis" session at ASGCT's Policy Summit on Sept. 23 and 24, 2024, covered current hot topics in clinical development, focusing on risk-benefit analysis for cell and gene therapies. Discussions included the use of surrogate endpoints and biomarkers, the role of patient experience data and the risk/benefit considerations for novel technologies. Additional topics included ultra-rare and n-of-1 diseases, as well as real-world evidence and clinical trial design. The panelists for this session included Matthew Porteus, MD, PhD, professor at Standford University School of Medicine; Timothy Miller, PhD, co-founder, president and CEO of Forge Biologics and Lola Fashoyin-Aje, MD, MPH, a medical oncologist and deputy division director in the division of oncology 3 in the Office of Oncologic Diseases at FDA.

FDA approved CRISPR Therapeutics' CASGEVY in 2023, the first-ever approved CRISPR-based therapy. CASGEVY is a CRISPR/Cas9 gene-edited therapy for patients 12 years and older who have sickle cell disease (SCD) or transfusion-dependent beta thalassemia (TDT). The company also has five clinical and 10 preclinical programs across hemoglobinopathies, oncology, diabetes and cardiovascular disease.

CASGEVY is a one-time therapy used to treat patients with SCD who have frequent vaso-occlusive crises (VOCs) and patients who have TDT who need regular blood transfusions. CASGEVY is made specifically for each patient, using the patient's own edited blood stem cells, and increases the production of a special type of hemoglobin called hemoglobin F (fetal hemoglobin or HbF). Having more HbF increases overall hemoglobin levels and has been shown to improve the production and function of red blood cells. This can eliminate VOCs in patients with SCD and eliminate the need for regular blood transfusions in patients with TDT.

After receiving CASGEVY, SCD patients who had recurrent VOCs were VOC-free, had no in-patient hospitalization for VOCs and achieved no hospitalization out to 45.5 months, and TDT patients who were transfusion-dependent achieved transfusion independence out to 45 months.

In the clinical study, 93.5 percent (29 out of 31) of SCD patients aged 12 to 35 did not have a severe VOC for at least 12 months in a row after receiving CASGEVY. In the clinical study, 91.4 percent (32 out of 35) of TDT patients were transfusion-independent for at least 12 months in a row after receiving CASGEVY.

Pharmaceutical Company Websites

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- AstraZeneca: **www.AstraZeneca.com**
- CASGEVY: **www.casgevy.com**
- CRISPR Therapeutics: **crisprtx.com**
- CSL Behring: **www.csl.com**
- Krystal Biotech: **www.krystalbio.com**
- Pfizer: **www.pfizer.com**

CSL Behring

In November 2022, FDA approved CSL Behring's HEMGENIX, the first-ever FDA-approved gene therapy for hemophilia B. HEMGENIX is a one-time gene therapy for the treatment of adults 18 years and older with hemophilia B who currently use FIX prophylaxis therapy or have current or historical life-threatening bleeding or have repeated, serious spontaneous bleeding episodes. HEMGENIX is administered as a single intravenous infusion and can be administered only once. HEMGENIX is not intended for women or children.

Hemophilia B, a life-threatening rare disease caused by a mutation on the F9 gene, results in low levels of functional clotting FIX. Patients who have this condition are particularly vulnerable to bleeds in their joints, muscles and internal organs, leading to pain, swelling and joint damage. Current treatments for moderate to severe hemophilia B include lifelong prophylactic infusions of FIX to temporarily replace or supplement low levels of the blood-clotting factor.

HEMGENIX is a gene therapy that reduces the rate of abnormal bleeding in eligible patients with hemophilia B by enabling the body to continuously produce FIX, the deficient protein in hemophilia B. It uses an AAV5, a non-infectious viral vector. The AAV5 vector carries the naturally occurring Padua gene variant of FIX to the target cells in the liver, generating FIX proteins that are five to eight times more active than normal. These genetic instructions remain in the target cells but generally do not become a part of a patient's own DNA. Once delivered, the new genetic instructions allow the cellular machinery to produce stable levels of FIX.

Based on the Phase III HOPE-B clinical trial to evaluate the safety and efficacy of HEMGENIX, results have shown that 1) 37 percent of patients' average FIX activity was elevated and sustained for years; 2) patients had greater bleed protection versus routine FIX prophy; 3) 94 percent of patients discontinued FIX prophy and remained prophy-free in the clinical trial; and 4) annualized bleed rate for all bleeds decreased from an average of 4.1 for patients on prophy during the lead-in period to 1.9 (a 54 percent reduction) in months seven to 18 after treatment.

HEMGENIX does not eliminate hemophilia B; rather, it provides patients with hemophilia B with a working copy of the F9 gene and the ability to make their own FIX. Therefore, patients treated with HEMGENIX still have the mutation that causes hemophilia B.

AstraZeneca

Over the last several years, AstraZeneca has been building its CRISPR toolbox, including tools such as CRISPR GUARD, CRISPR VIVO and DISCOVER-Seq. These tools help establish how CRISPR can be used as a precise and effective gene therapy in the clinic.

Steve Rees, senior vice president of discovery sciences, biopharmaceuticals research and development at AstraZeneca, says, "CRISPR is the most exciting life science discovery in the last decade. It allows us to identify and validate new targets for medicine discovery, and as a medicine allows us to edit genes to enable the treatment and hopefully cure many genetic diseases."

More recently, the company's CRISPR toolbox has grown to include three new tools and technologies that have the

potential to further improve the efficacy and precision of CRISPR-based medicines.

In 2022, AstraZeneca's scientists developed Prime Editor nuclease (PEn) technology that can efficiently introduce precise genetic insertions through multiple double-stranded DNA repair pathways. In addition to enhancing the efficiency of generating insertions, editing with PEn leads to a reduction of unwanted large deletions, reducing the frequency of off-target effects. This new gene editing approach drives efficient genetic insertions, with a reduced risk of unwanted edits, advancing the potential for therapeutic use.

The company's scientists have also developed a strategy called 2iHDR, which aims to improve the success of gene editing by suppressing two pathways of gene repair — called non-homologous end joining (NHEJ) and microhomology-mediated end joining (MMEJ) — that can lead to imprecise gene editing. Using a combination of two inhibitors, the efficiency of CRISPR gene editing can be dramatically improved while reducing the risk of off-target effects. This strategy holds great promise for both cell therapies and gene therapy.

AstraZeneca's scientists have also developed an enhanced CRISPR system that utilizes an engineered enzyme, SpOT-ON. This enzyme cuts DNA with similar efficiency to the traditional enzyme, SpCas9, with enhanced specificity for the target site in the genome. In a proof-of-concept preclinical study of hypercholesterolemia, SpOT-ON successfully targeted the PCSK9 gene, resulting in reduced plasma levels of the associated PCSK9 protein. This recent research emphasizes the increasing safety features being built into CRISPR, making it more amenable to therapeutic applications and applying these in vivo for the first time.

"By altering DNA repair pathways with 2iHDR and harnessing a highly specific Cas9 variant with SpOT-ON, we can achieve targeted genetic modifications with enhanced precision and efficacy, driving further advancements in the field," says Sandra Wimberger, a senior scientist of discovery sciences, biopharmaceuticals research and development at AstraZeneca.

Looking Forward

David Barrett, JD, CEO of the American Society of Gene and Cell Therapy, says the top three issues facing gene therapy today are the adequate delivery of gene therapy in the clinical setting; creating additional manufacturing capacity for the rapid development of new gene therapy technology; and changes that need to be made on how payers provide coverage for one-time gene therapies.

Although gene therapy research has been conducted for more than 30 years, it was not until 2017 when gene therapies started to receive FDA approval. "Now that there are several FDA-approved gene therapies available, and many more are expected in the near future, we need the appropriate support infrastructure to get gene therapies from the manufacturer to the clinical setting in a cost-effective, efficient and safe manner," says Barrett.

With the rapid development of new technology, the addition of new manufacturing capacity needs to be created. "There has been enormous advancement in gene editing technology since 2016 when CRISPR was discovered. There are now four or five primary ways to edit a genome, which is a faster, more widely application to use, and in the last three or four years, there have been two new gene editing technologies — prime editing and base editing. After new gene therapies have been approved by FDA, we need to get them manufactured in a cost-effective, efficient and safe manner."

Unlike pharmaceuticals, which are taken regularly over long periods of time or a lifetime until a disease is cured or being managed well, gene therapy is usually a one-time application, and the entire cost of the gene therapy must be paid upfront. However, unlike pharmaceuticals, gene therapies usually last either many months or years or indefinitely, so the one-time cost of the gene therapy must be compared to the long-term cost of taking pharmaceuticals for long periods of time or a lifetime.

"Payers need to make changes to how they provide coverage for one-time gene therapies, as opposed to pharmaceuticals, as the cost for a one-time gene therapy does not fit the same mold as reimbursing a patient for pharmaceuticals, as a patient typically pays for pharmaceuticals over a long period of time or a lifetime, not all at once," says Barrett. "There are 7,000-plus genetic diseases that currently have no treatment. Through genetic testing, we need to identify faulty genes and what causes the genes to become faulty, then we need to develop an appropriate tool(s) to find the faulty genes, and then we need to apply the most applicable gene-editing tool to find and replace or correct the faulty genes."

ASGCT is very hopeful researchers will make breakthroughs in the next five to 10 years. "We never know when a breakthrough might happen that could advance research tremendously and very quickly move us forward to the next stage of gene therapy that could help to diagnose and cure more people of their genetic diseases," adds Barrett. ❖

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Advances in Treating **Menopause**

Menopause is a normal, natural event in every woman's life, but it can cause a variety of uncomfortable symptoms. New therapies show promise for bringing relief and an improved quality of life.

By Jim Trageser

PEOPLE HAVE had theories about menopause long before we possessed the medical knowledge to actually understand it. With cultures across the ancient world all fascinated by fertility (as well they might, given their shorter average lifespans and the need to have children to carry a community into the future), the late-in-life loss of fertility that visited any woman who lived long enough was equally a source of fascination.

In fact, menstruation and menopause were observed with a mix of both suspicion and curiosity. Ancient Judaism viewed menstruation as unclean. In the fourth century B.C., Aristotle wrote about the idea of menopause, citing that women experienced it at an average age of 50. During the Roman empire, Pliny the Elder ascribed the power to dull blades and kill crops to menstrual blood. Much later in 1821, French physician Charles-Pierre-Louis de Gardanne came up with the term "menopause" from a combination of the Greek words for "monthly" and "cessation." From that point on, our attempts to understand the biological changes associated with menopause became steadily more scientific and less superstitious.[1]

In today's popular culture, menopause is understood to refer to the entire stretch of a woman's life as she both approaches menopause and then moves past it, but menopause is actually the moment that marks the time in a woman's life when her body no longer has the ability to conceive a child. While some symptoms of this transitional time are merely uncomfortable, other conditions that emerge postmenopause such as osteoporosis and cardiovascular

disease can pose significant health and even mortality risks to women. Fortunately, researchers continue to make new advances in both understanding the processes behind menopause and in developing new therapies to ameliorate both the discomfort and risks associated with it.

What Is Menopause?

The National Institutes of Health defines menopause as the moment a woman has gone 12 months without having a menstrual period.[2] Colloquially, the word "menopause" is generally understood as the stretch of a woman's life as she both approaches that moment and then moves past it, but the technical terms for these stages are "perimenopause" and "postmenopause."

Perimenopause is the time during which a woman's body naturally transitions to menopause, which marks the end of her reproductive years. This is also known as the menopausal transition.[3]

Postmenopause is the time after a woman's body has been without a menstrual period for 12 months.[4]

Technically, a woman transitions straight from perimenopause to postmenopause without ever actually being "in menopause."

Causes and Symptoms of Menopause

As a woman ages, the reproductive period of her life comes to a normal, natural end. Perimenopause typically begins in a woman's mid-40s and can last between two to eight years (on average, it lasts for four years); the average age of menopause is 51 years.[5] During perimenopause, the amount of hormones produced by a woman's ovaries begins to decrease, and as a result, her periods become less regular, both in terms of timing and amount of menstrual blood passed. Ovulation becomes less regular as well. (However, pregnancy is still possible as long as she is still having periods.) A woman's body may experience unpleasant symptoms such as hot flashes; night sweats; vaginal dryness and painful sexual intercourse; mood swings, depression or irritability; insomnia; weight gain; and urinary incontinence.[6] Women who have their ovaries surgically removed will experience immediate menopause after surgery, and will effectively enter the postmenopausal phase of life. They will then be subject to postmenopausal symptoms, which often include weakening of bone density and an increase in blood pressure.[5]

Menopause cannot be prevented or "cured," but there are treatments available to help ease the discomfort of symptoms associated with perimenopause and postmenopause.

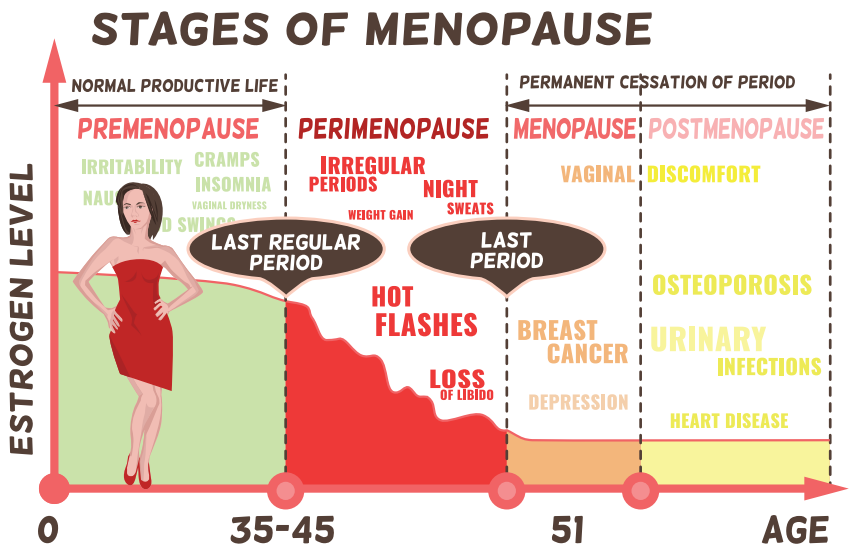
Menopause cannot be prevented or "cured," but there are treatments available to help ease the discomfort of symptoms associated with perimenopause and postmenopause. Symptoms of perimenopause are not life-threatening or dangerous, but instead affect women's quality of life. Postmenopausal women may continue to experience some of the same symptoms common during perimenopause, and their risk of some medical conditions increases, most notably osteoporosis and/or cardiovascular disease, which may quietly begin (postmenopausal women are at a higher risk of these conditions). Therefore, working with women to identify and address their symptoms is important not only for quality of life, but the length of life as well.

Perimenopausal Therapies

Medical intervention is not required for perimenopausal women unless symptoms are interfering with their quality of life. When that happens, patients have several options to discuss with their healthcare provider:

- *Hormone replacement therapy (HRT).* HRT replaces the natural hormones a woman's body no longer makes. There are two types of HRT: estrogen therapy and combination therapy. Estrogen therapy involves taking estrogen only; combination therapy involves taking a combination of estrogen and progesterone. Estrogen therapy may be administered through an oral pill, patch, topical gel, topical spray, vaginal ring, vaginal cream or vaginal tablets. Combination therapy may be administered through an oral pill, topical patch or an intrauterine device. Estrogen therapy should be used at the lowest dose needed to alleviate symptoms. Combination therapy is best for women who have not had a hysterectomy, as estrogen and progesterone are important for uterine health.

HRT is the most common therapy prescribed to ease the many uncomfortable symptoms of perimenopause. However, HRT does carry some risks, including an increased risk of uterine cancer, breast cancer, cardiovascular disease, gallbladder disease, blood clots and stroke. Risks of complications from HRT are lower when HRT is started before age 60 or within 10 years of menopause. Taking HRT when a woman is in her 40s and 50s is not typically associated with an increased risk of cardiovascular disease.[6,7,8] Recommendations for HRT are based on



women's symptoms and medical history, their family history and their overall health.[9]

• *Bioidentical hormone replacement therapy (BHRT).* A growing number of patients have been exploring BHRT as a natural alternative to traditional HRT. HRT uses synthetic hormones with a chemical structure similar to human hormones; BHRT uses hormones that come from plants, usually from wild yams, cactus or soy. The structure and function of these hormones is identical to human hormones. The hormones are extracted in a lab and then sent either to compounding pharmacies where individualized dosages are made according to patient need, or to pharmaceutical companies where proprietary formulas and products such as pills, patches, gels and creams are developed under strict U.S. Food and Drug Administration (FDA) regulations.[10]

FDA has approved many BHRT products that have been reviewed for safety and efficacy and are indicated for treating symptoms resulting from hormonal changes associated with menopause.[11] Examples of these products include Bijuva capsules and Imvexxy vaginal inserts. FDA-approved BHRT carries the same risks as HRT (increased risk for certain cancers, cardiovascular disease, blood clots, stroke, gallbladder disease). Compounded BHRTs are not produced under FDA's strict regulations, so they have not been evaluated for safety or effectiveness. However, compounding pharmacies must adhere to state pharmacy board regulations. In some patients, compounded BHRT may be a better choice because dosage can be customized according to individual patients' needs.[10,12,13] (See "Innovations in Bioidentical Hormone Replacement Therapy" on p.36.)

• *Antidepressants.* While less efficacious than hormone replacement, selective serotonin reuptake inhibitors (SSRIs) may reduce discomfort from hot flashes in some women. Various SSRIs have been used off-label with varying levels of effectiveness, but FDA has approved the low-dosage form of the antidepressant paroxetine (Brisdelle) specifically for treating hot flashes. This option is helpful for women who cannot use hormone therapies for health reasons.[14]

• *Fezolinetant (Veozah).* Approved by FDA in May 2023, Fezolinetant (Veozah) is the first nonhormonal drug designed specifically to treat hot flashes and night sweats. It works by addressing the brain's regulation of body temperature. It does carry the risk of liver damage, so ongoing blood testing is a requirement (similar to the use of statins in treating cholesterol).[15]

• *Professional counseling and lifestyle changes.* Mood changes are a major concern during perimenopause. In fact, about four in 10 women have mood changes during perimenopause that leave them feeling irritable, tearful or low on energy; some also experience difficulty concentrating. Studies show the risk of depression increases during this transitional time, too. Antidepressants and antianxiety drugs may be considered when symptoms are more pronounced and interfering with daily life, but sometimes mood changes can be addressed through professional therapy or lifestyle changes. Maintaining a healthy diet, exercising regularly, getting regular sleep and cutting back on caffeine can also help reduce the intensity of these symptoms.[16]

Postmenopausal Risks and Therapies

After menopause, women's risk of developing osteoporosis and cardiovascular disease increases because their bodies are making smaller amounts of estrogen, which is a critical component of building and maintaining healthy bones and guarding against heart attacks, cardiovascular disease and stroke.[4] Both osteoporosis and cardiovascular disease can be silent and go unnoticed by patients because they cause no immediate distress or discomfort. However, falls remain a major cause of mortality among the elderly, and osteoporosis disproportionately increases the danger of a fall.[17,18,19] Testing for both osteoporosis and cardiovascular conditions should be conducted as part of regular postmenopausal women's healthcare.

Some therapies may help mitigate against these conditions. Options include:

• *HRT*. Using estrogen for preventing and slowing osteoporosis is the frontline treatment in many parts of the world. It was first approved for use in the United States during World War II. While the side effects led European authorities to recommend against HRT more than two decades ago, some researchers believe that decision was in error and its benefits continue to outweigh its risks. HRT may also offer benefits in treating postmenopausal cardiovascular disease. (A recent study says HRT does not improve long-term outcomes, so more study is clearly needed to give physicians clear guidance.) However, drugs that lower blood pressure and cholesterol levels can also be considered to treat women with postmenopausal cardiovascular disease.[4]

• *Bisphosphonates*. While HRT may be helpful, the most widely prescribed treatment for postmenopausal osteoporosis is a family of drugs known as bisphosphonates, which have been in use since the 1990s. Bisphosphonates slow bone loss by inhibiting the activity of osteoclast cells, which break down old bone to make room for new bone. As new bone generation slows during postmenopause, bisphosphonates can help balance the process to preserve bone density and thus strength. Some commonly used bisphosphonates include alendronate (Fosamax), ibandronate (Boniva) and risedronate (Actonel), all of which can be taken orally. Pamidronate (Aredia) and zoledronic acid (Reclast, Zometa) are given via intravenous (IV) administration, and ibandronate can also be given both intravenously and orally. Mild side effects of oral bisphosphonates are esophageal and stomach reactions, while mild side effects of IV bisphosphonates include flu-like symptoms such as fever and achiness.[20,21]

• *Denosumab (Prolia, Jubbonti)*. Denosumab gained FDA approval in 2010. It may be a better fit for women who suffer significant side effects from or otherwise need to avoid bisphosphonates (those with kidney disease, for instance). Denosumab is administered via subcutaneous injection and works by blocking a protein the osteoclast cells require. However, denosumab can result in dangerously low calcium levels in the blood; calcium levels must be tested during the course of the treatment.[22]

• *Human parathyroid hormone (teriparatide, abaloparatide)*. For women at high risk of a fracture, doctors may prescribe a bone anabolic drug that promotes new bone growth. Currently, two synthetic forms of the human parathyroid hormone (teriparatide and abaloparatide) are available. However, because of side effects and a waning effectiveness over time, these can be used only on a limited basis.[23,24]

• *Romosozumab-aqqg (Evenity)*. Approved just five years ago, an even newer treatment for osteoporosis is the combination anabolic plus antiresorptive drug romosozumab (Evenity). However, there may be significant cardiovascular side effects with romosozumab, and the drug loses its effectiveness at promoting new bone growth after 12 monthly injections, so it is not a long-term treatment.[24,25]

Looking Ahead

As a very natural part of human life, menopause will be with us for the foreseeable future. But new therapies for managing uncomfortable side effects of perimenopause and mitigating more serious conditions that may occur during postmenopause offer physicians new tools for helping women elevate the quality and extend the length of their lives. ❖

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Innovations in Bioidentical Hormone Replacement Therapy

Touted as a more natural approach to hormone replacement therapy, this plant-based anti-aging remedy has evolved from an unregulated safety concern to a mainstay of modern medicine.

By Trudie Mitschang

HORMONES PLAY A huge role in how the body functions on every level, from weight management and mental alertness to stamina, bone health and quality of sleep. With aging, optimal hormone levels begin to decline or even deplete, so it's no surprise that hormone replacement therapy (HRT) has emerged as an increasingly popular method to turn back the clock and improve quality of life as people age.

HRT is typically used to treat symptoms associated with menopause, including hot flashes, accelerated skin aging, vaginal dryness, decreased muscle mass and osteoporosis. These symptoms are mostly caused by low levels of estrogen and progestogens.

While the popularity of HRT has surged in recent years, it is far from a new idea. History documents early attempts at hormone therapy back to ancient China, where aging Chinese women routinely ingested young women's dried urine to counteract health symptoms associated with menopause (the belief was that young women's urine contained high levels of metabolic waste products such as progesterone, estrogen and testosterone).[1]

Fast forward to modern times and HRT can be traced to the mid-20th century when researchers began investigating it for menopausal women.

Initially, synthetic hormones derived from the urine of pregnant horses were commonly prescribed, but concerns arose regarding their safety, including research findings linking HRT with an increased risk of breast cancer and heart disease. This led to the exploration of bioidentical HRT (BHRT). BHRT uses manufactured compounds said to have exactly the same chemical and molecular structure as hormones produced in the human body and are derived from plants.

In the 1980s and 1990s, interest in BHRT surged as more studies highlighted its potential benefits and safety profile. Patients who sought alternatives to traditional HRTs were drawn to the idea of what was promoted as a "natural" alternative. By the early 2000s, BHRT had gained widespread attention, with clinics across the country offering these therapies to address various hormonal imbalances, including menopause, thyroid disorders and adrenal insufficiency. And with growing demand, medical professionals continued to refine BHRT protocols and formulations to optimize patient outcomes.[2]

Safety and Risk Factors

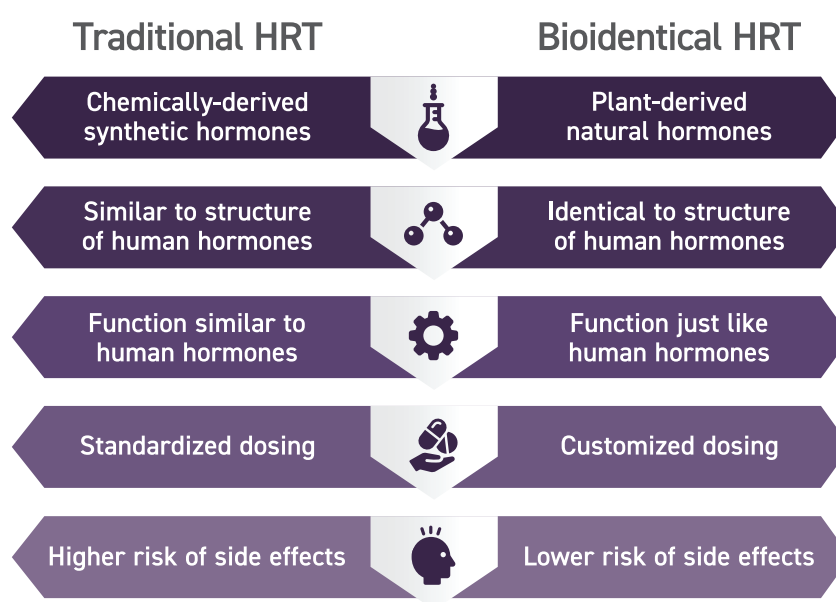
BHRT uses chemicals derived from plants such as soy and wild yams that contain compounds called phytoestrogens, which are chemically similar to estradiol, a form of estrogen produced in the ovaries. In a laboratory, scientists can extract these phytoestrogens and chemically convert them into bioidentical hormones that have the same structure and function as the hormones produced by the body. The primary hormones used in BHRT are estrogen, progesterone and testosterone, which can be administered in various forms, including pills, patches, creams, gels and injections. BHRT is often used to treat hormonal imbalances and relieve symptoms of menopause in women or andropause in men.

This similar makeup of bioidentical hormones to those found in the human body is believed to enhance their effectiveness and reduce the side effects associated with synthetic hormones. Erika Schwartz, MD, a prominent advocate of BHRT, states, "Bioidentical hormones are more effective because they mimic the hormones our bodies naturally produce."

When it comes to safety, doubts were raised over the safety of conventional HRT in 2002, when studies linked their extended use to a risk of breast cancer and heart disease. But is BHRT really a safer alternative? Detractors contend there have not been sufficient studies to evaluate the safety of soy- and yam-based hormones. Other concerns include the risk that hormones compounded by a specialty pharmacy can be inconsistent in terms of strength and dosage. Here is what the research shows:

- A 2009 California study asserted that the use of natural hormones is associated with a lower risk of breast cancer and cardiovascular disease, and that they are more effective than synthetic and animal-derived versions. (It also conceded that scientific trials were needed to investigate these differences.)[3]
- A 2012 clinical trial in Denmark demonstrated that healthy women taking BHRT for a decade immediately after menopause had a reduced risk of dying from heart disease.[3]
- The conclusion of a recent study published in the medical journal *JAMA* states: "The benefits of hormone therapy for the treatment of menopause symptoms outweigh the risks."[4] "Among women below the age of 60, we found hormone therapy has low risk of adverse events and [is] safe for treating bothersome hot flashes, night sweats and other menopausal symptoms," said study author JoAnn Manson, MD, MPH, DrPH, chief of preventive medicine at Brigham and Women's Hospital. "This is a departure from the advice many women have been given in the past."[4]

The recent study's analysis is based on two decades of follow-up data from the 1991 Women's Health Initiative study, which followed thousands of women taking



Source: Dr. B's Blog. Traditional or Bioidentical: Understanding the Differences Between Hormone Therapies. Accessed at www.drbnaples.com/traditional-or-bioidentical-understanding-the-differences-between-hormone-therapies.

HRT. The study was halted after it found that women taking Prempro (which is a combination of estrogen and progestin) had higher risks of breast cancer and stroke. "The findings were surprising," Dr. Manson notes, pointing out that the reason the randomized trial was conducted was because scientists were trying to determine if hormone therapy decreased the risk of heart disease and other conditions.

After the initial findings came out, many women abruptly stopped the therapy. Prescriptions plummeted, and many healthcare providers hesitated to recommend hormone therapy. But menopause experts say it's time to reconsider, because there's a lot known now that wasn't known two decades ago. Most significantly, there are now different types of hormones — delivered at lower doses — that are shown to be safer.

"Women should know that hormone therapy is safe and beneficial," says Lauren Streicher, MD, a clinical professor of obstetrics and gynecology at Northwestern University Feinberg School of Medicine. In hindsight, Dr. Streicher believes the Women's Health Initiative study was flawed and that some of the risks that were identified were linked to the type of hormones women were given, as well as the age of the women enrolled (they were all over 60). "We know that there is a window of opportunity when it is the safest to start hormone therapy and that you get the most benefit. That window is typically between ages 50 and 60," she adds.[4]

Exploring the Options

Individuals interested in BHRT have a number of choices when it comes to choosing the treatment option that is right for their specific symptoms:

- Lab-made bioidentical hormones that are chemically similar to the hormones in the body but are derived from a plant steroid found in soy and wild yams.
- Compounded bioidentical hormones custom-created at a compounding pharmacy.
- Food and Drug Administration (FDA)-approved bioidentical hormone products manufactured by pharmaceutical companies and prescribed under brand names.

All bioidentical hormones begin in a laboratory where phytoestrogens are extracted from plants. Compounding pharmacies and pharmaceutical companies both obtain those same bioidentical hormone products from the same chemical laboratory companies, but their paths then diverge. The pharmaceutical companies prepare their products (pills, gels, creams or patches) under strict FDA regulations. The compounding pharmacies take the same bioidentical hormone preparations and develop them into their own preparations based on individual lab tests and prescriptions. The advantage of the compounding pharmacy is that it can tailor the dosage delivered to the patient, while pharmaceutical companies have a more restricted dose range of the hormones they can offer, making the prescriptions more of a one-size-fits-all approach. In terms of oversight, pharmaceutical companies are under strict safety rules, while compounding pharmacies must report only to their state pharmacy boards and do not require FDA approval.

A compounded hormone product may contain one hormone or a combination of a few different hormones. For example, some healthcare providers will combine more than one type of estrogen together, and depending on the woman's symptoms, they may add progesterone as well. Compounded bioidentical hormone therapies (CBHTs) may be a good choice for those unable to take an FDA-approved product due to an allergy (such as peanut oil) or for those who did not find symptom relief from a commercial product. In some cases, a healthcare provider might prefer a compounded product and try that as a first course of treatment.

A study analyzing why women choose compounded BHRT found women are "not only seeking alternatives to

Hormone	Product	Formulation
Estradiol	Estrace	Cream; tablet
	Vivelle-Dot	Patch
	Climara	Patch
	Divigel	Gel
	EstroGel	Gel
	Imvexxy	Vaginal insert
	Vagifem	Vaginal tablet
Progesterone	Prometrium	Capsule
	Crinone	Vaginal gel
Testosterone	AndroGel	Gel
	Testim	Gel
	Fortesta	Gel
	Axiron	Solution
	Depo-Testosterone	Injection

conventional pharmaceuticals, but alternatives to conventional care where their menopausal experience is solicited, their treatment goals are heard, and they are engaged as agents in managing their own menopause."[5] The study concluded that "women making menopause treatment decisions of all kinds would benefit from greater shared decision-making in the clinical context in which they are explicitly invited to share their experiences, priorities and preferences. This would also provide an opportunity for clinicians to discuss the pros and cons of conventional HT, CBHT and other approaches to managing menopause."

Those with safety and efficacy concerns may prefer FDA-approved bioidentical hormones that are manufactured under strict guidelines by pharmaceutical companies prior to being released into the market. In 2018, FDA granted its first BHRT approval, a combination of estradiol and progesterone for moderate to severe vasomotor symptoms associated with menopause. The approval of Bijuva came on the heels of a clinical trial that demonstrated a combination of 17beta-estradiol and progesterone appeared to be safe and effective for reducing hot flash frequency and severity in menopausal women with a uterus.[6] Today, there are a number of FDA-approved hormone products that meet the definition of bioidentical. (See Table for list of available products.)

What's on the Horizon?

HRT has been proven to help any number of age-related health issues, and in a culture in which anti-aging remedies are increasingly in high demand, its popularity will likely continue to grow. Moving beyond the current use cases, new and promising research is now linking HRT to a reduced risk of Alzheimer's disease and dementia. "There's a window of opportunity," said lead study author Lisa Mosconi, PhD, director of the Alzheimer's Prevention Program and the Women's Brain Initiative at Weill Cornell Medicine in New York City. "Hormones work best for the brain when taken in midlife in presence of menopausal symptoms to support women through the menopause condition."[7]

Individuals interested in BHRT have a number of choices when it comes to choosing the treatment option that is right for their specific symptoms.

In fact, the brain has a higher chance of being protected if hormone replacement is started soon after menopausal symptoms begin, according to the analysis recently published in the journal *Frontiers in Aging Neuroscience*.[8] The length of time a woman undergoes therapy also matters: As long as a woman began hormones while she was in menopause, there was a 26 percent reduced risk of dementia if hormones were taken for more than 10 years, the study found.

"While there is not a clear one-size-fits-all approach, in the right woman, at the right dose and for the right duration of time, I believe that hormone replacement therapy can be one of our most powerful tools to reduce a woman's risk for cognitive decline and to slow down Alzheimer's pathology," said Richard Isaacson, MD, director of research at the Institute for Neurodegenerative Diseases in Florida. "I believe this may be especially true for women with one or more copies of the APOE4 genetic variant, which is present in about 25 percent of people. It's essential for neurologists and primary care physicians to work closely with gynecologists … and monitor treatment outcomes over time."[7]

This study and others show that BHRT continues to offer healthcare breakthroughs, and researchers continue to uncover potential treatment outcomes. Dr. Streicher agrees: "Hormone therapy is beneficial way beyond the benefits to just helping with hot flashes. Ongoing research points to protection against bone loss and even heart disease."[4]

Patients considering BHRT should engage in thorough discussions with their healthcare providers, weigh the potential benefits and risks, and consider their personal health history and needs. Ongoing research and more rigorous clinical trials will be essential in providing clearer guidance and improving the safety and efficacy of what is becoming a common defense in the arsenal against aging. ❖

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Myths & Facts: Prenatal Care

With almost a quarter of women receiving inadequate prenatal care in the U.S., more needs to be done to inform women about the myths surrounding this essential healthcare service.

By Ronale Tucker Rhodes, MS

A HEALTHY PREGNANCY is one of the best ways to promote a healthy birth. But, the chances of a healthy pregnancy are dependent upon getting early and regular prenatal care, which can begin even before pregnancy with a pre-pregnancy care visit to a healthcare provider and extend through birth, as well as following prenatal healthcare guidelines.

The recommendations for prenatal care doctor visits date back to the 19th century when new data revealed high rates of infant and maternal mortalities. These discoveries culminated in the first codification of a prenatal visit schedule in 1930 by the Children's Bureau, which recommended 12 to 14 prenatal visits during pregnancy. It was hoped the Bureau's schedule could prevent harm to mothers and babies. And, until the American College of Obstetricians and Gynecologists (ACOG) was founded, resulting in technological advancements in laboratory testing and ultrasonography, as well as calls from the National Institutes of Health Task Force for changes in prenatal care delivery in 1989, prenatal care recommendations continued to be the same as they had been since 1930: monthly visits until 28 weeks' gestation, bimonthly visits until 36 weeks' gestation and weekly visits until delivery.[1] Since then, that schedule remained essentially unchanged for almost a century until the pandemic in 2020 that changed in-person prenatal care visits to a multimodal model of in-office and telemedicine visits.[2]

In 2022, there were 3,667,758 births in the United States, or a birth rate of 11.0 per 1,000 population (the latest available data as of this writing).[3] Also in 2022, 77 percent of live births in the United States were to women receiving early prenatal care, 16.3 percent were

to women beginning care in the second trimester and 6.8 percent were to women receiving late or no prenatal care. Inadequate prenatal care is pregnancy-related care beginning in the fifth month of pregnancy or later or less than 50 percent of the appropriate number of visits for an infant's gestational age. In 2022, about one in seven infants (15.5 percent of live births) was born to a woman receiving inadequate prenatal care in the United States,[4] which can lead to premature pregnancy, intrauterine growth retardation, low weight at birth, and maternal and child mortality as a result of infections in the perinatal and postnatal periods.[5]

What's more, in addition to inadequate prenatal care among almost a quarter of pregnant women in the United States, the many myths surrounding healthcare recommendations such as alcohol consumption, exercise, nutrition and more result in other pregnancy complications. As such, during prenatal visits, physicians should encourage regular checkups and help to dispel the many myths surrounding pregnancy to ensure their patients have healthy pregnancies.

Separating Myth from Fact

Myth: Prenatal care starts after a positive pregnancy test.

Fact: Women should schedule their first prenatal appointment as soon as they find out they are pregnant, but women can benefit from prepregnancy care, too. According to ACOG, a prepregnancy care checkup can find things that could affect a woman's pregnancy, which is important because the first eight weeks of pregnancy is the time when major organs develop in a fetus. During the prepregnancy visit, the OB-GYN will discuss diet and lifestyle, medical and family history, medications and past pregnancies. He or she will also review vaccination history to be sure all vaccines recommended for a women's age group have been received. In addition, sexually transmitted infections and how to protect against them will be discussed.[6]

Myth: Women over age 35 are at high risk for pregnancy.

Fact: The truth is that most women 35 or older have a normal pregnancy and healthy baby. Plus, there are some advantages to being an older mom, including financial stability and having more life experience that can help during the parenting journey. Nevertheless, women should talk to their OB-GYN about the types of complications that can occur from underlying health issues that arise more often with age, including diabetes and high blood pressure. Getting proper treatment for these issues can better women's chances of having a healthy pregnancy.[7] That said, while the risks are low, there is a higher risk of pregnancy-related complications that might lead to a C-section delivery. The risk of chromosomal conditions is higher, and babies born to older mothers have a higher risk of certain chromosomal conditions such as Down syndrome. In addition, the risk of pregnancy loss is higher.[8]

Myth: All bleeding during the first trimester means a miscarriage.

Fact: Women who experience bleeding during any stage of pregnancy should talk to their OB-GYN to assess what's going on. This is because vaginal bleeding during pregnancy has many causes, some of which are serious and others that are not. In fact, bleeding can occur early or later in pregnancy.[9] However, bleeding, even during the first trimester, is not always associated with a miscarriage. Vaginal bleeding is extremely common in the first trimester, occurring in 20 percent to 40 percent of women.[7]

According to ACOG, "Light bleeding or spotting can occur one to two weeks after fertilization when the fertilized egg implants in the lining of the uterus. [And], the cervix may bleed more easily during pregnancy because more blood vessels are developing in this area."[9]

Myth: It's OK for women to eat as much as they want while pregnant.

Fact: Eating for two is a cute adage often used during pregnancy, but eating twice as much can put women at increased risk of pregnancy complications. According to a 2015 government report, 47 percent of American moms gain too much weight during pregnancy.[10]

Many women find it difficult to figure out the right balance of food intake. Most physicians recommend eating an extra 200 to 400 calories a day in the second trimester and about 500 calories a day more in the third trimester, but that may vary for women who are overweight or underweight. Of course, those expecting twins or triplets will need to eat more.[10]

Medline calorie guidelines for most

Recommended Micronutrients During Pregnancy[19]

Micronutrient	Recommended Daily Intake	Common Amount in Prenatal Vitamins
Calcium	1,000 mg	200 to 300 mg
Elemental iron	30 mg	27 mg
Folic acid	400 to 1,000 mcg*	600 mcg
Omega-3 fatty acids	650 mg**	0 to 450 mg
Vitamin D	600 IU	200 to 600 IU

* 4,000 mcg per day recommended for people with a history of neural tube defects
** 300 mg should be in the form of docosahexaenoic acid

Key Events in the Evolution of Prenatal Care Delivery Guidelines Since 1930

- **1930:** The Children's Bureau released a second prenatal care booklet, with specific recommendations for physician visit schedule; the American Board of Obstetricians and Gynecologists first provided specialty certification.
- **1951:** American Association of Obstetricians and Gynecologists (AAOG) was formed.
- **1955:** The American College of Nurse-Midwives was founded.
- **1957:** AAOG changed its name to the American College of Obstetricians and Gynecologists (ACOG).
- **1959:** ACOG released the first "Manual of Standards in Obstetric-Gynecologic Practice," which maintains the original prenatal visit schedule.
- **1970:** The Kessner Index was introduced to assess the adequacy of prenatal care.
- **1985:** Findings from the Institute of Medicine Committee to Study the Prevention of Low Birthweight were released, supporting the causal relationship between prenatal care and reduction of low birthweight infants.
- **1989:** The National Institutes of Health Public Health Service Expert Panel on the Content of Prenatal Care recommended a schedule of prenatal visits based on medical and social risk factors; Medicaid expansion occurred to improve prenatal care access.
- **1990s:** Clinical trials demonstrated the safety of reduced visit schedules for low-risk patients; group prenatal care was first introduced.
- **2019:** The first randomized controlled trial of the prenatal care model integrating telemedicine was published.
- **2020:** Outbreak of COVID-19, which resulted in a pandemic, which resulted in a pandemic, that changed in-person prenatal care visits to a multimodal model of in-office and telemedicine visits.

Adapted from: Peahl, AF, and Howell, JD. The Evolution of Prenatal Care Delivery Guidelines in the United States. *American Journal of Obstetrics & Gynecology*, 2021 Apr; 224(4): 339–347. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC9745905.

normal-weight pregnant women are about 1,800 calories per day during the first trimester, about 2,200 calories per day during the second trimester and about 2,400 calories per day during the third trimester. Medline's general guidelines for healthy weight gain are:[11]

- Normal total weight gain for a healthy woman is 25 to 35 pounds (11 to 16 kilograms) during pregnancy.
- Overweight women should gain only 10 to 20 pounds (4 to 9 kilograms) during pregnancy.
- Underweight women should gain more (28 to 40 pounds or 13 to 18 kilograms) during pregnancy.
- Women with multiples (twins or more) should gain 37 to 54 pounds (16.5 to 24.5 kilograms) during pregnancy.

Myth: It's OK for women to have an occasional glass of wine during pregnancy.

Fact: This topic is actually debated today. For years, women have been told to abstain completely from alcohol during pregnancy. But, more recently, many women are being told by their OB-GYNs that on an individual basis, the occasional glass of wine would unlikely harm the baby due to the limited amount of alcohol being introducing into the body.[12]

According to the Centers for Disease Control and Prevention, "There is no safe time for alcohol use during pregnancy." And that includes all types of alcohol, including red or white wine, beer and liquor since it "is associated with an increased risk of miscarriage, preterm birth, stillbirth and sudden infant death syndrome. Alcohol use during pregnancy can cause a range of lifelong behavioral, intellectual and physical disabilities known as fetal alcohol spectrum (FAS) disorders."[13]

But, says the American Pregnancy Association, while it is known that excessive drinking is the cause of many of the complications that can occur during pregnancy as a result of alcohol, these risks may not be associated as strongly with occasional drinking. FAS occurs when the pregnant mother drinks excessive amounts of alcohol. Unfortunately, there is no specific amount that has been determined to cause FAS, which is why the safest answer to whether or not a woman should drink during pregnancy is that it should be avoided, if at all possible.[12]

Myth: Pregnancy women should fly/travel by air.

Fact: According to ACOG, "In most cases, pregnant women can travel safely until close to their due dates." During a healthy pregnancy, occasional air travel is almost always safe, and most airlines allow women to fly domestically until about 36 weeks of pregnancy. However, pregnant women should avoid flying if they have a medical or pregnancy condition that may be made worse by flying or could require emergency medical care (most common pregnancy emergencies usually happen in the first and third trimesters).

That said, research shows that any type of travel lasting four hours or more — whether by car, train, bus or plane — doubles the risk of deep vein thrombosis (DVT), and being pregnant is an extra risk factor for DVT. But this risk can be mitigated by drinking lots of fluids without caffeine, wearing loose-fitting clothing, walking and stretching at regular intervals, and wearing special stockings that compress the legs, either below the knee or full length, to help prevent blood clots from forming.[14]

Myth: Pregnant women shouldn't exercise.

Fact: Exercise is important during pregnancy for weight control, stress

management and overall health. According to ACOG, women should try performing 150 minutes of moderate physical activity each week, along with muscle-strengthening activities on two days or more a week. The number of minutes can be divided into shorter workout sessions throughout the week. The number of minutes can be divided into shorter workout sessions throughout the week, for example, performing a 30-minute workout five days per week.[15]

According to an expert review of current literature published in the *American Journal of Obstetrics and Gynecology*, "Conclusive data from both validated activity questionnaires and accelerometers indicate that physical activity is safe during pregnancy. In addition, studies of physical activity during pregnancy that evaluate pregnancy outcomes have found reduced risks of preterm birth, preeclampsia and gestational diabetes and improved mental health among individuals who regularly engage in physical activity." According to the experts, "Providers should encourage physical activity before and during pregnancy and educate patients regarding the benefits and safety of physical activity."[16]

Myth: Sex during pregnancy can be harmful for the baby.

Fact: In most cases, sex during pregnancy poses no risk to the mother or baby. Many studies have concluded that vaginal sex during pregnancy has no increased risk of preterm labor or premature birth. However, if a doctor considers someone to be at high risk, he or she may recommend that the woman avoids sexual intercourse during the pregnancy or just in the later stages.[17]

Myth: Pregnant women should not take over-the-counter (OTC) and/or prescription medicines or supplements.

Fact: A common concern about prenatal care involves the use of OTC medications. Unfortunately, high-quality research on the safety and effectiveness of OTC medications in pregnancy is limited. In fact, "fewer than 10 percent of medicines approved since 1980 have enough information to determine their safety during pregnancy. This is because pregnant people are often not included in studies that determine the safety of new medicines. As a result, pregnant people and healthcare professionals have limited information to make informed treatment decisions during pregnancy."[18]

Nevertheless, medicine use during pregnancy is common. "About nine in 10 women report taking some type of medicine during pregnancy. About seven in 10 report taking at least one prescription medicine."[18] According to studies, in the first trimester, the most common OTC medications taken are ibuprofen, acetaminophen, aspirin, naproxen, pseudoephedrine and docusate.[19]

Eating for two is a cute adage often used during pregnancy, but eating twice as much can put women at increased risk of pregnancy complications.

Therefore, CDC recommends pregnant women discuss all medicines they take, including prescriptions, OTC medicines, herbal and dietary supplements and vitamins with their healthcare providers.[18]

According to the American Academy of Family Physicians (AAFP), "A well-balanced diet rich in vitamin D, folic acid, iron, calcium, omega-3 fatty acids and other micronutrients should be encouraged for pregnant patients. Prenatal vitamins are recommended because they provide folic acid, iron, calcium and vitamin D. Ideally, they should be started before conception and should contain at least 400 mcg of folic acid, 30 mg of elemental iron, 200 to 300 mg of calcium and 400 IU of vitamin D."[19] (See table for recommended micronutrients.) Prenatal vitamins can be obtained OTC or by prescription. Some examples of prescription prenatal vitamins include VitaMedMD One RX, VitaPearl and VitaTrue.

Myth: It's dangerous if a pregnant woman is past her due date.

Fact: It's normal for women to give birth before or after their set due date. The due date is merely a calculated estimate of when the baby has been developing in the womb for 40 weeks. A pregnancy that goes beyond the 40 week mark and lasts between 41 or 42 weeks is called "late term." A pregnancy that lasts longer than 42 weeks is called "postterm."

Women most likely to have a postterm pregnancy are those who are in their first pregnancy, if the baby is a boy, if the woman's body mass index is 30 or higher (obese), if the woman has had a prior postterm pregnancy, or if the due date was calculated wrong due to confusion about the last menstrual period. An OB-GYN will closely watch the baby's size, heart, weight and position if a woman goes past her due date. If necessary, the OB-GYN will recommend a labor induction to help promote a vaginal birth if the health of the mother or fetus is at stake.[7,20]

Most women who give birth after their due dates have uncomplicated labor and give birth to healthy babies. Risks associated with postterm pregnancy include stillbirth, macrosomia, postmaturity syndrome, meconium in the lungs of the fetus (which can cause serious breathing problems after birth) and decreased amniotic fluid (which can cause the umbilical cord to pinch and restrict the flow of oxygen to the fetus). However, problems occur in only a small number of postterm pregnancies.[20]

Myth: Women who opt for telehealth visits vs. in-person office visits receive inadequate prenatal care.

Fact: Postpandemic, it is now known that in-person prenatal visits are not all necessarily superior to telehealth visits. This came to light in the 2023 study mentioned previously that examined the multimodal model of in-office and telemedicine visits. In the cohort study of 151,464 pregnant individuals, after implementation of a multimodal prenatal healthcare model with telemedicine and in-office visits during the pandemic, there were no changes in rates of preeclampsia and eclampsia, severe maternal morbidity, cesarean delivery and preterm birth compared with the prepandemic rates; however, there was an increase in the rate of neonatal intensive care unit admissions during the second pandemic period. These findings suggest that a multimodal prenatal healthcare model combining in-office and telemedicine visits performed adequately compared with in-office only prenatal healthcare, supporting its continued use after the pandemic.[2]

Dispelling the Myths Now

It may seem a bit unbelievable, and no doubt disturbing, but women in the United States are more likely to die from childbirth than women living in other developed countries. Therefore, Healthy People 2030 is focusing on preventing pregnancy complications and maternal deaths and helping women stay healthy before, during and after pregnancy.[21] One of the goals of Healthy People 2030 is to increase the proportion of pregnant women who receive early and adequate prenatal care to 80.5 percent of the population (vs. 77 percent currently).[4] According to Healthy People 2030, women who receive recommended healthcare services before they get pregnant are more likely to be healthy during pregnancy and to have healthy babies. And, strategies to help pregnant women get medical care and avoid risky behaviors — such as smoking or drinking alcohol — can also improve health outcomes for infants.[21]

Unfortunately, whether the Healthy People 2030 initiative becomes reality seems in jeopardy. A report released by CDC's National Center for Health Statistics in August showed that the number of women going through pregnancy without prenatal care is growing — even though the overall number of babies born in the U.S. is falling. In fact, an analysis of birth certificates revealed "the percentage of mothers without any prenatal care rose from 2.2 percent in 2022 to 2.3 percent in 2023." According to the authors of the report, the lopsided trend may reflect, in part, a growing number of women unable to access OB-GYN care after the U.S. Supreme Court overturned Roe v. Wade in 2022. "In many counties, you can't even find a prenatal care provider," said Brenna Hughes, MD, MSc, executive vice chair of the department of obstetrics and gynecology at Duke University in Durham, N.C. "If you have limited resources and have to travel to be able to access prenatal care, it is going to be a deterrent."[22]

Therefore, now more than ever, timely intervention, including dispelling the many myths concerning prenatal care, from doctors can significantly cure or prevent problems, improving outcomes for unborn babies and mothers. ❖

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Menopause: *A Patient's Perspective*

By Trudie Mitschang

SHARON MACARTHUR is a menopause educator and the founder of Miss Menopause UK, an organization that focuses on corporate education about menopause. Her own journey through this life change inspired her to help others — particularly women in the workforce — navigate the symptoms and repercussions with knowledge and self-empowerment.

BSTQ: Tell us about your experience with menopause.

Sharon: My journey began at age 47 with night terrors: waking up at 4 a.m. with a feeling of impending doom. I began to feel exhausted. I just didn't feel like me. Things I could do without thinking suddenly became really difficult. I couldn't remember people's names, and I was tired all of the time. I felt anxious about meeting people and didn't want to go out. Then the disturbed sleep began. I seemed to wake up every hour, leaving me feeling totally drained. I took to Google to see if I could figure out what was happening to me. After hours of research, I realized I was probably going though perimenopause. This meant that menopause was on the way. I felt sad and confused. I was sure I was too young. Sadly, it turns out I wasn't.

BSTQ: Tell us about what you called your "final straw" experience.

Sharon: I fell asleep at the wheel of my car while driving at full speed. Fortunately, I didn't swerve or crash, but I was terrified when I nodded awake and realized what had happened. For many months after that, when I was driving, I would pull over every half hour for a power nap, petrified I would fall asleep and die. I knew it was my hormones, but I couldn't control it: Menopause was causing this. Shocked, I began to ask my friends and family to see who might be going through the same thing. Surprisingly, older women I asked said they "just got on with it" but they hadn't worked at the time. Friends my age didn't seem to know what to expect. I was on my own.

BSTQ: What inspired you to start Miss Menopause?

Sharon: I found that there wasn't enough information readily available for women like me experiencing such a huge life event. When I attended mental health courses to find out more information, I was shocked to hear that menopause is never even considered a talking point. It was then I decided to start Miss Menopause to create an outlet to both educate and support women through this time in their life. I am keen to educate employers on how they can educate all of their workforce about this subject and, most importantly, equip women with the skills as to what to expect and how to deal with this life event.

BSTQ: Why did you decide this was a corporate conversation?

Sharon: I was speaking to women who had left their jobs because they didn't know what was happening to them, and the companies they worked for weren't stopping them from going. They'd lost their confidence, didn't feel as capable and some even thought they had early-onset Alzheimer's. It frustrated me because men in their mid-40s are powering through their careers, enhancing their pensions and looking to take on more responsibility. At that age, so many women should also be hitting their professional stride — but then the menopause symptoms begin and throw them off kilter.

BSTQ: What workplace changes do you advocate?

Sharon: I don't necessarily think companies need to create policies around menopause; they just need to educate their staff — including men — and demonstrate through action that it's not an unspoken taboo. I'm sharing this information in male-dominated fields, and men are thanking me, saying it's saving their relationships. Giving people space and permission to talk about their experiences is important. Many women suffer in silence and feel a deep sense of loneliness, and often shame, about their menopausal symptoms.

BSTQ: Why is talking about menopause important?

Sharon: When we talk about menopause, we have the opportunity to share advice. It took nearly 18 months and much trial and error for me to find a menopause treatment that worked for me.

BSTQ: How did you eventually manage your symptoms?

Sharon: After experimenting with sage tablets, magnesium baths and being wrongly prescribed antidepressants, I asked my doctor for hormone replacement therapy (HRT) after researching it extensively, and it completely changed my life. My symptoms faded away — it was a miracle. HRT often gets such bad press but [...] it's your body, your choice, and you must do your research, get the facts. On average, menopause lasts between five and seven years. Do you really want to put your life on hold for all that time?" ❖

Menopause: *A Physician's Perspective*

ERIKA SCHWARTZ, MD, is the founder of Evolved Science, a world-renowned medical practice based in New York City, built on the recognition that bioidentical hormones are the foundation for better health. Having experienced early menopause herself, Dr. Schwartz is a pioneer in the use of bioidentical hormone replacement therapy (BHRT) for preventing illness and recognizing its direct link to overall wellness and interconnection with diet, sleep and stress management.

BSTQ: What is the root of troublesome menopausal symptoms?

Dr. Schwartz: Menopause symptoms such as hot flashes, insomnia and mood swings are the result of a hormonal imbalance, and it is important to know what causes this imbalance. It could be anything or a combination of factors, some of which include diet, exercise regimen, stress level and your ability to manage stress, the amount of sleep you're getting, and overall lifestyle. All of these affect hormonal balance, and if any of these factors are not well taken care of, it will throw off your balance, which could spell trouble.

BSTQ: How did your personal experience with menopause lead to your discovery of BHRT as a treatment option?

Dr. Schwartz: I went into menopause quite early at age 46. I tried the synthetic HRT I was trained to recommend to my patients and also birth control pills. I felt horrible. It was like an alien entered my body. My moods were out of control, I developed terrible irregular periods with heavy bleeding, I gained weight and I didn't recognize myself. This was not how I wanted to age. One of my patients had asked me to write a prescription at a compounding pharmacy for what turned out to be BHRT a few years before. I knew nothing about it because we were never taught in school about the existence of these preparations of hormones identical to the hormones our bodies make. My patient loved them and swore by them. I read up on them and scoured the scientific literature for information on them. It was all there since the early 1930s. I ordered some for myself and felt much better. Then I decided to take a deeper dive into the hormones themselves and learn more about compounding pharmacies. I took three years to develop my own formulations and work with my own patients and myself to figure out solutions that worked.

BSTQ: You're considered a respected expert on BHRT. Tell us about your personal protocol and how you teach it to other physicians.

Dr. Schwartz: I have been working with BHRT for 30 years and have treated thousands of women and still do. I also still take the hormones myself. Many of my patients are with me since the beginning and are thriving. It's such an honor and a gift to see women be able to age feeling great. I am a faculty member of American Academy of Anti-Aging Medicine, which is the only organization that provides teaching, certification and serious scientific and clinical foundation for BHRT treatments. I also write scholarly articles on the topic and provide information on social media and host a podcast for practitioners.

BSTQ: In your opinion, why should menopausal women be prescribed testosterone as part of a hormone replacement plan?

Dr. Schwartz: Testosterone is a very important hormone women manufacture, and it has been scientifically proven in numerous scholarly articles over the course of the past five decades that it protects the brain, bones, heart, libido and muscles to just name a few. Testosterone is crucial to maintaining healthy, optimal metabolic function as we age. It improves overall health, which is crucial to anyone who wants to stay youthful and enjoy the aging process.

BSTQ: What connection have you seen between hormone therapy and depression and antidepressant use during menopause?

Dr. Schwartz: Women in perimenopause or menopause are often prescribed antidepressants, when in reality, they may just need to balance their hormones. Estradiol, progesterone and testosterone along with thyroid and adrenal hormones improve mood by increasing dopamine and serotonin production in the brain. The lack of hormones is what may cause depression, not the lack of antidepressants. I spend much time weaning women off antidepressants that are extremely addictive and don't help. Balancing hormones helps. Antidepressants may serve a purpose for acute events and very short duration of use. Using them for decades is not helpful and may actually harm the brain by increasing the likelihood of dementia and Alzheimer's.

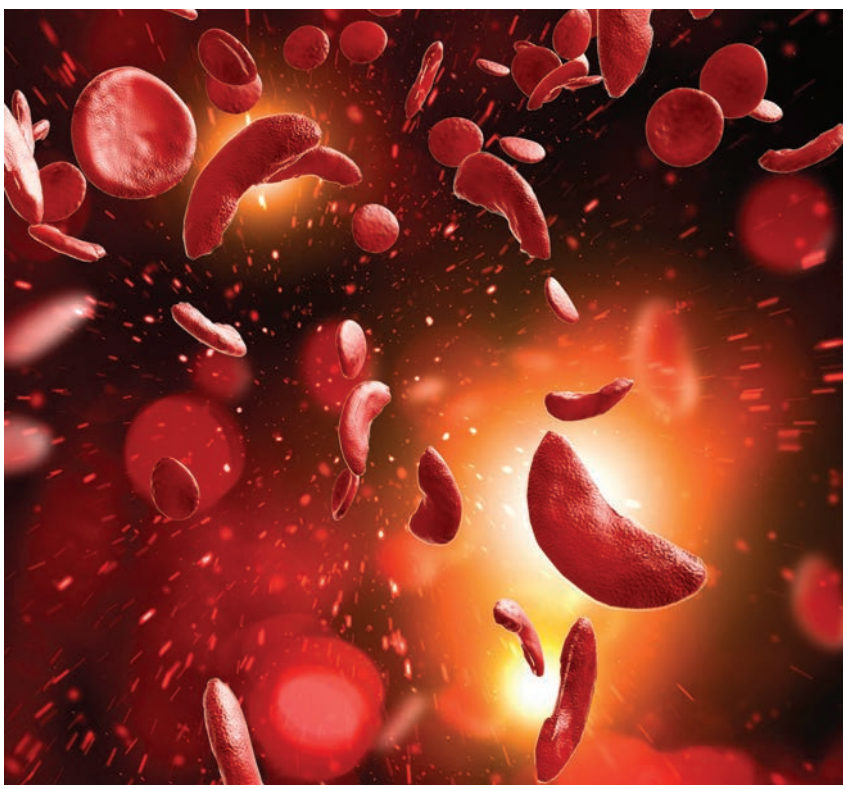
BSTQ: Are there any interesting new studies on BHRT in the pipeline?

Dr. Schwartz: There are many studies that have already proven the importance and safety of BHRT. In fact, there isn't one study that showed bioidenticals to be dangerous or ineffective if given in correct doses for the patient. ❖

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

New Gene Therapies Are Transformative for People with Sickle Cell Disease and Frequent Vaso-Occlusive Crises

By Keith Berman, MPH, MBA



AFFECTING MORE than 100,000 American children and adults, sickle cell disease (SCD) is an inherited hemoglobinopathy that results when a single-nucleotide mutation in the ß-globin gene yields an abnormal "sickle" hemoglobin (HbS). In a low oxygenation state commonly triggered by infection, dehydration, stress or extreme temperatures, HbS forms rigid polymers that cause normally biconcave red blood cells (RBCs) to become elongated, rigid and curved on the ends, resembling a sickle shape.

These stiff, severely deformed sickle RBCs tend to stick together and block or restrict blood flow. Because sickle RBCs are prone to hemolysis, they have a far shorter circulating lifespan than normal RBCs, resulting in chronic anemia.

Most severely affected are individuals with the HbSS (sickle cell anemia) or HbS-ß0-thalassemia genotypes, in whom high levels of HbS and hypoxic trigger events lead to recurrent bouts of severely painful vaso-occlusive crises (VOCs). Acute chest syndrome, severely painful joints, splenic sequestration and stroke head a long list of common serious acute and chronic complications of severe SCD (Table).

Expanding SCD Treatment Options

Two mainstay treatments have been used for many years in SCD patients in an effort to limit VOCs and reduce other serious complications. The first is RBC transfusion to acutely or chronically reduce the level of circulating HbS and improve oxygen delivery. The other is hydroxyurea, potent oral antimetabolite used in higher doses to treat certain cancers. Through an incompletely understood means, hydroxyurea induces production of fetal hemoglobin (HbF), which inhibits intracellular HbS polymerization and the sickling phenomenon. In adults, hydroxyurea can substantially reduce the frequency of severe painful vaso-occlusive episodes, acute chest syndrome, hospitalizations and blood transfusion requirements.[1] In children with SCD ages 2 years and older, hydroxyurea has been shown to decrease the frequency of pain crisis and childhood hospitalization.[2]

But the limited benefits of hydroxyurea and transfusion to reduce VOCs and other SCD complications have spurred development of newer treatments. By blocking a protein that causes stickiness between vascular endothelial cells, RBCs, platelets and leukocytes, the humanized monoclonal antibody crizanlizumab (ADAKVEO) has been shown to further reduce VOC incidence in subjects both treated and not treated with hydroxyurea. The U.S. Food and Drug Administration (FDA) approved ADAKVEO in 2017 after a pivotal trial showed that addition

Table. Common Acute and Chronic Complications of Sickle Cell Disease

System	Complications
Circulatory	Vaso-occlusive crisis
	Anemia secondary to hemolysis
	Splenic sequestration; abdominal pain
	Bacterial sepsis
Pulmonary	Acute chest syndrome
	Pulmonary infection
Cerebrovascular	Cerebrovascular
	Silent cerebral infarcts
	Learning and cognitive difficulties
Genitourinary	Chronic renal dysfunction
	Priapism (painful sustained erection)
Hepatobiliary	Cholelithiasis
	Hepatic fibrosis
Ocular	Retinopathy and decreased vision
Skeletal	Osteonecrosis; severe joint pain
	Dactylitis

of the drug achieved a 45 percent reduction in the median annual rate of VOCs, from 2.98 to 1.63 events.[3]

Supplementation of hydroxyurea with twice-daily oral L-glutamine (ENDARI), also approved by FDA in 2017, was separately proven to reduce the median number of VOCs by about one-quarter in a placebo-controlled study in 230 adults and children with sickle cell anemia or HbS-ß0-thalassemia. ENDARI therapy also resulted in fewer hospitalizations due to sickle cell pain and a lower incidence of acute chest syndrome.[4,5]

Two years later in 2019, FDA approved voxelotor (OXBRYTA), another oral medication that, by increasing hemoglobin affinity for oxygen, inhibits HbS polymerization, thereby reducing RBC sickling and hemolysis-associated anemia.[6]

These newer treatment options have proven utility in reducing VOCs and other comorbidities, but they are far from a cure, particularly for more severely affected children and adults with more frequent VOCs. According to the U.S. Centers for Disease Control and Prevention (CDC), the average life expectancy for persons with SCD is still shortened by more than 20 years compared with the general population; when factoring in quality of life, more than 30 years are lost.[7] So despite the availability of several drug treatment options that didn't exist a decade ago, many patients with SCD continue to suffer from severe morbidity and shortened lifespan.

Limitations of Donor Stem Cell Transplantation

In children and qualifying young adults with SCD who have the HbSS or HbS-ß0-thalassemia genotypes and one or more specific manifestations of severe disease,* allogeneic hematopoietic stem cell transplantation (HSCT) is curative in more than 90 percent of cases.[8] But outside of investigational clinical trials, HSCT is appropriate only for SCD patients who have a fully HLA-matched sibling without SCD in order to avoid major risks of potentially life-threatening graft-versus-host disease (GVHD).

Unfortunately, fewer than one in five children with SCD have an HLA-matched sibling, leaving all others without access to HSCT. And even in the optimal circumstance where the donor is an HLA-matched sibling, allogeneic HSCT has real risks, including:

- A roughly 15 percent overall risk of developing acute or chronic GVHD, increasing with transplant age;[9]
- A risk of future infertility resulting from myeloablative conditioning;[10,11] and
- A risk of premature death (an overall seven percent probability of five-year mortality, increasing about 10 percent with each one-year increase in transplant age).[9]

Fortunately, a second curative strategy for SCD has finally arrived: gene therapy. And because it involves use of autologous hematopoietic stem cells (HSCs), this novel treatment approach isn't burdened by the HSCT-associated risks of serious or potentially life-threatening GVHD, nor restricted to a small subpopulation of SCD patients fortunate enough to have an HLA-matched full sibling.

*Stroke, recurrent acute chest syndrome, recurrent severe crisis pain, recurrent priapism, impaired neuropsychological function with evidence of cerebral infarction, sickle cell nephropathy, stage I or II sickle lung disease, bilateral proliferative retinopathy and major visual impairment, osteonecrosis of multiple joints, and red cell alloimmunization with more than two antibodies during long-term transfusion therapy. [Walters MC, De Castro LM, Sullivan KM, et al. Indications and results of HLA-identical sibling hematopoietic cell transplantation for sickle cell disease. *Biol Blood Marrow Transplant* 2016 Feb;22(2):207-11].

Two SCD Gene Therapies, Two Approaches

Conventional gene therapies exert their therapeutic effect through insertion of a gene encoding a missing protein that plays a critical role in an enzymatic or metabolic pathway. Novartis' ZOLGENSMA, for example, is an adeno-associated viral (AAV) vector-based gene therapy that stops the progression of spinal muscular atrophy by replacing the missing or nonworking human survival motor neuron (SMN1) gene. BioMarin Pharmaceuticals' ROCTAVIAN and CSL Behring's HEMGENIX similarly use an AAV vector to deliver genes respectively encoding functional coagulation factors VIII and IX missing in persons with hemophilia A and B.

In December 2023, FDA approved not one but two novel, single-treatment gene therapies for the treatment of SCD patients age 12 years and older with a history of VOCs. One of these two therapies (LYFGENIA) applies the classical functional protein replacement model, while the other (CASGEVY) employs an entirely novel approach to overcoming HbS-mediated RBC pathophysiology.

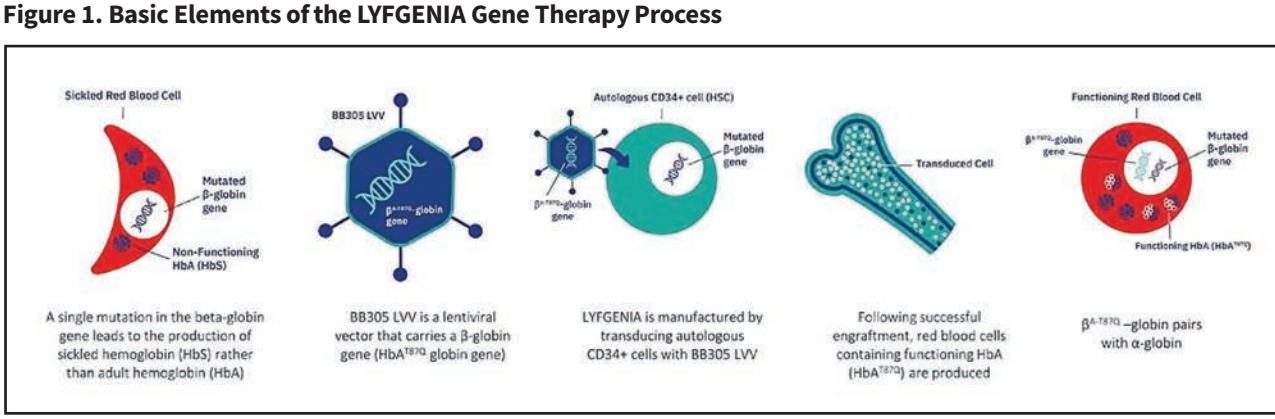
LYFGENIA (lovotibeglogene autotemcel) (bluebird bio). Similarly to the way that approved hemophilia gene therapies work through insertion of genes encoding functional factor VIII and IX, the LYFGENIA procedure employs a recombinant replication-defective lentiviral vector (LVV) to introduce copies of a modified ß-globin gene ($ß^{A\text{-}T87Q}$) into the genome of the patient's bone marrow-harvested autologous CD34+ cell-enriched HSCs (Figure 1). $ß^{A\text{-}T87Q}$ combines with native ß-globin to yield an anti-sickling hemoglobin variant (HbA^{T87Q}) whose oxygen-binding affinity and dissociation properties are similar to normal hemoglobin. And because this generated HbA^{T87Q} both reduces intracellular and total HbS levels and acts to inhibit polymerization of HbS, it also limits the sickling of RBCs.

A pair of clinical trials that treated a total of 47 SCD patients with a history of recurrent VOCs or stroke through up to five years of follow-up (median of 35.5 months) generated these key results:[12,13]

- All 47 patients exhibited strong, stable production of the anti-sickling hemoglobin variant, with a median HbA^{T87Q} exceeding 40 percent.
- Median total hemoglobin increased from 8.7 g/dL at pre-treatment baseline to 11.8 g/dL at the last visit.
- Of 34 evaluable patients, 32 (94 percent) had complete resolution of severe VOCs; 30 had complete resolution of all VOCs; this compares to a median of 3.0 severe VOCs and 3.5 total VOCs per year in the two years prior to LYFGENIA treatment.
- Patients reported sustained improvements in pain intensity, pain interference and fatigue, up to 48 months of follow-up.
- No evidence of graft failure, replication-competent lentivirus or vector-mediated oncogenesis was observed in any patient enrolled in the LYFGENIA clinical development program, extending back more than eight years.

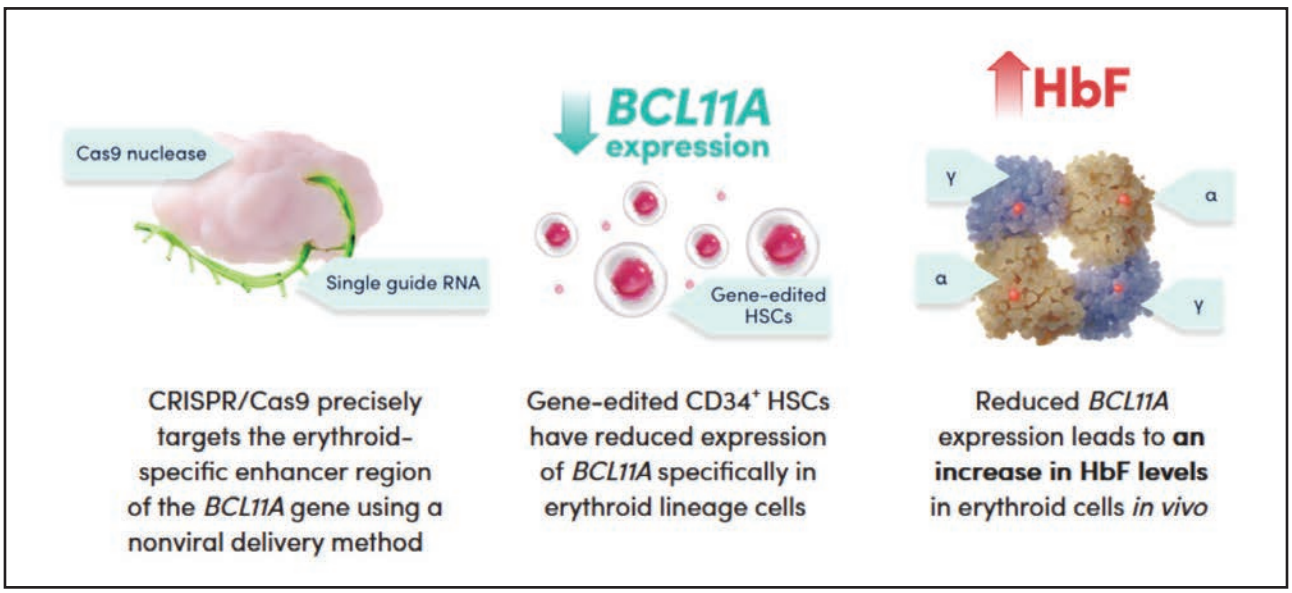
CASGEVY (exagamglogene autotemcel) (Vertex Pharmaceuticals). While LYFGENIA reduces RBC sickling by inserting functional copies of a modified functional ß-globin gene, the CASGEVY procedure instead employs an entirely new nonviral gene editing strategy to reactivate dormant fetal hemoglobin

Figure 1. Basic Elements of the LYFGENIA Gene Therapy Process



Source: LYFGENIA FDA Approval. Accessed at www.sec.gov/Archives/edgar/data/1293971/000119312523292087/d84993dex991.htm.

Figure 2. Basic Elements of the CASGEVY Gene Therapy Process



Source: CASGEVY® is a CRISPR/Cas9-modified autologous CD34+ cellular gene therapy. Accessed at www.casgevyhcp.com/transfusion-dependent-beta-thalassemia/mechanism-of-action.

(HbF) production and drive down HbS levels (Figure 2).

Harvested autologous CD34+ cell-enriched HSCs are collected from the patient and edited by a technology called "clustered regularly interspaced short palindromic repeats" (CRISPR). Sometimes referred to as "genetic scissors," CRISPR directs an enzyme called Cas9 to a specific region of a gene called *BCL11A*, whose function is to shut off the production of the fetal form of human hemoglobin (HbF) following birth. CRISPR-Cas9 deactivates *BCL11A* by cutting its DNA, resulting in reactivated HbF production by these gene-edited HSCs.

In June of this year, Vertex reported results from CLIMB SCD-121, a 24-month Phase III trial of CASGEVY in patients ages 12 to 35 years with a history of ≥2 VOCs per year. Here are key findings in 46 SCD patients who received CASGEVY, including 17 patients who completed at least two years of follow-up:[14]

- Twenty-nine of 31 (93.5 percent) evaluable patients were free of severe VOCs for ≥12 consecutive months (VF12); all 31 patients (100 percent) were free from hospitalizations for VOCs for ≥12 consecutive months.
- In patients achieving VF12, the mean VOC-free duration was 25.4 months (range 18.0-48.7 months).
- For all treated patients, the mean total hemoglobin was 11.9 g/dL at month 3 and ≥11 g/dL from month 6 onward.
- The mean HbF as a percentage of total hemoglobin was 37.1 percent at month 3 and generally ≥40.0% from month 6 onward with pancellular distribution (≥95 percent of RBCs express HbF).
- Patients reported sustained and clinically meaningful improvements in their health-related quality of life, across physical, emotional, social/family and functional well-being parameters, pain experience and overall health status.
- No patients had serious adverse events considered related to CASGEVY therapy.

While CRISPR technology is being investigated for a variety of therapeutic applications, CASGEVY has the distinction of being the first-ever CRISPR-based gene editing therapy to be approved in the U.S.

A second one-time CRISPR-based autologous gene editing therapy, Editas Medicine's renizgamglogene autogedtemcel ("reni-cel"), is also in late-stage clinical development for treatment of SCD. Like CASGEVY, reni-cel introduces edits that reactivate production of HbF.

While just two of 18 adult severe SCD patients dosed with reni-cel have been monitored for more than a year, none of these 18 patients have experienced a VOC over a mean of six months. Following reni-cel infusion, total hemoglobin levels rapidly normalized, with a sustained HbF level exceeding 40 percent through the last follow-up.[15] Massachusetts-based Editas plans to enroll a total of 45 severe SCD patients to evaluate reni-cel's efficacy, safety and tolerability.

Implementing SCD Gene Therapy

Both the CASGEVY and LYFGENIA therapy procedures require providers with specialized experience in stem cell transplantation. Individualized decisions must be made at each treatment phase, including mobilization of autologous HSCs, myeloablative drug conditioning to create space for the gene-modified HSCs to engraft in the bone marrow, use of RBC transfusions to reduce the risk of SCD-related complications, and management of adverse events that may follow infusion of gene-modified HSCs.

Vertex and bluebird bio are each engaging with carefully selected hospitals to qualify them for inclusion in their participating treatment center networks. To date, bluebird bio has activated — or is in the process of activating — at least 55 "Qualified Treatment Centers," including 25 children's hospitals. Vertex is on track to activate a similar number of "Authorized Treatment Centers."

Like other gene therapies licensed to date, CASGEVY and LYFGENIA are expensive, with list prices of $2.2 million and $3.1 million, respectively. However, less than a week after FDA approval, bluebird bio disclosed that it had reached an outcomes-based agreement with a third party payer organization representing approximately 100 million covered lives, and was in discussions with other large commercial payers and more than 15 state Medicaid agencies representing 80 percent of individuals with SCD in the U.S.[16] Under its announced Cell and Gene Therapy Access Model, beginning next year the U.S. government's Centers for Medicare and Medicaid Services (CMS) similarly plans to negotiate outcomes-based agreements with the two manufacturers on behalf of participating state Medicaid agencies; between 50 percent and 60 percent of SCD patients are covered by the Medicaid program, according to CMS.[17]

Modeling CASGEVY and LYFGENIA against the current standard of care, the Institute for Clinical and Economic Review (ICER) calculated a Health Benefit Price Benchmark ranging between $1.35 million and $2.05 million. More importantly, ICER concluded that, while acknowledging uncertainties about long-term outcomes, "both CASGEVY and LYFGENIA are likely to substantially improve quality and length of life among patients with SCD."[18]

Vertex estimates that some 16,000 U.S. SCD patients may be eligible for a one-time gene therapy that offers the potential of a durable functional cure by eliminating severe VOCs and associated hospitalizations.[19] While the evidence to date is highly promising, it remains to be seen whether a single infusion of genetically modified HSCs can actually provide a long-term cure. In the meantime, it is up to providers, insurers and government policymakers to work together to assure every qualifying individual with severe SCD has access to these therapies and the opportunity to live a long, healthy life. ❖

> Both the CASGEVY and LYFGENIA therapy procedures require providers with specialized experience in stem cell transplantation.

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

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[1]https://www.cdc.gov/poxvirus/molluscum-contagiosum/index.html
[2]https://www.fda.gov/consumers/consumer-updates/safely-treating-molluscum-common-skin-condition#:~:text=The%20FDA%20has%20approved%20Ycanth,only%20by%20health%20care%20professionals.

AI-Driven Healthcare Common Sense & Predictive Modeling : Healthcare Optimization Quick Reference Guide to Actionable Insights

Author: Salimah Muhammad

AI-Driven Healthcare explores how predictive modeling and common sense can optimize healthcare delivery, improve patient outcomes and streamline operations. This book delves into real-world examples, case studies and practical applications, making it an indispensable resource for healthcare professionals, leaders and anyone interested in the future of healthcare. Readers can discover how AI can enhance decision-making, address social determinants of health and generate significant return on investment in healthcare settings.

www.amazon.com/AI-Driven-Healthcare-Common-Predictive-Modeling-ebook/dp/B0CZ4G4F1D

Putting Social Media to Work in Healthcare: A Beginner's Guide to Digital Success, 1st Edition

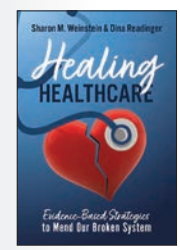
Author: Kevin R. Campbell

This is the first practical textbook for healthcare professionals demonstrating how to use social media in medicine. It focuses on the very basics of social media, providing a step-by-step approach for creating a social media presence and guiding readers through the process of setting up individual accounts on multiple social media platforms. The book will help professionals create a social media strategy and develop a consistent, effective online presence. In addition, it addresses important ethical and regulatory considerations for social media use by healthcare professionals, while real world examples show how social media engagement can improve health outcomes.

www.amazon.com/Putting-Social-Media-Work-Healthcare/dp/1138065862

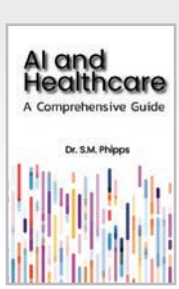
Healing Healthcare: Evidence-Based Strategies to Mend Our Broken System

Authors: Sharon M. Weinstein, MS, RN, CRNI-R, CSP, CVP, FACW, FAAN, and Dina Readinger, EMBA



Healing Healthcare is an exploration of the intricate challenges within the healthcare landscape post-pandemic and solutions for change. Faced with shortages and systemic upheavals, the healthcare system currently teeters on the brink of collapse, prompting responses from a respected group of healthcare professionals who each spotlight evidence-based strategies for recovery. With a diverse set of contributors from academia, practice and the community, this text is a collaborative effort that serves as a beacon of hope, paving the way for a truly healed and resilient healthcare ecosystem.

www.amazon.com/Healing-Healthcare-Evidence-Based-Strategies-Broken/dp/1637559666



AI and Healthcare: A Comprehensive Guide

Author: S. M. Phipps, PhD

AI and Healthcare: A Comprehensive Guide explores the revolutionary intersection of artificial intelligence and modern medicine. This authoritative volume offers readers a deep dive into how AI is transforming every aspect of healthcare, from diagnosis and treatment to drug discovery and patient care. It covers the latest developments in machine learning, deep learning and natural language processing as applied to healthcare, while also addressing critical ethical, legal and societal implications. Key features include in-depth explanations of AI technologies and their specific applications in healthcare; real-world case studies showcasing successful AI implementations in hospitals and research institutions; discussions on the future of AI in personalized medicine, telemedicine and public health; exploration of challenges and potential solutions in data privacy, algorithmic bias and regulatory compliance; and insights into emerging trends such as AI-powered wearables, robotics in surgery and AI in mental health.

www.amazon.com/Healthcare-Comprehensive-Dr-Phipps-PhD/dp/B0DB38CW6G

Addition of IVIG May Be Superior to Addition of Plasmapheresis in Corticosteroid-Resistant Optic Neuritis: Systematic Review

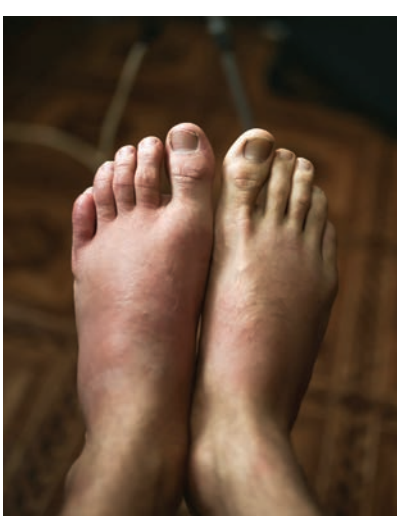
While the efficacy of corticosteroids (CS) is well-established as first-line treatment of optic neuritis (ON) in demyelinating disease, there is no consensus on second-line treatment. A team of French investigators conducted a meta-analysis and systematic review to compare the efficacy of CS alone against CS combined with intravenous immune globulin (IVIG) or CS combined with plasmapheresis (PP) in patients with steroid-resistant ON.

A total of six comparative studies, representing 209 patients, were identified from a systematic review of all studies published on PubMed between January 2000 and June 2022 that compared at least two of the three treatment options for steroid-resistant ON. Respective rates of significant visual recovery following acute treatment of ON with CS alone, CS plus PP and CS plus IVIG were 30 percent, 45 percent and 77 percent, yielding respective odds ratios of 12.81, 2.47 and 0.19.

The investigators concluded that treatment of steroid-resistant ON with CS plus IVIG or CS with PP is more effective than treatment with CS alone. And, while no study has directly compared the two treatments, IVIG may be more effective than PP in this clinical setting. ❖

Gaulier, A, Hardouin, JB, Wiertlewski, S, et al. Efficacy and Comparison of Corticosteroids Only and Corticosteroids with Plasmapheresis or Intravenous Immunoglobulin for the Treatment of Optic Neuritis in Demyelinating Disease: A Systematic Review and Network Meta-Analysis. *Multiple Sclerosis or Related Disorders*, 2024 May;85:105521.

Investigational Plasma Kallikrein Inhibitor (Sebetralstat) Reduces Time to Relief from Hereditary Angioedema Attacks



In a Phase III, double-blind, three-way crossover trial, sebetralstat given on-demand for treatment of hereditary angioedema (HAE) attacks was shown to result in faster times to the start of symptom relief, reduction in attack severity and complete attack resolution than placebo treatment. Sebetralstat is an orally administered plasma kallikrein inhibitor currently being developed by KalVista Pharmaceuticals.

A total of 136 participants at least 12 years of age with type 1 or type 2 HAE were randomly assigned to take up to two oral doses of sebetralstat (300 mg or 600 mg) or placebo for an angioedema attack. The median time to the start of symptom relief was 1.61 and 1.79 hours, respectively, in the 300 mg and 600 mg sebetralstat groups, compared to 6.72 hours in subjects given placebo.

The median time to a reduction in attack severity was 9.27 and 7.75 hours in the 300 mg and 600 mg sebetralstat groups, while it exceeded 12 hours in the placebo group. The percentage of attacks with complete resolution within 24 hours was 42.5 percent and 49.5 percent with the 300 mg and 600 mg dosages, and 27.4 percent with placebo.

Sebetralstat and placebo exhibited similar safety profiles, and no serious adverse events related to the trial agents were reported. The study authors noted that sebetralstat's oral route of administration could confer a therapeutic advantage over approved on-demand treatments for HAE attacks, whose parenteral route of administration is "associated with delays in treatment or withholding of therapy." ❖

Riedl, MA, Farkas, H, Aygören-Pürsün, E, et al. Oral Sebetralstat for On-Demand Treatment of Hereditary Angioedema Attacks. *New England Journal of Medicine,* 2024 May 31;391:32-43.

Medicare Immune Globulin Reimbursement Rates

Rates are effective Sept. 1, 2024, through Dec. 31, 2024

	Product	Manufacturer	J Codes	ASP + 6% (before sequestration)	ASP + 4.3% (after sequestration)
IVIG	ALYGLO	GC Biopharma	J1599	*	*
	ASCENIV	ADMA Biologics	J1554	$982.81	$967.05
	BIVIGAM	ADMA Biologics	J1556	$150.34	$147.93
	GAMMAGARD SD	Takeda	J1566	$164.38	$161.75
	GAMMAPLEX	BPL	J1557	$115.85	$113.99
	OCTAGAM	Octapharma	J1568	$97.99	$96.42
	PANZYGA	Octapharma/Pfizer	J1576	$134.92	$132.76
	PRIVIGEN	CSL Behring	J1459	$97.16	$95.60
	YUMMIGO	Kedrion	J1599	*	*
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$99.38	$97.79
	GAMMAKED	Kedrion	J1561	$97.61	$96.04
	GAMUNEX-C	Grifols	J1561	$97.61	$96.04
SCIG	CUTAQUIG	Octapharma	J1551	$144.98	$142.65
	CUVITRU	Takeda	J1555	$168.20	$165.50
	HIZENTRA	CSL Behring	J1559	$132.32	$130.20
	HYQVIA	Takeda	J1575	$175.03	$172.22
	XEMBIFY	Grifols	J1558	$142.95	$140.66

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

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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
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

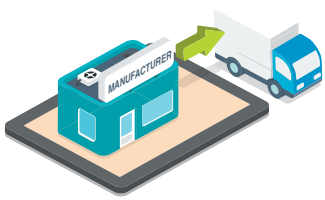
GuaranteedChannelIntegrity®

Guaranteed Channel Integrity®
8 Critical Steps

STEP 1

Purchasing

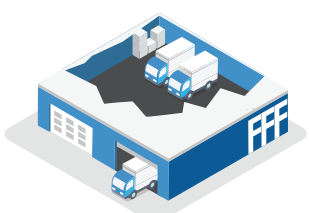
At FFF, we only purchase product from the manufacturer–never from another distributor or source–so the integrity of our products is never in question.



STEP 2

Storage

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



STEP 3

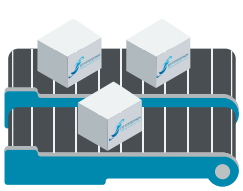
Specialty Packaging

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

STEP 4

Interactive Allocation

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



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

800.843.7477 | Emergency Ordering 24/7

STEP 5

Delivery

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

STEP 6

Methods of Delivery

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

STEP 7

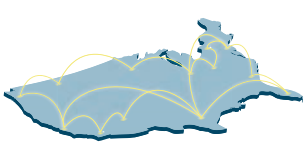
Verification

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

STEP 8

Tracking

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



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