SPRING 2020

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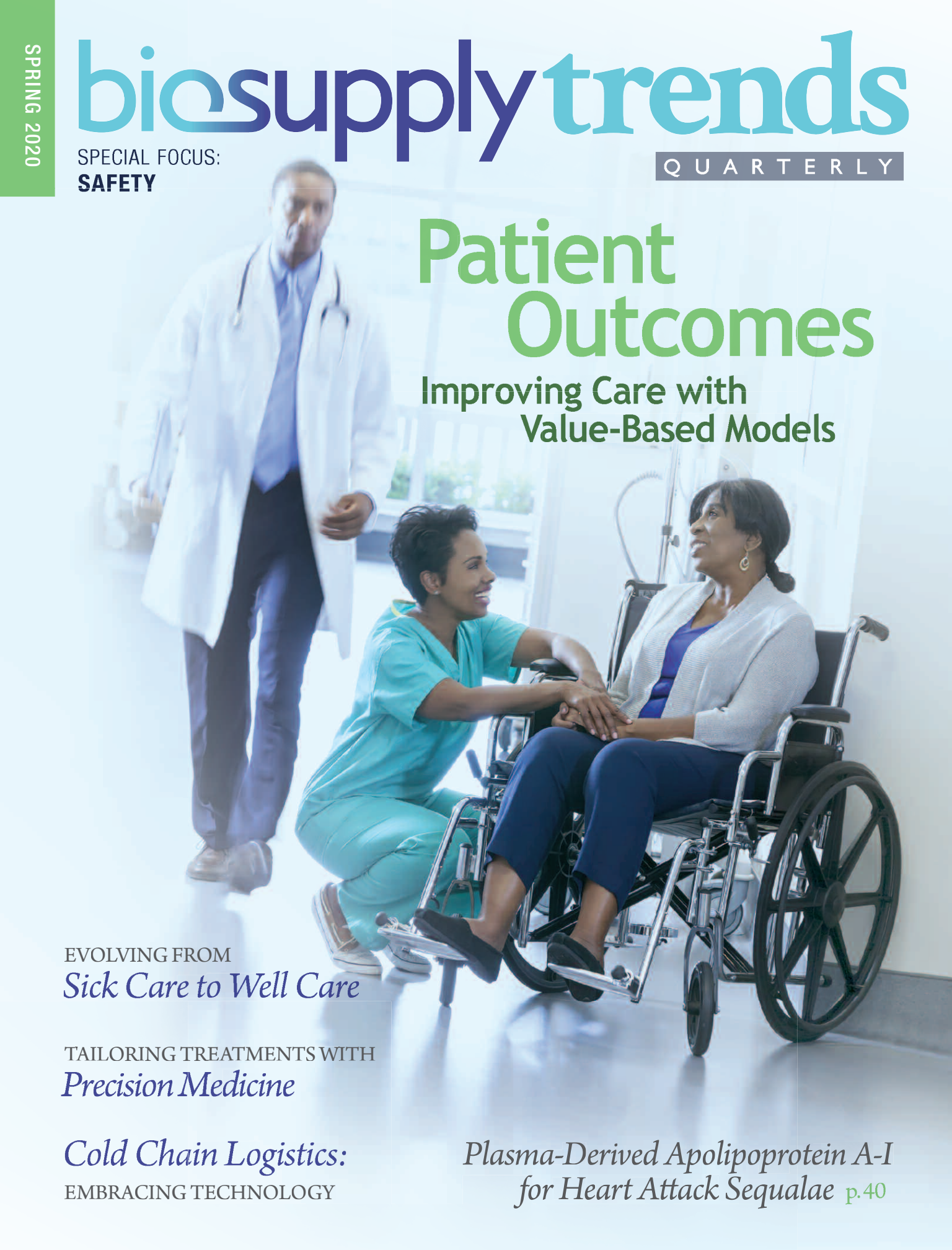
QUARTERLY

SPECIAL FOCUS:
SAFETY

Patient Outcomes

Improving Care with Value-Based Models



EVOLVING FROM
Sick Care to Well Care

TAILORING TREATMENTS WITH
Precision Medicine

Cold Chain Logistics:
EMBRACING TECHNOLOGY

Plasma-Derived Apolipoprotein A-I for Heart Attack Sequalae p.40

8 Critical Steps

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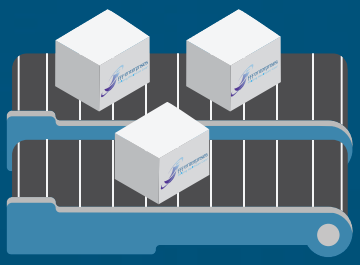

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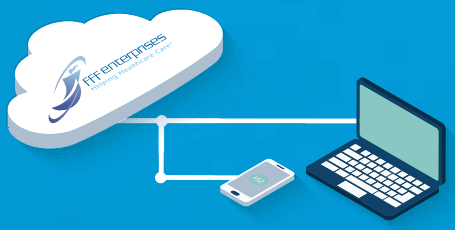

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BioSupply Trends Quarterly is the definitive source for industry trends, news and information for healthcare professionals in the biopharmaceuticals marketplace.

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Improving Patient Outcomes with Evolving Medical Models

UNDER THE Affordable Care Act, improving patient outcomes has become a central goal set for the U.S. healthcare system. In accordance, medical care is rapidly transitioning from traditional models toward those that prevent illness rather than treat it and that reward providers based on efficiency and effectiveness. The goals are to improve patient wellness and satisfaction and lower costs.

One of the biggest shifts in treatment models is from fee-for-service to value-based care. As explained in "The Changing Face of Primary Care" (p.16), value-based care changes the care delivery focus from volume to value and redefines financial incentives toward reduced costs. Under the Centers for Disease Control and Prevention's (CDC) Primary Cares Initiative, this change gives providers five payment options with varying levels of financial responsibility. But, value-based care is just one way in which primary care models are adapting to improve outcomes. Other models include collaborative care that integrates behavioral health and general medical services; the transition to more convenient care such as urgent care, telemedicine and drugstore retail clinics; and team-based care, especially for treating chronically ill patients, which can also reduce physician burnout.

Another major transformation in treatment models is the pivot from a sick-care to a well-care system. According to CDC, the U.S. ranks No. 1 in the world for medical spending, but only 37th in the world for health outcomes. As pointed out in our article "Evolving from Sick Care to Well Care" (p.20), for this revolution to occur, medical providers must address the whole patient from psychological, social and economic standpoints, payers must begin tying reimbursement to outcomes versus reimbursement, and patients must take responsibility for their health by seeking preventive care services and reducing risk factors.

On the healthcare horizon, a new development that shows great promise is precision medicine, an approach to patient care that allows doctors to select treatments most likely to help patients based on a genetic understanding of their disease. According to our article "Tailor-Made Medicine: An Evolution in Precision Cures" (p.29), studies to date have concentrated on pharmacogenomics and metabolomics, which focus on developing medicines based on individuals' specific genetic markers, medical history, environmental health and other lifestyle factors. It is hoped big data and artificial intelligence will help to capture information about the causes of diseases and who will be most affected before people become sick. But, there is still much to be done to create the vast networks necessary for collaborative research.

For now, providers can do much to make patient satisfaction a priority. For some practical techniques, see our article "How to Improve Patient Satisfaction" (p.10).

As always, we hope you enjoy this issue of *BioSupply Trends Quarterly*, and find it 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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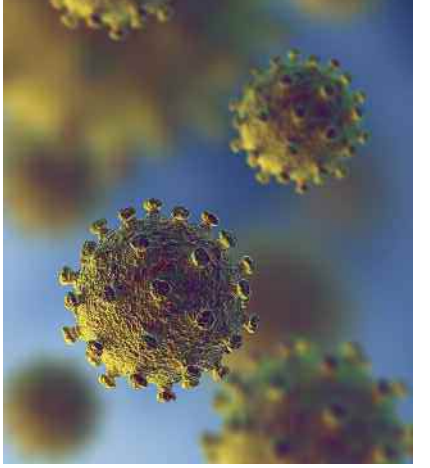
NIAID Awards $30 Million to Develop Tuberculosis Vaccine

The National Institute of Allergy and Infectious Diseases (NIAID) has awarded $30 million in first-year funding to establish new centers for immunology research to accelerate progress in tuberculosis (TB) vaccine development. The awards establish and provide up to seven years of support for three Immune Mechanisms of Protection Against Mycobacterium Tuberculosis (IMPAc-TB) Centers to elucidate the immune responses needed to protect against Mtb infection. The IMPAc-TB program aims to develop a comprehensive understanding of the immune responses required to prevent initial infection with Mtb, establishment of latent infection and transition to active TB disease. The existing Bacillus Calmette–Guérin (BCG) vaccines provide some protection for infants and young children against disseminated TB disease in which the infection has spread to multiple organs. However, they do not prevent lung infections or provide long-term protection against Mtb infection. ❖

NIH Awards Contracts to Advance Tuberculosis Immunology Research. National Institute of Allergy and Infectious Diseases press release, Sept. 26, 2019. Accessed at www.eurekalert.org/pub_releases/2019-09/nioa-nac092619.php.

FDA Initiates Coronavirus Medical Countermeasures



The U.S. Food and Drug Administration (FDA) is taking critical actions to advance development of novel coronavirus medical countermeasures. As with any emerging public health threat, FDA will collaborate with interagency partners, product developers, international partners and global regulators to expedite the development and availability of medical products needed to diagnose, treat, mitigate and prevent outbreaks. The agency is also sharing updates on processes in place to help developers understand the pathways, including Emergency Use Authorization (EUA), that may be available to more rapidly advance and make medical countermeasures available for this virus, including diagnostic tests. In addition, FDA is issuing key information for the public to help support the timely development of medical products to respond to the current outbreak.

To support efficient medical product development for novel coronavirus medical countermeasures, FDA launched a landing page that provides key information for the public, including product developers, on the agency's efforts in response to this outbreak. FDA is also requesting diagnostic test sponsors interested in potential EUA for tests to detect the current coronavirus to contact CDRH-EUA-Templates@fda.hhs.gov for further information and templates. Sponsors wishing to develop therapeutics for the coronavirus are encouraged to submit information and questions via the FDA's Pre-IND Consultation program.

"We have a vital mission to protect and promote public health, and the FDA is closely collaborating with our domestic and international public health partners to mitigate the impact of the novel coronavirus that emerged in Wuhan, China," said FDA Commissioner Stephen M. Hahn, MD. "We are actively leveraging the vast breadth of the FDA's expertise and have begun employing the full range of our public health authorities to facilitate the development and availability of investigational medical products to help address this urgent public health situation." ❖

FDA Announces Key Actions to Advance Development of Novel Coronavirus Medical Countermeasures. U.S. Food and Drug Administration press release, Jan. 27, 2020. Accessed at www.fda.gov/news-events/press-announcements/fda-announces-key-actions-advance-development-novel-coronavirus-medical-countermeasures.

Finalized Health Care Price Transparency Rule Unveiled

Under a rule finalized by the White House, hospitals will soon have to share price information they have long kept obscured, including how big a discount they offer cash-paying patients and rates negotiated with insurers. In a companion proposal, the administration announced it is also planning to require health insurers to spell out beforehand how much patients may owe in out-of-pocket costs for all services.

The hospital rule is part of an effort by the administration to increase price transparency in hopes of lowering healthcare costs on everything from hospital services to prescription drugs. The information required to be disclosed includes gross charges, negotiated rates and cash prices for the thousands of services offered, which will be required to be updated annually. The rule also requires each hospital to include a list of 300 "shoppable" services, described in plain language, with all the ancillary costs included. It is slated to go into effect in January 2021.

Under the proposed insurer rule, insurers would have to disclose the rates they negotiate with providers such as hospitals. They would also be required to create online tools to calculate for individual consumers the amount of their estimated out-of-pocket costs for all services, including any deductible they may owe, and make that information available before the consumer goes to the hospital or doctor. That rule would go into effect one year after it is finalized, although it is not known when that will occur. ❖

Appleby J. White House Unveils Finalized Health Care Price Transparency Rule. *Kaiser Health News*, Nov. 15, 2019. Accessed at khn.org/news/white-house-unveils-finalized-health-care-price-transparency-rule.

Medicare Will Now Cover Acupuncture for Chronic Low Back Pain

In January, the Centers for Medicare and Medicaid Services (CMS) finalized a decision to cover acupuncture for Medicare patients with chronic low back pain. Previously, acupuncture was nationally not covered by Medicare. The change in coverage takes into account an assessment of benefits and harms and the opioid public health crisis. While a small number of adults 65 years or older have been enrolled in published acupuncture studies, patients with chronic low back pain in these studies showed improvements in function and pain. The decision supports clinical strategies that include nonpharmacologic therapies for chronic low back pain. And, CMS notes that while there

is variation in covered indications and frequency of services, a number of large private payers provide some coverage of acupuncture for certain indications.

"We are dedicated to increasing access to alternatives to prescription opioids and believe that covering acupuncture for chronic low back pain is in the best interest of Medicare patients," said CMS Principal Deputy Administrator of Operations and Policy Kimberly Brandt. "We are building on important lessons learned from the private sector in this critical aspect of patient care. Over-reliance on opioids for people with chronic pain is one of the factors that led to the crisis, so it is vital that we offer a range of treatment options for our beneficiaries." ❖

CMS Finalizes Decision to Cover Acupuncture for Chronic Low Back Pain for Medicare Beneficiaries. Centers for Medicare and Medicaid Services press release, Jan. 21, 2020. Accessed at www.cms.gov/newsroom/press-releases/cms-finalizes-decision-cover-acupuncture-chronic-low-back-pain-medicare-beneficiaries.

CMS Launches Healthy Adult Opportunity Demonstration Initiative

The Centers for Medicare and Medicaid Services (CMS) has launched the Healthy Adult Opportunity (HAO) optional demonstration initiative designed to give states tools to design innovative health coverage programs tailored to the unique needs of adult beneficiaries, while holding states accountable for results and maintaining strong protections for the most at-risk populations. Specifically, the HAO provides states an opportunity to meet the needs of adult beneficiaries under age 65 who aren't eligible on the basis of a disability or their need for long-term care and for whom Medicaid coverage is optional. Other low-income adults, children, pregnant women, elderly adults and people with disabilities will not be directly affected.

"Vulnerable populations deserve better care. Data shows that barely half of adults on the Medicaid program report getting the care they need," said CMS Administrator Seema Verma. "This opportunity is designed to promote the program's objectives while furthering its sustainability for current and future beneficiaries, and achieving better health outcomes by increasing the accountability for delivering results. We've built in strong protections for our most vulnerable beneficiaries, and included opportunities for states to earn savings that have to be reinvested in strengthening the program so that it can remain a lifeline for our most vulnerable."

For the first time, participating states will have more negotiating power to manage drug costs by adopting a formulary similar to those provided in the commercial market, with special protections for individuals with HIV and behavioral health conditions. In exchange for increased flexibility offered through the HAO, states must accept increased accountability for the program's results.

The HAO also provides the opportunity for a full array of flexibilities that CMS has historically provided through section 1115 demonstrations, including flexibilities to waive requirements like retroactive coverage periods and the ability to engage beneficiaries through nominal premiums and cost-sharing. Subject to comprehensive

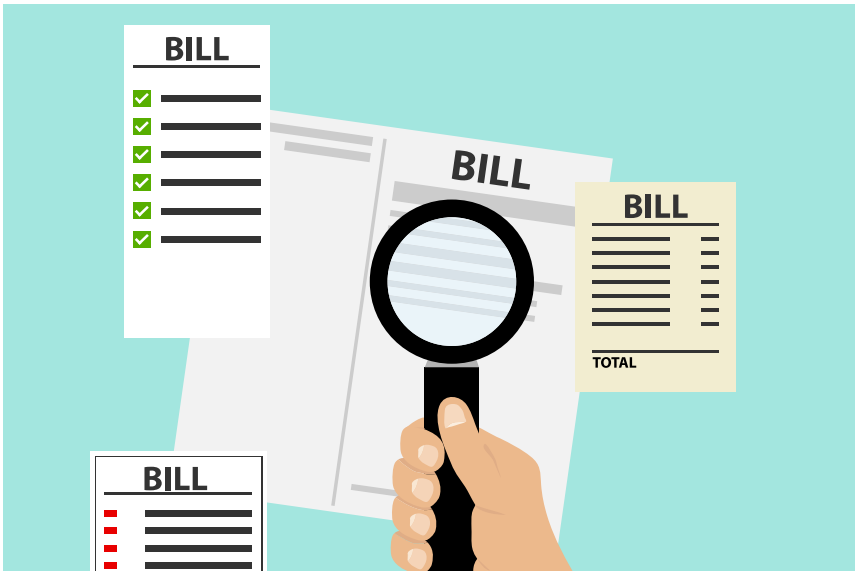
expectations for minimum standards for approval of an HAO demonstration, states will also have the opportunity to customize the benefit package for those covered and make needed program adjustments in real-time without lengthy federal bureaucratic negotiations or interference. ❖

Trump Administration Announces Transformative Medicaid Healthy Adult Opportunity. Centers for Medicare and Medicaid Services press release, Jan. 30, 2020. Accessed at www.cms.gov/newsroom/press-releases/trump-administration-announces-transformative-medicaid-healthy-adult-opportunity.

CMS Price Transparency: The Basics

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

NOV. 27, 2019, was a momentous day for transparency in healthcare pricing when the Centers for Medicare and Medicaid Services (CMS) released its final rule requiring hospitals to disclose payer-specific negotiated rates effective Jan. 1, 2021. The rule's goal is to create price pressure to lower healthcare costs by enabling consumers to more actively compare prices and proactively shop for care. Rather than perceiving transparency as an unwelcome burden, healthcare facilities should appreciate that this new rule presents opportunities for them to showcase services they provide and engage patients while meeting its requirements.



What does this transparency rule mean for healthcare facilities? The two major tenets are comprehensive machine-readable files and shoppable services. The rule requires hospitals, in comprehensive and machine-readable format, to post on their websites their gross charges, negotiated rates, minimum and maximum negotiated rates with payers, and discounted cash prices for all items and services. The data must be easily accessible and presented without barriers.

Posting similar information for 300 shoppable services in a consumer-friendly way is also required. CMS considers shoppable services to be those that can be scheduled in advance. Seventy of these shoppable services are divided into four categories (evaluation and management, laboratory and pathology, radiology, and medicine and surgery) and are published in the rule. The remaining 230 shoppable services are hospital-determined. The goal is to allow patients to be more informed about what they might pay for hospital items and services and, thus, to choose sites of care accordingly.

Simultaneously released by CMS, the Transparency in Coverage Proposed Rule requires most employer-based group health plans and health insurance issuers offering group and individual coverage to disclose price and cost-sharing information to participants, beneficiaries and enrollees up front.

Price Transparency Rule Definitions

Becoming familiar with the rule's definitions will assist in making necessary changes to be compliant.

Hospital definition. A hospital is an institution in any state in which the state or applicable local law provides for the licensing or is licensed pursuant to such law, or is approved by the agency of such state or locality responsible for licensing hospitals, as meeting the standards established for such licensing. A state is defined as each of the states, the District of Columbia, Puerto Rico, the Virgin Islands, Guam, American Samoa and the Northern Mariana Islands.

Hospitals include all Medicare-enrolled institutions licensed as hospitals (or approved as meeting licensing requirements), as well any non-Medicare-enrolled institutions licensed as a hospital (or approved as meeting licensing requirements). Federally owned/operated hospitals (e.g., Indian Health Program, Veterans Affairs or Department of Defense) are deemed compliant with making public standard charges requirements.

Hospital standard charges. These include:

- Gross charge: a charge for an individual item or service reflected on a hospital's charge description master (CDM), absent any discounts (the CDM price);
- Discounted cash price: a charge that applies to an individual who pays cash, or cash equivalent, for a hospital item or service;
- Payer-specific negotiated charge: a charge a hospital has negotiated with a third-party payer for an item or service (includes all negotiated rates with individual payers);
- De-identified minimum negotiated charge: the lowest charge a hospital has negotiated with all third-party payers for an item or service; and
- De-identified maximum negotiated

charge: the highest charge a hospital has negotiated with all third-party payers for an item or service.

Hospital items and services. These include all items and services, including individual items and services and service packages, that could be provided by a hospital to a patient in connection with an inpatient admission or an outpatient department visit for which the hospital has established a standard charge. Examples include, but are not limited to, supplies and procedures, room and board, use of the facility and other items (generally described as facility fees), services of employed physicians and nonphysician practitioners (generally reflected as professional charges), and any other items or services for which a hospital has established a standard charge.

Required data elements. These include:

- A description of each item or service;
- All standard charges (gross charges, payer-specific negotiated charges, discounted cash prices, minimum and maximum negotiated charges) that apply to each item or service when provided in, as applicable, hospital inpatient and outpatient department settings; and
- Any code used by the hospital for purposes of accounting or billing for the item or service (e.g., Healthcare Common Procedural Coding System (HCPCS) codes, diagnosis-related group (DRG) codes or other common payer identifiers).

Making standard charges public. These include:

- Comprehensive machine-readable file: A single machine-readable file containing all five types of standard charges for all items and services provided by the hospital that is useful for employers, providers and tool developers to use in consumer-friendly price transparency tools they develop or that may integrate the data into electronic medical records and shared decision-making tools at the point of care.
- Consumer-friendly shoppable services: A consumer-friendly list of some types of standard charges for a limited set of shoppable services (including 70 CMS-specified and 230 hospital-selected) provided by the hospital. This would be used by a healthcare consumer for a service that can be scheduled in advance.

Monitoring and enforcement. CMS has the authority to monitor hospital compliance by evaluating complaints made by individuals or entities to CMS, reviewing individuals' or entities' analyses of noncompliance, and auditing hospitals' websites. Should CMS conclude a hospital is noncompliant with one or more of the requirements to make standard charges public, CMS may assess a monetary penalty after providing a warning notice to the hospital or after requesting a corrective action plan from the hospital if its noncompliance constitutes a material violation of one or more requirements. If the hospital fails to respond to CMS' request to submit a corrective action plan or comply with the requirements of a corrective action plan, CMS may impose a civil monetary penalty on the hospital not in excess of $300 per day, and publicize the penalty on a CMS website. The rule establishes an appeals process for hospitals to request a hearing before an administrative law judge (ALJ) of the civil monetary penalty, and the administrator of CMS may review in whole or in part the ALJ's decision.

Price Transparency Resources

- CMS fact sheet. Hospital Price Transparency Requirements: go.cms.gov/2PCSlDz
- CMS fact sheet. Transparency in Coverage Proposed Rule: go.cms.gov/2PyWi1r
- CMS call transcript: go.cms.gov/2EERaCw
- CMS press release: go.cms.gov/2PCtbKN

Conduct a Financial Data Analysis

Healthcare facilities should conduct a financial data analysis to identify the true cost of care. From a pharmacy perspective, the CDM is front and center of transparency in drug and intravenous therapy pricing, and it will need to focus on simplicity of use and accuracy. As a major contributor of cost to some of the shoppable services likely to be chosen, pharmacy needs to be a part of pricing. Using infusion services as an example, templates can be created to address what contributes to the cost of a patient receiving a drug in the infusion center or a botulinum product in a clinic setting. It's important to get accurate and complete data, and to keep it simple using plain language descriptions with corresponding billing codes (Current Procedural Terminology, HCPCS, DRG) and applicable revenue codes. Locations in the facility where services are performed are important as is a listing of any ancillary items and services that will contribute to costs. Patients want and need more transparency, and facilities will miss the mark if there's a significant gap between patients' expectations of transparency and accuracy of pricing information available to them. ❖

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

How to Improve Patient Satisfaction

By Ronale Tucker Rhodes, MS

SINCE THE Centers for Medicare and Medicaid Services' implementation of pay-for-performance programs and financial incentives, increasing patient satisfaction has become a main priority among healthcare providers. But, avoiding financial penalties for falling below in the Hospital Consumer Assessment of Healthcare Providers and Systems quality-of-service survey is only one benefit to boosting patient satisfaction ratings. Healthcare providers also stand to benefit from an improved reputation, reduced malpractice costs and being chosen by patients over other facilities.

How can facilities improve patient satisfaction? Aside from providing customer service training to staff or hiring patient experience consultants, some relatively simple techniques can put a smile on patients' faces and keep them coming back.

Understand What Patients Want

Recognizing patients have choices for their care, then-Cleveland Clinic Health System's Chief Experience Officer James Merlino, MD, hired an outside firm to address the health system's low patient satisfaction scores, which ranked among the lowest for physician communication with patients. The firm found patients' top concerns were far from what staff perceived (Table):[1]

1) *Respect.* According to Dr. Merlino, "Respect is important to patients because they want providers to treat them like individuals and engage with them personally," which goes against everything providers have learned, since they are taught to be objective and unemotional. Yet, having a personal experience with their doctors and nurses makes patients feel providers will make fewer mistakes.

2) *Communication between caregivers.* Patients use proxy measures (indirect measures of desired outcomes) such as communication between physicians and nurses to assess the type of care they receive, says Dr. Merlino. For example, a doctor comes into a patient's room to speak with the patient, and later a nurse is asked by the patient to repeat what the doctor said, but the nurse doesn't know. Such an unmet expectation, he explains, is perceived as a lack of communication between the doctor and nurse, causing some patients to believe they are receiving substandard care.

3) *Happy providers.* Providers who appear happy are perceived by patients as more approachable. Patients are less likely to engage or ask questions of doctors or nurses who appear to be angry or in a hurry because patients don't want to contribute to whatever the providers are dealing with or make the providers more angry.

Table. Scale of Importance for Patient Satisfaction

Most Important	Less Important
Staff cared	Wait time before doctor
Doctor concern for comfort	Nurse courtesy
Doctor explained	Nurse concern for privacy
Information to care for self at home	Staff permitted family and friends to be with patient
Doctor kept patient informed	Cleanliness
Nurse kept patient informed	Helpfulness of first person asking about condition
Information about delays	Wait time for radiology
Family and friends kept informed	Comfort during blood draw
Nurses attention to needs	Wait time before treatment area
Doctor listened	Comfort during radiology
Pain control	Personal insurance privacy
Doctor courtesy	Radiology staff courtesy
Respect for privacy	Waiting area comfort
Nurses listened	Ease to provide insurance
Courtesy to family and friends	Courtesy taking insurance
	Wait time of staff notice

Treat Patients with Care and Concern

The best way providers can give patients what they want is by treating them with care and concern. Here are some suggestions for how to accomplish just that:

- *Smile and say hello when patients arrive.* People want to be acknowledged, so this should be an expectation by all staff.[2]
- *Spend time with patients.* Even if visits are shorter than what patients expect, a study found that "perceived" visit lengths create the highest satisfaction levels. The study also found patients' expectations of visit lengths predicted their satisfaction.[3]
- *Sit down during the visit.* One study found 52 percent of patients want their doctor to be seated versus 8 percent who want their doctor to stand and 40 percent who don't care. The study also found sitting translates into a perception of the visit lasting nearly 25 percent longer.[3]
- *Dress the part.* A review of clothing for healthcare personnel found patients express preferences for certain types of attire, including a white coat and no jeans.[3]
- *Be an expert communicator.* This can be accomplished by 1) using patients' names at least once during each conversation to emphasize they are viewed as individuals; 2) listening to patients without interrupting them, and looking for cues that may

indicate they are not satisfied or are concerned about something; 3) expressing empathy by observing patients' communication style and responding in a manner that makes them feel comfortable;[2] and 4) meeting patients' expectations for why they came to the appointment, including explaining why symptoms are occurring and what is causing them (patients are looking for answers), and providing guidance on the possible length of the condition and outcome (if possible).[3]

Embrace Technology

With more than 79 percent of the U.S. population using social media,[4] healthcare personnel have an opportunity for two-way communication and interaction with patients. Providers can use social media platforms to post health education videos, share new and relevant studies and statistics, answer general questions from patients, and advertise and promote upcoming events.

Online patient portals are another way patients prefer to access personal health information and communicate with their physicians. These allow patients to view notes from office visits, lab results and lists of medications and immunizations. And, most portals allow patients to email physicians or nurses, request prescription refills, schedule appointments, complete medical forms, read educational material and make payments.[5]

Similar to patient portals are smartphone apps. Known as mHealth, these apps are designed to ease clinical communication between providers and patients and allow for 24/7 management of patients' conditions along with the ability to personalize healthcare with patients. A few examples are:[6]

- AirStrip, a mobile, interoperable platform that allows care coordination between multiple devices and multiple care settings;
- Ambulatory EHR, which allows providers to access complete web charts, giving them instant access to patient records across healthcare organizations on a single mobile device; and
- MyChart, which allows patients to download health data from previous in-office visits, including test results, immunizations, medication and health conditions indicated by a provider.

Create a 'Halo Effect'

What all this comes down to, says Michael Solomon, a customer service consultant, is creating an overall experience of caring that translates into a better individual assessment of the facility. In essence, this means leaving a generally positive impression even if, for example, wait times are long and physician visits are too short. This can be accomplished, Solomon explains, with these eight tips:[7]

1) Not giving off cues of indifference and caring such as failing to make eye contact with patients, or talking about non-work-related topics such as vacations;

2) Experiencing care the way patients do such as parking where patients park to see how easy it is or isn't to get into the front door on crutches, and taking a tour of the facility to see if it's easy or difficult to find where an appointment is located;

3) Ensuring employees understand the purpose of the practice and why their jobs exist such as "to create successful medical outcomes and hospitable human experiences for patients";

4) Learning how to say "sorry," without defensiveness or apathy, to resolve issues;

5) Teaching every employee how to handle patient complaints rather than having to find the "right" person to address them;

6) Striving to create a blame-free environment (if it happens once, it may be the employee's fault, but if it happens twice, it is likely the fault of the system);

7) Understanding genuine warmth and smiles are of value; and

8) Benchmarking customer service on the best-in-service industries rather than just on other healthcare facilities.

Use Data to Put Patients First

When Dr. Merlino decided to tackle his facility's patient satisfaction problem at Cleveland Clinic, he recognized that using patient satisfaction and outcome data was key. In his article "The Glaring Omission in Healthcare: Patient Satisfaction and Outcome Data," Dr. Merlino talked about his experience at Toyota: "My Toyota maintenance guy sends me a customer satisfaction email automatically after each 'clinical encounter' with my cars. He asks me to rate the quality of the service he provided, as well as the quality of the outcome (Did we fix your problem?) and the cost effectiveness (Do you feel that our prices were fair, clearly explained beforehand and understandable?). Toyota corporate offices review these results in detail, and they hold those dealerships totally accountable, with consequences for bad numbers. You would think that the functionality of electronic medical records that cost millions of dollars could at least match my Toyota maintenance guy."

Unfortunately, says Dr. Merlino, now serving as Cleveland Clinic's first chief clinical transformation officer, the healthcare industry is different: "We're afraid to ask the patient what they think of our services and treatments, and we veil that fear in false claims of complexity and scientific validity. In the words of Jack Nicholson in a *Few Good Men*, we can't handle the truth, so we avoid the vulnerability."[1] ❖

RONALE TUCKER RHODES, MS, is the editor of *BioSupply Trends Quarterly* magazine.

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Medicines

FDA Approves Sandoz's Ziextenzo as 24th Biosimilar

The U.S. Food and Drug Administration (FDA) has approved Ziextenzo (pegfilgrastim-bmez), the 24th biosimilar approval in the U.S. and the third biosimilar of Amgen's Neulasta. Ziextenzo is a long-lasting form of filgrastim indicated to decrease the incidence of infection, as manifested by a low white blood cell count with fever, in patients with nonmyeloid malignancies who take myelosuppressive oncology drugs. Approval was granted based on results of a three-way pharmacokinetics and pharmacodynamics study in which no clinically meaningful differences were seen for safety and immunogenicity between the drug and other versions of pegfilgrastim. Sandoz launched the biosimilar in the U.S. in late 2019. It has been approved in Europe under the same name since 2018. ❖

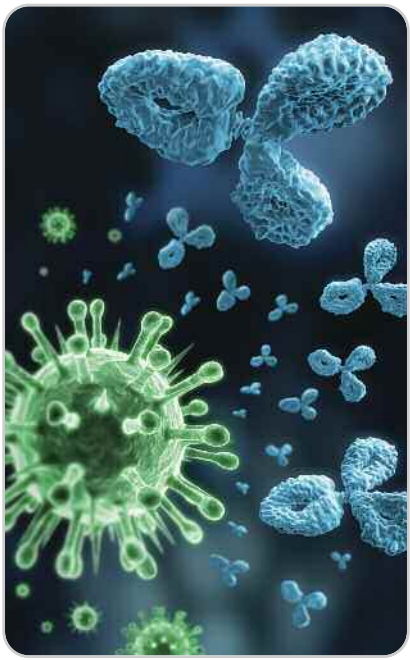
FDA Approves Sandoz's Ziextenzo as 24th Biosimilar. U.S. Food and Drug Administration press release, Nov. 15, 2019. Accessed at www.fdanews.com/articles/193451-fda-approves-sandozs-ziextenzo-as-24th-biosimilar?utm_campaign=Drug%20Daily%20Bulletin&utm_source=hs_email&utm_medium=email&utm_content=79444647&_hsenc=p2ANqtz-_6fMWI62oPfVJtflOMONrPO9_bC7jbTOZo74MF2DcOknm6I0XUDJ1ikJSv9Al4cIrw3uHoCP-pbSQBdbXBKBnRZy2xDA&_hsmi=79444647.

Research

Researchers Uncover How Human Immunity Evades Influenza Virus

A new study that looked at how the influenza (flu) virus escapes antibodies found the site of the escape mutation varies among most individuals' sera. As part of the study, Juhye Lee, a former PhD student of Jesse Bloom, PhD, a biochemist at the Fred Hutchinson Cancer Research Center in Seattle, Wash., designed a means of examining which mutations help the viruses overcome immunity and infect cells. Dr. Lee used polymerase chain reaction to make approximately 10,000 different mutations to the amino acid building blocks of the HA protein in a strain of the H3N2 virus that was isolated from a human in 2009. The mutant viruses were exposed to different concentrations of antibody-rich blood serum of four individuals ranging in age from 21 years to 65 years. They then infected canine kidney cells with the viruses-antibody mixtures and used high-throughput sequencing to determine which mutant viruses were able to replicate in the presence of serum antibodies.

Findings showed that in the serum of subjects aged 21 years and 65 years, viruses with a mutation at site F193D on the HA protein could replicate. In the serum of the 64-year-old, viruses with a mutation at site F159G were able to replicate. In all three



sera, the single mutations reduced immunity by 10-fold, meaning 10 times more antibodies were needed to stop the viruses from infecting cells compared to that required by the original nonmutated virus. In a subject aged 53 years, a single mutation at site L157D reduced immunity by five times.

According to the researchers, these findings show human immunity is focused and may come from just one or a few antibodies that target a specific region of the virus protein. It also demonstrates one mutation is capable of helping the virus evade antibodies in one person but not in another, said Dr. Bloom, co-author of the study's paper. "Despite the fact that our immune system can potentially make antibodies that target all over the viral protein, the results show that human immunity is instead very focused on just one part of the protein," he says. "Mutations that are strongly selected by one person's serum often aren't selected by another person's serum."

This variation in the ability of mutations to escape immunity could boil down to people's histories of flu strain infection. To see if the variations persist, the team is now repeating its experiments with the blood serum of young children who have had a single influenza infection with hopes the findings from both studies can help researchers develop better targeted vaccines against influenza. ❖

Gilbert N. New Insights Into How Influenza Evades Human Immunity. *Proceedings of the National Academy of Sciences*, Sept. 14, 2019. Accessed at blog.pnas.org/2019/09/journal-club-new-insights-into-how-influenza-evades-human-immunity.

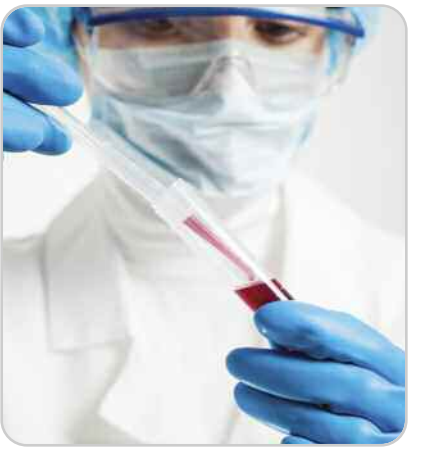
Medicines

FDA Expands Indication for Octapharma's WILATE to Hemophilia A

The U.S. Food and Drug Administration (FDA) has approved WILATE for treatment of adults and adolescents with hemophilia A for routine prophylaxis to reduce the frequency of bleeding episodes and on-demand treatment and control of bleeding episodes. WILATE was previously approved by FDA in 2009 for treatment of children and adults with von Willebrand disease for on-demand treatment and control of bleeding episodes, as well as for perioperative management of bleeding.

This expanded indication of WILATE is based on results of the Clinical Study to Investigate the PK, Efficacy and Safety of WILATE in Patients with Severe Hemophilia. In the study, 136 previously treated patients with hemophilia A (aged 11 years to 66 years) received WILATE in five clinical studies that involved prophylactic use, treatment on demand, surgery and/or pharmacokinetics. All subjects were male. Overall, subjects received 19,317,004 international units (IU) of WILATE during 9,001 exposure days. The most common adverse reaction was pyrexia (two subjects; 1.5 percent). Further adverse reactions included pruritus, headache and sleeping disorder (one subject; 0.75 percent). Two out of 55 subjects (3.6 percent) in the pivotal study of routine prophylaxis in severe hemophilia A had unexplained transient worsening of pre-existing thrombocytosis while on the study.

"Octapharma has been committed to providing U.S. hemophilia A patients with complete access to the company product portfolio since our inception," said Octapharma USA President Flemming Nielsen. "We are excited for providers and patients who have been looking forward to the day when WILATE would be indicated for hemophilia A. Octapharma is dedicated



to providing the bleeding disorders community with the therapies and programs that enhance patient lives every day."

FDA Approves Octapharma's Wilate for Hemophilia A in Adult and Adolescent Patients. Octapharma press release, Oct. 9, 2019. Accessed at www.hemophiliafed.org/news-stories/2019/10/fda-approves-octapharmas-wilate-for-hemophilia-a-in-adult-and-adolescent-patients.

Research

Skin Patch Shows Promise for Delivery of Influenza Vaccine

Researchers at the University of Rochester Medical Center in New York City have developed a new type of skin patch that could replace needles as a method to deliver the influenza (flu) vaccine. While previous flu vaccine skin patches used microneedles and electroporation, which are difficult to implement on a large scale for mass vaccination, this new patch uses a protein to make the skin barrier that normally prevents toxins and allergens from entering the body more permeable. The approach came to researchers when they investigated the biology of eczema. People with eczema have low levels of claudin-1 that causes the skin to become "leaky."

In the study, the researchers created a skin patch containing a peptide (small protein) that binds to and blocks claudin-1, and a recombinant flu vaccine and tested it in two ways on mice. In the first test, they applied the skin patch and then gave the mice a flu vaccine by injection to prime the immune system with the patch and then boost immunity with the vaccine. In the second test, the researchers gave the mice the flu vaccine first and then applied the skin patch to prime the immune system with the vaccine and then boost it with the skin patch. In both tests, the patch opened the skin barrier, which was confirmed by monitoring the amount of water the mice lost through their skin. When they applied the patch, the mice's skin became permeable, and when they removed it, the skin began to close, getting back to normal within 24 hours. While the immune response to the patch in the first test was insignificant, there was a robust immune response to the patch in the second test.

According to the researchers, since humans are exposed to influenza as young as 6 months of age and, therefore, most people's immune systems are already primed to the virus, the second test best mimics a real-world scenario, suggesting the patch could serve as a delivery mechanism for the regular seasonal flu vaccine. Notably, there were no side effects. After monitoring the mice for three months, there was no physical change in their skin such as might arise from infections. Studies are still needed to determine how long the patch should remain on the skin for optimum results. ❖

Paddock C. New Flu Vaccine Skin Patch Could Do Away with Needles. Medical News Today, Sept. 18, 2019. Accessed at www.medicalnewstoday.com/articles/326382.php.

Vaccines

Flu Vaccine May Reduce Risk of Heart Attack and Stroke in Hypertensive Individuals

A new study shows cardiovascular outcomes may improve in individuals with hypertension if they receive the influenza (flu) vaccine during the flu season. In the study, the researchers analyzed data from 608,452 people aged 18 years to 100 years who had hypertension and then followed them during nine flu seasons (2007 to 2016), comparing those who had a flu shot and those who did not. Throughout the follow-up period, the researchers looked at death from any cause, cardiovascular death and death from a heart attack and stroke. They also examined the link between getting the flu shot before the flu season and death risk during the flu season. Age, other medical conditions, medications and socioeconomic status were accounted for. The study

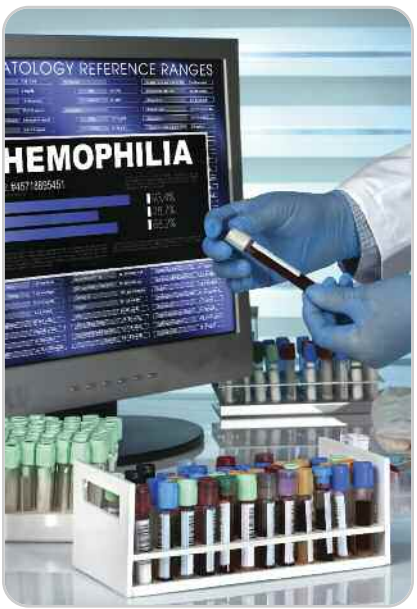
revealed an association between vaccination during the flu season and an 18 percent reduction in relative risk of dying from all causes, a 16 percent less relative risk of dying from a cardiovascular event and a 10 percent lower relative risk of dying from a heart attack or stroke.

"During the nine flu seasons we studied, vaccine coverage ranged from 26 percent to 36 percent, meaning that many patients with high blood pressure were not vaccinated," said lead researcher Daniel Modin, a research associate at the University of Copenhagen, Denmark. "Heart attacks and strokes are caused by the rupture of atherosclerotic plaques in the arteries leading to the heart or the brain. After a rupture, a blood clot forms and cuts off the blood supply. It is thought that the high levels of acute inflammation induced by influenza infection reduce the stability of plaques and make them more likely to rupture." ❖

Field P. Flu Shot May Lower Death Risk in People with Hypertension. Medical News Today, Sept. 2, 2019. Accessed at www.medicalnewstoday.com/articles/326218.php.

Research

Study Finds Safe Treatment for Children with Severe Hemophilia A with Inhibitors



Researchers have found combining immune tolerance induction (ITI) with Hemlibra (emicizumab, Roche) is a feasible and safe way of treating children with severe hemophilia A. Hemlibra is a non-factor replacement therapy to treat hemophilia A patients with or without inhibitors; however, it does not help rid a person of factor VIII (FVIII) inhibitors against FVIII treatments that neutralize their effectiveness. ITI, in which FVIII is given regularly over a period of time until the body is trained to recognize the product without reacting against it, is the only effective strategy for removing inhibitors and restoring a normal response to FVIII replacement therapy.

In the study, seven children between 21 months and 12 years old were started on a combination of ITI with FVIII infusions three times a week plus Hemlibra, and they were followed for a median time of 35 weeks. Results showed treatment for three of the seven led to either a complete clearing of inhibitors or a drop to unmeasurable levels. Three patients (43 percent) also had no bleeding events, and nine bleeding events were reported among the other four during follow-up. No adverse effects such as blood clots were reported. Six children underwent surgery during the study with no major complications or excess bleedings during or after. Length of hospital stays also decreased, changing from an average of three days to seven days to one day to two days.

According to the researchers, their work is the first to demonstrate "immune tolerance induction while on emicizumab (Hemlibra) prophylaxis is a feasible approach in pediatric hemophilia A patients with inhibitors." ❖

Mumal I. Hemlibra Given with Immune Tolerance Induction Safely Treats Children with Severe Hemophilia A, Study Finds. *Hemophilia News Today,* Sept. 9, 2019. Accessed at hemophilianewstoday.com/2019/09/09/atlanta-protocol-hemlibra-plus-iti-safe-for-severe-hemophilia-a-study-says.

Research

Trivalent HBV Vaccine Superior in Efficacy in Adults 45 Years and Older

A Phase III study has found a trivalent hepatitis B virus (HBV) vaccine demonstrated superiority in adults 45 years and older and noninferior in adults older than 18 years compared with a monovalent vaccine. In the study, researchers compared the immunogenicity of a 10 gram dose of a trivalent vaccine (Sci-B-Vac, VBI Vaccines) with a 20 gram dose of monovalent vaccine (Engerix-B, GlaxoSmithKline) given at days 0, 28 and 168 in 1,607 individuals randomly assigned to one of the two vaccines and then tracked for safety outcomes to day 336. Participants were stratified by study center and age group: 18 years to 44 years and 45 years to 65 years and older. They found the seroprotection rate among recipients 18 years or older who received the trivalent vaccine was 91.4 percent compared with 76.5 percent for monovalent vaccine recipients. And, among individuals 45 years and older, the seroprotection rate was 89.4 percent with the trivalent vaccine versus 73.1 percent for the monovalent vaccine.

"When compared to Engerix-B, Sci-B-Vac tends to have higher rates of protection among adults over age 18 with superiority in those older than 45," said Joanne M. Langley, MD, division head for infectious diseases and a professor of pediatrics and community health and epidemiology at Dalhousie University in Canada. "It also shows that all the subpopulations had higher seroprotection rates. Next steps are to write up the study and submit to regulators." Another study underway will expand the safety data and provide additional seroprotection data in the 18- to 45-year-old age group. ❖

Trivalent HBV Vaccine Noninferior to Monovalent Vaccine in Adults. ID Week, Oct. 5, 2019. Accessed at www.healio.com/infectious-disease/vaccine-preventable-diseases/news/online/%7B9741230a-3a04-44c1-b5d1-216a819192b3%7D/trivalent-hbv-vaccine-noninferior-to-monovalent-vaccine-in-adults.

Research

CDC Analyses Show Flu Vaccine Reduces Risk of Hospitalization in Children and Death in Adults

Two analyses by the Centers for Disease Control and Prevention (CDC) show the influenza (flu) vaccine can reduce the likelihood of hospitalization in children and death in adults.

In the first study, conducted by seven pediatric medical centers comprising the New Vaccine Surveillance Network, researchers analyzed flu test results from 3,600 children aged 6 months to 17 years who were hospitalized with acute respiratory illness over two seasons in which influenza A(H3N2) viruses were the predominantly circulating virus. Patients were tested for influenza using molecular diagnostic tests, which found 163 out of 1,714 (10 percent) during the 2016-2017 season and 218 out of 1,916 (11 percent) during the 2017-2018 season tested positive for flu, including A(H3N2), A(H1N1) and B viruses. They then estimated how well the flu vaccine worked to reduce hospitalizations due to laboratory-confirmed influenza by comparing the frequency of flu vaccination among children who tested positive for flu to vaccination among children without flu, adjusting for age, race/ethnicity, enrollment month, study site and underlying medical

conditions. Based on this information, the vaccine effectiveness against influenza-associated hospitalizations was 50 percent over the two seasons (49 percent for the first season and 51 percent the second), meaning vaccination reduced the risk of hospitalization with flu by about half.

In the second study, researchers looked at five flu seasons using the U.S. Influenza Hospitalization Surveillance Network and identified 43,608 adults (18 and older) hospitalized with laboratory-confirmed flu. Overall, 38 percent of those 18 years to 64 years old and 65 percent of those 65 years or older had received a flu vaccine. Researchers assessed vaccination status among hospitalized patients to determine the reduction in the odds of severe outcomes among vaccinated patients compared to those who were unvaccinated. Findings showed that in patients diagnosed with influenza A(H1N1), flu vaccination reduced their odds of severe outcomes, including death (36 percent), pneumonia (17 percent), intensive care unit (ICU) (19 percent) and mechanical ventilation (34 percent). Vaccination also was associated with a shorter ICU length of stay. And, in those 65 years or older, flu vaccination was associated with reduced risk of ICU admission (28 percent) and mechanical ventilation (46 percent).

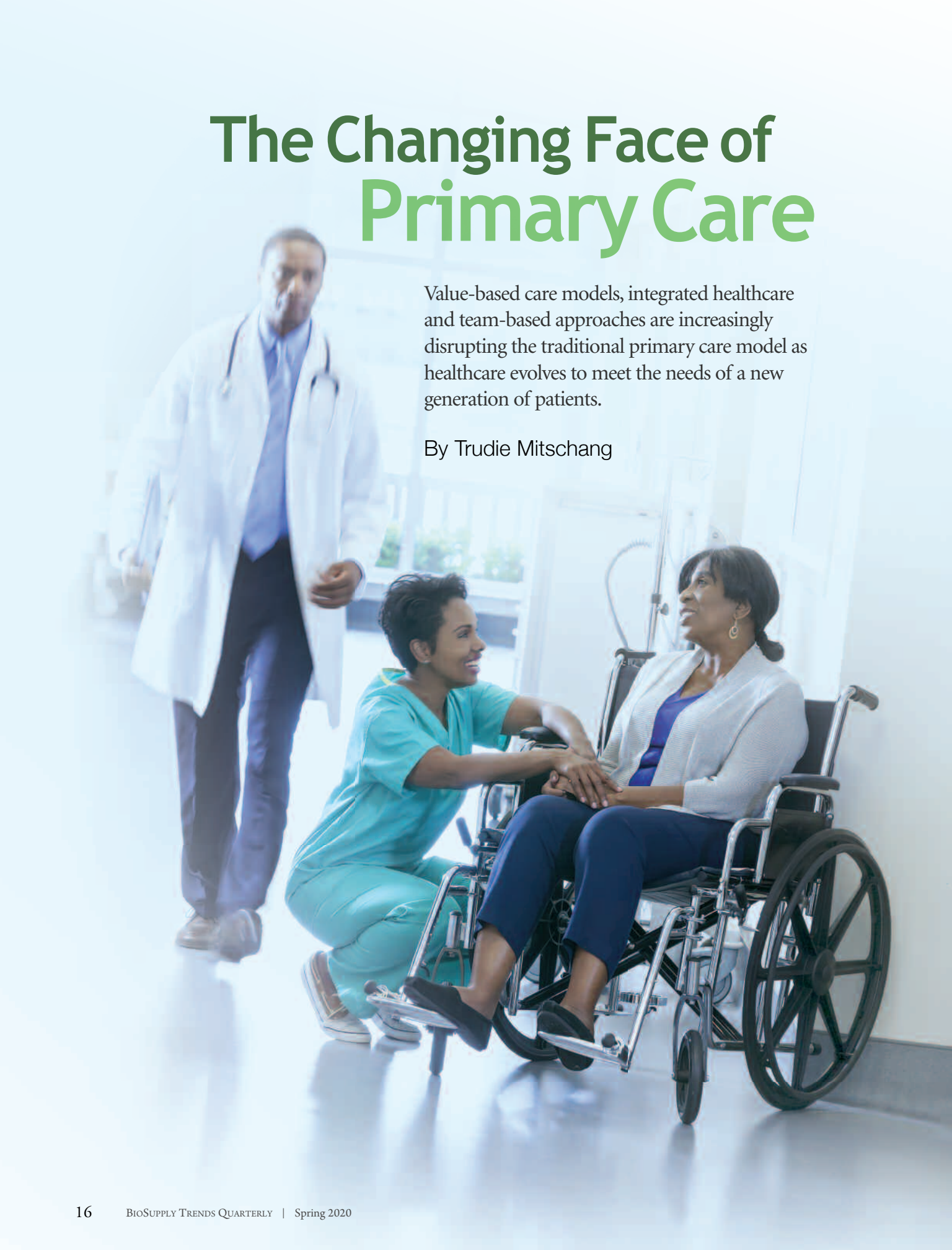
"These studies add to the evidence that influenza vaccines prevent serious complications from flu," said Angela P. Campbell, MD, MPH, FIDSA, FPIDS, lead author of the study in children and medical officer in the epidemiology and prevention branch of the influenza division at CDC. "They show just how important it is that everyone 6 months and older who is eligible to get a flu vaccine does so every year." ❖

Studies Show Flu Vaccine Reduces Risk of Hospitalization in Children and Death in Adults: National Flu Surveillance Research. Infectious Diseases Society of America press release, Oct. 8, 2019. Accessed at www.idsociety.org/news--publications-new/articles/2019/studies-show-flu-vaccine-reduces-risk-of-hospitalization-in-children-and-death-in-adults.

The Changing Face of Primary Care

Value-based care models, integrated healthcare and team-based approaches are increasingly disrupting the traditional primary care model as healthcare evolves to meet the needs of a new generation of patients.

By Trudie Mitschang



IN 2019, FEDERAL health officials unveiled a new primary care experiment that proposed to pay doctors for providing an elevated level of service designed to keep patients healthy and reduce hospital visits. Proponents of the value-based care model believe the efforts could transform the way medical services are delivered for millions of Americans. The Centers for Medicare and Medicaid Services (CMS) Primary Cares Initiative includes five payment options for both small and large providers, allowing them to take varying levels of financial responsibility for improving care and lowering costs. The core of the initiative seeks to overhaul how primary care is delivered by rewarding physicians for improving care for patients, especially those with chronic illnesses such as high blood pressure and diabetes. "This initiative will radically elevate the importance of primary care in American medicine," said Health and Human Services Secretary Alex Azar.[1] He went on to note that creating a system that rewards providers for outcomes rather than procedures has the potential to free up doctors to focus on the patients in front of them, rather than the subsequent paperwork.

An Incentivized Approach

For many patients, the primary care physician is their first point of contact with the healthcare system. Research indicates that when incentives for primary care providers are structured to reward high-caliber care, the quality and cost effectiveness of patient care improves. "As we seek to unleash innovation in our healthcare system, we recognize that the road to value must have as many lanes as possible," said CMS Administrator Seema Verma. "Our Primary Cares Initiative is designed to give clinicians different options that advance our goal to deliver better care at a lower cost, while allowing clinicians to focus on what they do best: treating patients."[2]

Accountability is also a factor; value-based reimbursements are calculated by using numerous measures of quality and determining the overall health of populations. Unlike the traditional model, value-based care is driven by data because providers must report to payers on specific metrics and demonstrate improvement. Providers may have to track and report on hospital readmissions, adverse events, population health, patient engagement and more.

Because value-based care reimbursement ties payments for care delivery to the quality of care provided and rewards providers for both efficiency and effectiveness, it may offer an alternative — and potential replacement — for fee-for-service reimbursement, which pays providers retrospectively for services delivered based on bill charges or annual fee schedules. Fee-for-service encourages many providers to order more tests and procedures, as well as manage more patients to get paid more.

Additionally, under fee-for-service models, cost variations for procedures and tests increased and the healthcare industry was spending more to treat patients even though patient outcomes were not necessarily improving. The model also challenged provider workflows because physicians were seeing more patients and each claim had to be processed in a fragmented network.

A State Health Care Cost Containment Committee report sums it up this way: "The opportunity exists to transform how healthcare is delivered. The goal is straightforward but ambitious: Replace the nation's reliance on fragmented, fee-for-service care with comprehensive, coordinated care using payment models that hold organizations accountable for cost control and quality gains."[3]

Advantages of Collaborative Care

Another care model altering the delivery of primary care is the integrated approach. Essentially, integrated care combines primary healthcare and mental healthcare in one setting. Over the past decade, the integration of behavioral health and general medical services has been shown to improve patient outcomes, save money and reduce stigma related to mental health.

Research indicates that when incentives for primary care providers are structured to reward high-caliber care, the quality and cost effectiveness of patient care improves.

Significant research spanning three decades has identified the collaborative care model as being effective and efficient in delivering integrated care. A report titled Dissemination of Integrated Care Within Adult Primary Care Settings: The Collaborative Care Model, developed jointly by the American Psychiatric Association and Academy of Psychosomatic Medicine, offers insights into this approach, including recommendations for how to advance its use to better meet the whole health needs of people with mental health conditions. "Bringing mental health services to primary care normalizes and destigmatizes treatment for behavioral health disorders, simultaneously increasing access for patients by making evidence-based mental health services available in their regular primary care clinics," the report states. "The delivery of primary care services to mental health settings also can overcome barriers to receiving medical and preventive care, offering increased convenience and familiarity with services. Merging

mental health services within primary care services is more studied than the reverse; the science around effective health services delivery is greater for these models."[4]

According to the National Institutes of Health,[5] the integrated model is valuable because:

• Primary care settings, like doctor offices, provide about half of all mental healthcare for common psychiatric disorders.

• Adults with serious mental illnesses and substance use disorders also have higher rates of chronic physical illnesses and die earlier than the general population.

• People with common physical health conditions also have higher rates of mental health issues.

This approach is unique in that it addresses the whole person with the belief that a patient's physical and behavioral health are both essential for the achievement of lasting, positive outcomes and cost-effective care.

Significant research spanning three decades has identified the collaborative care model as being effective and efficient in delivering integrated care.

Historically, it has been difficult for a primary care provider to offer effective, high-quality mental healthcare when working alone, and although most primary care providers can treat mental disorders, particularly through medication, that may not be the most effective, long-term treatment plan for a patient. Integrated care is structured to meet all of a patient's health needs in one setting, and it can be delivered in multiple ways depending on who is providing the care, what type of care is being provided, where the care is taking place and how services are being coordinated. Options for integrated care include a behavioral health setting, a primary care office, a specialty clinic or a home health setting.

Identifying the appropriate type of integrated care is often determined using a system called the Four Quadrant model that prescribes integration levels based on diagnosis complexity and risk. Basically, the location, types of providers and services vary depending on the complexity of a patient's condition. For instance, individuals with mild-to-moderate physical and/or behavioral health issues may be best cared for in a primary care setting with integrated behavioral health providers. Likewise, patients with complex general medical conditions coupled with mild-to-moderate behavioral health disorders may benefit from a medical specialty setting with integrated behavioral health providers. Finally, patients with severe behavioral problems, as well as medical conditions, may receive the most comprehensive care in a specialty behavioral health center with integrated general medical providers, or in a health home.[5]

Primary Care in the Age of Millennials

Behavioral trends and generational preferences are also influencing the future of primary healthcare. A recent poll of 1,200 adults conducted by the Kaiser Family Foundation found 45 percent of 18- to 29-year-olds had no primary care physician compared with 28 percent of those aged 30 years to 49 years. The study's authors state, "Millennials are foregoing the time-bound model of office-based primary care in favor of more convenient care such as urgent care centers, telemedicine and drugstore retail clinics."[6]

Another factor influencing millennial healthcare choices is that most young people have been on their parents' insurance plans since birth. That means as they transition to their own insurance plans, they are suddenly responsible for their own health at a time when they are managing student loans, first jobs and becoming independent. All of that coupled with a tendency to feel healthy and invincible can result in letting primary medical care fall by the wayside.

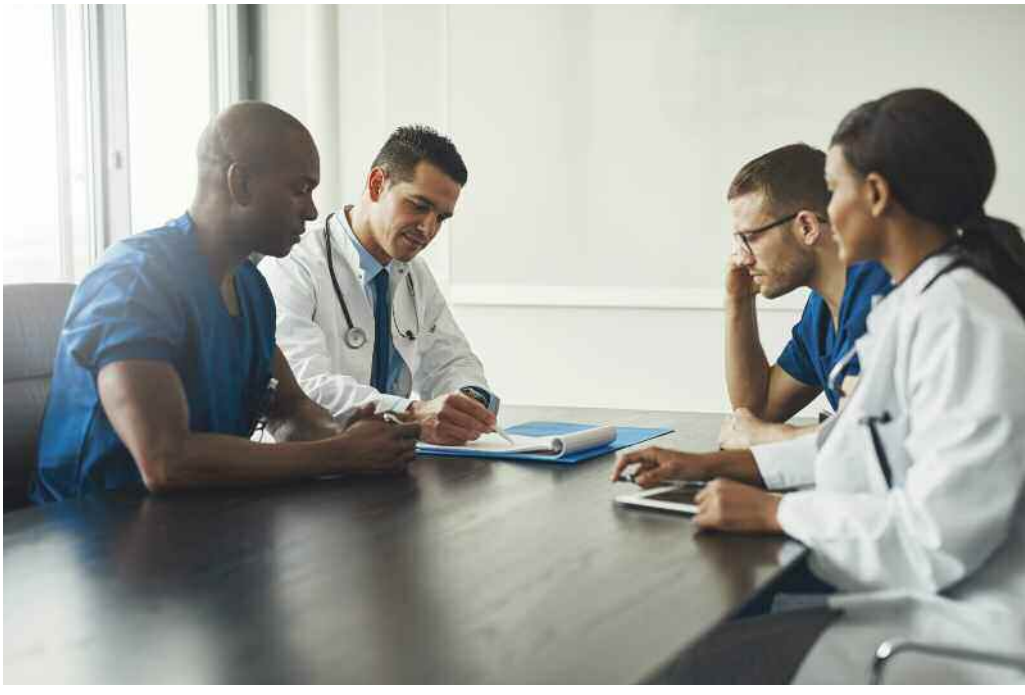
In an attempt to capture this demographic, physicians are increasingly looking to technology to make everything from scheduling appointments to asking questions both quicker and easier for patients. "We're all relying on smartphones," says Susanne Madden, MBA, PCMH CCE, CEO of The Verden Group, a consulting firm for healthcare providers. "The difference is that the older generations are a lot more tolerant of not having that technology. Millennials, because they're the connected generation, they've directed that change. There really is a groundswell demanding this, but millennials are just leading the charge."[7]

And, it's not just millennials who are shifting their focus away from primary care. A study by the nonpartisan Health Care Cost Institute found fewer adults are seeing their primary care physicians and opting more often to see a nurse practitioner or physician assistant. In fact, visits to primary care physicians have been declining since 2012, and the trend has not abated. The message seems to be that convenience and ready access are the desired qualities younger Americans value in engaging the health system.[8]

Team-Based Care Alleviates Burnout

Physician burnout in the primary care setting has also been an issue for a number of years, and it is fueling a desire to change the model of primary care delivery. According to a new study by

InCrowd, some 79 percent of primary care physicians say they have experienced symptoms of burnout, compared to 68 percent among all physicians surveyed.[9] "The alarming persistence of physician burnout over the years and across multiple studies, unfortunately, demonstrates that we have not yet turned the tide on this problematic issue," said Diane Hayes, PhD, co-founder and president of InCrowd. Dr. Hayes notes that since InCrowd last surveyed physician burnout in 2016, there have been no noticeable improvements. "The healthcare industry would benefit from refining and expanding current initiatives to assure adequate staffing levels needed to deliver the quality care patients deserve," she says.



Team-based care has become a popular healthcare goal in the wake of the industry's move toward value-based care models, and it may be a viable means of reducing physician burnout. Because value-based care models are cost-cutting and outcomes-based, industry experts believe teamwork between various providers is essential for long-range success. For example, value-based care puts a heavy emphasis on patients with chronic illness or other complex health needs. These patients typically see a number of providers, including primary care physicians, specialists, pharmacists, nurse practitioners and physician assistants who may all be practicing in those facilities. A team-based model can improve the quality of healthcare, minimize incongruities in care and potentially reduce physician burnout.[10]

According to the National Academy of Medicine (NAM), "The existing evidence demonstrates a generally positive association between team-based care and clinician well-being." Reducing physician burnout can improve the quality of care patients receive because their physicians will be less tired, more attuned to patient needs and able to create better relationships with patients.[11]

Although evidence is currently limited, researchers at NAM say team-based care may be one key solution to physician burnout. Team-based care can also positively impact the patient experience. Research has shown that patients who believe their medical team works well together also perceive they have received a higher level of care.

As the primary healthcare industry continues to adapt to changing fee structures, adjust delivery methods to meet patient preferences and seek new ways of reducing costs and improving outcomes, it will be essential for organizations to embrace innovation and reinvention. While advances in technology and the shift toward value-based care may permanently alter the primary care delivery landscape, the future depends on collaboration between the many industry stakeholders, including PCPs, specialists, politicians, Medicare, Medicaid, commercial insurers and healthcare systems. Now more than ever, healthcare providers must rethink the primary care paradigm and introduce new, innovative ways to deliver care and, ultimately, improve the patient experience. ❖

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

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Evolving from **Sick Care to Well Care**

Embracing a preventive healthcare model can help to reduce spending and improve patient outcomes, but it will require a seismic shift in mindset by patients, providers and payers.

By Abbie Cornett

MOST AMERICANS have always regarded the U.S. healthcare system as the best in the world. And, while that is largely true, what the U.S. has is a great sick care system. Also known as the acute care model, the sick care system was designed to treat illness and disease rather than promote good health.[1] In essence, it is reactive to illness rather than proactive to prevent it. For obvious reasons, this model doesn't make sense in the long run, but change is never easy. The acute care model and its cultural basis has been in place since the Stone Age, when man first treated a wound, set a bone or identified which plants helped relieve pain or soothe a fever.

Basically, the current healthcare model is unsustainable for many societal and economic reasons. For one, because it is tailored to treat illness rather than prevent it, many modifiable risk factors for chronic diseases are not addressed adequately by medical providers. Therefore, evolution to a preventive model focused on forestalling the development of diseases before symptoms or life-threatening events occur is long overdue.

Secondly, according to the Centers for Disease Control and Prevention (CDC), the U.S. spent $10,739 per person for healthcare in 2017, for a total spending of $3.5 trillion, or 17.9 percent of the total gross domestic product.[2] This puts the U.S. No. 1 in spending in the world for medical expenses, which might be acceptable if the U.S. were No. 1 in health outcomes, but it's not. The U.S. ranks number 37th in health outcomes among world health systems. The question is: How did we get into this position, and how do we cure it?

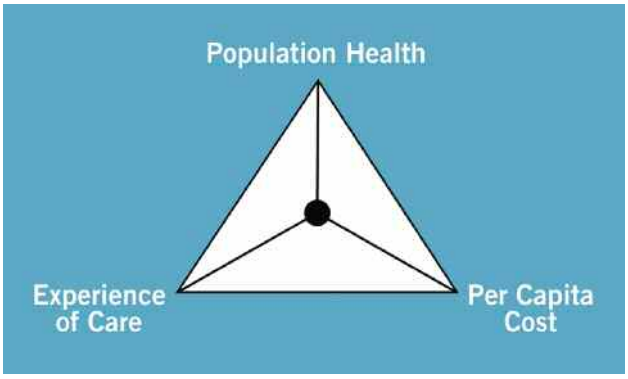
Changing the current model means changing its political, social and economic underpinnings. And, the biggest roadblocks are how patients, providers and payers in the U.S. view the current system. In response, the Institute for Healthcare Improvement introduced the Triple Aim initiative (Figure) that implements programs designed to improve the patient care experience and the health of patient populations and to reduce the per capita cost of healthcare. Yet, while these sound like simple concepts, they will require a significant change in the healthcare culture and investment in technology.

Embracing a Holistic Approach

Currently, Western medicine uses the reductionism method to diagnose, treat and prevent diseases. According to KevinMD.com, "The basic premise of reductionism is that by breaking down (or reducing) complex biological or medical phenomena into their many parts, one is much more likely to understand a single cause and devise a cure." Yet, while this method has been responsible for tremendous successes in modern medicine, it has its limits. These traditional medical care interventions contribute only about 10 percent to reducing premature deaths compared to interventions such as genetic predisposition, social factors and individual health behaviors.[3] Chronic diseases, for instance, have multiple causes that must be considered. Therefore, future medical providers must be taught to address the whole patient from a psychological, social and economic standpoint. This means medical schools must teach prevention strategies alongside treatment approaches with a focus on lifestyle modification.[2] The whole-body approach is particularly important when treating chronic disease patients.

Currently, Western medicine uses the reductionism method to diagnose, treat and prevent diseases.

Figure. Institute for Healthcare Improvement's Triple Aim Initiative



Reimbursing for Well Care vs. Sick Care

Payers must also shift their way of thinking by reimbursing for well care rather than just for treatment. Reimbursing only for treatment incentivizes providers to conduct numerous tests, procedures and medications when the patient is ill, instead of incentivizing providers to educate patients about how to stay healthy. The result is the overuse of medical procedures rather than behavior-change education and counseling.

Payers can reduce costs and improve quality of life by offering insurance plans that cover chronic care and whole-person disease management programs, wellness education, smoking cessation and other preventive healthcare programs. Tying reimbursement to improved outcomes can also help.

Some payers are recognizing the benefits of changing the current healthcare model. In 2018, Stephen Cassell, Cigna's vice president of global branding, announced the company wanted to change its dialogue regarding healthcare to recognize the multiple factors that challenge people's health, including not only the physical factors but also the emotional, financial, social and spiritual components.[4] According to Cassell, the company realized it had an opportunity to save the lives of thousands of people every year who were not getting the preventive care they needed.

To encourage a change in the sick care mindset, Cigna introduced the "Say Ahhh" and "Job Swap" campaigns, which used social influencers to motivate people to take better care of their health by getting annual checkups. The shift from the sick care to the well care model at Cigna increased the number of adult preventive care checkups by 18 percent,[5] or literally millions of people. The company's approach was met with support from both customers and healthcare professionals.

Taking Responsibility for Health

If well care is going to succeed, it's not just providers and payers who need to rethink what healthcare means. It's also everyone else, too. Under the sick care system, people go to the doctor only

when they are sick. This needs to change. They need to seek out medical care prior to becoming ill or developing a chronic disease. Further, people need to reduce their risk factors for disease by maintaining a healthier lifestyle. This includes managing risk factors such as obesity, lack of exercise, stress, alcohol consumption, use of tobacco products and substance abuse.

According to CDC, chronic diseases that are avoidable through preventive care services account for 75 percent of the nation's healthcare spending, and they lower economic output in the U.S. by $260 billion a year. If everyone in the country received the recommended clinical care, the healthcare system could save more than 100,000 lives a year.[5]

For people with chronic diseases, well care equals disease management.

Diabetes is one example of the cost savings and improvement in a population's health that a preventive approach can achieve. The cost of treating a diabetic patient each year is roughly $6,000. However, many cases of diabetes can be prevented by modest behavioral changes such as increased exercise and a healthier diet. In one study, a group that was able to implement lifestyle changes developed diabetes at a 58 percent lower rate than a group with no interventions.[1]

With an aging population, the shift in the burden of disease toward chronic conditions has accelerated. The most prevalent preventable causes of death today are obesity and smoking, which result in delayed but progressive disease. Currently, about half of all Americans have at least one chronic condition. Patients with a chronic illness need to take an active role in their own treatment by educating themselves about their illness. The more knowledge patients gain, the better able they are to interact with their healthcare providers during medical visits. Active participation by patients allows healthcare providers to spend more time during medical visits educating patients about appropriate actions to take at home to control or even cure diseases.[6]

For people with chronic diseases, well care equals disease management. A large component of disease management is patient education, behavior modifications and involving patients' families in assisting them at home to follow through on necessary changes. For this to work, patients must be engaged and active in their healthcare. Patient empowerment is an essential component in changing any part of the healthcare system.

Applying Technology

A big part of the transition to well care can be aided by developments in technology aimed at improving individual patient outcomes and quality of life, while reducing costs. Tech companies are currently developing programs to help medical providers streamline services such as urgent care, behavioral health, radiology and chronic care verticals.[7]

Some examples of how technology can help reduce costs and improve outcomes are the use of patient portals that allow quicker access to care providers, the development of medical devices and apps that allow patients to be monitored remotely, and the use of portable medical records aimed at reducing overlapping medical procedures and testing.

But, the medical community isn't the only sector where changes in technology need to occur. To reduce costs and improve patient outcomes, payers also need to adopt new technology such as the rapidly growing role of telemedicine (the use of telecommunication technologies to deliver health services over a distance) to provide care for the underserved, those at a distance or for whom care is inaccessible. Telemedicine applications have demonstrated dramatic growth during the past decade, particularly in rural areas for clinical specialty applications, the most common being radiology, cardiology, orthopedics and mental health services. Reimbursement for teleservices by payers has emerged as a crucial issue to the development of these services. For projects to evolve from the demonstration stage to a mainstream component of health delivery,[8] payers must adapt how reimbursement is viewed.

Preventive Care Is Key

Healthcare in the U.S. has reached a critical tipping point where it must evolve from sick care to well care. The long-established model of treating disease rather than preventing it is not sustainable. For change to occur, there needs to be a shift in the established culture of sick care to more time and effort spent on preventive care that results in less time and money spent on patients. Moving toward a well-care model focused on prevention is the best solution! ❖

ABBIE CORNETT is the patient advocate for *IG Living* magazine.

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The Challenge of **Cold Chain Logistics**

While some of the guidelines for the transportation, handling, storage and delivery of temperature-sensitive medications are basic and vague, advances in technology help to ensure these drugs are safe and effective when they reach their site of administration.

By Ronale Tucker Rhodes, MS

THE PHARMACEUTICAL cold chain, a temperature-controlled system required to preserve and maintain the usability of pharmaceutical products, is a critical part of today's healthcare supply chain. The cold chain involves constant refrigeration of a product from the time of its production through its transportation, handling, storage and delivery.[1] Responsibility for cold chain logistics originates at the manufacturer of origin and ends at the healthcare facility where the medications are stored until used for patients.

The cold chain was inspired by the World Health Organization (WHO) after it launched a global campaign in 1966 to eradicate smallpox. As part of that campaign, WHO established the Expanded Programme on Immunization (EPI) to assess the feasibility of implementing a single global immunization schedule for six antigens: tuberculosis, polio, diphtheria, pertussis, tetanus and measles. It found, however, that a key challenge of the EPI was the safe delivery of these vaccines, which are temperature-sensitive biological products. To meet this challenge, WHO developed the technologies, systems and guidance toward a vaccine cold chain to distribute vaccines.[2]

Over the past several decades, the need for cold chain activities has substantially increased with the growth of biologics (blood products and vaccines), which require both temperature- and time-controlled distribution, as well as other precision medicine breakthroughs such as cellular therapies, biomarker testing and regenerative medicine (stem cells).[1] According to Pharmaceutical Commerce's annual *BioPharma Cold Chain Sourcebook*, the transport of temperature-sensitive products along a supply chain through thermal and refrigerated packaging methods and the logistical planning to protect the integrity of these shipments is predicted to be a $16.6 billion industry by 2021.[3]

Who Regulates Cold Chain Logistics?

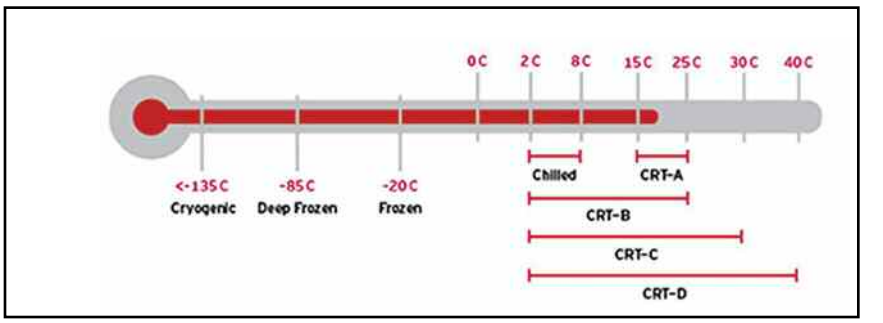
While there are many parties involved in overseeing cold chain logistics, the main regulatory forces are the U.S. Food and Drug Administration (FDA) and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). FDA co-founded ICH with the European community in 1990 "to decrease unnecessary replication of costly regulatory processes, thereby promoting more efficient manufacturing, processing and distribution methods for regulated products on a global scale." FDA's jurisdiction is primarily in the U.S. and Puerto Rico, while ICH's jurisdiction is over the U.S., Japan and the European Union.[4]

The Complexities of the Cold Chain

Drug safety is heavily reliant on cold chain logistics to manage temperature-sensitive products as they move through the supply chain. Depending on the type of pharmaceutical products, their optimal temperature ranges include between 35 degrees and 46 degrees Fahrenheit (2 degrees and 8 degrees Celsius), sub-zero and cryogenic temperatures, with the majority of drugs requiring refrigeration at between 2 degrees to 8 degrees Celsius. Cryogenic products have their own specifications ranging from –35 degrees to –15 degrees Celsius, –65 degrees Celsius, –120 degrees Celsius and –150 degrees Celsius (see Figure).[1] Exposure to temperatures outside these ranges may result in reduced potency of medicines or the need to discard them, which can result in patients being untreated or, in the case of vaccines, an increased risk of vaccine-preventable diseases.[5] In fact, too much exposure to heat, cold or light at any step in the cold chain can damage medicines and result in loss of potency. In addition, exposure to freezing temperatures could destroy some medicines.[6]

To ensure medicines are maintained at the proper temperatures, monitoring them through the supply chain process is essential and can be accomplished in several ways. The most basic includes packing discrete devices called temperature data loggers with the shipment that will record a temperature reading of the products that can be manually uploaded into a system. However, more sophisticated data loggers have the ability to measure temperature, shock, humidity, vibration and other attributes. And, some have GPS capability with real-time tracking and reporting. Radio-frequency identification (RFID) technology utilizing electromagnetic fields to automatically identify and track tags attached to packages can be used with software to monitor temperature.[1] Even more advanced and perhaps the newest and most effective monitoring technology is smart refrigeration systems for storage, handling and inventory (see Monitoring the Storage and Handling of Vaccines and Biologics: MinibarRx).

Figure. Common Product Temperature Ranges within a Controlled Supply Chain



CRT = Controlled Room Temperature
Source: DHL Global Forwarding, 2015

Transportation Guidelines

Even though the cold chain is regulated, there isn't "a single standard, guidance, regulator, document or arbiter with the final say on a compliant cold chain for a given region." Therefore, distributors must rely on only basic requirements for pharmaceutical distribution, as well as other sources such as conferences, technical reports and recommendations from companies that specialize in cold chain logistics.[4]

That being said, one set of rules is becoming the "de-facto standard around the world" and has resulted in stepped-up regulation of cold chain logistics. This is the "European Commission Guidelines on Good Distribution Practices of Medicinal Products for Human Use," which was revised in 2013 and established good distribution practices (GDP) requirements for pharmaceutical products.[7] Items outlined in the GDP are quality management; personnel; premises and equipment; documentation; operations; complaints, returns, suspected falsified medicinal products and medicinal product recalls; outsourced activities; self-inspections; transportation; specific provisions for brokers; and final provisions. The guidelines can be found at ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/2013_c343_01/2013_c343_01_en.pdf.[8]

The European Commission transportation guidelines specifically state it is the "responsibility of the supplying wholesale distributor to protect medicinal products against breakage, adulteration and theft, and to ensure that temperature conditions are maintained within acceptable limits during transport." This includes ensuring vehicles and equipment used to distribute, store or handle products are suitable for their use and appropriately equipped to prevent exposure to conditions that could affect their quality and packaging integrity; written procedures are in place for the operation and maintenance of all vehicles and equipment; and risk assessment is conducted of delivery routes.[8]

Yet, these and other guidelines, as mentioned previously, are merely basic requirements; they don't dictate specifically how these guidelines should be accomplished to comply with cold chain logistics. So, one supply chain consultant suggests distributors, logistic providers and carriers coordinate actions to address the ongoing challenges of cold chain logistics. And, distributors should be able to answer some key questions that should ensure they are in compliance:[3]

- What is the strategy for ensuring end-to-end cold chain visibility?
- How is temperature monitored through the delivery cycle?
- Are logistics providers prequalified for cold chain?
- What processes are in place to assure proper handling and storage once product leaves the facility?
- How is compliance measured?

CDC Storage and Inventory Guidelines

While the handling of vaccines and other medicines begins with the manufacturer, once they arrive at the facility, healthcare providers are responsible for storage, handling and administration. Following is a brief breakdown of the Centers for Disease Control and Prevention (CDC) guidelines for storing vaccines, which can be applied to other medicines requiring refrigeration:[5]

1) Medicine packages should be opened immediately to assess for damage and temperature. Damaged or incorrect temperature drugs should be segregated in a separate location, and the supplier should be contacted for advice on how to proceed.

2) Medicines should immediately be stored at the recommended storage temperature. To assist with this, it is recommended a sign be placed on the refrigerator that lists the appropriate storage temperatures.

3) Medicines should be stored in the middle of refrigerators, never in doors, and in their original packaging inside designated storage trays positioned 2 inches to 3 inches from refrigerator walls. When new product arrives, the stock should be rotated by placing newer medicines behind older ones.

4) Temperature inside refrigerators should be monitored and recorded at least twice a day to ensure they are within the proper range.

5) It is recommended to place temperature log sheets on refrigerators and document the twice-daily checks.

6) If it is suspected medicines have been exposed to out-of-range temperatures or have been left out of refrigerators, they should be marked with "Do Not Use" and transferred to a functional refrigerator at the proper storage temperature while determining whether the medicine is still viable.

CDC also has step-by-step guidelines for inventorying medicines. Briefly described, these include:[6]

1) A stock record should be used to keep track of inventory. The record can be in paper or electronic form, or it can be part of an information system with the capacity to manage drug inventory. The stock record should be updated weekly, and it should account for and document every dose of the medicine, including:

- Date of delivery (and initials of the person who unpacked the delivery)
- Medication and diluent name and manufacturer
- Number and expiration date for each lot (including expiration dates based on beyond-use-date guidance in the product information)
- Number of doses received
- Condition of each medication and diluent upon arrival
- Center for Comparative Medicine reading if included in the shipping container (and actions taken if the monitor was triggered, signaling a possible temperature excursion)
- Number of doses used (i.e., administered, wasted, compromised, expired or transferred [and destination])
- Balance of remaining doses after subtracting the amount used

2) At least once a month and before placing any order, all medications and diluent doses should be counted to ensure the number of doses in the storage unit matches the number of doses documented in the stock record. At the end of each month, the total number of medications and diluent doses used during the month and the amount of stock still available should be determined. And, at the end of the year, the stock record should be used to determine the number of doses received and used during the year to help minimize future waste.

3) Expiration dates on medications and diluents should be checked at least once a week. And, expired medications should be immediately removed to avoid inadvertently administering them. Expired medications should be documented on the stock record.

It should be noted that many of these processes can now be automated with more sophisticated storage and inventorying technologies.

The Future of the Cold Chain

As the pharmaceutical industry becomes more regulated to ensure compliance with cold chain logistics, the need grows for more sophisticated methods of ensuring drug safety as medicines are transported from manufacture to dispensing. Innovation has inspired great strides over the past several decades, but it stands to make even greater improvements with advancing technologies. This is especially true now with advanced therapies such as regenerative medicine and cellular therapies.

Today, next-generation technology, artificial intelligence (AI) and intelligent packaging and software solutions are paving the way for improvements in cold chain logistics. Next-generation shippers and data management devices can report on chain of custody and condition, as well as interact with a user and be reprogrammed instantly to update documentation and airway bills or provide real-time visibility of environmental conditions. Enhanced tracking technology is made possible with augmented GPS (Bluetooth, WiFi, IoT), next-generation data loggers and enhanced software management capabilities. RFID technology and 5G-enabled sensors are next-generation technologies that are improving the safety of cold chain medicines. AI-enabled robotics can analyze and track data, as well as generate predictions to improve the supply chain. And, intelligent packaging solutions can be integrated into driver management or freight management platforms to integrate and optimize supply chain performance.[9]

Even though the cold chain is regulated, there isn't 'a single standard, guidance, regulator, document or arbiter with the final say on a compliant cold chain for a given region.'

To meet the rising demand for biopharmaceuticals, reliance on cold chain logistics is expected to increase substantially. In light of many recent technological breakthroughs, as well as increased regulatory oversight, the safety of cold chain medicines as they travel from manufacturer to site of administration is projected to vastly improve aided by the implementation of smart technology. ❖

RONALE TUCKER RHODES, MS, is the editor of *BioSupply Trends Quarterly*.

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Monitoring the Storage and Handling of Vaccines and Biologics: MinibarRx

BEYOND MANUALLY trying to tackle the tasks of cold chain logistics, the only feasible solution to simplifying the complexities of inventorying and storing biopharma products is with the use of smart refrigeration technology. Shay Reid, chief operating officer at FFF Enterprises, who leads development of the smart refrigerator technology, explains how a smart refrigerator system guarantees medicines are both safe and accessible.

How does smart refrigeration technology help pharma companies comply with the cold chain process?

Smart refrigeration technology, such as our MinibarRx units, complies with the Centers for Disease Control and Prevention's regulatory requirements for storage and handling of vaccines and biologics, making the purchase and management of inventory worry-free. It is a medical-grade refrigeration system designed specifically for vaccine and biologics storage, handling and inventory management for the pharma industry and other healthcare providers.

Features of MinibarRx smart refrigerators include 24/7 temperature monitoring and reporting, password protection, automation of the management of first-in/first-out inventory to reduce risk for expired products, customization to align with the current vaccines and biologics portfolio, emergency medical record connection to reduce data entry and improve vaccine billing accuracy, and a customer portal for real-time reporting capabilities.

The customer portal tracks the visibility of current inventory, usage data and products approaching expiry. In addition, it will record inventory usage each time a product is dispensed, and which user dispensed the item. When products are replenished, this information is automatically captured in the facility's inventory reports. Along with inventory data reports, the portal also provides real-time temperature readings. If a temperature reading is outside of the designated range, an audible alarm is triggered on the system that sends an email notification to the MinibarRx support staff and all designated practice managers. The portal also offers visibility when managing multiple MinibarRx sites through one dashboard to improve key performance indicators such as temperature, expiry, inventory and lot numbers.

What is PAR (periodic automatic replenishment) management, and why is it so important?

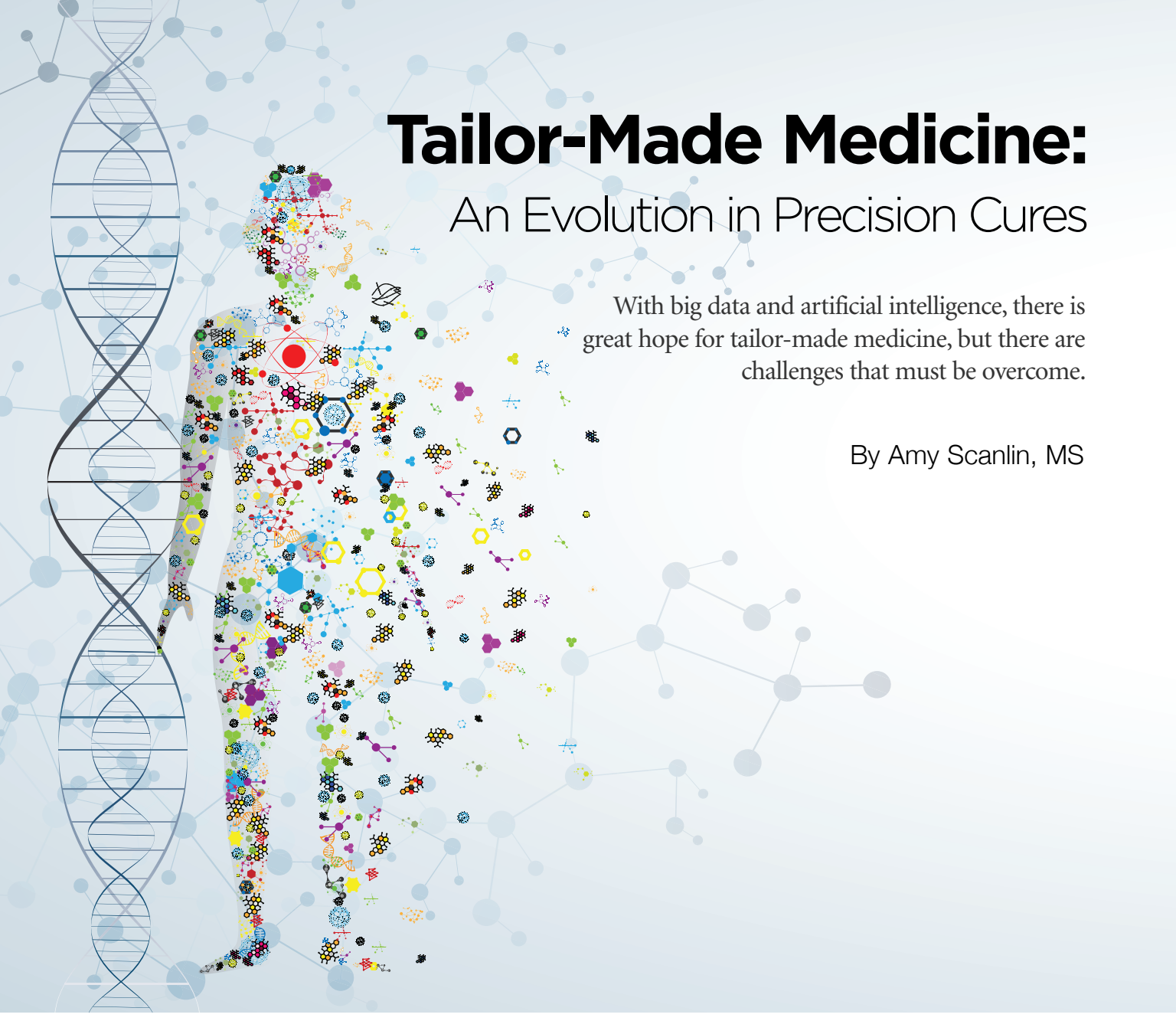
MinibarRx relies on PAR management that is managed through proprietary software designed to allow healthcare providers to set bookend values for each product that represents the minimum amount to stock to meet clinical needs and the maximum to place in the machine. The PAR management algorithms then monitor usage of each item to calculate the most appropriate minimum and maximum stocking level between the bookend values. The software also improves restocking efficiency and further ensures availability by identifying opportunity replenishments so more product is shipped in one container. This sophisticated software that manages the MinibarRx inventory eliminates the manual process of counting and reordering of inventory; think of our refrigerators as having an expert inventory management resource on staff.

Most important concerning PAR management is the medicine is always on-hand. While most companies are trying to ship product out to deliver the next day, MinibarRx ensures the medicine is already there.

What are the differences between MinibarRx and other smart refrigeration technologies?

MinibarRx does not require any additional product labeling such as the use of RFID tags. MinibarRx is also an interactive technology capable of presenting temperature and inventory information on screen to the user, as well as directing the user to dispense first expiring products to help eliminate product expiry in the machine. Additionally, MinibarRx's unique design helps to maintain the temperature and block light even when the main door is open to further protect the very sensitive inventory the machine dispenses without limiting accessibility.

In addition, we use forward deployed inventory (FDI), a business model FFF owns. FDI gives our customers the option of being billed when an individual vial or single syringe of the drug is dispensed versus being billed for a full pack when the drug is shipped from a local or regional distribution center. In essence, this relieves the provider of a higher inventory carrying cost. As a result, the quantity and variety of drugs a facility can provide to patients is no longer limited by its capital. The facility only pays for what it uses.



Tailor-Made Medicine:

An Evolution in Precision Cures

With big data and artificial intelligence, there is great hope for tailor-made medicine, but there are challenges that must be overcome.

By Amy Scanlin, MS

PRECISION MEDICINE, offering pinpoint accuracy in tailored healthcare treatments, is the latest iteration in evidenced-based health. Powered by a rapidly expanding knowledge of genes, genomes and their variabilities, the ability to identify a condition's underlying genetic cause in combination with environmental and lifestyle factors can help to determine the best opportunity for targeted treatments. The pace of genetic research, enhanced by the ability to collect, manipulate and study data for the benefit of both individual care and the larger public health, is opening new doors and making early and positive improvements in patient health.

Efficiency and cost-effective methodologies for assessing disease markers, both static and dynamic, are improving every day, making this evolution to tailored care a reality, particularly in cancer care, where it has been most widely used to date. Costs of genome-wide and partial sequencing have come down significantly, as has the cost of data and data storage. The ability to churn through that data for rapid and accurate assessments will have profound impacts on the success of treatments and long-term health outcomes. Precision medicine must link and learn from all source data, including genetic, behavioral and environmental data,[1] so prediction modeling of health status in combination with treatment options, both pharmacologic and behavioral, can identify outcomes most likely to have greatest impact.

The greater our understanding of disease and its mechanics, including genetics, the greater likelihood patients will have better prescribed treatments, with a high expectation of efficacy and low risk of adverse events. By reaching further and digging deeper to understand etiology and drug targets, science is building opportunity for more proactive and effective treatments based on individualized makeup.

Pharmacogenomics

Most studies in tailor-made medicine have so far focused on pharmacogenomics, or the development of medicines and drug delivery systems based on patients' specific genetic markers. But, the road to tailor-made medicines in this "golden age" of drug discovery has not been without its speed bumps. As genomics became the focus of drug development in the 1990s due to significant advancements in biotechnology and computational capabilities, the discovery of expressed sequencing tags, which enabled a shift from alleviating symptoms of disease to attacking the mechanics of disease, led to a massive increase in research spending but with a subsequent increase in clinical trial failures.

In 2003, the publication of the human genome sequence significantly increased understanding of disease etiology, including how genomic variations interact with complex diseases. But this massive potential has, so far, not met expectations for targeted drug development. Genome-wide association studies (GWAS), for example, enabled a better understanding of diseases, but offered little insight into potential causes. With nearly three million single nucleotide polymorphisms (SNPs) for many human traits and diseases, there are as many as 100,000 contributing SNPs throughout the genome. In fact, between the years 2007 and 2012, nearly 2,000 potential drug leads for almost 2,000 associated loci of complex diseases and traits were identified, some of which were associated with multiple diseases and several autoimmune conditions, including psoriasis, inflammatory bowel disease and ankylosing spondylitis. However, despite these findings, a lack of biological explanation still exists because GWAS most often point to a group of genes close to the signal rather than identifying specifics. This lack of a strong cause-and-effect relationship between a gene and disease means GWAS have, as yet, had little impact on new drug development.[2]

The promise of tailor-made medicine runs across the continuum of care, from dynamic disease risk and prediction modeling to diagnosis and optimized treatments.

Yet, despite these setbacks, evolution away from medicine for the masses in favor of targeted treatments that focus on patients' underlying disease continues to advance, particularly for disorders with strong genetic components such as neurological diseases and cancer. In fact, the disruption of pathways and introduction of immunotherapy has coincided with rapid advancements in companion diagnostics, enabling matching of patients and specific targeted therapies.[2]

Metabolomics

Of course, variability in drug response is not solely genetic and, therefore, cannot be predicted by the genome alone. Patients' medical history, the environmental health of their surroundings, their gut and other lifestyle factors must also be considered to determine which drug will be most effective and at what dose. This is made possible with metabolomics, which is an understanding of the metabolome, or the biochemicals present in cells, tissues and body fluids, and their influence on the genome. By collecting metabolome and genome data, creating a map of underlying molecular disease mechanisms, and identifying biomarkers for drug response phenotypes, better diagnostic capabilities are possible, allowing for more accurate treatments and toxicity risk predictions.

With more input comes more complicated assessment due to integration challenges. So, the next step in research is merging multiple domain risk studies with anonymized data in its original context and meaning with other inputs, while preserving all multivariate statistical properties.[1] For example, assessments of patients' metabotypes prior, during and posttreatment may give powerful clues to pharmaceutical intervention response variability. Metabolomics is a valuable tool and is complementary to precision medicine with the potential to identify factors fundamental to disease, facilitate the discovery of new biomarkers and, thus, identify new targets for clinical intervention.[3]

Inherent Biases of Big Data

The promise of tailor-made medicine runs across the continuum of care, from dynamic disease risk and prediction modeling to diagnosis and optimized treatments. But, for disease prediction to be most effective, it must include not only static factors (genes, age and race), but dynamic factors (behavioral, social, environmental). This holistic, multi-domain approach offers the best opportunity for meaningful intervention as disease etiology, phenotypes and their subclasses, etc., have profound impacts on treatment choices. The inclusion of patients' own-generated data through wearables and apps that capture blood pressure, activity level, dietary intake and more can further enhance valuable clinical data.

Particularly as technologies advance, the ability to integrate genomic data with electronic health record (EHR) and personal health record data provides opportunity, albeit with its own set of challenges. As the capability for capturing and using data grows, the opportunities of precision medicine grow with it. Enter artificial intelligence (AI) and big data, which many believe are key to advancing precision medicine through their ability to understand diseases, their causes and in what patients they are most likely to occur before showing symptoms.

Moving beyond the significant barriers of competing data systems — with differing coding, access protocols, semantic integration and bias — these vast networks can facilitate multi-domain studies, sequencing large numbers of genes simultaneously. For instance, the bias introduced through EHR data is important to recognize and mitigate to the extent possible, as patient populations, the frequency of healthcare visits, diagnostics and care, including prescriptions, may inherently flaw outputs, making big data prediction modeling, in some respects, of limited value. Examples of bias that could be addressed are the use of gender, race and ethnicity as risk modifiers, with the replacement of environmental categories such as lifestyle and diet.

With so much available data that is linkable and comes from a variety of sources, a real challenge is parsing through that which has the greatest statistical significance and clinical relevance to gain actionable knowledge. Thus far, genomic and other "omic" studies have, understandably, been limited by small and heterogeneous sample sizes.[1]

Even so, it is largely thought that without big data and AI, the ability to grow tailor-made healthcare would be curtailed. For example, biomarker identification through digitally enabled technologies is expected to benefit new product label extensions and rationale for reimbursement of diagnostic tests and targeted therapies. More than a third of healthcare settings are expected to invest in personalizing clinical care recommendations, including drug therapies, with the use of AI as a clinical decision support tool.[4]

Advancement of Precision Public Health

Criticisms of precision medicine, based on a perceived lack of broader benefit, include locationally driven concerns, economic segmentation and ethics such as religious and political views. Another challenge is diversity. With the majority of genomic data obtained from those of European descent, research is missing key markers of minority and understudied populations, according to the Population Architecture using Genomics and Epidemiology study funded by the National Human Genome Research Institute and National Institute on Minority Health and Health Disparities. As precision medicine grows, the gap widens to pinpoint care for these racially and ethnically diverse populations that have been understudied. Case in point: Sixty-five new or previously unknown genetic associations along a chromosome where genetic variants are located were recently uncovered in a study of nonwhite Americans. With the potential for information coded in biomarkers to be transferable to additional groups who share genetic lineage, the risk for missing important information and misunderstanding how this information may be attributed in the larger population is an oversight, but one that can be corrected.[5]

There are many examples of drugs that are effective in treating disease, but not for all, and in some cases not for the population with the highest risk for the disease. One example is asthma, which is predominantly seen in African-Americans and Latinos, yet both groups do not respond as readily as others to the most common drugs used in inhalers.

The 2018 launch of the National Institutes of Health's "All of Us" is working to correct the underrepresentation of minorities in research through partnership and sharing of health data of more than one million participants of all races and ethnicities. Prior to All of Us, for example, just 3 percent of African-Americans and less than one percent of Hispanics were represented in genome databases, even though they make up 13 percent and 18 percent of the U.S. population. In All of Us, to date, 21.5 percent of participants are African-American and 17.6 percent are Hispanic, offering an opportunity to better understand complex traits and disease causes and effects.[6]

Criticisms of precision medicine, based on a perceived lack of broader benefit, include locationally driven concerns, economic segmentation and ethics such as religious and political views.

The opportunity to expand precision medicine to a larger construct of public health is growing by incorporating not only genetic and genomic data, but by combining it with other health-related factors that can help to develop a more complete picture of disease and targeted therapies that best suit the individual. There is much work still to be done, but the future looks promising for this collaborative world of health research. ❖

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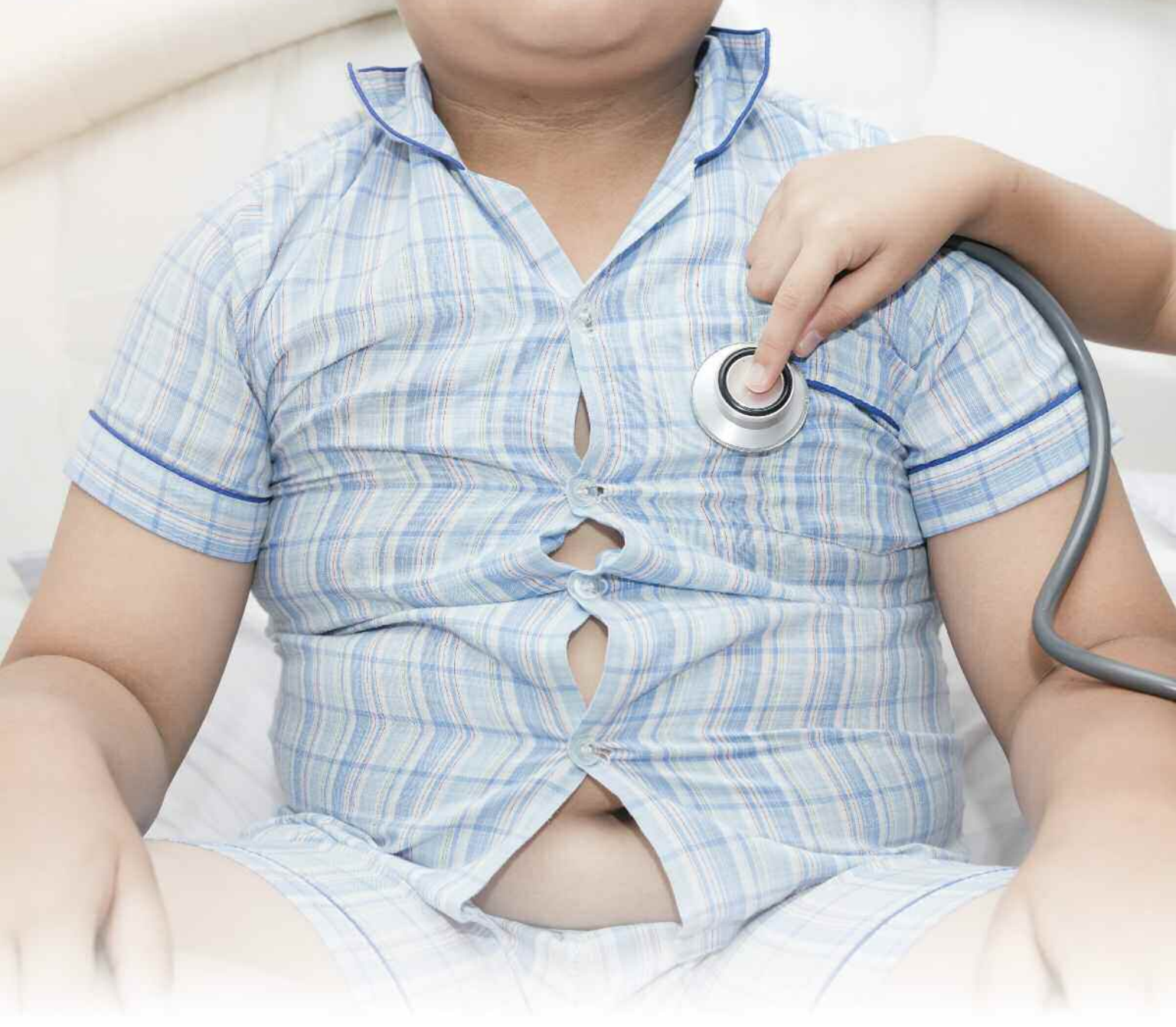


Childhood Obesity: *An Expanding Epidemic*

With the childhood obesity epidemic escalating, pediatricians can help to prevent and treat it.

By Diane L.M. Cook

CHILDHOOD OBESITY RATES in the United States have consistently escalated over the past five decades. These higher childhood obesity rates continue to adversely affect the overall physical and mental health of the nation's children and continue to burden our healthcare system. And, until this trend slows and reverses, more children will become obese, and many will become obese adults.

According to the Centers for Disease Control and Prevention (CDC), obesity is defined as a body mass index (BMI) at or above the 95th percentile of the CDC sex-specific BMI-for-age growth charts (Figures 1 and 2).[1] However, a new classification system recognizes BMI above the 95th percentile as class I obesity, BMI greater than 120 percent of the 95th percentile as class II obesity, and BMI greater than 140 percent of the 95th percentile as class III obesity.[2] And, while not all children who carry extra pounds are obese (some children have larger-than-average body frames, and children normally carry different amounts of body fat at various stages of development[3]), BMI is still the accepted measure to diagnose obesity.

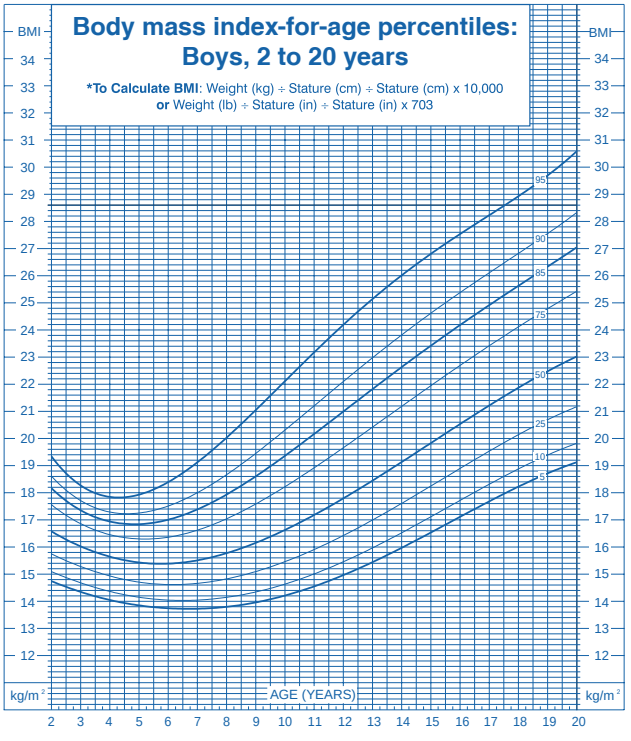
The percentage of children and adolescents affected by obesity has more than tripled since the 1970s. Data shows nearly one in five school-age children and young people (6 years to 19 years) is obese,[4] affecting about 13.7 million children and adolescents.[1] Data from the National Health and Nutrition Examination Survey (NHANES) found in 2015-2016 the prevalence of obesity was 18.5 percent in youth. The survey also found the prevalence of obesity was higher among youth aged 6 years to 11 years (18.4 percent) and adolescents aged 12 years to 19 years (20.6 percent) compared with children aged 2 years to 5 years (13.9 percent). And, from 1999-2000 through 2015-2016, a significantly increasing trend in obesity was observed in youth.[5]

The reason for the dramatic increase in childhood obesity in the U.S. can be directly correlated to the period of time when women started to enter the workforce in large numbers in the 1970s. At that time, homemade meals became less prevalent in families' homes, and there was a definitive uptick in the consumption of processed food, fast food and restaurant food, resulting in many children eating unhealthfully.

Other attributable causes include electronic games such as Atari, Gameboy, Nintendo and Sega Genesis, which became popular in the 1980s, and Xbox, PlayStation and Wii in later years. Today, computers, smartphones and tablets have become ubiquitous among children and adolescents, with electronic games and devices resulting in increased indoor activity time for children and adolescents and, hence, decreased outdoor activity time, leading to an untold number of children who lack regular exercise or physical activity.

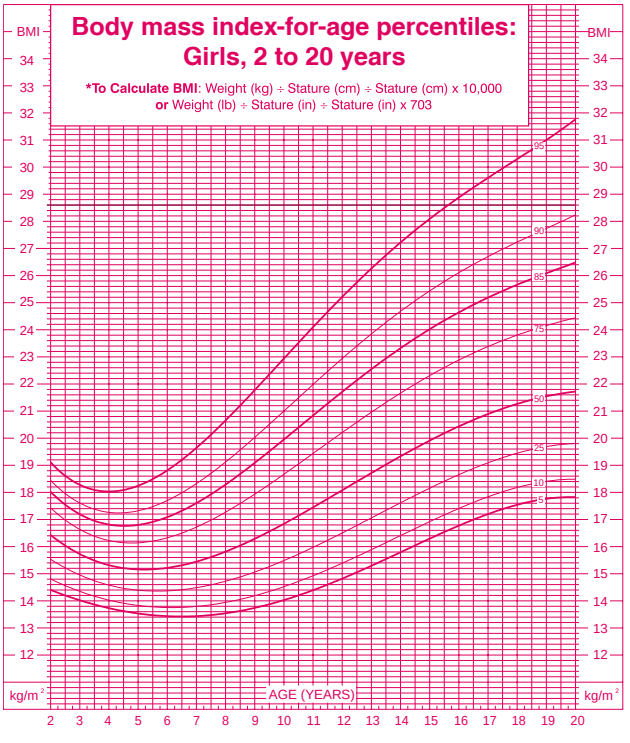
Yet, while there are myriad causes, symptoms and consequences

Figure 1



Source: Centers for Disease Control and Prevention.

Figure 2



of childhood obesity, it is preventable and treatable. And, pediatricians can play an active role.

Causes of Childhood Obesity

The causes of childhood obesity can include physical, psychological and socioeconomic factors or a combination of these factors. However, the most common causes of childhood obesity are excessive and/or unhealthy food consumption and a lack of exercise or physical activity, which can sometimes be caused by a lack of available heathy food and opportunities for exercise or physical activity. In rare cases, childhood obesity can be caused by medical or genetic factors, both of which can be ruled out with a physical exam and blood tests.

Set-point (the weight range in which the body is programmed to function optimally) theory suggests a person's weight is determined by complex interactions of genetic, hormonal and metabolic factors. However, this theory would account only for children who are slightly to moderately overweight, not for children who are obese or morbidly obese.

Perhaps the greatest consequence of childhood obesity is the propensity for becoming obese adults who suffer exacerbated symptoms.

Symptoms of Obesity

According to Boston Children's Hospital, each obese child may experience different symptoms, but some of the most common include stretch marks on the hips and abdomen; dark, velvety skin (known as acanthosis nigricans) around the neck and in other areas; fatty tissue deposition in breast area (an especially troublesome issue for boys); poor self-esteem and eating disorders; shortness of breath when physically active and sleep apnea; constipation and gastroesophageal reflux disease; early puberty and irregular menstrual cycles in girls and delayed puberty in boys, as well as disproportionately small genitals in males; and flat feet, knock knees or dislocated hips.[6]

Consequences of Childhood Obesity

Obese children are at a much greater risk for myriad health conditions, which can include high cholesterol, high blood pressure, early heart disease, stroke, type 2 diabetes, nonalcoholic fatty liver disease, asthma, chronic obstructive pulmonary disease, gall bladder issues, osteoarthritis, bone fractures, and pain in the knees and lower back. In addition to suffering from adverse health conditions, obese children also suffer from emotional and social conditions.

Obesity can also lead to low self-esteem and a higher risk of being bullied. "Children often tease or bully their overweight peers, who suffer a loss of self-esteem and an increased risk of depression as a result," reports the Mayo Clinic. Obese children also suffer from behavior and learning problems: "Overweight children tend to have more anxiety and poorer social skills than normal-weight children do. These problems might lead children who are overweight either to act out and disrupt their classrooms or to withdraw socially." Lastly, obese children also suffer from depression: "Low self-esteem can create overwhelming feelings of hopelessness, which can lead to depression in some children who are overweight."[1]

Perhaps the greatest consequence of childhood obesity is the propensity for becoming obese adults who suffer exacerbated symptoms. According to the World Health Organization, "Childhood obesity is associated with a higher chance of premature death and disability in adulthood. Overweight and obese children are more likely to stay obese into adulthood and to develop noncommunicable diseases (NCDs) like diabetes and cardiovascular diseases at a younger age. For most NCDs resulting from obesity, the risks depend partly on the age of onset and on the duration of obesity. Obese children and adolescents suffer from both short-term and long-term health consequences."[7]

The Role of Pediatricians

As a second line of defense behind parents, pediatricians are the most qualified to assist patients with preventing and treating obesity. Depending on the age and maturity level of the child, pediatricians can disseminate guidelines either to their child patients or parents of the child about how to plan a healthy diet and exercise program to prevent children from becoming overweight or obese or who are currently overweight or obese.

The U.S. Department of Health and Human Services (HHS) published the "2015-2020 Dietary Guidelines for Americans," which includes sections for children and adolescents and shows types of healthy foods; how to build a healthy meal; how to limit calories by eliminating added sugars, saturated fats and sodium; how to make healthier food and beverage choices; and how to include everyone in choosing and preparing healthy meals from home to school to work to communities.[8]

Pediatricians can also encourage parents to keep a daily food log of what their children eat and the associated calories to gauge food and caloric intake over time. This can help parents adjust their children's diet if they continue to gain weight or do not lose the recommended weight as prescribed by their pediatrician.

HHS has also published the "Physical Activity Guidelines for Americans," which can help children improve their body composition

by reducing overall levels of body fat, as well as abdominal fat, through regular exercise. The guidelines outline types of activities (aerobic, muscle strengthening and bone strengthening) for age groups (preschool-aged children ages 3 years through 5 years and school-aged youth and adolescents ages 6 years through 17), and recommends each age group perform 60 minutes of moderate-to-vigorous physical activity three times per week.[9] Based on these recommendations, parents can plan weekly exercise programs for their children and adjust them, if required, to meet their weight goals as prescribed by their pediatrician.

In 2013, the American Academy of Pediatrics launched the Institute for Healthy Childhood Weight (IHCW) to address the complex problem of childhood obesity from prevention through treatment. IHCW's focus is on translating policy, research and best practices into action within healthcare, communities and families, and emphasizing strategic and methodological innovation and evaluation.

One of IHCW's goals is to improve healthy weight assessments during health supervision visits. To accomplish this, it has partnered with the Bright Futures Guidelines, which is currently in progress, by supporting training and implementation tools on best practices for effective weight assessment and counseling for nutrition and physical activity for children from birth to 21 years of age.[10]

IHCW also supports healthcare providers in the delivery of anticipatory guidance around early feeding and nutrition by being part of the Building a Foundation for Healthy Active Living (BFHAL) project. BFHAL includes a portfolio of resources, including a series of online continuous medical education and maintenance of certification modules to help healthcare providers improve delivery of key content during the first 11 well visits, and a suite of family engagement resources (videos, infographics and social media graphics) to create awareness and engage families in the importance of sound nutrition and healthy behaviors.[10]

Through its Healthy Active Living for Families (HALF) project, IHCW also supports healthcare providers in delivering anticipatory guidance about early obesity prevention. Resources in the HALF project were designed to support the implementation of early obesity prevention (infancy through age 5 years) at the point of primary care by leveraging parent focus groups and the latest evidence. Resources include an implementation guide, an app and web-based patient engagement tools for providers' websites.[10]

Lastly, the Childhood Obesity Foundation recommends obese children LIVE 5-2-1-0!: Eat five or more veggies and fruits per day; get no more than two hours of screen time per day; get at least one hour of physical activity or more per day; and drink zero sugary drinks per day.[11]

Moving Forward

In the article "Prevalence of Obesity and Severe Obesity in U.S. Children, 1999-2016" by Ashley Cockrell Skinner, PhD, whose mandate was to provide updated prevalence data on obesity trends among U.S. children and adolescents aged 2 years to 19 years from a nationally representative sample, Dr. Skinner concluded: "Despite previous reports that obesity in children and adolescents has remained stable or decreased in recent years, we found no evidence of a decline in obesity prevalence at any age. In contrast, we report a significant increase in severe obesity among children aged 2 to 5 years since the 2013-2014 cycle, a trend that continued upward for many subgroups."

Dr. Skinner also reported: "Nationally representative data provided by the NHANES demonstrates clearly that childhood obesity continues to be a significant concern for the United States. The past 18 years have seen increases in the levels of severe obesity in all ages and populations despite increased attention and efforts across numerous domains of public health and individual care. Present efforts must continue, as must innovation, research [and] … collaboration among clinicians, public health leaders, hospitals and all levels of government."[2]

To quote the African proverb, "It takes a village to raise a child," which means an entire community of people must interact with children for them to experience and grow in a safe and healthy environment. To address the United States' high childhood obesity rates, not only are parents responsible for the health and well-being of their children, but the entire community — healthcare practitioners (pediatricians), teachers (school cafeterias) and government officials (state lawmakers) — is responsible for the health of the nation's children. All need to work together to ensure all children are provided with the healthy food and regular exercise they require to grow to become healthy adults. ❖

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Myths and Facts: **Chronic Inflammation**

This elusive condition often goes undetected, and when left untreated, it can contribute to a host of serious health risks.

By Jim Trageser

"**INFLAMMATION" IS A** handy catchall for the visible and other tangible signs of the body's immune response when injured or under attack from infectious agents. There is swelling, of course, and often redness, pain, elevated localized temperature and what patients often describe as a throbbing sensation. All of these symptoms are the result of the body's immune system flooding the affected area with white blood cells, dilating blood vessels in the area to increase blood flow, and churning out prostaglandins (compounds with varying hormone-like effects) to help direct the healing.

In fact, while inflammation can be uncomfortable and patients often want to reduce the associated swelling and pain, both are evidence of the ongoing healing process. However, chronic inflammation is not a sign of healing. It is an immune system gone off the rails, rallying the body's defenses to fight a nonexistent threat. Lasting months or even years, chronic inflammation can lead to other serious, often life-threatening conditions.

The World Health Organization now lists chronic diseases, including those associated with chronic inflammation, as the single greatest threat to health.[1] It can be a challenge to impart the seriousness of chronic inflammation to patients because symptoms are often mild (and sometimes nonexistent), and when they are present, they are easily confused with the normal aches and pains of everyday life. To effectively treat chronic inflammation, physicians sometimes have to first overcome the cultural myths surrounding this disease.

Separating Myth from Fact

Myth: Chronic inflammation is no different than acute inflammation.

Fact: Acute inflammation is the body's normal, healthy reaction to injury or infection. When a person gets a splinter or beesting, the body rallies to isolate the intrusion and begin healing the damaged tissue. When a person contracts the flu or a bacterial infection, the immune system mobilizes itself to hunt down the invaders. Once the splinter is out and the puncture healed, or once the flu or infection is over, the immune system winds down and things return to normal.

Chronic inflammation, on the other hand, is an ongoing condition in which the body is reacting to a benign stimulus in a destructive way. Since there is no injury or infection to treat or attack, the white blood cells can, in some cases, begin attacking the body itself, leading to an autoimmune condition such as multiple sclerosis, lupus, Crohn's disease or rheumatoid arthritis.

In addition, while acute inflammation will subside as the injury heals or infection abates, chronic inflammation will, in many cases, persist indefinitely if left untreated.

Myth: Chronic inflammation is no big deal.

Fact: In addition to the autoimmune diseases listed above (often referred to as chronic inflammatory systemic diseases[2]), untreated chronic inflammation can also lead or contribute to a host of other serious health challenges, including:

• Cardiovascular disease, including heart attack and stroke. In particular, chronic inflammation has been shown to contribute to atherosclerosis, the buildup of fatty plaque in the blood vessels.[3] If the body misidentifies the plaque as a foreign substance, it will attempt to build a barrier around it, further constricting the interior dimensions of the blood vessels.

• Cancer, specifically colorectal cancer. Those with inflammatory bowel disease (IBD), including Crohn's and ulcerative colitis, are at heightened risk of developing colorectal cancer. And, chronic inflammation is a known risk factor for IBD.[4]

• Type 2 diabetes. Clinical obesity is a suspected trigger for chronic inflammation, and that inflammation can interfere with the body's production of and reaction to insulin.[5]

• Alzheimer's disease. A study at Johns Hopkins followed 1,500 participants for more than two decades, and tracked C-reactive protein (associated with chronic inflammation) against brain damage associated with Alzheimer's disease, finding a strong correlation between the two.[6] While this doesn't definitively establish a causal relationship, the correlation was strong enough to warrant further study.

Because of its role in autoimmune diseases, cardiovascular disease, cancer, diabetes and dementia, chronic inflammation is an especially dangerous condition that needs to be treated and managed.

Myth: It's easy to know if a person has chronic inflammation.

Fact: While any kind of inflammation — acute or chronic — can cause symptoms of swelling, pain, redness and/or fever, many times there are no symptoms or they are not immediately obvious. Patients may report a lingering fatigue, soreness or weakness in their muscles or joints, or a sense of malaise.[7] But the symptoms may be mild or only noticeable some of the time and are general enough that they can be attributed to other causes.

If a patient reports any of these symptoms, or if a physician notices a patient is having frequent or recurring infections, chronic inflammation may be suspected. Ongoing or repeated gastrointestinal problems can also be a clue. The only way to know for certain if a patient has chronic inflammation is through a clinical blood test. A physician will generally diagnose chronic inflammation by ordering an hsCRP blood test to look for the C-reactive protein, which is associated with chronic inflammation.[3]

The World Health Organization now lists chronic diseases, including those associated with chronic inflammation, as the single greatest threat to health.

Myth: Chronic inflammation is easily treated with diet and lifestyle changes.

Fact: Eating healthy, ceasing smoking and regularly exercising are important components in effectively treating chronic inflammation, but they are not always enough. Still, good dietary and lifestyle habits will amplify any other treatment's efficacy and should be encouraged.

The first step is to manage a healthy weight. Obesity is a critical risk factor for developing chronic inflammation, and reducing

weight to a healthy level can also reduce the seriousness of any chronic inflammation. Foods high in omega-3 fatty acids are particularly useful in fighting chronic inflammation, according to the Scripps Clinic in San Diego, Calif. Cold water fish, grapes, celery, blueberries, olive oil and tea all contain nutrients useful to the body for keeping chronic inflammation at bay. Scripps doctors also recommend limiting fried foods and trans fats, and avoiding processed sugar as much as possible.[8]

Since a variety of underlying causes can trigger chronic inflammation, there is no one way to prevent its onset.

Regularly scheduling exercise can be the most challenging lifestyle change. After all, everyone is already going to take the time to eat each day, so dietary modifications can be handled without giving up other activities. But in an age when too many people are overbooked, finding time for aerobic workouts and weight training can be a challenge. Nevertheless, Scripps staff recommends about an hour to an hour and a half of exercise four to five times a week, with about two-thirds of that aerobic and the rest working with weights.

Obviously, patients who smoke or use other tobacco products should be encouraged to stop since tobacco increases stress on the body and can lead to chronic inflammation.[9]

Finally, Scripps doctors recommend finding ways to practice stress reduction throughout the day, whether it's meditation, yoga, breathing exercises or another technique.

Myth: There is no treatment for chronic inflammation.

Fact: In addition to dietary and lifestyle changes, other treatments can help reduce both the symptoms and the existence of chronic inflammation. Non-steroidal anti-inflammatory drugs such as naproxen, ibuprofen and aspirin can be taken to treat the swelling and pain associated with inflammation — although they do not address the underlying cause of chronic inflammation. In addition to lowering cholesterol levels, statins also reduce inflammation. Steroids can be used to help not only treat the symptoms of inflammation, but suppress the immune system to reduce the processes of inflammation. However, long-term steroid use carries the risk of serious complications, including increased risk of infection, vision problems, elevated blood pressure and increased blood sugar levels.[10]

Myth: Only old people develop chronic inflammation.

Fact: While age is a risk factor for developing chronic inflammation, it is only one factor, and plenty of young people have chronic inflammation. However, older patients are at greater risk of developing chronic inflammation. One likely reason is that as people age, their immune system becomes less and less efficient, and thus more prone to dysfunction.[11] Other possible reasons chronic inflammation becomes more common as people age are an increase in body fat, mitochondrial decay or accumulation of free radicals.[1]

Myth: Doctors and researchers don't know what causes chronic inflammation.

Fact: While the specific triggers that can cause chronic inflammation may never be known in many patients, there is understanding about what can lead to chronic inflammation in a general sense. In some cases, chronic inflammation starts out as acute inflammation. A bacterial, viral or fungal infection is successfully fought off, but somehow the body doesn't get the message that the infection is gone, and it remains in fight mode. In other instances, chronic inflammation may develop from exposure to poisonous substances or microparticles the body cannot process or dispose of (for instance, inhaled silica dust). Since these foreign substances cannot be expelled or broken down, the body will stay in continuous inflammation. And, as mentioned earlier, some conditions such as obesity increase chances the body's immune system will go into a state of chronic inflammation.

But, the reality remains that in many cases, perhaps most, doctors simply won't know what caused a specific patient to develop chronic inflammation.

Myth: Doctors can easily cure chronic inflammation.

Fact: Since the specific cause of patients' long-term inflammation may not be known, there is generally no one-stop cure to reverse the condition. Rather, doctors and patients work together to improve patients' underlying health so their bodies can restore themselves to balance and shut down unnecessary inflammation. This is accomplished through a combined regimen that may include changes in diet, exercise, lifestyle and/or medications.

At the same time, any other conditions that arise due to chronic inflammation must also be treated simultaneously. And, unfortunately, if patients develop an autoimmune disease or cardiovascular disease as a result of chronic inflammation, it can become more challenging to address the inflammation itself.

Myth: There is a vaccine to prevent chronic inflammation.

Fact: Since a variety of underlying causes can trigger chronic inflammation, there is no one way to prevent its onset. And, at this time, there is no pharmaceutical preventive for chronic inflammation. However, patients who proactively adopt a balanced diet, exercise regularly, avoid tobacco use, maintain a healthy weight and avoid exposure to environmental toxins have a good chance of not developing chronic inflammation.

Myth: Scientists will soon know the specific causes of chronic inflammation, and how to cure and prevent it.

Fact: While the Centers for Disease Control and Prevention lists several hundred recent and ongoing research studies on chronic inflammation, the fact remains that the human body's immune system is tremendously complex, and much about it remains a mystery. While some studies are looking into the root causes of chronic inflammation, and others are exploring new treatment options, the odds of a cure or a vaccine in the near future remain long.

Dispelling the Myths Now

Chronic inflammation is not only dangerous, it is cumulatively dangerous. The longer patients suffer from untreated chronic inflammation, the higher their risk of developing an associated subcondition. Clearly, the cost of ignorance regarding chronic inflammation can be staggeringly high.

It is imperative patients be given accurate information regarding chronic inflammation, and that they be encouraged to work on a plan of treatment with their physician. With so many sources of information now available to patients, they often feel empowered to participate in decision-making regarding their own health, but they can be overwhelmed by the amount of misinformation proliferating online.

Asking patients questions about their understanding of chronic inflammation can help physicians determine which popular myths about the disease may be coloring patients' resistance to diagnosis or effective treatment. At the same time, including them in the design of a plan of attack can go a long way toward lowering that resistance and gaining patient buy-in. ❖

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Plasma-Derived ApoA-1: Could It Protect Against Recurrent Cardiovascular Events Following Heart Attack?

By Keith Berman, MPH, MBA

SOME 800,000 American adults will experience a myocardial infarction (MI) this year.[1] Of the 85 percent who survive their heart attack, many are at high risk for a recurrent MI, stroke or other major adverse cardiovascular event, particularly over the first few months of their event.

Following acute-phase management of post-MI patients with drug and mechanical revascularization interventions, maintenance pharmacotherapy, cardiac rehabilitation and lifestyle modification prescriptions all help to moderate the risk of a recurrent cardiovascular event. But across all cases, there remains a roughly 10 percent risk of re-infarction, stroke and cardiovascular death over the first year following an MI.[2] Approximately two-thirds of these recurrent cardiovascular events occur in the first 90 days.

This high prevalence of early post-MI cardiovascular events clearly represents an important unmet medical need, and has attracted much interest and investment in potential protective treatments to reduce this recurrent disease burden. Most of these treatments target the key mediator of atherosclerotic disease itself: the low-density lipoprotein cholesterol (LDL) that builds up in the arterial walls, producing atherosclerosis that eventually can lead to MI and stroke.

Perhaps the most intriguing LDL-focused approach involves the development of products intended to mimic the physiologic activity of high-density lipoprotein cholesterol (HDL), the so-called "good cholesterol" that mediates the continuous removal, or "efflux," of atherogenic LDL from vascular cells.

HDL and Reverse Cholesterol Transport

HDLs are actually a range of globular particles containing both proteins and lipids. The outer layer of HDL includes the more polar lipids, phospholipids and free cholesterol, while more hydrophobic lipids reside in the core of the particle. Apolipoprotein A-I (apoA-I), a 243-amino acid protein embedded in the outer layer, is the active mediator of cholesterol efflux, the first step in reverse cholesterol transport — a physiologic repair effort involving removal of atherogenic LDL from arterial cells and its elimination from the body.

The reverse cholesterol transport process occurs in three stages:

1) Cholesterol efflux mediated by apoA-I, which removes excess cholesterol contained in lipid-laden cellular macrophages;

2) Lipoprotein remodeling, where HDL undergoes structural modifications with possible impact on its functional activity; and

3) Hepatic lipid uptake, where HDL releases cholesterol to the liver for excretion into bile and feces.

HDL particles can contain variable numbers of apoA-I protein molecules.[3] Further, despite having similar or slightly higher apoA-I levels than healthy individuals, individuals with stable atherosclerotic disease exhibit significantly lower cholesterol efflux capacity, the functional measure of how effectively harmful cholesterol can be removed by HDL from vascular tissues. This suggests the physiologic status of these patients somehow may be altering their circulating HDL to render it less

functional or even dysfunctional.[4]

Consistent with these findings, a study of more than 1,600 patients with ST-elevation myocardial infarction (STEMI) requiring percutaneous intervention found that those with the highest HDL-mediated cholesterol efflux capacity had markedly lower 30-day and long-term mortality rates following their MI event than those with the lowest efflux capacity, after adjusting for serum HDL level.[5] HDL cholesterol efflux capacity is thus an inverse marker of incident cardiovascular disease risk.

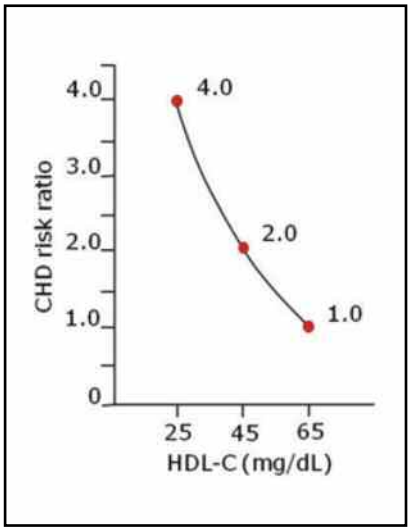
It turns out the functionality of HDL in post-MI patients, entirely apart from the HDL serum level, may be key to successful development of HDL-based therapeutics to reduce major cardiovascular events following MI.

The Conceptual Basis for an HDL-Based Therapeutic

Data from the landmark Framingham Heart Study in the 1970s first established that, across a large population, the serum level of HDL cholesterol is inversely related to the risk of coronary heart disease (CHD). This independent protective effect of HDL may be even more potent than is LDL as a CHD risk factor: In the Framingham population, every 10 mg/dl increase in HDL was found to be associated with a roughly 50 percent reduction in CHD risk[6,7] (Figure 1). HDL is now incorporated into standard patient cardiovascular risk formulas — the ratio of total cholesterol to HDL, for example — to provide better predictive power for CHD.

This strong relationship between HDL level and cardiovascular event risk prompted two large clinical trials to learn whether oral niacin supplementation, which modestly elevates serum HDL by 15 percent to 20 percent in low-HDL patients with established atherosclerotic disease, could potentially reduce stroke or CHD-related hospitalizations, revascularization procedures or deaths.[8,9] Surprisingly,

Figure 1. Relationship Between HDL Cholesterol Level and Coronary Heart Disease Risk[6,7]



both studies failed to show a significant effect of niacin treatment on the incidence of major cardiovascular events. Several drugmakers later pursued testing of novel compounds with the capacity to more robustly boost HDL levels. Once again, large Phase III clinical trials failed to show long-term treatment with these more potent HDL-boosting drugs had a meaningful effect on the cardiovascular event rate compared to placebo.[10,11]

Why would classical epidemiological studies show a strong association between higher HDL levels and lower cardiovascular event risk, while drugs used to increase circulating HDL levels fail to have a clearly demonstrable effect? The answer is thought to involve the distinction between simply raising serum HDL, particularly in people with existing atherosclerosis, and introducing more functional HDL particles that actually mediate reverse transport of cholesterol out of vascular tissues.[12]

Studies measuring cholesterol efflux capacity, again an independent predictor of cardiovascular event risk apart from the HDL level itself,[13,14] have revealed that blood sera from individuals with the same HDL levels can widely differ in their ability to promote the efflux of cholesterol bound up in macrophages.[15] These and other findings have spurred interest in developing apoA-I — the key functional portion of HDL — as a potential therapeutic to boost cholesterol efflux capacity during the critical days and weeks following an MI, with the goal of reducing recurrent event rate.

Two recombinant apoA-I-based HDL mimetics have advanced from bench and preclinical testing to clinical trials, but once again with surprisingly disappointing results:

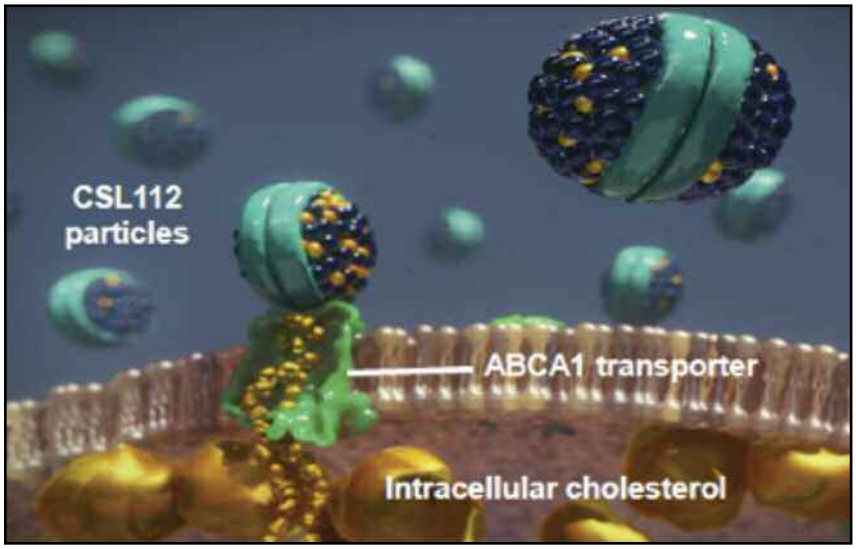
• ApoA-I Milano (MDCO-216) is a recombinant version of a high-functioning apoA-I variant isolated from residents of a village in Italy who have an unusually low prevalence of CHD. In a double-blind pilot study, 122 post-acute coronary syndrome patients placed on statin therapy were randomized to receive five weekly infusions of apoA-I Milano or placebo. At day 36, there was no significant difference in the mean change in atheroma volume between apoA-I Milano and placebo groups; this HDL mimetic failed to produce incremental plaque regression beyond the benefit produced by statin therapy alone.[16]

In late 2016, the sponsor (The Medicines Company) announced it discontinued further investment in the clinical development of apoA-I Milano/MDCO-216.

• CER-001 is an engineered complex of recombinant human apoA-I and phospholipids designed to mimic the structure and function of natural HDL. In a double-blind trial, 272 patients with acute coronary syndrome and extensive coronary atheroma were randomized to receive 10 weekly infusions of CER-001 or placebo in addition to statins. Between baseline and day 78, mean atheroma volume decreased slightly in placebo group patients, but not at all in those in the CER-001 group; similar percentages in both groups demonstrated any measurable atheroma regression.[17]

The sponsor (ABIONYX Pharma) abandoned development of CER-001 for

Figure 2. Graphic Depiction of CSL112 Mediating ABCA1-Dependent Cholesterol Efflux from Vascular Cells



Source: CSL Limited

this clinical application in early 2017.

Australia-based CSL Behring has taken a different tack. In a research and development program now spanning well over a decade, the company has been investigating a novel formulation of apoA-I (CSL112) purified directly from donor human plasma. This naturally-derived apoA-I product has consistently produced strong, immediate and roughly comparable increases in cholesterol efflux capacity both in studies of healthy volunteers and in individuals with CHD.

CSL112: Human Plasma-Derived ApoA-I

Among the world's leading manufacturers of human plasma-derived medicinal products, CSL Behring purifies intravenous and subcutaneous immune globulin, albumin and other therapeutics from millions of liters of donor plasma each year. In the early plasma fractionation process steps, HDL partitions to lipid-rich fraction IV. The native apoA-I protein is further purified from this fraction, lyophilized with specific stabilizers and reconstituted to form a preparation (CSL112) suitable for infusion.

In vitro studies of CSL112 have shown it undergoes remodeling steps that involve transient fusion with endogenous HDL and subsequent rapid fission to spontaneously yield two small-diameter and one large-diameter HDL molecular species, all containing CSL112. The smaller lipid-poor apoA-I HDL species demonstrates both highly functional cholesterol efflux capacity and significant anti-inflammatory effects.[18]

Like endogenous HDL, CSL112 acts as a scavenger, removing LDL from the coronary plaque and transporting it to the liver for eventual excretion. CSL112 was designed to optimize cholesterol efflux by the ATP-binding cassette transporter (ABCA1); this membrane "transporter" is induced by excess cellular cholesterol present in the atherosclerotic plaque (Figure 2).

Infusions of CSL112 into healthy volunteers have been shown to rapidly induce cholesterol efflux, the first step in reverse cholesterol transport. A single 6-gram dose of CSL112 induced a 2.5-fold average increase in total cholesterol efflux capacity compared to baseline, and was safe and well-tolerated in volunteers with both normal and moderately impaired renal function.[19] Importantly, CSL112 performed similarly in persons with high and low endogenous HDL functionality. Further, pooled data from studies in 93 healthy subjects and 44 patients with stable atherosclerotic disease documented strong, quantitatively similar elevations in cholesterol efflux capacity, independent of disease status or baseline cholesterol efflux activity.[20]

As worsening cardiovascular disease is associated with declining cholesterol efflux capacity, these findings suggested CSL112 can robustly boost cholesterol efflux capacity in patients with impaired endogenous HDL function. Encouragingly, several studies have documented the ability of CSL112 (as well as CSL111, a predecessor version) to reduce atherosclerotic plaque volume. In particular, a study randomizing 20 patients with femoral artery claudication, a single infusion of CSL111 resulted in acute changes in plaque characteristics and significantly reduced plaque lipid content and measures of inflammation compared to placebo.[21]

Assessing CSL112 in Post-MI Patients

Conducted in 2015 at treatment sites in 16 countries, CSL Behring's Phase IIa AEGIS-I study randomized a total of 1,258 post-MI patients on a 1:1:1 basis to receive four weekly infusions of a low dose (2 grams apoA-I) or a high dose (6 grams apoA-I) of CSL112, or placebo. The higher dose of CSL112 was associated with well over a 100 percent increase in cholesterol efflux activity (Table), similar to that achieved in patients with stable coronary artery disease. There were no significant alterations in liver or kidney function or other safety concerns.

At 12-month follow-up, the rate of major adverse cardiovascular events — a composite of cardiovascular death, non-fatal MI, ischemic stroke and hospitaliza-

tion for unstable angina — was similar between the low- and high-dose CSL112 treatment groups and the placebo group (respectively 6.4 percent, 5.7 percent and 5.5 percent). Nonfatal MI rates were the same — about 3 percent — in all three treatment groups. Two and four cardiovascular deaths were reported in the 2-gram and 6-gram CSL112 groups, and none in the placebo group; this one-year mortality rate was considered too small to be evaluable.

In early 2018, CSL Behring initiated its pivotal Phase III AEGIS-II study randomizing adult patients diagnosed with either STEMI or non-STEMI to receive four consecutive weekly infusions of 6 grams (170 mL) of CSL112 or a 4.4 percent albumin placebo solution. Study participants may be either medically managed or managed with percutaneous coronary intervention. Some 1,000 U.S. and international study sites are participating in this Phase III, double-blind, randomized, placebo-controlled, parallel-group study. With a 17,400-subject enrollment target, this is by far the largest and most ambitious clinical investigation of any plasma-derived therapeutic in history. AEGIS-II is scheduled to be completed in about two years.

An Opportunity to Make a Difference

CSL Behring and its clinical collaborators across the globe are hoping CSL112's demonstrated ability to strongly boost cholesterol efflux capacity and reduce lipid content in atherosclerotic plaques will translate into a clinically meaningful reduction in a composite of fatal and nonfatal cardiovascular events over the critical 90-day period following MI.

For its pivotal AEGIS-II study, the company is focusing on a higher-risk subpopulation of MI patients with multivessel coronary artery disease and at least one of the following: age greater than 65 years, a history of prior MI, diabetes mellitus and/or peripheral artery disease. In this "enriched" AEGIS-II study population, CSL Behring anticipates a post-MI recurrent cardiovascular event rate of about 10 percent over the first 90 days in its placebo control arm.

An interim efficacy analysis will be completed next year. If analysis of the final results confirm CSL112 can meaningfully reduce that 90-day recurrent event rate with an acceptable safety profile, the product will immediately establish itself as a standard treatment for this high-risk segment of the 800,000 Americans who experience an MI each year.

The AEGIS-II trial is now past the halfway point. CSL Behring will spend roughly $800 million altogether to learn if its faith in CSL112 was justified. With thoughts of countless patients whose weeks and months following their heart attack are lived in fear, the medical community is hopeful too that CSL112 turns out to be a winning bet. ❖

Table. AEGIS-I Study: Cholesterol Efflux, HDL Cholesterol and ApoA-I Values Immediately After Infusion of CSL112

	CSL112 2 g	CSL112 6 g	Placebo
Total cholesterol efflux capacity, %/4h	15.8±3.8	20.8±3.8	8.3±2.7
Fold elevation vs. baseline	**1.87**	**2.45**	0.94
Apolipoprotein A-I (apoA-I), mg/dL	161±33.4	263±58.2	121±25.7
Fold elevation vs. baseline	**1.29**	**2.06**	0.96
HDL cholesterol, mg/dL	43.9±11.8	52.5±12.1	39.3±10.9
Fold elevation vs. baseline	**1.09**	**1.27**	0.97

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After his sister's death due to obesity, Tommy Tomlinson finally confronted his own 460 pounds, writing a book about his struggles and finally finding a lifestyle plan that has helped him to lose weight and keep it off.

Obesity: *A Patient's Perspective*

By Trudie Mitschang

TOMMY TOMLINSON was 50 years old when he was forced to face his own mortality and his lifelong battle with obesity. Topping the scales at 460 pounds, the successful journalist was not only at risk for heart disease, diabetes and stroke, he was unable to climb a flight of stairs without having to catch his breath, or travel on an airplane without buying two seats. A simple trip to a local diner required a stressful, advanced assessment of whether there was an available seat that could support him.

Raised in the South by a family that loved food, he had been aware of his health problem for years, seeing doctors and trying diets from the time he was a preteen. But nothing worked, and every time he tried to make a change, it didn't go the way he planned. Tomlinson says it was his older sister's sudden death on Christmas Eve in 2014 that provided the wake-up call he needed to address the problem head on. "She died of an infection that was basically caused by her size," he recalls. "I went to her funeral and I could see my future: I was 50 years old when she died, and guys like me don't make it to 60. I knew then, in a way I never really felt as deeply and emotionally, that I had to change."

Tomlinson's successful career as a longtime columnist for the *Charlotte Observer* includes being a Pulitzer Prize finalist and a Nieman Fellow at Harvard. Although he has written about everything from music to sports, he only recently tackled the personal and difficult subject of his weight in his first book titled *The Elephant in the Room: One Fat Man's Quest to Get Smaller in a Growing America*, published in January 2020. In it, Tomlinson bares the physical and emotional struggles he and millions of Americans face each day. "My weight is the biggest story of my life, but I hadn't told it because I was embarrassed, because I was afraid, because I knew I didn't understand myself."

When putting pen to paper, Tomlinson says the statement "I weigh 460 pounds" was the most terrifying yet cathartic truth to share. "Those were the hardest words I've ever had to write. Nobody knew that number — not my wife, not my doctor, not my closest friends. It felt like confessing a crime," he says. "The average American male weighs about 195 pounds; I'm two of those guys, with a 10-year-old left over. I'm the biggest human being most people who know me have ever met, or ever will."

In the book, Tomlinson talks about growing up in a culture where food — and lots of it — was considered expressions of both affluence and love. He also describes an addiction to fast food that created a downward spiral for him in terms of weight gain. After the loss of his sister, Tomlinson began confronting his relationship with food and says he believes he's been successful at losing weight because he finally chose a method that was sustainable for him. He wanted a plan that would bring him slow, steady results, and he describes his regimen as "the three-step diet," which consists of exercise, using a Fitbit to calculate how many calories he burns daily and then calculating his exact calorie intake. "If I burn more than I bring in, eventually I'm bound to lose weight. It's very slow and steady," he says. "I'm still a big guy several years into this plan, but I do think it's something that I can live with."

Tomlinson confides near the end of his book that his ultimate goal is to weigh 230 pounds — half his original size, and he's feeling positive about his weight-loss journey to date. Although reticent to say how much, he admits he's lost a substantial amount of weight and has kept it off for the first time in his life. He also recently embarked on a book tour and is already contemplating what life will be like as someone who is not defined only by body size.

"I've never been anything but fat. One of the things I'm curious about, and a little worried about, is how my personality will change as my body changes. In terms of personality, I kind of like who I am," he says. "Part of what I feel is positive about my personality is that I've always had a lot of empathy for other people. Whatever other strengths I have as a journalist, my ability to step into someone else's shoes and understand their issues is something I can easily do. I assume that losing weight will not make me less empathetic, because I will remember that person I used to be. But I don't know." ❖

Dr. Rekha Kumar chose to specialize in obesity when she recognized the condition was a contributing factor to most other diseases.

Obesity: *A Physician's Perspective*

REKHA KUMAR, MD, is an assistant professor of medicine at the Weill Cornell Medical College and an attending endocrinologist specializing in the diagnosis and treatment of various endocrinology disorders, including obesity and weight management. Dr. Kumar currently serves as the medical director of the American Board of Obesity Medicine (ABOM) and is certified as an ABOM diplomate. She is also board-certified in internal medicine, endocrinology, diabetes and metabolism.

The author of several papers and textbook chapters on obesity management, Dr. Kumar enjoys educating physicians on various aspects of obesity medicine ranging from etiologies of obesity to new pharmacologic therapies. She has lectured throughout the United States and has addressed policymakers on Capitol Hill on the importance of treating obesity as a disease.

BSTQ: How did you choose this area of medicine?

Dr. Kumar: While training as an internal medicine doctor and endocrinologist, I observed obesity was a contributing factor to most diseases. As a result, we were often treating complications of obesity without addressing the actual underlying condition of excess weight gain.

BSTQ: What are the most common misconceptions about obesity?

Dr. Kumar: Most common misconceptions are that obesity is a just a behavioral problem or that people with obesity are lazy. There is a behavioral component of the disease, but our biology does influence our behavior. For example, if we have dysregulated weight-regulating hormones or are taking medicines that affect appetite and/or metabolism, we will be inclined to eat more.

BSTQ: How common is obesity in the U.S.?

Dr. Kumar: Unfortunately, obesity is extremely common in the United States. Currently, approximately 40 percent of our population is obese. It is so extremely common that it has become normalized in certain populations.

BSTQ: What is the distinction between obesity and morbid obesity?

Dr. Kumar: Obesity begins at a body mass index (BMI) of 30, while severe or morbid obesity is a BMI of 40 or greater.

BSTQ: What treatment options have you found to be most effective for obesity?

Dr. Kumar: The most effective approach typically includes a combination of support for behavioral change, a calorie-reduced nonprocessed low-glycemic diet, increased exercise and, occasionally, the use of medicines or surgery to help reduce body weight.

BSTQ: How do obesity treatment options differ for adults versus children?

Dr. Kumar: Many interventions in childhood are focused on diet and exercise along with family interventions, whereas in adults, there is more use of medicines and surgery.

BSTQ: What are your thoughts about treating the mental/emotional issues related to overeating and obesity?

Dr. Kumar: It's actually a very important component. Obesity is associated with depression, and depression is associated with obesity. When dealing with a condition like obesity, it's always vital to treat the whole person, and it can be beneficial to address any potential mood disorders while also focusing on behavior modification.

BSTQ: When is medication recommended for weight loss?

Dr. Kumar: Lifestyle interventions, including a calorie-deficit diet and physical activity, remain the cornerstone of treatment for people who are obese. However, lifestyle modifications are not always effective in providing lasting weight loss. The National Heart, Lung and Blood Institute of the National Institutes of Health recommends individuals diagnosed with obesity who fail to respond to lifestyle interventions, have a BMI of greater than 30 and present with a weight-induced comorbidity may benefit from having weight-loss medication added to their treatment plan. The goal of pharmacotherapy is not only to reduce weight, but more importantly, to improve the comorbid conditions associated with obesity such as hyperglycemia, hyperlipidemia and atherosclerotic heart disease.

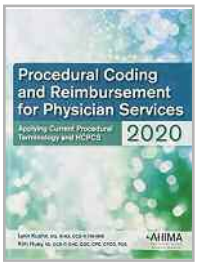
BSTQ: When is weight-loss surgery recommended?

Dr. Kumar: Surgery is recommended for a BMI of 35 or greater if there is a weight-related complication such as prediabetes or hypertension, and it is commonly recommended when a person has a BMI of 40 or greater.

BSTQ: Are there any new studies in obesity medicine that you find promising?

Dr. Kumar: There are a number of new medicines in clinical trials that look promising. There are also more digital health companies focused on addressing the obesity epidemic through apps and telehealth that will make doctor visits for obesity care more accessible. ❖

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



Procedural Coding and Reimbursement for Physician Services, 2020

Authors: Lynn Kuehn, MS, RHIA, CCS-P, FAHIMA, and Kimberly Huey, CCS-P, PCS, MJ, CPC, CPCO, CHC, COC

This book introduces the basic principles and conventions of Current Procedural Terminology and Healthcare Common Procedure Coding System coding while delivering the experience-based knowledge needed to code confidently and efficiently. Included are self-assessment exercises based on actual case documentation providing hands-on experience analyzing and coding clinical data; the latest code sets for immediate comprehension; chapters targeting systems, procedures and practice settings; and odd-numbered answers for chapter review exercises in appendix E. Also included are an expanded test bank; document checkups to progress student understanding; five online appendices, including a printable CMS-1500 claim form; more than 80 case-based coding scenarios to apply coding knowledge and skills; hundreds of practice questions, including chapter exercises, chapter tests and test bank items in the instructor's guide; and answer keys (provided only to verified instructors).

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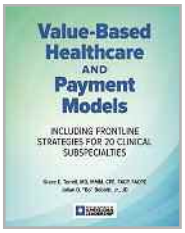
Value-Based Healthcare and Payment Models: Including Frontline Strategies for 20 Clinical Subspecialties

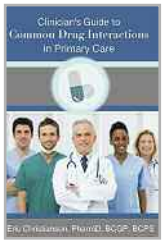
Authors: Grace E. Terrell, MD, MMM, CPE, FACP, FACPE, and Julian D. Bo Bobbitt Jr., JD



This book is filled with practical advice on how to shift to value-based care in both the private and public healthcare sectors. In the complicated world of payment and delivery system reform, the authors deconstruct the most challenging concepts for the novice, yet provide sophisticated insights for even the most seasoned executive. The book fills an important need by providing concrete and proven strategies to aid in an organization's successful transformation. The authors also lay out high-value strategies for 20 different subspecialties with specialty-specific changes in the way medicine is practiced and paid for.

www.amazon.com/Value-Based-Healthcare-Payment-Models-Subspecialties/dp/0984831010/ref=sr_1_2?keywords=Physicians&qid=1581018069&s=books&sr=1-2

Clinician's Guide to Common Drug Interactions in Primary Care



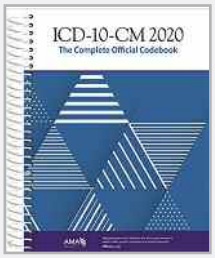
Author: Eric Christianson, MD

For many, drug interactions are one of the most frustrating challenges in family medicine, geriatrics and ambulatory care practice. Even if one is up to speed on what drugs interact with one another, it is often unknown how to manage that specific interaction. Throughout the book, the author shares some of his management tips and pearls to help physicians feel more comfortable with managing drug interactions. This book is an educational resource for pharmacists, nurse practitioners, physicians, physician assistants and nurses who are looking to pick up clinical, real-world practice pearls.

www.amazon.com/dp/1651812187/ref=sr_1_1?qid=1581018497&refinements=p_27%3ADr.+Eric+Christianson&s=books&sr=1-1&text=Dr.+Eric+Christianson

ICD-10-CM 2020: The Complete Official Codebook

Author: American Medical Association



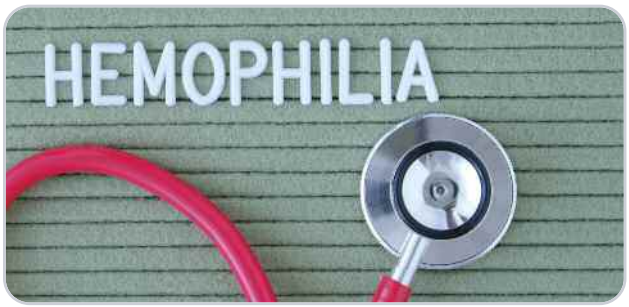
This official codebook provides the entire updated code set for diagnostic coding, organized to make the challenge of accurate coding easier. It is the cornerstone for establishing medical necessity, determining coverage and ensuring appropriate reimbursement. Each of the 21 chapters in the Tabular List of Diseases and Injuries is organized to provide quick and simple navigation to facilitate accurate coding. The book also contains supplementary appendixes including a coding tutorial, pharmacology listings, a list of valid three-character codes and additional information on Z-codes for long-term drug use and Z-codes that can only be used as a principal diagnosis. Official coding guidelines for 2020 are bound into this codebook.

www.amazon.com/ICD-10-CM-2020-Complete-Official-Codebook

High-Titer Inhibitors Reduced in PUPs with Severe Hemophilia A Treated with Fourth Generation Recombinant Factor VIII

A prospective, multinational, open-label Phase III study in previously untreated patients (PUPs) with severe hemophilia A found replacement therapy with simoctocog alfa (Nuwiq; Octapharma USA), a fourth-generation recombinant factor VIII (FVIII) product, was associated with an incidence of high-titer inhibitors similar to the rate seen in a landmark trial evaluating plasma-derived FVIII products, and significantly lower than the rate seen in PUPs treated with earlier-generation recombinant FVIII products in that same trial.

A total of 105 PUPs evaluable for inhibitor development received on-demand or prophylactic treatment with simoctocog alfa for a median of 101 exposure days (range one to 1,164), with 96 patients treated for greater than or equal to 100 exposure days. The cumulative high-titer inhibitor incidence was 17.6 percent (95 percent confidence interval [CI]: 10.0 percent to 25.5 percent), and 27.9 percent for cumulative inhibitors. This compares closely with the SIPPET study, which reported high-titer and any inhibitors in 18.6 percent and 26.8 percent of PUPs treated with plasma-derived FVIII products naturally containing von Willebrand factor. By contrast, SIPPET study patients treated with earlier-generation recombinant FVIII products had high-titer and



cumulative inhibitor rates of 28.4 percent and 44.5 percent.

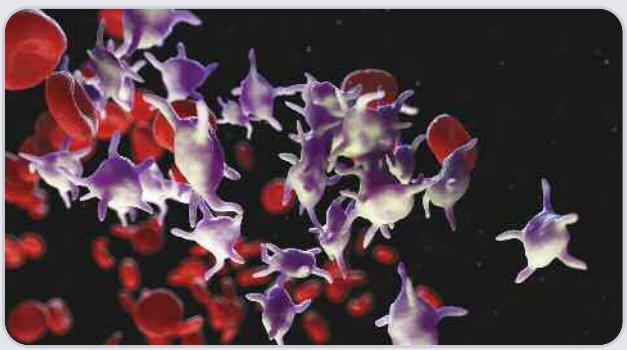
Simoctogoc alfa had a median spontaneous annualized bleeding rate of 0 during prophylaxis and was successful in the treatment of 92.9 percent of bleeding events and in 94.7 percent of surgical procedures. "These results complement results in previously treated patients (PTPs) and support the use of simoctocog alfa in the prevention and treatment of bleeding events in PUPs and PTPs," the investigators concluded.

Liesner R and Neufeld EJ. Inhibitor development with simoctocog alfa in previously untreated patients with severe hemophilia A: Final results of the NuProtect study. Blood *2019 Nov 13;134(Supplement 1):903.*

FcRn Antagonist Boosts Platelet Counts, Reduces Bleeding Risk in Patients with Immune Thrombocytopenic Purpura

Efgartigimod, an investigational human IgG1 Fc fragment, induced a rapid reduction in total IgG levels and clinically relevant increases in platelet counts in patients with primary immune thrombocytopenia (ITP), according to findings from a Phase II, placebo-controlled multinational study.

In this randomized, double-blinded, placebo-controlled study, 38 ITP patients at 19 European study centers were randomized 1:1:1 to receive four weekly intravenous infusions of either placebo or efgartigimod at a dose of 5 mg/kg or 10 mg/kg body weight.



Patients were followed for up to 21 weeks. Most patients enrolled in this study were refractory to previous lines of therapy.

Forty-six percent of patients on efgartigimod experienced platelet counts of greater than or equal to 50 x 109/L on at least two occasions, compared with 25 percent of those who received placebo; 38 percent of efgartigimod-treated patients achieved greater than or equal to 50 x 109/L on at least 10 cumulative days.

The proportion of patients with bleeding decreased in both the efgartigimod 5 and 10 mg/kg groups, from 46.2 percent at baseline to a minimum of 7.7 percent at day 64, and from 38.5 percent at baseline to a minimum of 7.7 percent at day 29. In the placebo group, the proportion with bleeding decreased from 33.3 percent at baseline to a minimum of 25.0 percent at day 50.

Taken together, these data "suggest that targeted IgG reduction with efgartigimod is a potential new treatment modality in primary ITP and warrants further evaluation of longer-term treatment in a larger Phase III study," the investigators concluded.

Newland AC, Sánchez-Gonzáles B, Egyed M, et al. Phase 2 study of efgartigimod, a novel FcRn antagonist, in adult patients with primary immune thrombocytopenia. Am J Hematol *2020 Feb;95(2):178-187.*

Medicare Immune Globulin Reimbursement Rates

Rates are effective April 1, 2020, through June 30, 2020

	Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
IVIG	FLEBOGAMMA	Grifols	J1572	$72.03	$70.88
	GAMMAGARD SD	Takeda	J1566	$128.18	$126.12
	GAMMAPLEX	BPL	J1557	$110.42	$108.65
	OCTAGAM	Octapharma	J1568	$80.94	$79.64
	PANZYGA	Pfizer	90283/J1599	**	**
	PRIVIGEN	CSL Behring	J1459	$82.43	$81.11
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$79.50	$78.23
	GAMMAKED	Kedrion	J1561	$81.65	$80.34
	GAMUNEX-C	Grifols	J1561	$81.65	$80.34
SCIG	CUTAQUIG	Octapharma	90284/J3590	**	**
	CUVITRU	Takeda	J1555	$138.85	$136.62
	HIZENTRA	CSL Behring	J1559	$104.97	$103.29
	HYQVIA	Takeda	J1575	$141.37	$139.10
	XEMBIFY	Grifols	90284/J3590	**	**

* Reflects 2% sequestration reduction applied to 80% Medicare payment portion as required under the Budget Control Act of 2011.

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

Immune Globulin Reference Table

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

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

2020-2021 Influenza Vaccine

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

Product	Manufacturer	Presentation	Age Group	Code
Trivalent				
FLUAD (aIIV3)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90653
Quadrivalent				
AFLURIA (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	3 years and older	90686
AFLURIA (IIV4)	SEQIRUS	5 mL MDV	6 months and older	90688
AFLURIA PEDIATRIC (IIV4)	SEQIRUS	0.25 mL PFS 10-BX	6-35 months	90685
FLUAD (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90694
FLUARIX (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUBLOK (ccIIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	18 years and older	90682
FLUCELVAX (ccIIV4)	SEQIRUS	0.5 mL PFS 10-BX	4 years and older	90674
FLUCELVAX (ccIIV4)	SEQIRUS	5 mL MDV	4 years and older	90756*
FLULAVAL (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUMIST (LAIV4)	ASTRAZENECA	0.2 mL nasal spray 10-BX	2-49 years	90672
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL SDV 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	5 mL MDV	6 months and older	90688
FLUZONE HIGH-DOSE (IIV4)	SANOFI PASTEUR	0.7 mL PFS 10-BX	65 years and older	90662
FLUZONE PEDIATRIC (IIV4)	SANOFI PASTEUR	0.25 mL PFS 10-BX	6-35 months	90685/90687

aIIV3 MF59-adjuvanted trivalent inactivated injectable
ccIIV4 Cell culture-based quadrivalent inactivated injectable
IIV4 Egg-based quadrivalent inactivated injectable
LAIV4 Egg-based live attenuated quadrivalent nasal spray

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

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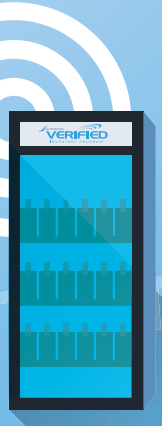

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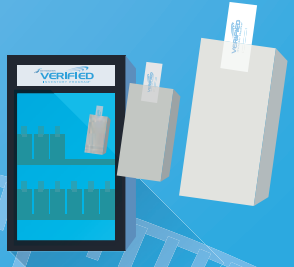

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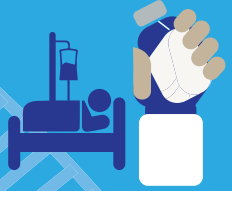

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