biosupplytrends
QUARTERLY
FALL 2023 INNOVATION

Personalized Medicine

Mining Genomic Sequencing Data

MANAGING DISEASE WITH
Digital Therapeutics

Healthcare Consolidation:
THE PROS AND CONS

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Guaranteed Channel Integrity®

8 Critical Steps

STEP 1

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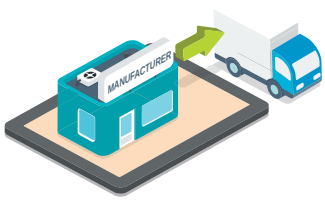

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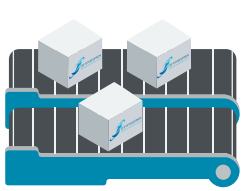

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STEP 6

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STEP 7

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STEP 8

Tracking

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

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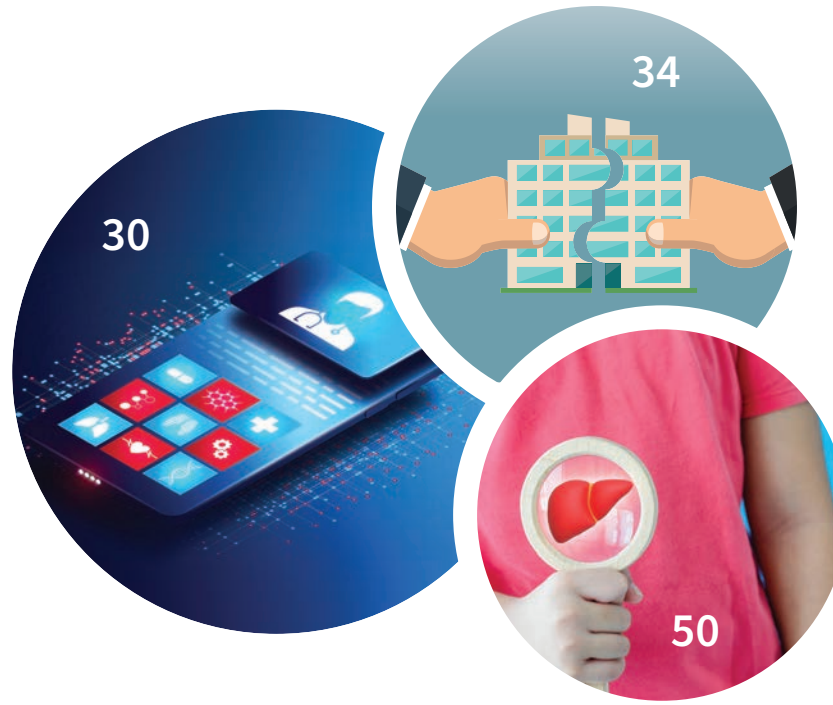

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Reconfiguring the Healthcare Landscape

THE NEED to provide high-quality, personalized care in the U.S. has never been greater due to an aging population with changing needs, the increasingly common occurrence of chronic disorders and digitization. All of these things amid the further stressing of the healthcare system caused by the COVID-19 pandemic are reconfiguring the way services are delivered.

Precision medicine, also known as personalized healthcare, dates back to 2004 with the launch of the Personalized Medicine Coalition that brought together innovators, scientists, patients, providers and payers to promote "the understanding and adoption of personalized medicine concepts, services and products to benefit patients and health systems." Today, many milestones have been achieved in the field of personalized medicine. We provide an overview of these in our article "Personalized Healthcare" (p.24), including the human genome research programs developed by the National Institutes of Health and genetic tests developed by researchers at the U.S. Food and Drug Administration. Yet, while the role of personalized medicine is still relatively limited, it is hoped that it will soon expand to achieve the goal of matching the right treatments at the right dosages for individual patients at the right time.

What could possibly be considered a form of personalized healthcare is the growing field of digital technology, specifically digital therapeutics (DTx), which are evidence-based therapeutic interventions driven by software to prevent, manage or treat medical disorders or diseases. As we explain in our article "Digital Therapeutics: The Next Frontier" (p.30), while DTx don't replace healthcare providers, these prescription-based products and services encourage collaboration between providers and patients, allowing providers to adjust patient treatments, medication doses and other needs according to the information gathered from the DTx, and providing patients more control over their care. As the field of DTx continues to grow, they will provide doctors more information, efficiency and efficacy, and patients with more independence, privacy and comfort.

Still, even with better testing and technologies, the effects of the COVID-19 pandemic have left a heavy strain on the healthcare industry with rising costs, provider burnout and increased patient expectations. One result of this has been healthcare consolidation, with a surge in mergers this year alone. But, whether consolidation is good or bad for the healthcare industry is a matter of debate, as we highlight in our article "Pros and Cons of Healthcare Consolidation" (p.34). Proponents claim consolidation provides access to quality patient care at an affordable price with more efficient, reliable organizations. Opponents, however, claim it hurts patients because of decreased competition that raises the cost of care, decreased access to and quality of care, workforce inefficiencies and movement away from facilities' missions. Which side is correct remains to be seen.

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

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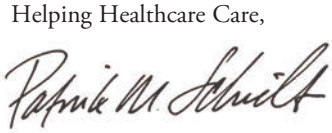

Patrick M. Schmidt
Publisher

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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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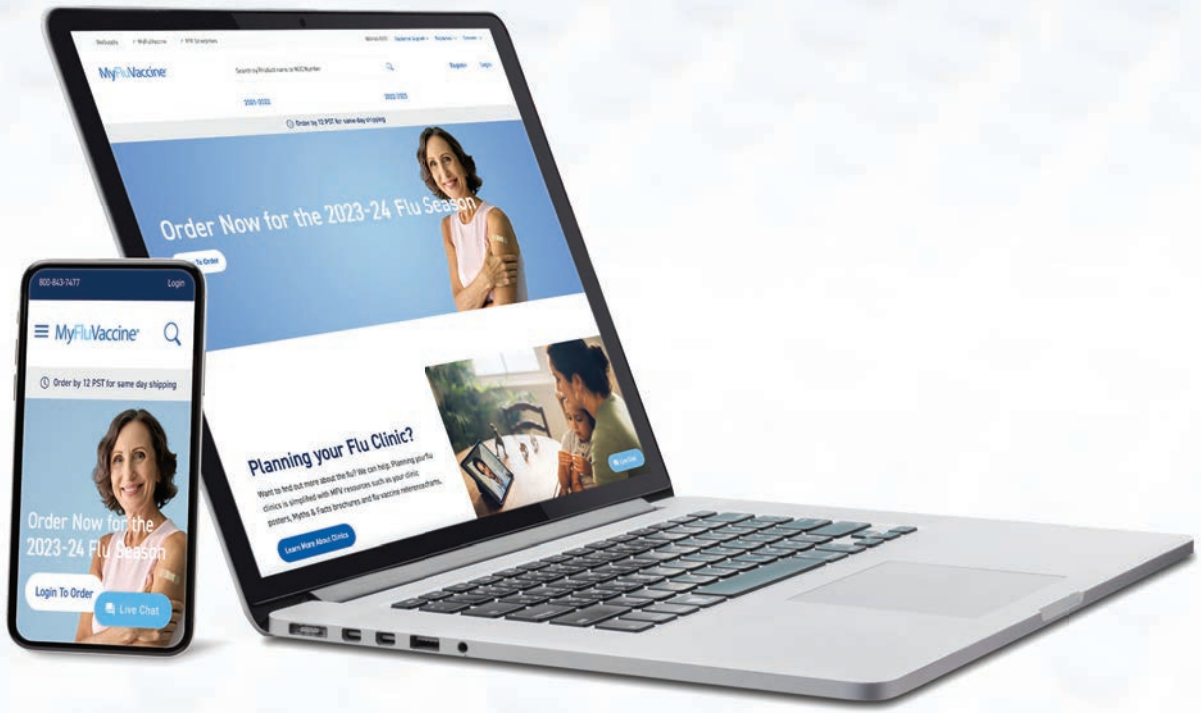

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Medicare Dementia Care Model Is Established by HHS

The Guiding an Improved Dementia Experience (GUIDE) Model, which aims to improve the quality of life for people living with dementia, reduce strain on unpaid caregivers, and help people remain in their homes and communities through a package of care coordination and management, caregiver education and support, and respite services has been established by the U.S. Department of Health and Human Services.

Through the GUIDE Model, the Centers for Medicare and Medicaid Services (CMS) will test an alternative payment for participants who deliver key supportive services to people with dementia, including comprehensive, person-centered assessments and care plans, care coordination and 24/7 access to a support line. Under the model, people with dementia and their caregivers will have access to a care navigator who will help them access services and supports, including clinical services and nonclinical services such as meals and transportation through community-based organizations.

The model is also designed to enhance access to the assistance and resources caregivers need. Evidence-based models of support for caregivers of people with dementia and dementia-capable community-based providers have been expanded over the last decade through investments in research and services by HHS and others. The model will provide a link between the clinical healthcare system and community-based providers to help people with dementia and their caregivers access education and support such as training programs on best practices for caring for a loved one living with dementia. Model participants will also help caregivers access respite services, which enable them to take temporary breaks from their caregiving responsibilities. Respite has been found to help caregivers continue to care for their loved ones at home, preventing or delaying the need for facility care.

"While we have made tremendous progress in improving care for people with dementia through the National Plan to Address Alzheimer's Disease, people living with dementia and their caregivers too often struggle to manage their healthcare and connect with key supports that can allow them to remain in their homes and communities. Fragmented care contributes to the mental and physical health strain of caring for someone with dementia, as well as the substantial financial burden," said CMS Administrator Chiquita Brooks-LaSure. "We know that Black, Hispanic and Asian Americans, Native Hawaiian and Pacific Islander populations have been particularly disadvantaged in receiving dementia care. The GUIDE Model will provide new resources and greater access to specialty dementia care in underserved populations and communities." ❖

Biden-Harris Administration Announces Medicare Dementia Care Model. U.S. Department of Health and Human Services press release, July 31, 2023. Accessed at www.hhs.gov/about/news/2023/07/31/biden-harris-administration-announces-medicare-dementia-care-model.html.

HHS Makes $25 Million Available to Expand Primary Care Services in Schools

Through the Health Resources and Services Administration (HRSA), the U.S. Department of Health and Human Services (HHS) has announced the availability of approximately $25 million to expand primary healthcare, including mental health services, in schools. For the first time, applicants will be required to add or expand mental health services to receive school-based funding. HRSA-funded health centers currently operate more than 3,400 school-based service sites in schools across the country.

School-based service sites provide convenient access to primary healthcare for children and adolescents. HRSA-funded health centers will use this funding to expand access to general primary medical and mental healthcare through both new school-based sites and expand existing sites. HRSA anticipates funding 70 awards.

The $25 million funding opportunity for health centers builds on the $30 million HRSA has awarded since September 2021 to increase access to health center services in schools. Further, it advances the department's shared commitment to expand school-based health services as outlined in their joint letter to governors. In addition, this funding is part of the ongoing effort to strengthen the nation's mental health. ❖

HHS Announces the Availability of $25 Million to Expand Primary Care — Including Mental Health — Services in Schools. U.S. Department of Health and Human Services press release, March 10, 2023. Accessed at www.hhs.gov/about/news/2023/03/10/hhs-announces-the-availability-of-25-million-dollars-to-expand-primary-care.html?utm_source=news-releases-email&utm_medium=email&utm_campaign=march-12-2023.

$147 Million Awarded to Help End the HIV Epidemic in the U.S.

The U.S. Department of Health and Human Services (HHS) has awarded more than $147 million to 49 recipients to advance the Ending the HIV Epidemic in the U.S. (EHE) initiative, which is part of ongoing efforts to reduce the number of new HIV infections in the United States by at least 90 percent by 2030. This funding will help states and metropolitan areas with the highest levels of HIV transmission link people with HIV to essential care, support and treatment, as well as support training and other resources for these jurisdictions.

The awards include:

- Nearly $139.1 million to metropolitan areas and states to implement strategies and interventions to provide medical and support services to reduce new HIV infections in the U.S.
- $8 million to two nonprofit organizations to provide training and other resources to recipients of EHE funds.

The EHE initiative focuses on four key strategies:

- Diagnose all people with HIV as early as possible.
- Treat people with HIV rapidly and effectively to reach sustained viral suppression.
- Prevent new HIV transmissions by using proven interventions.
- Respond quickly to potential HIV outbreaks.

These strategies build on the continued success of the Ryan White HIV/AIDS Program, which supports medical care, medications and other essential support services to help more than 576,000 people stay in care. Nearly 90 percent of Ryan White clients who receive care reach viral suppression, meaning they cannot transmit HIV and can also live healthier lives. This rate exceeds the national viral suppression average of 64.6 percent.

"Ending the HIV epidemic requires us to reach people living with the virus where they are, and that's exactly what this program allows us to do," said HHS Secretary Xavier Becerra. "Through this program and others, we will continue our work to destigmatize this deadly disease and ensure equitable access to testing and treatment." ❖

HHS Awards $147 Million to Support Ending the HIV Epidemic in the United States. U.S. Department of Health and Human Services press release, April 27, 2023. Accessed at www.hhs.gov/about/news/2023/04/27/hhs-awards-147-million-support-ending-hiv-epidemic-united-states.html?utm_source=news-releases-email&utm_medium=email&utm_campaign=april-30-2023.

HHS Forms the Office of Long COVID Research and Practice and Launch of Long COVID Clinical Trials

The U.S. Department of Health and Human Services (HHS) has founded the Office of Long COVID Research and Practice to lead the Long COVID response and coordination across the federal government. In addition, the National Institutes of Health (NIH) launched Long COVID clinical trials through the RECOVER Initiative.

The Office of Long COVID Research and Practice will be located within HHS's Office of the Assistant Secretary for Health under the leadership of the HHS Assistant Secretary for Health Admiral Rachel Levine, MD. The office is charged with ongoing coordination of the whole-of-government response to the longer-term effects of COVID-19, including Long COVID and associated conditions and the implementation of the National Research Action Plan on Long COVID. Currently, 14 federal departments engage on Long COVID, including more than a dozen HHS operating and staff divisions with a goal to reduce the impacts of Long COVID by improving quality of life for people living with Long COVID and reducing disparities related to Long COVID.

The NIH RECOVER Initiative is a $1.15 billion nationwide research program designed to understand, treat and prevent Long COVID, which describes long-term symptoms following infection by SARS-CoV-2, the virus that causes COVID-19. More than 200 symptoms are associated with Long COVID, and the condition can cause problems throughout the body, affecting nearly all body systems, including the nervous, cardiovascular, gastrointestinal, pulmonary, autonomic and immune systems.

"The Office of Long COVID Research and Practice will enhance efforts being

undertaken across the U.S. government to improve the lives of those who continue to experience the long-term impacts of the worst public health crisis in a century," said Admiral Levine, "bringing together the resources and expertise of federal, state and local partners, patients, providers, researchers and the business sector to answer the American [people's] most urgent calls to action." ❖

HHS Announces the Formation of the Office of Long COVID Research and Practice and Launch of Long COVID Clinical Trials Through the RECOVER Initiative. U.S. Department of Health and Human Services press release, July 31, 2023. Accessed at www.hhs.gov/about/news/2023/07/31/hhs-announces-formation-office-long-covid-research-practice-launch-long-covid-clinical-trials-through-recover-initiative.html.

2024 OPPS, ASC and PFS Proposed Payments

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

THE PROPOSED calendar year 2024 Outpatient Prospective Payment System (OPPS), Ambulatory Surgery Center (ASC) and Physician Fee Schedule (PFS) payment rule sets are being finalized to begin Jan. 1, 2024. Their scope covers healthcare in all outpatient settings, including ASCs and physician offices, allowing for shifts among various sites of care to best meet patients' needs and achieve cost savings that are critical with costs rapidly spiraling to new heights. Inpatient healthcare in a variety of settings is covered by its own payment rules, which follow a fiscal year beginning Oct. 1, 2023.

Several other pieces of legislation are being debated that will also significantly impact practices' revenue streams, operations and clinical services. Common prevailing themes include prior authorizations, pharmacy benefit managers (PBMs), transparency and site-of-care changes, among others.

Equity and quality are major factors used to determine payment rates. These rules update and refine the requirements for the hospital Outpatient Quality Reporting, ASC Quality Reporting and Rural Emergency Hospital Quality Reporting programs. They also establish payment for certain intensive outpatient services under Medicare beginning Jan. 1, 2024, and update and refine requirements for hospitals to make public their standard charge information and enforcement of hospital price transparency.

2024 Proposed Payment Rule Sets

Small molecule drugs and biologicals. Small molecule drugs and biologicals are paid for in one of four ways: new drugs not yet assigned unique healthcare common procedure coding system (HCPCS) codes; new pass-through drugs; non-pass-through, separately payable drugs less than $140 per day based on average sales price (ASP); and policy packaged or lower-cost packaged products costing equal or less than $140 per day based on ASP (Table).

Three-year transitional pass-through payment period for all pass-through drugs, biologicals and radiopharmaceuticals and quarterly expiration of pass-through status. The pass-through payment provision requires additional payment under Part B for current orphan drugs, current drugs and biologicals and brachytherapy sources used in cancer therapy, and current radiopharmaceutical drugs and biologicals. For at least two years, they also are provided for certain "new" drugs and biologicals whose cost is "not insignificant" in relation to OPPS payments for the procedures or services associated with the new drug or biological. For pass-through payment purposes, radiopharmaceuticals are included as "drugs."

Non-opioid pain management in ASC settings. Four drugs will receive separate payment at ASP+6%. These include HCPCS codes C9290 (injection, bupivacaine liposome, 1 mg); J1096 (dexamethasone, lacrimal ophthalmic insert, 0.1 mg); J1097 (phenylephrine 10.16 mg/ml and ketorolac 2.88 mg/ml ophthalmic irrigation solution, 1 ml); and C9089 (bupivacaine, collagen-matrix implant, 1 mg).

Note: HCPCS C9144 (injection, bupivacaine [posimir], 1mg) will have transitional pass-through payment, making it separately payable in both the OPPS and ASC setting.

Proposed remedy to 340B ruling. The Centers for Medicare and Medicaid Services (CMS) is proposing to make a one-time lump-sum payment to each 340B-covered hospital that was paid less due to the now-invalidated policy for 2018 through 2022. The proposed one-time payment to hospitals involves:

1) A one-time $9 billion lump sum budget neutral payment (includes beneficiary co-payment amounts) divided among 1,649 covered entities impacted by reimbursement cuts. Claims won't be reprocessed. Through their Medicare administrative contractors, hospitals will be remitted the calculated difference between paid ASP-22.5% rates and ASP+6% rates. Methods for disputing CMS-determined amounts owed aren't included.

2) Budget neutrality will cut non-drug services reimbursement by 0.5 percent over 16 years.

3) Hospitals enrolled in Medicare after 2018 will be exempted from the proposed cuts to non-drug services reimbursement.

Additionally, the Senate issued a bipartisan request for information on the 340B Drug Pricing Program covering multiple areas, including Health Resources and Services Administration oversight, contract pharmacies, duplicate discounts and specific patient benefits.

PBM oversight. The Senate Finance Committee advanced legislation reigning in PBM abuses in the Medicare and Medicaid programs, consistent with American Society of Health System Pharmacists' recommendations. The Modernizing and Ensuring PBM

Table. 2024 OPPS Proposed Payment for Drugs and Biologicals ($5 Threshold Increase)

New drugs not yet assigned unique HCPCS codes	New pass-through drugs*	Non pass-through separately payable drugs >$140/day based on ASP	Policy packaged or lower-cost packaged products costing ≤$140/day based on ASP
	Status Indicator G	Status Indicator K	Status Indicator N
95 percent of average wholesale price may apply	On the bill as separate line items	On the bill as separate line items	Not on the bill as separate line items; paid as part of the service bundle
See Addendum B for specific payment	ASP+6% Policy packaged offsets may apply	ASP+6%	No change from 2023
	Payment based on wholesale acquisition cost (WAC)+3% until enough ASP data is gathered	Payment based on WAC+3% until enough ASP data is gathered	No separate reimbursement; drug costs are bundled into the procedure: 1) due to threshold price of $140/day or 2) due to statute -Contrast agents -Anesthesia drugs -Implantable biologicals -Diagnostic radiopharmaceuticals (CMS seeking input on possible changes) -Drugs, biologicals, radiopharmaceuticals used as supplies in a diagnostic test or procedure -Drugs, biologicals used as supplies or implantable devices in surgical procedures
	*All biosimilars eligible for pass-through, not just the first one for each reference product	Biosimilars excepted from the OPPS threshold packaging policy when their reference biologicals are separately paid. Pay separately for biosimilars even if per-day cost is < threshold packaging policy	

Accountability Act seeks to limit fees imposed on pharmacies, bring greater transparency to PBM practices, including those related to white bagging, and prohibit PBMs from spread pricing in Medicaid.

2024 PFS key proposed focus areas. Key 2024 PFS areas of focus include a $1.14 reduction in the 2024 conversion factor with a 1.25 percent decrease in overall proposed payment amounts compared with 2023, coupled with a proposed 2024 PFS conversion factor of $32.75 — a decrease of 3.34 percent, or $1.14, from 2023. However, CMS also proposed payment increases for some visit services such as primary care. Part B coverage in a physician office setting remains at ASP+6% by statute.

Telehealth services and practitioners. The proposed new rule will:

• Add health and well-being coaching services; continue to allow telehealth services in any geographic area and in any originating site, including the beneficiary's home; and allow certain services to be furnished via audio-only telecommunications.

• Add new telehealth Medicare-eligible qualified practitioners, including occupational therapists, physical therapists and speech-language pathologists. Pharmacists currently aren't included.

• Extend the flexibility of allowing institutional providers to bill for diabetes self-management training, outpatient therapy and medical nutrition therapy when provided remotely, and virtual supervision flexibility through 2024.

• Allow diabetes prevention programs to continue to provide services remotely if providers maintain an in-person Centers for Disease Control and Prevention organization code through 20267.

Opioid treatment programs. The proposed rule extends flexibilities for audio-only telecommunications

providing periodic assessments "when video is not available to the beneficiary, to the extent that use of audio-only communications technology is permitted under the applicable (Substance Abuse and Mental Health Services Administration) and (Drug Enforcement Administration) requirements at the time service is furnished and all other applicable requirements are met."

Vaccine provision and reimbursement. The proposed rule extends additional add-on payment for in-home vaccination for COVID-19 and pneumococcal, influenza and hepatitis B vaccines when provided in a beneficiary's home. The one-time add-on payment applies even if multiple vaccines are provided. Vaccine administration payment applies for each vaccine given.

Evaluation and management coding. A new separate add-on code for G2211 will recognize costs associated with evaluation and management visits for primary and longitudinal care with complex patients, billed with a modifier to denote an office or outpatient visit unbundled from another service. Current split/shared billing practices will be continued to give clinicians a choice of using history, physical exam, medical decision-making or time to determine who bills for the visit.

Complex drug administration coding. CMS is seeking stakeholder feedback on coding and payment policies for complex, non-chemotherapeutic drugs to "promote coding and payment consistency and patient access to infusion services" for certain Part B drugs that are usually self-administered.

Manufacturer refunds for medication waste. The new rule will implement a provision of the Infrastructure and Investment Jobs Act of 2021 requiring "manufacturers to provide a refund to CMS for certain discarded amounts from a refundable single-dose container or single-use package drug" once the amount of waste reaches a certain threshold of a product's total allowed charges (at least 10 percent) in a quarter.

Additional policies include timelines for the initial and subsequent discarded drug refund reports to manufacturers; the method of calculating refunds for discarded amounts from lagged claims data; the method of calculating refunds when there are multiple manufacturers for a refundable drug; increased applicable percentages for certain drugs with unique circumstances; and an application process by which manufacturers may request an increased applicable percentage for a drug with unique circumstances.

Site-of-care neutral reimbursement. The House Ways and Means Committee advanced HR 4822, the Health Care Price Transparency Act of 2023. Among other provisions, the bill requires off-campus outpatient hospital departments to use separate and unique provider identifiers for billing Medicare and be reimbursed for clinician-administered drugs at the same level as the Medicare physician fee schedule. Allowances for a phase-in apply to health professional shortage areas, rural areas and cancer hospitals.

Proposed Medicare payment for intensive outpatient programs. This new concept would establish payment for intensive outpatient programs (IOPs) under Medicare with defined scope of benefits, physician certification requirements, coding and billing, and payment rates under the IOP benefit. The IOP services may be furnished in hospital outpatient departments, community mental health centers, federally qualified health centers and rural health clinics. It also establishes payment for intensive outpatient services provided by opioid treatment programs (OTPs) under the existing OTP benefit.

Request for public comments for establishing and maintaining access to essential medicines. CMS is seeking comment on separate payment under the Integrated Personnel Payment System (IPPS) for establishing and maintaining access to a three-month buffer stock of essential medicines to foster a more reliable, resilient supply of these medicines. Based on the review of comments received, this could be finalized early for cost-reporting to CMS beginning on or after Jan. 1, 2024, with an OPPS adjustment considered for future years. The essential medicines include the 86 products on the Administration for Strategic Preparedness and Response list in its Essential Medicines Supply Chain and Manufacturing Resilience Assessment. Possible buffer supply payment could be based on the "IPPS shares of the additional reasonable costs of a hospital to establish and maintain access to its buffer stock." Reasonable costs could include "costs to hold essential medicines directly at the hospital, arrange contractually for a distributor to hold, or arrange contractually with a wholesaler for a manufacturer to hold" the stock, but won't include medication costs. ❖

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

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Utilizing Virtual Services and Workforces

The future of healthcare is here. Identifying new tools that will best serve both employees and patients — and learning how to use them efficiently — is critical for moving forward.

By Amy Scanlin, MS

TECHNOLOGY IS moving fast, increasing business opportunities and efficiencies by enabling hybrid work environments and outsourcing virtual workforces. Considered a major pivot in healthcare just a few years ago, 76 percent of hospitals now connect digitally through video teleconferencing or other technologies,[1] normalizing what was, pre-pandemic, nearly unchartered territory.

Today, virtual workforces fill critical healthcare needs, and sometimes, despite the infrastructure costs, do so more efficiently and cost effectively than on-site employees. But, setting up successful virtual workforces comes with a unique set of challenges, one of which is establishing and maintaining workflow cohesiveness when the team is geographically scattered. Other challenges include validating that training is not only completed but learning objectives are also met; meeting the immense, non-negotiable demands of IT infrastructure; and measuring the effectiveness of these collective efforts as they work in tandem.

Traditional in-house workforces are a thing of the past. Reimagining the team to adapt to the opportunities and demands of a virtual environment and equipping them to do so is critical to long-term success.

Reimagine the Team

These days, people can work from just about anywhere. Surgeons perform operations via robots; providers meet patients on computer screens; and much of the support staff can just as easily perform their tasks from a home office as a cubicle. Services such as scheduling, billing, marketing and training can all be transitioned to a virtual environment. The flexibility this affords can be a real benefit to businesses since it allows for attracting the best talent available anywhere, not just the best talent available locally.

But, virtual work environments also present cohesiveness challenges because team building can't happen as organically online. There is also the question of productivity and trust with remote workers — trust on the part of the manager and trust on the part of the employee(s). That trust can be harder to earn in a virtual environment. Therefore, expectations on both sides of the aisle must be clearly articulated, provided in writing and signed by all parties, including the evaluation process.

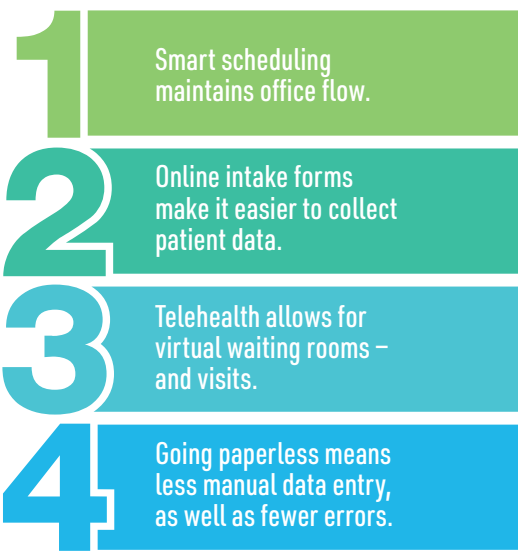
Retool the Training

Training can be done just about anywhere, too. Numerous online employee training services cover HIPAA, CPR and more, making outsourcing training to a virtual environment easy. In fact, third-party vendors can create customized training that includes verification of learning assessments and enables remedial and refresher trainings as needed. Some companies' employee training may already be outsourced, but other opportunities might be available.

And, it's not just employees who need training: Patients using web-based applications may need help learning how to navigate new patient portals or e-communications. Therefore, facility managers should consider implementing patient training for tasks such as how to access electronic health records, how to schedule an appointment online or how to join an online appointment.

Regardless of how much or how little work is outsourced, training should always include an optional human component. When questions are raised or extra hand-holding is needed, it is important to remember that different learning styles require different interventions. As effective as outsourced training is, for some, the personal touch is sometimes most effective.

4 Ways Telehealth Technology Improves Clinical Workflow



Source: Curogram. How Telehealth Technology Improves Clinical Workflow. Accessed at blog.curogram.com/how-telehealth-technology-improves-clinical-workflow.

Consider IT and Cyber Concerns

Cyber risks are receiving much well-deserved attention, particularly as

healthcare is increasingly under attack. Network security threats are everywhere, from legitimate looking but nefarious emails from a familiar company or person to text messages with embedded code that take hold of the device used to access network files. The manner in which data is collected, managed, stored and secured is as vitally important as the accessibility and interoperability of that data. As workforces move outside the physical walls of an organization, the challenges of keeping networks safe increases exponentially.

When deciding to expand virtual operations, facility managers should consider utilizing data governance, virtual private networks, multi-factor authentication, third-party vendor agreements and employee policies that clearly define acceptable and unacceptable use of company equipment. Outsourcing digital security services to third-party vendors with the specific expertise needed to set up systems and protect them from dangers such as malware and ransomware can help bolster an already stretched IT department while ensuring essential workflows remain uninterrupted.

Prioritize Patients

Even before the pandemic, it was widely thought that the traditional model of healthcare was unsustainable. With too many patients and too few providers, new care alternatives such as those found in big box stores or community care centers were filling gaps with great success. Post-pandemic, the challenges of healthcare have continued. Patients attempting to return to the exam table have been met with exacerbated capacity challenges due to provider burnout after a tremendously difficult few years.

But patients still need access to care. Think about utilizing new models that can help offset demand versus supply: Telemedicine and remote patient monitoring are emerging as great options. Virtual appointments between patients and providers are convenient for patients, and they save time and money. Wearables (digital medical devices such as electrocardiogram monitors, blood pressure monitors, pulse oximeters and more) with real-time remote patient monitoring send reports to a third-party, specialized team. These new models of care can be beneficial for both providers and patients, saving time and lowering costs. In fact, patients can be seen more quickly, and telehealth care can cost less than in-person care.[2]

While these time and cost savings seem like a win, it takes digital literacy and interest on the part of staff and patients, as well as broadband access for these tools to be effective. Staying on top of licensing requirements if choosing to offer telemedicine to those out of state, regulatory and insurance requirements, as well as coding and billing to ensure proper payment for telemedicine and remote patient monitoring are necessary parts of doing business.

Evaluate Metrics

Even the best-laid plans must ensure evaluation tools accurately measure accountability, connectivity and effectiveness. Whether training current workforces in a new virtual world or asking on-site staff to operate daily tasks alongside a virtual team, it should be ensured that patient and employee satisfaction are not diminished by efforts to increase efficiencies. This can be accomplished by a detailed look at data trends.

Patient and employee surveys should include objective questions such as the software's ease of use, as well as unbiased, real-time analytics measuring trends such as how many patients actually choose to seek virtual care options or whether doctor-prescribed patient wearables are performing, etc. While there are measurements for just about everything under the sun, use caution when deciding what data to collect, both from a legality standpoint, as well as information overload. Also, always remember that for many patients, data can't replace the personal connection of partnering with a provider to manage their health.

Careful Planning Is Key

Planning is crucial. Some effective, in-person workflows may be less effective when transitioned to a virtual environment. Take time to consider which important business elements and functions might best translate to a virtual world — and how they might adapt to a virtual environment — before jumping into one.

Still, telemedicine and virtual workforces are here to stay, with some expectations that this $87.8 billion dollar industry will grow to $285.7 billion by 2027.[3] But with this upward trend also come challenges that must be met head-on for success. Careful planning for the hows and whys of this newly envisioned virtual work environment, as well as employing the tools to make this vision a reality, are just the start. With the help of outsourced expertise, virtual services and workforces may provide healthcare operations the efficiencies needed to advance further into the digital age. ❖

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3. McBride, A. How Virtual and In-person Care Merge for a Healthier, Sustainable Future. Ernst and Young, Jan. 24, 2023. Accessed at www.ey.com/en_gl/health/how-virtual-and-in-person-care-merge-for-a-healthier-and-more-sustainable-future.

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

Medicines

FDA Approves Pfizer's ABRYSVO Vaccine for the Prevention of RSV

Pfizer's ABRYSVO, a respiratory syncytial virus vaccine, has been approved by the U.S. Food and Drug Administration (FDA) for the prevention of lower respiratory tract disease (LRTD) and severe LRTD caused by RSV in infants from birth up to 6 months of age by active immunization of pregnant women at 32 through 36 weeks gestational age. ABRYSVO is unadjuvanted and composed of two preF proteins selected to optimize protection against RSV A and B strains and was observed to be safe and effective.

The approval was based on the data from the pivotal Phase III clinical trial (NCT04424316) MATISSE (MATernal Immunization Study for Safety and Efficacy), a randomized, double-blinded, placebo-controlled study designed to evaluate the efficacy, safety and immunogenicity of the vaccine against LRTD and severe LRTD due to RSV in infants born to healthy women vaccinated during pregnancy.

"ABRYSVO's approval as the first and only maternal immunization to help protect newborns immediately at birth through 6 months from RSV marks a significant milestone for the scientific community and for public health," said Annaliesa Anderson, PhD, senior vice president and chief scientific officer of vaccine research and development at Pfizer. "We are incredibly grateful to the clinical trial participants and study investigator teams around the world, as well as our Pfizer colleagues, for their commitment to making this vaccine available. Today, a long-sought-after goal to deliver a maternal vaccine that will help protect infants 6 months of age or younger — when they are at greatest risk of possible serious consequences from RSV — has been achieved."

In May, FDA approved ABRYSVO for the prevention of LRTD caused by RSV in individuals 60 years and older. That decision was based on data from the pivotal Phase III clinical trial, RENOIR (RSV vaccine Efficacy study iNOlder adults Immunized against RSV disease), a global, randomized, double-blind, placebo-controlled study designed to assess the efficacy, immunogenicity and safety of a single dose of the vaccine in adults 60 years of age and older. RENOIR has enrolled approximately 37,000 participants, randomized to receive RSVpreF 120 µg or placebo in a 1:1 ratio. Results showed positive top-line results when co-administered with seasonal inactivated influenza vaccine in adults 65 years and older.

Pfizer has initiated two additional clinical trials evaluating ABRYSVO. One trial is being conducted in children at higher risk for RSV disease ages 2 year to less than 18 years. A second trial is evaluating adults ages 18 to 60 at higher risk for RSV due to underlying medical conditions such as asthma, diabetes and chronic obstructive pulmonary disease, and adults ages 18 and older who are immunocompromised and at high-risk for RSV. Pfizer also plans postmarketing studies and surveillance programs to further describe the safety of the vaccine. ❖

U.S. FDA Approves ABRYSVO, Pfizer's Vaccine for the Prevention of Respiratory Syncytial Virus (RSV) in Infants Through Active Immunization of Pregnant Individuals 32-36 Weeks of Gestational Age. Pfizer press release, Aug. 21, 2023. Accessed at www.pfizer.com/news/press-release/press-release-detail/us-fda-approves-abrysvotm-pfizers-vaccine-prevention-0.

U.S. FDA Approves ABRYSVO, Pfizer's Vaccine for the Prevention of Respiratory Syncytial Virus (RSV) in Older Adults. Pfizer press release, May 31, 2023. Accessed at www.pfizer.com/news/press-release/press-release-detail/us-fda-approves-abrysvotm-pfizers-vaccine-prevention.

Medicines

First Over-the-Counter Contraceptive Pill Gets FDA Approval

The U.S. Food and Drug Administration (FDA) has approved the birth control pill Opill (norgestrel), manufactured by Perrigo, to be available over-the-counter — the first nonprescription birth control pill in the United States. The pill needs to be taken at the same time every day for it to be effective. Opill is expected to be available over-the-counter in stores by the end of March 2024.

"Today's approval is a groundbreaking expansion for women's health in the U.S., and a significant milestone toward addressing a key unmet need for contraceptive access," said Frederique Welgryn, Perrigo global vice president for women's health. ❖

Hassan, C. FDA Approves First Over-the-Counter Birth Control Pill. CNN Health, July 13, 2023. Accessed at www.cnn.com/2023/07/13/health/fda-otc-birth-control-opill.

Research

Study Finds Adult Vaccines Potentially Protect Against Alzheimer's

A new study conducted at the University of Texas Health Science Center at Houston found that people who received shingles and pneumonia vaccines — along with tetanus and diphtheria — had as much as a 30 percent reduced risk of developing Alzheimer's, the most common type of dementia. It also found patients who received the pneumococcal vaccine — which protects against the bacteria that can lead to pneumonia, meningitis and sepsis — demonstrated a 27 percent lower chance of having an Alzheimer's diagnosis. Further, it found the shingles vaccine was linked to a 25 percent reduced risk.

The researchers followed patients who were at least 65 years old at the start of the eight-year study period who did not have dementia in the prior two years. They then compared groups of vaccinated and unvaccinated patients for each of the vaccines, looking at the occurrence of Alzheimer's diagnoses. Prior to this study, the same research team published another study that showed people who got at least one influenza vaccine showed a 40 percent lower rate of Alzheimer's than their unvaccinated peers. "We were wondering whether the influenza finding was specific to the flu vaccine," said senior author Paul E. Schulz, MD, the Umphrey family professor in neurodegenerative diseases and director of the Neurocognitive Disorders Center at McGovern Medical School. "This data revealed that several additional adult vaccines were also associated with a reduction in the risk of Alzheimer's." ❖

Rudy, M. These Adult Vaccines Could Reduce Seniors' Risk of Alzheimer's, Study Finds: 'Heightened Immune Response.' Fox News, Aug. 21, 2023. Accessed at www.foxnews.com/health/these-adult-vaccines-could-reduce-seniors-risk-alzheimers-study-finds-heightened-immune-response.

Research

IVIG May Improve Neurological Symptoms in MIS-C

Recent case series findings, as well as previous studies, show that children with multisystem inflammatory syndrome (MIS-C) who present with signs of acute neurological symptoms may show improvement with intravenous immune globulin (IVIG) and corticosteroids.

In the recent case series findings, 12 children were diagnosed with acute neurological symptoms and MIS-C in two hospitals in the Isfahan province in Iran between March 1, 2020, and Dec. 28, 2021. Diagnosis of MIS-C was made according to World Health Organization criteria and recommendations from the American College of Rheumatology, in addition to prior detection of SARS-CoV-2. The median age of the patients was 4.5 years, and three patients were aged 1 year or younger. Underlying diseases included chronic neurological disorders (neurodegenerative disease and seizure disorder), cardiac disease and malignancy. Immunodeficiency was not observed in any patient.

All patients were treated per the Iranian treatment protocol for children with MIS-C. Two patients were admitted to the intensive care unit during their hospitalization, and one patient experienced myocarditis and vegetation-like lesions in the endocardium. Eleven patients were ultimately discharged in good condition, and in four-week follow-ups, 10 of them showed no complaints. One patient suffered from short-term memory loss.

Notably, relapses of MIS-C occurred in two patients due to rapid tapering of corticosteroids at two weeks instead of the standard protocol of four to six weeks. One patient who suffered from cobalamin deficiency died after full recovery from acute neurological symptoms, attributed to irreversible shock due to cobalamin deficiency.

Based on their observations, the investigators said central nervous system involvement is a non-rare associating condition with MIS-C. Acute neurological symptoms are life-threatening, although the epidemiology, pathophysiology and prognosis of acute neurological symptoms in children with MIS-C are still unclear. Cerebrospinal fluid (CSF) analysis of the cases was almost insignificant. However, one case had pleocytosis in the CSF analysis, which has been noted previously in other patients with COVID-19. Importantly, however, lumbar puncture of cases was performed within 24 hours of admission, which may not be enough time for white blood cells to migrate to the CSF.

According to the investigators, limitations included 1) the retrospective nature of the study meant that investigations of patients were dissimilar and dependent on the current guidelines at the time, although neurologic evaluation was performed for all patients in the same way and 2) because MIS-C is a clinical diagnosis and diagnostic tests are lacking, it is not possible to distinguish between acute neurological symptoms as part of MIS-C and as a coincidence. Yet, despite these limitations and the remaining gaps in knowledge about MIS-C, the investigators concluded that immunomodulatory agents such as IVIG and corticosteroids can significantly improve patients' prognosis. ❖

Antrim, A. Case Studies Show IVIG May Improve Neurological Symptoms in Pediatric Multisystem Inflammatory Syndrome. Pharmacy Times, Aug. 23, 2023. Accessed at www.pharmacytimes.com/view/case-studies-show-ivig-may-improve-neurological-symptoms-in-pediatric-multisystem-inflammatory-syndrome.

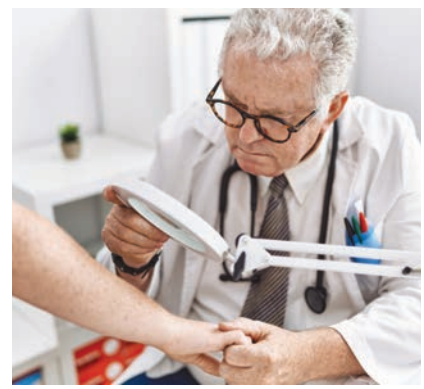
Research

Study Finds Immunotherapy Causes Chronic Side Effects

A recent study has found chronic immune-related side effects are common in patients with skin cancer who are treated with postsurgical Opdivo (nivolumab) or Keytruda (pembrolizumab), although for some individuals, these toxicities resolve by the 18-month mark.

In the study, researchers analyzed data from 318 patients who were treated with Opdivo or Keytruda after undergoing surgery for advanced or metastatic melanoma. Findings showed 147 patients (46.2 percent) experienced at least one chronic (lasting three months or longer) immune-related side effect. This included 74 grade 2 or higher side effects and six grade 3 through 5 (moderate, severe or fatal). All side effects were symptomatic. Common immunotherapy side effects that sometimes became chronic included adrenal insufficiency, arthritis or joint pain, skin inflammation, thyroid issues and colitis/diarrhea.

At a longer follow-up (average of 34.7 months), 54 patients (36.7 percent)



experienced resolution of their chronic side effects, with an average of 11.2 months between ending their immunotherapy treatment and having their toxicity resolve. For those still experiencing side effects at the long-term follow-up, 59.1 percent had grade 2 or higher side effects, while 44.1 percent were symptomatic and 25.8 percent were using therapeutic steroid treatment.

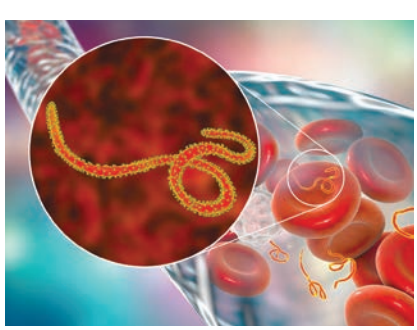
Among the 48 patients who experienced chronic side effects, 32.7 percent experienced disease recurrence, including 18 cases (12.2 percent) of regional recurrence and 30 (20.4 percent) of metastatic recurrence, meaning the cancer spread to another part of the body. Additionally, some patients (32.4 percent) experienced a flare of the toxicity when they were retreated with immunotherapy.

"(Immunotherapy drugs) targeting … PD-1/PD-L1 prolong recurrence-free survival when used as adjuvant therapy. … Anti–PD-1 also causes widespread T-cell activation and results in autoimmune side effects involving multiple organs, termed immune-related adverse events," the researchers wrote. "While most severe (immune-related adverse events) are acute and resolve with glucocorticoids, we recently reported that up to 43 percent of (immune-related adverse events) persist for at least 12 weeks following therapy cessation in patients with melanoma treated with adjuvant anti–PD-1." ❖

Benyon, B. Immunotherapy May Lead to Chronic Side Effects. Cure, Aug. 8, 2023. Accessed at www.curetoday.com/view/immunotherapy-may-lead-to-chronic-side-effects.

Medicines

Merck's Ebola Vaccine Approved for the Pediatric Population



An expanded indication for ERVEBO for the prevention of disease caused by Zaire ebolavirus in individuals 12 months of age and older has been approved by the U.S. Food and Drug Administration. The vaccine was previously approved for use in individuals 18 years of age and older.

ERVEBO does not protect against other species of Ebolavirus or Marburgvirus, and the duration of protection conferred by ERVEBO is unknown. The effectiveness of the vaccine when administered concurrently with antiviral medication, immune globulin and/or blood or plasma transfusions is unknown. ERVEBO includes a contraindication for individuals with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine, including rice protein.

"Ebola virus disease is contagious and potentially deadly in both children and adults. We're proud of the approval of ERVEBO for the prevention of disease caused by Zaire ebolavirus in children as young as 12 months old, which is another milestone in our continued commitment to help address the global health threat caused by Zaire ebolavirus," said Eliav Barr, MD, senior vice president, head of global clinical development and chief medical officer at Merck Research Laboratories. ❖

U.S. FDA Approves Merck's ERVEBO® (Ebola Zaire Vaccine, Live) for Use in Children 12 Months of Age and Older. Merck press release, Aug. 3, 2023. Accessed at www.merck.com/news/u-s-fda-approves-mercks-ervebo-ebola-zaire-vaccine-live-for-use-in-children-12-months-of-age-and-older/#:~:text=U.S.%20FDA%20Approves%20Merck%27s%20ERVEBO,Age%20and%20Older%20%2D%20Merck.com.

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Research

Immunotherapy May Treat ALS, Says Study

A study led by scientists at Oregon Health & Science University (OHSU) has found that a type of monoclonal antibody already tested in certain forms of cancer may be a promising treatment in stopping the progression of amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative disease. The study, which involved a mouse model and was confirmed in the tissue of human brains affected by ALS and donated after death, revealed for the first time that modulating immune cells can slow the progression of the disease.

The researchers used a monoclonal antibody targeting a5 integrin, which has already been developed and used in treating certain forms of cancer. Using postmortem tissue from 139 brains donated for research, scientists confirmed the presence of a5 integrin within areas of the brain associated with motor function. Specifically, they found a5 integrin expressed by microglial cells and macrophages in blood — cells associated with the immune system — to be highly pronounced in the spinal cord, motor cortex and peripheral nerves during ALS. They then tested the monoclonal antibody targeting a5 integrin in mice genetically predisposed to carry ALS and found that it protected motor function, delayed disease progression and increased mouse survival.

"When we blocked its expression in mice, we were able to slow down the disease," said senior author Bahareh Ajami, PhD, assistant professor of molecular microbiology and immunology and behavioral neuroscience in the OHSU School of Medicine. "We hope that it will get to the clinic very soon." However, Dr. Ajami added, "At this point, we cannot say it's a cure but it's a very interesting start. It may be similar to what immunotherapy did for cancer or will do for Alzheimer's by targeting immune cells." ❖

Robinson, E. Study Raises Possibility of Immunotherapy Treatment for ALS. Oregon Health & Science University, July 31, 2023. Accessed at news.ohsu.edu/2023/07/31/study-raises-possibility-of-immunotherapy-treatment-for-als.

Medicines

FDA Approves First Postpartum Depression Oral Treatment

The U.S. Food and Drug Administration has approved Zurzuvae (zuranolone), the first oral medication indicated to treat postpartum depression (PPD) in adults. PPD is a major depressive episode that typically occurs after childbirth but can also begin during the later stages of pregnancy. Until now, treatment for PPD was only available as an IV injection given by a healthcare provider in certain healthcare facilities.

The efficacy of Zurzuvae for the treatment of PPD in adults was demonstrated in two randomized, double-blind, placebo-controlled, multicenter studies. Trial participants were women with PPD who met the Diagnostic and Statistical Manual of Mental Disorders criteria for a major depressive episode and whose symptoms began in the third trimester or within four weeks of delivery. In the first study, patients received 50 mg of Zurzuvae or placebo once daily in the evening for 14 days. In the second study, patients received another zuranolone product that was approximately equal to 40 mg of Zurzuvae or placebo, also for 14 days. Patients in both studies were monitored for at least four weeks after the 14-day treatment. The primary endpoint of both studies was the change in depressive symptoms using the total score from the 17-item Hamilton depression rating scale (HAMD-17), measured at day 15. Patients in the Zurzuvae groups showed significantly more improvement in their symptoms compared to those in the placebo groups. The treatment effect was maintained at day 42 — four weeks after the last dose of Zurzuvae.

The most common side effects include drowsiness, dizziness, diarrhea, fatigue, nasopharyngitis (the common cold) and urinary tract infection. According to the labeling, use of Zurzuvae may cause suicidal thoughts and behavior and fetal harm. The daily recommended dose for Zurzuvae is 50 mg once daily for 14 days in the evening with a fatty meal.

"Postpartum depression is a serious and potentially life-threatening condition in which women experience sadness, guilt, worthlessness — even, in severe cases, thoughts of harming themselves or their child. And, because postpartum depression can disrupt the maternal-infant bond, it can also have consequences for the child's physical and emotional development," said Tiffany R. Farchione, MD, director of the Division of Psychiatry in the FDA's Center for Drug Evaluation and Research. "Having access to an oral medication will be a beneficial option for many of these women coping with extreme, and sometimes life-threatening, feelings." ❖

FDA Approves First Oral Treatment for Postpartum Depression. U.S. Food and Drug Administration news release, Aug. 4, 2023. Accessed at www.fda.gov/news-events/press-announcements/fda-approves-first-oral-treatment-postpartum-depression.

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Medicines

FDA Approves Antibody to Protect Infants Against RSV

The U.S. Food and Drug Administration (FDA) has approved nirsevimab to protect newborns from respiratory syncytial virus (RSV). The drug, which will be sold under the brand name Beyfortus, is a ready-made antibody that can bind to the virus and block it from infecting healthy cells. Rather than a vaccine that prompts the body to make antibodies to defend against pathogens, with nirsevimab, the immune system doesn't have to make anything. It's given as a single injection to an infant before RSV season, which usually peaks in the fall and winter months. The FDA approval also allows a second injection for infants up to 24 months of age who remain vulnerable through their second RSV season.

"RSV can cause serious disease in infants and some children and results in a large number of emergency department and physician office visits each year," said John Farley, MD, MPH, director of the Office of Infectious Diseases in the FDA's Center for Drug Evaluation and Research. "Today's approval addresses the great need for products to help reduce the impact of RSV disease on children, families and the healthcare system." ❖

Goodman, B. FDA Approves Antibody to Protect Infants from RSV. CNN Health, July 17, 2023. Accessed at www.cnn.com/2023/07/17/health/rsv-antibody-nirsevimab/index.html.

Medicines

New mRNA-Based Therapy Effective in Treating Melanoma in Mouse Models

Investigators at the Icahn School of Medicine at Mount Sinai have designed an RNA-based strategy to activate dendritic cells, which play a key role in immune response, that eradicated tumors and prevented their recurrence in mouse models of melanoma. The findings suggest that the approach has the potential to be effective against tumors that have already spread to other parts of the body and against different cancer types.

Cancer cells employ strategies to switch off various stages of the cancer-immunity cycle, the process by which dendritic cells educate T cells to kill cancer cells. This immunosuppressive environment that impedes activation of cancer-killing T cells allows tumors to grow. As part of the regimen, the researchers used new types of lipid nanoparticles to deliver two mRNA therapeutics to ensure the dendritic cells were sufficiently activated to enhance the cancer-immunity cycle in established tumors.

The researchers named their approach CATCH. Using multiple bioassays to gain insights on the effects of the CATCH regimen on different types of immune cells, the researchers showed their strategy not only reactivated the cycle but also removed obstacles at other stages. This caused a change in the tumor's microenvironment, shifting it from having cell types that weaken T cells' ability to fight cancer to having cell types that actually support and enhance their ability to fight tumors.

Beyond the positive findings in mouse models of melanoma, the researchers conducted further tests to evaluate the effectiveness of the CATCH regimen in restarting the cancer immunity cycle more broadly. Their investigations revealed encouraging results, as the regimen reduced tumors in mouse models of B cell lymphoma by 83 percent. They also tested it in mouse models of breast cancer, where approximately half of the mice favorably responded.

Next, the researchers plan feasibility and safety testing for using the CATCH regimen in early-phase clinical trials for patients.

"Dendritic cells have been a key focus for the development of new cancer therapies as these cells organize the cancer-immunity cycle. In theory, the CATCH regimen using this particular RNA-based technology has the potential to provide a much more effective approach for using dendritic cells for cancer immunotherapy to treat a wide range of solid tumors," said Brian Brown, PhD, director of the Icahn Genomics Institute and associate director of the Marc and Jennifer Lipschultz Precision Immunology Institute at Icahn Mount Sinai. ❖

New RNA-Based Therapy Combats Melanoma in Mouse Models. Mount Sinai School of Medicine news release, July 27, 2023. Accessed at www.eurekalert.org/news-releases/996545.

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KEDRION BIOPHARMA

Personalized Healthcare

Precise, personal treatment is the way of the future. Here's how experts are using genetic sequencing to forge a revolutionary new way of practicing medicine.

By Diane L.M. Cook

THE "ONE-SIZE-FITS-ALL" approach to healthcare might soon be a thing of the past. A novel approach called precision medicine is expected to usher in a new era of healthcare that is specifically tailored to a person's genes. The adoption of precision medicine will help save more lives from cancer, and in the future, from rare genetic diseases, chronic conditions and infectious diseases.

Precision medicine (which is used interchangeably with "personalized medicine") is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle for each person. This approach will allow doctors and researchers to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people.[1]

Precision medicine is being advanced through data from the Human Genome Project (HGP). Conducted between 1990 and 2003, the HGP generated the first sequence of the human genome. Then, the HGP sequenced all the DNA, which involved determining the exact order of the bases in DNA that improved the methods for DNA sequencing.[2]

The potential long-term benefits of research in precision medicine include:[1]

1) a wider ability of doctors to use patients' genetic and other molecular information as part of routine medical care;

2) an improved ability to predict which treatments will work best for specific patients;

3) a better understanding of the underlying mechanisms by which various diseases occur;

4) improved approaches to preventing, diagnosing and treating a wide range of diseases; and

5) better integration of electronic health records in patient care, which will allow doctors and researchers to access medical data more easily.

The U.S. Department of Health and Human Services and the private healthcare industry are working together to move the precision medicine field forward for the betterment of everyone's health.

Personalized Medicine Coalition — Plans, Studies and a Conference

Launched in 2004, the Personalized Medicine Coalition (PMC) represents innovators, scientists, patients, providers and payers, and promotes the understanding and adoption of personalized medicine concepts, services and products to benefit patients and health systems.

PMC explains that personalized medicine is an evolving field in which physicians use diagnostic tests to determine which medical treatments will work best for each patient or use medical interventions to alter molecular mechanisms that impact health. By combining data from diagnostic tests with individuals' medical histories, circumstances and values, healthcare providers can develop targeted treatment and prevention plans with their patients.

PMC President Edward Abrams says its Strategic Plan for Advancing Personalized Medicine in 2023 "arrives at a moment when the contention upon which PMC was founded — that a paradigm shift toward personalized medicine will not occur just because new tests and treatments have become available — is more evident than ever."

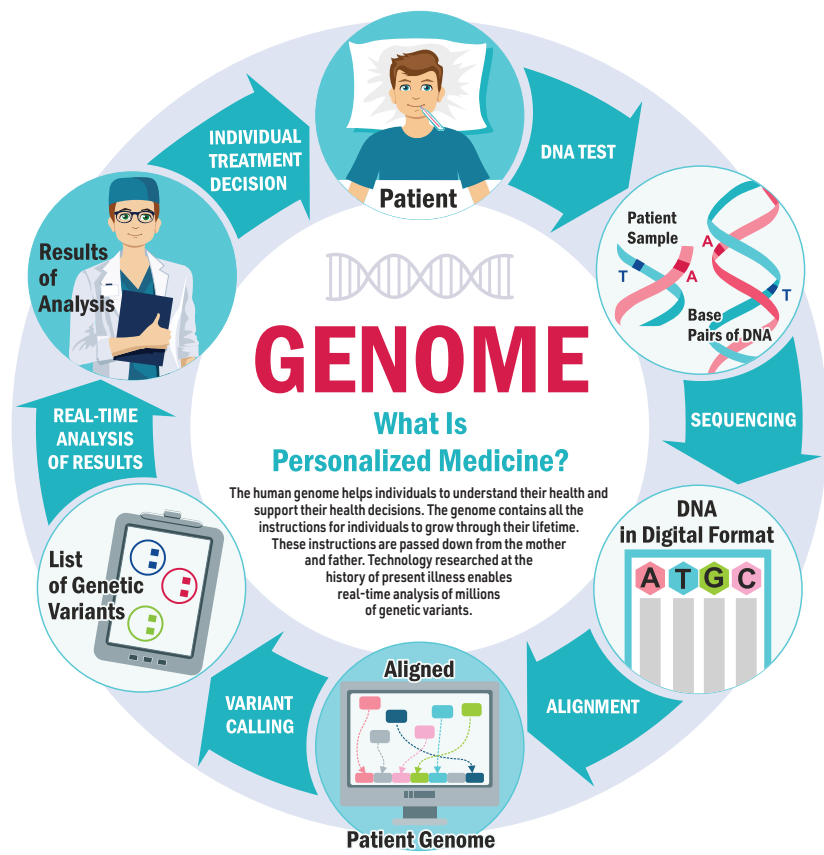
PMC research shows that due to the influence of testing and treatment difficulties occurring at each of seven steps in the precision oncology pathway, personalized medicine benefited only 36 percent of a cohort of 38,068 patients diagnosed in 2019 with advanced non-small cell lung cancer, a disease that presents major opportunities for a genetically personalized approach. According to PMC, with more than 100,000 genetic testing products and 300 personalized medicines now on the market, we know we can do better than this to help turn the tide against many of humanity's most dreadful biological foes.

In this context, PMC's three-part strategic plan explains what the coalition aspires to do in 2023 to increase investment in personalized medicine and help close the gap between what is possible and what is practiced in modern medicine.[3]

In 2022, PMC said the U.S. Food and Drug Administration (FDA) achieved many milestones in the field of personalized medicine. FDA approved 12 personalized medicines (therapeutic molecular entities); approved five new gene or cell-based therapies; cleared or approved new or expanded indications for 12 diagnostic testing systems; approved a new therapy to treat non-small cell lung cancers characterized by tumors with KRAS G12C genetic mutations; released a draft guidance document titled Human Gene Therapy Products Incorporating Human Genome Editing; and approved a new personalized therapy for a rare eye cancer.[4]

According to PMC's Strategic Plan for Advancing Personalized Medicine in 2023, the Coalition will explore the evolving value proposition of personalized medicine across multiple disease states. Member-facing communications will help decision-makers track and tackle key challenges facing personalized medicine. And, patient-facing educational initiatives will prompt more point-of-care conversations about molecularly targeted treatments and the ways in which various medical interventions may alter patients' lives.

PMC's advocacy efforts will continue



to address emerging questions about how and when to regulate, pay for and integrate the innovative diagnostics and treatments underpinning personalized medicine into health systems whose capacity is already stretched by efforts to develop and equitably deploy "one-size-fits-all" medical interventions.

And, PMC's research portfolio will continue to focus on generating evidence to support the clinical adoption of personalized medicine.[5]

According to PMC Senior Vice President of Public Affairs Chris Wells, "PMC's programs promise to help address the growing gap between what is possible and what is practiced in personalized medicine. By educating patients and providers about opportunities in personalized medicine, the PMC helps prompt conversations about it in clinical settings. By advocating for supportive public policies, the coalition helps to make it easier for business leaders and clinicians to develop and integrate the tests and treatments underpinning personalized medicine into clinical practices. And, by examining clinical integration opportunities and challenges, the PMC's research helps to direct the field's leaders toward the most pressing obstacles slowing the pace of progress in the field. All of this is designed to bring us one step closer to the day when every patient can benefit from the right prevention or treatment strategy at the right time."

PMC also plans to conduct three studies in 2023. The first study will evaluate progress in healthcare by studying payer policies and perspectives on personalized medicine and provide a landscape analysis of what they find. The second study will assess clinical and economic value of personalized medicine by studying the improvements in clinical care associated with personalized medicine. The third study will examine clinical integration strategies by addressing disparities in research advancing personalized medicine.[6]

And, on Nov. 30 and Dec. 1, 2023, PMC will hold its 17th annual personalized medicine conference. "By examining the opportunities and challenges facing the industries whose work drives progress in personalized medicine, this year's conference is designed to provide a comprehensive overview of the status and outlook for the field 20 years after scientists announced the completion of the Human Genome Project in 2003," says Wells.

NIH's CSER/IGNITE/SPARK/All of Us Research Program

The Clinical Sequencing Evidence-Generating Research (CSER) consortium, founded in 2010 by the National Institutes of Health (NIH), is rapidly advancing the knowledge necessary to develop best practices for the implementation of genomic sequence data into clinical care.

Anna Rogers, MA, a science writer with the NIH Office of Communications, says, "Currently, the second phase of CSER, which started in 2017, includes six clinical sites and the National Human Genome Research Institute Intramural ClinSeq Study Coordinating Center. An additional focus has been placed on clinical utility and the recruitment of ancestrally diverse and medically underserved populations. As of June 2022, CSER had recruited [fewer than] 5,200 participants, 75 percent of whom are from underserved populations."

The first phase of the Implementing Genomics in Practice (IGNITE) Pragmatic Trials Network (PTN), founded in 2013, is an NIH-funded network dedicated to supporting the implementation of genomics in healthcare and includes new genomic medicine studies.

The goal of the first phase of IGNITE was to expand the implementation of genomic medicine across different clinical settings and in diverse populations. These pragmatic clinical trials aimed to incorporate genomic information into electronic medical records and to provide clinical decision support for the implementation of appropriate interventions or clinical advice.

The second phase of IGNITE began in 2018. The PTN is comprised of five multi-site clinical groups and one coordinating center involving diverse settings and populations to conduct clinical trials of genomic medicine interventions.[7]

"IGNITE is currently conducting two large, network-wide, genomic medicine [pragmatic clinical trials (PCTs)], which will allow for bigger, more efficient clinical trials and help researchers and clinicians understand what to expect in real-world clinical settings. These PCTs are ADOPT-PGx, a depression and opioid trial in pharmacogenomics, and GUARDD-US, genetic testing to understand renal disease disparities," says Rogers.

The IGNITE Genomic Demonstration Projects incorporated genomic information into electronic medical records and provided clinical decision support for providers across diverse healthcare settings. The sites worked together to develop new methods and projects and disseminated their findings to the public.

One outlet for public distribution is the SPARK Toolbox, which provides genomic medicine resources for clinicians and researchers. Dissemination of these methods and developing best practices for implementation is a key goal so that the information generated from the program will contribute to the growing knowledge base of using genomic information in patient care.

Another NIH research program known as All of Us has a goal to invite more than one million diverse people from across

the United States to help build a database that can inform thousands of studies on a variety of health conditions. This creates more opportunities to 1) know the risk factors for certain diseases; 2) figure out which treatments work best for people of different backgrounds; 3) connect people with the right clinical studies for their needs; and 4) learn how technologies can help us take steps to be healthier. Researchers will use the data to learn how biology, lifestyle and environment affect health, which will help them find ways to treat and prevent disease.[8]

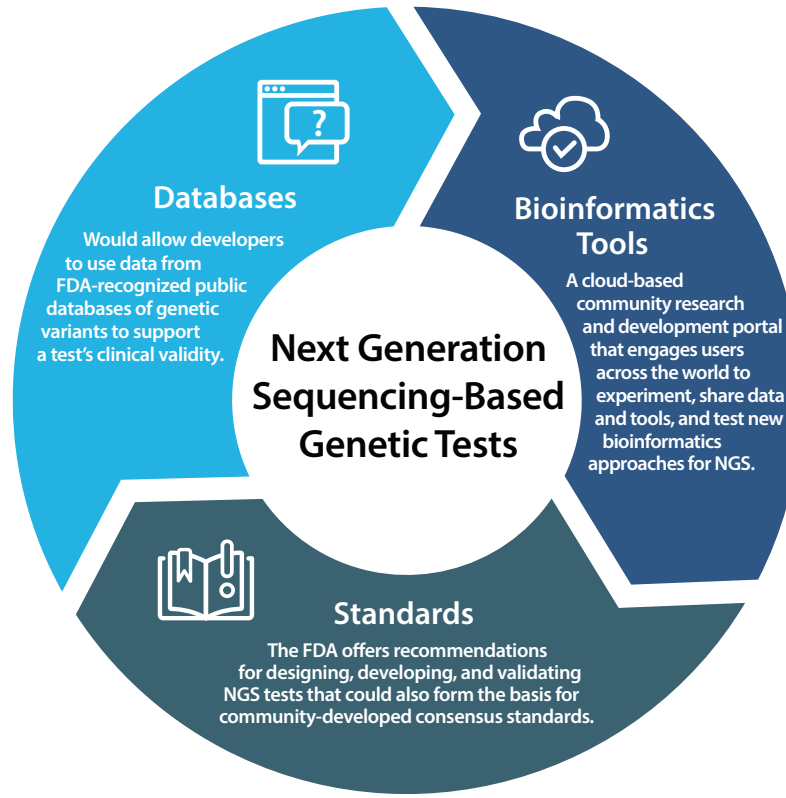
FDA's Next Generation Sequencing Tests and precisionFDA

FDA says the goal of precision medicine is to match the right treatments at the right dosages for individual patients at the right time. Precision medicine is generally comprised of two elements: One is the drug, biologic or other therapeutic intervention and the second is the diagnostic test. However, FDA says precision medicine will only be as good as the tests that guide diagnosis and treatment. The challenge of precision medicine is to identify the mechanistic basis for adverse events such as why the body reacts negatively to a treatment (such as breaking out in a rash) and differences in efficacy (why a drug works better in some patients than others).[9]

The agency's role in advancing precision medicine is to ensure the accuracy of Next Generation Sequencing (NGS) tests so patients and clinicians receive accurate and clinically meaningful test results. And, FDA's flexible regulatory approach to approving NGS tests will enable innovation in testing and research and speed access to accurate, reliable genetic tests.

NGS tests are capable of rapidly identifying or sequencing large sections of a person's genome and are important

Streamlining FDA's Regulatory Oversight of NGS Tests[11]



advances in the clinical applications of precision medicine. NGS can scan a person's DNA to detect genomic variations that might determine whether a person has or is at risk of disease or might help to inform treatment decisions.[10]

In 2018, FDA issued two final guidances that recommend approaches to streamline the submission and review of data supporting the clinical and analytical validity of NGS-based tests. The first guidance titled "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics" allows developers to use data from FDA-recognized public databases of genetic variants to help support a test's clinical validity, and the second titled "Considerations for Design, Development and Analytical Validation of Next Generation Sequencing-Based In Vitro Diagnostics Intended to Aid in the Diagnosis of Suspected Germline Diseases" offers recommendations for designing, developing and validating NGS tests.[11]

In addition to approving NGS tests and personalized medicines, in 2015, FDA created "precisionFDA," a public cloud-based portal for community research and development that allows users worldwide to share data and tools to test, pilot and validate existing and new bioinformatics approaches to NGS processing.

precisionFDA helps to drive critical precision medicine initiatives. It offers a variety of foundational capabilities, according to James McKinney, an FDA press officer, which include reference data, analysis apps and workflows; public and private workspaces; a community

discussion forum; the Global Substance Registration System; Common Data Model for Harmonization; and public challenges and app-a-thons. "Since the launch of FDA's Data Modernization Action Plan, precisionFDA capabilities have grown to provide data orchestration, transformation, cleansing, analytics and business intelligence in support of regulatory operations and for experiential training of FDA data scientists and data collaborators. precisionFDA now aligns with DMAP [Data Modernization Action Plan] goals to support a robust internal talent network, standardize data practices and use of artificial intelligence to improve efficiency and user experience."

Looking Forward

Although the term precision medicine is relatively new, NIH says the concept has been a part of healthcare for many years, and while examples [of precision medicine] can be found in several areas of medicine, its role in day-to-day healthcare is relatively limited. Researchers hope this approach will expand to many areas of health and healthcare in the coming years.

Precision medicine holds promise for improving many aspects of health and healthcare. Some of these benefits will be apparent soon as the All of Us research program continues and new tools and approaches for managing data are developed. However, other benefits will result from long-term research in precision medicine and may not be realized for years.[1] ❖

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Digital Therapeutics: **The Next Frontier**

This growing field of intervention-based therapeutics promises to enhance patient health and make healthcare more proactive.

By Meredith Whitmore

IT'S NOT SURPRISING healthcare professionals are unfamiliar with or confused by the rapidly evolving digital technologies employed in medicine today. Because of their current and future revolutionary impacts on healthcare, and their complicated, expansive components, professionals are likely overwhelmed by and unable to make sense of the tangle. Still, the field is growing exponentially, with no end in sight. Therefore, a quick overview of terms, categories and specific uses of each digital healthcare category might add clarity. And, although this article focuses specifically on digital therapeutics (DTx), a tech family tree is in order.

Distinctions Among Branches of Digital Healthcare

Fundamentally, there are three branches of digital technologies in healthcare: digital health, digital medicine and DTx (Table).

Digital health pertains to the field of evidence-based digital health tools that measure and/or intervene in the service of health to support practices of medicine broadly. This includes treatment, recovery, disease prevention and health promotion. Broadly put, digital technologies track health information.

Digital medicine deals with the development of interconnected health systems to improve the use of computational technologies, smart devices, computational analysis techniques and communication media to aid healthcare professionals and their clients manage illnesses and healthcare risks to improve health and well-being. In a nutshell, it tracks health information and collects or measures health data that can be used to manage a health condition.

DTx use digital and Internet-based technologies to encourage positive and necessary changes in patient behavior. These web- and design-based applications allow patients and providers to collaborate outside of a clinic or hospital. DTx products, prescribed by a healthcare provider, use the best possible software to offer evidence-based therapeutic interventions that can prevent, manage and treat a wide variety of physical, mental and behavioral conditions. DTx allow medical providers to track, collect, measure and interpret health data and make treatment changes based on real-time health information. In other words, DTx are a combination of each branch of digital technologies used in healthcare, making it the most well-rounded medical technological field.[1,2]

DTx are expected to benefit the development of medical products, including pharmaceuticals. Innovations in DTx such as electronic sensors, computing platforms and information technology offer opportunities for clinicians to collect clinical trial data directly from patients. Portable DTx are worn, implanted, swallowed or placed in an environment that allows data collection from patients who are at home or in otherwise remote locations apart from clinical settings.[3]

DTx use digital and Internet-based technologies to encourage positive and necessary changes in patient behavior.

Specific DTx Characteristics

Beyond identifying the branches of digital healthcare, there's also the task of precisely deciphering DTx characteristics. DTx are even more accurately identified by the following components:[4]

- They have been designed and produced using quality best practices.
- They engage end users in product development and usability processes.

Table. Digital Health, Digital Medicine and Digital Therapeutics: What's the Difference?

	Digital Health	Digital Medicine	Digital Therapeutics (DTx)
Relation	Includes digital medicine and DTx	Subset of digital health	Subset of digital medicine
Types of products	Different health-related products	Products to measure human health	Products to deliver therapeutic interventions
Clinical evidence	Not always required	Required	Required
Regulatory oversight	Not required	Requirements vary	Always required
Examples	• Electronic health record platforms • Health information portals	• Blood glucose sensors • Heart rate monitoring tools	• Behavior programs • Self-care programs

Source: Altexsoft. Digital Therapeutics: How Software Can Treat Diseases, Aug. 17, 2021. Accessed at www.altexsoft.com/blog/digital-therapeutics.

• They incorporate patient privacy and security protections.

• They apply product deployment, management and maintenance best practices.

• They publish trial results inclusive of clinically meaningful outcomes in peer-reviewed journals.

• They are authorized by a regulatory body as required to support product claims of risk, efficacy and intended use.

• They have made medical claims appropriate to clinical evaluation and regulatory status.

Freedom for Patients, Improved Resources for Providers

With a more specific description, perhaps it's easier to see just how valuable and innovative the most emergent branch in digital healthcare really is. For the first time, patients' healthcare treatments and decisions — not simply their data to collect and interpret — are put in patients' own hands, which providers oversee. And when patients and providers utilize DTx, they may access an ever-growing range of tools. This includes wearables that monitor heart health or glucose levels. Other DTx can improve musculoskeletal performance and chronic pain by using a smartphone camera to guide patients through physical therapy. Additional DTx treatment possibilities still in the works include but are not limited to management, treatment and prevention of atopic dermatitis, substance abuse disorders, sleep disorders and even cancer. In such scenarios, DTx devices are providing patients' performance information to healthcare workers. Some DTx will even help people decrease or better manage mental conditions such as anxiety, depression, insomnia, bipolar disorder and attention deficit hyperactivity disorder. For mental health conditions, artificial intelligence and DTx are a powerful combination that will offer people with such illnesses more power and hope. For the sake of illustration, consider this powerful combination being a means to reduce negative thoughts and behavior. Theoretically, improvement might only take 12 weeks, with one or two 30-minute sessions a week.[3]

DTx also offer a route beyond traditional medicine that provides more flexibility and innovation for providers with fewer obstacles such as making appointments, reducing travel time and costs and managing health conditions that limit patients' mobility. DTx improve not only patients' physical health, but their mental health through the empowerment they obtain. Being personally involved in their own healthcare choices offers patients "buy-in," so to speak, which often fosters motivation to be compliant with treatment and promote healing and prevention of their personal health issues.[5]

And apart from being tailored to accommodate each patients' needs, behavior and even language, DTx provide patients privacy, confidentiality and the ease of utilizing healthcare in the comfort of their homes. Such therapeutics also break down barriers to healthcare such as distance, disabilities and lack of transportation. Thus, DTx provide more efficacy and improved healthcare management for both healthcare workers and patients.[2]

Providers Are Still Crucial

Even so, it's critical to recognize that DTx do not replace healthcare providers. Medical professionals must keep a watchful eye on patients, carefully monitoring their symptoms and healthcare needs. And providers must prescribe DTx, making sure they will be a beneficial fit for each patient. Most if not all DTx, for the record, aren't over-the-counter treatments. They require a physician's thorough physical and/or mental examination and diagnosis. In addition, providers must administer such technologies without training and resources to refine treatment to monitor patient needs and information. In fact, DTx providers augment their ability to personalize patients' care more frequently and with increased precision.

Providers, of course, must check the devices or therapies to ensure they are working effectively. For example, patients would continue to see their provider for regular appointments, but therapeutics could improve providers' abilities to adjust patient treatments, medication doses and other needs according to the information gathered from the DTx. Providers need not be involved in each therapy session, however. While providers will monitor data

What Are Digital Therapeutics (DTx)?

DTx, a subset of digital health, are evidence-based therapeutic interventions driven by high-quality software programs to prevent, manage or treat a medical disorder or disease. DTx:

- are mobile software applications that treat a disease or condition.
- are therapeutic programs that go through clinical trials and regulatory review, similar to a traditional drug or medical device.
- use the strengths of mobile software to deliver an engaging and personalized treatment, right on patients' phones.
- may be prescribed by a physician as a stand-alone treatment or alongside a drug or therapy.

from a DTx product or therapy prescribed for a condition such as chronic pain management, patients are able to adhere to the treatment plan on their own — perhaps through video exercises or therapy for pain management via an electronic device such as a phone or laptop.[2,4,5]

U.S. Food and Drug Administration (FDA) Approval

Because the field is so broad and still so exploratory, regulatory agencies continue to be involved in clinical testing of DTx applications to demonstrate that any medical claims made about the devices are true. While FDA doesn't typically regulate wellness applications and devices currently on the market, it does become involved when developers of new wellness apps make medical claims about their inventions. For instance, if a developer states an app can monitor exercise amount and times, there is no medical claim. But, if a developer claims their app or device can improve blood sugar levels, that medical claim requires FDA involvement. As DTx expand their uses and devices, FDA will no doubt be more involved to monitor and determine which studies and trials are required to prove such claims.[3]

Potential Roadblocks

As with most technologies, there are obstacles to the development of DTx. There remain, for example, challenging questions regarding how DTx will or will not be covered by insurance reimbursement. Not only does this affect patients, it is notable for providers as well. As an illustration, during a provider shortage, patient access to DTx would be limited. Regulations might also lead to FDA control, which could lead to exorbitant prices for patient access to DTx. As such, healthcare workers' support is necessary to regulate DTx to ensure treatment is paid for by insurance companies. Unfortunately, in the majority of cases, there is yet a clear definition of and consensus for how DTx are or will be reimbursed by insurance.[3,5]

Beyond financial and insurance issues, DTx are still so new and ever-changing that there is not yet a lot of buy-in from patients who have not had access to them. Nor do DTx have the marketing expertise of the tried-and-true pharmaceutical therapeutics, which people are much more prone to understand and trust. Many providers, too, might not want to test this emerging field because they are either unsure of it or are afraid of the perceived risk involved for themselves and their patients. Other providers might feel as though their role is less effective in their patients' treatment via digital means.[5]

The Future of DTx

Despite critics and potential difficulties, interest in the field and the number of DTx available is increasing and will continue to do so. In fact, by 2020, even before the COVID-19 pandemic, investment in DTx products grew by 40 percent per year, and DTx are expected to be a global opportunity of $56 billion by 2025.[5]

Providers are increasingly seeing DTx' potential for growth. A recent survey of healthcare executives responsible for pharmaceutical decisions found that while only 25 percent of their organizations' formularies paid for DTx, another 45 percent were intrigued by it and expected to do so in the future. There is also a lot of opportunity for virtual first-care companies to use and improve DTx products while helping providers to further reach and improve their engagement with patients.[2,5] So, as regulatory agencies clinically test more and more devices and methods, and expand the availability and quality of DTx, providers and patients will profit professionally, physically and emotionally.

The future of the healthcare industry is clearly increasingly digital. DTx, along with the other branches under the umbrella of digital technology, are providing doctors with more information, efficiency and efficacy, and they are providing patients with more independence, privacy and comfort. Therefore, while the DTx field is still developing, it is certainly here to stay. Healthcare professionals who haven't yet explored or taken time to understand these tools would be wise to proactively find out more about the field and examine its advantages for patients and professionals. After all, several years from now, medical clinics and offices will look different than they do today as technologies continue to work together with and for everyone. Welcome to the radical future of better health and more interconnected healthcare. ❖

It's critical to recognize that DTx do not replace healthcare providers.

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Pros and Cons of Healthcare Consolidation

Do mergers help or hurt the healing industry?

By Rachel Maier, MS

THE HEALTHCARE INDUSTRY is changing, and it's changing fast. Independent practices and community hospitals are being snatched up by larger, more robust health systems; large local hospital systems are crossing state lines to create "premier" healthcare destinations; hospitals systems are buying outpatient centers and merging with health plans; private practices are joining forces to stay afloat; insurance providers are even linking arms as a strategy to remain competitive — the list goes on and on. Private equity firms are even getting in on the trend.

Reports of healthcare mergers and acquisitions flood news feeds, with announcements of new partnerships seemingly every week. In fact, 20 deals generating more than $13.3 billion were announced in the second quarter of 2023 alone, the highest number since before the COVID-19 pandemic.[1]

Perhaps it's not surprising. After all, the healthcare industry as a whole continues to strain to meet the ever-increasing demand of rising costs, provider burnout and patient expectations, among other things, and teaming up to face an uncertain future sounds like a good idea.

But not everyone sees healthcare consolidation as a good thing. Arguments for and against healthcare consolidation agree access to quality patient care at an

affordable price in an efficient, reliable organization is the goal, but while some believe consolidation is the key to moving forward, others raise very real concerns about it.

A Bird's Eye View

In broad terms, healthcare consolidation is the practice of two or more healthcare companies coming together to form a new, more robust entity.

- *Horizontal consolidation* refers to the merger of entities that perform similar functions such as when two hospitals merge into one or when two or more physician practices come together to form a larger group.[2]
- *Vertical consolidation*, or integration, occurs between companies 1) that do business with each other or 2) whose services complement each other such as when a hospital purchases an outpatient center or a health plan merges with a hospital system.[3]
- *Cross-market consolidation* refers to hospital systems' expansion into broader geographical locations, often in multiple states, by acquiring entities in that location. Notably, a recent analysis shows that 55 percent of the 1,500 hospitals targeted for merger or acquisition between 2010 and 2019 were located in a separate geographic market than the acquirer.[4]
- *Private equity roll-ups* refer to when private equity firms acquire and merge multiple small businesses into one larger company.[5] These "megadeals" have grown increasingly common in the healthcare sector, especially in nursing homes and rural hospitals.[5]

Proponents of healthcare consolidation in all forms sing its praises, saying things such as hospital mergers increase access to resources that smaller hospitals wouldn't otherwise have, making better patient care available at a lower cost.[6] But critics disagree, saying consolidation decreases quality of care and raises prices. So far, studies have been largely inconclusive as to which side is "right."

Pros of Consolidation

The rationale for healthcare consolidation seems logical enough: When existing or potential competitors such as physician practices, hospitals, surgery centers, insurance companies or pharmacies join forces, it creates new, more financially sound entities better able to meet the needs of a larger population. The partnerships increase access to capital and other important resources; reduce costs; standardize clinical protocols; aim to improve efficiency; and emphasize the promise of increasing access to care. Some large companies are merging their already-robust entities to become premier destinations with the promise of offering patients best-in-class care.

The launch of Risant Health, for example — the result of a 2023 merger between Kaiser Foundation Hospitals and Geisinger Health — is an "innovative move designed to improve the health of communities, achieve better healthcare outcomes and improve healthcare affordability," according to a Geisinger Health press release.[7] On its heels came an announcement from BJC HealthCare of St. Louis and Saint Luke's Health System of Kansas City, which released a letter of intent to consolidate the companies into one entity. The announcement touts the companies' shared vision of "becoming the premier Midwest destination for patient care, clinical research and medical education and the region's most exceptional place to work and practice medicine."[8]

Mergers such as these appear to have clear advantages, including:[6]

- *Augmented access to capital and resources.* When entities merge, the smaller company has access to the larger company's capital, and the larger company has access to the smaller company's resources. This can benefit both parties. For example, if a specialty practice merges with a large medical system, the large system covers the costs of the smaller specialty practice, which keeps the practice financially viable, while the larger system benefits from having specialists in-house.
- *Shared financial burden*. Mergers take advantage of economies of scale. Sharing

the cost of property, utilities, facility maintenance and equipment, and staff salaries and benefits reduces overhead for both entities. This makes it possible for both entities to be more financially viable.

• *Improved workflow.* From human resources to inventory management, day-to-day operations strain hospital systems. Mergers give struggling hospitals access to proven protocols that streamline policies, workflow and management.

Misgivings about healthcare consolidation are gaining traction, so much so that the U.S. Senate Committee on Finance held a hearing on June 8, 2023, to discuss the growing concern.

• *Better bargaining power.* Large systems with higher patient populations have more power to negotiate lower costs with insurers and pharmaceutical companies than systems with lower patient populations.

• *Upgraded access to care.* Mergers expand the type of care and services a given entity is able to offer patients. For example, when a large healthcare system acquires a small specialty practice, existing patients automatically have access to the specialists acquired by the health system. Mergers give patients more comprehensive options for care.

• *Improved care coordination.* Mergers reduce duplication of clinical services. Standardized clinical protocols are thought to help minimize patient expense and maximize patient experience.

Cons of Consolidation

But critics are skeptical, saying consolidation will hurt patients, both in terms of value and outcomes. In fact, a new study from Harvard University and the National Bureau of Economic Research investigated whether claims that consolidation will improve healthcare are actually bearing out. "One of the key arguments for hospital mergers and practice acquisition was that health systems would deliver better-value care for patients," said Nancy Beaulieu, PhD, the study's lead author and a research associate in the Blavatnik Institute at Harvard Medical School.[9] "This study provides the most comprehensive evidence yet that this isn't happening."[9]

The biggest problems with consolidation seem to be:

• *Decreased competition and higher costs.* When there are fewer healthcare entities, patients have fewer options. Highly concentrated markets enable hospitals to charge higher prices and negotiate higher prices from health insurance plans.[10] A recent study found that the prices of hospitals that do not have competitors within a 15-mile radius are 12 percent higher than markets with four or more competing hospitals.[10] Further, a study published in *Health Affairs* in May 2022 found that vertical consolidation between physicians and health systems led to a 12 percent increase in primary care physician prices and a six percent increase in specialist prices between 2013 and 2017.[10] Further, "Evidence is accumulating that cross-market mergers may sometimes enable hospital systems to increase prices through cross-market power such as from tying hospitals across markets that have common customers (primarily insurers) or because of multi-market contact that leads to mutual forbearance."[4]

• *Diminished access to and quality of care.* Decreased competition increases incentives to raise costs to patients while decreasing incentives to create value for patients. Patient choice becomes limited, quality of care goes down and patients' overall experience is worsened. A study published in 2020 in the *New England Journal of Medicine* illustrates this: The study showed that hospital mergers were associated with worsened patient experiences and no significant changes in readmission or mortality rates.[11]

• *Workforce challenges and inefficiencies.* Mergers are often viewed as a sign of financial instability and, as such, retaining reputable physicians isn't easy: They often seek employment elsewhere in the wake of consolidation. Also, it's hard to recruit top-tier talent when systems are in a state of flux.[12] Further, transforming two distinct entities with unique workflows into one unified company with a smooth, new workflow is challenging. Supply chain concerns, autonomy of units, clash of corporate cultures and regulatory compliance all contribute to the hiccups.[12]

• *Movement away from mission*. A study looking at the impacts of consolidation in Pittsburgh, Pa., showed concerns that acquisition by large health systems fundamentally shifts smaller hospitals away from their original mission, most notably for nonprofit hospitals. "Stakeholders claimed that hospitals acquired by systems are less mission-driven, especially in terms of providing care, regardless of ability to pay. Some brought up the [University of Pittsburgh Medical Center's] acquisition of the

only remaining independent faith-based healthcare provider [in the area], Mercy Hospital. Even though the acquisition was sanctioned by the Pittsburgh Catholic Diocese and is now overseen by it, stakeholders claimed that they perceived less charity care provided at Mercy than before."[13]

Consumer Cost vs. Value and Delivery

Misgivings about healthcare consolidation are gaining traction, so much so that the U.S. Senate Committee on Finance held a hearing on June 8, 2023, to discuss the growing concern. Of primary importance: the effect healthcare consolidation has on consumer cost versus value and delivery. Specifically, the committee examined whether healthcare consolidation and private equity investments are favoring mega-corporations at the expense of patients and taxpayers.

"Too many hospital mergers lead to jacked-up prices and diminished care for patients most in need," said Federal Trade Commission (FTC) Office of Public Affairs Director Lindsay Kryzak.[14] R. Shawn Martin, the executive vice president and chief executive officer of the American Academy of Family Physicians, who provided testimony at the hearing, agrees, saying there is sufficient evidence showing that vertical integration also leads to higher prices and costs, including insurance premiums, without improving quality of care or patient outcomes.[15] Zach Cooper, PhD, associate professor of public health and associate professor of economics at Yale University, also provided testimony at the hearing, adding that increased consolidation "raises provider prices (thus increasing health spending) and harms access to healthcare services (by increasing insurance premiums and out-of-pocket costs)."[16]

In July 2023, FTC and the Department of Justice (DOJ) announced they are working to update federal merger guidelines. "Unchecked consolidation threatens free and fair markets," said U.S. Attorney General Merrick B. Garland. The goal of the update is to better reflect how both FTC and DOJ determine a merger's effect on competition in the modern economy, as well as evaluate proposed mergers under the law.[17] According to Mr. Garland, updated merger guidelines will help protect Americans from the effects of anticompetitive mergers.[17]

Concerns Continue

While healthcare consolidation aims to make medical companies better-equipped to serve patients, as well as more financially secure, critics say it doesn't achieve the goal and ends up costing patients much more than just money (but it also happens to cost them a lot of that, too).

Consolidating healthcare entities for the altruistic sake of improving access to and quality of healthcare seems reasonable, even ideal. And some mergers bear out that mission. But in practice, the change is benefiting large corporations, not patients. It is causing very real challenges, perhaps the most profound of which is carrying out the act of actual caring. At its heart, healthcare is an act of stewardship: It's the responsible overseeing and protection of something considered worth caring for and preserving — people's lives. Finding the best way to do that remains elusive.

What lies ahead for healthcare consolidation and the true value it brings to patients remains to be seen. "We need to examine the drivers of consolidation, as well as its effects on care quality and costs, both for patients and taxpayers," said Senator Mike Crapo, ranking member of the U.S. Senate Finance Committee. "As we look to strike a productive balance, we should consider not just consolidation, but also quality, access and innovation."[18] ❖

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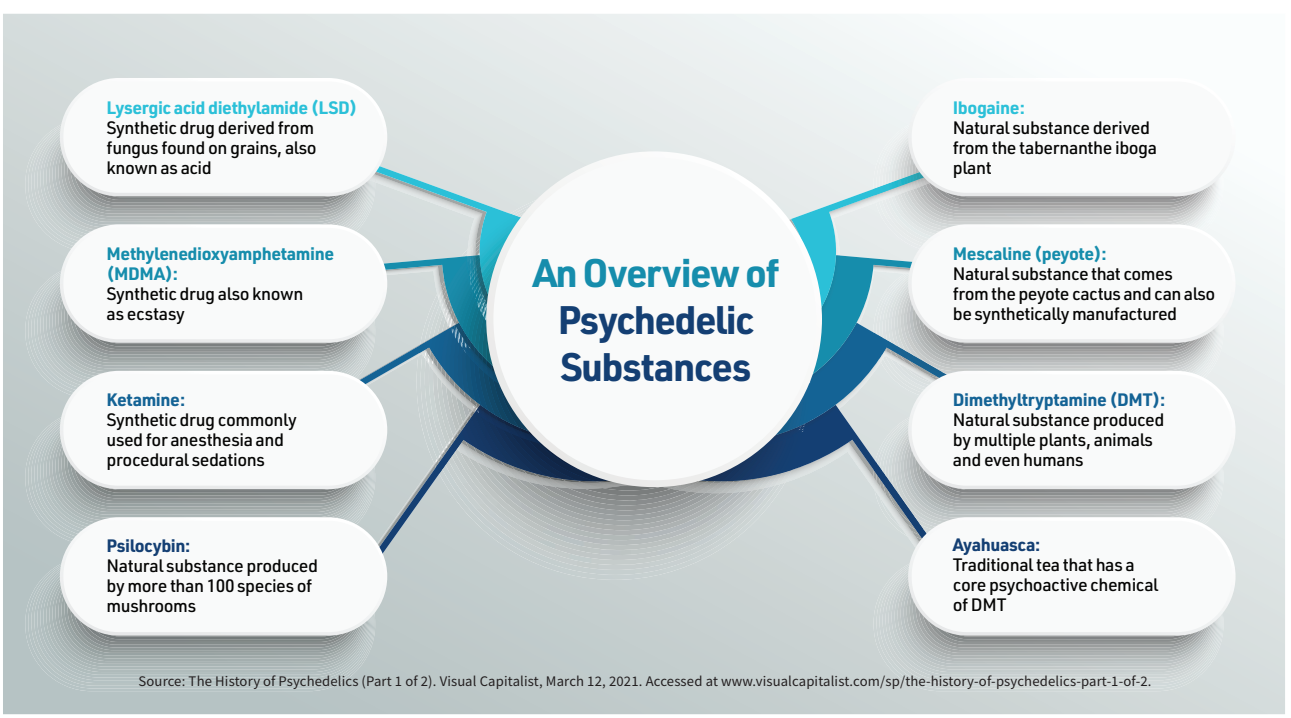
Psychedelic Medicines: The Future?

Renewed interest and research in psychedelic compounds is giving formerly illicit drugs a 21st century image makeover. Are they really breakthrough solutions for treatment-resistant conditions such as depression and PTSD? At this point, the data looks promising.

By Trudie Mitschang

THE UPTICK of interest in psychedelic medicines has launched a once-taboo topic into the medical mainstream. With respected academic and research institutions diving into comprehensive studies that chronicle the therapeutic uses of psychedelics (substances that can temporarily alter a person's mood, thoughts and perceptions of reality[1]), plus popular books and documentaries touting their benefits, it's easy to wonder what all the buzz is about. While much of the research is focused on their reported benefits for mental health, researchers are increasingly looking at the use of psychedelics — primarily psilocybin, the psychedelic compound in mushrooms — for the treatment of everything from nicotine addiction and anorexia to Alzheimer's disease.[2]

"One of the remarkably interesting features of working with psychedelics is they're likely to have transdiagnostic applicability," says Roland Griffiths, PhD, who heads the Johns Hopkins University Center for Psychedelic and Consciousness Research (a facility that has led some of the most promising studies evaluating psilocybin for treating depression and alcoholism). "The myriad applications suggested for these drugs may be a big part of what makes them sound, to many, like snake oil — but the data is very compelling." Dr. Griffiths goes on to note that psychedelics provide an opportunity to "peer into the basic neuroscience of how these drugs affect brain activity and worldview in a way that is ultimately very healthy."[2]



Source: The History of Psychedelics (Part 1 of 2). Visual Capitalist, March 12, 2021. Accessed at www.visualcapitalist.com/sp/the-history-of-psychedelics-part-1-of-2.

A Brief History of Psychedelics

For thousands of years, humans have used plant compounds capable of producing abnormal psychic effects to create altered states of consciousness for religious, mind expansion and recreational purposes. The earliest evidence of psychedelic use can be found in a cave in the Tassili-n-Ajjer region of the Sahara desert in Algeria. The cave features a mural depicting what is referred to as the "mushroom man" or "mushroom shaman," a bee-headed figure with mushrooms sprouting out of his body. The mushrooms pictured are Psilocybe mairei psychedelic mushrooms, which are native to that region. The mural is estimated to be 7,000 to 9,000 years old; clearly, psychedelic use is nothing new.[3]

As far as Western culture's history with psychedelics and the scientific study of their therapeutic uses, here are some timeline highlights:

- 1895: The first scientific trial was conducted for peyote in Washington, D.C., at Columbian University (now George Washington University).
- 1912: Anton Köllisch, a German chemist, became the first person to synthesize 3,4-methylenedioxyamphetamine (MDMA).
- 1931: Richard Manske, a Canadian chemist, was the first to synthesize dimethyltryptamine (DMT).
- 1947: Sandoz Laboratories marketed lysergic acid diethylamide (LSD) under the brand name Delysid and distributed it as a treatment for psychiatric disorders.
- 1949: Psychiatrist Max Rinkel carried out the first LSD experiment in the United States, giving the substance to 100 volunteers at the Boston Psychopathic Institute.
- 1952: Charles Savage, MD, published the first study looking at LSD as a treatment for depression.
- 1958: Swiss chemist Albert Hofmann isolated and identified the structure of psilocybin and psilocin, the two psychoactive compounds in magic mushrooms.
- 1960-1967: Stanislav Grof, MD, a Czech psychedelic pioneer, conducted more than 4,000 LSD therapy sessions and reported that LSD could relieve anxiety and despair in terminal cancer patients.

The scientific interest in psychedelics shifted in the 1970s when LSD, DMT, MDMA, psilocybin, psilocin, mescaline, peyote and cannabis were all classified as schedule I drugs under the United States Controlled Substances Act. In a nutshell, psychedelics were legally said to have no recognized medical value and a high potential for abuse. As a result, the scientific study of psychedelics was ground to a halt.[3] It would be another two decades before sanctioned research into psychedelics ramped up again.

Starting in the 1990s there was a resurgence of government-approved studies about psychedelic substances. Then, a landmark 2006 Johns Hopkins study demonstrated that psilocybin can generate positive changes in attitude and behavior lasting several months, reigniting interest in psychedelics as a psychiatric treatment. Subsequent studies affirmed and expanded on these findings.[4]

In 2019, Imperial College London launched the world's first Centre for Psychedelics Research, and months later, Johns Hopkins launched its own: the Center for Psychedelic and Consciousness Research. Both centers focused on what psychedelics reveal about consciousness and how these compounds can help treat conditions such as depression, addiction and post-traumatic stress disorder (PTSD).

A Shift Toward Social Acceptance

While the study of psychedelics as medicine is inching toward mainstream acceptance, it still remains somewhat controversial thanks to their solidly counterculture reputation. But, opinions may be shifting. In 2019, the U.S. Food and Drug Administration (FDA) approved the psychedelic drug esketamine for use in treading depression. Additionally, in 2021, FDA granted "breakthrough therapy" status to study the medical benefits of psychedelics.[5]

"The resurgence in interest in psychedelic medicine is likely related to multiple factors, including decreasing societal stigma regarding drugs like hallucinogens and cannabis, increasing awareness of the potential therapeutic compounds found naturally occurring in plants and fungi and the growing mental health crisis our nation faces," said University of Nevada neuroscientist, Dustin Hines, PhD. "Because of the intersection between the great need for innovation and wider social acceptance, researchers have started to explore psychedelics as novel treatments for depressive disorders, including work with compounds that have been used for millennia."[6]

The question of how psychedelics change the brain is not fully understood. The secret seems to lie in a neurological system called the default mode network (DMN). The DMN switches on when the brain is engaged in activities such as daydreaming or ruminating. For many, this function can lead to habitual worrying and obsessing about past mistakes, precursors to anxiety and depression. It's thought that psychedelics can temporarily quiet the DMN and activate connections between other regions of the brain. Whereas the mind normally follows well-worn roads, psychedelics essentially open alternative routes, potentially offering

refreshed perspectives. Studies have shown that the psychological changes sparked by controlled psychedelics can linger for months or even years, leading to long-term improvements in a range of mental-health disorders,[4] including:

- Depression: A study of individuals diagnosed with major depressive disorder found that two sessions of psilocybin coupled with psychotherapy yields rapid, substantial and sustained easing of symptoms.
- Substance use: Eight in 10 cigarette smokers who received two or three sessions of psilocybin alongside traditional smoking-cessation treatment remained fully abstinent six months later. Another psychedelic, ibogaine, was found to reduce or eliminate opioid use after a single session.
- PTSD: In one study, MDMA diminished symptoms of PTSD so dramatically that after two sessions, 83 percent of study participants no longer met criteria for the disorder.
- Terminal illness: Several studies have shown that cancer patients treated with LSD and other psychedelics experienced significantly lower anxiety and depression stemming from their diagnosis. Participants also reported less fear of death.

While psychedelics do not have the same addictive properties as other drugs, they must be handled with care and administered in a controlled setting by a trained professional. Additionally, they're not for everyone; individuals predisposed to certain mental illnesses such as schizophrenia may experience adverse reactions.

FDA Introduces Guidelines for Clinical Trials

In June 2023, FDA published a new draft guidance to highlight fundamental considerations for researchers investigating the use of psychedelic drugs for potential treatment of medical conditions, including psychiatric or substance use disorders. It is the first FDA draft guidance that presents considerations for designing clinical trials for psychedelic drugs.[7]

"Psychedelic drugs show initial promise as potential treatments for mood, anxiety and substance use disorders. However, these are still investigational products. Sponsors evaluating the therapeutic potential of these drugs should consider their unique characteristics when designing clinical studies," said Tiffany Farchione, MD, director of the Division of Psychiatry in FDA's Center for Drug Evaluation and Research. "By publishing this draft guidance, [FDA] hopes to outline the challenges inherent in designing psychedelic drug development programs and provide information on how to address these challenges. The goal is to help researchers design studies that will yield interpretable results that will be capable of supporting future drug applications."[7]

Among the many safeguards the guidelines put in place, FDA suggests clinical trials may be subject to a clinical hold if they don't include safety monitoring according to FDA's recommendations. For example, the guidelines state that subjects receiving active treatment with psychedelic drugs remain in a vulnerable state for as long as 12 hours, and that safety monitoring should involve a healthcare provider with graduate-level professional training and clinical experience in psychotherapy, and an assistant monitor with a bachelor's degree and at least one year of clinical experience in a licensed mental healthcare setting.

Considerations for Prescribing Psychedelics

Consideration	Relevant Factors
Screening for patients likely to have a challenging or adverse experience ("bad trip")	In clinical trials, researchers have largely screened out participants with a personal or family history of psychotic or bipolar disorders. It remains unclear if psychedelic sessions can cause de novo psychotic disorders or trigger psychotic episodes in vulnerable patients.
Managing acute medical and psychiatric complications	There have been case reports of patients experiencing limb ischemia and rhabdomyolysis with subsequent renal failure from the use of LSD (lysergic acid diethylamide) and psilocybin, respectively. Although less likely, patients may become agitated and violent during a challenging experience, and may require a sedative or physical restraint to maintain safety.
Informed consent	Patients should understand the potential serious risks of undergoing psychedelic treatment. Patients will likely lose capacity to make medical decisions once a psychedelic session begins. Patients' wishes regarding certain scenarios should be known prior to initiating treatment (for example, whether they allow supportive touch during a session).
The use of guides	Due to time constraints, psychiatrists are not likely to be present during a patient's psychedelic session, but supportive staff or "guides" should be present. Guides should be trained and up to date on published recommendations from leading organizations involved in community psychedelic practice.

Source: Adapted from The Rebirth of Psychedelic Psychiatry. *Current Psychiatry*, 2021 January;20(01):13-16, 18-19. Accessed at www.mdedge.com/psychiatry/article/233919/depression/rebirth-psychedelic-psychiatry/page/0/3?reg=1&icd=login_success_email_match_norm.

According to the report, the purpose of the draft guidance is to advise researchers on study design and other considerations as they develop medications that contain psychedelics. Within the draft guidance, the term psychedelics refers to "classic psychedelics," typically understood to be drugs such as psilocybin and LSD that act on the brain's serotonin system, as well as "entactogens" or "empathogens" such as MDMA.[7]

Understanding the Research

From a research perspective, one priority is to understand why only certain drugs work for some disorders and not for others, isolate those effective drug mechanisms and focus research efforts around those mechanisms to develop far more targeted, disorder-specific treatments.[8] Scientists are now beginning to tease out the brain mechanisms behind the distinctive mind-altering properties of these different drug families, a critical step in turning them into mainstream treatments.

Researchers have already identified that certain psychedelics seem to work by binding to the serotonin 2a receptor, one of the 15 specialized receptor molecules the serotonin system uses to coordinate brain activity. Entactogens and dissociative anesthetics don't directly act on this receptor, which is why they "feel" different from hallucinogens. By comparison, ketamine, a dissociative anesthetic that has some hallucinogenic effects, has been linked to a specific receptor in the brain's glutamate system.[7]

"We need more research using the same rigorous methods applied to many other promising compounds for mental illnesses. By studying both efficacy and mechanisms, we can be more precise in developing better treatments with fewer side effects," said Carolyn Rodriguez, MD, a professor of psychiatry and behavioral sciences who co-authored a July 2022 position statement by the American Psychiatric Association on the mental health uses of psychedelics and empathogens.[7]

Dr. Rodriguez, who directs Stanford Translational Therapeutics, is leading studies on the mechanisms underlying ketamine's effects, a crucial component of her work on ketamine as a potential therapy for obsessive compulsive disorder (OCD). Her study on ketamine's mechanism of action aims to better understand how ketamine helps OCD patients — one stepping stone toward a targeted OCD treatment.

Another key question is how these drugs change the brain itself to produce their unique mental states. Karl Deisseroth, MD, PhD, D.H. Chen Professor, professor of bioengineering and professor of psychiatry and behavioral sciences at Stanford and a Howard Hughes Medical Institute investigator, has studied how ketamine alters brain dynamics to produce the characteristic "dissociative" state that appears to help some patients with depression and other disorders. In a 2020 study, the Deisseroth lab linked these dissociative states to a specific rhythm of activity in particular circuits in the mouse brain. When the team artificially reproduced this rhythm in normal mice, they found they could directly trigger dissociation, even without ketamine.[7]

What the Future May Hold

With the field of psychedelics booming, researchers are operating in a high-stakes environment. On the one hand, it's never been a better time to study these compounds: FDA has indicated its intent to approve both MDMA and psilocybin as mental health treatments in the next two years. The downside, according to Robert Malenka, MD, PhD, Nancy Friend Pritzker professor of psychiatry and behavioral sciences, is the risk that widespread medical legalization of these substances might lead to rampant misuse, which could threaten the future of psychedelic medicine altogether. "As soon as something bad happens, the pendulum will swing the other way," he said. "We don't want to return to the early 70s, where some individuals and communities used these substances inappropriately and bad things happened."[8]

It remains to be seen how regulators will scale up and facilitate this pipeline from lab breakthrough to mainstream treatment. But for now, many researchers are excited to begin exploring and utilizing innovative options to help treat mental disorders that have long resisted traditional treatments. If these once-taboo drugs prove to deliver beneficial and lasting results, it could usher in a whole new era for medicine. And, while it's been decades in the making, all signs indicate that even the medical field's most conventional thinkers may be opening their minds to the possibilities psychedelics have to offer. ❖

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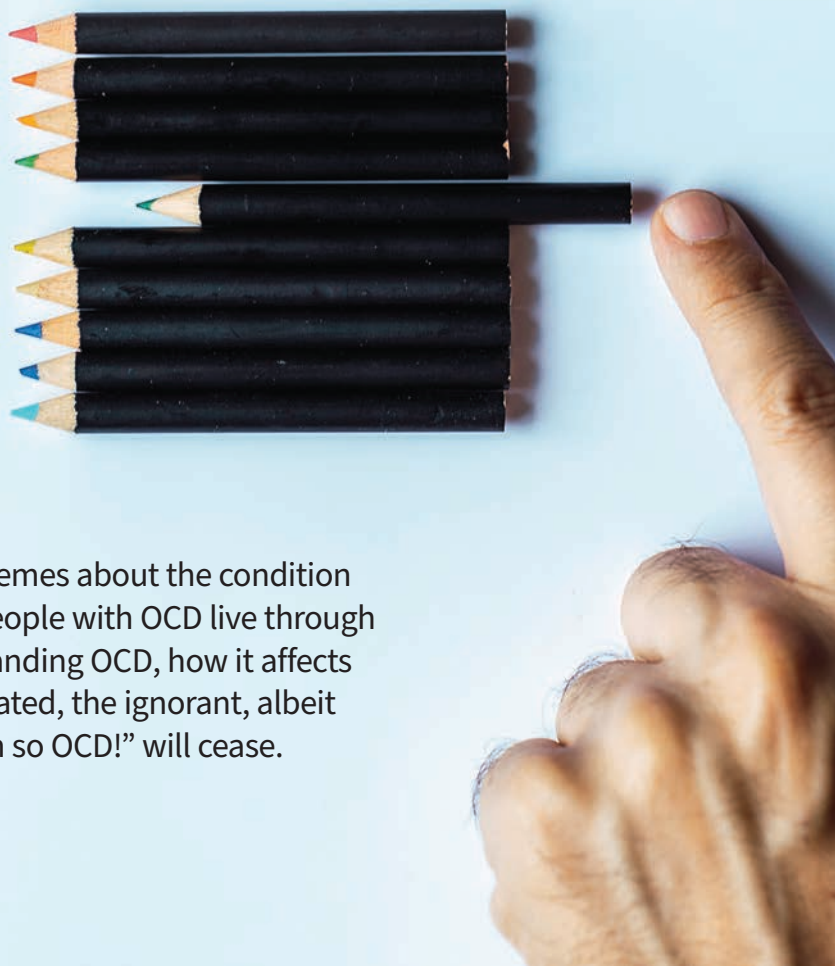
Myths & Facts:

Obsessive-Compulsive Disorder



OCD is no joke, and the rash of hurtful memes about the condition minimize the amount of suffering that people with OCD live through on a daily basis. But perhaps by understanding OCD, how it affects those who suffer from it and how it is treated, the ignorant, albeit mostly innocent, statements such as "I'm so OCD!" will cease.

By Ronale Tucker Rhodes, MS

MANY PEOPLE have heard of obsessive-compulsive disorder (OCD), but few really understand what it is. In fact, despite its prevalence, OCD is one of the most misunderstood health conditions, and many people have ideas about it that simply aren't true. According to Nystrom and Associates, a group of professional care providers, the disorder is commonly stereotypically portrayed, and misused catchphrases from individuals who don't understand it minimize OCD as a mental health condition.[1]

But, OCD is not a mental health condition; it's a chronic anxiety disorder that causes people to experience unreasonable, uncontrollable or recurring thoughts followed by a behavioral response. The repeatedly obsessive thoughts cause anxiety that results in repetitive behaviors. And the behaviors persist due to "operant conditioning," which means the compulsions, or behavioral responses, reduce anxiety. In fact, the responses are so effective, they negatively reinforce the behavior.[2]

According to BeyondOCD.org, OCD is a disorder that has a neurobiological basis, which means there is a connection between the nervous system and how the brain works. In the United States, about one in 40 adults and one in 100 children have OCD. And according to the World Health Organization, OCD is one of the top-20 causes of illness-related disability worldwide for individuals between 15 and 44 years of age.[3] Indeed, the National Institute of Mental Health noted that OCD was once ranked in the top-10 most disabling illnesses by lost income and decreased quality of life.[4]

Therefore, because OCD is such a complex, chronic disorder, it's important to clear up misconceptions, reduce stigmatization and set the facts straight.

Separating Myth from Fact

Myth: OCD is not that big of a deal.

Fact: OCD is a big deal. OCD isn't just an overreaction to stressors in life. It causes severe and often debilitating anxiety resulting in overwhelming obsessions that can limit individuals' ability to function.[5]

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), considered the "gold standard" by most mental health professionals in the United States, the clinical definition of OCD is:[6]

A) Presence of obsessions, compulsions or both. Obsessions are defined by 1) recurrent and persistent thoughts, urges or impulses that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress and 2) the individual attempts to ignore or suppress such thoughts, urges or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion).

Compulsions are defined by 1) repetitive behaviors or mental acts that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly and 2) the behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.

B) The obsessions or compulsions are time-consuming (e.g., take more than one hour per day) or cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

C) The obsessive-compulsive symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

D) The disturbance is not better explained by the symptoms of another mental disorder (e.g., excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possessions, as in hoarding disorder; hair pulling, as in trichotillomania [hair-pulling disorder]; skin picking, as in excoriation [skin-picking disorder]; stereotypes, as in stereotypic movement disorder; ritualized eating behavior, as in eating disorders; preoccupation with substances or gambling, as in substance-related and addictive disorders; preoccupation with having an illness, as in illness anxiety disorder; sexual urges or fantasies, as in paraphilic disorders; impulses, as in disruptive, impulse-control and conduct disorders; guilty ruminations, as in major depressive disorder; thought insertion or delusional preoccupations, as in schizophrenia spectrum and other psychotic disorders; or repetitive patterns of behavior, as in autism spectrum disorder).

According to Menije Boduryan-Turner, PsyD, a psychologist based in California, there are four categories of OCD behaviors (called compulsions):[2]

1) Acting compulsive such as checking, hand washing, locking, moving objects, staring, praying or seeking symmetry.

2) Seeking reassurance from loved ones, typing a search in Google or asking Siri.

3) Avoiding triggers such as social interaction, objects or walking around things.

4) Mental compulsions such as repeating words, counting, mental checking, rumination, visualization, thought suppression, neutralizing (replacing an unpleasant thought with a pleasant one) and mental reviewing (reviewing past actions).

Myth: Only women have OCD.

Fact: It may seem like more women than men would have an anxiety disorder such as OCD, but OCD equally affects men, women and children of all races, ethnicities and socioeconomic backgrounds. However, according to the most recent statistic, the prevalence of OCD in a 12-month period *is* higher in females (1.8 percent) than males (0.5 percent).[2]

According to BeyondOCD.org, OCD is a disorder that has a neurobiological basis, which means there is a connection between the nervous system and how the brain works.

Myth: OCD is just about cleanliness.

Fact: Obviously, the clinical definition of OCD proves that OCD is much more than obsessing over cleanliness. And, not all "neat freaks" have OCD.

Myth: Everyone is a little OCD at times.

Fact: Every person does *not* have some level of OCD. In fact, only just over 2 percent of the population has been diagnosed with OCD. Perpetuating the myth that everyone has some form of OCD makes it much more difficult for

OCD Statistics[2]

- Approximately 2.3 percent of the population has OCD, which is about one in 40 adults and one in 100 children in the U.S.
- The prevalence of OCD in a 12-month period is higher in females (1.8 percent) than males (0.5 percent).
- One study in 1992 found that nearly two-thirds of people with OCD had major symptoms before the age of 25.
- In families with a history of OCD, there's a 25 percent chance that another immediate family member will develop symptoms.

those who actually have it to receive the necessary assistance in treating it.[7]

Myth: OCD begins in childhood.

Fact: OCD can begin at any time from preschool to adulthood. Yet, according to the International OCD Foundation, there are generally two age ranges when OCD tends to first appear: 1) between age 8 and 12 years old and 2) between the late teen years and early adulthood.[9] The average age of onset of OCD is 19.5 years old. Males make up the majority of very early-onset cases, with almost a quarter of males having onset before age 10. On the other hand, most females are diagnosed with OCD during adolescence (after age 10). In addition, people with early age of onset have more severe symptoms of OCD and higher rates of attention-deficit/hyperactivity disorder and bipolar disorder.[2]

The foundation also points out that in rare cases, symptoms of OCD "may develop seemingly 'overnight' with a rapid change in behavior and mood and sudden appearance of severe anxiety." In this case, it is a subtype of pediatric OCD caused by an infection (e.g., strep throat) that confuses the child's immune system into attacking the brain instead of the infection. This causes the child to begin having severe symptoms of OCD, often seemingly all at once, in contrast to the gradual onset seen in most cases of pediatric OCD. This type of OCD is called pediatric autoimmune neuropsychiatric disorder associated with streptococcus if it is a strep infection, or pediatric acute-onset neuropsychiatric syndrome if it is any other infection.[8]

Myth: OCD is rooted in childhood.

Fact: A common belief by many is that OCD is caused by growing up in dysfunctional homes and having poor self-esteem as a result. But, "what happens in childhood has very little to do with having OCD when you grow up," explains Jeff Szymanski, PhD, executive director of the International OCD Foundation. However, he notes, OCD does run in families, and researchers believe genetics may play at least some part in its development, as well as experiences.[9]

Myth: It's easy to tell if a person has OCD.

Fact: Actually, it can be difficult to tell if someone has OCD. This is because "people experiencing intrusive thoughts often don't share with others what they are feeling or thinking and try to control it themselves, which can create anxiety and build up stress, guilt and even shame," explains Cara Maksimow, LCSW, CPC. "Those negative feelings can reinforce the person's need to keep the thoughts and behaviors a secret from those around them."[10]

Myth: Stress causes OCD.

Fact: While stressful situations can make things worse for people with OCD, stress is not a cause of OCD. However, according to the Anxiety and Depression Association of America (ADAA), in persons who are genetically predisposed to OCD or who have a subclinical case of the disorder, "a stress trigger or trauma may precipitate symptoms, which also sometimes begin after a severe trauma such as the death of a loved one. Other stress triggers include the birth of a sibling, a marriage or divorce, a move to a new home or new community, a transition to a new school or new school year, or a natural disaster such as an earthquake or tornado." In addition, ADAA says if OCD symptoms are already present, stress can worsen them, as can anxiety, fatigue, illness and even stress associated with holidays, vacations and other positive events.[11]

Myth: Tests can confirm OCD.

Fact: Unfortunately, there are no blood or physical tests, nor are there brain scans to confirm a diagnosis of OCD. But, there are tests and techniques used by mental health professionals. "To diagnose OCD, trained therapists will ask questions to determine if you meet the criteria outlined in the DSM-5 for the disorder," Keara Valentine, PsyD, a postdoctoral fellow at Stanford University School of Medicine in the OCD and Related Disorders Track, says.

Within DSM-5, many therapists will turn to SCID-5, which stands for Structured Clinical Interview for DSM-5. These therapists use structured diagnostic interviews or other inventories to assess symptoms of various mental health diagnoses to rule out other differential diagnoses, Dr. Valentine explains. However, in most OCD-suspected cases, trained OCD therapists will administer the Yale-Brown Obsessive Compulsive Scales (Y-BOCS) to assess individuals' obsessions and compulsions, as well as the severity of symptoms.

Therapists want to determine how time-consuming the obsessions and compulsions are. According to Dr. Valentine, an hour per day might be a red flag, as well as if they're roadblocks in any way to daily life (work, play, etc.).

Further, they need to determine that these acts are not connected in any way to substance abuse, including alcohol and prescription medication, as well as rule out any other mental disorder that may be causing the obsessive behaviors such as generalized anxiety disorder.

It's important to note that while a 2013 study published in *Depression & Anxiety* found that the risk of OCD was significantly increased when first-degree family members had either OCD, tic disorders, affective disorders or anxiety disorders, just because a parent or sibling has the disorder doesn't mean a child or sibling will also. And, researchers have not identified specific genes associated with OCD.[12]

Myth: OCD isn't treatable.

Fact: OCD can be treated depending on how it is affecting individuals' lives. The two main treatments are a type of cognitive behavioral therapy called exposure and response prevention (ERP) and medicine.

ERP, which has the strongest evidence supporting its use in the treatment of OCD, is typically performed by a licensed mental health professional (such as a psychologist, social worker or mental health counselor) in an outpatient setting. The exposure component of ERP refers to practicing confronting the thoughts, images, objects and situations that make individuals anxious and/or provoke their obsessions. The response prevention part of ERP refers to making a choice not to perform a compulsive behavior once the anxiety or obsessions have been "triggered." All of this is done under the guidance of a therapist at the beginning — although individuals usually eventually learn to do their own ERP exercises to help manage symptoms. Over time, the treatment will "retrain the brain" to no longer see the object of the obsession as a threat.[13]

Only approximately seven out of 10 people with OCD will benefit from ERP. For the other three out of 10 people, medicine is needed. The main medicines prescribed are a type of antidepressant called serotonin reuptake inhibitors (SRIs), which can help improve OCD symptoms by increasing the levels of a chemical called serotonin in the brain. And, while not all antidepressants are effective for treating OCD, eight SRIs have been identified that are (see Serotonin Reuptake Inhibitors for OCD). One of these, anafranil, has been around the longest and is also the best-studied for OCD. However, no studies have shown any significant differences in how all of these drugs work to treat OCD. So, it is suggested by the International OCD Foundation that the only way to tell which drug will be the most helpful with the least side effects is to try each drug for about three months. And, there are side effects with these medications, which most patients will experience.

There are also hundreds of case reports of other drugs that can be effective for treating OCD such as duloxetine (Cymbalta), which has been reported to help OCD patients who have not responded to these other medications.[14]

In addition to these, some newer treatments are being researched. As reported in the *NIH Record*, Carolyn Rodriguez, PhD, associate dean at Stanford University and professor of psychiatry and behavioral sciences, has been researching ketamine, which has previously been shown to relieve symptoms of depression within hours, and Dr. Rodriguez believed there was a mechanistic rationale to test the drug in OCD patients as well. Ketamine is a U.S. Food and Drug Administration-approved anesthetic that affects the brain's glutamate system, which is involved in important brain functions such as learning and memory. Glutamate is the brain's most common excitatory neurotransmitter. The drug blocks the NMDA receptor, which receives glutamate signals.

In a small pilot study, patients with OCD received a low dose of ketamine or saline via infusion. Those who received the ketamine reported a rapid decrease in OCD symptoms compared to those who received saline. One patient who received ketamine felt he had a vacation from his symptoms. Others reported they tried to have OCD thoughts but couldn't.

In another study, Dr. Rodriguez partnered with a team to study ketamine's effect on brain activity in people with OCD. To determine whether ketamine changed levels of glutamate in an area of the brain called the prefrontal cortex, researchers gave patients a dose of ketamine and imaged their brains using

Serotonin Reuptake Inhibitors for OCD[15]

Drug	Dose
citalopram (Celexa)	up to 40 mg/day*
clomipramine (Anafranil)	up to 250 mg/day
escitalopram (Lexapro)	up to 40 mg/day
fluvoxamine (Luvox)	up to 300 mg/day
fluoxetine (Prozac)	40-80 mg/day
paroxetine (Paxil)	40-60 mg/day
sertraline (Zoloft)	up to 200 mg/day
venlafaxine (Effexor)	up to 375 mg/day

*High doses are often needed for these drugs to work in most people.

magnetic resonance spectroscopy. After an hour, they didn't see any changes in glutamate, but they did see elevated levels of an inhibitory neurotransmitter called Gamma-aminobutyric acid, which blocks chemical messages in the brain and decreases the stimulation of nerve cells.

Dr. Rodriguez is also studying the potential of accelerated theta burst stimulation, a type of neuromodulation therapy, to treat OCD. She conducted an open-label study in seven patients who received five consecutive days of accelerated stimulation. Ten sessions were applied per day (18,000 pulses/day, hourly) or 90,000 total pulses. After five-days, patients experienced a robust and rapid response in five of the seven (71 percent), with at least a 50 percent reduction in OCD symptoms within seven to 14 days.[15]

Artificial intelligence (AI) has also been making great strides in the field of depression treatment, and is showing promising results for OCD. OCD-focused AI studies are seeking to discover which particular protein (or proteins) are involved in the appearance of the condition's adverse symptoms, and which molecular medication can regulate it. To date, a cell surface protein called 5-HTIA has been implicated: Normally, 5-HTIA is activated by the neurotransmitter serotonin, which has already been found to be related to the appearance of this condition. By calculating which molecular drug this protein will respond to, AI research is attempting to effectively decrease OCD severity, even in cases in which serotonin activation is below the normal rate.[16]

Myth: People with OCD can't live normal lives.

Fact: It is completely possible for people to live their daily lives normally with OCD, especially with suitable treatment. ERP has had a fantastic success rate in reducing the symptoms of OCD by exposing patients to things that may activate their obsession and instructing them on how to avoid following through with a compulsion. And other forms of CBT have also been proven to be extremely helpful in overcoming certain struggles that those with OCD face.[7]

Indeed, there are many examples of prominent individuals with OCD who are living normal and successful lives, including Leonardo DiCaprio, Howie Mandel, Lena Dunham, Justin Timberlake and Camila Cabello.[17]

Myth: OCD remains the same forever.

Fact: OCD is a lifelong condition. However, the severity of OCD symptoms can and do fluctuate over a person's lifetime, which means individuals may have times when their symptoms are worse and times when they ease up. This can be related to stress level, environment, the treatment methods being used and many other factors.[18]

Dispelling the Myths Now

OCD is a debilitating condition for millions of individuals in the U.S. While treatments have been shown to be successful for approximately two-thirds of those suffering from OCD, other treatments are needed to help the other one-third who don't respond to mainstay treatments.

The International OCD Foundation is offering research grants to scientists investigating OCD and related disorders in 2023. In 2022, donations to the foundation provided more than $1.5 million in research funding.[19] In addition, the Center for OCD, Anxiety and Related Disorders, with support from the Brooke Professorship and the McKnight Brain Institute at the University of Florida, is offering funding for pilot projects designed specifically for applicants proposing research that is related to OCD, anxiety or related disorders.[20]

Even though there will never be a cure, individuals with OCD can still live a great life. In their book, *Everyday Mindfulness for OCD*, Jon Hershfield, MFT, and Shala Nicely, LPC, have a section titled "Chronic, Not Terminal." And, according to Nicely, that's "the best way to think about OCD."[21] ❖

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Update on Child Hepatitis

An unusual uptick in pediatric hepatitis recently put the medical community on edge. Here's what we know, why it matters and what to do to mitigate the condition going forward.

By Jim Trageser

HISTORICALLY, HEPATITIS (inflammation of the liver) has not been a disease front and center in pediatric care. It happens, but only very rarely — and the source (maternal transmission, food poisoning, toxic exposure) is normally easily established. Thus, when in the midst of the COVID-19 pandemic the World Health Organization (WHO) noticed what appeared to be a spike in cases of hepatitis of unknown cause in young children (many toddlers), the news sent shock waves throughout both the popular media and the medical community.

Notably, the patients were not testing positive for viral hepatitis or toxins linked to hepatitis, nor were they newborns who may have contracted the condition in utero. So, health officials were left to categorize these cases as "acute hepatitis of unknown etiology."[1] By July 2022, the number of such cases had grown to more than 1,000 — with four dozen children needing liver transplants, and more than 20 dying from the condition.[2]

In response, WHO and national health organizations, including the U.S. Centers for Disease Control and Prevention, immediately tried to determine what was causing this sudden spike. From that effort came two breakthrough understandings regarding childhood hepatitis:

• First, a subsequent re-examination of the medical record suggested there had not been a spike: Instead, due to COVID-19, there may have been a heightened awareness about and increased reporting of cases. (It seems a small number of cases of childhood hepatitis with no known cause has been happening for years.[3])

• Second, infection by a combination of common childhood viruses may, in rare cases, lead to inflammation of the liver.[4]

Concurrent with these developments are ongoing advances in treatment of hepatitis in general, including new drugs that can offer the hope of a cure for some types of hepatitis that were previously incurable.

Causes of Hepatitis

Looking at the most common causes of hepatitis, it is clear that most young children are at very low risk for most types.

Infectious:

• Hepatitis A: spreads via contaminated food or water, sexual contact or sharing a hypodermic needle

• Hepatitis B: spreads via sexual contact, sharing a needle or from a mother to her child during pregnancy

• Hepatitis C: spreads via sharing a needle or from a mother to her child during pregnancy

• Hepatitis D: spreads via sexual contact, sharing a needle or from a mother to her child during pregnancy (notably, it can only infect those already infected with hepatitis B)

• Hepatitis E: spreads via contaminated drinking water

Toxin exposure:

• Alcohol: Excessive alcohol consumption for many years can cause hepatitis.

• Industrial chemicals: Exposure to chemicals ranging from tetrachloride to vinyl chloride, paraquat to polychlorinated biphenyls can result in hepatitis.[5]

• Over-the-counter pain relievers: Aspirin, acetaminophen, ibuprofen and naproxen can all damage the liver if taken frequently or in high doses.

• Prescription medications: Statins, some antivirals and anabolic steroids (among many others) can all cause hepatitis.

• Herbs and supplements: Aloe vera, chaparral and other plants can cause liver damage; children can develop hepatitis if they mistake vitamins for candy and ingest large amounts.

Autoimmune:

• People who have already been diagnosed with an autoimmune condition such as thyroiditis, Grave's disease, celiac disease and immune thrombocytopenia, among others, can develop hepatitis.[6]

Viruses:

• Epstein-Barr virus, cytomegalovirus, rubella, enteroviruses, varicella zoster virus, herpes simplex virus and parvovirus can all cause hepatitis. However, while hepatitis is a possible side effect or complication of these infections, it is extremely rare.[7]

Pediatric Hepatitis

Until recently, most cases of noninfant pediatric hepatitis in the West were caused by the hepatitis A virus, contracted via contaminated food.[8]

Sadly, a growing source of hepatitis in children is maternal transmission of hepatitis C, which is associated with expectant mothers who have injected illegal street drugs.[9] More than 700 babies are born with hepatitis C in the United States each year, a number that has grown significantly and correlates strongly with the opioid crisis.[10] (Johns Hopkins points out, however, that only 20 percent of all neonatal cases of hepatitis can be specifically traced to a viral infection in the mother; the rest are of unknown cause.[11])

In the developing world, hepatitis E (contracted from untreated water) remains a leading cause of hepatitis in children. Hepatitis B is also still a significant source of hepatitis in Africa, where it is passed from mother to child.[12]

Autoimmune hepatitis is categorized into types I and II. Type I tends to appear in school-age children or older and is the most common type. Type II can appear earlier, and is more difficult to treat.[13]

Cracking the Mystery?

As noted previously, most of the children diagnosed with hepatitis during the past 18 months or so tested negative for the hepatitis viruses, tested negative for toxins associated with hepatitis and tested negative for autoimmune disorders. What one group of researchers found, though, is that a large percentage of these patients did test positive for an adenovirus. While this specific virus, adeno-associated virus type 2 (AAV2), is not known to cause hepatitis on its own, researchers speculate that it may cause liver inflammation in conjunction with

Ongoing advances in treatment of hepatitis in general include new drugs that can offer the hope of a cure for some types of hepatitis that were previously incurable.

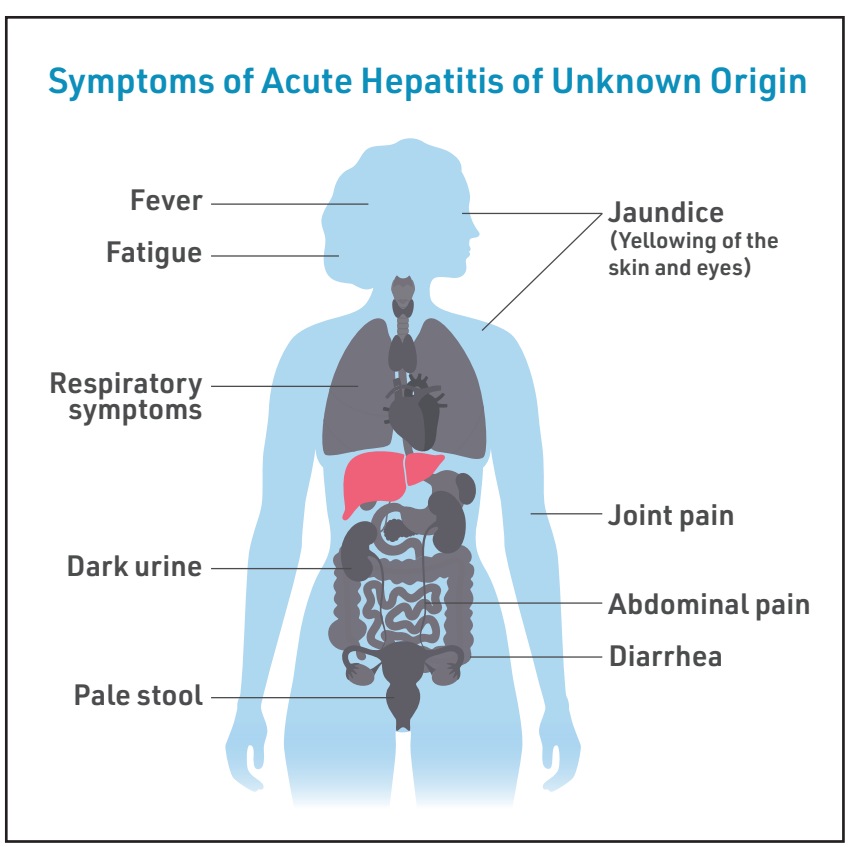
other viral infections.[14] Among the other viruses found in the subjects' specimens were human adenoviruses (HadVs), Epstein-Barr, herpes and enterovirus. The average age of the children in the study was 3 years old.

One of the study's lead authors, Charles Chiu, MD, PhD, director of the Clinical Microbiology Laboratory at the University of California, San Francisco, said, "We were surprised by the fact that the infections we detected in these children were caused not by an unusual, emerging virus, but by common childhood viral pathogens."[15] The researchers think that the social isolation the children experienced during the COVID-19 lockdowns may have made them more susceptible to these common viruses when they returned to normal social interactions.[16]

Researchers are unsure of the mechanisms by which multiple adenoviruses might create liver inflammation, and little is understood of adenoviruses in general. With more than 100 types of adenoviruses already identified, and more continuing to be discovered, scientists are urging that more resources be dedicated to studying adenoviruses and their pathology.[17]

Diagnosis and Treatment

Diagnosis of pediatric hepatitis is no different than with adults — with the caveat that very young children will be unable to articulate pain, so it is incumbent upon physicians to work with parents to notice any other symptoms consistent with hepatitis, including changes in color of urine or feces, jaundice, fever, fatigue or itchy skin.



With immunocompromised patients receiving immune globulin treatments, false positives for hepatitis B are possible due to the presence of hepatitis B antibodies in donors' plasma.[18] Additional screening may be necessary to confirm a diagnosis.

Treatment is also the same as for adults with hepatitis. Acute hepatitis is treated with palliative care, including rest, fluids and avoiding medications that might further stress the liver.[19]

For hepatitis B, quick treatment with immune globulin immediately after exposure can help prevent the onset of chronic hepatitis. If the hepatitis B infection does become chronic, antivirals, including tenofovir (Viread), lamivudine (Epivir) and adefovir (Hepsera) may be prescribed to slow the virus' growth. Interferon alfa-2b may also be given in conjunction with an antiviral.[20] There are also reports that hepatitis E can be cleared from immunocompromised patients with antiviral drugs.[21]

Further, there is good news in that it is now possible to cure hepatitis C via antiviral drugs — with a success rate of more than 95 percent. A dozen antiviral drugs are approved by the U.S. Food and Drug Administration to treat hepatitis C, ranging from sofosbuvir (Sovaldi) to ribavirin (RibaPak).[22]

Hepatitis D, which can only be contracted by someone who already has hepatitis B, will be treated alongside hepatitis B. Hepatitis D is usually treated with a 48-week regimen of pegylated interferon alpha.[23]

Toxic hepatitis is generally treated similarly to hepatitis A: with rest and liquids. In the case of an overdose of acetaminophen, a drug called acetylcysteine can be administered to limit the damage to the liver — but only if administered within 16 hours of the original acetaminophen exposure.[5]

CDC Guidance for Clinicians, Parents and Caregivers of Children with Potential Acute Hepatitis

1) Clinicians should continue to perform the standard diagnostic workup for children with acute hepatitis.
2) Clinicians should also be testing patients for the adenovirus.
3) Children should be up to date in all their vaccinations.
4) Parents and caregivers should follow everyday actions already recommended for prevention of other infections such as washing hands and avoiding people who are sick, covering coughs and sneezes and avoiding touching the eyes, nose or mouth.

Autoimmune hepatitis is approached with the goal of inducing remission. Steroids (prednisone) can stop the body's immune system from attacking the liver. They can be used in conjunction with immunosuppressants such as azathioprine or mercaptopurine.[13]

Treatment for hepatitis of unknown origin is more involved than in other cases in order to head off possible complications. As with acute hepatitis, rest and liquids are called for. In addition, limiting protein intake and watching for a decline in liver function, as well as maintaining blood electrolyte levels and watching coagulation function, are important.[24] If patients test positive for an adenovirus, that infection can be addressed with antivirals, including cidofovir, ganciclovir and ribavirin.[25]

Treatment for chronic hepatitis will depend upon the specific cause.

In all instances of hepatitis, a liver transplant may become necessary if the inflammation cannot be controlled and there is significant damage. In younger children especially, the transplant may need to be only a portion of an adult donor liver, which makes it possible to utilize a living donor.

Prevention

Effective vaccinations are available for hepatitis A and B, and these should be administered as outlined by public health authorities. If traveling to areas where hepatitis E outbreaks are known to occur, individuals should drink only treated water, or boil or chlorinate water before drinking it.

To prevent toxic hepatitis, keeping all medications away from children is crucial. This includes vitamins and over-the-counter pain killers.

Women who are pregnant or may become pregnant should avoid sharing needles (or even using recreational drugs), and should be tested for hepatitis during pregnancy.

To prevent hepatitis of unknown cause, parents should use normal hygienic routines to inhibit the spread of adenoviruses. For instance, children should be reminded to wash their hands thoroughly with warm water and soap before meals and after using the bathroom, and if practical, wear a face mask in social settings where respiratory illness is known to be circulating.

Reporting Is Necessary

With information scarce and research still ramping up on the possible links between adenoviruses and hepatitis of unknown cause, physicians should report any such patients to public health authorities to help build our body of knowledge. ❖

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Childhood Hepatitis: *A Patient's Perspective*

By Trudie Mitschang

WHEN KELSEA Schwab's then 2-year-old daughter Baelyn became ill in April 2022, Kelsea attributed her runny nose and hives to an allergic reaction and scheduled a routine visit to their primary care physician. It was the next day as Baelyn's symptoms worsened that Kelsea began to suspect something else was wrong. "I noticed that her eyes were more yellow than usual. I thought it could be due to the allergy medication, but they kept getting worse."

That weekend, another family member pointed out how strange Baelyn's eyes looked. Her suspicions confirmed, Kelsea brought her daughter into the doctor the following Tuesday. She was shocked when the doctor called after performing blood tests and diagnosed Baelyn with acute hepatitis and possible liver failure. Their physician referred the family to M Health Masonic Children's Hospital in Minneapolis for treatment and told them to get there as soon as possible. Baelyn was airlifted to Minnesota later that day.

Prepping for Transplant

Once the family arrived at the hospital, a multidisciplinary team that ran tests on Baelyn found her liver failure was severe. Baelyn's care team — and family — held out hope that her liver would recover on its own without the need for transplant. Srinath Chinnakotla, MD, MCh, FACS, MBA, surgical director of liver transplantation and professor of surgery at University of Minnesota Medical School, was assigned to Baelyn's case and visited her daily to monitor the ammonia levels in her liver to see if they stabilized on their own. "When her ammonia levels started climbing, that's when I got nervous," Dr. Chinnakotla said. Not wanting to wait any longer, the medical team placed Baelyn on the transplant waiting list on April 29, less than a week after Kelsea first noticed that Baelyn's eyes had turned yellow.

In preparation for transplant, Baelyn was put on an antiviral medication to treat her for adenovirus. Adenovirus is a common illness that presents in the majority of hepatitis patients, and typically only causes cold or flu-like symptoms. Since Baelyn's doctors found the virus was active in her bloodstream, and because transplant severely weakens a person's immune system, it was important to prevent the virus from spreading after transplant and attacking her healthy new liver.

The Road to Recovery

Baelyn was fortunate that her time on the waiting list was short. A matching donor liver became available quickly and she underwent transplant surgery on May 5, just over a week after being admitted to the hospital. Dr. Chinnakotla performed the operation, his second pediatric transplant for liver failure that year. "The number of pediatric transplants done for acute liver failure [is] typically a few every year," he noted. "This year, we've already seen two children with liver failure and transplanted two children with liver failure. This is very unusual for us."

Baelyn also had an unusual anatomy: She had two small vessels supplying blood to her liver instead of one larger one. Dr. Chinnakotla used blood vessels from the same liver donor to create a unique bridge graft, known as an aortohepatic conduit. Despite the challenges, the surgery was successful, and Kelsea noticed an almost immediate difference in her daughter. Before transplant, Baelyn's skin had turned a dark yellow — almost orange — color. By the time she woke up, it had returned to normal. A short time later, Kelsea recalls, Baelyn's fiery personality returned as well, and she began to play, walk and become her normal, rambunctious self.

"Baelyn has been such a trooper through everything. She has always had such a positive attitude and doesn't struggle at all with the many appointments, pokes or anything of [the like]," says Kelsea. "Pretransplant, I was working full time and was the primary earner in the home. Since transplant, I have had to take a step back from work, and my full-time job is taking care of Baelyn and advocating for her. It hasn't always been easy, but [we connect] with other pediatric transplant families and [utilize] the hospital's resources such as biweekly caregiver calls. We all stick together and are bonded through the medical life."

Baelyn's story, though unusual, was one of nearly 200 hepatitis outbreaks that affected children in 36 states between November 2021 and May 2022.[1] Public health experts are still researching the causes, but for the Schwab family, it's a health scare they are thankful to finally put behind them. Since the operation, Baelyn has gotten a gastrostomy tube and continues to receive full nutrition through that because of a recent diagnosis of gastroparesis. She also receives speech, occupational and physical therapy multiple times per week, and is excited to start preschool this fall. ❖

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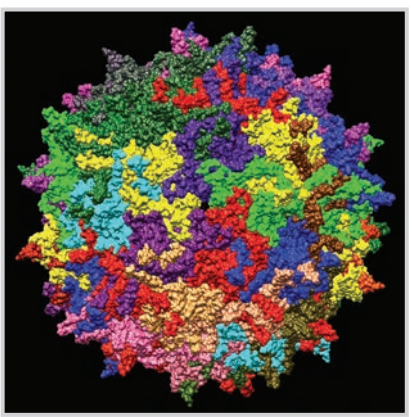
The 2022 Childhood Hepatitis Outbreak:

What We Know Now



IN 2022, A MYSTERIOUS and unexplained outbreak of acute severe hepatitis began striking previously healthy children. As cases began to escalate between April and July of that year, more than 1,000 children globally (and at least 350 children in the United States) were diagnosed with hepatitis. The hallmark of the disease is liver inflammation. According to the World Health Organization, nearly 50 children who were infected ended up needing liver transplants; 22 of the infected children died from the disease.[1]

The mystery behind this sudden outbreak left families devastated and the medical community puzzled, sparking a number of research studies aimed at uncovering the root cause. Finally, nearly a year later in January 2023, it was learned that three independent studies published in the multidisciplinary science journal *Nature* all came to a similar conclusion: The presence of the adeno-associated virus 2 (AAV2) in the blood and livers of infected children might be the clue researchers were looking for.[2]

AAV2 is a common childhood virus that the study authors found was present among nearly all of the children with unexplained acute hepatitis; many were also infected with multiple "helper" viruses. And, although the researchers can't say for sure, the timing of the outbreak may have been associated with the global loosening of COVID-19 pandemic restrictions after periods of relative isolation.

"Children were suddenly exposed to a barrage of viruses after lockdowns, or had poorly trained immune systems that led to an increased susceptibility to otherwise harmless viruses," said Frank Tacke, MD, PhD, associate professor for hepato-gastroenterology and executive senior physician at the Department of Medicine III of the University Hospital Aachen, Germany, in an editorial published alongside the new studies. "The fact that three independent groups found this from different areas of the world actually makes it really convincing."[3]

One of the studies conducted at the University of California, San Francisco (UCSF) analyzed tissue samples from children in the United States and detected AAV2 in 93 percent of 14 cases. The researchers also found that all children infected with AAV2 had co-infection with a "helper" virus — either human herpes virus 6 or Epstein-Barr virus — that might promote AAV2 replication. The UCSF study concluded that for a small subset of these children, getting more than one infection at the same time may have made them more vulnerable to severe hepatitis.

"We were surprised by the fact that the infections we detected in these children were caused not by an unusual, emerging virus, but by common childhood viral pathogens," said Charles Chiu, MD, PhD, professor of laboratory medicine in the Division of Infectious Diseases, director of the UCSF Clinical Microbiology Laboratory and senior author of the paper. "That's what led us to speculate that the timing of the outbreak was probably related to the really unusual situations we were going through with COVID-19-related school and daycare closures and social restrictions. It may have been an unintended consequence of what we have experienced during the last two to three years of the pandemic."[4]

The findings from the UCSF study mirrored the results of two concurrent studies conducted in the United Kingdom, Dr. Chiu said. These identified the same AAV2 strain. All three studies also identified co-infections from multiple viruses and about 75 percent of the children in the U.S. study had at least three or four viral infections.

Other key takeaways included:

- Children may be especially vulnerable to more severe hepatitis triggered by co-infections.
- While infections from adeno-associated viruses can occur at any age, the peak is typically between ages 1 and 5 years.
- The median age of the affected children in the study was 3 years old.
- The findings from all of these studies were published in March 2023. ❖

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Just Arrived: A Trio of Active and Passive Vaccines Against RSV

By Keith Berman, MPH, MBA

FOR DECADES, respiratory syncytial virus (RSV) — a leading cause of serious lower respiratory tract disease (LRTD) in infants and older individuals — has defied the best efforts of vaccine makers to bring it to heel. Now over a span of less than three months between May and July of this year, U.S. marketing approvals of two novel, highly targeted RSV vaccines and a human RSV monoclonal antibody product have finally ended that long record of research futility.

Available in time for this fall/winter 2023-2024 RSV season, these three new agents offer the potential to importantly cut the annual toll in illness, death, healthcare costs and broader economic costs attributable to RSV.

The RSV Disease Burden

Most children and adults infected with RSV experience only minor cold-like symptoms, including rhinorrhea, coughing and sneezing, which generally resolve on their own within a week or two. But this is not the case for infants entering the RSV season within their first six months of life, for young children with congenital pulmonary or heart disease, or for older adults, particularly those with a long list of chronic comorbidities. All are at sharply increased risk for their RSV infection to progress to severe LRTD.

Each year among young children, RSV accounts for at least 57,000 hospitalizations, 500,000 emergency department visits and one-and-a-half million outpatient clinic visits.[1] The U.S. Centers for Disease Control and Prevention (CDC) estimates that RSV infection may be associated with up to 20 percent of hospitalizations and 18 percent of emergency department visits for acute respiratory infections in children under 5 years of age.[2]

A separate CDC analysis of U.S. hospital discharges over a 10-year period found the RSV-related disease burden falls most heavily on very young infants, with 26 LRTD-related hospitalizations per 1,000 infants under age 1 year dropping more than 10-fold to 1.8 per 1,000 children between ages 1 and 5 years. RSV additionally accounts for about 100 to several hundred deaths annually among infants under 1 year of age.[3]

In adults, it is estimated that RSV infections result in between 60,000 and 160,000 hospitalizations of older adults each year, and 6,000 to 10,000 deaths. Adults at highest risk for severe RSV infection and its complications include those over age 60, and those with chronic heart or lung disease, compromised immunity and certain other underlying health conditions, including diabetes, asthma and chronic kidney disease.[4] The most serious complications secondary to RSV infection include pneumonia, congestive heart failure and exacerbations of chronic obstructive pulmonary disease or asthma symptoms.

A landmark study that prospectively followed separate cohorts of healthy elderly adults and high-risk U.S. adults found nearly 30 percent of high-risk RSV-infected patients made a physician office visit, more than 50 percent higher than the visit rate for generally healthy elderly patients who contracted RSV. But more tellingly, nine percent of high-risk RSV-infected patients made an emergency room (ER) visit and 16 percent were hospitalized, while none of the RSV-infected healthy elderly patients required an ER visit or hospitalization. Nevertheless, RSV infection can infrequently result in serious lower respiratory tract infections (LRTIs) in generally healthy elderly adults.[5]

Decades of Vaccine False Starts

Since RSV was first discovered in 1956, all past attempts to develop safe and effective RSV vaccines have proven unsuccessful. Clinical testing of an early inactivated form of RSV in the mid-1960s proved disastrous when 80 percent of vaccinated children in one study were hospitalized and two toddlers died when they contracted the virus. Later research revealed antibodies produced by the children's immune systems bound to RSV but did not neutralize it, instead triggering a cascade of events leading to inflammation and lung tissue damage. This phenomenon, called antibody-dependent enhancement, occurs when the body produces antibodies that fail to confer adequate protection and instead act to exacerbate the infection.

Over the following decades, most vaccine development has focused on the RSV F antigen, which facilitates membrane fusion and viral penetration into the host cell. But progress continued to stagnate until a molecular biologist at the National Institutes of Health Vaccine Center applied atomic structure mapping to show that the F protein has distinct prefusion and postfusion conformations.[6] It was subsequently determined that antibodies against the prefusion F (preF) conformation effectively neutralize the circulating form of the virus before it fuses to cells, while those against the postfusion protein shape do not.

New RSV Vaccines Approved for Older Adults

Additional research resulted in the isolation of a potent RSV-neutralizing antibody against a highly conserved epitope on preF that effectively blocks viral fusion and entry into host cells. After 50 years of futility, these discoveries led directly to the development and licensure, in May of this year, of the first two RSV vaccines approved for the prevention of LRTD in individuals aged 60 years and older: GlaxoSmithKline's Arexvy and Pfizer's ABRYSVO (Table 1).

AREXVY (GlaxoSmithKline [GSK]). The first-ever RSV vaccine to be approved in the U.S., GSK's recombinant subunit preF glycoprotein antigen vaccine is combined with the company's proprietary AS-01 adjuvant system incorporated into several licensed GSK vaccines. AREXVY (previously RSVPreF3) is administered as a single intramuscular (IM) dose.

The U.S. Food and Drug Administration's (FDA) approval of AREXVY is based on safety and efficacy findings from the pivotal AReSVi-006 Phase III trial conducted in adults ≥60 years of age at 275 sites in the U.S. and 16 other countries. Over a median follow-up of 6.7 months, vaccine efficacy against RSV LRTD was 82.6 percent (96.95 percent confidence interval [CI], 57.9 to 94.1), with seven cases of RSV-LRTD in the vaccinated group (n = 14,467), compared to 40 cases in the placebo group (n = 14,499). Vaccine efficacy (VE) against severe RSV-LRTD, defined as an RSV-associated LRTD episode preventing normal everyday activities, was 94.1 percent, with just a single case in vaccinated subjects versus 17 cases in placebo-treated subjects.[7]

AREXVY was well-tolerated; most observed adverse events included injection site pain, fatigue, myalgia, headache and arthralgia, all of which were generally mild to moderate and transient. However, two South African study participants in a separate smaller trial developed acute disseminated encephalomyelitis (ADEM) seven and 22 days after receiving AREXVY concomitantly with a seasonal influenza vaccine, and a Japanese patient in a second trial was diagnosed with Guillain-Barré syndrome (GBS) nine days after receiving AREXVY.[8] GSK

Table 1. New FDA Approvals of Active and Passive Immunotherapies for the Prevention of RSV-Caused Lower Respiratory Tract Disease (LRTD) in Infants and Older Adults

Approval	Product (Manufacturer)	Indication(s)
5/3/2023	AREXVY Respiratory Syncytial Virus Vaccine, Adjuvanted (GlaxoSmithKline)	Active immunization for the prevention of lower respiratory tract disease (LRTD) caused by RSV in individuals 60 years of age and older
5/31/2023	ABRYSVO Respiratory Syncytial Virus Vaccine (Pfizer)	Active immunization for the prevention of LRTD caused by RSV in individuals 60 years of age and older
8/21/2023		Active immunization of pregnant women at 32 through 36 weeks gestational age for the prevention of LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age
7/17/2023	Beyfortus Nirsevimab-alip (AstraZeneca/Sanofi)	Prevention of RSV LRTD in 1) neonates and infants born during or entering their first RSV season and 2) children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season

will conduct a postmarketing study to identify any signals of serious risks for ADEM and GBS.

ABRYSVO (Pfizer). Encouraged by an earlier study showing 87 percent protective efficacy against symptomatic RSV infection in healthy volunteers intranasally inoculated with the live virus,[9] Pfizer investigated its own RSV prefusion F antigen vaccine (RSVPreF) in the Phase III randomized, placebo-controlled RENOIR trial in adults ≥60 years of age. ABRYVSO is an unadjuvanted bivalent preF vaccine; the two preF proteins were selected to optimize protection against both RSV A and B strains.

At data cutoff, more than 34,000 participants were enrolled at 240 clinical sites in seven countries. RSV-associated acute respiratory illness occurred in 22 participants in the vaccine group (2.38 cases per 1,000 person-years of observation) and 58 participants in the placebo group (6.30 cases per 1,000 person-years), translating in VE of 62.1 percent (95 percent CI, 37.1 to 77.9).[10]

RSV LRTD with at least two signs or symptoms occurred in 11 participants in the vaccine group (1.19 cases per 1,000 person-years) and 33 participants in the placebo group (3.58 cases per 1,000 person-years), for a VE of 66.7 percent (96.66 percent CI, 28.8 to 85.8). RSV LRTD with at least three signs or symptoms occurred in just two and 14 cases in the vaccine and placebo groups, respectively, for a VE of 85.7 percent (96.66 percent CI, 32.0 to 98.7). Very similar rates of adverse events and severe adverse events were reported for both treatment arms.

Pfizer plans to initiate additional clinical trials to evaluate ABRYVSO in healthy children ages 2 to 5, children ages 5 to 18 at high risk for LRTD due to underlying medical conditions, and immunocompromised adults 18 and older who are at high risk for LRTD.

In early August, GSK filed a lawsuit against Pfizer in U.S. court, alleging ABRYSVO infringes four of its patents related to recombinant RSV antigens used in Arexvy, as well as the methods used to create this and other vaccine components.[11] GSK has requested a jury trial and is seeking monetary damages, including lost profits and royalties. The United Kingdom drugmaker is also asking a judge to prevent Pfizer from manufacturing and selling ABRYSVO in the U.S. for adults aged 60 and older.

Pfizer responded that it "is confident in its intellectual property position and will strongly defend its right to bring its innovative RSV vaccine ABRYSVO to patients."[11]

Meanwhile, both GSK and Pfizer have launched public awareness campaigns targeting Americans age 60 and older (Figure 1), particularly those living with chronic health conditions associated with increased risk of severe RSV disease.

Passive Immunotherapy for Preterm and High-Risk Infants

Because of the immaturity of antibody-mediated immunity in the first months of life, active immunization with an RSV vaccine cannot confer adequate protection against RSV-associated LRTD.

With this in mind, scientists at MedImmune, now part of AstraZeneca, developed nirsevimab (formerly MEDI8897), a highly potent recombinant human monoclonal antibody (MAb) that targets a highly conserved site of the prefusion conformation of the RSV fusion (F) protein. Additionally, a substitution of three amino acids in the Fc domain of nirsevimab extends its half-life three-fold, allowing for a single IM dose of this long-acting MAb to cover a typical five-month RSV season.

Nirsevimab has been shown to neutralize a diverse panel of RSV A and B strains, with more than 50-fold higher activity than palivizumab (Synagis), another MedImmune-developed anti-RSV MAb approved in

Figure 1. Pfizer and GSK Promotional Materials Encouraging Persons 60 and Older to Inquire About RSV Vaccination

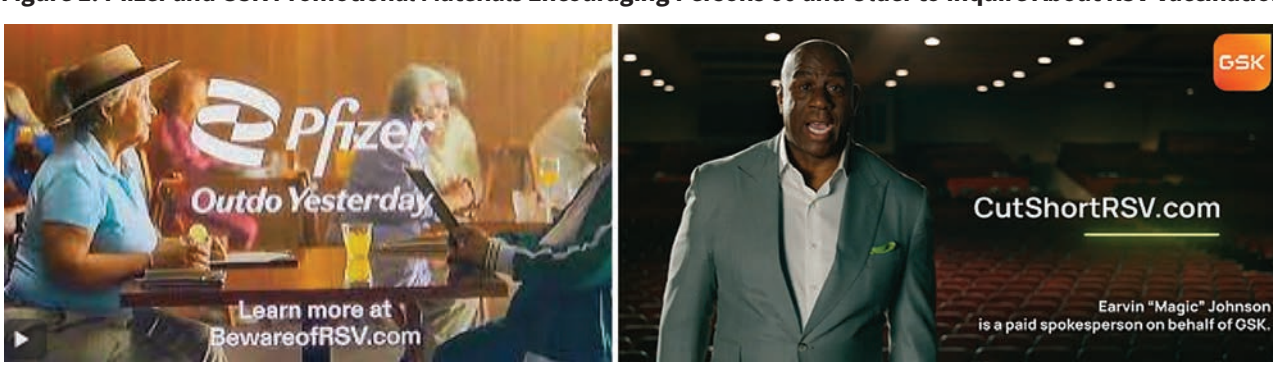


Table 2. Phase IIb and Phase III Clinical Study Findings Documenting Efficacy of Beyfortus (nirsevimab) for Prevention of RSV-Related Lower Respiratory Tract Infection

Trial	Target Population	Study Design (n)	Risk Reduction with Nirsevimab vs. Placebo
Study 03 (Phase IIb)	Preterm infants (born at ≥29 to <35 weeks gestational age) born during or entering their first RSV season	Medically attended RSV lower respiratory tract infection (LRTI); infants randomized 2:1 to receive a single dose of Beyfortus or placebo (n = 1,453)	70% (2.6% vs. 9.5%)
Study 04 (Phase III)	Term and late preterm infants (born at >35 weeks gestational age)	Medically attended RSV LRTI; infants randomized 2:1 to receive a single dose of Beyfortus or placebo (n = 1,490)	75% (1.2% vs. 5.0%)

1998 for the prevention of serious LRTD in premature infants (≤35 weeks gestational age) and children with bronchopulmonary dysplasia or congenital heart disease.

Approved in July and brand-named Beyfortus, nirsevimab is indicated for the prevention of RSV LRTD in neonates and infants born during or entering their first RSV season, and in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. Beyfortus will be manufactured by AstraZeneca and distributed through Sanofi, and will be available ahead of the upcoming 2023-2024 RSV season.

Two key clinical studies have demonstrated the ability of a single dose of Beyfortus to achieve a 70 to 75 percent reduction in the risk of medically attended LRTI in preterm and full-term infants, as well as infants with pulmonary or cardiac conditions placing them at high risk for LRTI (Table 2).

In addition to a 70 percent reduction in risk of bronchiolitis, pneumonia and other medically attended LRTIs, preterm infants enrolled in a Phase IIb study (Study 03) who received a single prophylactic dose of Beyfortus experienced a 78.4 percent lower incidence of hospitalization (0.8 percent versus 4.1 percent) than those given placebo.[12] The Phase II/III MEDLEY trial documented a similar safety and tolerability profile for nirsevimab compared to palivizumab treatment when administered to preterm infants or those with chronic lung disease or congenital heart disease entering their first RSV season.[13]

Subsequently, a multinational Phase III study (Study 04) demonstrated that, compared to placebo injection, a single IM injection of nirsevimab achieved a 74.5 percent reduction in the incidence of LRTI caused by RSV in healthy preterm (≥35 weeks gestational age) and term infants entering their first RSV season (1.2 percent versus 5.0 percent; P<0.001).[14]

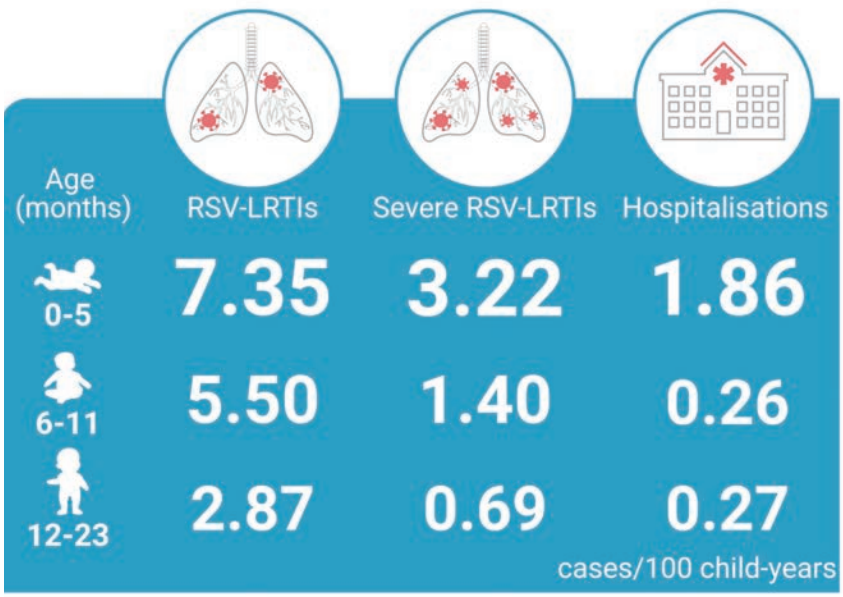
In a pooled post-hoc analysis, blood samples taken from infants dosed with nirsevimab exhibited RSV neutralizing antibodies roughly 50-fold higher than baseline at Day 151 post-dose. RSV neutralizing antibody levels remained greater than 19-fold higher than levels in placebo recipients, with no known RSV infection through Day 361, suggesting protection could extend beyond Day 151.

In addition, real-world data from the Phase IIIb HARMONIE study documented an 83.2 percent (95 percent CI, 67.77 to 92.04) reduction in hospitalizations due to RSV-related LRTD in infants under 12 months of age who received a single dose of nirsevimab, compared to infants who received no RSV intervention.[15]

This clinical trial, which recruited more than 8,000 infants at nearly 250 sites across France, the United Kingdom and Germany, also documented a 58 percent lower incidence of all-cause hospitalizations in infants who received a single dose of nirsevimab. "This means the overall burden on healthcare systems could be reduced significantly if all infants receive nirsevimab," Sanofi said in an announcement of its HARMONIE study findings.[16]

> The first-ever RSV vaccine to be approved in the U.S., GSK's recombinant subunit preF glycoprotein antigen vaccine is combined with the company's proprietary AS-01 adjuvant system incorporated into several licensed GSK vaccines.

Figure 2. Incidence Rates of RSV-LRTIs, Severe RSV-LRTIs and Resulting Hospitalizations in Three Infant Age Cohorts



Source: Langley JM, Bianco V, Domachowske JB, et al. *J Infect Dis* 2022 Aug 26;226(3):374-85.

Young Infant RSV Protection by Maternal Vaccination

A recent multinational investigation of clinical RSV infection in children under age 2 years has confirmed what one would expect: The highest rate of RSV LRTI occurs in infants under 6 months of age. The incidence of first-episode RSV-LRTIs at age 0 to 5 months was one-third higher than the incidence at age 6 to 11 months, and more than 2.5-fold higher than at age 12 to 23 months.[17]

But more importantly, the incidence rates of both severe RSV-LRTIs and RSV-related hospitalization were many-fold higher over the first six months than the following 18 months of life (Figure 2).[17] This owes both to the immaturity of immune defenses in very young infants and the high surface-to-volume ratios in their still-developing airways. Because nearly all pulmonary airways and alveoli are present at birth, the bronchiolar lumen size in young infants is smaller relative to that of an adult and thus more prone to obstruction.[18]

It is now well-established that exogenously administered anti-RSV MAbs like nirsevimab can protect very young infants who are unable to self-generate sufficiently protective antibody titers against RSV. However, Pfizer and other RSV vaccine developers have instead pursued an entirely different protective antibody prophylaxis strategy: RSV vaccination of pregnant women to effect transplacental transport of their anti-RSV antibodies to the maturing fetus.

Three months after FDA approval of Pfizer's ABRYSVO for prevention of LRTD caused by RSV in persons 60 years of age and older, the vaccine received a second approval for active vaccination of pregnant women at 32 to 36 weeks gestational age for the prevention of RSV-caused LRTD and severe LRTD from birth through 6 months of age.

"Newborns and young infants — whose immune systems are still developing and are not yet strong enough to defend against infections — may now be protected from RSV from the moment of birth through maternal immunization," said Eric A.F. Simões, MD, a MATISSE study investigator.

FDA approval for this novel indication was based on data from the pivotal Phase III MATISSE trial, which randomly assigned more than 7,300 maternal participants at 24 through 36 weeks' gestation to receive a single IM injection.[19] Within the first 90 days after birth, severe LRTI occurred in just six infants in the vaccine group and 33 infants in the placebo group, for a VE of 81.8 percent (95 percent CI, 40.6 to 96.3); 19 cases and 62 cases, respectively, occurred within 180 days after birth, translating into a VE of 69.4 percent.

But while ABRYVSO was judged to be efficacious at protecting infants during their first six months from severe RSV disease, there was a non-statistically significant imbalance in the number of premature births: 201 in the vaccinated group versus 169 in the placebo group, or about one percent higher.

While most preterm births had already reached 33 weeks of pregnancy and prematurity rates in both treatment arms fell below the overall U.S. population average, it still raised concerns with some FDA advisory panel members, particularly in light of GSK's decision last year to abandon a similar clinical trial program for its investigational RSV vaccine,* after observing an increased

* Licensed in May 2023 under the brand name Arexvy for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older.

incidence of premature deliveries compared to placebo.[20]

After careful review of the MATISSE study data, FDA decided to address this concern over a possible risk of vaccine-related prematurity by restricting the maternal vaccination window to gestational weeks 32 to 36. In addition, using Medicaid and commercial insurance claims databases, Pfizer will conduct a postmarketing study to follow multiple safety endpoints, including rates of premature births and low birth weight at delivery.

Putting RSV Preventive Tools Into Practice

While both the GSK and Pfizer RSV vaccines are broadly indicated for the prevention of LRTD caused by RSV in individuals age 60 and older, the CDC's Advisory Committee on Immunization Practices (ACIP) has recommended "shared clinical decision-making" between providers and patients.[21] The decision about whether or not to vaccinate, according to ACIP, should be based on a discussion about "the patient's risk for disease and their characteristics, values and preferences; the provider's clinical discretion; and the characteristics of the vaccine."

This differs from ACIP's recommendation of routine seasonal influenza vaccination for all age groups, including older adults. A recommendation of shared clinical decision-making reflects the fact that persons ≥60 years of age with chronic lung, cardiovascular, kidney, liver, hematologic and certain other medical conditions are at highest risk for severe RSV disease and are most likely to benefit from RSV vaccination. Additionally, the AREXVY and ABRYSVO trials were underpowered to estimate efficacy against RSV-associated hospitalization and death.

Still, according to ACIP, "prevention of LRTD, including medically attended LRTD, suggests that vaccination might prevent considerable morbidity from RSV disease among adults aged ≥60 years."[21] CDC says it will prioritize estimating VE against RSV-associated hospitalization, which may provide further guidance for shared decision-making between physicians and patients.

Separately, ACIP has recommended Beyfortus (nirsevimab) specifically for infants aged less than 8 months born during or entering their first RSV season, and for infants and children aged 8 to 10 months who are at increased risk of severe RSV disease entering their second RSV season.[22] But this new recommendation was published the very same week that Pfizer's ABRYSVO received its second approval for immunization of pregnant women to prevent RSV LRTD in infants in their first six months of life.

Will young infants delivered from mothers immunized with ABRYSVO experience meaningful added protective benefit from passive immunization with Beyfortus? Which adults over age 60 experience clinically meaningful benefit from RSV vaccination? Will periodic booster shots be needed, and when? The answers to these questions and more must await real-world experience. In the meantime, we all can be thankful for the extraordinary science and the considerable investments that made these products possible. ❖

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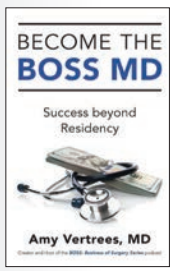

Become the BOSS MD: Success Beyond Residency

Author: Amy Vertrees, MD

In *Become the BOSS MD*, surgeon and certified life coach Amy Vertrees, MD, helps physicians navigate the processes and pitfalls of a career in medicine. This five-part guide offers fresh perspectives and sage advice for physicians in all stages of their career. Readers will learn how to match their strengths with available options, market their practice, lobby for causes, measure performance, budget clinical resources and protect personal assets. This book reveals the secret to empowerment and the joy possible when physicians become their own advocate.

www.amazon.com/Become-BOSS-MD-Success-Residency/dp/1544542933

New Suite of Compounding Pharmacy Manuals

Author: ACHCU

ACHCU, the educational and training division of Accreditation Commission for Health Care Inc. (ACHC), is introducing a suite of resource manuals to help compounding pharmacies align their practices with recently updated requirements from the United States Pharmacopeia (USP). The four newly available manuals support specific compliance needs within the profession: non-sterile non-hazardous compounding, non-sterile hazardous compounding, sterile non-hazardous compounding and sterile hazardous compounding. Available as a complete resource for all compounding services or as individual manuals, each one comes complete with guidelines that adhere to USP requirements for policies and procedures, standard operating procedures, specific job descriptions, competency assessments and various forms to evaluate efficiency.

www.achc.org/wp-content/uploads/2023/04/2023.04.04_ACHCU_Compounding-Pharmacy-Manuals_New-Product.pdf

Peripheral Brain for the Pharmacist 2023-24

Author: Ananda Chatterjee

Peripheral Brain for the Pharmacist is a pocket-sized collection of resources for student pharmacists and pharmacists alike. This book provides quick references to commonly accessed clinical information required in a variety of pharmacy practice settings. APhA's new 2023-24 edition includes more than 90 individual core reference pages, including new content on considerations for emergency room care, new presentation of important information for transplant pharmacy and expansions of resources for psychiatric medications.

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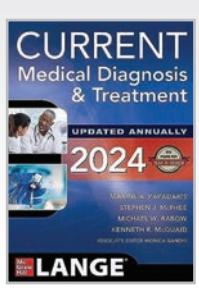
CURRENT Medical Diagnosis and Treatment 2024, 63rd Edition

Authors: Maxine Papadakis, MD, Stephen McPhee, MD, Michael Rabow, MD, Kenneth McQuaid, MD, and Monica Gandhi, MD



In *CURRENT Medical Diagnosis and Treatment 2024*, students, residents and clinicians will find authoritative, evidence-based coverage of more than 1,000 diseases and disorders, along with concise yet thorough synopses of diagnosis and treatment. This book covers all aspects of outpatient and inpatient care and includes discussion of new developments and breakthroughs in medicine. New to this edition are the latest USPSFT recommendations for cardiovascular risk prevention; new opioid prescribing guidelines from CDC; clarification on the distinction between uncontrolled hypertensive and hypertension emergency; latest classification of lymphomas released by WHO; recommendations for the initiation and titration of treatment for chronic hypertension in pregnancy; current treatment guidelines and medications for H pylori infection; classification of the role, dosing and potential risks of JAK inhibitors and anti-23 antibody (risankizumab) in the treatment of IBD; updates that underscore the growing utility of combination treatments for high LDL levels, especially among high and very high-risk patients; and the WHO revision of the pathological classification of renal cell carcinoma to assist with prognosis prediction and treatment decisions.

wwww.amazon.com/CURRENT-Medical-Diagnosis-Treatment-2024/dp/1265556032

Early Albumin Administration May Reduce Mortality in Septic Shock and ARDS: Retrospective MIMIC III Database Study

Acute respiratory distress syndrome (ARDS), a frequent complication of septic shock (SS), involves the rapid onset of hypoxemia and bilateral pulmonary edema caused by increased alveolocapillary permeability. ARDS patients have the characteristics of hypoalbuminemia, which may impact the progression of pulmonary edema. While a recent meta-analysis indicated that early administration of albumin to ARDS patients could decrease alveolar-capillary leakage and improve oxygenation, it is also known that tissue edema may be exacerbated by the extravasation of colloid molecules in patients with high capillary leakage.

The investigators, therefore, aimed to determine if early human albumin administration can improve survival in septic shock patients with ARDS using the Medical Information Mart for Intensive Care (MIMIC) III database, a large open-source U.S. medical record database publicly available in PhysioNet.

The 28-day mortality rate in 135 patients who received albumin was significantly lower than in 730 patients not treated with albumin (37% versus 47%, $p = 0.018$). After propensity matching, the difference between the two groups remained significant (34.8% versus 48.1%, $p = 0.031$). At 90 days, mortality in the albumin group remained lower than in the non-albumin group (42.2% versus 68.2%, $p < 0.01$).

The relationship between early albumin treatment and lower mortality remained significant in prespecified subgroups, including age <75 or ≥75 years; presence or absence of heart failure; absence of renal failure; non-glucocorticoid use; a SOFA score ≤10; or mild or moderate hypoxemia. However, the association was insignificant in subgroups with glucocorticoid use, renal failure, severe hypoxemia or a SOFA score >10.

The investigators concluded that early albumin administration in septic shock patients with ARDS was independently associated with a reduction in 28-day mortality, and that its survival benefit appeared to be more pronounced in patients with a SOFA score of ≤10. ❖

Wang, X, Zhang, T, Gao, X, et al. Early Human Albumin Administration Is Associated with Reduced Mortality in Septic Shock Patients with Acute Respiratory Distress Syndrome: A Retrospective Study from the MIMIC-III Database. *Frontiers in Physiology,* 2023 Apr 7;14:1142329.

Combination of IVIG and Corticosteroids Superior to Respective Monotherapies for Treatment of Relapsed ITP in Adults

Chinese investigators conducted a retrospective analysis of clinical data on adult patients with relapsed immune thrombocytopenic purpura (ITP) who received first-line combination therapy with intravenous immune globulin (IVIG) and corticosteroids or their respective monotherapies. Clinical characteristics, efficacy and safety of these three treatment alternatives were captured on 205 patients at multiple centers across the country from 2010 through 2022.

The proportion of patients with platelet count elevations consistent with a complete response was significantly higher in the combination therapy group (71.83%) compared with the IVIG group (43.38%) and the corticosteroids group (23.08%). The mean maximum platelet count in the combination therapy group was also significantly higher (178 x 10^9/L) than in the IVIG group (109 x 10^9/L) and the corticosteroids group (76 x 10^9/L).

Additionally, the average time for platelet counts to first reach 30 x 10^9/L, 50 x 10^9/L and 100 x 10^9/L in the combination group was significantly shorter than in the two monotherapy groups. No significant difference was observed in adverse event rates between the three treatment groups. The study authors concluded that "the combination of IVIG and corticosteroids is a more efficient and rapid treatment for relapsed ITP in adults compared with the use of either therapy alone." ❖

Fang, L, Sun, J, Zhao, Y, et al. Efficacy and Safety Analysis of Combination Therapy Consisting of Intravenous Immunoglobulin and Corticosteroids Versus Respective Monotherapies in the Treatment of Relapsed ITP in Adults. *Global Medical Genetics,* 2023 Jun; 10(2):87-96.

Medicare Immune Globulin Reimbursement Rates

Rates are effective Oct. 1, 2023, through Dec. 31, 2023

	Product	Manufacturer	J Codes	ASP + 6% (before sequestration)	ASP + 4.3% (after sequestration)
IVIG	ASCENIV	ADMA Biologics	J1554	$982.81	$967.05
	BIVIGAM	ADMA Biologics	J1556	$145.92	$143.58
	GAMMAGARD SD	Takeda	J1566	$153.13	$150.68
	GAMMAPLEX	BPL	J1557	$114.02	$112.19
	OCTAGAM	Octapharma	J1568	$89.57	$88.14
	PANZYGA	Octapharma/Pfizer	J1576	$131.41	$129.30
	PRIVIGEN	CSL Behring	J1459	$95.18	$93.65
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$88.92	$87.49
	GAMMAKED	Kedrion	J1561	$98.52	$96.94
	GAMUNEX-C	Grifols	J1561	$98.52	$96.94
SCIG	CUTAQUIG	Octapharma	J1551	$140.42	$138.17
	CUVITRU	Takeda	J1555	$157.25	$154.73
	HIZENTRA	CSL Behring	J1559	$127.28	$125.24
	HYQVIA	Takeda	J1575	$168.88	$166.17
	XEMBIFY	Grifols	J1558	$139.71	$137.47

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Immune Globulin Reference Table

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

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

2023-2024 Influenza Vaccine

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

Product	Manufacturer	Presentation	Age Group	Code
Quadrivalent				
AFLURIA (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	3 years and older	90685
AFLURIA (IIV4)	SEQIRUS	5 mL MDV	6 months and older	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	0.5 mL PFS 10-BX	18 years and older	90682
FLUCELVAX (ccIIV4)	SEQIRUS	0.5 mL PFS 10-BX	6 months and older	90674
FLUCELVAX (ccIIV4)	SEQIRUS	5 mL MDV	6 months and older	90756*
FLULAVAL (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUMIST (LAIV4)	ASTRAZENECA	0.2 mL nasal spray 10-BX	2-49 years	90672
FLUZONE (IIV4)	SANOFI	0.5 mL PFS 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI	5 mL MDV	6 months and older	90685
FLUZONE HIGH-DOSE (IIV4)	SANOFI	0.7 mL PFS 10-BX	65 years and older	90662

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

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

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