DRUGS IN THE PIPELINE mRNA vaccines | POPULATION HEALTH Centenarians

Managed Healthcare EXECUTIVE®

The C-Suite Advisor

Weathering the GLP-1 storm

How health plans and self-insured employers are coping with all the prescriptions for Ozempic and the other GLP-1 drugs

February 2024 VOL. 34 NO. 2

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TECHNOLOGY

xCures and AI

For LDL-C reduction in patients with primary hyperlipidemia along with diet and statin therapy[1]

LEQVIO IS PROVEN TO LOWER LDL-C WITH JUST 2 DOSES A YEAR[1*]

*After 2 initial doses and taken with statin therapy.[1]

HCP ADMINISTRATION GIVES YOU CONFIDENCE YOUR PATIENTS RECEIVED THEIR DOSE[1]

HCP, health care provider; LDL-C, low-density lipoprotein cholesterol.

INDICATION

LEQVIO® injection is indicated as an adjunct to diet and statin therapy for the treatment of adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce low-density lipoprotein cholesterol (LDL-C).

IMPORTANT SAFETY INFORMATION

Adverse reactions in clinical trials (≥3% of patients treated with LEQVIO and more frequently than placebo) were injection site reaction, arthralgia, and bronchitis.

Brief Summary of Prescribing Information on adjacent page.

LEQVIO®

(inclisiran) injection 284 mg/1.5 mL

2 LEQVIO® maintenance doses[1]* (HCP-administered)

1 YEAR OF DOSING

VS 12 Evolocumab monthly doses[2] (self-injected)

1 YEAR OF DOSING

26 Evolocumab every 2 weeks[2] (self-injected)

1 YEAR OF DOSING

This is not a complete list of all the available treatments for patients with primary hyperlipidemia who have elevated LDL-C. The comparison pertains only to differences in dosing and administration and should not be considered a comparison of efficacy or safety.

WHICH WOULD YOUR PATIENTS PREFER?

LEQVIO IS BROADLY COVERED AND AFFORDABLE FOR MOST PATIENTS[3]

Please scan to learn more at LEQVIOhcp.com

References: 1. Leqvio. Prescribing information. Novartis Pharmaceuticals Corp. **2.** Repatha. Prescribing information. Amgen, Inc. **3.** Data on file. LEQVIO Coverage and Affordability. Novartis Pharmaceuticals Corp; 2023.

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NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

8/23 296143

LEQVIO® (inclisiran) injection, for subcutaneous use
Initial U.S. Approval: 2021

BRIEF SUMMARY: See package insert for full prescribing information.

1 INDICATIONS AND USAGE

LEQVIO® is indicated as an adjunct to diet and statin therapy for the treatment of adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce low-density lipoprotein cholesterol (LDL-C).

4 CONTRAINDICATIONS

None.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in Table 1 are derived from 3 placebo-controlled trials that included 1,833 patients treated with LEQVIO, including 1,682 exposed for 18 months (median treatment duration of 77 weeks) *[see Clinical Studies (14) in the full prescribing information]*. The mean age of the population was 64 years, 32% of the population were women, 92% were White, 6% were Black or African American, 1% were Asian, and < 1% were other races; 6% identified as Hispanic or Latino ethnicity. At baseline, 12% of patients had a diagnosis of HeFH and 85% had clinical atherosclerotic cardiovascular disease (ASCVD).

Adverse reactions reported in at least 3% of LEQVIO-treated patients, and more frequently than in placebo-treated patients, are shown in Table 1.

Table 1: Adverse Reactions Occurring in Greater Than or Equal to 3% of LEQVIO-treated Patients and More Frequently than with Placebo (Studies 1, 2, and 3)

Adverse Reactions	Placebo (N = 1,822) %	LEQVIO (N = 1,833) %
Injection site reaction†	2	8
Arthralgia	4	5
Bronchitis	3	4

†includes related terms such as: injection site pain, erythema and rash

Adverse reactions led to discontinuation of treatment in 2.5% of patients treated with LEQVIO and 1.9% of patients treated with placebo. The most common adverse reactions leading to treatment discontinuation in patients treated with LEQVIO were injection site reactions (0.2% versus 0% for LEQVIO and placebo, respectively).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Discontinue LEQVIO when pregnancy is recognized. Alternatively, consider the ongoing therapeutic needs of the individual patient. Inclisiran increases LDL-C uptake and lowers LDL-C levels in the circulation, thus decreasing cholesterol and possibly other biologically active substances derived from cholesterol; therefore, LEQVIO may cause fetal harm when administered to pregnant patients based on the mechanism of action *[see Clinical Pharmacology (12.1) in the full prescribing information]*. In addition, treatment of hyperlipidemia is not generally necessary during pregnancy. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hyperlipidemia for most patients.

There are no available data on the use of LEQVIO in pregnant patients to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

In animal reproduction studies, no adverse developmental effects were observed in rats and rabbits with subcutaneous administration of inclisiran during organogenesis at doses up to 5 to 10 times the maximum recommended human dose (MRHD) based on body surface area (BSA) comparison *(see Data)*. No adverse developmental outcomes were observed in offspring of rats administered inclisiran from organogenesis through lactation at 5 times the MRHD based on BSA comparison *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

Data

Animal Data

In embryo-fetal development studies conducted in Sprague-Dawley rats and New Zealand White rabbits, inclisiran was administered by subcutaneous injection at dose levels of 50, 100, and 150 mg/kg once daily during organogenesis (rats: Gestation Days 6 to 17; rabbits: Gestation Days 7 to 19). There was no evidence of embryo-fetal toxicity or teratogenicity at doses up to 5 and 10 times, respectively, the MRHD based on BSA comparison/dose. Inclisiran crosses the placenta and was detected in rat fetal plasma at concentrations that were 65 to 154 times lower than maternal levels.

In a pre- and postnatal development study conducted in Sprague-Dawley rats, inclisiran was administered once daily by subcutaneous injection at levels of 50, 100, and 150 mg/kg from Gestation Day 6 through Lactation Day 20. Inclisiran was well-tolerated in maternal rats, with no evidence of maternal toxicity and no effects on maternal performance. There were no effects on the development of the F1 generation, including survival, growth, physical and reflexological development, behavior, and reproductive performance at doses up to 5 times the MRHD, based on BSA comparison/dose.

8.2 Lactation

Risk Summary

There is no information on the presence of inclisiran in human milk, the effects on the breastfed infant, or the effects on milk production. Inclisiran was present in the milk of lactating rats in all dose groups. When a drug is present in animal milk, it is likely that the drug will be present in human milk *(see Data)*. Oligonucleotide-based products typically have poor oral bioavailability; therefore, it is considered unlikely that low levels of inclisiran present in milk will adversely impact an infant's development during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LEQVIO and any potential adverse effects on the breastfed infant from LEQVIO or from the underlying maternal condition.

Data

In lactating rats, inclisiran was detected in milk at mean maternal plasma:milk ratios that ranged between 0.361 and 1.79. However, there is no evidence of systemic absorption in the suckling rat neonates.

8.4 Pediatric Use

The safety and effectiveness of LEQVIO have not been established in pediatric patients.

8.5 Geriatric Use

Of the 1,833 patients treated with LEQVIO in clinical studies, 981 (54%) patients were 65 years of age and older, while 239 (13%) patients were 75 years of age and older. No overall differences in safety or effectiveness were observed between patients 65 years of age and older and younger adult patients.

8.6 Renal Impairment

No dose adjustments are necessary for patients with mild, moderate, or severe renal impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*. LEQVIO has not been studied in patients with end stage renal disease *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

8.7 Hepatic Impairment

No dose adjustment is necessary in patients with mild to moderate hepatic impairment. LEQVIO has not been studied in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Distributed by:
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For more information, visit www.leqvio.com or call 1-833-LEQVIO2 (1-833-537-8462).

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Paying for the GLP-1s

Ozempic, once a drug that only diabetes specialists and perhaps people with the disease were aware of, has become a household word. Since last year, it has been all over TikTok and other social media platforms. Celebrities plugged it on X, formerly known as Twitter. Jimmy Kimmel joked about Ozempic at last year's Oscars, and it was used in a punchline in a "Saturday Night Live" skit about the movie awards.

The consequences of the huge demand for Ozempic and other drugs in the glucagon-like peptide 1 (GLP-1) class don't stop with name recognition and jokes. Their popularity has upended the weight loss industry. WeightWatchers has long depended on its points system and group support. In December, the company launched a program designed to support people taking GLP-1s. Noom, which sells a behavioral, app-based approach to weight loss, also put a GLP-1 program on the market last year

But neither WeightWatchers nor Noom are covering the cost of the drugs themselves. With list prices of $1,000 or more for a month's supply, the GLP-1s are too expensive for most people to buy without some kind of insurance coverage.

If anyone is going to foot the GLP-1 bill, it is going to be payers, not individuals.

Our cover story this month is a look at how payers are dealing with GLP-1s. It is not entirely clear, but some studies suggest that people who lose weight with a GLP-1 will need to keep taking the drug if they are to keep the weight off. Insurers and self-insured plans are facing the prospect of many of their members taking these drugs for long periods, perhaps indefinitely. That will be expensive. True, weight loss has all kinds of health benefits, but often the effects are not immediate. The payer who covered the cost of a GLP-1 may not be the same payer who benefits from a member with fewer obesity-related healthcare expenses. The law that created Medicare Part D explicitly forbids the coverage of weight loss drugs. Will Congress change the law?

A new, effective treatment for obesity is something to celebrate, not regret. But as is often the case with new treatments, the GLP-1s are stirring up difficult questions about cost, waste, payment and coverage. We don't have the answers, but we can help by shedding light on the some of these issues in these pages. ■

Mike Hennessy Jr.
President and CEO
of MJH Life Sciences

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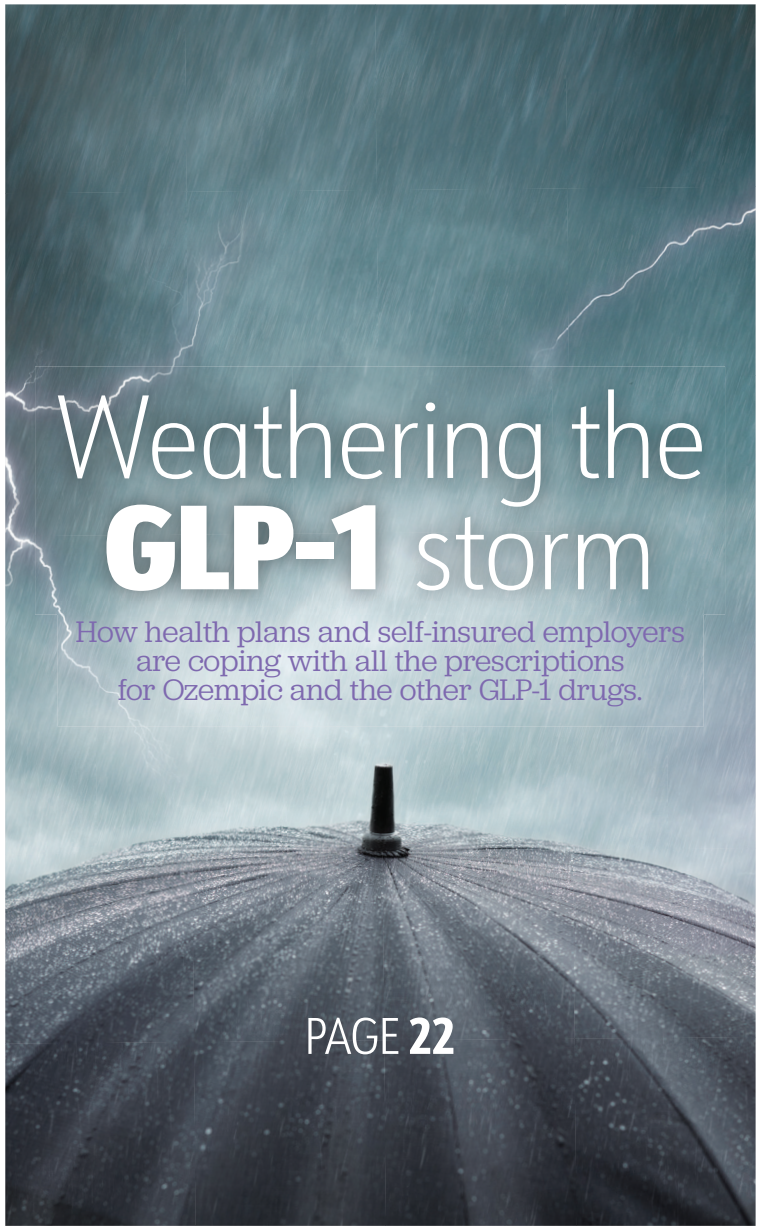
FEBRUARY 2024



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TARPEYO®
(budesonide) delayed release capsules • 4 mg

TARPEYO was studied under the name NEFECON.

NEW INDICATION based on 2-year study results[1]

NOW FDA APPROVED to reduce the loss of kidney function in adults with IgA Nephropathy (IgAN)[1]

TARPEYO is the first and only FDA-approved treatment for IgAN to reduce the loss of kidney function[1,2]

INDICATION

TARPEYO is indicated to reduce the loss of kidney function in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression.

IMPORTANT SAFETY INFORMATION

Contraindications: TARPEYO is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of TARPEYO. Serious hypersensitivity reactions, including anaphylaxis, have occurred with other budesonide formulations.

Warnings and Precautions

Hypercorticism and adrenal axis suppression: When corticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Corticosteroids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic corticosteroid is recommended. When discontinuing therapy or switching between corticosteroids, monitor for signs of adrenal axis suppression.

Patients with moderate to severe hepatic impairment (Child-Pugh Class B and C respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure to oral budesonide. Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). Monitor for increased signs and/or symptoms of hypercorticism in patients with moderate hepatic impairment (Child-Pugh Class B).

Risks of immunosuppression: Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressive doses of corticosteroids. Avoid corticosteroid therapy in patients with active or quiescent tuberculosis infection; untreated fungal, bacterial, systemic viral, or parasitic infections, or ocular herpes simplex. Avoid exposure to active, easily-transmitted infections (e.g., chicken pox, measles). Corticosteroid therapy may decrease the immune response to some vaccines.

Other corticosteroid effects: TARPEYO is a systemically available corticosteroid and is expected to cause related adverse reactions. Monitor patients with hypertension, prediabetes, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where corticosteroids may have unwanted effects.

Adverse reactions: In clinical studies, the most common adverse reactions with TARPEYO (occurring in ≥5% of TARPEYO treated patients, and ≥2% higher than placebo) were peripheral edema (17%), hypertension (12%), muscle spasms (12%), acne (11%), headache (10%), upper respiratory tract infection (8%), face edema (8%), weight increased (7%), dyspepsia (7%), dermatitis (6%), arthralgia (6%), and white blood cell count increased (6%).

Drug interactions: Budesonide is a substrate for CYP3A4. Avoid use with potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, and cyclosporine. Avoid ingestion of grapefruit juice with TARPEYO. Intake of grapefruit juice, which inhibits CYP3A4 activity, can increase the systemic exposure to budesonide.

Use in specific populations

Pregnancy: The available data from published case series, epidemiological studies, and reviews with oral budesonide use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with IgAN. Infants exposed to in-utero corticosteroids, including budesonide, are at risk for hypoadrenalism.

Please see Full Prescribing Information and accompanying Brief Summary on adjacent page.

References: 1. TARPEYO. Prescribing Information. Calliditas Therapeutics AB; December 2023. **2.** Lafayette R, Kristensen J, Stone A, et al. Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial. *Lancet*. 2023. https://doi.org/10.1016/S0140-6736(23)01554-4

calliditas THERAPEUTICS

01/24 US-TAR-2300229

See what the data can mean for your patients

TARPEYO® (budesonide) delayed release capsules
Brief Summary of Prescribing Information

4 CONTRAINDICATIONS

TARPEYO is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of TARPEYO. Serious hypersensitivity reactions, including anaphylaxis have occurred with other budesonide formulations.

5 WARNINGS AND PRECAUTIONS

5.1 Hypercorticism and Adrenal Axis Suppression

When corticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Corticosteroids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic corticosteroid is recommended. When discontinuing therapy *[see Dosing and Administration (2)]* or switching between corticosteroids, monitor for signs of adrenal axis suppression.

Patients with moderate to severe hepatic impairment (Child-Pugh Class B and C respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure of oral budesonide. Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). Monitor for increased signs and/or symptoms of hypercorticism in patients with moderate hepatic impairment (Child-Pugh Class B) *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

5.2 Risks of Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressant doses of corticosteroids. Avoid corticosteroid therapy in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections, or ocular herpes simplex. Avoid exposure to active, easily-transmitted infections (e.g., chicken pox, measles). Corticosteroid therapy may decrease the immune response to some vaccines.

How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, consider therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG). If exposed to measles, consider prophylaxis with pooled intramuscular immunoglobulin (IG). If chickenpox develops, consider treatment with antiviral agents.

5.3 Other Corticosteroid Effects

TARPEYO is a systemically available corticosteroid and is expected to cause related adverse reactions. Monitor patients with hypertension, prediabetes, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where corticosteroids may have unwanted effects.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.1)]*
- Risks of immunosuppression *[see Warnings and Precautions (5.2)]*
- Other corticosteroid effects *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TARPEYO was evaluated in 389 patients in the randomized, double-blind, placebo-controlled study, NefIgArd (NCT: 03643965, Phase 3 clinical study in adults with primary IgAN). The data below reflect TARPEYO exposure in 195 patients with a median duration of 41 weeks, compared with comparable exposure to placebo in 194 patients.

The most common adverse reactions, reported in greater than or equal to 5% of TARPEYO-treated patients and greater than or equal to 2% higher than placebo, in the 9-month treatment period are listed in *Table 1*.

Most adverse reactions that occurred at a greater incidence for TARPEYO compared to placebo were consistent with hypercortisolism and reversible, resolving within 3 months after discontinuation.

Table 1: Reported adverse reactions occurring in greater than or equal to 5% of TARPEYO treated patients, and greater than or equal to 2% higher than Placebo

Adverse Reaction	TARPEYO 16 mg (N=195)	Placebo (N=194)
	n (%)	n (%)
Peripheral edema	33 (17)	10 (5)
Hypertension	23 (12)	6 (3)
Muscle spasms	23 (12)	8 (4)
Acne	22 (11)	2 (1)
Headache	19 (10)	14 (7)
Upper respiratory tract infection	16 (8)	12 (6)
Face edema	15 (8)	1 (0.5)
Weight increased	13 (7)	6 (3)
Dyspepsia	13 (7)	4 (2)
Dermatitis	12 (6)	2 (1)
Arthralgia	12 (6)	4 (2)
White blood cell count increased	11 (6)	1 (0.5)

7 DRUG INTERACTIONS

7.1 Interaction with CYP3A4 Inhibitors

Budesonide is a substrate for CYP3A4. Avoid use with potent CYP3A4 inhibitors; e.g. ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, and cyclosporine *[see Clinical Pharmacology (12.3)]*.

Avoid ingestion of grapefruit juice with TARPEYO. Intake of grapefruit juice, which inhibits CYP3A4 activity, can increase the systemic exposure to budesonide *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary The available data from published case series, epidemiological studies and reviews with oral budesonide use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with IgA Nephropathy. Infants exposed to in-utero corticosteroids, including budesonide, are at risk for hypoadrenalism *(see Clinical Considerations)*. In animal reproduction studies with pregnant rats and rabbits, administration of subcutaneous budesonide during organogenesis at doses approximately 0.3 times or 0.03 times, respectively, the maximum recommended human dose (MRHD), resulted in increased fetal loss, decreased pup weights, and skeletal abnormalities. Maternal toxicity was observed in both rats and rabbits at these dose levels *(see Data)*.

The estimated background risk of major birth defects and miscarriage of the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations *Disease-Associated Maternal and/or Embryo/Fetal Risk* IgA nephropathy in pregnancy is associated with adverse maternal outcomes, including increased rates of cesarean section, pregnancy-induced hypertension, pre-eclampsia and preterm delivery, and adverse fetal/neonatal outcomes, including stillbirth and low birth weight.

Fetal/Neonatal Adverse Reactions Hypoadrenalism may occur in infants born to mothers receiving corticosteroids during pregnancy. Infants should be carefully observed for signs of hypoadrenalism, such as poor feeding, irritability, weakness, and vomiting, and managed accordingly *[see Warnings and Precautions (5.1)]*.

Data

Animal Data Budesonide was teratogenic and embryo-lethal in rabbits and rats.

In an embryo-fetal development study in pregnant rats dosed subcutaneously with budesonide during the period of organogenesis on gestation days 6 to 15 there were effects on fetal development and survival at subcutaneous doses up to approximately 500 mcg/kg in rats (approximately 0.3 times the maximum recommended human dose (MRHD) on a body surface area basis).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis on gestation days 6 to 18, there was an increase in maternal abortion, and effects on fetal development and reduction in litter weights at subcutaneous doses from approximately 25 mcg/kg (approximately 0.03 times the MRHD on a body surface area basis).

Maternal toxicity, including reduction in body weight gain, was observed at subcutaneous doses of 5 mcg/kg in rabbits (approximately 0.006 times the maximum recommended human dose on a body surface area basis) and 500 mcg/kg in rats (approximately 0.3 times the maximum recommended human dose on a body surface area basis).

In a peri- and post-natal development study, subcutaneous treatment of pregnant rats with budesonide during the period from Day 15 post coitum to Day 21 post partum, budesonide had no effects on delivery, but did have an effect on growth and development of offspring. In addition, offspring survival was reduced and surviving offspring had decreased mean body weights at birth and during lactation at exposures ≥ 0.012 times the MRHD (on a mg/m^2 basis at maternal subcutaneous doses of 20 mcg/kg/day and higher). These findings occurred in the presence of maternal toxicity.

8.2 Lactation

Risk Summary Breastfeeding is not expected to result in significant exposure of the infant to TARPEYO. Lactation studies have not been conducted with oral budesonide, including TARPEYO, and no information is available on the effects of the drug on the breastfed infant or the effects on the drug on milk production. One published study reports that budesonide is present in human milk following maternal inhalation of budesonide *(see Data)*. Routine monitoring of linear growth in infants is recommended with chronic use of budesonide in the nursing mother. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TARPEYO and any potential adverse effects on the breastfed infant from TARPEYO, or from the underlying maternal condition.

Data One published study reports that budesonide is present in human milk following maternal inhalation of budesonide, which resulted in infant doses approximately 0.3% to 1% of the maternal weight-adjusted dosage and a milk to plasma ratio was approximately 0.5. Budesonide was not detected in plasma, and no adverse events were noted in the breastfed infants following maternal use of inhaled budesonide.

Assuming a daily average milk intake of about 150 mL/kg/day and a milk to plasma ratio of 0.5, the estimated oral dose of budesonide for a 5 kg infant is expected to be less than 2 mcg/day for a maternal dose of 16 mg TARPEYO. Assuming 100% bio-availability in the infant this is about 0.1% of the maternal dose and about 3% of the highest inhaled dose used clinically for asthma in infants.

8.4 Pediatric Use

The safety and efficacy of TARPEYO in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of TARPEYO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Patients with moderate to severe hepatic impairment (Child-Pugh Class B and C, respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure to budesonide *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*. Avoid use in patients with severe hepatic impairments (Child-Pugh Class C). Monitor for increased signs and/or symptoms of hypercorticism in patients with moderate hepatic impairment (Child-Pugh Class B).

10 OVERDOSAGE

Reports of acute toxicity and/or death following overdosage of corticoids are rare.

In the event of acute overdosage, no specific antidote is available. Treatment consists of supportive and symptomatic therapy.

Please see Full Prescribing Information for TARPEYO at TARPEYOhcp.com

US-TAR-2300219

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A conversation with Don Hall, M.P.H.

On public health, Medicaid and Medicaid managed care, and profit seeking in healthcare

Don Hall, M.P.H., who joined the Managed Healthcare Executive *editorial advisory board in 2007, is winding down his consulting business, DeltaSigma LLC, and stepping down from the board. We caught up with him recently and asked him to discuss his career and reflect on the condition of U.S. healthcare.*

Peter Wehrwein, the managing editor, conducted this interview. This transcript has been edited for clarity and length.

I took a look at your LinkedIn profile and saw that you majored in zoology and psychology and then got your master's degree in public health. What motivated you to go into public health?

I worked my way through college, which you could do back in the '70s; I don't think you could now. One of the jobs I had was I drove an ambulance in Norman, Oklahoma, and that was before the EMT era, so it was really load and go. I was struck by a number of things. One was most of our calls were not emergency calls. We were taking people from nursing homes to the hospital and back again. We would pick somebody up at a nursing home, take them in to have their kidneys checked, and they would stay the number of days they were allowed, and then we'd pick them up and take them back. Many of these people — and I don't mean to be negative at all — were not fully cognizant of what was going on. I mean, we were basically picking up a body — a living, breathing body — taking [them] to the hospital, getting [them] checked and taking [them] back. I thought, "This is not healthcare."

I also remember one intersection where there were multiple very serious traffic accidents. The intersection begged for a stoplight. But the city didn't have the money for a stoplight. But there was no end to the money to pay for all the chaos, damage [and] injuries from that.

Between those two, it seemed like we needed a more global look at where we were putting our dollars.

At that point in time, many children were not covered by insurance. The very people who would grow up and take care of us … were not being taken care of. But the people in the nursing homes were getting care upon care.

I've heard that from other people who trained in public health — that their motivation came from something that showed so much illness or injury could be prevented. But your career wasn't in traditional public health.

When I got out of graduate school, I went into public health and maternal/child health and spent three years there. But there was one incident that was really exciting to me, and it made me move out of public health. Jimmy Carter was president, and he thought that people should start paying for family planning services based on their income, so I was charged with helping to set up this fee system that was graduated based on income and so on.

We were collecting absolutely no money; the nurses and

social workers who go into public health are not there to collect money. But there was this one county in Oklahoma where I noticed we had lots of people who were fairly well off. I looked at where they worked, and they worked at this Uniroyal tire plant in Ardmore, Oklahoma. So I contacted the tire plant, and I said, "You know, you have a lot of people who come to our clinic for care." And at that time, when you went to the clinic, it took about a day. They ended up saying, "Well, I'll tell you what: We'll give you money to put a clinic in our building." We were able to get patients through in an hour, and the program made more money in that one county than it made in the rest of the state.

It was a business that was saying, "This makes sense." In the public health mindset, you don't … [create clinics in businesses]. It made me aware of the role that business plays in healthcare. If you can save time and can get people to care, it's in the interest of the organization, the company, to do that. So that got me going.

You worked for several different companies before hanging your shingle as a consultant.

Over time, I went from one company to another. The companies would build up and sell, build up and sell, and I got frustrated.

I ended up at Blue Cross and Blue Shield of Texas, and they had no managed care, and I was head of managed care, product development [and] market development. That's really where I got stung by the Medicaid bug. Ross Perot had worked at Blue Cross and Blue Shield of Texas at the time that Medicaid came out, and he put together an organization that basically bid against the organization even though he was working for them and took the contract away from them. And our president wanted to get back into Medicaid, so I was charged with that. I realized that Medicaid could have so much impact on the healthcare of this country. The way Medicaid was set up then, it was truly for the poorest people.

At the time, deliveries were barely paid for, so medical schools and public hospitals were handling them. Because there were so many problems with pregnancies, Medicaid started paying the rate that commercial would pay for them, and suddenly, every hospital was taking care of women covered by Medicaid.

Of course, one of the chief features of the ACA has been Medicaid expansion. I assume that you think that Medicaid expansion has been a good thing for American healthcare.

It has been a great thing for healthcare. I think it's absolutely insane that the politics in Texas and Florida prohibit them from caring enough about their people [to expand Medicaid].

I do want to say that one of the frustrations I've always had — and Medicaid is part of it — is that as we start to move into really doing something, oftentimes you see companies coming into that space and they go, "Whoa, look at the money we can make here." They start getting into it, but not for the reason of taking care of people but for the reason that they can figure out how to make it to their advantage economically.

As a consulting group, one of the things we did was help companies expand what they were doing in healthcare: private health plans and public health plans. [We got calls] from foreign investors who looked at healthcare in the United States as easy pickings — people from Europe, from the Middle East — who wanted to buy into some company or start something to make money.

With our system, unfortunately, the more money we put into trying to take care of things, the more money gets sucked out in the form of profits for things that may not benefit anybody.

You see Medicaid expansion as a great thing. Despite your background in managing Medicaid, do you now see managed Medicaid as being counterproductive and another avenue for profiteering?

I don't think managed Medicaid, per se, is bad, and I will tell you why. If somebody wanted to go to the doctor, we were required to make sure they could get to the doctor in so many days. We were required to follow up on certain conditions. We were required to make sure if they needed a specialist, they could get a specialist. We were required to provide behavioral health.

Without a managed care system, those things fall apart. I mean, poor people are just out there without anything.

I've studied a number of healthcare systems around the world. We're the only one that is for profit. I think when you put the for-profit element into healthcare, you change the dynamic greatly. There are a number of not-for-

profit Medicaid plans that I think are really focused on the population. But the for-profit plans are focused pretty much on profit, and I think that's been [a] detriment.

What do you say to people who say for-profit enterprises in healthcare find efficiencies because they're motivated to create margin?

I see a general problem, even with hospitals.

I recall being at a meeting when I was with HCA [Healthcare] of all the hospitals in the Southeast region. The chairman of the board was there, and they had people stand up who had an average of 80% census during the year — 80% of the beds were full. Wild applause. 90% and then 95%. Well, there were a few hospitals where there was over 100% [census] because the hospitals didn't have enough beds, and they were using the ER [emergency room] to supplement beds. Those people got wild ovations. I kept thinking, do these people not have grandmothers? Do they not have people who are sick? Do they not understand that every bed is filled with somebody who has had cancer, has had a heart attack, has been in a bad accident? We had shifted the hospital's role of taking care of these people to how much profitable bed space you were using.

I feel like healthcare is a different industry and should not be profit based. And with a lot of the nonprofit health plans and nonprofit hospitals, as you know, it's just a tax twist. It's not really nonprofit. I mean, there are nonprofit CEOs who make a ton of money.

The theory that you can go in and economize, figure out twists that make things work, makes sense. But it becomes more for the profit than doing it to economize.

When I went to Colorado Access, it was nonprofit. We had presidents of the biggest hospitals, all nonprofit, on board, and it was driven by money. The sense was no money, no mission. Well, money became the mission. I have seen that too much in healthcare.

I'll tell you an interesting story. We had some issues with our reserves at Colorado Access. We had a meeting with the division of insurance, and we had this $3 million claim. We had a premature baby who did not have fully functioning organs and needed multiple organ transplants. We ended up sending the child to Little Rock [Arkansas] because that was where they could do whatever was needed. Our reinsurance wouldn't cover it because it was experimental; we went ahead and covered it because it did look like the baby would survive. I looked up as I was talking about it, and this division of insurance auditor was crying and asked whether the baby was alive, and I said, "Oh, the baby is doing fine." She said, "I've never heard a story like that where an insurance company would do that." And the truth is too many times we don't. The measure [is often] are we making money, and she actually jumped over it and said, "You saved the baby's life." I think we forget that's what it should be all about.

One couldn't banish for-profit enterprises in healthcare. Do you have any notions about practical steps that could be taken to counteract some of these tendencies?

I'm an optimist, so I don't think there's nothing we can do. I mean, frankly, one of the worst things is the Supreme Court allowing so much money to go into elections, which then allows pharmaceutical companies, insurance companies to really dominate the discussion. I do feel like there's grassroots activity going on; that could change that. I also think that states can start picking it up on their own and move the ball a little bit.

I think we're going to enter a period where money simply isn't going to be there. As the population ages, we don't have as many people working and putting money into the system. You're going to face a crisis in healthcare because there's just not going to be enough money to do everything you need to do.

If we could make healthcare truly a nonprofit industry, I think that would change things greatly. If we could make health plan boards include more people who are the ones being taken care of, I think that would change things. How many boards have investors on them? When you have an investor sitting on the board, it's all about what we are going to make this month. You don't have a discussion about the quality care, about excess deaths, about surgical infections and things like that. ◘

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CVS Caremark to remove branded Humira from formularies

Effective April 1, 2024, CVS Caremark will remove Humira (adalimumab) from its national commercial template formularies. Instead, the pharmacy benefit manager says it will include Humira biosimilars.

Humira is used to treat several immune conditions, including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, ulcerative colitis, Crohn's disease, uveitis and hidradenitis suppurativa. It has a monthly price of $7,299 according to Drugs.com, up from $6,922 last year.

CVS Caremark's move is related to the company's launch of Cordavis in August 2023, which is working directly with pharmaceutical manufacturers to produce a number of biosimilar products.

CVS Caremark has announced that AbbVie, the manufacturer of Humira, long one of the top selling drugs in the world, has entered into an agreement to supply Cordavis with a committed volume of cobranded Humira.

Cordavis has also contracted with Sandoz to commercialize and bring to market Hyrimoz (adalimumab-adaz) in the first quarter of 2024 under a Cordavis private label. Antonio Ciaccia, president of 3 Axis Advisors, told *Formulary Watch* the wholesale acquisition cost of CVS' product is more than double the price that Mark Cuban Cost Plus Drug Company received for Yusimry (adalimumab-aqvh), another Humira biosimilar. "They're not being transparent about their pricing and are likely are going to use formulary status to direct patients to their more expensive product offering over cheaper products in the market," Ciaccia comments.

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FDA accepts Accord's BLA for Stelara biosimilar

In early January, the FDA accepted Accord BioPharma's biologic license application (BLA) for DMB-3115, a biosimilar to Johnson & Johnson (J&J)'s Stelara (ustekinumab). Stelara is prescribed as a treatment for several autoimmune conditions including Crohn's disease, ulcerative colitis, plaque psoriasis and psoriatic arthritis.

Accord BioPharma is the U.S. specialty division of Intas Pharmaceuticals, which has a partnership with Dong-A Socio Holdings and Meiji Seika Pharma to develop DMB-3115. Intas has commercialization rights for the biosimilar.

The BLA submission for DMB-3115 is based on results from phase 3 clinical trials in patients with plaque psoriasis, in which the primary end point was the rate of change in the Psoriasis Area and Severity Index for skin symptoms. The clinical results demonstrated that DMB-3115 and its reference product, ustekinumab, are highly similar and have no clinically meaningful differences in terms of quality, safety and efficacy.

In October 2023, Accord BioPharma reached a settlement with Janssen Biotech, a J&J company, under confidential terms that would allow Accord BioPharma to launch its proposed ustekinumab biosimilar no later than May 15, 2025.

A marketing application of DMB-3115 is also being received by the European Medicines Agency.

In November 2023, the FDA approved Amgen's Wezlana (ustekinumab-auub), the first interchangeable biosimilar to Stelara. Wezlana is expected to launch no later than Jan. 1, 2025, after an agreement with J&J.

Have a tip, some news or a suggestion for a topic that *Formulary Watch* should cover?

Email us at dmyshko@mjhlifesciences.com.

Andrey Cherkasov - stock.adobe.com

Coherus launches Loqtorzi for nasopharyngeal carcinoma

Coherus BioSciences announced in January 2024 that it had launched Loqtorzi (toripalimab-tpzi) to treat patients with recurrent or metastatic nasopharyngeal carcinoma (NPC). Loqtorzi is an anti-PD-1 monoclonal antibody developed by Coherus and Shanghai Junshi Biosciences.

Loqtorzi is available for purchase through several specialty distributors including Cencora (formerly AmerisourceBergen), Cardinal Health and McKesson. Billing will occur under the medical benefit using an unclassified Healthcare Common Procedure Coding System code J3490 or J3590 with the National Drug Code number of 70114-0340-01. Coherus expects a product-specific, permanent J-code to be assigned in mid-2024.

Loqtorzi has a list price of $8,892.03 per single-use vial. As a single agent, it is dosed every two weeks. When used in combination with chemotherapy, Loqtorzi is given every three weeks. Coherus provides patient assistance and copay assistance. Patients with insurance may be eligible for $0 copay, with a limit of $30,000 a year.

Coherus' market access team has engaged with all top commercial payers and Medicare for coverage of Loqtorzi nationally and regionally, according to Paul Reider, Coherus' chief commercial officer.

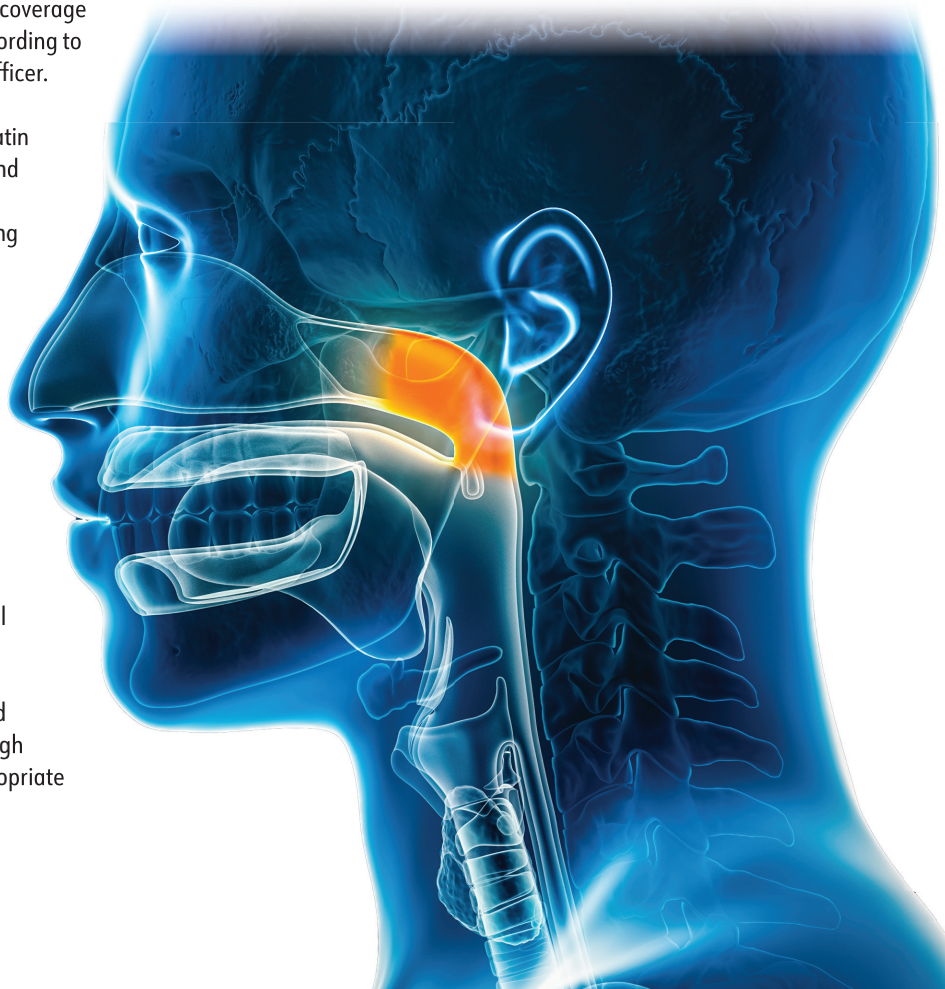
The FDA approved Loqtorzi in October 2023 to be used in combination with cisplatin and gemcitabine for first-line treatment and as monotherapy in patients with disease progression on or after platinum-containing chemotherapy. NPC is an aggressive cancer that starts in the nasopharynx, the upper part of the throat behind the nose and near the base of skull. It affects approximately 2,000 people in the United States annually, and patients are treated primarily with radiation and chemotherapy. The five-year survival rate for all patients diagnosed with NPC is approximately 60%; however, those who are diagnosed with advanced disease have a five-year survival rate of approximately 49%.

The National Comprehensive Cancer Network classified Loqtorzi as a preferred category 1 therapy, meaning there is a high level of evidence that the therapy is appropriate for this cancer.

Loqtorzi was approved based on data from the POLARIS-02 and JUPITER-02 studies. In the phase 3 JUPITER-02 study results, Loqtorzi combined with chemotherapy improved progression-free survival, reducing the risk of disease progression or death by 48% compared with chemotherapy alone. Loqtorzi also reduced the risk of death by 37% versus chemotherapy alone. Results from JUPITER-02 were published online in *JAMA*.

In the phase 2 POLARIS-02 clinical study results, Loqtorzi demonstrated durable antitumor activity in patients with recurrent or metastatic NPC whose disease did not respond to previous chemotherapy, with an objective response rate of 20.5%, a disease control rate of 40% and a median overall survival of 17.4 months.

The safety profile of Loqtorzi was consistent with the PD-1 inhibitor class. Adverse events leading to discontinuation of Loqtorzi were 11.6% compared with 4.9% with placebo. Immune-related adverse events of grade 3 or above were more frequent in the Loqtorzi arm. ■



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CHIEF HEALTHCARE EXECUTIVE®

Chief Healthcare Executive (www.chiefhealthcareexecutive.com), a sibling publication of *Managed Healthcare Executive*, covers issues facing hospitals and health systems. The digital outlet publishes news, features and analysis daily.

More hospitals revive mask policies as influenza, COVID-19, RSV cases rise

With more patients being admitted to hospitals with influenza, COVID-19 and respiratory syncytial virus (RSV), more hospitals and health systems returned to requiring masking beginning in late December 2023. Perhaps anticipating pushback from individuals who object to masking, some health systems stressed that policies were temporary.

At the end of December, more than 235,000 patients visited emergency departments nationwide due to influenza, COVID-19 or RSV, according to data from the Centers for Disease Control and Prevention. Data for the first week in January showed a sharp drop in hospital admissions for RSV, a moderate decline for flu but a continuing increase for COVID-19.

NYC Health + Hospitals, which operates the 11 public hospitals in New York, New York, reinstated its mask policy. New York City Health Commissioner Ashwin Vasan told a local TV station that masks are required in areas where patients are being treated and the policy is designed to ensure the system can maintain staffing because more patients are getting sick.

Mass General Brigham in Boston, Massachusetts, started requiring that all its clinicians and staff wear masks while interacting with patients in the beginning of January. Patients and visitors were encouraged to wear masks when interacting with staff but weren't required to do so. Duke Health in North Carolina, Lifespan Health System in Rhode Island, Main Line Health in the Philadelphia area and Hackensack Meridian Health in New Jersey were the among the hospital systems that started to implement various kinds of mask requirements.

Two Missouri hospital systems complete merger, forming $10B system

On the first day of 2024, BJC HealthCare and Saint Luke's Health System completed their merger of the Missouri hospital systems.

The combined organization is now moving forward as BJC Health System. The integrated academic health system boasts $10 billion in revenue and operates 24 hospitals and more than 250 clinics and healthcare locations. BJC Health System currently has 44,000 employees, making it one of the largest employers in Missouri.

Despite the merger, the two individual brands will remain in place in their respective markets. The merged system will operate as BJC in the St. Louis area, its longtime base, and southern Illinois. The system will retain the Saint Luke's name in the Kansas City, Missouri, area and in eastern Kansas.

The systems announced in late November 2023 that they had reached a formal agreement to merge and had completed the necessary steps in the regulatory process.

Richard J. Liekweg, M.H.S.A., MBA, is CEO of BJC Health System. Nick Barto, MBA, is serving as president of BJC Health System as well as president of BJC's Eastern region. Julie Quirin, M.A., who became president of Saint Luke's in November, will serve as president of BJC's Western region.

Leaders of the system touted the potential to offer better care and greater access to clinical trials as a result of the merger. BJC is managing more than 3,500 clinical trials.

As a combined system, BJC says it will provide an estimated $1 billion in community benefits.

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Hospitals continue to wrestle with supply chain challenges

Hospitals and health systems aren't facing the dire shortages of supplies they endured during the early stages of the COVID-19 pandemic, but they continue to encounter supply chain headaches, analysts say.

Kyle MacKinnon is senior director of operational excellence with Premier Inc., which purchases drugs and medical supplies for more than 4,300 hospitals. He says health systems are seeing some product shortages.

MacKINNON

"I think hospitals and health systems do continue to see and experience supply chain challenges," MacKinnon tells *Chief Healthcare Executive.*

Gregg Lambert, senior vice president of Kaufman Hall, also says supply chain difficulties continue for many health systems. But he says they are different from the widespread shortages of masks, gowns or even crutches early in the pandemic.

"Today, it seems to be much more random," Lambert tells *Chief Healthcare Executive.* "Instead of just a product category, now … this fairly specialized product used in this procedure isn't available."

A Kaufman Hall report in October found that 71% of healthcare executives said they are dealing with distribution delays in their supply chain. More than half (55%) of executives said they were grappling with raw product and sourcing availability.

Although not as widespread as in the past, some shortages of drugs and medical supplies are delaying surgeries and chemotherapy for patients with cancer, according to results from a recent survey by ECRI, a patient safety organization, and its affiliate, the Institute for Safe Medication Practices.

During the previous six months before the survey, 60% of the participants said they experienced shortages of more than 20 drugs, single-use supplies or other medical devices.

In spring 2023, the American Cancer Society warned that shortages of some chemotherapy drugs posed a life-threatening issue for some patients with cancer.

Some hospitals and healthcare organizations are moving from the just-in-time model to a just-in-case approach to supplies, MacKinnon says. More health systems are stockpiling critical supplies to ensure that they are ready for an unexpected shortage, he says. More than half of healthcare organizations (57%) said they are raising their inventory levels, according to Kaufman Hall's report.

In addition, more hospitals are looking at acceptable substitutes for certain drugs and products. Lambert says that's not a new strategy but that it's gained more traction in the past couple of years.

Lambert stresses the importance of supply chain leaders working with clinicians to have their input on clinically acceptable substitutes for certain medications in the event of a shortage.

"Working with the clinicians is huge," Lambert says. "If they're used to opening a blue box during surgery and all of a sudden they get a red one, that should not surprise them. They should know way before, and they should have been part of that decision-making process."

More hospitals and health organizations are looking to find suppliers inside the United States or sources from countries that are closer to home.

"We're seeing more nearshoring or friendshoring," MacKinnon says. "I think we're going to see more of that going into 2024."

Many hospitals and health systems are looking to avoid shortages tied to disruptions across the globe. In 2022, hospitals dealt with shortages of contrast dye used in medical imaging due to a shutdown of a key plant in Shanghai, China.

MacKinnon says it's not realistic to expect to avoid using supplies produced in Asia.

"I do think there's still going to be a portion that is going to be in China or is going to be in Malaysia or Indonesia or some of these other low-cost manufacturing countries," he says. "I think that's inevitable."

But he says more hospitals are looking at geographical diversification and ensuring they have options for some supplies from domestic suppliers or others closer to the U.S.

Increasingly, hospitals are also employing different approaches to dealing with suppliers. In the past, organizations may have relied on one or two suppliers in order to get better deals on pricing as preferred customers. Now, some hospitals are branching out to a bigger number of suppliers, even if it means they have to absorb some higher costs. "Providers and the industry are willing to pay a little bit more just to have that redundancy, where it makes sense," MacKinnon says. ■

Have a news tip or a story idea that *Chief Healthcare Executive* should cover?

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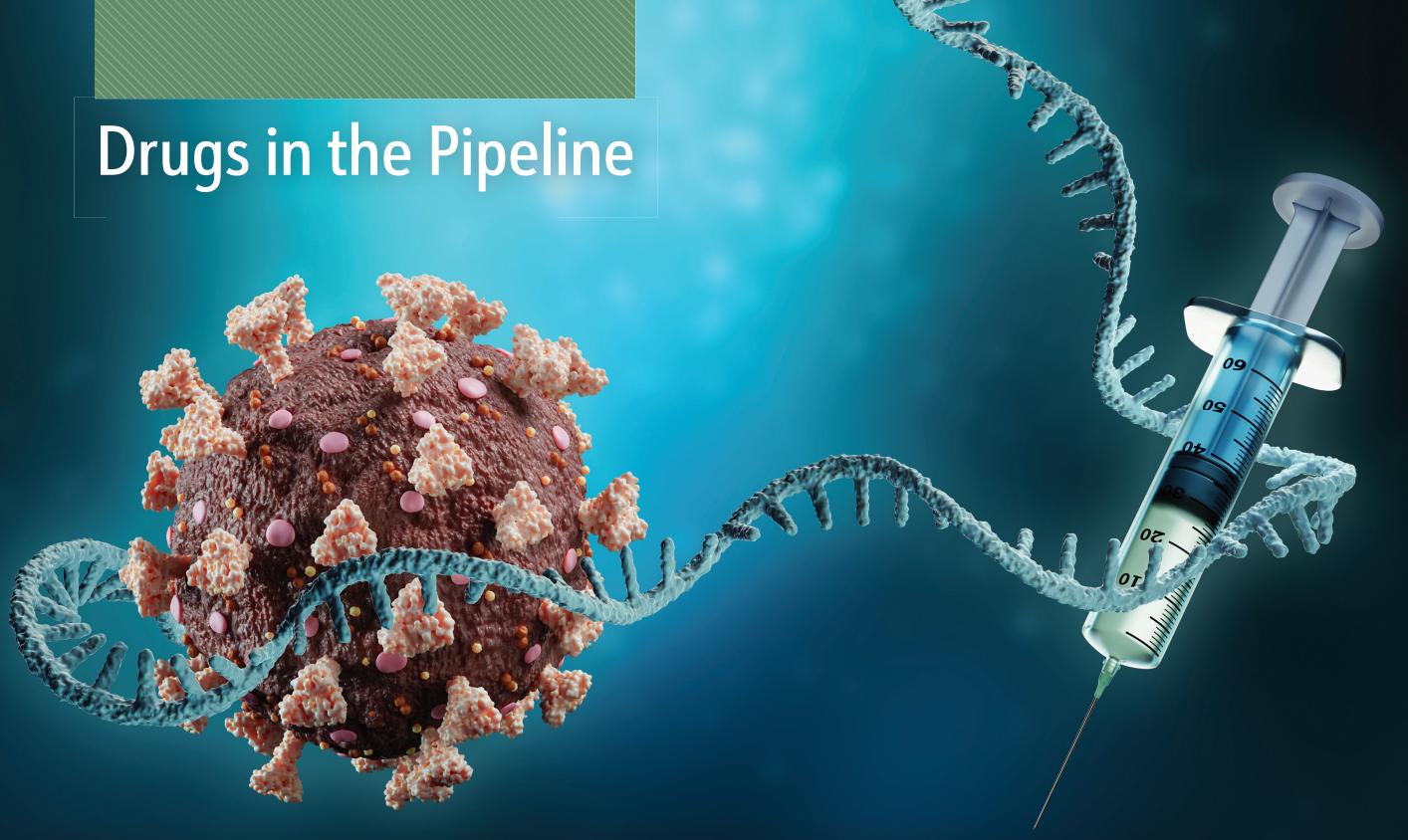

mRNA vaccine momentum

The success of mRNA vaccines against COVID-19 has led to a surge of mRNA vaccines being developed for other diseases.

By **ROSANNA SUTHERBY, PHARM.D.**

Before December 2020, when the FDA authorized the use of two COVID-19 messenger RNA (mRNA) vaccines developed by Pfizer and Moderna, the science behind mRNA vaccines had been researched for over 30 years. After the success of the two pioneering COVID-19 vaccines, these companies have been investigating the mRNA technology for its potential use in vaccines against other infections. These include seasonal influenza (flu), cytomegalovirus (CMV), Zika virus, genital herpes and HIV.

What makes mRNA vaccines different?

mRNA vaccines differ from other types of vaccines in their mechanism of action. Non-mRNA vaccines typically contain attenuated virus, inactivated virus or part of the virus they are formulated to protect against. Upon encountering the benign viral element in these vaccines, the immune system mounts a response and develops memory cells that will fight off the actual virus if it infects the person in the future.

mRNA vaccines do not contain viruses or any part of them. Instead, they deliver mRNA that instructs the cells to make certain proteins that may be present in the virus of concern and those proteins serve as the antigens that activate the immune system. For example, mRNA COVID-19 vaccines carry instructions to make the spike protein sprouting from the surface of the SARS-CoV-2 virus that causes COVID-19.

Because producing mRNA-based vaccines does not require growing viruses, they can typically be manufactured more rapidly than attenuated or inactivated vaccines. They are also relatively easy to modify, so manufacturers can quickly adjust the mRNA vaccine to match the pathogens in circulation.

mRNA vaccines for seasonal influenza

Current flu vaccines have an efficacy rate of approximately 40% to 60% when circulating strains are well matched to those in the vaccines. Several biopharmaceutical companies are aiming to improve those numbers with mRNA flu vaccines. Moderna and Pfizer both have candidates in late stages of development.

Moderna reported positive phase 3 trial results for its seasonal flu vaccine candidate mRNA-1010. The trial,

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which enrolled 6,102 participants, compared antibody titer levels and side effects versus Fluarix Quadrivalent, the inactivated seasonal flu vaccine marketed by GSK.

When stacked against Fluarix, Moderna's mRNA candidate demonstrated higher titer levels and seroconversion rates for A and B flu strains, including A/H1N1, A/H3N2, B/Yamagata and B/Victoria. Similar results were seen in a separate phase 1/2 study comparing mRNA-1010 with Sanofi Pasteur's Fluzone High-Dose Quadrivalent, a flu vaccine indicated for use in adults 65 years or older.

The investigational vaccine showed an acceptable safety and tolerability profile, raising no safety concerns from data and safety monitoring boards.

Based on these positive results, Moderna plans to meet with regulators and hopes to launch the vaccine in time for the 2024-2025 Northern Hemisphere flu season.

As for Pfizer, the company has enrolled 46,180 adults in a phase 3 study evaluating the safety, efficacy, tolerability and immunogenicity of its modified RNA quadrivalent flu vaccine candidate modFlu. Primary end points include the incidence of laboratory-confirmed flu cases, antibody titer levels and adverse reactions compared with a standard licensed quadrivalent inactivated flu vaccine.

The vaccine candidate met all primary end points during primary analysis, demonstrating superiority to the comparator vaccine and maintaining efficacy through the 2022-2023 flu season. The company expects to complete the trial in March 2024.

Moderna and Pfizer are also developing combination flu and COVID-19 mRNA vaccines. Moderna's combination candidate is currently in phase 3 trials, whereas Pfizer's is in phase 2 studies.

mRNA vaccine for cytomegalovirus

CMV is a common virus that causes few to no symptoms in healthy individuals but may lead to serious complications involving the eyes, liver, lungs and other organs in patients who are immunocompromised. Furthermore, CMV can be passed from an infected woman to an infant during pregnancy or childbirth and through breast milk. Congenital CMV infection can lead to hearing loss and other serious sequelae in the infant. Currently, there is no vaccine available to protect against CMV infection.

Once again leveraging the mRNA technology from its COVID-19 vaccine, Moderna is developing a CMV vaccine candidate targeted for females aged 16 to 40 years. The goal is to prevent congenital CMV infection by protecting females of childbearing age.

The investigational vaccine, named mRNA-1647, contains six mRNA sequences encoding glycoprotein B and a pentameric glycoprotein complex, both of which are significant CMV antigens.

The candidate is currently in a phase 3 trial enrolling 6,900 females aged 16 to 40 years. Primary outcomes include antigen-specific seroconversion and adverse events. Trial completion is expected in April 2026.

mRNA vaccine for Zika virus

The Zika virus is another pathogen that can lead to congenital defects, stillbirths or miscarriage if contracted during pregnancy. As with CMV, there are no approved vaccines for Zika virus infection.

Moderna's mRNA-1893 is an mRNA vaccine candidate currently in a phase 2 trial investigating the safety, tolerability and reactogenicity of a two-dose regimen of the investigational vaccine. The study's researchers randomly assigned 809 participants aged 18 to 65 years to receive the study vaccine or placebo. Primary outcomes include antigen-specific neutralizing antibodies and adverse events. The study's estimated completion date is in July 2024.

mRNA vaccines for genital herpes

Herpes simplex virus type 2 (HSV-2) is the leading cause of genital herpes. After primary infection, the virus lies dormant in nerve cells. Periodic reactivation often results in painful lesions in the genital or other mucosal areas.

Moderna and BioNTech are using mRNA technology to develop vaccines to prevent genital herpes lesions in adults infected with HSV-2.

Moderna's candidate, mRNA-1608, is in a phase 1/2 trial, and BioNTech's candidate, BNT163, is in a phase 1 study. Both trials have estimated completion dates in June 2025.

mRNA vaccines for HIV

HIV, the virus that causes AIDS, was first identified in 1984. After 40 years and numerous attempts to develop a vaccine, an effective vaccine against the virus does not exist. HIV/AIDS prevention strategies currently rely on fast and effective treatment with antiviral or preexposure prophylaxis with some of the same drugs.

Moderna, in partnership with the National Institute of Allergy and Infectious Diseases, is evaluating the mRNA HIV vaccine candidate mRNA-1574 in the phase 1 HVTN 302 trial. The company has also partnered with the International AIDS Vaccine Initiative (IAVI) in the development of another potential mRNA HIV vaccine, which is a phase 1 trial sponsored by the Bill & Melinda Gates Foundation.

Both trials are enrolling HIV-negative adults. Study locations for the HVTN 302 trial are only in the United States. The other trial's locations include sites in the United States, Rwanda and South Africa. ◘

Rosanna Sutherby, Pharm.D., *is an independent medical writer and community pharmacist in High Point, North Carolina.*

Weathering the **GLP-1** storm

How health plans and self-insured employers are coping with all the prescriptions for Ozempic and the other GLP-1 drugs

By **PETER WEHRWEIN**

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David Lassen, who has decades of experience managing drug costs, has never seen anything like it. Neither has another pharmacy benefit veteran, Renee Rayburg, R.Ph.

"I don't think we've ever seen something like this in terms of the impact on overall pharmacy spend and trend in my 30 years," David Lassen, chief clinical officer for Prime Therapeutics, the Minnesota-based pharmacy benefit manager, says.

Rayburg, vice president of specialty clinical consulting at Pharmaceutical Strategies Group, a consulting firm, says the interest in off-label use of Ozempic (semaglutide) was unprecedented as were all the headlines and cultural references to the drug. "I have been a pharmacist for 35 years, and I have never seen that type of response from patients," Rayburg says, with a somewhat rueful laugh escaping. "I laugh because I think everyone, whether you are in healthcare or not, knows the word Ozempic."

For their manufacturers, this demand for the weight loss medications, off- and on-label, has produced a surge of sales revenue. Ozempic and Wegovy, the version of semaglutide approved for weight loss, brought sales revenue of $4.8 billion to Novo Nordisk, the Danish drugmaker, in the third quarter of 2023 alone, and the semaglutide pair accounted for half the company's revenue during the first nine months of the year.

Meanwhile, Eli Lilly's coffers bulged with $2.9 billion in revenue from Mounjaro (tirzepatide), a drug that is similar to semaglutide, during the first nine months of 2023. Like Ozempic, Mounjaro was approved as a diabetes drug that was used off-label for weight loss. The FDA approved tirzepatide for weight loss in November 2023, and Lilly is now marketing tirzepatide for weight loss purposes as Zepbound.

Of course, the flip side to all this revenue for drugmakers is mushrooming drug spend for health insurers and self-insured employers. Payers have responded in various ways. Some employers have taken a blunt approach and simply axed coverage of weight loss drugs. The University of Texas, for example, announced last summer that its employee and retiree health plans were going to stop covering weight loss medications in September. Ascension, a large hospital system headquartered in St. Louis, made a similar decision to stop coverage of weight loss drugs. Others have taken a more nuanced approach.

Predictably, some dishonest people saw an opportunity in the weight loss gold rush. "When you have something of this magnitude, there's going to be fraud and abuse," says Lassen. Prime Therapeutics' special investigation unit worked to identify cases when patients were falsely identified as having diabetes in order to receive Ozempic. Lassen says the fraud was often associated with patients receiving care through telehealth, although he cautioned that he didn't want to generalize all telehealth options. The company terminated some contracts and cooperated with some criminal investigations.

LASSEN

RAYBURG

"Sadly, we started out the year [2023] with full trust," Lassen says. "As we moved through the year, we were forced to put in validation steps because we could not trust without verifying the information we were receiving and getting for requests for coverage was true and accurate." It wasn't just prescribers, Lassen notes. "We had individuals working with their prescribers to seek coverage so they would flag in the system and make it look like they [had diabetes when] they didn't." Lassen says that as Prime Therapeutics was working to ferret out fraud,

it was taking steps to reduce waste in the form of time- and bandwidth-consuming prior authorizations. According to Lassen, in June 2023, Prime Therapeutics implemented a system that tapped into a database of diagnosis codes that allowed a claim to be processed at the point of sale "rather than having to force that member and provider down the path of a prior authorization."

"In fact," Lassen continues, "we reduced our prior authorizations overnight by 20%, and millions of dollars of waste were taken out of system by automating and reducing friction at the point of sale because this is such a high-volume situation."

Rayburg says that early on, many payers didn't recognize that so many prescriptions for Ozempic were being written off-label for weight loss. Patients were urging physicians to write the prescription and then hoping the insurance company's guard would be down so that the Ozempic claim would go through.

Figuring it out

The surge of weight loss prescriptions storm may have forced payers to respond on the fly in 2023. Now they are adjusting to the reality of the popularity of the drugs and sorting out how to cover them.

Attitudes and approaches are mixed. Accolade, a virtual health company, published the results of a survey of 500 human resources managers involved in benefits decisions late last year that showed that less than one-third (30%) of employers cover weight loss drugs and less than that (25%) covered the glucagon-like peptide 1 (GLP-1) class that includes Ozempic and Wegovy. (Mounjaro and Zepbound are lumped into the GLP-1 class, although they have an additional mechanism of action, activation of the glucose-dependent insulinotropic polypeptide receptor.) But the survey results also showed that 43% of employers that weren't covering the GLP-1 drugs in 2023 were considering coverage this year. The reluctant majority (57%) picked cost, lack of research and lack of public payer as reasons for holding back.

Rayburg says it is important to distinguish between deciding to cover GLP-1 drugs as a treatment for diabetes and deciding to cover them for weight loss. She noted that the FDA approved the first GLP-1, exenatide, marketed as Byetta, back in 2005, and coverage of the GLP-1s for diabetes hasn't been controversial.

"In the beginning, there was not a lot of push to limit these drugs, because why would you ever limit diabetes drugs that are beneficial and working? But as expenses go up, you look at the cost, you look at the utilization," she says.

"All of a sudden," Rayburg continues, "your costs are kind of getting out of control and you are wondering, 'Is this all related to diabetes?' And when you start to look into it, you are finding that there is probably just as many people getting it off-label for weight loss as there are for diabetes."

Even as GLP-1s' profile as weight-loss drugs has grown, many payers view coverage for diabetes as a priority, according to Rayburg. "There's a finite number of healthcare dollars. We say that all the time, right? So if you've got limited dollars to spend, you definitely would put your money toward your patients with diabetes first and then figure out the second part [weight loss]."

The manufacturers are offering rebates on the GLP-1 drugs that offset some of the costs associated with the flood of prescriptions. But Rayburg says her company worked with one client who tightened up coverage and wound up saving five times more through decreased use than they would have realized through rebates.

One variable in the math of covering the drugs for weight loss is proportion of those with overweight or obesity. Some national statistics suggest that 40% of Americans have obesity, which is defined as a body mass index (BMI) of 30 or more, and almost 10% have severe obesity (a BMI of 40 or more). Rayburg says her company usually has access to data that it can analyze to tell a health plan or self-insured employer how many of its members have obesity. "If you have a tremendous number of people who have obesity, we may make a recommendation to start small and maybe cover those who would benefit the most," she says.

Rayburg says research has shown that weight loss of 5% or more yields an array of health benefits and that the GLP-1s have been shown to produce weight loss of 15% or more. "The unknown is how long that takes," she says. As a result, the payer who foots the bill for the GLP-1 may not be the same payer who reaps the benefits of improved health from weight loss and presumably lower use of medical services.

Lassen also sees considerable uncertainty about the supposed payback from the weight loss from GLP-1s. Last year, Prime Therapeutics published data showing that only 1 in 4 patients who started taking a GLP-1 or weight loss was taking the drug a year later. Research results reported in *JAMA* in December 2023 underscored that patients may need to stay on these weight loss medications to keep the lost weight off. Louis Aronne, M.D., an obesity specialist at NewYork-Presbyterian Hospital in New York, and colleagues reported that after 36 weeks, participants in an open-label study of tirzepatide experienced an average weight reduction of just over 20%. However, those who were switched to a placebo experienced a 14% weight regain during a yearlong follow-up period whereas those who were assigned to continued treatment with the drug experienced an additional 5.5% in weight reduction. Executives at payer orga-

nizations are wondering if a large percentage of their members are going to be taking a GLP-1 indefinitely, saddling their organizations with a year-in, year-out cost with major question marks about offsetting savings from reductions in obesity-related illness.

Lassen also notes that trials that led to FDA approval of the GLP-1 drugs for weight loss enrolled participants in lifestyle medication programs and that their adherence was monitored. Lassen said for him and his colleagues at Prime Therapeutics, all this stirs up apprehension about what will happen with GLP-1 drugs outside the cosseted circumstances of industry-sponsored clinical trials. "Our chief concern with these drugs right now is how do we best manage the waste, because there's a real potential if people in real-world practice are not staying on these medications, then they are not going to do anything but promote cost and temporary weight loss," he says. "If we just simply cover the medication and say, 'Have at it,' what is the likelihood of having success with that? Slim to none."

Lassen is making a case for a new product that he says Prime Therapeutics will unveil sometime in the early part of 2024 that includes assistance from healthcare professionals, coaching and other features. In advance of the official announcement, Lassen was reluctant about sharing too many details, such as the organizations or companies that Prime Therapeutics is partnering with. But he says the program will not be organized as a step program that requires lifestyle modification before receiving a GLP-1 drug prescription.

"We're not looking at this as another barrier to care, a step through lifestyle medication before you get the golden egg. That's not the right approach," Lassen says. "The right approach is if you're going to cover the benefit, then let's make it as successful as possible and let's also help mitigate the friction and confusion that is out there."

"We're excited because doing this is more than just a weight loss program and a lifestyle modification program. It's a cardiometabolic program," Lassen continues. "Our objective is to offer something different and unique that our customers can offer to their members to engage and get care."

Lack of Medicare coverage

Time will tell whether Prime Therapeutics' potential customers will see it that way or as bells and whistles. But the plain fact is that many employers have steered clear of covering weight loss drugs. Lassen says that only 22% of the 30 million lives in its current book of business have a benefit design that covers weight loss (the proportion is slightly higher among self-insured employers). The demand for GLP-1s may cut both ways: Employers may be even more wary of covering weight loss drugs because of the cost, but they may be more willing to cover them because of the evidence of their efficacy and the potential of weight loss benefits may have for attracting and retaining valued employees.

The 65-million beneficiary gorilla of benefit coverage in the U.S. is Medicare. When Medicare Part D was created in 2003, drugs for weight loss and some other conditions, such as hair loss, were explicitly excluded. Legislation that would overturn that ban was first introduced in Congress in 2012 and has been reintroduced in subsequent years with a growing number of sponsors but has not moved forward.

The lack of Medicare coverage affects not only Medicare beneficiaries but also, indirectly, people covered by employer plans and Medicaid because other payers tend to take their coverage cues from Medicare. James Wantuck, M.D., associate chief medical officer for Accolade, says the lack of coverage for weight loss extends beyond drugs to physician visits. "If you [have obesity], you can't go your doctor and talk to them about how to lose weight and have it paid for by your insurance. That seems counterproductive with the crisis we're in," he says. Rayburg says lobbyists are actively working to get the Medicare rules changed.

Another piece in the coverage puzzle may be additional indications for the GLP-1 drugs. If the FDA decides that the GLP-1 drugs can be prescribed on-label for, say, reducing cardiovascular disease risk factors, Medicare might cover the GLP-1s for that reason. Regardless, Rayburg says, cost will be a factor. "At the end of the day, in order for CMS to agree to cover these drugs, they're going to have to figure out how they're going to afford it. So will they put price pressure on the manufacturers? I am not sure."

Coverage by Medicaid is a state-by-state choice. Weight loss drugs are not among the drugs that states must cover under the Medicaid Drug Rebate Program. Even so, Medicaid spending on GLP-1 drugs has increased. KFF, formerly known as the Kaiser Family Foundation, published a report in September 2023 that showed Medicaid spending, in aggregate and before any rebate calculations, on GLP-1s had increased from $547 million in 2021 to $1.2 billion in 2022. Still, the GLP-1 drugs account for a tiny if growing fraction of Medicaid spending on drugs. In 2022, they accounted for just 1.3% of Medicaid drug spending. Patient advocates and others are pushing for more generous coverage. Rayburg says that some states have been sued for not covering the GLP-1 drugs, with the plaintiffs arguing that the drugs must be covered because obesity is a disability.

Peter Wehrwein *is managing editor of* Managed Healthcare Executive.

Meet the superstars of aging: CENTENARIANS

The number of people living to 100 is growing in the U.S. and around the world. Defying the overall trend of older people having more health issues, they are not major users of healthcare.

By **DEBORAH ABRAMS KAPLAN**

While working at a senior care facility with several levels of care in the 1990s, Thomas Perls, M.D., M.P.H., wanted to meet with several centenarians in the independent living section. Perls, then a geriatrics fellow at the beginning of his career, had a hard time making arrangements. "They were never around," he says, and he assumed that they were occupied with medical visits. Perls later realized he was wrong. They were keeping busy with nonmedical activities. One 102-year-old resident was an accomplished pianist who was giving concerts that included complicated Chopin arrangements. Another was a 101-year-old former tailor spending time in the occupational therapy clinic but not for therapy; he was mending people's clothes. Or he was spending time with his young (85-year-old) girlfriend.

PERLS

Perls had an epiphany that maybe there was something special about this group that allowed them to delay or escape aging-related diseases, prompting him to start the New England Centenarian Study (NECS) in 1995, the largest study of its kind in the world. He is the director of the Boston University study and a professor at the university's medical school.

Centenarians are still the exception, the elite pack in the marathon of old age, but their numbers are growing. In 2021, there were nearly 90,000 centenarians in the U.S., almost double the number two decades prior and close to the time when Perls made it his career to study centenarians and look for reasons for their longevity. As the centenarian population expands, other questions have come up, including ones about healthcare utilization and costs.

These insights will come in handy as 100 becomes the new 90 or even 85. The Pew Research Center projects that by 2050, there will be 3.7 million centenarians globally, with the U.S. centenarian population in the lead.

The secrets

Life expectancy at birth in the U.S. rose to 77.5 years in 2022, but that was an exception. *The Washington Post* published a series of articles in 2023 exploring why gains in life expectancy have stagnated and even reversed since about 2010. The newspaper's reporting identified the growing number of middle-aged people with chronic illness, wealth and income disparity, and childhood obesity as among the reasons. For older people, the picture is brighter. Before the COVID-19 epidemic, life expectancy for people at the ages of 65 and 75 had been getting longer. As for centenarians, the NECS research supports the "compression of morbidity" theory of James Fries, M.D., a professor

at Stanford University in California, who researched healthy aging. Fries, who died at age 83 in 2021, argued that good health can stretch into old age and that the onset of infirmity can be postponed so ill health is squeezed into a relatively short period.

Perls and his NECS study have found that most centenarians aren't spared from age-related diseases, but researchers found 90% of them function independently at an average age of 93 and they live with their diseases and handle them better than their peers. The study's researchers say their research has shown that 43% of centenarians are what they call "survivors" who were diagnosed with age-related diseases before the age of 80 and about the same percentage are "delayers" who were diagnosed after 80. "Escapers," who have no mortality-associated disease, make up the remaining 15%.

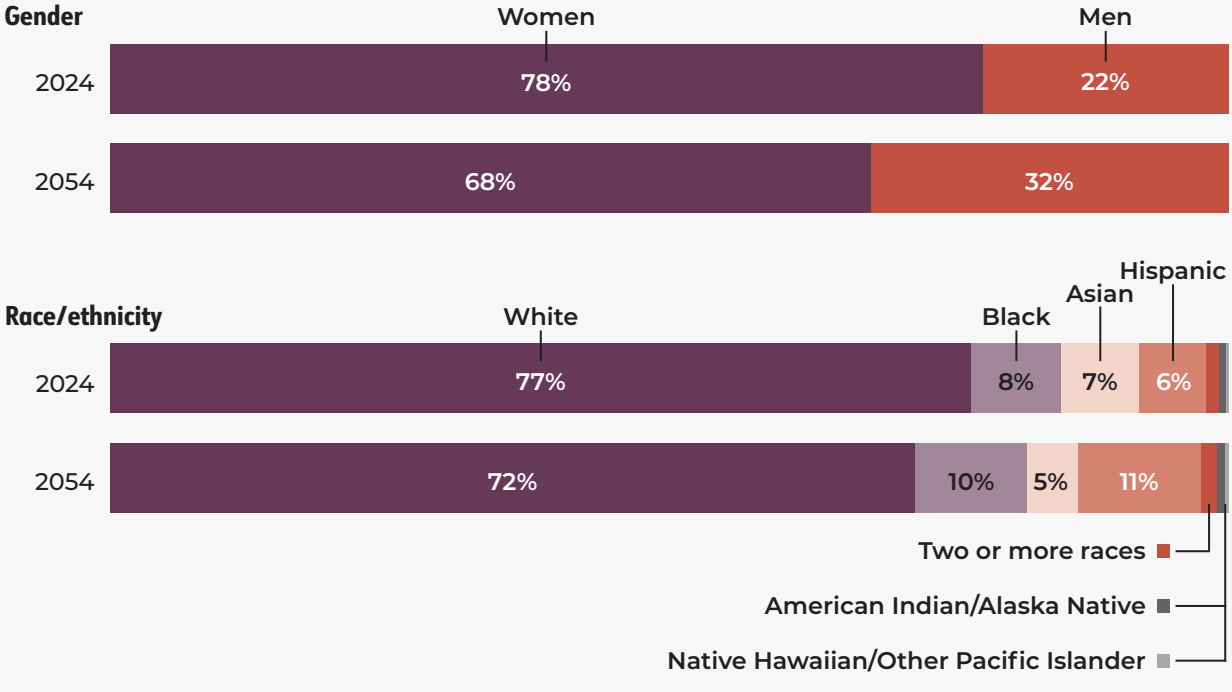

PETERMANN

Cynthia Petermann, a certified geriatric nurse practitioner at CenterWell Senior Primary Care in Anderson, South Carolina, has taken care of numerous centenarians during her career. She's noticed that most centenarians have some kind of chronic disease, such as peripheral vascular disease, osteoarthritis or osteoporosis. Generally, however, they do not have more debilitating disorders such as diabetes or chronic obstructive pulmonary disease. And there is nary a smoker. "I've never had a centenarian I cared for who has been a smoker or used any kind of tobacco. I thought [that] was interesting," she says. Her experience aligns with research, with findings from one study showing that 23% of centenarians have no major chronic diseases and 18% have no disability.

Petermann has noticed other commonalities. She has not seen any centenarians who are overweight — most are actually underweight. All her centenarian patients have been active and ambulatory, mostly residing in assisted living. They have all been involved with their communities and have good support there and with their families, an observation

GENDER AND RACE OF CENTENARIANS IN THE U.S.

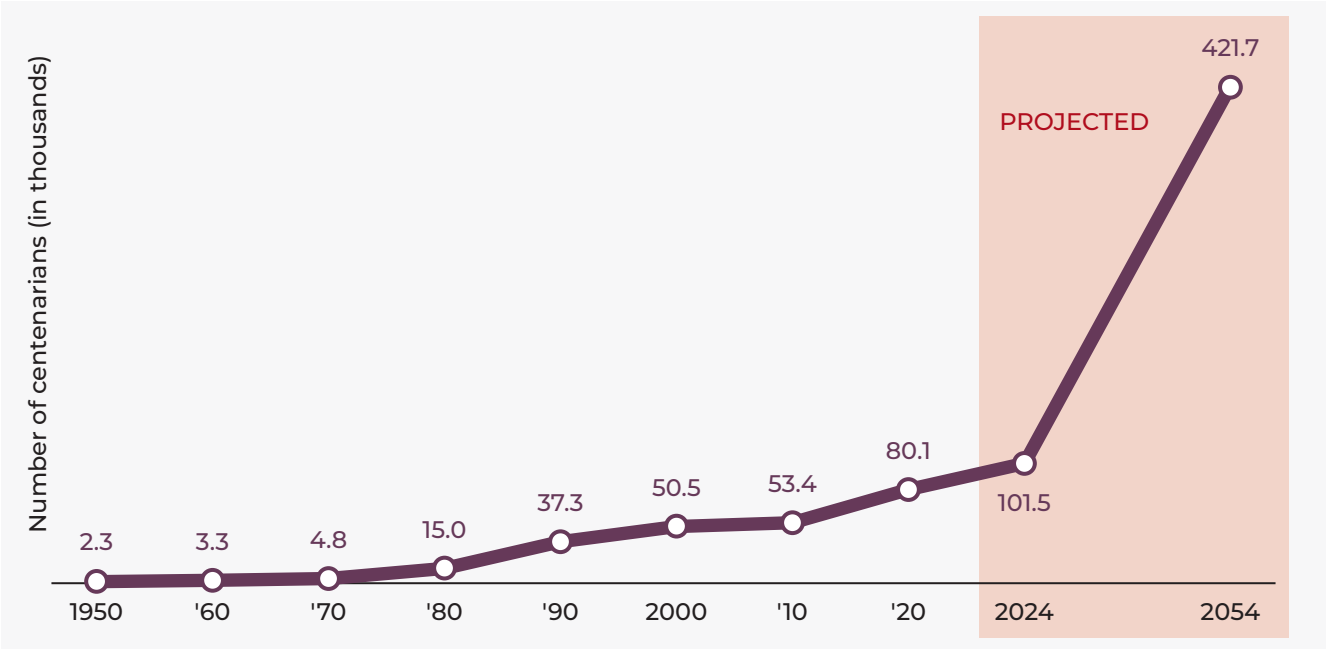
Most of the centenarians in the U.S. are currently White women, but the composition of the group is projected to become more male and less White over the next 30 years.



Source: Pew Research Center

NUMBER OF CENTENARIANS TO SOAR

The number of centenarians in the U.S. is projected to quadruple over the next 30 years.



Source: Pew Research Center

that fits with the research that shows a strong association between good health in old age and social networks.

Not expensive

Medicare data analyzed by KFF, formerly known as the Kaiser Family Foundation, found that although Medicare spending per capita increased with age, the spending topped out at the age of 96, gradually declining for those living longer. For noncentenarians, inpatient hospital care was the largest proportion of the spending. For centenarians, the largest proportion of Medicare spending was on hospice care.

Though centenarians live longer than their peers, healthcare costs for this population tend to be lower, Perls observes. "Generally speaking, centenarians should be the least of our worries when it comes to healthcare costs because of two things," he says: If they get sick, they usually have fewer diseases and are taking fewer medications. And when they get an illness that could be expensive, it's toward the end of their lives. "When they have a high mortality-risk disease, they generally don't choose to go into an ICU [intensive care unit], where care becomes very expensive," Perls says. Delaying those diseases to relatively short periods of their lives — at the ends of their long lives — means lower treatment costs.

Petermann says that last year, one of her centenarian patients went to the hospital for the first time in five years; the patient had a heart disease issue that needed medical attention.

"A lot of people, when they get to that point, don't want to be connected to any machines, life support or tube feedings." This is Perls' experience as well. "Many choose not to go to ICU — they don't want heroic measures. They have a much more realistic idea about their mortality and their quality of life. Aggressive vascular support is not something they're interested in," he says.

As the NECS research matures, Perls is noticing that centenarians' children "very much follow in the footsteps of their parents. They demonstrate an uncanny ability to age slowly and escape diseases associated with aging." The Boston University study is now following some of these people as participants as well. "When you want to live much beyond 90, I'd say choosing your parents well or grandparents well becomes more and more important," Perls says.

Deborah Abrams Kaplan *writes about business, insurance and healthcare.*

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Medical records can be messy. One company says AI can bring clarity

xCures says artificial intelligence and machine learning can help make sense of disparate medical records.

By **JARED KALTWASSER**

Blame it on Deep Blue.

Ever since IBM's Deep Blue computer defeated chess champion Garry Kasparov in 1997 humans have wondered — and fretted about — whether computers could outperform humans in a wide range of areas.

At xCures, a California-based healthcare technology startup, the question took the form of a competition between artificial intelligence (AI) and expert panels of physicians (known as tumor boards) to see which could make better treatment decisions for patients with advanced cancer.

xCures built an AI-based decision support application, and soon it was able to match the performance of human tumor boards, Mika Newton, CEO of xCures, said.


NEWTON

"I get asked, 'Would you still want a tumor board with humans on it?'" Newton told *Managed Healthcare Executive*. "And the answer is, yeah, maybe there's some magic in there sometimes, though I think that actually happens less than people expect."

The humans versus computers question occupied much of xCures' first two years after its founding in 2018. However, Newton said it also exposed another problem that has led to the company's growth since then. "And that problem was access to sufficiently sophisticated medical records — medical data — to make those decisions," he said.

Nonprofit origins

xCures has firsthand knowledge of the difficulty of making meaning out of disparate medical records, because it used to do it the old-fashioned way. The company grew out of Cancer Commons, a nonprofit organization that provides navigation and advocacy services for patients with advanced cancer. Such work has historically been human labor-intensive, relying on individuals to stay up to date on the latest trials and therapies and the details of individual patients' cases. The work helped connect patients to cures, but it had logistical limits.

"They were starting to look at what was the type of technology that you would need to build in order to really be able to scale that nationally," Newton said.

To achieve scale, Cancer Commons launched a for-profit company, xCures. The challenge xCures faced was finding a tool that could give them all-comers data on patients with advanced cancer nationwide as well as the comprehensive medical histories of individual patients. "And we couldn't find such a platform," he said, "so we ended up building one."

What xCures built is software that uses AI and machine learning (ML) to pull together all available medical records on a patient within 15 minutes, giving physicians the information needed to best advise patients.

"Then the last part is that the data [are] now sufficiently organized and structured so that you could do something useful with [them]," Newton said.

The average patient has 1,400 files from 30 different provider locations, he said. xCures provides reports that summarize the data and also link to the original files in case a provider wants to double-check a piece of information or dig deeper into it. In some cases, records are based on facsimiles or scans or include jargon specific to a particular health system or region, Newton noted. AI and ML can sort through those anomalies and make sense of such data.

Other companies

xCures is not alone in seeing the potential of AI to make sense of disparate medical records. Back in 2021, Sidhartha R. Sinha, M.D., of Stanford University in California, and colleagues developed an AI model to organize and display referral records

for new patients. They then recruited a dozen physicians and gave them one set of records that had been organized by the AI system and one set of records in the standard, nonoptimized format. After reviewing the records, physicians were given a list of 22 questions to answer based on the records. The investigators found the AI-based system cut the amount of time it took to answer the questions by 18%.

"The AI system helped physicians extract relevant patient information in less time while maintaining high accuracy," Sinha and colleagues said in a write-up of the results published in *JAMA Network Open* in July 2021. "This is particularly relevant in an era in which practitioners are confronting increasing volumes of EHR [electronic health record] data and the loss of face-to-face interaction with patients."

In fact, results from a 2018 survey of physicians conducted by The Harris Poll for Stanford Medicine suggested physicians spend approximately 62% of their time allotted to each patient referring to EHRs.

Even as xCures has built out its technology platform, public perceptions of AI have changed rapidly. In 2022, the technology firm OpenAI released a public version of its ChatGPT chatbot, ushering in a world in which the public could use AI to create everything from travel itineraries to haikus and 10th-grade history essays. "I think that really sparked everyone's imagination that AI could now move faster and we actually have enough computing power to do these really startling things," Newton said.

It also raised concerns about potential harms that could come from AI. The straightforward nature of xCures' service puts it in the relatively noncontroversial corner of the AI world; everything the company produces can be easily verified and its provenance documented.

Still, even relatively straightforward uses of AI in healthcare raise significant concerns. Saad Abdullah, Ph.D., of Mälardalen University in Sweden, and colleagues noted in a 2023 paper in *Biomedical Materials & Devices* that medical records are "seldom organized neatly" and are "often erroneous." Abdullah and colleagues noted that healthcare datasets such as those used and created by AI systems raise significant privacy concerns and are also vulnerable to hackers and ransomware attacks.

They pointed out that a number of countries have enacted laws and regulations designed to protect patient privacy, but they said such laws can have unintended consequences.

> **"I get asked, 'Would you still want a tumor board with humans on it?' And the answer is, yeah, maybe there's some magic in there sometimes, though I think that actually happens less than people expect."**
>
> MIKA NEWTON, XCURES

"Because various laws passed by various countries make problems of collaboration and cooperative research more difficult, data privacy regulations established to solve this issue may restrict the quantity of data accessible to train AI systems on a national and global scale," they wrote.

Newton said the healthcare sector is not unique in needing to navigate the intersection of AI and privacy. He noted that any time a person applies for a credit card, for instance, a host of personal financial records are used to verify the applicant's identity and assess their creditworthiness.

When meeting with potential clients, Newton said their concerns are generally less about the technology and more about liability when errors occur. Specifically, if a physician misses a key piece of a patient's medical history or makes a decision based on erroneous data, is the physician liable for any resulting harm or is the AI company liable? "That stuff is really hard to tease apart," Newton said.

'Scary idea'

Sometimes such mistakes are due to negligence or a lack of sufficient governance. Other times, mistakes are just mistakes. So far, Newton said he is unaware of any court cases testing such questions. However, he said similar issues arise regarding self-driving cars and that litigation over accidents caused by self-driving vehicles might create some legal clarity for the healthcare industry.

In the meantime, Newton said xCures plans to expand its market beyond cancer and begin looking for other types of illnesses in which its technology can make a meaningful difference. He said he understands the concerns some have about AI and healthcare.

"It's just a scary idea," he said, "because you don't know what's really possible or not." Newton pointed to a recent article in a national newspaper questioning whether AI would be able to match the quality of human-made art, thus rendering it redundant. While it's fun to ponder such questions, Newton thinks such juxtapositions might be missing the point.

"As a technologist, I'm just not sure it needs to go that far," he said. "I think we should say, 'These are the tools we have. These are the problems we want to solve. What are the right tools for the problem?'" ◘

Jared Kaltwasser *is a healthcare writer in Iowa and a regular contributor to* Managed Healthcare Executive.

K-Cast

What a new treatment means for patients with Demodex blepharitis

In this Managed Healthcare Executive *K-Cast video series, Christopher Starr, M.D., provides an overview of the symptoms and diagnosis of Demodex blepharitis and discusses the consequences of the first FDA-approved treatment. Starr is an associate professor of ophthalmology at the Weill Cornell Medical College in New York. You can view the video series at www.managedhealthcare executive.com/k-cast.*

This transcript of Starr's remarks has been edited for clarity and length.

Demodex blepharitis has had a very substantial impact on people's quality of life for a number of reasons. The eyes can be red, and the eyelid margin can be swollen, red, crusty and flaky. That doesn't look great, and people get very self-conscious. People pay a lot of money for long, full eyelashes, and this condition can lead to loss of those eyelashes, which, of course, has cosmetic implications. Also, the eyelashes are important for protecting the ocular surface: They are there for a reason. When you lose your eyelashes, things can get into your eye and your eyes can be more irritated.

Both forms of Demodex blepharitis — follicular and brevis — can lead to recurrent chalazion or hordeolum. When those are present, you have big bumps on the eyelids, and in some cases, they can cause preseptal cellulitis.

We know that Demodex blepharitis goes hand in hand with dry eye disease, and dry eye disease can have a major impact on quality of life, on people's wellness and well-being. It can also be very expensive.

Types of blepharitis

Blepharitis is Latin for inflammation of the eyelids, which is very nonspecific. Anterior blepharitis and posterior blepharitis are two ways it can be categorized, and Demodex blepharitis is probably the most common cause of anterior blepharitis. Posterior blepharitis is often called meibomian gland dysfunction, and Demodex brevis is related to that.

When there is blepharitis from Demodex — really any form of blepharitis — that can lead to ocular surface issues [such as] pterygium or pinguecula.

Risk of blindness

When there's Demodex blepharitis, there is often bacterial overload as well. The bacteria generally tend to be the [staphylococcal] and [streptococcal] gram-positive bacteria. Those are the same bacteria that lead to one of the most horrific complications of cataract surgery, which is endophthalmitis. If you see Demodex blepharitis, anterior blepharitis or collarettes prior to surgery, you have a pretty good idea that there's an extra load of bacteria on those lids and it behooves you, as the surgeon, to reverse that, to treat it aggressively prior to not only finalizing your ocular surgery measurements but certainly before making any incisions and doing the surgery itself. Usually, it's not Demodex but rather the bacteria that go hand in hand with Demodex that cause the infection. In a lot of those cases, the majority of [patients in those] cases do end up legally blind. We have to do everything we can to prevent that from happening.

Common symptoms and a vicious cycle

Patients with blepharitis will probably have a lot of the same symptoms as a patient [with] dry eye, as the person with exposure keratitis, as a person with allergic conjunctivitis or infectious conjunctivitis, and so on and so forth. When these patients come in with these symptoms — dryness, itchiness, redness, my eyes are itchy, they're gritty, they get a foreign body [in the eye] sensation, my vision fluctuates — those symptoms can be attributable to virtually any of the ocular surface diseases. Many practitioners will just say, "You have dry eye, so go take some artificial tears and you'll be fine" and sweep it under the rug.

We need to isolate the symptoms and try to pin each symptom to an actual diagnosis. The best way to do that is certainly with a very careful and thoughtful examination.

Pearls for patients

Itching is something that we hear a lot. [My approach is to ask] whether it is your eyes that are itchy or is it your eyelids. Show me how you [rub] your eyes when they get itchy, and when somebody does this, it's probably allergy. But when somebody takes their finger down and goes across their eyelashes, that to me is eyelid itching. That kind of scratching with the fingernail on the lashes is, in my experience, almost assuredly related to anterior blepharitis, and in most cases, that's going to be Demodex. I think that's a great little pearl for all practitioners and patients.

When you're seeing 50, 60, 70 patients a day, you have

very limited time. A lot of doctors will recoil at anything that's related to the ocular surface. They won't take that extra five seconds and ask a couple of pointed little questions about the symptoms or the way they itch or the signs. And that's all it takes.

Challenges to diagnosis

One of the biggest challenges with diagnosing Demodex blepharitis has been the guaranteed kind of diagnosis. The way that diagnosis was guaranteed was you would have to remove an eyelash or a few eyelashes, which never feels good for the patient, [and look at them under a microscope for Demodex]. It's time consuming and costly. A lot of times, you might pluck a few eyelashes and not see Demodex. Then you have these false-negative diagnoses.

The second challenge has always been this uncomfortable discussion [about infestation with mites]. When you're having that conversation with somebody, when there wasn't an FDA-approved medication to treat it, that conversation is really uncomfortable. So uncomfortable that, and I'm guilty of this too, you just don't discuss it at all.

We would recommend the same treatments that we would recommend for everybody with any form of blepharitis: warm compresses … a little baby shampoo on your eyelids, maybe an antibiotic here or there, a little ointment, and so on and so forth. [And] maybe [don't] mention the fact that there are mites.

Easier to talk about

Now that we do have an FDA-approved treatment, we have an effective treatment, I'm much more likely to bring it up when I see Demodex.

We know that collarettes now are pathognomonic; you don't have to pluck the eyelashes, you don't need a microscope in your office, you don't need glass slides and all that cumbersome stuff. If you see the collarettes, then the best way to diagnose is have the patient look down when you're looking at them under the slit lamp. [If] you see the collarettes, you've got your diagnosis.

It's still uncomfortable [to tell patients about the diagnosis] because anytime you talk about mites and infestation, it's uncomfortable, plain and simple. But it's much more comfortable now that there's a prescription medication that can treat this effectively.

Christopher Starr, M.D., an associate professor of ophthalmology at Weill Cornell Medical College in New York, discussed a new FDA-approved treatment for Demodex blepharitis in a *Managed Healthcare Executive* K-cast video.

Scan the QR code to watch the full video series.

New FDA-approved treatment

The lotilaner eyedrops differ substantially [from treatments used in the past]. Probably the most important distinction is that they are FDA approved.

They are also an eyedrop. [The other treatments I have mentioned] were scrubs and ointments, procedural things, oral medication, and so on and so forth. This is really the first eyedrop. It's a twice-a-day eyedrop for a six-week course. It was, at least in the phase 3 clinical trial, very well tolerated, very comfortable. I think 90% of patients considered it to be a neutral or very comfortable drop. [The results] showed, compared with the placebo, a highly statistically significant improvement in the eradication of mites, reduction in collarettes, and reduction in eyelid redness or erythema.

Education needed

I think that there's a lot of education to be had around Demodex blepharitis for practitioners, patients, healthcare systems, hospitals and insurance companies because this is an extremely common condition. It might have been underreported and underdiagnosed in prior times for all the reasons that I mentioned. Now that there's FDA treatment approved, we're going to be seeing more and more [Demodex blepharitis diagnoses]. [It's] not that the prevalence of it is going up. It's just that we're going to be diagnosing it more because we have effective treatments for it now.

For practitioners, I think the most important educational tip here is very simply to make the diagnosis. It might require a slight change to the way we practice because a lot of doctors don't necessarily have patients always look down. It's also important to educate providers that there is an FDA-approved treatment. There's a lot of new stuff happening in all aspects of eye care. A lot of people might not even know that we have an FDA-approved product now for Demodex blepharitis.

For healthcare systems [and insurers], it will save time and money in the long run if we look for [Demodex blepharitis], diagnose it and treat it on [the first] visit rather than [the 12th] visit after the patient has tried a zillion other prescription medications, wipes, surgical procedures and so on. ■

K-Cast

Innovations in reproductive medicine: AI, broadening access

In this Managed Healthcare Executive *K-Cast video series, Joseph Chervenak, M.D., MBA, discussed the challenges of making infertility treatment available to more people and the potential of using artificial intelligence and other strategies to overcome them. Chervenak is a clinical fellow in reproductive endocrinology and infertility at the Montefiore Health System in New York. You can find this K-Cast video series at www.managedhealthcareexecutive.com/k-cast.*

Financial barriers, limits on insurance coverage and other hurdles loom large for people seeking fertility treatment, which has historically been viewed as an elective service that reaches a small, affluent population, Joseph Chervenak, M.D., MBA, said in a *Managed Healthcare Executive* K-Cast video series. Meanwhile, specialists are reconceiving infertility to encompass more people and in a greater variety of circumstances, Chervenak, a clinical fellow in reproductive endocrinology and infertility at the Montefiore Health System in New York, noted. Broadening access while also expanding the population viewed as needing services will require greater scale and capacity, he said. "I think as a society, as we've recognized the potential need for fertility services is much larger than it used to be, there has and will be a focus on the technologies and innovations that will allow us to deliver care at scale to more people," Chervenak said.

Applying AI

Application of artificial intelligence (AI) holds great potential for a field of medicine that has traditionally embraced innovation, Chervenak noted. Currently, embryologists visually inspect and grade embryos. "This is something, in theory, a high-quality camera with an algorithm should be able to do better, and there has been exciting research that suggests tools like this are viable," Chervenak said.

Chervenak was the first author of a study published in the journal *Fertility and Sterility* in September 2023 that examined ChatGPT responses to fertility-related prompts. The results showed that 9 (6%) of 147 ChatGPT factual statements were categorized as incorrect, and only one statement cited a reference. Chervenak and his colleagues concluded that although ChatGPT "demonstrates the ability of generative artificial intelligence to produce relevant, meaningful responses to fertility-related clinical queries," its limitations, such as the "the unpredictable possibility of fabricated information," may limit its clinical use.

Navigating insurance coverage of IVF

"When talking about the challenges of treatment, I think the No. 1 problem is expense and burden of our most effective treatment option," which is in vitro fertilization (IVF), Chervenak said. IVF involves receiving injectable medications for a couple of weeks, during which there is frequent monitoring with ultrasounds and bloodwork, he explained, and that is followed by the other steps in the IVF process (egg retrieval, in vitro fertilization, embryo transfer). "Not everyone has a great support system in place for this process through family or friends, so it may be more difficult to manage for some than others. And there's always a chance that this process could fail at different stages," Chervenak said.

Some states, such as a New York, have mandated that health insurers cover IVF. But Chervenak said that even with mandates, there is variability in exactly what is covered. For example, insurance mandates may not apply to employees for smaller employers who have small-group insurance, he said. "Reviewing each patient's situation with the financial department becomes a necessity for almost every individual," even in states with coverage mandates, he said.

> "When talking about the challenges of treatment, I think the No. 1 problem is **expense and burden** of our most effective treatment option **[IVF]**."
>
> JOSEPH CHERVENAK, M.D., MBA, MONTEFIORE HEALTH SYSTEM

Some insurers will require patients to first try cycles of intrauterine insemination (IUI), which involves placing sperm directly into the uterus.

"That can be problematic for patients," Chervenak said. "A patient for whom you determine IVF is the best option, they have to do IUI cycles before an IVF cycle will be covered. And in our field, [that] is not just a burden on the patient, but also IVF becomes less successful with aging." ◘

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