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# MEDICAL FORUM™

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# Editorial



**Dear Doctor**

It is our immense pleasure to present **"Medical Forum-January 2023"**. In this issue, we have incorporated one of the biggest achievements of Eskayef Pharmaceuticals ltd. We have ensured to mention some of the medical concern of current times as well.

Hope these topics will present as interesting, enjoyable and informative to you.

Wish you a happy reading…


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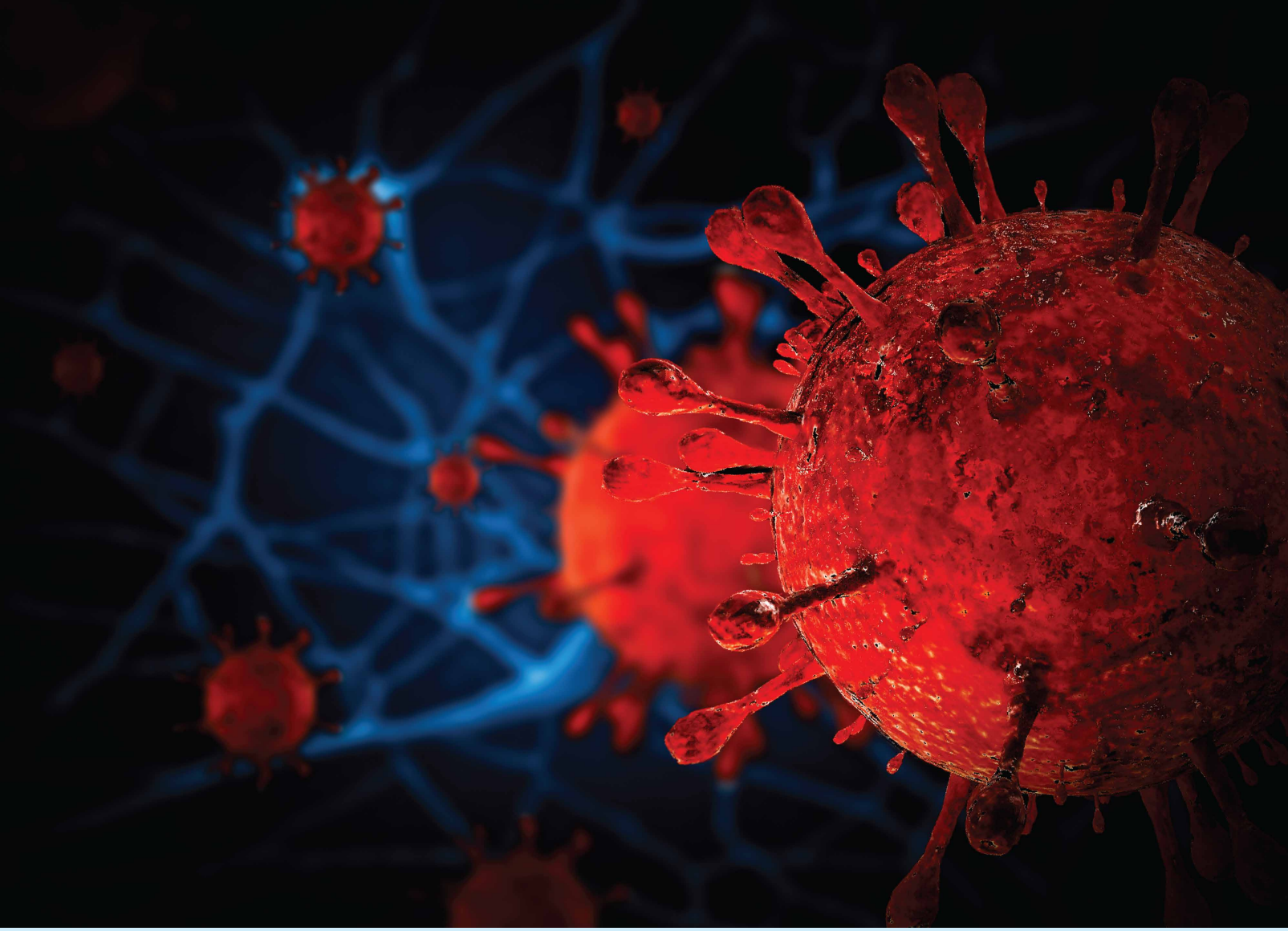
# STOP THE SPREAD OF SUPERBUGS

For nearly a century, bacteria-fighting drugs known as antibiotics have helped to control and destroy many of the harmful bacteria that can make us sick. But in recent decades, antibiotics have been losing their punch against some types of bacteria. In fact, certain bacteria are now unbeatable with today's medicines. Sadly, the way we've been using antibiotics is helping to create new drug-resistant "superbugs."

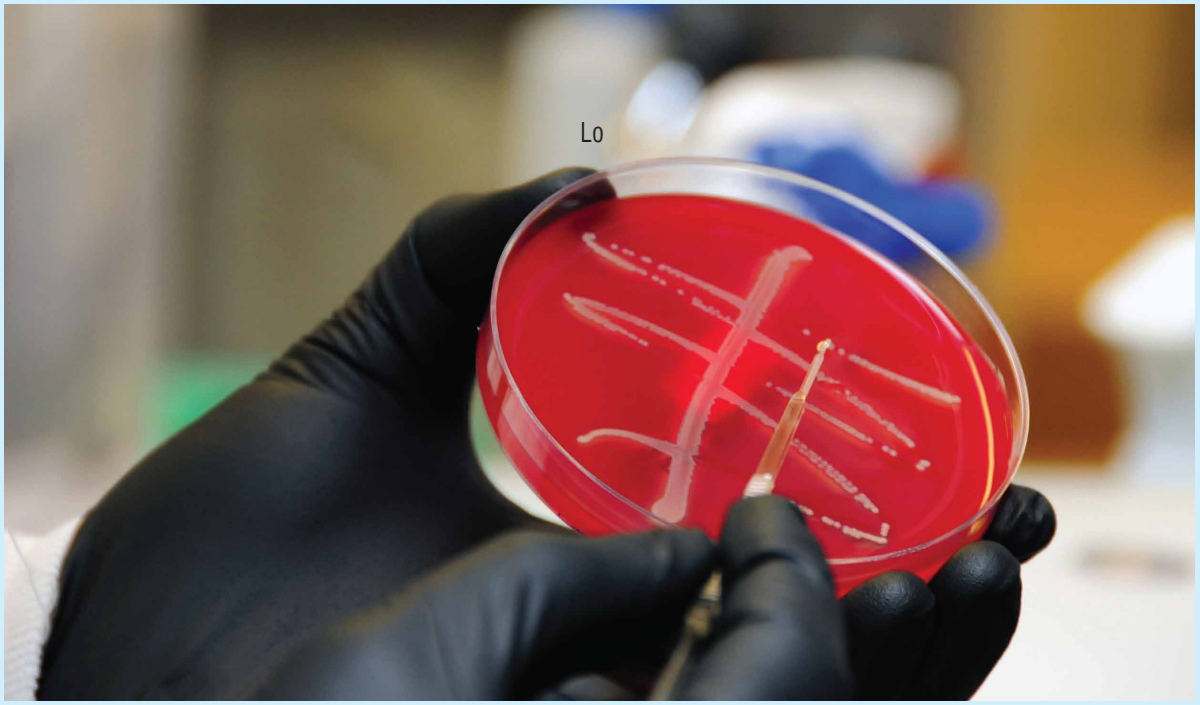
Superbugs are strains of bacteria that are resistant to several types of antibiotics. Each year these drug-resistant bacteria infect more than 2 million people nationwide and kill at least 23,000, according to the U.S. Centers for Disease Control and Prevention (CDC). Drug-resistant forms of tuberculosis, gonorrhea, and staph infections are just a few of the dangers we now face.

Antibiotics are among the most commonly prescribed drugs for people. They're also given to livestock to prevent disease and promote growth. Antibiotics are effective against bacterial infections, such as strep throat and some types of pneumonia, diarrheal diseases, and ear infections. But these drugs don't work at all against viruses, such as those that cause colds or flu.



Unfortunately, many antibiotics prescribed to people and to animals are unnecessary. And the overuse and misuse of antibiotics helps to create drug-resistant bacteria.

Here's how that might happen. When used properly, antibiotics can help destroy disease-causing bacteria. But if you take an antibiotic when you have a viral infection like the flu, the drug won't affect the viruses making you sick. Instead, it'll destroy a wide variety of bacteria in your body, including some of the "good" bacteria that help you digest food, fight infection, and stay healthy. Bacteria that are tough enough to survive the drug will have a chance to grow and quickly multiply. These drug-resistant strains may even spread to other people.




Over time, if more and more people take antibiotics when not necessary, drug-resistant bacteria can continue to thrive and spread. They may even share their drug-resistant traits with other bacteria. Drugs may become less effective or not work at all against certain disease-causing bacteria.

"Bacterial infections that were treatable for decades are no longer responding to antibiotics, even the newer ones," says Dr. Dennis Dixon, an NIH expert in bacterial and fungal diseases. Scientists have been trying to keep ahead of newly emerging drug-resistant bacteria by developing new drugs, but it's a tough task.

"We need to make the best use of the drugs we have, as there aren't many in the antibiotic development pipeline," says Dr. Jane Knisely, who oversees studies of drug-resistant bacteria at NIH. "It's important to understand the best way to use these drugs to increase their effectiveness and decrease the chances of resistance to emerge."

You can help slow the spread of drug-resistant bacteria by taking antibiotics properly and only when needed. Don't insist on an antibiotic if your health care provider advises otherwise. For example, many parents expect doctors to prescribe antibiotics for a child's ear infection. But experts recommend delaying for a time in certain situations, as many ear infections get better without antibiotics.

NIH researchers have been looking at whether antibiotics are effective for treating certain conditions in the first place. One recent study showed that antibiotics may be less effective than previously thought for treating a common type of sinus infection. This kind of research can help prevent the misuse and overuse of antibiotics.

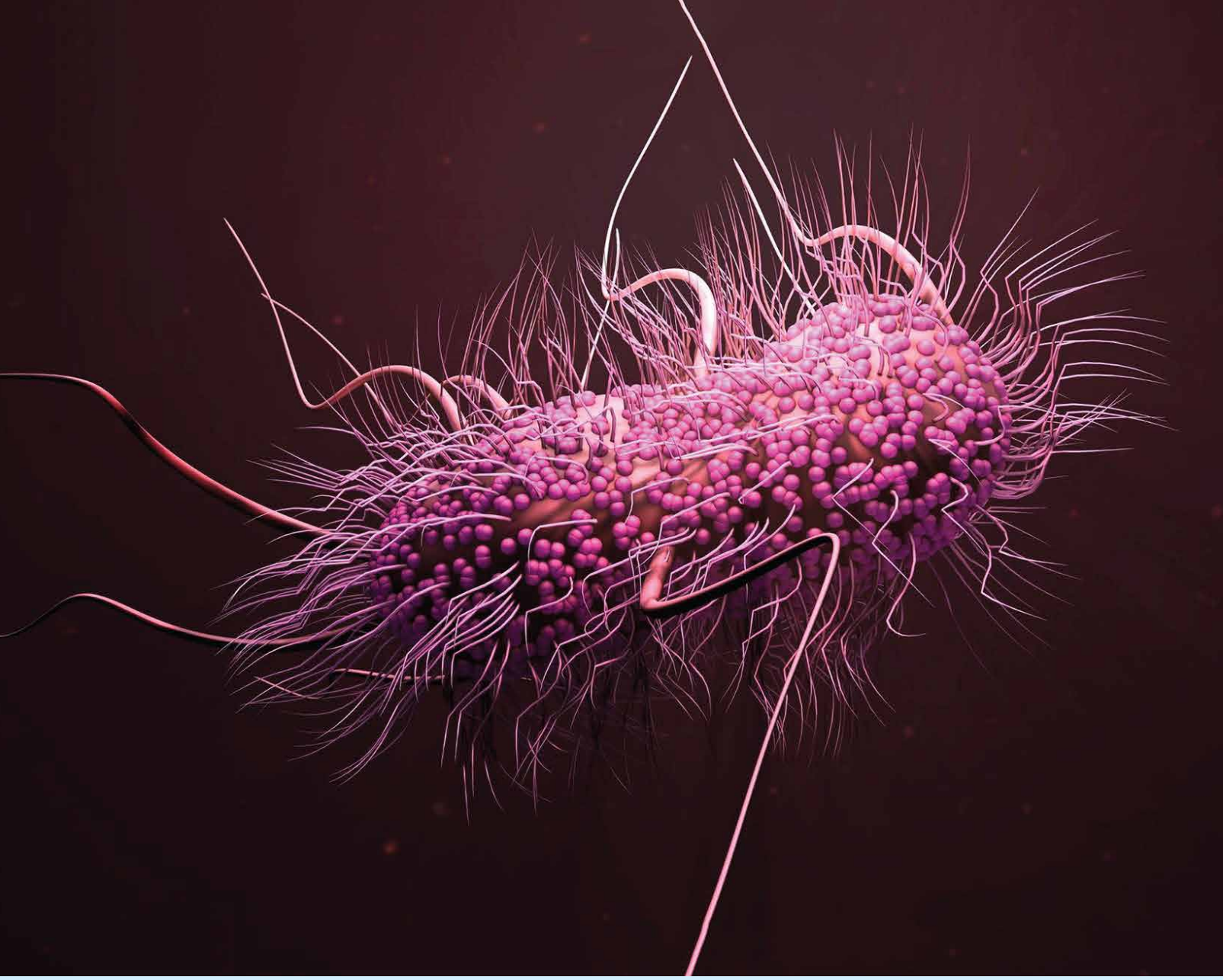
“Treating infections with antibiotics is something we want to preserve for generations to come, so we shouldn’t misuse them,” says Dr. Julie Segre, a senior investigator at NIH.

In the past, some of the most dangerous superbugs have been confined to health care settings. That’s because people who are sick or in a weakened state are more susceptible to picking up infections. But superbug infections aren’t limited to hospitals. Some strains are out in the community and anyone, even healthy people, can become infected.

One common superbug increasingly seen outside hospitals is methicillin-resistant Staphylococcus aureus (MRSA). These bacteria don’t respond to methicillin and related antibiotics. MRSA can cause skin infections and, in more serious cases, pneumonia or bloodstream infections.

A MRSA skin infection can appear as one or more pimples or boils that are swollen, painful, or hot to the touch. The infection can spread through even a tiny cut or scrape that comes into contact with these bacteria. Many people recover from MRSA infections, but some cases can be life-threatening. The CDC estimates that more than 80,000 aggressive MRSA infections and 11,000 related deaths occur each year in the United States.

When antibiotics are needed, doctors usually prescribe a mild one before trying something more aggressive like vancomycin. Such newer



antibiotics can be more toxic and more expensive than older ones. Eventually, bacteria will develop resistance to even the new drugs. In recent years, some superbugs, such as vancomycin-resistant Enterococci bacteria, remain unaffected by even this antibiotic of last resort.

“We rely on antibiotics to deliver modern health care,” Segre says. But with the rise of drug-resistant bacteria, “we’re running out of new antibiotics to treat bacterial infections,” and some of the more potent ones aren’t working as well.

Ideally, doctors would be able to quickly identify the right antibiotic to treat a particular infection. But labs need days or even weeks to test and identify the bacteria strain. Until the lab results come in, antibiotic treatment is often an educated guess.

“We need to know how to treat for a favorable outcome, but knowledge about the infection can be several days away,” explains Dr. Vance Fowler, an infectious disease expert at Duke University School of Medicine.

Fowler says faster diagnostic testing offers one of the best hopes for treating infectious diseases. Technology is catching up, he says, and new research in this area looks promising.

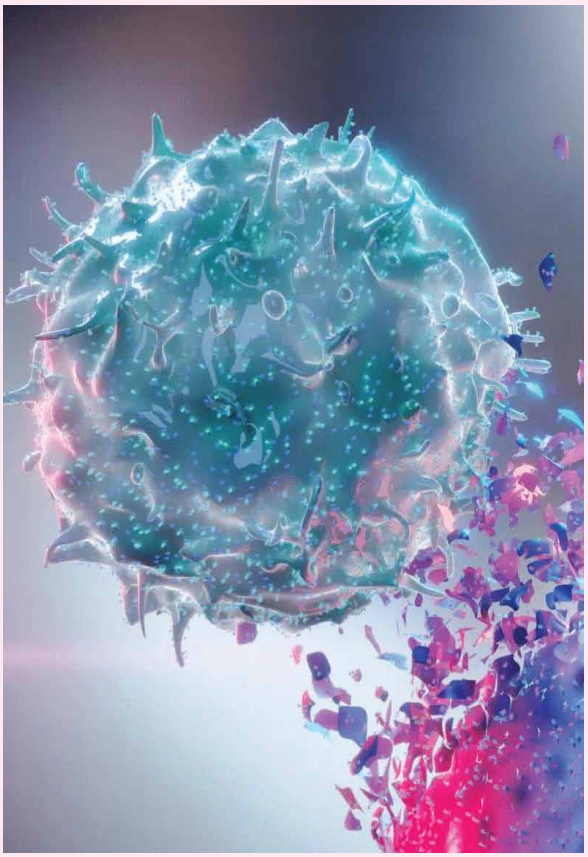
Genetic studies by NIH-supported researchers such as Segre and Fowler are also helping us understand the unique characteristics of antibiotic-resistant bacteria. Their findings could point the way to innovative new treatments.

While scientists search for ways to beat back these stubborn bacteria, you can help by preventing the spread of germs so we depend less on antibiotics in the first place.

The best way to prevent bacterial infections is by washing your hands frequently with soap and water. It's also a good idea not to share personal items such as towels or razors. And use antibiotics only as directed. We can all do our part to fight drug-resistant bacteria.

## Next Generation of mRNA Vaccinology

Advancements in the generation, purification and cellular delivery of RNA have enabled the development of mRNA vaccines across a broad array of applications, such as cancer and Zika virus infection. The technology is cost-effective, relatively simple to manufacture, and elicits immunity in a novel way. Furthermore, the emergence of the COVID-19 pandemic demonstrated that the world needed rapid development of a vaccine that was deployable around the globe. Because of previous research that laid the groundwork for this technology, an effective COVID-19 vaccine was developed, produced, approved and deployed in less than a year. This landscape-changing technology has the potential to be used to manage some of healthcare's most challenging diseases quickly and efficiently.



## PSMA-Targeted Therapy in Prostate Cancer

Each year, more than 200,000 American men receive a diagnosis of prostate cancer – making it the most commonly diagnosed cancer among men in the United States. Accurate imaging is critical for tumor localization, staging the disease and detecting recurrences. PSMA, an antigen found in high levels on the surface of prostate cancer cells, is a potential biomarker for the disease. PMSA PET scans use a radioactive tracer to attach to PSMA proteins, which are then combined with CT or MRI scans to visualize the location of prostate cancer cells. In 2020, this technology received FDA approval based on phase III clinical trials, which showed substantially increased accuracy for detecting prostate cancer metastasis compared to conventional imaging with bone and CT scans. When detected early by PSMA PET scans, recurrent prostate cancer can be treated through a targeted approach with stereotactic body radiation therapy, surgery and/or systemic therapy in a personalized manner.

## New Treatment for the Reduction of LDL

High levels of blood cholesterol, particularly low-density lipoproteins (LDL-C), are known to be a significant contributor to cardiovascular disease. In 2019, the FDA reviewed the application for inclisiran in treating primary hyperlipidemia in adults who have elevated LDL-C while on a maximally tolerated dose of statin therapy. Inclisiran is an injectable small interfering RNA that targets the PCSK9 protein. In contrast to statins, it requires infrequent dosing (twice per year) and provides effective and sustained LDL-C reduction in conjunction along with statins. Its prolonged effect may help alleviate medication non-compliance, one of the leading causes of failure to lower cholesterol levels. Inclisiran was FDA approved in December 2021 and is widely considered a game-changer for heart disease patients.

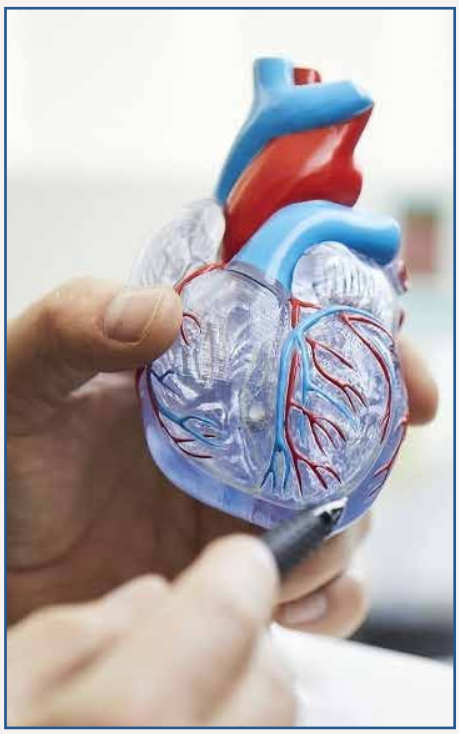


## Novel Drug for Treatment of Type 2 Diabetes

In the United States, 1 in 10 individuals has diabetes, which affects how the body processes food into energy. One potential therapy is a once-weekly injectable dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide receptor agonist (GLP-1) that aims to control blood sugar. Injected under the skin, GLP-1 and GIP receptors cause the pancreas to release insulin and block the hormone glucagon, limiting blood sugar spikes after a meal. Additionally, it slows digestion, resulting in individuals remaining full longer and eating less. Thus far, late phase III clinical trials reveal that the treatment significantly reduces hemoglobin A1C in type 2 diabetes and supports weight loss, making it potentially the most effective therapy for diabetes and obesity yet developed.

## Breakthrough Treatment for Postpartum Depression

Experts believe the rate of postpartum depression could be at least twice as high as what current statistics reveal because many cases go undiagnosed. Currently, counseling and anti-depressant medications are the primary treatments but some women do not respond to these therapies. In 2019, the FDA approved an intravenous infusion treatment designed to treat postpartum depression specifically. This novel therapy, administered around the clock for 60 hours, uses a neurosteroid to control the brain's response to stress. This treatment design is groundbreaking as it targets the signaling thought to be deficient in hormone-sensitive postpartum depression. Additionally, this treatment appears to show benefits very quickly, while traditional anti-depressants typically take two to four weeks to have a significant effect. This rapid treatment option would be a breakthrough for women with this often overlooked condition.



## Targeted Medication for Hypertrophic Cardiomyopathy

For decades, clinicians have only been able to treat patients' hypertrophic cardiomyopathy (HCM) symptoms—using drugs developed to treat other heart conditions—with limited effectiveness. Currently, non-specific medications are prescribed to treat some of the symptoms that HCM shares with other cardiovascular diseases. These therapies include beta-blockers, anti-arrhythmic drugs, calcium channel blockers and anticoagulants. A new treatment, however, works to reduce the root cause of the problem in many patients. A first-in-class medication specifically targets heart muscle to reduce abnormal contractions caused by genetic variants that put the heart into overdrive. By acting specifically on this mechanism in HCM patients, this novel treatment not only improves symptoms and quality of life, but potentially could slow progression of the disease. The FDA has assigned a target action date for this therapy of April 28, 2022. If approved, this would be the first medication explicitly dedicated to treating HCM and providing new hope to patients and physicians.

## Non-Hormonal Alternatives for Menopause

More than 50 percent of all menopausal women experience hot flashes, which can persist for an average of seven years. While effective and safe when used appropriately, hormone therapy involves some risk and not all patients are appropriate candidates or ready to try this treatment option. Fortunately, a new group of non-hormonal drugs, called NK3R antagonists, have emerged as a viable alternative to hormone therapy. These drugs disrupt a signaling pathway in the brain that has been linked to the development of hot flashes and have shown promise in clinical trials for relieving moderate to severe menopausal hot flashes as effectively as hormones. While additional studies are needed to fully understand the effectiveness and safety of these new drugs, it is clear that the next generation of non-hormonal treatments for menopausal hot flashes is on the horizon.

## Implantable for Severe Paralysis

Approximately one in 50 Americans, or 5.4 million people, have some form of paralysis. Most patients experience a significant decline in their overall health. Recently, a team has offered new hope for these patients by leveraging implanted brain-computer interface technology to recover lost motor control and enable patients to control digital devices. The technology uses implanted electrodes to collect movement signals from the brain and decode them into movement commands. It has been shown to restore voluntary motor impulses in patients with severe paralysis due to brain, spinal cord, peripheral nerve or muscle dysfunction. While the interface technology is in its infancy, the FDA has designated the implantable a “breakthrough device,” reinforcing the need to move this technology to the bedside of patients who need it most.

## AI for Early Detection of Sepsis

Sepsis is a severe inflammatory response to infection and a leading cause of hospitalization and death worldwide. Because septic shock has a very high mortality rate, early diagnosis of sepsis is critical. Diagnosis can be complicated because early symptoms are common across other conditions, and the current standard for diagnosis is non-specific. Artificial intelligence (AI) has surfaced as a new tool that can help rapidly detect sepsis. Using AI algorithms, the tool detects several key risk factors in real time by monitoring patients' electronic medical records as physicians input information. Flagging high-risk patients can help facilitate early intervention, which can improve outcomes, lower healthcare costs and save lives.

## Predictive Analytics and Hypertension

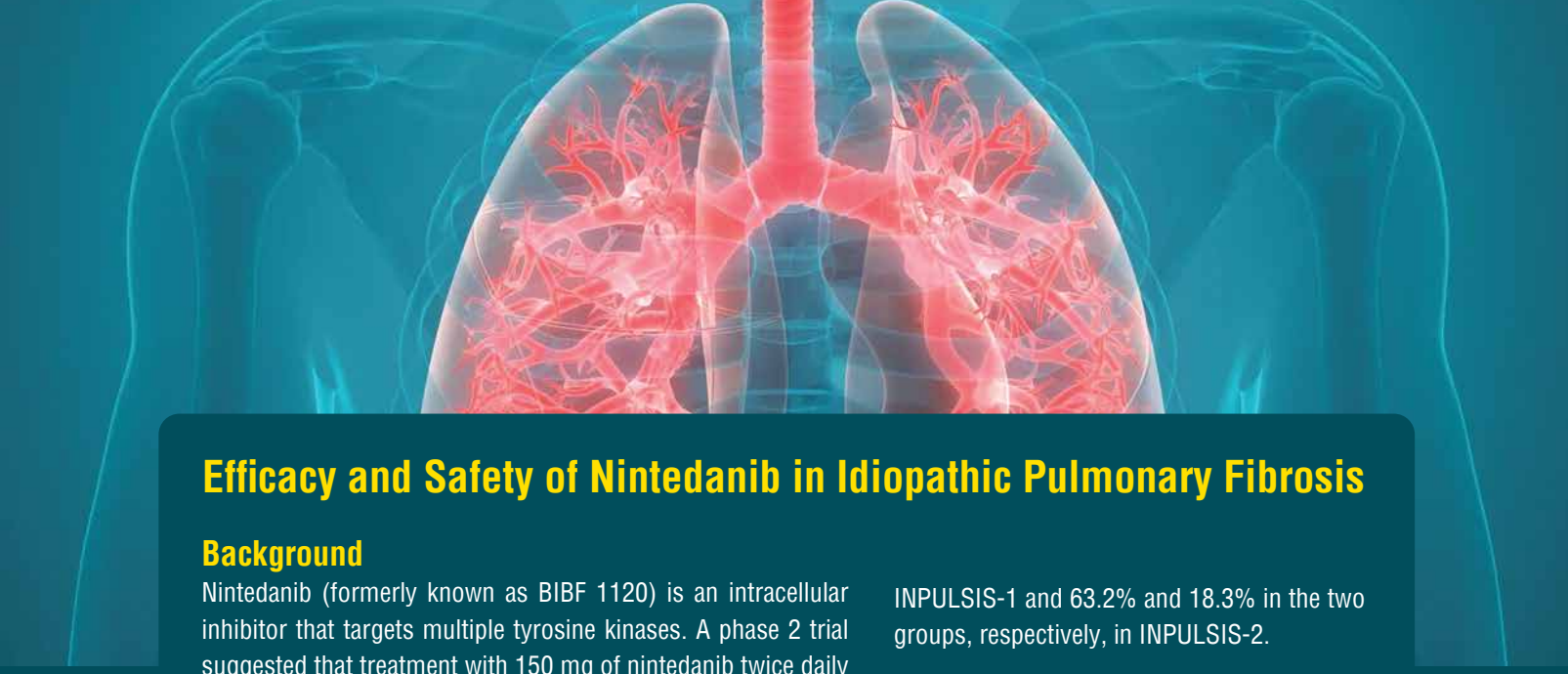
Often referred to as the "silent killer," hypertension, or high blood pressure, usually shows no symptoms while increasing risk for serious health problems, including heart disease, heart failure and stroke. Effective treatment options exist; however, many adults remain unaware that they have hypertension until they experience a significant health crisis. Using machine learning, a type of artificial intelligence, physicians are able to better select more effective medications, medication combinations, and dosages to improve control of hypertension. AI also will allow physicians to predict cardiovascular morbidities and enable physicians to focus on interventions before they occur. Predictive analytics equip providers with the key that could open the door to preventing hypertension and many other diseases.

## Protein supplementation for fracture healing (July 2022)

While general guidance for patients recovering from a fracture often includes ensuring that protein intake is adequate, very few controlled trials have assessed the role of protein in fracture healing. In a single-center trial of 400 patients with pelvic or extremity fractures requiring surgical repair, those assigned to receive essential amino acid supplementation had lower overall complication rates (30.5 versus 43.8 percent) and significantly less early skeletal muscle wasting than those assigned to standard care and nutrition [12]. While the trial was not completely blinded and further study is needed, these results support guidance for adequate daily protein intake in patients with healing fractures.

## Intensive insulin therapy in type 1 diabetes and risk of foot ulcers (April 2022)

In the Diabetes Control and Complications Trial (DCCT), more intensive insulin therapy (achieved mean glycated hemoglobin [A1C] of 7.2 percent) compared with conventional therapy (achieved mean A1C of 9.1 percent) decreased rates of neuropathy and macrovascular disease, although there have been few data on foot ulcers. In the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study to the DCCT, the incidence of diabetic foot ulcers 23 years post-DCCT was also lower in the group that was originally randomized to intensive insulin therapy (7.3 versus 9.6 per 1000 person-years) [17]. There were relatively few lower extremity amputations (almost all involving toes) reported during EDIC follow-up. Selecting an appropriate target A1C should be individualized, balancing the anticipated reduction in microvascular and macrovascular complications over time with the immediate risks of hypoglycemia and weight gain.



NINTEDANIB

# Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

## Background

Nintedanib (formerly known as BIBF 1120) is an intracellular inhibitor that targets multiple tyrosine kinases. A phase 2 trial suggested that treatment with 150 mg of nintedanib twice daily reduced lung-function decline and acute exacerbations in patients with idiopathic pulmonary fibrosis.

## Methods

We conducted two replicate 52-week, randomized, double-blind, phase 3 trials (INPULSIS-1 and INPULSIS-2) to evaluate the efficacy and safety of 150 mg of nintedanib twice daily as compared with placebo in patients with idiopathic pulmonary fibrosis. The primary end point was the annual rate of decline in forced vital capacity (FVC). Key secondary end points were the time to the first acute exacerbation and the change from baseline in the total score on the St. George's Respiratory Questionnaire, both assessed over a 52-week period.

## Results

A total of 1066 patients were randomly assigned in a 3:2 ratio to receive nintedanib or placebo. The adjusted annual rate of change in FVC was –114.7 ml with nintedanib versus –239.9 ml with placebo (difference, 125.3 ml; 95% confidence interval [CI], 77.7 to 172.8; P<0.001) in INPULSIS-1 and –113.6 ml with nintedanib versus –207.3 ml with placebo (difference, 93.7 ml; 95% CI, 44.8 to 142.7; P<0.001) in INPULSIS-2. In INPULSIS-1, there was no significant difference between the nintedanib and placebo groups in the time to the first acute exacerbation (hazard ratio with nintedanib, 1.15; 95% CI, 0.54 to 2.42; P=0.67); in INPULSIS-2, there was a significant benefit with nintedanib versus placebo (hazard ratio, 0.38; 95% CI, 0.19 to 0.77; P=0.005). The most frequent adverse event in the nintedanib groups was diarrhea, with rates of 61.5% and 18.6% in the nintedanib and placebo groups, respectively, in INPULSIS-1 and 63.2% and 18.3% in the two groups, respectively, in INPULSIS-2.

## Conclusions

In patients with idiopathic pulmonary fibrosis, nintedanib reduced the decline in FVC, which is consistent with a slowing of disease progression; nintedanib was frequently associated with diarrhea, which led to discontinuation of the study medication in less than 5% of patients.

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