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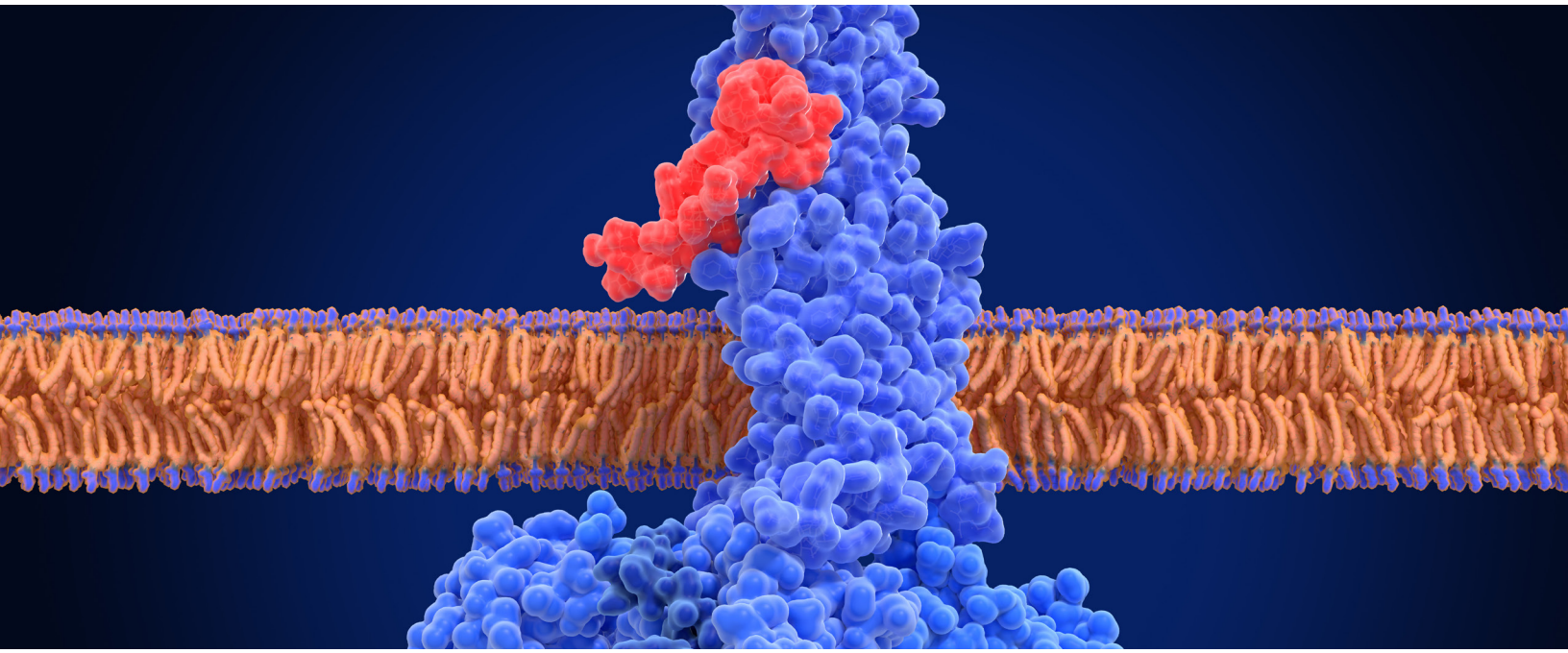
# GLP-1 receptor agonists– **A case for precision**

by Yuri Fesko, MD, Vice President, Medical Affairs

Let me start with a slight disclaimer: I cannot possibly discuss all the hot issues surrounding the GLP-1 receptor agonist (GLP-I RA) craze. In fact, I'm not sure there is a more divisive topic, with the possible exception of the upcoming presidential election. Some love this class of drugs for their unprecedented results across multiple conditions, while others fear their cost and other multifaceted, long-term implications. As a long-serving oncologist who has performed double duty in the diagnostic testing world promoting precision medicine, I see nearly limitless possibility (* with a notable asterisk).



As with any other seemingly overnight sensation, the GLP-1 story is a decades-long tale of struggle, failure, and eventual redemption. Although the story is fascinating, featuring an ensemble cast—almost certainly including some future Nobel Prize winners—it's also beyond the scope of my discussion and covered exceptionally well by STAT News here.

The short version of the story is that GLP-1, which stands for glucagon-like peptide-1, is a naturally occurring hormone that is produced in the small intestine, particularly in response to food intake. It's part of the endocrine response to eating and plays a significant role in the incretin effect, where oral ingestion of glucose leads to a greater insulin response than intravenous glucose.

GLP-1 has several key actions that help regulate blood glucose levels:

- It stimulates the pancreas to produce insulin in a glucose-dependent manner, meaning that it helps the body to secrete insulin when blood glucose levels are high
- It inhibits the secretion of glucagon, a hormone that increases blood sugar levels
- It slows gastric emptying, which leads to a more gradual absorption of glucose into the bloodstream
- It promotes a feeling of satiety or fullness, which can help reduce food intake

In other words, GLP-1 sounds pretty amazing if you're interested in regulating glucose levels with the side benefit of reducing body weight. The problem is that naturally occurring GLP-1 has a very short half-life in the bloodstream, typically lasting only a few minutes. In order to stimulate the benefits of GLP-1, researchers created a modified, or engineered, version of the hormone, known as a GLP-I RA. These agonists are synthetic peptides that mimic the action of natural GLP-1 but are designed to be more resistant to degradation by the enzyme dipeptidyl peptidase-4 (DPP-4), thereby extending their duration of action in the body.

Amylin Pharmaceuticals®, in partnership with Eli Lilly®, was the first-to-marketwith a GLP-I RA in 2005 called exenatide, which was marketed under the brand name Byetta. Byetta requires twice-daily injections and has proven effective at lowering blood glucose levels (reduction in hemoglobin A1c of 0.5%–0.8%). It has helped patients with type 2 diabetes achieve better control of their blood sugar levels, particularly postprandial glucose (blood sugar levels after eating). Exenatide's mechanism of stimulating insulin release in a glucose-dependent manner also reduces the risk of hypoglycemia, a common side effect of some diabetes treatments. It was further discovered that exenatide is associated with weight loss; however, the results have varied significantly across multiple studies.

The success of Byetta created a whole new class of diabetes and weight management drugs. (See Figure 1) Subsequent drugs have improved and expanded in 3 areas, across 2 different primary indications: type 2 diabetes and weight management.

The first area of improvement was to extend the half-life of GLP-1 in the bloodstream. Different drugs employ different strategies for extending the release period of GLP-1. AstraZeneca® gained FDA approval for Bydureon in 2012, which utilized exenatide, the same active drug used in Byetta, but as a once-weekly injection instead of twice daily.[2]

| Drug Name | Agonist(s) | Brand | Company | Indication | Date Approved | Frequency | Dosage | Route |
|---|---|---|---|---|---|---|---|---|
| Exenatide | GLP-1 | Byetta | Amylin & Eli Lilly | Type-2 Diabetes | Apr-2005 | twice daily | 5mcg, 10mcg | Injection, subcutaneous |
| | | Bydureon | AstraZeneca | Type-2 Diabetes | Jan-2012 | once weekly | 2mg | Injection, subcutaneous |
| Liraglutide | GLP-1 | Victoza | Novo Nordisk | Type-2 Diabetes | Jan-2010 | once daily | 0.6mg, 1.2mg, 1.8mg | Injection, subcutaneous |
| | | Saxenda | | Obesity | Dec-2014 | once daily | 3mg | Injection, subcutaneous |
| Albiglutide | GLP-1 | Tanzeum | GlaxoSmithKline | Type-2 Diabetes | Apr-2014 | once weekly | 30mg, 50mg | Injection, subcutaneous |
| Dulaglutide | GLP-1 | Trulicity | Eli Lilly | Type-2 Diabetes | Sep-2014 | once weekly | 0.75mg, 1.5mg | Injection, subcutaneous |
| Lixisenatide | GLP-1 | Adlyxin | Sanofi | Type-2 Diabetes | Jul-2016 | once daily | 10mcg, 20mcg | Injection, subcutaneous |
| Semaglutide | GLP-1 | Ozempic | Novo Nordisk | Type-2 Diabetes | Dec-2017 | once weekly | 0.5mg, 1.0mg, 2.0mg | Injection, subcutaneous |
| | | Rybelsus | | Type-2 Diabetes | Sep-2019 | once daily | 7mg, 14mg | Pill, oral |
| | | Wegovy | | Obesity | Jun-2021 | once weekly | 1.7mg, 2.4mg | Injection, subcutaneous |
| | | *TBD* | | Obesity | *2024 (est)* | once daily | 50mg | Pill, oral |
| Tirzepatide | GLP-1 + GIP | Mounjaro | Eli Lilly | Type-2 Diabetes | May-2022 | once weekly | 2.5mg, 15mg | Injection, subcutaneous |
| | | Zepbound | | Obesity | Nov-2023 | once weekly | 5mg, 10mg, 15mg | Injection, subcutaneous |
| Petrelintide | GLP-1 + Glucagon | Survodutide | Zealand + Boehringer Ingelheim | Obesity | *2026 (est)* | once weekly | *TBD* | Injection, subcutaneous |
| Semaglutide + Cagrilintide | GLP1 + [amylin + calcitonin] | CagriSema | Novo Nordisk | Obesity + Diabetes | *2026 (est)* | once weekly | *TBD* | Injection, subcutaneous |
| Retatrutide | GLP-1 + GIP + Glucagon | *TBD* | Eli Lilly | Obesity + Diabetes | *2026 (est)* | once weekly | *TBD* | Injection, subcutaneous |

Figure 1

The second goal, which is arguably the primary goal in all R&D efforts, is to improve efficacy. Bydureon, in the prior example, in addition to extending the half-life of GLP-1, also demonstrated notable improvements in HbA1c reductions over Byetta, using the same active drug.[3]


Novo Nordisk's® liraglutide then showed significant improvements over exenatide, also as a once-daily injection. Novo won FDA approval for the brand Victoza (liraglutide) in 2010 for type 2 diabetes.[4] In December 2014, they were able to secure the first FDA approval for a GLP-1 agonist specifically for weight management for Saxenda (a higher-dose version of Victoza).[5]

The third goal was to move to a more convenient, less-painful delivery route. Novo Nordisk was the first to gain FDA approval of a GLP-1 agonist in the form of an oral pill, which they did as Rybelsus (semaglutide) for type 2 diabetes in 2019. Building on this innovation, Novo Nordisk has continued to advance the convenience of GLP-1 therapy by introducing a 50 mg dosage of oral semaglutide, specifically indicated for weight loss.[6] This further exemplifies the commitment to making GLP-1 treatment more accessible and easier for patients to incorporate into their daily lives.

So generally speaking, the path thus far for GLP-I RA has followed the pattern: improved efficacy, improved delivery (a combination of medication route and frequency), and expanded indications (initially starting with type 2 diabetes and moving to weight management, with additional indications on the horizon).

Although there is not, to my knowledge, a formal classification of GLP-I RA drugs by generation, I would characterize them as follows: eexenatide, first generation; liraglutide, second generation; semaglutide, third generation; and tirzepatide, fourth generation.

These drugs continue to get more effective while largely maintaining a similar adverse effect profile. Subsequent generations of GLP-1s have continued to show improvements in both glucose reduction and weight loss. Although, arguably, their relative effectiveness in weight loss seems to garner the most attention. Exenatide use has had associated weight loss, but as previously noted, the amount has been highly variable across multiple studies. Liraglutide is associated with an average weight loss of 5% of body weight after 1 year.[7] Semaglutide shows an average loss of 14.9% of body weight at 68 weeks, while tirzepatide reports indicate a 20.9% average loss of body weight at 72 weeks.[8,9]

Tirzepatide was the first dual-agonist GLP-1 drug, incorporating both GLP-1 and gastric inhibitory polypeptide (GIP) agonists. GIP is also produced in the small intestine and plays a complementary role in insulin secretion and glucose regulation. By simultaneously addressing both agonists in appropriate balance,

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Eli Lilly has demonstrated a significant leap forward. Despite Novo Nordisk's success with semaglutide (Ozempic, Rybelsus, and Wegovy), many believe that Eli Lilly's tirzepatide drugs Mounjaro (type 2 diabetes) and Zepbound (weight management) are poised to gain significant traction during 2024.

Although the next wave of GLP-1s are still in clinical trials, early results are promising. Retatrutide, Eli Lilly's triple agonist currently in phase 3 trials, which adds glucagon to GIP and GLP-1, has shown average loss of body weight of 25.9% at 48 weeks.[10] Novo Nordisk's next generation drug, CagriSema, a combination of semaglutide and cagrilintide, has shown an average decrease in body weight of 15.6% at 32 weeks.[11]

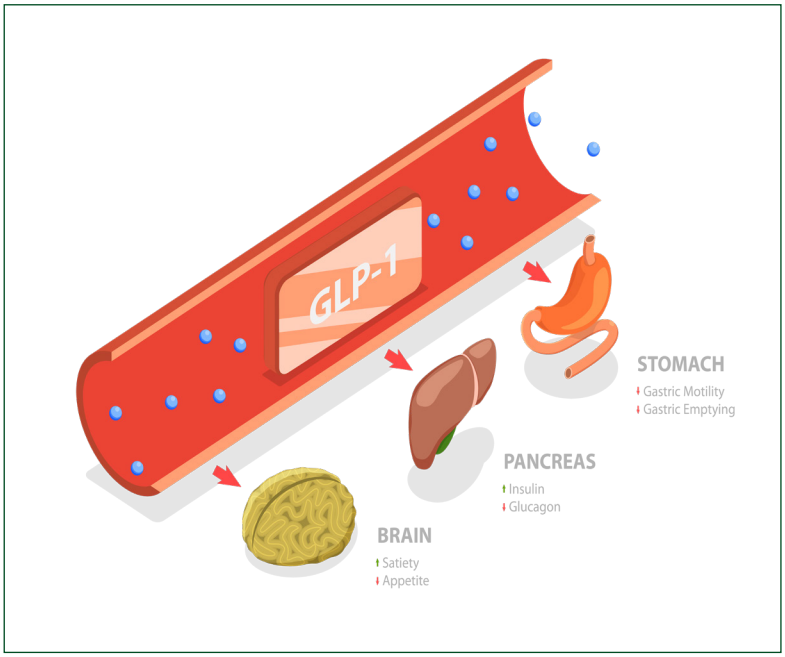
There are a host of new GLP-1 agonists in the pipeline and many are either multi-agonists, combination drugs, or both. The only certainty is that drug development is going to continue to push the boundaries of efficacy, expand indications, strive to minimize side effects, and otherwise reduce adherence frictions.

Although frequently glossed over because they are seldom life-threatening, the side effects of GLP-I RA are nevertheless significant and have a direct impact on long-term drug adherence. The most common side effects are gastrointestinal issues (nausea, vomiting, diarrhea, and constipation), hypoglycemia (particularly when used in combination with other glucose-lowering medications like sulfonylureas or insulin), and appetite changes and weight loss. Although less common, there is a risk of gastroparesis and pancreatitis, and the FDA requires GLP-I RA to carry a black-box warning for the risk of thyroid C-cell tumors.[12] Additionally, the American Association of Anesthesiologists recommends patients stop taking GLP-1s at least as long as their medication's half-life (typically a week) prior to surgery to minimize risks of aspiration during surgery.[13]

The primary indications for GLP-I RA are decreased blood glucose levels in support of type 2 diabetes management and weight loss for obesity. Additional benefits that have been demonstrated in various clinical trials include reduction in major cardiovascular events, improved beta-cell function in the pancreas, potentially improved lipid profiles, renal benefits, reduction in inflammatory markers, and potential neuroprotective benefits that could be effective against neurodegenerative diseases like Parkinson's and Alzheimer's. In other words, a veritable treasure trove of potential benefits.

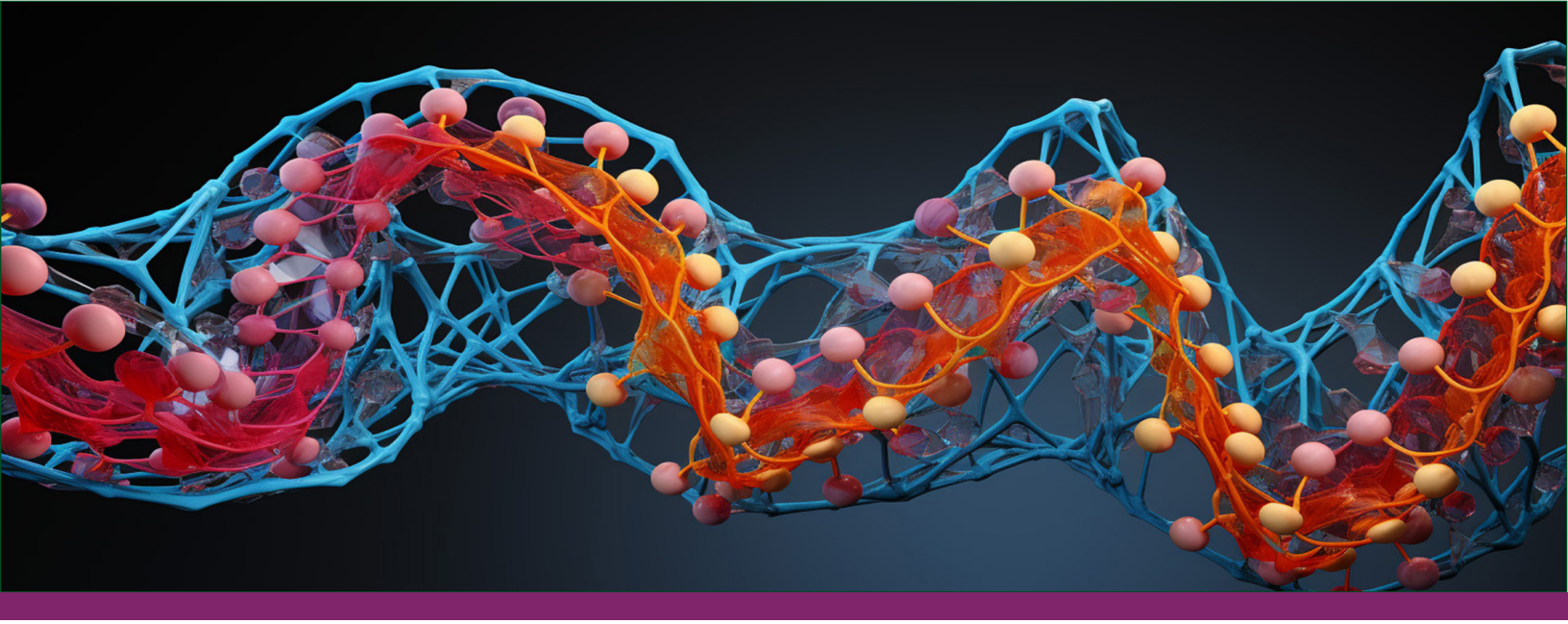
In many ways, the success of GLP-1s seems like impossibly good news. Don't get me wrong, the drugs are not perfect. The side-effects are real and typically lead more than 50% of people to stop taking them within 1 year.[14]

However, the progress and the rate of progress we are witnessing within this class of drug is completely unprecedented and portends amazing strides in our fight against obesity - a fight against obesity—which up to this point has been worsening for decades.




According to the CDC, obesity is now responsible for more than $173 billion in healthcare costs per year.[15] And that very well may be a conservative figure. Obesity is highly correlated with type 2 diabetes. It increases the risk of heart disease, hypertension, and stroke. It is linked to respiratory problems and certain forms of cancer. It's probably not too much of a stretch to say that obesity is the single largest preventable contributor to human disease.

Right up to this point, I think most people are in agreement. Obesity is a big problem, and GLP-1s hold enormous potential. Things pretty much go off the rails when you add 2 additional pieces of information. First, the benefits that GLP-1s provide go away if you stop taking the medications, which means they are intended to be taken for life, and second, current list price for these medications is roughly $10,000 per year per person. If you consider that more than 70%



of Americans are overweight, with 42% characterized as obese, you can easily rationalize a world in which more than 100 million Americans would benefit from GLP-1 drugs at a cost of more than $1 trillion a year.[16] Obviously, that can't happen, and it's about at this point where perspectives really begin to diverge.

Although GLP-1s trigger a number of fascinating discussions, many of which I also have strong opinions about, I'd prefer to focus on something near and dear to my heart as an oncologist who has spent the better part of the last 2 decades embracing and promoting precision medicine. In some ways, it's a little ironic that after declaring the age of blockbuster drugs a thing of the past, perhaps the single greatest blockbuster drug of all time is beginning to send shockwaves across the industry.

Before we throw up our hands and admit defeat, I think it might be worth digging our heels in a little here. We have learned an enormous amount in the last 20 years about how disease works. While mapping the human genome may not have solved all the problems we had hoped, we continue to learn and continue to dig deeper. We have made enormous progress in the field of oncology that only a few years ago seemed impossible. Much of this progress has been driven by a perspective that we didn't have just 20-30 years ago.

I would argue, that while the success of GLP-1s demonstrates that we still have the capacity to make significant progress in population-wide therapeutics, the lessons we have learned in precision medicine are both enormously relevant and applicable, and should be used to help guide the evolution of GLP-I RA over the next decade.

The journey of precision medicine in oncology, a field where complex biological processes intertwine with individual variability, reveals a path that can be mirrored in the evolution of GLP-I RA. The narrative of GLP-1s, much like the journey of cancer therapeutics, suggests that the next leap forward lies not just in broadening the scope of these drugs but in refining their application through the lens of precision medicine.

Just as oncology has embraced biomarkers for personalized treatment strategies, the same paradigm can be applied to GLP-I RA. The development of biomarkers for risk stratification could dramatically reshape the landscape of type 2 diabetes and obesity management. By understanding the potential cost and benefits of therapy based on genetic and epigenetic factors, we can identify those patients who are most likely to benefit from GLP-1 therapies, ensuring a more targeted and cost-effective approach.

One of the key learnings from precision medicine is the influence of genetic and epigenetic factors on drug efficacy and tolerability. Identifying these factors in the context of GLP-I RA could allow us to predict individual responses, both in terms of therapeutic efficacy and the risk of adverse effects. This understanding could lead to the development of next-generation GLP-1s with improved safety profiles and enhanced effectiveness.

Incorporating pharmacogenomic data into clinical decision-making can revolutionize how GLP-I RA are prescribed. Similar to oncology, where treatment decisions are increasingly guided by genetic profiling, GLP-1 therapies could be tailored based on an individual's pharmacogenomic data. This approach would optimize therapy choice, dosage, and predict responses, making treatment more efficient and effective.

Finally, the potential financial burden of widespread GLP-1 usage is a significant concern. Here, precision medicine offers a strategic approach to resource allocation. Diagnostics can help identify subpopulations where GLP-1 therapies would be most effective or where alternative treatments might be more suitable. This targeted approach ensures that healthcare resources are utilized where they can have the greatest impact.

The success of GLP-I RA is indeed a testament to our ability to make significant strides in understanding and managing complex biological processes. However, the true potential of these therapies lies in our ability to apply the precision medicine framework, where knowledge has been hard-won over decades of cancer research. By integrating diagnostics, genetic profiling, and patient-specific data, we can guide the evolution of GLP-I RA, ensuring that they not only continue to be highly effective but also become integral components of personalized healthcare.

As we look to the future, it's clear that the journey of GLP-1 receptor agonists is far from complete. The lessons from precision medicine provide a roadmap for their evolution, promising a future where these therapies are as nuanced and individualized as the patients they aim to treat. The opportunity is immense, and the time to act is now, to ensure that the promise of GLP-I RA is fully realized in the coming decade.

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Dr. Yuri Fesko is the Chief Medical Officer at Quest Diagnostics, where he leads the medical affairs group, clinical development, and internal analytics, among other responsibilities. With a rich background in oncology, hematology, and internal medicine, he has pioneered several diagnostic and clinical trial innovations since joining Quest in 2016. Dr. Fesko, a published author and sought-after speaker at healthcare conferences, brings deep expertise in clinical practice, business leadership, and academic research to his role. A native New Yorker, he is committed to enhancing patient and physician experiences through diagnostic innovations that promote better care, insights, and affordability.

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