Medical Science

To Cite:
Górska M, Janowski M, Górski J, Czyż P, Strzałkowska A. mRNA Therapeutics Beyond Vaccines: Emerging Applications in Rare and Chronic Diseases. *Medical Science* 2025; 29: e150ms3698
doi: https://doi.org/10.54905/disssi.v29i162.e150ms3698

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Peer-Review History
Received: 18 June 2025
Reviewed & Revised: 25/June2025 to 18/August/2025
Accepted: 25 August 2025
Published: 30 August 2025

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Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

DISCOVERY SCIENTIFIC SOCIETY

mRNA Therapeutics Beyond Vaccines: Emerging Applications in Rare and Chronic Diseases

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ABSTRACT

Messenger RNA (mRNA) isn't just about COVID-19 vaccines anymore, far from it. In just the past few years (especially starting around 2015), mRNA technology has begun to change the way we think about treating disease, not just some diseases, but a wide range: rare ones, chronic ones, even a few that used to be considered untreatable. This review takes a closer look at where mRNA might be headed next, not just beyond COVID-19, but beyond infectious diseases altogether. We're talking about cancer (with a big focus on personalized, tailor-made immunotherapies), rare inherited metabolic disorders (conditions such as cystic fibrosis and propionic acidemia have always limited treatment options), and autoimmune diseases too (like multiple sclerosis or type 1 diabetes, which affect millions but still lack accurate long-term solutions). In other words, mRNA isn't just a pandemic story - it's becoming a much bigger story (a much more exciting one) across medicine. We examine not only what these therapies entail, but also how they are delivered (with lipid nanoparticles playing a significant role), how they are being tested (including ongoing clinical trials), and their safety and scalability (a critical consideration). The spotlight is on research and clinical trials spanning january 2015 to May 2025 - all aimed at giving us a clearer sense of what truly works, what's still experimental, and what's just about to break through. mRNA, which not so long ago was thought of mainly as a vaccine tool, is now (quite rapidly) transforming into something bigger: a broad therapeutic platform, and maybe - even more exciting - a real game-changer for the future of medicine.

Keywords: mRNA therapeutics, lipid nanoparticles, CRISPR-Cas9 delivery, VEGF mRNA

1. INTRODUCTION

Over the last decade, especially since 2015, mRNA has evolved from a lab curiosity to one of the most versatile therapeutic tools in modern medicine. While nearly everyone knows it from the COVID 19 vaccine experience, that's only the tip of the iceberg. Since the early 2020s, research has rapidly expanded mRNA's reach into areas far beyond infectious diseases, targeting cancer, protein deficiency disorders,

genetic or metabolic diseases, and even autoimmune conditions (Rohner et al., 2022; Swetha et al., 2023; Hou et al., 2021).

What makes mRNA particularly exciting and compelling to scientists, clinicians, and biotechnology companies? It's the fact that it's programmable. Researchers can (quite precisely) design strands of mRNA that tell your cells what proteins to make and when. And not just one type of protein, but virtually any protein your body might be missing, lacking, or in need of. mRNA is an incredibly flexible tool - modular, fast, adaptable, and futuristic. Instead of handing over the finished drug (the way we usually do with traditional medicine), mRNA therapy gives the body something different: a set of custom-written instructions - a kind of molecular blueprint - so that your own cells do the work and make the proteins themselves. It's not just treatment; it feels more like teaching, or even reprogramming, the body from the inside out - safely, temporarily, and with real precision (Rohner et al., 2022).

A striking example is in oncology. The personalized neoantigen vaccine mRNA 4157/V940, developed by Moderna and Merck, has shown impressive early results. In the Phase IIb KEYNOTE-942 trial (focused on people with high-risk stage III/IV melanoma), researchers tested what happens when you add mRNA-4157 to pembrolizumab. The results were significant: the risk of the cancer coming back or the patient dying dropped by almost 44%. After about two and a half years, roughly 75% of patients on the combination were still recurrence-free, compared to only ~56% for those on pembrolizumab alone. Efficiently delivering mRNA to the right tissues, achieving therapeutic protein levels (often much higher than needed in vaccines), and avoiding unwanted immune activation are key obstacles (Swetha et al., 2023; Rohner et al., 2022). Innovations in lipid nanoparticle (LNP) design, including emerging machine learning guided optimization, are crucial to overcoming these hurdles (Ding et al., 2023).

There's even groundbreaking progress in genetic disease treatment, such as delivering CRISPR Cas9 via LNPs to correct rare liver disorders in vivo, and using mRNA-encoded VEGF for heart failure, both emerging from early human trials (Rohner et al., 2022). In this review, we explore the rapid evolution of mRNA therapeutics (January 2015– May 2025), focusing on mechanisms, delivery strategies, clinical progress, and future applications beyond vaccines, highlighting how this platform is becoming one of the most promising vectors for treating a wide array of conditions.

2. REVIEW METHODS

To explore how mRNA therapeutics have evolved (especially beyond vaccines), we reviewed literature published between January 2015 and May 2025. A comprehensive literature search was performed across PubMed, Scopus, Web of Science, and ClinicalTrials.gov (to ensure all relevant studies were included), with the goal of capturing the most complete and current body of evidence, employing keywords including: "mRNA therapeutics," "lipid nanoparticles," "CRISPR-Cas9 delivery," "VEGF mRNA," and "mRNA cancer vaccines."

We focused on peer-reviewed and preprint studies published in English that examined non-infectious applications of mRNA, particularly in oncology, genetic disorders, cardiovascular disease, and autoimmune disease.

Papers were grouped by:

- Delivery strategies (e.g., LNPs)
- Disease target
- Development stage (preclinical to clinical)
- Mechanistic approach

We excluded studies on infectious disease vaccines from this analysis. Final sources were gathered and screened.

The screening process followed the PRISMA guidelines (Figure 1). Our aim was not simply to collect the most technical studies, but rather the most relevant and impactful ones. To ensure completeness, we also checked the reference lists of key articles to capture any studies that might have been overlooked in database searches. We gave additional priority to papers that were widely cited or highlighted in other authoritative reviews.

3. RESULTS AND DISCUSSION

The past decade, particularly from January 2015 to May 2025, has been something of a turning point for mRNA therapeutics. What once felt speculative or experimental is now (in many cases) becoming real, becoming clinical, becoming tangible. From early-stage lab trials to real-world human data, mRNA is now showing measurable, often striking results across multiple fields of medicine, most notably in oncology, rare genetic disorders, and (more recently) autoimmune diseases (Parhiz et al., 2024; Qin et al., 2022).

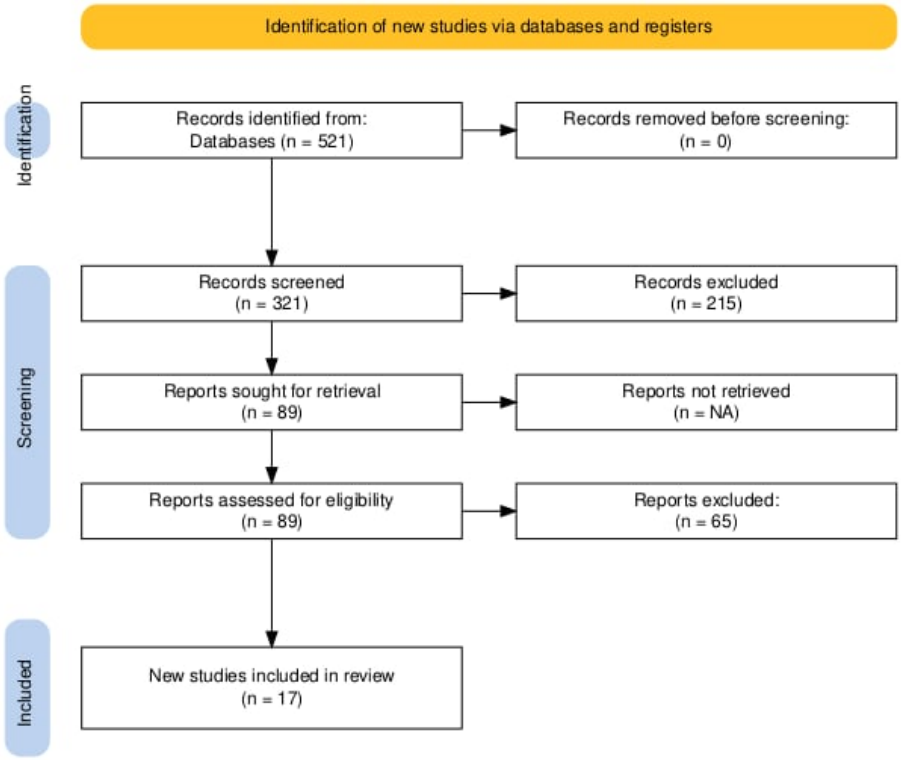

Figure 1 PRISMA flow diagram

Oncology: A New Era of Personalized Cancer Immunotherapy

Among the most compelling evidence of mRNA's clinical potential is its application in oncology, particularly in the treatment of melanoma. In the KEYNOTE 942 Phase IIb trial, patients with resected stage III/IV melanoma received either pembrolizumab alone or pembrolizumab paired with the personalized mRNA vaccine mRNA 4157/V940. The results? Not just statistically significant, but (in many ways) clinically persuasive. Patients receiving the combination of mRNA 4157/V940 and pembrolizumab didn't just see a statistically significant improvement - they experienced a clinically meaningful shift in outcomes (a shift that really can't be ignored, really hard to overlook). In other words, the difference wasn't just numbers on a page; it was something you could actually see in the results. By the 18-month mark, recurrence-free survival (RFS) had climbed to 78.6% in the combination group, a noticeable and substantial improvement over the 62.2% seen in the monotherapy arm (Weber et al., 2024)

But perhaps even more striking and worth highlighting were the results for distant metastasis-free survival (DMFS). In the same time frame, 91.8% of patients in the combination group remained free of distant metastases, compared to just 76.8% in those who received pembrolizumab alone (HR = 0.347; p = 0.0063).

Just as importantly, the safety profile was favorable. Most of the side effects reported were mild to moderate (grade 1 or 2), and importantly, the trial didn't reveal any new safety concerns at all (nothing unexpected, nothing alarming). The rates of serious adverse events were much the same in both treatment groups (Choueiri et al., 2024), (so neither group ran into noticeably more severe side effects), which is really worth keeping in mind when thinking about how this therapy might perform outside the carefully controlled world of a clinical trial - especially when it's combined with a well-established checkpoint inhibitor.

What makes these results stand out and what's genuinely exciting is how consistent the benefits were across a variety of patient subgroups. The positive effects didn't seem to depend much on PD-L1 expression, tumor mutational burden (TMB), or whether circulating tumor DNA (ctDNA) was detectable or not. This broad applicability and versatility suggest that mRNA-based treatments like mRNA-4157/V940 could potentially help a much wider range of patients than initially expected.

Genetic & Metabolic Disorders: Treating What Was Once Untreatable

Outside the spotlight of oncology, mRNA's quietly expanding role in treating rare monogenic diseases is beginning to show (real) promise, and it's something worth paying attention to. Disorders like propionic acidemia and methylmalonic acidemia, for example, have long been notoriously difficult to manage because of their underlying protein deficiencies. But here's where mRNA comes into its own: rather than simply replacing the missing enzyme from the outside, this technology (quite literally) teaches the body through mRNA to produce that crucial enzyme on its own.

In preclinical models, delivering mRNA systemically—mRNA that encodes these key metabolic enzymes—produced sustained expression and meaningful biochemical correction (Baek et al., 2024). Now, several companies (Moderna among them) are beginning to push these strategies into human trials.

The scope of the mRNA platform stretches well beyond vaccines and protein replacement - it now reaches into the realm of in vivo CRISPR-Cas9 delivery, making direct gene editing in patients possible. One powerful example is transthyretin amyloidosis, where a single intravenous dose can sharply and durably reduce the production of the harmful protein (Gillmore et al., 2021). This isn't just innovation, it isn't just progress - it's a genuine therapeutic breakthrough (a shift that could rewrite what modern medicine can do).

Cardiovascular and Autoimmune Trials: The Next Frontier

Though we're still in the early days, the fields of cardiovascular and autoimmune medicine are beginning to show real, tangible momentum with mRNA technology. Take the EPICCURE trial as a prime example: researchers delivered VEGF-A–encoded mRNA directly into the heart muscle of patients undergoing bypass surgery. The results showed not just a modest step forward, not just a small incremental gain, but a real and significant boost in blood flow along with actual recovery of damaged (ischemic) heart tissue (something that once seemed out of reach) (Anttila et al., 2023). Although the study was relatively small, we should not underestimate its findings. It could very well be the first glimpse of something far bigger: mRNA's potential not just to replace missing proteins, but actually repair and regenerate tissue.

Over in autoimmune disease research, the excitement is just as palpable. Scientists are now exploring how mRNA could help "retrain" immune tolerance, teaching the immune system to calm down in specific ways, rather than just suppressing it across the board. One striking mouse study demonstrated that delivering autoantigen-encoding mRNA in a tolerizing context effectively prevented autoimmune diabetes, and importantly, did so without triggering the typical issue of broad immunosuppression (Krienke et al., 2021). Human trials are on the horizon, and if these early findings hold up (and there's good reason to think they might), we could soon be entering a new era where mRNA therapies don't just treat autoimmune diseases, they reprogram the immune system itself.

Lipid Nanoparticles (LNPs): The Unsung Hero

None of this would work without delivery systems—and lipid nanoparticles (LNPs) remain at the heart of it all. The recent improvements are impressive, ranging from organ-specific targeting to machine-learning-guided formulation. LNPs are now enabling a wider range of applications than ever before. Better delivery means bigger possibilities—and the possibilities just keep growing (Ding et al., 2023). Liver delivery is now routine. However, other organs remain a challenge.

As LNPs become more efficient and, significantly, less immunogenic, the tolerability of mRNA therapies improves. But challenges remain: repeat dosing, antibody formation, and off-target accumulation still need to be carefully addressed in each new indication (Münter et al., 2023)

Table 1 gives an overview of the latest clinical and preclinical advances in mRNA therapeutics, spanning oncology, genetic disorders, cardiovascular disease, and autoimmune disease (basically, almost every major area of medicine). It also highlights something crucial: the essential role of lipid nanoparticle (LNP) delivery systems—the unsung heroes making all this possible.

Table 1. Summary of key mRNA therapeutic applications and outcomes across multiple fields.

Field	Application / Trial	Key Outcomes / Findings
Oncology	KEYNOTE-942: mRNA-4157/V940 + pembrolizumab	44% reduced recurrence/death; RFS 78.6% vs 62.2%; DMFS 91.8% vs 76.8%; strong results across subgroups
Genetic & Metabolic Disorders	mRNA therapy for propionic and methylmalonic acidemia	Sustained enzyme production; meaningful biochemical correction in preclinical models.
Gene Editing	CRISPR-Cas9 mRNA delivery for	A single IV dose led to permanent harmful

Field	Application / Trial	Key Outcomes / Findings
	transthyretin amyloidosis.	protein reduction.
Cardiovascular	EPICCURE trial: VEGF-A mRNA into heart muscle.	Improved blood flow and ischemic tissue recovery; early but promising.
Autoimmune	mRNA tolerizing therapy for autoimmune diabetes.	prevented disease in mice without causing systemic immunosuppression.
Lipid Nanoparticles (LNPs)	Advanced LNPs with organ-specific targeting & machine learning formulation.	Improved delivery, less immunogenicity; issues remain with dosing, antibodies, and off-target accumulation.

4. CONCLUSION

In recent years, mRNA has emerged as a pivotal tool in medical research and therapeutics. The development of mRNA therapeutics began with COVID-19 vaccines, but it has since expanded to include significant advances in cancer immunotherapy, the treatment of rare genetic diseases, cardiovascular repair, and, notably, the reprogramming of the immune system itself—rather than merely suppressing it, re-educating it.

The real driver of this change isn't just the clever design of mRNA. What truly makes all this possible is delivering mRNA exactly where it's needed (to the right cells, at the right time, so it can actually do its job). Lipid nanoparticles (LNPs) are small but essential carriers – they do the hard work. They discreetly encapsulate delicate mRNA molecules and safely guide them to the right cells (delivering the payload exactly where and when it's needed). Thanks to advances in machine learning, scientists are now refining LNPs to target specific organs and optimize delivery with near-surgical precision. While drug delivery to the liver has become relatively routine, the true challenges and opportunities for future breakthroughs lie in targeting more complex organs, such as the brain. Still, we are not without obstacles. Immune reactions, the need for repeated doses, and bothersome side effects remain challenges that are difficult to overcome. Personalized cancer vaccines have already demonstrated the ability to reduce relapse rates. Enzyme therapies based on mRNA are improving lives in ways once thought impossible for people with rare, inherited conditions. Perhaps most compelling is that mRNA doesn't just tell the body what to fight. It's beginning to show us that it can teach the body how to heal itself and repair itself from within.

Acknowledgments

The authors have no acknowledgments to disclose.

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Informed consent

Not applicable.

Ethical approval

Not applicable.

Funding
This study has not received any external funding.

Conflict of interest
The authors declare that there is no conflict of interest.

Data and materials availability
All data associated with this work are present in the paper.

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