

mRNA Vaccine Platforms and Lipid Nanoparticle Delivery Systems: Molecular Advances, Clinical Breakthroughs, and Regulatory Perspectives (2020–2025)

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Systematic Review

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Abstract

Background: The success of mRNA vaccines against COVID-19 has catalyzed a paradigm shift in vaccinology. Messenger RNA (mRNA)-based platforms offer exceptional design flexibility, rapid manufacturing, and antigen-agnostic modularity, yet their full translational potential — spanning infectious disease prophylaxis, personalized cancer immunotherapy, and regulatory implementation in low- and middle-income countries — remains incompletely synthesized from a regulatory science perspective.

Main body: This systematic review, conducted in accordance with PRISMA 2020 guidelines across PubMed/MEDLINE, Scopus, Web of Science, and ClinicalTrials.gov (January 2020–February 2025), synthesizes 68 peer-reviewed studies on four thematic pillars: (1) mRNA platform biology and engineering; (2) lipid nanoparticle (LNP) formulation and targeted delivery; (3) clinical-stage mRNA vaccines for HIV, RSV, influenza, CMV, and emerging pathogens; and (4) personalized cancer vaccines. Key findings include: the individualized neoantigen therapy mRNA-4157 (V940) plus pembrolizumab demonstrated a 44% reduction in recurrence or death in resected melanoma (KEYNOTE-942, Phase IIb); mRNA-1345 (mRESVIA) achieved 83.7% efficacy against RSV lower respiratory tract disease and received EMA approval in June 2024; eOD-GT8 60mer induced HIV broadly neutralizing antibody precursors in 97% of Phase I participants; and next-generation selective organ-targeting (SORT) LNPs now enable tissue-specific mRNA delivery beyond hepatic default. Critically, this review — authored by scientists at Indonesia’s BPOM, one of the largest NMRAs among LMICs — is the first to systematically integrate regulatory science into an mRNA vaccine evidence synthesis, evaluating approval pathways, cold-chain constraints, pharmacovigilance requirements, and equitable access challenges from the standpoint of an LMIC NMRA: a dimension entirely absent from all five most recent systematic reviews in this field.

Conclusion: mRNA-LNP technology represents a transformative and versatile vaccine platform with proven efficacy across oncology and infectious disease. Realizing its full global potential demands coordinated advances in thermostable formulation, manufacturing scalability, and fit-for-purpose regulatory frameworks in LMICs. The evidence synthesized here provides a molecular and regulatory roadmap for the next generation of mRNA vaccine development and approval through 2030.

1. Introduction

Vaccination stands as one of the most impactful public health interventions in human history. From Edward Jenner's pioneering smallpox inoculation in 1796 to the global eradication of poliomyelitis and measles control, vaccines have fundamentally altered the burden of infectious disease. Yet, for decades, a handful of pathogens—HIV, respiratory syncytial virus (RSV), cytomegalovirus (CMV), and numerous cancers—remained beyond the reach of effective immunization, largely due to the biological complexity of their antigens or the limitations of conventional vaccine platforms.[1][2]

The COVID-19 pandemic catalyzed an unprecedented acceleration in vaccine innovation. The emergency authorization of BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) in late 2020—less than twelve months after SARS-CoV-2 genomic sequencing—marked the first-ever commercial deployment of messenger RNA (mRNA)-based vaccines and validated the platform at global scale.[56][26][27][53][3][4]

The mRNA vaccine platform offers several intrinsic advantages over traditional approaches. It does not require live or attenuated pathogens, eliminating associated biosafety concerns during manufacturing. It enables cell-free, fully synthetic production that is readily scalable. Crucially, the platform is antigen-agnostic: the same manufacturing infrastructure can produce vaccines for any target by simply substituting the encoded sequence. This modularity provides an unparalleled speed advantage in responding to emerging pathogens and supports the development of highly individualized therapeutic applications.[68][24][25][2][5]

Central to the clinical success of mRNA vaccines is the lipid nanoparticle (LNP) delivery system. Naked mRNA is susceptible to rapid nuclease degradation, poorly taken up by cells, and highly immunostimulatory. LNPs protect the mRNA cargo, facilitate endosomal escape, and enable efficient cytoplasmic delivery, making them indispensable to the translational pipeline.[36][52][11][17]

Despite a rapidly expanding body of mRNA vaccine literature, existing reviews share a critical blind spot: they are written exclusively from the perspective of academic or industrial researchers in high-income settings. No prior systematic review has evaluated the mRNA-LNP landscape through the lens of a national medicines regulatory authority (NMRA) operating in a lower-middle-income country (LMIC), where approval frameworks, cold-chain infrastructure, manufacturing capacity, and health technology assessment processes differ fundamentally from those in Europe or North America. The present review addresses this gap directly. Authored by scientists at the Indonesian Food and Drug Authority (BPOM) — the NMRA of the world’s fourth most populous nation and a middle-income country with over 275 million people — this work uniquely integrates molecular and clinical evidence with regulatory science, offering translational insights applicable to NMRAs across ASEAN, Sub-Saharan Africa, and Latin America, and informing how mRNA vaccine technology can be evaluated, approved, and deployed equitably in LMIC contexts. Furthermore, this review is the first to simultaneously synthesize the three-year KEYNOTE-942 follow-up data (2025), the EMA conditional approval of mRESVIA, and the IAVI G001 HIV immunogenicity findings within a single PRISMA-compliant systematic framework covering January 2020 to February 2025.

The present review provides a comprehensive and critical synthesis of the most recent advances in mRNA vaccine research, organized around four thematic pillars: (1) the fundamental biology and engineering of mRNA platforms; (2) innovations in LNP formulation and targeted delivery; (3) clinical-stage mRNA vaccines for major infectious diseases; and (4) the rapidly evolving field of personalized cancer vaccines. We further address key translational challenges and delineate the projected research trajectory through 2030, with particular attention to regulatory implications for NMRAs in LMICs. This

review targets an audience of immunologists, vaccinologists, translational researchers, clinicians, and regulatory scientists engaged in next-generation vaccine development and approval.

2. Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The study selection process is presented in Fig. 1. A structured literature search was independently performed by two reviewers across PubMed/MEDLINE, Scopus, Web of Science (Core Collection), and ClinicalTrials.gov, covering the period from January 1, 2020, to February 15, 2025.

Search terms, applied in Boolean combinations (AND/OR), included: "mRNA vaccine," "messenger RNA vaccine," "lipid nanoparticles," "LNP delivery," "cancer vaccine," "personalized vaccine," "neoantigen vaccine," "individualized neoantigen therapy," "HIV mRNA vaccine," "RSV mRNA vaccine," "self-amplifying RNA," "saRNA vaccine," "circular RNA vaccine," "broadly neutralizing antibody," "immunotherapy cancer," "mRNA-4157," "mRESVIA," and "eOD-GT8." Reference lists of included articles were hand-searched to identify additional eligible studies.

Inclusion criteria comprised: (a) original research articles, systematic reviews, meta-analyses, or high-quality narrative reviews published in Q1-ranked journals; (b) clinical trials (Phase I–III) of mRNA vaccine candidates in human participants; (c) preclinical studies demonstrating mechanistic or translational significance; and (d) publications in English with accessible full text. Exclusion criteria included single case reports, conference abstracts without peer review, and articles with incomplete outcome data.

As illustrated in Fig. 1, a total of 412 records were initially identified. After duplicate removal and title/abstract screening, 95 full-text articles were assessed for eligibility. Following full-text evaluation, 68 articles met the final inclusion criteria and were included in the qualitative synthesis..

3. The mRNA vaccine platform: biology and engineering

3.1 Mechanism of action

Upon intramuscular injection, LNP-encapsulated mRNA is endocytosed primarily by dendritic cells and myocytes at the injection site. Following endosomal escape, the mRNA is translated by cytoplasmic ribosomes into the encoded antigen protein. Endogenously produced antigen is processed and presented via MHC class I molecules to CD8 + cytotoxic T lymphocytes (CTLs) and, following cross-presentation, via MHC class II to CD4 + T helper cells. The latter provide cognate help to B cells, driving antibody class-switching, affinity maturation in germinal centers, and the generation of long-lived plasma cells and memory B cells.[24][46][3][5]

This dual engagement of cellular and humoral immunity is a defining advantage of the mRNA platform. Unlike subunit vaccines, which predominantly stimulate humoral responses, mRNA vaccines stimulate

CTL responses essential for eliminating virus-infected or malignant cells. Furthermore, the LNP carrier itself acts as an endogenous adjuvant by activating innate immune sensors, including Toll-like receptors (TLR7/8) and the STING pathway, amplifying the adaptive immune response without the need for exogenous adjuvants.[2][7]

3.2 Nucleoside modification and mRNA optimization

A critical obstacle in early mRNA vaccine development was the potent innate immunostimulatory activity of synthetic mRNA, mediated through pattern recognition receptors, which suppressed translation efficiency and caused systemic reactogenicity. The seminal discovery by Karikó and Weissman demonstrated that substitution of uridine with N1-methylpseudouridine (m1Ψ) dramatically reduced TLR-mediated innate immune activation while simultaneously increasing translational efficiency and protein yield.[21][22][23][3][6]

Beyond nucleoside modification, contemporary mRNA optimization encompasses multiple engineering layers: (1) ARCA (anti-reverse cap analog) or CleanCap® chemistry for efficient 5'-cap incorporation, enhancing ribosomal recognition; (2) codon optimization based on human codon-usage frequency tables to maximize translational fidelity; (3) optimization of 5' and 3' untranslated regions (UTRs) to incorporate regulatory elements that enhance mRNA stability and translational efficiency; and (4) addition of a poly(A) tail of optimal length (typically 100–150 adenosines) to prevent deadenylation-mediated degradation.[47][2]

3.3 Next-generation RNA platforms

Beyond conventional mRNA, several next-generation RNA modalities are under active development. Self-amplifying RNA (saRNA) incorporates the alphavirus replicase machinery, enabling intracellular amplification of the RNA and thereby achieving high-level antigen expression from microgram-range doses, compared with the milligram-range doses required for conventional mRNA.[10] Trans-amplifying RNA (taRNA) further improves the safety profile by encoding the replicase and the antigen of interest on separate molecules, preventing inadvertent expression of viral replicase proteins. Circular RNA (circRNA), a more nascent platform, offers resistance to exonucleolytic degradation by virtue of its covalently closed structure, potentially enabling sustained antigen expression in vivo.[1][31][33][32]

The fundamental immunological mechanism underlying these RNA platforms is illustrated in Fig. 2. Following intramuscular administration, lipid nanoparticle (LNP)-encapsulated mRNA is internalized by antigen-presenting cells via endocytosis. Subsequent endosomal escape releases mRNA into the cytoplasm, where ribosomal translation produces the encoded antigen. Processed peptides are presented through major histocompatibility complex (MHC) class I molecules to CD8 + cytotoxic T lymphocytes (CTLs) and via MHC class II molecules to CD4 + T helper cells. This coordinated activation promotes B-cell differentiation into antibody-secreting plasma cells and the generation of long-lived memory B and T cells.

4. Lipid nanoparticle delivery systems: advances and innovations

4.1 Composition and architecture of LNPs

Lipid nanoparticles represent the most clinically advanced mRNA delivery technology and form the backbone of all approved mRNA vaccines. A canonical LNP formulation comprises four lipid components, each serving a distinct functional role:[38][11][17]

(1) An ionizable lipid, the most critical component, which is protonated at acidic endosomal pH (~ 4–5), facilitating membrane destabilization and mRNA endosomal escape, while remaining neutral at physiological pH (~ 7.4), minimizing systemic toxicity. (2) A helper phospholipid (e.g., DSPC or DOPE), which provides structural bilayer integrity and modulates membrane fusion properties. (3) Cholesterol, which enhances membrane fluidity, structural stability, and endosomal membrane fusion efficiency. (4) A PEGylated lipid (PEG-lipid), which coats the particle surface, reducing aggregation, shielding immune recognition, and prolonging systemic circulation by preventing opsonization and clearance by the mononuclear phagocyte system.[36][37][15][16]

LNP size, typically between 80 and 200 nm, is a critical parameter governing biodistribution, cellular uptake, and immunogenicity. Particles below 200 nm diffuse passively into lymphatic capillaries, enabling efficient drainage to regional lymph nodes for direct antigen presentation, whereas larger particles depend more on local phagocytic cell uptake.[14]

4.2 Ionizable lipid engineering: the critical variable

The ionizable lipid is the single most important determinant of LNP efficacy and is the focus of the most intensive engineering efforts. Unlike early cationic lipids, which bear permanent positive charges associated with membrane toxicity and complement activation, ionizable lipids are designed with a pKa between 6.2 and 6.8 to optimize endosomal activity while maintaining near-neutral charge at physiological pH.[11][18]

High-throughput screening combined with machine-learning models has dramatically accelerated the discovery of novel ionizable lipid structures. Key structural parameters include the lipid tail structure (degree of branching and unsaturation, which modulates membrane cone geometry and fusogenicity), the headgroup chemistry (which determines pKa and endosomal activity), and the linker region (which affects biodegradability and clearance kinetics). Degradable ester linkages in the lipid tail have been incorporated in several next-generation LNP formulations to facilitate rapid hepatic clearance and reduce long-term accumulation, improving the tolerability profile.[49][50][51][12]

4.3 Selective organ targeting and active targeting

A major limitation of first-generation LNP formulations is preferential hepatic accumulation following systemic administration, driven by apolipoprotein E (ApoE) adsorption from serum and hepatocyte-selective LDL receptor-mediated uptake. For vaccine applications, delivery to lymph nodes and splenic immune cells is paramount, while for therapeutic RNA applications, targeting to tissues such as the lung, kidney, or brain is desirable.[14][19]

The Selective ORgan Targeting (SORT) platform addresses this limitation by demonstrating that the addition of a supplemental charged lipid component predictably shifts LNP tropism toward specific tissues: cationic additives favor lung delivery, whereas zwitterionic additives redirect biodistribution toward the spleen.[14] Active targeting strategies under development include surface decoration of LNPs with mannose ligands for dendritic cell–specific targeting via the mannose receptor (CD206), anti-CD4 or anti-CD8 antibody fragments for lymphocyte-directed delivery, and DEC-205–targeting approaches to enhance follicular dendritic cell engagement, which is critical for germinal center reactions and durable memory B-cell formation.[19][48][52]

A comparative overview of current RNA-based vaccine platforms, including their advantages, limitations, and representative clinical examples, is summarized in Table 1.

Table 1
Comparative overview of RNA-based vaccine delivery platforms.

Platform	Key Advantages	Limitations	Clinical Examples
Conventional mRNA + LNP	Clinically validated; rapid manufacturing; strong dual immunity	Ultra-cold storage; transient expression; production cost	BNT162b2, mRNA-1273 (COVID-19); mRESVIA (RSV); mRNA-4157 (melanoma)
Self-amplifying RNA (saRNA)	Microgram doses sufficient; prolonged antigen expression	Larger construct; replicase immunogenicity risk; complex manufacture	Phase I/II: influenza, HIV (IAVI G001)
Trans-amplifying RNA (taRNA)	Improved safety vs saRNA; replicase delivered separately	Two-component delivery complexity; still preclinical for most targets	Preclinical: RSV, influenza models
Circular RNA (circRNA)	Exonuclease-resistant; potentially very durable expression	Unique translation initiation (IRES); largely preclinical stage	Preclinical: cancer models, SARS-CoV-2

LNP: lipid nanoparticle; saRNA: self-amplifying RNA; taRNA: trans-amplifying RNA; circRNA: circular RNA; IRES: internal ribosome entry site.

5. mRNA vaccines for infectious diseases: clinical advances

5.1 Respiratory syncytial virus (RSV)

RSV is the foremost viral cause of acute lower respiratory tract disease in infants, young children, older adults, and immunocompromised individuals, accounting for approximately 33 million acute lower respiratory infections and 3.6 million hospitalizations annually worldwide.[61][7] Despite more than four decades of unsuccessful vaccine development, largely derailed by the catastrophic enhancement observed with formalin-inactivated RSV in the 1960s, two major structural insights—the identification of

the prefusion conformation of the RSV F protein as the dominant target for potentially neutralizing antibodies, and structural stabilization strategies—enabled a new wave of successful vaccine candidates.[9]

Moderna's mRNA-1345 encodes a stabilized prefusion F (DS-Cav1) protein delivered in an LNP. The pivotal Phase III randomized controlled trial enrolled 35,541 adults aged 60 years or older across 22 countries. Vaccine efficacy against RSV-associated lower respiratory tract disease with two or more signs and symptoms was 83.7% (96.36% CI: 66.1–92.2%) in the primary analysis. The safety profile was acceptable, with solicited injection-site and systemic reactions being mild to moderate and transient. Grade 3 adverse events occurred in 8.1% of vaccine recipients versus 4.3% of placebo recipients.[58][60][9]

In June 2024, the European Medicines Agency (EMA) granted conditional marketing authorization to mRNA-1345 (trade name mRESVIA) for adults aged 60 years and above—marking the world's first regulatory approval of an mRNA vaccine for any indication beyond COVID-19 and representing a watershed moment in the field. Parallel programs are now evaluating maternal immunization strategies with mRNA RSV vaccines to confer passive antibody protection to neonates, a population with the highest RSV mortality burden.[3][6]

5.2 Human immunodeficiency virus (HIV)

HIV-1 has resisted effective vaccine development for more than 40 years due to its extraordinary sequence diversity, continuous antigenic evolution driven by error-prone reverse transcription ($\sim 3 \times 10^{-5}$ errors per base per replication cycle), the early establishment of latent reservoirs, and a dense glycan shield that sterically occludes conserved epitopes on the Env trimer from antibody recognition.[7] The mRNA platform is uniquely suited to address these challenges, enabling rapid iteration of immunogen design and precise control of antigen conformation.

The International AIDS Vaccine Initiative (IAVI) G001 Phase I trial evaluated an mRNA-LNP vaccine encoding the engineered immunogen eOD-GT8 60mer—a self-assembling nanoparticle designed to engage the rare B cell precursors bearing the unmutated common ancestor of VRC01-class broadly neutralizing antibodies (bnAbs). The trial demonstrated induction of bnAb precursor B cells in 97% of vaccine recipients (35 of 36 evaluable participants), a remarkable immunological result that exceeded preclinical expectations. These precursor B cells are the necessary starting point for the sequential immunization strategies intended to guide their maturation into mature bnAb-secreting cells.[2][20][30][2][5]

In parallel, preclinical studies in non-human primates have demonstrated sustained reduction in SHIV acquisition following mRNA-LNP Env vaccination, with sequential heterologous boosting strategies under evaluation to achieve tier-2 virus neutralization breadth.[29][2] The convergence of structure-guided immunogen design, germline-targeting strategies, and the modularity of the mRNA platform may finally render a broadly protective HIV vaccine tractable.[3]

5.3 Influenza: toward a universal vaccine

Seasonal influenza vaccines require annual reformulation based on strain surveillance and incur variable efficacy (typically 20–60%) due to antigenic mismatch. The mRNA platform offers two transformative advantages: a rapid-response capability enabling strain-specific sequence updates within days of surveillance data, and the potential to encode multiple conserved antigenic targets across influenza subtypes (hemagglutinin stalk, neuraminidase, M2 ectodomain, nucleoprotein) to confer broad cross-reactive immunity—the concept of a "universal" influenza vaccine.[4][6]

Moderna's quadrivalent mRNA influenza vaccine candidate (mRNA-1010) has completed Phase III clinical trials. Additional next-generation programs encode combinations of conserved internal antigens alongside the hemagglutinin head to broaden subtype coverage and reduce the annual vaccine strain selection dependency. A NIAID-sponsored program targeting pre-pandemic influenza subtypes (H5, H7) is evaluating mRNA vaccines as pandemic preparedness countermeasures.[45][6]

5.4 Cytomegalovirus, Zika, and emerging pathogens

Cytomegalovirus (CMV) is the most common congenital infection worldwide and a major cause of morbidity in solid-organ and hematopoietic stem cell transplant recipients. Moderna's mRNA-1647 encodes six CMV antigens—including the gB protein and the pentameric complex essential for non-fibroblast cell entry—and demonstrated 42.0% efficacy against primary CMV infection in seronegative women in a Phase II trial, with Phase III enrollment now complete.[3]

For emerging pathogens with pandemic potential, the mRNA platform's most decisive advantage is speed. Vaccine candidates against Nipah virus, Ebola virus, Marburg virus, Zika virus, and monkeypox have all been advanced to pre-clinical or early clinical evaluation using mRNA-LNP technology. Zika mRNA vaccine candidates have induced durable neutralizing antibodies and sterilizing protection in murine and NHP models. The strategic stockpiling of GMP-grade mRNA components and LNP formulation materials is increasingly recognized as a critical element of global pandemic preparedness infrastructure.[34][35][5][9]

6. mRNA cancer vaccines: clinical breakthroughs

6.1 Principles of personalized neoantigen vaccines

Therapeutic cancer vaccines leverage the principle that tumor-specific somatic mutations generate neo-peptides—neoantigens—that are presented by tumor cell MHC molecules and recognized as foreign by the host T cell repertoire. Because each tumor harbors a unique mutational landscape, optimal neoantigen vaccines must be individually designed for each patient (individualized neoantigen therapy, INT), necessitating a manufacturing pipeline that integrates next-generation sequencing, bioinformatic neoantigen prediction, mRNA synthesis, and LNP formulation within a clinically actionable timeframe.[1][10][13][1][10]

The neoantigen selection pipeline involves: (1) deep whole-exome and transcriptome sequencing of matched tumor and normal tissue; (2) somatic variant calling and filtering; (3) neoantigen prediction integrating HLA typing, MHC-I/II binding affinity algorithms (NetMHCpan, MHCflurry), mRNA expression levels, and tumor clonality; (4) synthesis of a polyepitope mRNA encoding 20–34 predicted neoantigens flanked by flexible linkers; and (5) LNP formulation and GMP release testing. Advances in computational pipeline efficiency and manufacturing automation have reduced the turnaround from tumor biopsy to first dose from approximately nine weeks to fewer than four weeks.[42][54][1][8]

6.2 mRNA-4157 (V940) for melanoma: a Phase IIb breakthrough

The most clinically advanced personalized cancer vaccine is mRNA-4157 (V940; Moderna/Merck), currently in Phase III development. In the randomized, double-blind KEYNOTE-942 Phase IIb trial, 157 patients with completely resected high-risk Stage III/IV cutaneous melanoma were randomized 2:1 to receive mRNA-4157 plus pembrolizumab versus pembrolizumab monotherapy.[1][10]

At the primary analysis (median follow-up 18 months), the combination arm demonstrated a statistically and clinically significant 44% reduction in the risk of recurrence or death compared with pembrolizumab alone (HR 0.56, 95% CI: 0.31–1.02, one-sided $p = 0.053$, meeting the pre-specified significance threshold). Three-year follow-up data presented in 2025 confirmed durable benefit, with the recurrence-free survival advantage widening over time, consistent with the hypothesis that mRNA vaccination continuously restimulates memory T cells against evolving tumor clones.[40][41][10][8]

A global Phase III trial (KEYNOTE-942B) across multiple solid tumor indications (non-small cell lung cancer, bladder cancer, renal cell carcinoma) is now enrolling. Regulatory submissions for melanoma are anticipated in 2026, with potential first commercial approval of an mRNA cancer vaccine as early as 2028–2029.[1][10]

6.3 Targeting pancreatic cancer and glioblastoma

Pancreatic ductal adenocarcinoma (PDAC) and glioblastoma multiforme (GBM) represent two of the most lethal solid tumors and are characterized by profoundly immunosuppressive tumor microenvironments and historically negligible responses to checkpoint blockade immunotherapy, in part because of their relatively low tumor mutational burden (TMB).[10]

Nonetheless, early-phase clinical evidence suggests that mRNA neoantigen vaccines can generate neoantigen-specific T cell responses even in these immunologically cold tumors. A personalized mRNA-LNP vaccine for resected PDAC induced polyfunctional CD4 + and CD8 + T cell responses against patient-specific neoantigens in a subset of participants, with responders showing a trend toward improved relapse-free survival.[39][1] For GBM, blood-brain barrier penetrance remains the dominant delivery challenge; lipid-polymer hybrid nanoparticles and focused ultrasound-mediated LNP extravasation strategies are under preclinical investigation to enable intracranial mRNA delivery.[65][8]

6.4 The role of artificial intelligence in cancer vaccine design

Artificial intelligence (AI) and machine learning have become indispensable components of the cancer vaccine development pipeline. Deep learning models—including transformer-based architectures—trained on large-scale immunopeptidomic datasets can predict MHC class I and MHC class II binding affinities with substantially greater accuracy than earlier position-weight matrix approaches, thereby improving the precision of neoantigen prioritization.[1][10]

Beyond neoantigen prediction, AI applications extend to multiple stages of the development continuum. These include: (1) tumor immune microenvironment classification to identify patients most likely to benefit from vaccination; (2) codon optimization and mRNA secondary structure modeling to enhance translational efficiency and antigen expression; (3) lipid nanoparticle (LNP) formulation optimization using generative modeling frameworks; and (4) clinical trial outcome prediction to support adaptive trial design strategies. The integration of large-scale multi-omics datasets with AI-guided vaccine engineering represents a major frontier in precision immunotherapy.[1][43][44]

The end-to-end manufacturing workflow of personalized mRNA cancer vaccines is illustrated in Fig. 3. The process begins with tumor biopsy and germline DNA sampling, followed by whole-exome and transcriptomic sequencing. AI-driven neoantigen prediction informs the design of a personalized polypeptide-encoding mRNA construct, which is subsequently synthesized, formulated into LNPs, and subjected to quality control and Good Manufacturing Practice (GMP) release testing prior to patient administration. With current automation platforms, the complete manufacturing cycle has been reduced to fewer than four weeks.

7. Translational challenges and limitations

7.1 Cold-chain requirements and thermostability

First-generation mRNA vaccines required storage at -70°C or below (BNT162b2) or -20°C (mRNA-1273), constraining equitable global deployment to settings with robust ultra-cold chain infrastructure. Thermostability is primarily limited by mRNA hydrolysis through 2'-OH-mediated self-cleavage and LNP component degradation (ionizable lipid oxidation and PEG-lipid hydrolysis) at elevated temperatures.[11][15]

Significant progress has been achieved through lyophilization (freeze-drying) of LNP-mRNA formulations in the presence of cryoprotectants (sucrose, trehalose), which has yielded formulations stable at 2–8°C for 3–6 months without measurable loss of potency. Emerging approaches include spray-drying, solid lipid nanoparticle matrices, and encapsulation in carbohydrate glasses, each with the potential for room-temperature stable vaccine presentations suitable for low-resource settings.[60][62][15]

7.2 Manufacturing cost and equitable access

The per-patient manufacturing cost of individualized neoantigen mRNA vaccines currently ranges from approximately US\$50,000 to US\$300,000, reflecting the cost of tumor sequencing, bioinformatic analysis, individualized GMP mRNA synthesis, formulation, and release testing. At these price points, personalized cancer vaccines are inaccessible to the vast majority of patients in low- and middle-income countries (LMICs).[8][1]

Addressing this challenge requires parallel advances on multiple fronts: continuous improvement in synthesis automation and yields, reduction in sequencing costs (which have fallen ~ 10,000-fold since 2007), computational pipeline efficiency, regulatory pathways for accelerated release testing of individualized products, and innovative financing mechanisms. "Off-the-shelf" public neoantigen vaccines targeting shared driver mutations (e.g., mutant KRAS G12C/D/V in PDAC and non-small cell lung cancer) offer a complementary strategy that avoids individualized manufacturing entirely.[55][1]

7.3 Immunosuppressive tumor microenvironment

Even when a robust vaccine-induced T cell response is generated, functional efficacy in solid tumors can be abrogated by the immunosuppressive tumor microenvironment (TME). Key mechanisms include: regulatory T cell (Treg) infiltration, myeloid-derived suppressor cell (MDSC) accumulation, upregulation of inhibitory checkpoint ligands (PD-L1, CTLA-4 ligands) by tumor and stromal cells, adenosine pathway suppression, and TGF- β -mediated T cell exclusion and dysfunction.[10][8]

Rational combination strategies under clinical evaluation include: mRNA vaccines plus PD-1/PD-L1 checkpoint inhibitors (most advanced, as in KEYNOTE-942); plus CTLA-4 blockade (dual checkpoint combinations); plus agonistic CD40 antibodies or IL-2 cytokine variants to amplify T cell priming; and plus local intratumoral innate immune activators to remodel the TME toward a permissive phenotype. Combinations with adoptive cell therapies, including tumor-infiltrating lymphocyte (TIL) therapy, are also being explored.[67][10]

7.4 Reactogenicity and immunogenicity optimization of LNPs

While the overall safety profile of LNP-mRNA vaccines is well established following administration of hundreds of millions of COVID-19 vaccine doses, solicited reactogenicity—including injection-site pain, fatigue, fever, and myalgia—remains common and may limit vaccine acceptability, particularly in cancer vaccine regimens requiring repeated dosing. The intrinsic immunostimulatory properties of ionizable lipid components can activate innate immune pathways, contributing to reactogenicity and, if excessive, potentially suppressing mRNA translation and antigen-specific immunogenicity.[15][18].

Several engineering strategies are under active investigation to mitigate these effects. These include the development of next-generation ionizable lipids with reduced Toll-like receptor (TLR) activation, optimization of PEG-lipid density and PEG molecular weight to balance immune evasion with cellular uptake, co-encapsulation of anti-inflammatory agents, and refinement of formulation buffer systems. Additionally, although the rare adverse event of myocarditis—observed predominantly in young males

following mRNA COVID-19 vaccination—remains extremely uncommon (approximately 5 per 100,000 doses in the highest-risk group), continued pharmacovigilance and mechanistic investigation are essential to inform risk–benefit assessments for emerging mRNA vaccine indications.[18][63]

A broader overview of key translational barriers in mRNA vaccine development and corresponding mitigation strategies is summarized in Table 2.

Table 2

Key translational challenges in mRNA vaccine development and corresponding mitigation strategies.

Challenge	Current Status / Impact	Mitigation Strategy
Ultra-cold chain (storage at -70°C)	Limits deployment in LMICs and primary care settings	Lyophilization; spray-drying; thermostable LNP excipients enabling 2–8°C storage
High manufacturing cost (personalized vaccines)	US\$50,000–\$300,000 per patient; limits access globally	Automation; improved mRNA yield; off-the-shelf shared neoantigen approaches; value-based pricing
Immunosuppressive TME	Attenuates T cell function in solid tumors despite strong vaccine responses	Combination with checkpoint inhibitors, CD40 agonists, anti-MDSC agents
Hepatic LNP tropism after IV administration	Prevents delivery to target tissues (lung, lymph nodes, brain)	SORT technology; mannose surface targeting; ionizable lipid engineering
Reactogenicity and rare adverse events	Myocarditis risk; general reactogenicity limiting repeat dosing	Optimized ionizable lipid design; anti-inflammatory co-formulation; smaller mRNA modifications

LMIC: low- and middle-income country; TME: tumor microenvironment; MDSC: myeloid-derived suppressor cell; SORT: Selective ORgan Targeting; IV: intravenous.

8. Future directions and emerging research frontiers

The trajectory of mRNA vaccine research over the next five years is defined by several converging scientific and technological themes. With over 120 active clinical trials as of early 2025, the pipeline spans prophylactic vaccines for endemic and pandemic-threat pathogens, therapeutic vaccines for established and recurrent cancers, and novel applications in infectious disease prophylaxis combined with treatment.

From a regulatory science perspective — and particularly relevant to NMRAs in LMICs such as Indonesia’s BPOM — several strategic priorities emerge. First, the development of harmonized, fit-for-purpose regulatory guidance specifically for mRNA-based products is urgently needed. While the FDA has issued guidance under Breakthrough Therapy and accelerated approval frameworks, and ICH harmonization of mRNA product guidelines is anticipated within two years, most LMICs lack the technical infrastructure and precedents to evaluate mRNA vaccines independently.[6] Second, regional

regulatory reliance frameworks, in which LMICs rely on stringent regulatory authority (SRA) decisions from EMA, FDA, or WHO prequalification as the basis for their own approvals, offer a pragmatic near-term pathway for timely access – but require capacity building in pharmacovigilance, cold-chain oversight, and batch release testing. Third, the critical need for thermostable mRNA-LNP formulations cannot be overstated in LMIC contexts: without 2–8°C-stable presentations, equitable global deployment remains aspirational. The convergence of lyophilization advances, improved cryoprotectant formulations, and regional fill-finish manufacturing capacity building in ASEAN, Africa, and Latin America will determine the true global impact of the mRNA vaccine revolution.[64][63][66][1]

For cancer vaccines, the anticipated regulatory approval of mRNA-4157 for high-risk melanoma will establish the commercial and regulatory framework for subsequent indications. The transition from fully individualized to "semi-personalized" vaccines—which combine patient-specific neoantigens with pan-tumor shared antigens (e.g., mutant KRAS, TP53, or EGFR variants)—promises to reduce costs while retaining substantial personalization. Integration of therapeutic mRNA vaccines with cell therapies (CAR-T and TIL-based) represents a particularly compelling synergistic frontier.[10][8]

For infectious diseases, the goal of universal vaccines against influenza, HIV, and betacoronaviruses remains the north star. Mosaic antigens—engineered immunogens that simultaneously display conserved epitopes from multiple strains—are increasingly paired with mRNA platforms to induce breadth of neutralization not achievable with single-strain antigens.[57][59][2][3]

The regulatory landscape is evolving in parallel. The FDA's accelerated approval pathway, combined with the Breakthrough Therapy Designation granted to mRNA-4157, provides a roadmap for other personalized mRNA therapeutics. Harmonized international regulatory guidance specifically for mRNA-based products is expected to be issued by ICH (International Council for Harmonisation) within the next two years, reducing the burden of country-by-country approval.[43][44][1][6]

Finally, the application of mRNA technology is expanding beyond conventional vaccines into in vivo protein replacement therapy (e.g., for metabolic enzyme deficiencies), in vivo gene editing (co-delivery of CRISPR components), and in situ cellular reprogramming. These applications will benefit directly from advances in LNP delivery specificity and mRNA stability pioneered in the vaccine context, underscoring the fundamental importance of continued investment in mRNA platform science.[3][5]

9. Conclusions

mRNA vaccine technology has undergone a transformation from a laboratory curiosity to a globally deployed, life-saving platform within a single decade. The commercial validation provided by COVID-19 vaccines has catalyzed investment and scientific progress at a pace that could not have been anticipated prior to 2020. The regulatory approval of mRESVIA for RSV marks the first translation of this momentum into a new indication and heralds a broad expansion of the mRNA vaccine portfolio.[58][45][46]

The clinical evidence reviewed herein demonstrates the breadth of therapeutic potential: a 44% reduction in melanoma recurrence risk with mRNA-4157 plus pembrolizumab; 83.7% efficacy against RSV lower respiratory tract disease; induction of HIV broadly neutralizing antibody precursors in 97% of immunized volunteers; and next-generation LNP platforms enabling tissue-specific mRNA delivery beyond the hepatic default. These achievements, taken together, constitute a compelling proof of concept for mRNA as a universal vaccine modality.[26][27][28]

Substantial translational challenges remain: production cost and equitable access are primary concerns for individualized cancer vaccines; thermostability and cold-chain logistics constrain global deployment of infectious disease vaccines; and the immunosuppressive tumor microenvironment limits efficacy in immunologically cold tumors. Critically, from the perspective of NMRAs in LMICs, the regulatory science gap — encompassing adapted approval pathways, pharmacovigilance systems, and cold-chain governance — represents an equally pressing challenge that must be addressed in parallel with the scientific advances. Meeting these challenges will require sustained interdisciplinary collaboration among basic scientists, chemical engineers, computational biologists, clinicians, regulatory scientists, and health policy experts.

With over 120 active clinical trials spanning oncology and infectious disease, the first commercial cancer mRNA vaccine anticipated by 2029, and a rapidly maturing regulatory framework, the mRNA platform is poised to deliver a second generation of breakthroughs that may fundamentally reshape how humanity prevents and treats its most burdensome diseases.

Abbreviations

AI: Artificial intelligence; APC: Article processing charge; ApoE: Apolipoprotein E; ARCA: Anti-reverse cap analog; bnAb: Broadly neutralizing antibody; BPOM: Badan Pengawas Obat dan Makanan (Indonesian Food and Drug Authority); CAR-T: Chimeric antigen receptor T cell; circRNA: Circular RNA; CMV: Cytomegalovirus; CTL: Cytotoxic T lymphocyte; DC: Dendritic cell; DSPC: 1,2-distearoyl-sn-glycero-3-phosphocholine; DOPE: 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; EMA: European Medicines Agency; GBM: Glioblastoma multiforme; GMP: Good manufacturing practice; HLA: Human leukocyte antigen; HIV: Human immunodeficiency virus; IAVI: International AIDS Vaccine Initiative; INT: Individualized neoantigen therapy; IRES: Internal ribosome entry site; LDL: Low-density lipoprotein; LMIC: Lower-middle-income country; LNP: Lipid nanoparticle; m1Ψ: N1-methylpseudouridine; MDSC: Myeloid-derived suppressor cell; MHC: Major histocompatibility complex; mRNA: Messenger RNA; NIAID: National Institute of Allergy and Infectious Diseases; NMRA: National medicines regulatory authority; NHP: Non-human primate; PDAC: Pancreatic ductal adenocarcinoma; PEG: Polyethylene glycol; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RSV: Respiratory syncytial virus; saRNA: Self-amplifying RNA; SHIV: Simian-human immunodeficiency virus; SORT: Selective organ targeting; STING: Stimulator of interferon genes; taRNA: Trans-amplifying RNA; TGF-β: Transforming growth factor beta; TIL: Tumor-infiltrating lymphocyte; TLR: Toll-like receptor; TMB: Tumor mutational burden; TME: Tumor microenvironment; Treg: Regulatory T cell; UTR: Untranslated region.

Declarations

Ethics approval and consent to participate

Not applicable. This article is a systematic review of previously published studies and does not involve human participants, human data, or human tissue.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Authors' contributions

T.I.: Conceptualization, Methodology, Investigation, Writing – Original Draft; W.M.: Methodology, Investigation, Writing – Review & Editing; A.S.: Conceptualization, Investigation, Writing – Review & Editing, Supervision. All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

No new datasets were generated or analyzed during this study. All data referred to in this review are available in the original published sources cited herein.

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Figures

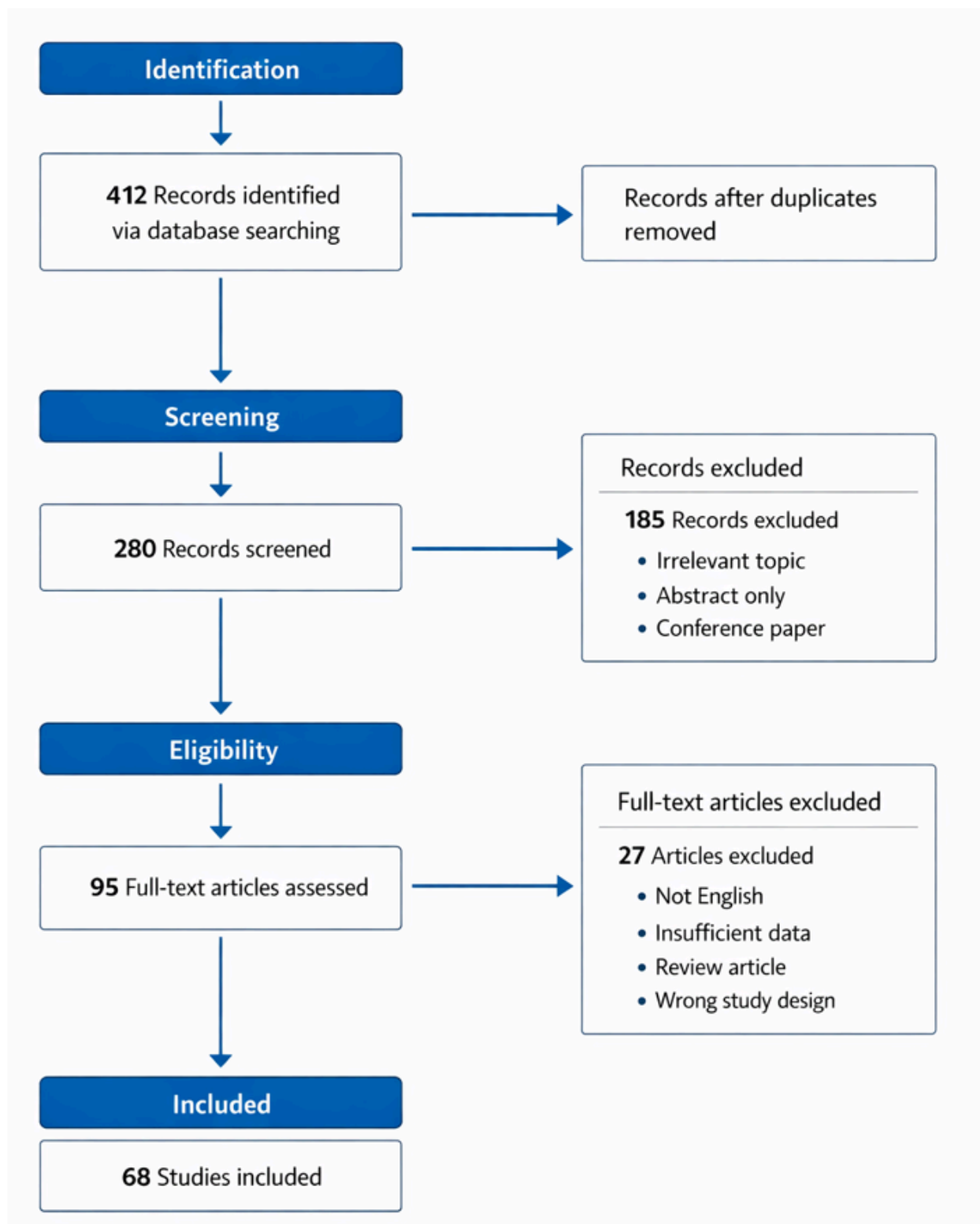


Figure 1

PRISMA 2020 flow diagram illustrating the systematic literature selection process. From 412 identified records, 68 articles met final inclusion criteria after successive screening stages.

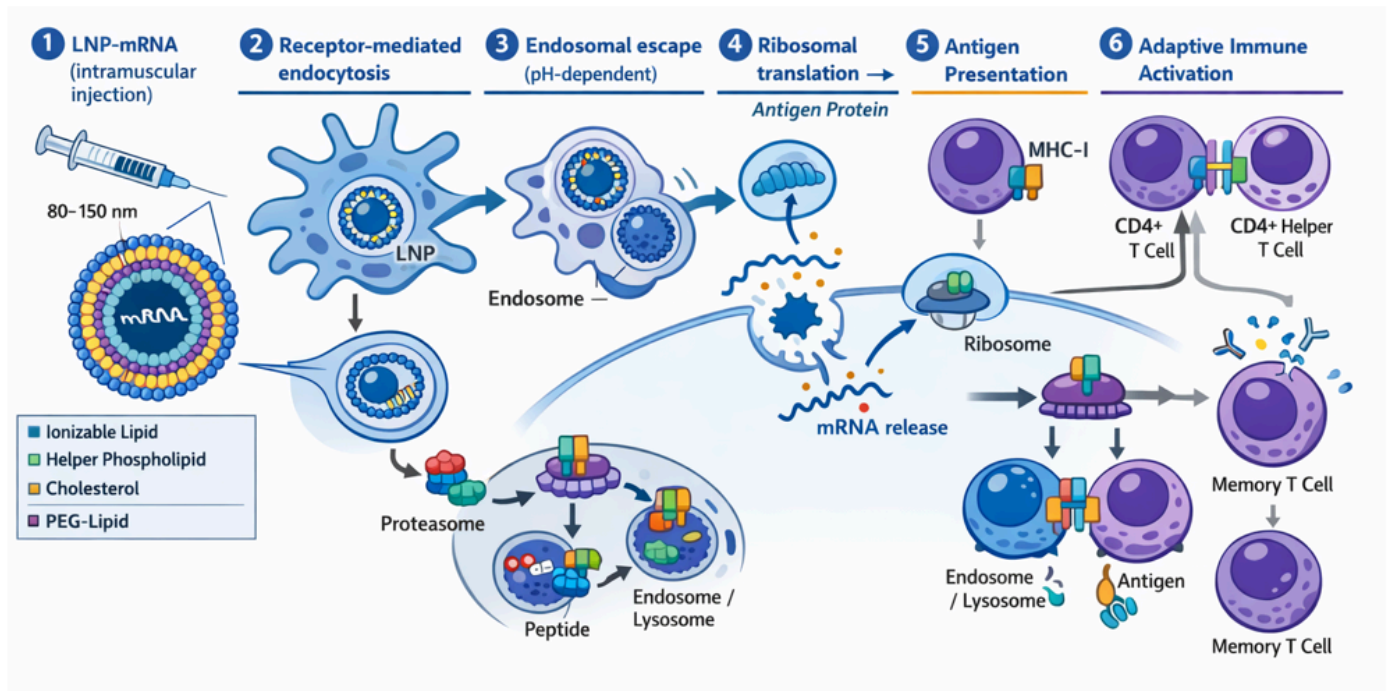


Figure 2

Schematic overview of the mRNA vaccine mechanism of action. Following LNP-mediated endosomal uptake and cytoplasmic mRNA release, the ribosome translates the encoded antigen. Processed peptides are presented via MHC class I to CD8+ CTLs and via MHC class II to CD4+ T helper cells. Activated B cells differentiate into antibody-secreting plasma cells and memory B cells.

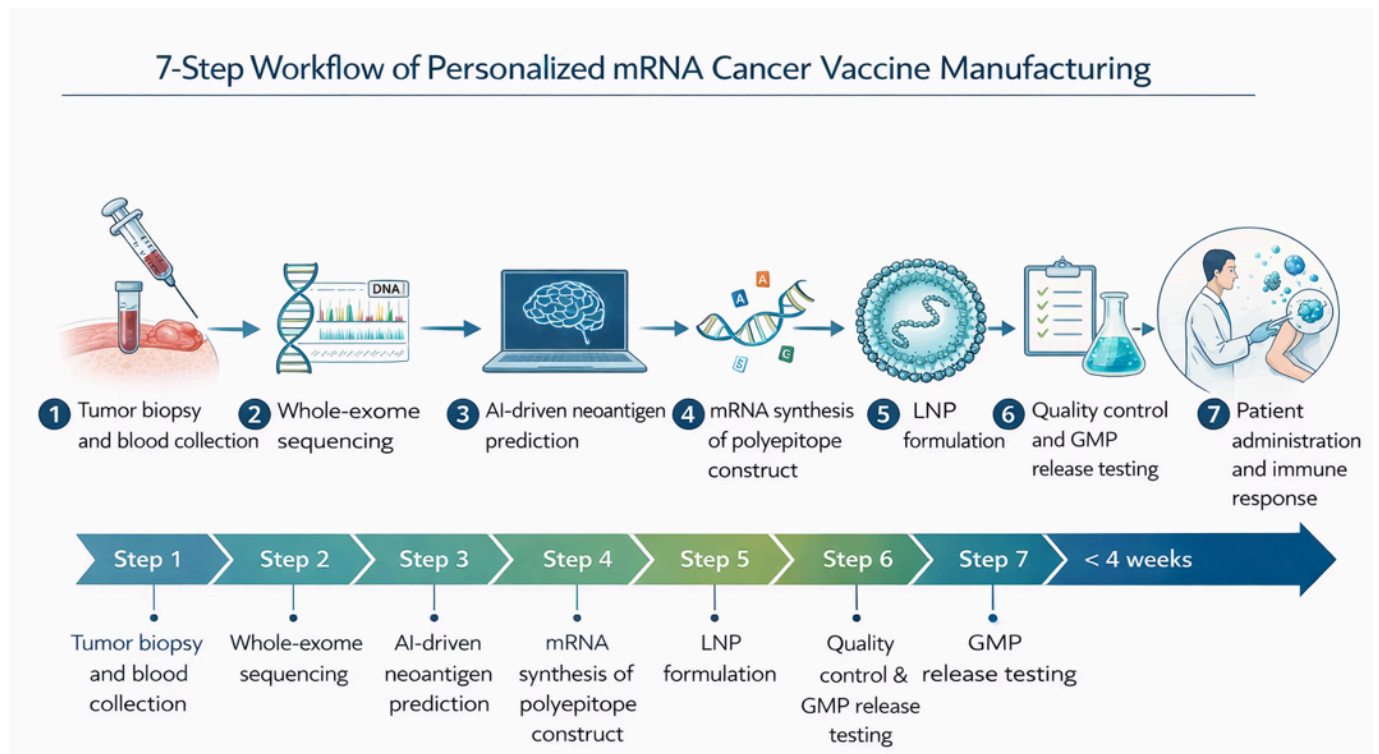


Figure 3

Workflow of personalized mRNA cancer vaccine manufacturing. The process encompasses tumor biopsy and germline DNA sampling, whole-exome and RNA sequencing, AI-driven neoantigen prediction, mRNA synthesis encoding a personalized polyepitope, LNP formulation, quality release testing, and patient administration. The complete cycle has been reduced to fewer than four weeks with current automated platforms.