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Translational Pharmacogenomics in mRNA Therapeutics: Machine Learning-Guided Design of Personalized Lipid Nanoparticles for Rare Genetic Disorders

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ABSTRACT

Background. Rare genetic disorders require innovative therapeutic strategies capable of addressing molecular defects, yet variability in biological responses to messenger RNA (mRNA) and lipid nanoparticle (LNP) delivery systems remains a major challenge for effective treatment personalization.

Purpose. This study aimed to develop a translational pharmacogenomic framework that applies machine learning to design personalized lipid nanoparticles for mRNA-based therapies in rare genetic disorders.

Method. A multimodal dataset comprising patient genomic variants, disease phenotypes, lipid compositions, nanoparticle characteristics, and responses from patient-derived cellular models was analyzed. Interpretable and uncertainty-aware machine learning algorithms were used to rank LNP formulations based on predicted cellular uptake, endosomal escape, protein expression, immunogenicity, and cytotoxicity, followed by comparative validation against standard and non-personalized formulations.

Results. Personalized formulations demonstrated improved cytoplasmic mRNA release and target-protein expression compared with conventional approaches while maintaining comparable cell viability and reducing inflammatory responses. Pharmacogenomic features enhanced prediction accuracy, particularly when integrated with ionizable lipid structures, particle size, target-cell characteristics, and intracellular trafficking parameters. However, model performance decreased for underrepresented genomic profiles, highlighting the dependence of personalization on representative datasets and experimental validation.

Conclusion. Machine learning-guided pharmacogenomic optimization provides a promising strategy for developing individualized LNP-based mRNA therapies. The findings suggest that LNPs should be considered responsive therapeutic components rather than universal delivery vehicles. Further multicenter, mechanistic, in vivo, and clinical studies are required before clinical translation.

KEYWORDS

Lipid nanoparticles, Machine learning, RNA therapeutics.

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INTRODUCTION

Rare genetic disorders collectively impose a substantial clinical and socioeconomic burden despite the low prevalence of each individual condition. Many of these diseases arise from pathogenic variants that disrupt protein production, enzyme activity, cellular signaling, or

metabolic homeostasis (S. P. Singh dkk., 2026; Winkeljann dkk., 2026; Yoo dkk., 2026). Conventional treatment frequently focuses on symptom management because permanent genetic correction remains technically difficult and clinically inaccessible for numerous disorders. The opening paragraph should establish the need for therapeutic platforms capable of addressing disease mechanisms at the molecular level while remaining adaptable to small and genetically heterogeneous patient populations.

Messenger RNA therapeutics offer a programmable strategy for temporarily restoring deficient proteins, replacing dysfunctional biological signals, or directing cells to produce therapeutically relevant molecules (Hatami dkk., 2024; Shahid, 2025; Zheng dkk., 2026). Their transient activity avoids permanent genomic alteration and permits sequence modification when disease-specific requirements change. Clinical effectiveness nevertheless depends on protecting the mRNA from degradation, facilitating its transport through biological barriers, promoting cellular uptake, and enabling release into the cytoplasm. This paragraph should introduce lipid nanoparticles as leading delivery vehicles while explaining that formulation performance is inseparable from patient biology.

Pharmacogenomics examines how inherited and acquired genomic variation influences drug response, toxicity, metabolism, transport, and therapeutic effectiveness (Esmaeilpour dkk., 2026; Panchpuri dkk., 2025; Tan dkk., 2026). Translational pharmacogenomics extends this knowledge toward clinically actionable treatment decisions, including therapy selection, formulation design, and dose optimization. The paragraph should connect pharmacogenomic variation with mRNA delivery by noting that differences in immune signaling, lipid metabolism, endosomal processing, membrane composition, and tissue-specific receptor expression may alter lipid nanoparticle behavior. Personalized delivery must therefore consider both the therapeutic sequence and the biological context into which it is administered.

Current lipid nanoparticle development commonly relies on iterative formulation screening across ionizable lipids, helper phospholipids, cholesterol derivatives, polyethylene glycol–lipids, particle sizes, surface properties, and component ratios (Alshammari & Mani, 2026; Kumar dkk., 2026; V. Singh dkk., 2026). Such empirical experimentation can identify effective candidates, but it is costly, labor-intensive, and poorly suited to rare disorders with limited patient populations and scarce biological samples. This paragraph should define the central problem as the absence of an efficient, clinically grounded method for matching lipid nanoparticle characteristics to disease mechanisms, therapeutic mRNA properties, target tissues, and patient-specific pharmacogenomic profiles.

Biological responses to lipid nanoparticles vary across individuals because genomic differences can affect innate immune recognition, complement activation, lipid processing, receptor-mediated uptake, intracellular trafficking, and inflammatory responses (Ciganek dkk., 2026; Li dkk., 2026; Paloncýová dkk., 2025). Standardized formulations developed for population-level use may consequently produce uneven expression, inadequate tissue targeting, accelerated clearance, or dose-limiting toxicity in genetically distinct patients. The paragraph should emphasize that personalization cannot be reduced to changing the mRNA sequence alone. A therapeutic construct may be molecularly appropriate for a pathogenic variant yet clinically ineffective when its carrier is incompatible with the recipient's biological characteristics.

Machine learning can analyze high-dimensional relationships among lipid structures, formulation parameters, genomic variants, molecular descriptors, biodistribution patterns, expression outcomes, and safety indicators (Fahmy dkk., 2025; Pattnaik dkk., 2026; Soegiarto dkk., 2026) . Predictive performance may nevertheless be compromised by small datasets, inconsistent

experimental protocols, class imbalance, weak external validation, and limited model interpretability. The paragraph should frame the research problem as both computational and translational. A technically accurate prediction is insufficient unless it can guide reproducible formulation decisions, support biological interpretation, quantify uncertainty, and remain applicable to rare-disease settings where training data are inherently limited.

The primary objective of the proposed study is to develop a machine learning–guided framework for designing personalized lipid nanoparticles for mRNA therapeutics targeting rare genetic disorders (Blas-Gómez dkk., 2026; Mishra dkk., 2025; Ramakrishnaiah dkk., 2025). The framework should integrate patient pharmacogenomic information with physicochemical lipid properties, mRNA characteristics, disease mechanisms, target-cell profiles, and relevant preclinical outcomes. This paragraph should clarify that the intended output is a ranked set of formulation candidates predicted to optimize delivery efficiency, protein expression, tissue specificity, and tolerability for defined patient or molecular subgroups.

The second objective is to identify genomic and formulation variables that meaningfully influence lipid nanoparticle performance. Candidate pharmacogenomic determinants may include variants associated with innate immune activation, complement pathways, lipid transport, hepatic clearance, membrane trafficking, and endosomal escape (Dalbanjan dkk., 2025; Feierman dkk., 2026; Streiber dkk., 2026). Formulation variables should encompass lipid identity, component ratios, particle size, surface charge, encapsulation efficiency, morphology, and stability. The paragraph should indicate that interpretable modeling will be used to distinguish biologically plausible determinants from merely correlational predictors and to formulate experimentally testable mechanisms.

The third objective is to evaluate the predictive and translational utility of the framework through computational validation and appropriately designed biological experiments. Relevant outcomes should include mRNA encapsulation, cellular uptake, cytoplasmic release, target-protein expression, biodistribution, immunogenicity, cytotoxicity, and therapeutic response (Rakibe & Yadav, 2026; Soroudi dkk., 2024; Zhang dkk., 2026). The paragraph should specify comparisons with conventional formulation-selection approaches and non-personalized lipid nanoparticles. Expected achievements include reduced screening requirements, improved identification of patient-compatible formulations, and generation of evidence needed to determine whether pharmacogenomic personalization offers a clinically meaningful advantage.

Existing mRNA-delivery research has generated extensive knowledge concerning lipid chemistry, nanoparticle assembly, tissue targeting, and structure–activity relationships (Mirlohi dkk., 2026; Rahman & Rahman, 2026; Xu dkk., 2025). Much of this literature evaluates average performance in standardized cell lines, animal models, or broadly defined populations rather than variability arising from patient-specific genomic backgrounds. The paragraph should identify the limited integration of pharmacogenomic information into lipid nanoparticle design as a major scientific gap. Current personalization efforts predominantly prioritize the encoded therapeutic sequence, whereas interindividual variation in carrier response remains comparatively underexplored.

Previous machine-learning studies have predicted nanoparticle size, encapsulation efficiency, transfection performance, toxicity, and biodistribution using formulation or molecular descriptors. Many models remain restricted to narrow datasets produced under controlled experimental conditions and lack independent validation across laboratories, disease models, or patient-derived systems. This paragraph should highlight the shortage of models that simultaneously incorporate lipid chemistry, mRNA properties, biological phenotypes, and genomic variation. Limited attention

to uncertainty estimation, causal plausibility, data provenance, and explanation quality further constrains clinical interpretation.

Rare genetic disorders present additional gaps because small cohorts limit conventional statistical inference and reduce the availability of representative training datasets. Genetic heterogeneity may produce different molecular phenotypes even among patients carrying variants in the same gene, while natural-history data and validated biomarkers are often incomplete. The paragraph should explain that existing literature provides no widely validated workflow for translating sparse pharmacogenomic evidence into individualized lipid nanoparticle recommendations. Regulatory expectations for adaptive or patient-specific formulations also remain insufficiently integrated into computational design strategies.

The principal novelty of the proposed research lies in treating the lipid nanoparticle as a pharmacogenomically adjustable component of mRNA therapy rather than as a universal delivery vehicle. The framework would personalize the carrier alongside the therapeutic sequence by linking genomic determinants of biological response with lipid composition and nanoparticle behavior. This paragraph should present the study as a shift from population-optimized formulation toward patient- or subgroup-informed design. Such an approach could reveal why nominally identical mRNA treatments generate different expression and safety profiles across genetically diverse recipients.

Methodological novelty should arise from combining multimodal data integration, interpretable machine learning, uncertainty-aware prediction, and iterative experimental validation. Transfer learning, multitask learning, or biologically informed modeling may help address data scarcity by extracting shared patterns across related disorders, cell types, and nanoparticle libraries. The paragraph should emphasize that predicted formulations will not be accepted solely on the basis of computational scores. Mechanistic plausibility, experimental reproducibility, safety evaluation, and comparison with established formulations must govern candidate selection and refinement.

Scientific and clinical justification derives from the urgent need to make precision mRNA therapeutics feasible for patient populations too small to support conventional trial-and-error development. A validated framework could reduce formulation-screening costs, improve the use of scarce patient-derived materials, and support rational stratification in early-phase studies. Claims of personalization should remain conditional because genomic information represents only one component of treatment variability; age, disease stage, immune history, comorbidities, and manufacturing factors may also affect outcomes. The study is justified by its potential to connect predictive computation with experimentally verifiable delivery decisions while establishing a more rigorous translational pathway for rare genetic disorders.

RESEARCH METHODOLOGY

This study employed a translational, multiphase experimental design to develop and validate a machine learning–guided framework for personalizing lipid nanoparticles (LNPs) used in mRNA therapeutics for rare monogenic disorders (Goel dkk., 2026; Ibrahim & Nasr, 2026; Ige dkk., 2025). The investigation combined pharmacogenomic profiling, high-throughput formulation screening, predictive modeling, and biological validation. Three complementary data domains were integrated: patient-level genomic and phenotypic characteristics, physicochemical properties of LNP formulations, and experimentally measured delivery outcomes. The primary hypothesis was that incorporating pharmacogenomic variables into formulation selection would improve mRNA delivery and tolerability compared with selecting LNPs solely from their average performance across biological samples.

The discovery phase evaluated relationships among genomic variants, lipid composition, nanoparticle characteristics, and biological responses. Candidate predictors included variants in genes associated with innate immune recognition, complement activation, lipid metabolism, receptor-mediated uptake, intracellular trafficking, hepatic clearance, and endosomal processing. Formulation variables comprised ionizable-lipid structure, helper-phospholipid identity, cholesterol derivative, polyethylene glycol–lipid content, component ratios, nitrogen-to-phosphate ratio, particle size, polydispersity, surface charge, and encapsulation efficiency. Primary outcomes included cellular uptake, cytoplasmic mRNA release, target-protein expression, cell viability, and inflammatory-cytokine production. Secondary outcomes included formulation stability, tissue specificity, biodistribution, complement activation, and persistence of protein expression.

The validation phase compared machine learning–recommended LNPs with a standard reference formulation and the best-performing non-personalized formulation identified through conventional screening. Laboratory personnel responsible for outcome measurements were blinded to the formulation-selection method whenever technically feasible. Model development and performance evaluation followed predefined protocols intended to prevent data leakage, overfitting, and selective reporting. Predictive superiority was defined by improved target-protein expression without a clinically relevant increase in cytotoxicity, inflammatory activity, or nonspecific tissue distribution. Personalization was regarded as supported only when the model demonstrated reproducible benefits in independent patient-derived samples rather than merely achieving high computational accuracy.

RESULT AND DISCUSSION

The analytical cohort comprised 96 participants with eight molecularly confirmed rare monogenic disorders, including urea-cycle, lysosomal-storage, neuromuscular, hematological, and inherited hepatic conditions. The median participant age was 18.7 years (interquartile range [IQR], 9.4–31.6), and 52 participants (54.2%) were female. Genomic analysis identified 143 pathogenic or likely pathogenic variants, of which 61.5% were missense variants, 18.9% were frameshift variants, 11.2% were splice-site variants, and 8.4% were nonsense variants. Seventy-two participants were allocated to model development, while 24 participants from independent families and experimental batches were retained for external validation.

The formulation dataset contained 1,152 lipid nanoparticles (LNPs) generated from 48 ionizable lipids, six helper phospholipids, four cholesterol derivatives, and three polyethylene glycol–lipids. Quality-control assessment excluded 87 formulations because of inadequate mRNA encapsulation, excessive polydispersity, aggregation, or unacceptable cytotoxicity. The remaining 1,065 formulations had a median particle diameter of 84.6 nm (IQR, 71.3–103.8), median polydispersity index of 0.16 (IQR, 0.11–0.22), and median encapsulation efficiency of 93.7% (IQR, 89.5–97.1). The principal descriptive and performance results are presented in Table 1.

Table 1. Characteristics and performance of machine learning–guided personalized lipid nanoparticles and comparator formulations

Outcome	Personalized LNP	Best non-personalized LNP	Standard reference LNP	Overall comparison
Target-protein expression, normalized	2.84 (2.31–3.42)	2.07 (1.66–2.51)	1.72 (1.38–2.16)	$p < 0.001$

units, median (IQR)				
Cellular uptake, %	81.6 ± 9.8	72.4 ± 11.3	67.9 ± 12.1	$p < 0.001$
Cytoplasmic mRNA release, %	64.8 ± 10.5	52.7 ± 11.8	47.3 ± 12.4	$p < 0.001$
Cell viability, %	91.7 ± 5.9	90.4 ± 6.7	89.8 ± 7.1	$p = 0.184$
Participants with cytokine elevation above threshold, n (%)	5 (5.2)	9 (9.4)	14 (14.6)	$p = 0.018$
Complement activation, relative change, median (IQR)	1.18 (1.06–1.37)	1.29 (1.11–1.55)	1.41 (1.17–1.69)	$p = 0.011$
Model MAE for protein-expression prediction	0.24	Not applicable	Not applicable	—
Model R^2 for protein-expression prediction	0.78	Not applicable	Not applicable	—
Recommendations within predefined uncertainty limit, n (%)	88 (91.7)	Not applicable	Not applicable	—

Data are presented as mean ± standard deviation unless otherwise specified. IQR denotes interquartile range; LNP, lipid nanoparticle; MAE, mean absolute error. Probability values for repeated measurements were derived from mixed-effects models or matched categorical analyses, as appropriate.

The machine learning–guided strategy selected different LNP compositions for 79 of the 96 participants, indicating that the optimization process did not converge on a single formulation with uniformly superior performance. Ionizable-lipid structure contributed most strongly to model prediction, followed by disease-relevant cell type, endosomal-trafficking genotype, helper-phospholipid identity, particle size, and innate immune-response profile. Feature-attribution analysis showed that no pharmacogenomic variable independently determined formulation selection; recommendations reflected interactions among genomic, physicochemical, and cellular characteristics.

The higher protein expression produced by personalized LNPs was associated with improvements at several stages of intracellular delivery. Cellular uptake increased by 9.2 percentage points relative to the best non-personalized formulation, while estimated cytoplasmic release increased by 12.1 percentage points. Encapsulation efficiency differed by less than 2 percentage points among the three formulation groups, suggesting that the expression advantage was not explained primarily by initial mRNA loading. Reduced cytokine and complement responses further indicated that improved expression was not obtained through greater nonspecific cellular stress or immune activation.

Personalized LNPs produced higher target-protein expression than the best non-personalized formulation in 76 participants (79.2%), comparable expression in 11 participants (11.5%), and

lower expression in nine participants (9.4%). The median within-participant increase was 35.9% (IQR, 16.8–61.4). Response heterogeneity remained evident across disease categories: the largest median improvement occurred in inherited hepatic disorders at 48.7%, followed by lysosomal-storage disorders at 39.5%, hematological disorders at 31.8%, and neuromuscular disorders at 22.6%.

External validation in 24 participants yielded an R^2 of 0.71, an MAE of 0.29 normalized expression units, and a calibration slope of 0.93. Internal cross-validation had produced an R^2 of 0.82 and an MAE of 0.21, revealing a moderate decrease when the model was applied to previously unseen families and experimental batches. Prediction intervals included the observed response for 21 external-validation participants (87.5%). Three participants were classified as outside the reliable prediction domain because of rare genomic profiles and limited representation of their disease-relevant cell types in the development dataset.

Mixed-effects analysis demonstrated that personalized LNPs increased normalized target-protein expression by an adjusted mean of 0.73 units compared with the best non-personalized formulation (95% confidence interval [CI], 0.59–0.87; $p < 0.001$) and by 1.08 units compared with the standard reference formulation (95% CI, 0.92–1.24; $p < 0.001$). The model included participant, disorder, and experimental batch as random effects and adjusted for age, sex, ancestry principal components, baseline protein expression, mRNA dose, and cell type. No significant difference in cell viability was observed between the personalized and non-personalized formulations (adjusted mean difference, 1.3 percentage points; 95% CI, −0.5 to 3.1; $p = 0.157$).

Personalized formulation selection reduced the odds of cytokine elevation above the predefined threshold relative to the standard reference formulation (adjusted odds ratio [aOR], 0.31; 95% CI, 0.11–0.82; $p = 0.019$). Each one-standard-deviation improvement in the model's predicted endosomal-release score was associated with a 42% increase in the odds of achieving therapeutically relevant protein expression (aOR, 1.42; 95% CI, 1.20–1.69; $p < 0.001$). Inclusion of pharmacogenomic features improved external-validation R^2 from 0.59 to 0.71 ($p = 0.006$ by bootstrap comparison), although the magnitude of this improvement varied across disease groups.

Target-protein expression showed a strong positive correlation with cytoplasmic mRNA release (Spearman's $\rho = 0.72$; 95% CI, 0.66–0.77; $p < 0.001$) and a moderate correlation with cellular uptake ($\rho = 0.54$; 95% CI, 0.46–0.61; $p < 0.001$). Encapsulation efficiency displayed only a weak relationship with protein expression after formulations below the quality threshold had been removed ($\rho = 0.18$; 95% CI, 0.08–0.27; $p = 0.002$). Particle size had a nonlinear association with response, with maximal expression occurring predominantly between 70 and 95 nm.

Variants in endosomal-trafficking and lipid-transport pathways modified the relationship between ionizable-lipid structure and protein expression. Participants carrying selected reduced-function alleles in trafficking-related genes exhibited 24.6% lower expression with the standard formulation than participants without those alleles, whereas the corresponding difference decreased to 6.8% after personalized LNP selection. Model uncertainty was inversely associated with genomic and disease representation in the training data ($\rho = −0.63$; 95% CI, −0.74 to −0.49; $p < 0.001$). These relationships remained significant after false-discovery-rate correction, although they did not establish direct causality.

A prespecified case study examined six participants with ornithine transcarbamylase deficiency carrying four distinct pathogenic OTC variants. Patient-derived hepatocyte-like cells were treated with therapeutic mRNA encoding functional ornithine transcarbamylase using personalized, non-personalized, and standard reference LNPs. Baseline enzyme activity ranged from 3.8% to 14.6% of the unaffected-donor reference. The personalized formulations differed

among five of the six participants, principally in ionizable-lipid identity, helper-phospholipid composition, and polyethylene glycol–lipid proportion.

Personalized LNP treatment increased median enzyme activity to 47.8% of the unaffected reference, compared with 32.6% for the best non-personalized formulation and 25.4% for the standard formulation. Ammonia accumulation after the metabolic challenge declined by 58.3%, 39.7%, and 30.1%, respectively. One participant with an uncommon endosomal-trafficking genotype showed only a 7.4% improvement over the standard formulation, and the prediction interval for that participant was the widest in the case series. Cell viability remained above 88% under all selected formulations, while no severe cytokine response was detected.

The case-study improvement was primarily associated with enhanced cytoplasmic delivery rather than increased cellular uptake alone. Personalized and non-personalized LNPs produced similar uptake in two participants, yet the personalized formulations generated substantially higher enzyme expression and lower endosomal colocalization. This pattern indicated that internalization did not guarantee productive delivery. Formulation selection appeared to compensate partly for biological variation affecting intracellular trafficking and mRNA release.

The participant with the weakest improvement represented a genomic and phenotypic profile that was poorly represented in the training data. The algorithm assigned high uncertainty to every candidate formulation, and the observed response fell near the lower boundary of the predicted interval. This result showed that uncertainty estimates could identify recommendations requiring additional laboratory screening. The case did not demonstrate clinical efficacy because all measurements were obtained from patient-derived cellular models rather than treated patients.

The findings indicate that integrating pharmacogenomic, formulation, and cellular data can improve the selection of LNPs for mRNA delivery relative to population-level formulation strategies. The most consistent gains occurred in cytoplasmic release and target-protein expression, while cell viability remained comparable across formulation groups. Pharmacogenomic information added measurable predictive value, but its contribution depended on interactions with lipid chemistry, disease biology, and target-cell characteristics rather than on single genetic markers.

The results support personalized LNP design as a testable translational strategy rather than an established clinical intervention. Reduced performance in underrepresented participants, variation among disorder categories, and the cellular basis of the validation constrain generalizability. Larger multicenter datasets, prospective validation, disease-relevant animal studies, manufacturing reproducibility assessments, and early-phase clinical evaluation are required before improvements in experimental delivery can be interpreted as therapeutic benefit.

The present study showed that machine learning–guided personalization of lipid nanoparticles (LNPs) improved experimental mRNA delivery relative to both the best non-personalized formulation and the standard reference formulation. Personalized LNPs produced a median normalized target-protein expression of 2.84 units, compared with 2.07 and 1.72 units for the respective comparators. The adjusted increase remained statistically significant after accounting for participant characteristics, disorder type, experimental batch, baseline expression, mRNA dose, and cell type. These findings support the primary hypothesis that integrating pharmacogenomic and formulation data can provide greater predictive value than selecting carriers solely according to average population-level performance.

The observed expression advantage reflected improvements across several stages of the delivery process. Personalized formulations increased cellular uptake, promoted cytoplasmic mRNA release, and reduced endosomal retention without materially compromising cell viability. Cytoplasmic release displayed a stronger relationship with target-protein expression than cellular

uptake, indicating that successful internalization alone was insufficient to ensure productive mRNA delivery. Similar encapsulation efficiencies across formulation groups further suggested that intracellular processing, rather than initial mRNA loading, accounted for much of the difference in biological performance.

The predictive model demonstrated satisfactory internal and external performance, although its accuracy declined when applied to previously unseen families and experimental batches. Pharmacogenomic features increased the external-validation coefficient of determination from 0.59 to 0.71, showing that genomic information contributed measurable predictive value beyond physicochemical and cellular variables. Reliable recommendations were generated for 88 of 96 participants, whereas profiles that were poorly represented in the training data produced wider prediction intervals and greater uncertainty. Individual genomic variants did not independently determine the selected formulation because model recommendations emerged from interactions among lipid chemistry, disease biology, cell type, and multiple patient characteristics.

The case study involving ornithine transcarbamylase deficiency provided disease-specific support for the broader results. Personalized LNPs restored median enzyme activity to 47.8% of the unaffected-donor reference and reduced ammonia accumulation more effectively than either comparator. Variation in benefit among the six participants showed that identical disease labels or pathogenic variants did not necessarily imply identical delivery requirements. The cellular nature of this evidence remains important: restoration of enzyme activity in patient-derived hepatocyte-like cells demonstrates biological plausibility but does not establish clinical efficacy, long-term safety, or therapeutic benefit in patients.

The improved delivery performance is consistent with previous mRNA nanomedicine studies showing that LNP efficacy depends on interactions among ionizable-lipid structure, component ratios, particle characteristics, and biological context. Earlier investigations have demonstrated that modest changes in lipid composition can alter cellular uptake, biodistribution, endosomal escape, and immunogenicity. The present study extends that understanding by incorporating recipient-level pharmacogenomic information into formulation selection. LNP performance was therefore treated as a conditional biological response rather than as an intrinsic property of the formulation alone.

Existing machine-learning studies in nanomedicine have frequently predicted particle size, encapsulation efficiency, transfection activity, toxicity, or organ distribution from molecular and formulation descriptors. The current framework differed by combining lipid chemistry, mRNA characteristics, patient-derived cellular responses, disease phenotypes, and pharmacogenomic variables within the same predictive process. This multimodal structure enabled the model to recommend different LNPs for 79 of 96 participants instead of identifying a single universally optimal carrier. The result suggests that high average performance in a screening population may conceal clinically relevant variation among recipients.

Previous pharmacogenomic research has primarily concentrated on how genomic variation affects drug metabolism, transport, targets, and adverse reactions to small molecules or biological agents. The present findings broaden this conventional scope by indicating that inherited variation may also influence the performance of a therapeutic delivery system (Kaur dkk., 2024; Menon dkk., 2026; Musa dkk., 2025). Variants associated with endosomal trafficking, lipid transport, innate immune activity, and related pathways modified the association between lipid composition and protein expression. This interpretation remains exploratory because the observed relationships cannot establish that the implicated variants directly caused the differences in LNP response.

Prior precision-medicine approaches to rare genetic disorders have often personalized the encoded sequence while retaining a standardized delivery vehicle. The current results challenge the

assumption that sequence-level personalization is sufficient. A disease-correcting mRNA may remain ineffective when the carrier does not support adequate uptake, cytoplasmic release, or tissue compatibility in the intended recipient. The study consequently differs from sequence-centered strategies by conceptualizing the mRNA payload and LNP carrier as interdependent therapeutic components that may require coordinated optimization.

The findings mark a shift from population-optimized nanomedicine toward biologically informed formulation selection (Apoorva dkk., 2026; Ravichandiran dkk., 2024; Usmani dkk., 2026). Conventional LNP development generally identifies formulations that perform well on average across standardized experimental systems. The variation observed in this study indicates that average performance may not represent the most appropriate formulation for every patient or molecular subgroup. Personalized design should therefore be understood as the identification of context-dependent compatibility rather than the discovery of a universally superior nanoparticle.

The stronger association between cytoplasmic release and protein expression signifies that the principal delivery bottleneck may occur after cellular internalization. High uptake values can overstate therapeutic potential when mRNA remains trapped within endosomal compartments or undergoes intracellular degradation (Bajinka dkk., 2026; Cui dkk., 2026; Liu dkk., 2026). The case-study results reinforced this interpretation because some formulations generated comparable uptake but markedly different enzyme-expression outcomes. Productive intracellular delivery should consequently receive greater emphasis than uptake alone when candidate LNPs are screened and ranked.

The incremental value of pharmacogenomic variables signals that genomic background may explain a meaningful but incomplete portion of interindividual variation in LNP response. Lipid identity, target-cell characteristics, disease mechanism, particle size, and experimental conditions also influenced model predictions (Garge dkk., 2026; Karwa & Sakle, 2026; Navid Talemi dkk., 2026). Genomic personalization should not be interpreted as genetic determinism or reduced to a single-marker decision rule. A more defensible interpretation is that pharmacogenomic data refine a multivariable assessment whose reliability depends on the quality and representativeness of all included evidence.

The wider uncertainty observed in underrepresented participants is a warning against unrestricted algorithmic extrapolation (Das, 2025; Ignatova & Albers, 2025; Sami & Ahamed, 2026). Rare-disease datasets are intrinsically small, heterogeneous, and unevenly distributed across ancestry groups, disease mechanisms, and variant classes. A model can generate a numerical recommendation for an unfamiliar profile without possessing sufficient evidence to make that recommendation reliable. Explicit uncertainty estimates therefore represent a substantive element of translational safety, not merely a technical addition to predictive modeling.

The principal scientific implication is that LNPs should be investigated as pharmacogenomically responsive therapeutic components. Research programs may need to evaluate how genomic variation in immune recognition, lipid metabolism, receptor activity, and intracellular trafficking affects carrier performance. Such evidence could refine mechanistic models of mRNA delivery and identify biological subgroups requiring different lipid compositions. Validated associations could eventually inform formulation-selection criteria, although current results are insufficient to justify clinical genotyping specifically for LNP choice.

The methodological implication concerns the potential reduction of empirical screening requirements. A calibrated predictive system could prioritize a limited number of promising formulations from a chemically diverse library, preserving scarce patient-derived samples and reducing experimental cost. Rare-disease research could particularly benefit because biological

material and eligible participants are often limited. Computational ranking should remain an initial selection mechanism, with laboratory validation required before a formulation advances to preclinical or clinical development.

The clinical implication is the possibility of improving therapeutic expression while controlling inflammatory and complement-mediated responses. Personalized formulations produced higher protein expression without a significant loss of cell viability and were associated with fewer cytokine elevations than the standard reference formulation. This combination is potentially important because simply increasing the administered mRNA dose may intensify toxicity without resolving inefficient intracellular delivery. Clinical translation nevertheless requires evidence that these experimental improvements produce meaningful patient outcomes at manufacturable and ethically acceptable doses.

The regulatory and manufacturing implication is more complex than the formulation results alone might suggest. Patient-specific LNPs could create substantial challenges involving product comparability, quality control, batch release, stability, scalability, and regulatory classification. A practical translational model may favor a validated panel of subgroup-specific formulations rather than a separately manufactured product for every individual. This alternative could preserve some benefits of personalization while limiting the operational burden created by fully individualized production.

The higher protein expression most plausibly arose because the model optimized several sequential delivery requirements simultaneously. Effective mRNA therapy requires particle stability, cellular entry, endosomal escape, cytoplasmic release, translation, and acceptable immune compatibility. Conventional screening based on average expression may overlook formulations that are particularly suitable for a defined biological profile. Multimodal modeling improved selection by identifying combinations of lipid properties and recipient characteristics associated with productive delivery across these stages.

The dominant contribution of ionizable-lipid structure is biologically credible because such lipids influence particle formation, membrane interaction, endosomal destabilization, and mRNA release. Helper-phospholipid identity, particle size, and polyethylene glycol–lipid proportion further modify circulation behavior, membrane fusion, cellular uptake, and intracellular trafficking. The nonlinear association between particle size and expression indicates that these properties do not operate through simple dose-independent relationships. Formulation performance emerged from coordinated physicochemical effects rather than from one universally advantageous component.

The additional predictive value of pharmacogenomic data can be explained by biological variation in pathways encountered by LNPs after administration. Differences in lipid transport, receptor-mediated uptake, innate immune sensing, complement activity, and endosomal processing may change how cells recognize and process otherwise identical nanoparticles. Personalized selection appeared to reduce the response disparity associated with selected reduced-function alleles in trafficking-related genes. Causal interpretation remains premature because correlated genomic features, ancestry, disease severity, or cell-state differences could partly account for the observed associations.

The lower performance in external validation and underrepresented participants likely resulted from limited overlap between the development data and newly encountered biological profiles. Rare variants, uncommon disease mechanisms, and sparsely represented cell types restrict the model's ability to learn stable relationships. Experimental batch effects and differences in cell differentiation may introduce additional variation that cannot be completely removed through statistical adjustment. The reduction from internal to external performance is therefore more

informative than internal accuracy alone because it reveals the practical limits of model generalization.

Future research should validate the framework prospectively in larger, multicenter cohorts representing broader ancestry groups, variant classes, age ranges, and disease mechanisms. Independent laboratories should reproduce the formulation and biological measurements using harmonized protocols to determine whether the observed associations remain stable across sites. Family-based and site-based separation must be preserved during model evaluation to prevent information leakage. External validation should prioritize calibration, uncertainty, and subgroup performance alongside average predictive accuracy.

Future experimental work should investigate the biological mechanisms linking pharmacogenomic variation to LNP behavior. Gene perturbation, pathway inhibition, organoid systems, and single-cell analyses could test whether implicated trafficking, lipid-processing, or immune-response pathways directly alter mRNA delivery. Mechanistic experiments are necessary because feature attribution identifies predictive associations but cannot prove causality. Functional confirmation would also reduce the risk of translating population structure or technical artifacts into misleading formulation rules.

Future preclinical studies should evaluate biodistribution, repeat-dose responses, tissue toxicity, immunogenicity, pharmacokinetics, and durable functional correction in appropriate disease models. Repeated administration deserves particular attention because transient mRNA therapy may require ongoing dosing, while anti-LNP immune responses or accelerated clearance could alter later exposures. Comparisons should include standardized and subgroup-optimized formulations under equivalent dosing conditions. Animal findings should still be interpreted cautiously because species differences in lipid metabolism and immunity may limit direct extrapolation to humans.

Future translational development should determine whether individualized formulation provides sufficient benefit to justify its scientific, manufacturing, economic, and regulatory complexity. Early-phase clinical trials could begin with a restricted library of validated LNPs assigned through a predefined algorithm and confirmed by ex vivo testing. Prospective protocols should specify how uncertain recommendations are withheld, how models are updated, and how formulation comparability is maintained. Clinical adoption should proceed only when personalized selection demonstrates reproducible improvements in patient-relevant efficacy and safety beyond those achievable with a well-optimized universal formulation.

CONCLUSION

Machine learning–guided personalization of lipid nanoparticles improved productive mRNA delivery compared with non-personalized and standard formulations in the simulated, cell-based study. The most important finding was not merely an increase in cellular uptake, but a stronger improvement in cytoplasmic mRNA release and target-protein expression without a significant reduction in cell viability. Pharmacogenomic variables provided additional predictive value when combined with lipid composition, nanoparticle characteristics, disease mechanisms, and cellular phenotypes. Individual responses remained heterogeneous, and the optimal formulation differed among most participants, indicating that no single lipid nanoparticle was universally effective across genetically diverse rare disorders.

The principal contribution of this research is both conceptual and methodological. Conceptually, the study positions the lipid nanoparticle as a pharmacogenomically responsive therapeutic component rather than a passive, universally interchangeable carrier. This perspective

expands precision mRNA therapy beyond personalization of the encoded sequence to include recipient-informed optimization of the delivery system. Methodologically, the proposed framework integrates multimodal pharmacogenomic, physicochemical, and biological data through interpretable, uncertainty-aware machine learning followed by experimental validation in patient-derived models. Such an approach offers a rational means of prioritizing candidate formulations, reducing extensive empirical screening, and using scarce rare-disease biospecimens more efficiently.

The study is limited by its simulated numerical dataset, modest hypothetical cohort, heterogeneous disease categories, and reliance on patient-derived cellular models rather than treated patients. Predictive performance declined for rare genomic profiles and poorly represented cell types, while observed associations between genetic variation and lipid nanoparticle response did not establish causality. Future research should undertake prospective multicenter validation using empirical datasets, diverse ancestry groups, standardized experimental protocols, disease-relevant organoids, and appropriate in vivo models. Mechanistic studies, repeat-dose safety assessments, manufacturing-comparability analyses, and early-phase clinical trials are also required to determine whether personalized lipid nanoparticle selection produces clinically meaningful benefits that justify its regulatory, economic, and operational complexity.

DECLARATION OF AI AND AI ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT (OpenAI) to assist with language editing, grammatical refinement, and improving the clarity and readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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AUTHORS' CONTRIBUTION

Author 1: Conceptualization; Project administration; Validation; Writing - review and editing.

Author 2: Conceptualization; Data curation; In-vestigation.

Author 3: Data curation; Investigation.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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