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EMERGING THERAPEUTIC STRATEGIES FOR POMPE DISEASE: A SYSTEMATIC REVIEW OF CURRENT ADVANCES AND FUTURE DIRECTIONS

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ABSTRACT
Emerging therapeutic strategies for Pompe disease have gained increasing attention as researchers seek to overcome the limitations of conventional enzyme replacement therapy (ERT), which include inadequate skeletal muscle uptake, immune responses, and lifelong dependence on intravenous infusions. Following the PRISMA 2020 guidelines, literature was retrieved from PubMed, ScienceDirect, Wiley Online Library, Taylor & Francis, MDPI, Frontiers, Cell Press, Bentham Science, and other peer-reviewed databases. Sixteen eligible studies consisting of systematic reviews, narrative reviews, clinical trials, and original research articles were analyzed to evaluate current and developing treatment approaches for Pompe disease. The reviewed evidence highlights significant advances in next-generation enzyme replacement therapies, adeno-associated virus (AAV)-mediated gene therapy, pharmacological chaperones, substrate reduction therapy, antisense oligonucleotide therapy, and prenatal therapeutic interventions. Gene therapy emerged as one of the most promising strategies because of its potential to provide sustained acid alpha-glucosidase (GAA) expression after a single administration, while combination therapies demonstrated improved enzyme stability and skeletal muscle targeting compared with conventional ERT. Although several emerging therapies have shown encouraging clinical and preclinical outcomes, long-term safety, efficacy, accessibility, and cost-effectiveness remain important challenges. Overall, these advances represent significant progress toward more effective and durable treatment options for Pompe disease while emphasizing the need for continued clinical research to optimize patient outcomes.

Keywords:
Pompe disease; acid alpha-glucosidase (GAA); enzyme replacement therapy; gene therapy; pharmacological chaperones; substrate reduction therapy; systematic review.

INTRODUCTION
Pompe disease, also known as glycogen storage disease type II (GSD II), is a rare autosomal recessive lysosomal storage disorder caused by pathogenic variants in the acid alpha-glucosidase (GAA) gene. These mutations result in a deficiency or complete absence of the lysosomal enzyme acid alpha-glucosidase, preventing the normal breakdown of glycogen into glucose. Consequently, glycogen progressively accumulates within lysosomes, particularly in skeletal, cardiac, and smooth muscle tissues, leading to cellular dysfunction and progressive muscle degeneration. The disease is clinically classified into infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD), both of which differ in age of onset, severity, and progression but share the same underlying enzymatic defect.

Enzyme replacement therapy (ERT), using recombinant human acid alpha-glucosidase, has been the standard treatment for Pompe disease for more than a decade. The introduction of ERT has significantly improved survival, cardiac function, and quality of life, particularly among patients with infantile-onset disease. Despite these advances, important therapeutic limitations remain. Conventional ERT demonstrates limited uptake into skeletal muscle, does not adequately cross the blood–brain barrier, may trigger immune responses that reduce treatment efficacy, and requires lifelong intravenous administration. As a result, many patients continue to experience progressive respiratory decline, muscle weakness, and reduced functional capacity despite continuous treatment.

These limitations have driven substantial research into novel therapeutic approaches that aim to improve treatment efficacy and address the underlying molecular mechanisms of the disease. Recent advances include next-generation enzyme replacement therapies with enhanced receptor targeting, adeno-associated virus (AAV)-

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mediated gene therapy designed to restore endogenous GAA production, pharmacological chaperones that stabilize enzyme activity, substrate reduction therapy to decrease glycogen accumulation, antisense oligonucleotide therapy for mutation correction, and emerging prenatal interventions. Many of these strategies have demonstrated encouraging results in preclinical studies and early clinical trials, suggesting the potential for improved long-term disease management.

Although numerous studies have investigated these emerging therapies individually, a comprehensive synthesis of the current evidence is essential to evaluate their therapeutic potential, clinical advantages, and remaining challenges. Therefore, this systematic review aims to examine the current literature on emerging therapeutic strategies for Pompe disease, compare their mechanisms of action and reported clinical outcomes, and identify future directions for improving patient care and disease management.

OBJECTIVES

General Objective

To systematically review the current evidence on emerging therapeutic strategies for Pompe disease and evaluate their effectiveness, mechanisms of action, and potential advantages over conventional enzyme replacement therapy.

Specific Objectives

This systematic review specifically aims to:

- Identify the current and emerging therapeutic approaches used in the treatment of Pompe disease.
- Compare the mechanisms of action of conventional enzyme replacement therapy and novel treatment strategies, including gene therapy, pharmacological chaperones, substrate reduction therapy, antisense oligonucleotide therapy, and prenatal interventions.
- Evaluate the reported clinical outcomes, therapeutic benefits, and limitations of emerging treatment approaches based on published literature.
- Determine the current challenges, research gaps, and future directions in the development of therapies for Pompe disease.

METHODOLOGY

This systematic review was conducted following the PRISMA 2020 guidelines to identify, evaluate, and synthesize current evidence on emerging therapeutic strategies for Pompe disease. A structured review process was employed to ensure the transparent selection, extraction, and analysis of relevant studies.

1. Research Design

This study employed a systematic literature review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review aimed to synthesize current evidence regarding emerging therapeutic strategies for Pompe disease, focusing on advances beyond conventional enzyme replacement therapy.

2. Literature Search Strategy

A comprehensive literature search was conducted using PubMed, ScienceDirect, Wiley Online Library, MDPI, Frontiers, Cell Press, Taylor & Francis Online, Bentham Science, and PubMed Central (PMC). Studies published between 2021 and 2025 were retrieved using combinations of the keywords "Pompe disease," "enzyme replacement therapy," "gene therapy," "pharmacological chaperone," "substrate reduction therapy," and "emerging therapy."Additional relevant articles were identified through manual screening of reference lists.

Inclusion Criteria

Studies were included if they:

- were published between 2021 and 2025;
- were written in English;
- focused on therapeutic approaches for Pompe disease;
- investigated emerging therapies or improvements to conventional enzyme replacement therapy;
- were clinical trials, systematic reviews, narrative reviews, or original research articles;
- were published in peer-reviewed journals.

Exclusion Criteria

Studies were excluded if they:

- focused solely on diagnosis, epidemiology, or genetics without discussing treatment;
- were conference abstracts, editorials, commentaries, or letters;

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- lacked sufficient methodological information;
- were duplicate publications.

Study Selection

The initial database search identified potentially relevant studies. Duplicate records were removed before titles and abstracts were screened for relevance. Full-text articles that met the eligibility criteria were subsequently assessed. Studies that satisfied the inclusion criteria were included in the final qualitative synthesis.
A total of 15 studies were included in this review.

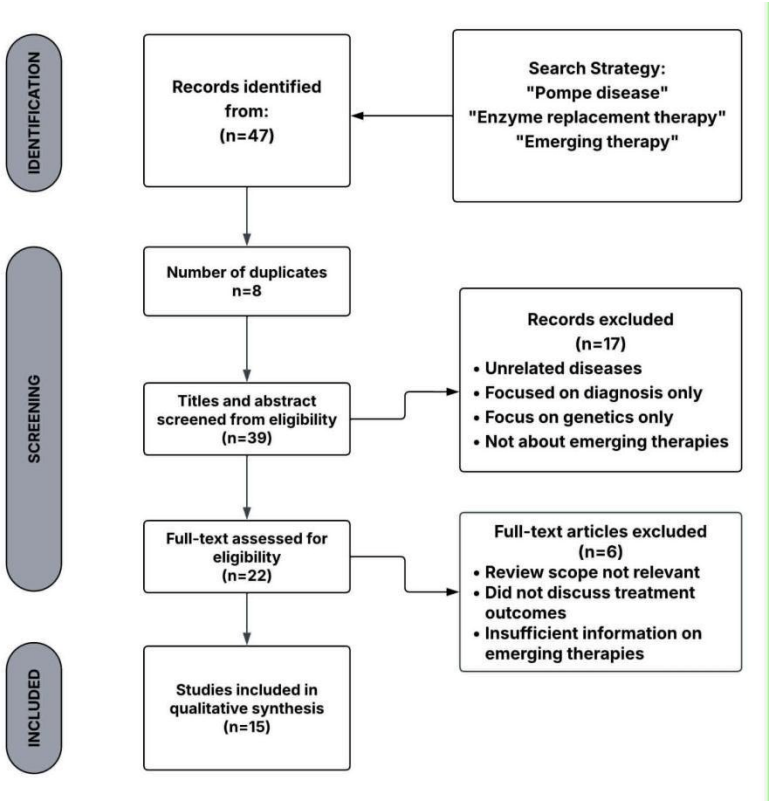

Figure 1. PRISMA 2020 Diagram for the systematic review of emerging therapeutic strategies for Pompe disease.

4. Data Extraction

Relevant data were systematically extracted from each eligible study using a standardized data extraction form. Information collected included the author(s), year of publication, study type, therapeutic approach, objectives, key findings, limitations, and conclusions. The extracted information was then summarized in tabular form to compare the effectiveness, advantages, and limitations of the different emerging therapies for Pompe disease.

5. Data Synthesis and Analysis

A narrative synthesis using thematic analysis was conducted to examine the findings of the included studies. The extracted data were categorized according to the therapeutic strategies investigated, and similarities, differences, clinical outcomes, advantages, and limitations were identified and synthesized to provide a comprehensive overview of emerging therapies for Pompe disease.

6. Limitations

This review is limited to English-language studies published between 2021 and 2025 and focuses solely on emerging therapeutic strategies for Pompe disease. A qualitative synthesis was conducted because of the variability in study designs and reported outcomes, making quantitative analysis inappropriate. Furthermore, several emerging therapies remain under investigation, and long-term clinical evidence is still limited.

RESULTS AND DISCUSSION

A total of 15 studies published between 2021 and 2025 met the inclusion criteria and were included in this systematic review. The selected literature consisted of systematic reviews, narrative reviews, clinical trials,

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preclinical animal studies, and original research articles. Most studies investigated strategies to overcome the limitations of conventional enzyme replacement therapy (ERT), with gene therapy being the most extensively explored approach. Other therapeutic strategies included next-generation ERT, pharmacological chaperones, substrate reduction therapy, anti sense oligonucleotide therapy, and multidisciplinary treatment approaches.

Table 1. Characteristics of the Included Studies

Author(s)	Year	Study Design	Therapeutic Strategy	Major Findings	Conclusion
Smith et al.	2023	Phase I Clinical Trial	Liver-directed AAV8 gene therapy	Sustained serum GAA activity, increased muscle GAA activity, successful withdrawal of ERT, and no treatment-related serious adverse events.	Liver-directed AAV8 gene therapy demonstrated promising safety and therapeutic potential for LOPD
Unnisa et al.	2022	Narrative Review	AAV and lentiviral gene therapy	Optimized viral vectors improved tissue targeting, secretion, and uptake of GAA while addressing ERT limitations.	Gene therapy has strong potential to become a long-term treatment for Pompe disease.
Roger et al.	2022	Systematic Review	AAV-mediated gene therapy	Gene therapy produced prolonged GAA expression and improved skeletal muscle and CNS targeting.	Advances in vector design may improve safety and reduce immune responses in future clinical applications.
Guémy & Laforêt	2023	Narrative Review	Next-generation ERT, gene therapy, antisense oligonucleotides, substrate reduction therapy	Novel therapies demonstrated improved enzyme delivery and therapeutic efficacy compared with conventional ERT.	Emerging therapies provide new treatment opportunities but require long-term evaluation.
Adadi & El Brouzi	2025	Review	ERT and gene therapy	Gene therapy enables endogenous GAA production, while next-generation ERT enhances skeletal muscle delivery.	Emerging therapies may overcome limitations of conventional ERT despite remaining clinical challenges.
Sellier et al.	2023	Preclinical Animal Study	Muscle-specific AAV gene therapy	Successfully corrected glycogen accumulation and rescued the Pompe phenotype in GAA-deficient mice.	Muscle-specific AAV vectors demonstrated strong therapeutic potential for future clinical translation.
Han et al.	2022	Preclinical Animal Study	Combination gene therapy	Testosterone improved GAA activity, reduced glycogen accumulation,	Hormonal adjunct therapy may enhance the effectiveness of gene therapy.

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				and enhanced muscle function.	
George et al.	2024	Review	Tissue-targeted ERT, substrate reduction therapy, gene therapy	Emerging therapies aim to improve tissue targeting, reduce glycogen accumulation, and restore endogenous enzyme production.	Innovative therapeutic strategies may substantially improve long-term patient outcomes.
Dornelles et al.	2023	Systematic Review & Meta-Analysis	Conventional ERT	ERT significantly improved survival, cardiac function, and ventilation with acceptable safety.	Alglucosidase alfa remains an effective first-line therapy despite persistent limitations.
Stevens et al.	2023	Narrative Review	Conventional and next-generation ERT, gene therapy	Recently approved ERTs and gene therapies demonstrated encouraging outcomes but limited CNS penetration remains a challenge.	Continued therapeutic innovation is needed to improve long-term disease management.
Leon Astudiolo et al.	2021	Review	Recombinant AAV and lentiviral gene therapy	Gene therapy showed favorable safety and efficacy in early studies while highlighting advances in vector engineering.	Gene therapy remains one of the most promising long-term treatment strategies for Pompe disease.
Borie-Guichot et al.	2021	Review	Pharmacological chaperone therapy	Pharmacological chaperones stabilize GAA and improve enzyme function, particularly when combined with ERT.	Chaperone therapy may serve as an effective adjunctive treatment.
Khan et al.	2025	Narrative Review	ERT, gene therapy, immune modulation, chaperone therapy	Adjunctive therapies improved enzyme delivery and addressed major limitations of conventional ERT.	Early diagnosis combined with emerging therapies may substantially improve clinical outcomes.
Risi et al.	2025	Narrative Review	ERT, gene therapy, rehabilitation, nutritional management	Integrated treatment approaches improved long-term management beyond pharmacological therapy alone.	Multidisciplinary care remains essential alongside emerging pharmacological treatments.
Kishnani et al.	2024	Review	Precision medicine, gene therapy, engineered enzymes	Precision therapies and engineered GAA enzymes may improve	Continued clinical research is needed to establish long-term

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				efficacy while minimizing adverse effects associated with current treatments.	safety and effectiveness of precision-based therapies.

A total of 15 studies published between 2021 and 2025 were included in this systematic review. The selected literature consisted of systematic reviews, narrative reviews, clinical trials, preclinical animal studies, and review articles investigating emerging therapeutic strategies for Pompe disease. Most studies focused on overcoming the limitations of conventional enzyme replacement therapy through the development of gene therapy, next-generation enzyme replacement therapy, pharmacological chaperones, substrate reduction therapy, and multidisciplinary management approaches. Overall, the findings demonstrated a growing emphasis on therapies that improve enzyme delivery, reduce glycogen accumulation, and provide long-term disease management.

Table 2. Summary of Emerging Therapeutic Strategies for Pompe Disease

Therapeutic Strategy	Mechanism of Action	Advantages	Current Limitations	Supporting Studies
Conventional Enzyme Replacement Therapy (ERT)	Replaces deficient acid α-glucosidase through intravenous recombinant enzyme administration.	Improves survival, cardiac function, and respiratory outcomes, especially in IOPD.	Poor skeletal muscle uptake, does not cross the blood-brain barrier, lifelong treatment, immunogenicity.	Dornelles et al. (2023); Stevens et al. (2023); Adadi & El Brouzi (2025)
Next-Generation ERT	Modified recombinant enzymes with enhanced mannose-6-phosphate receptor targeting.	Improved skeletal muscle uptake and glycogen clearance compared with conventional ERT.	Requires repeated infusions; long-term efficacy remains under investigation.	Guémy & Laforêt (2023); George et al. (2024); Stevens et al. (2023)
Gene Therapy	Delivers a functional GAA gene using viral vectors to enable endogenous enzyme production.	Sustained GAA expression, reduced dependence on ERT, potential CNS correction.	Immune responses, vector manufacturing, redosing limitations, limited long-term clinical data.	Smith et al. (2023); Roger et al. (2022); Unnisa et al. (2022); Leon-Astudillo et al. (2024); Sellier et al. (2023)
Pharmacological Chaperone Therapy	Stabilizes misfolded GAA proteins to improve enzyme activity and lysosomal trafficking.	Enhances enzyme stability and may improve ERT effectiveness.	Effective only for selected mutations; limited clinical evidence.	Borie-Guichot et al. (2021); Khan et al. (2025)
Combination Therapy	Combines ERT or gene therapy with immune modulation, hormones, or chaperones.	Improves enzyme uptake, reduces immune responses, and enhances therapeutic efficacy.	Most evidence comes from animal studies or early clinical research.	Han et al. (2022); Khan et al. (2025); Risi et al. (2025)

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Future Therapeutic Approaches	Includes substrate reduction therapy, antisense oligonucleotides, and precision medicine.	Targets multiple disease mechanisms and may improve long-term outcomes.	Most therapies remain in preclinical or early clinical development.	George et al. (2024); Guémy & Laforêt (2023); Adadi & El Brouzi (2025)

Table 2 summarizes the major emerging therapeutic strategies identified across the included studies. Although enzyme replacement therapy remains the cornerstone of Pompe disease management, recent evidence demonstrates increasing interest in therapies designed to improve enzyme delivery, enhance skeletal muscle uptake, reduce immune responses, and provide sustained endogenous GAA production. Among these strategies, gene therapy emerged as the most extensively investigated approach because of its potential to overcome many of the limitations associated with conventional enzyme replacement therapy.

1. Limitations of Conventional Enzyme Replacement Therapy

Enzyme replacement therapy (ERT) remains the standard treatment for Pompe disease and has significantly improved patient survival and cardiac outcomes since its introduction. However, the included studies consistently identified several limitations that reduce its long-term therapeutic effectiveness. Dornelles et al. (2023) reported that alglucosidase alfa significantly improves survival, cardiac function, and ventilatory outcomes in patients with infantile-onset Pompe disease, confirming its role as the current standard of care. Despite these benefits, the review also noted considerable heterogeneity among studies and emphasized the limited quality of evidence supporting long-term efficacy.

Several studies highlighted that conventional ERT demonstrates limited uptake in skeletal muscle and is unable to cross the blood-brain barrier, preventing adequate treatment of neurological manifestations. Stevens et al. (2023) and George et al. (2024) emphasized that although ERT slows disease progression, many patients continue to experience skeletal muscle deterioration and respiratory decline despite ongoing treatment. Similarly, Guémy and Laforêt (2023) observed that the therapeutic effectiveness of alglucosidase alfa gradually declines over time, creating the need for more efficient treatment approaches.

Another major concern identified across the literature is the development of immune responses against recombinant GAA, which may reduce treatment efficacy and contribute to variable clinical outcomes. Adadi and El Brouzi (2025) further explained that poor skeletal muscle uptake and immunogenicity remain major barriers despite advances in enzyme engineering. Collectively, these findings demonstrate that although conventional ERT has transformed the management of Pompe disease, its biological limitations have driven the development of innovative therapeutic strategies designed to improve enzyme delivery, reduce immune responses, and achieve more durable clinical benefits.

2. Advances in Next-Generation Enzyme Replacement Therapy

To address the shortcomings of conventional ERT, several studies investigated the development of next-generation enzyme replacement therapies designed to improve enzyme uptake and therapeutic efficacy. These modified recombinant enzymes incorporate enhanced mannose-6-phosphate receptor targeting, allowing more efficient delivery of acid α-glucosidase to skeletal muscle cells.

Guémy and Laforêt (2023) reported that recently developed therapies such as avalglucosidase alfa and cipaglucosidase alfa, particularly when combined with miglustat, demonstrated improved biochemical properties and enhanced uptake into target tissues compared with conventional alglucosidase alfa. Likewise, George et al. (2024) described tissue-targeted ERT as one of the most promising therapeutic developments, with the potential to improve glycogen clearance while minimizing disease progression in affected muscles.

Stevens et al. (2023) also reviewed newly approved ERT formulations and concluded that although these therapies provide incremental improvements in clinical outcomes, challenges related to central nervous system involvement and long-term treatment durability remain unresolved. Similarly, Adadi and El Brouzi (2025) highlighted that next-generation ERT enhances skeletal muscle targeting but still requires lifelong administration and continuous monitoring.

Overall, the reviewed studies suggest that next-generation ERT represents an important advancement over conventional therapy by improving enzyme delivery and clinical response. Nevertheless, these treatments continue to face limitations associated with repeated administration and incomplete correction of multisystem disease manifestations.

3. Gene Therapy as an Emerging Therapeutic Strategy

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Gene therapy emerged as the most extensively investigated therapeutic approach among the included studies because of its potential to provide sustained endogenous production of acid α-glucosidase following a single treatment. Unlike conventional ERT, gene therapy aims to correct the underlying genetic defect by delivering a functional GAA gene to target tissues, thereby reducing glycogen accumulation and minimizing the need for lifelong enzyme infusions.

The Phase I clinical trial conducted by Smith et al. (2023) provided encouraging evidence for liver-directed AAV8-mediated gene therapy in patients with late-onset Pompe disease. The treatment demonstrated sustained serum GAA activity, significantly increased muscle enzyme activity, and enabled participants to discontinue enzyme replacement therapy without treatment-related serious adverse events. These findings support the safety and biological activity of liver-directed gene therapy in clinical settings.

Consistent with these clinical findings, several review articles emphasized the therapeutic advantages of adeno-associated viral (AAV) and lentiviral vectors. Unnisa et al. (2022), Roger et al. (2022), and Leon-Astudillo et al. (2024) reported that optimized viral vectors improve tissue-specific gene expression, enhance GAA secretion, and potentially overcome limitations related to poor skeletal muscle uptake and central nervous system involvement. These studies also highlighted ongoing improvements in vector engineering, promoter optimization, and immune modulation strategies to enhance treatment efficacy and safety.

Evidence from preclinical animal studies further supports the clinical potential of gene therapy. Sellier et al. (2023) demonstrated that muscle-specific, liver-detargeted AAV vectors successfully corrected glycogen accumulation and restored muscle function in GAA-deficient mice. Likewise, Han et al. (2022) found that testosterone administration enhanced the effectiveness of AAV-mediated gene therapy by increasing GAA activity and improving muscle performance in female Pompe mice.

Despite these promising outcomes, the reviewed literature consistently identified several challenges, including immune responses against viral vectors, difficulties in vector manufacturing, limited opportunities for repeat dosing, and the need for larger clinical trials to establish long-term safety and efficacy. Nevertheless, gene therapy remains the most promising emerging therapeutic strategy because of its potential to provide long-lasting correction of the underlying enzymatic deficiency

4. Adjunctive and Combination Therapies

Beyond enzyme replacement and gene therapy, several studies explored adjunctive therapeutic approaches designed to enhance treatment efficacy. Pharmacological chaperones, immune modulation, hormonal therapy, and multidisciplinary management were identified as valuable complementary strategies for improving patient outcomes.

Borie-Guichot et al. (2021) reported that pharmacological chaperones stabilize acid α-glucosidase by promoting proper protein folding, thereby improving enzyme activity and enhancing the effectiveness of conventional ERT. These compounds appear particularly beneficial when administered alongside recombinant enzyme therapy.

Han et al. (2022) demonstrated that short-term androgen administration enhanced AAV-mediated gene therapy by increasing mannose-6-phosphate receptor expression, resulting in improved skeletal muscle uptake of GAA and greater glycogen clearance in animal models. Similarly, Khan et al. (2025) discussed immune modulation strategies that reduce antibody formation against recombinant enzymes, potentially improving long-term treatment response.

In addition to pharmacological interventions, Risi et al. (2025) emphasized the importance of multidisciplinary care, including respiratory management, nutritional support, rehabilitation, and physical therapy. The authors concluded that combining pharmacological treatments with comprehensive supportive care provides greater functional benefits than pharmacological therapy alone.

These findings indicate that adjunctive therapies may significantly enhance existing treatment strategies and should be considered as part of an integrated management approach for Pompe disease.

5. Future Directions and Remaining Challenges

Although substantial progress has been made in the development of emerging therapies for Pompe disease, several important challenges remain. Across the reviewed studies, long-term clinical efficacy, treatment durability, immune responses, manufacturing complexity, and accessibility were consistently identified as barriers to widespread implementation.

Many of the emerging therapies, particularly gene therapy, remain in early clinical development. Smith et al. (2023) demonstrated encouraging safety outcomes in a small Phase I trial; however, larger multicenter studies are still necessary to confirm long-term effectiveness. Likewise, Roger et al. (2022), Leon-Astudillo et al. (2024), and Unnisa et al. (2022) emphasized the need to optimize viral vectors, improve tissue targeting, and minimize immune responses before routine clinical application can be achieved.

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Several reviews also highlighted the importance of developing therapies capable of addressing neurological manifestations of Pompe disease, an area that remains largely unaffected by current ERT. George et al. (2024) and Stevens et al. (2023) suggested that tissue-targeted therapies, substrate reduction therapy, and advanced gene therapy platforms may provide more comprehensive disease correction in the future.
Overall, the evidence indicates that the future management of Pompe disease will likely rely on personalized and multimodal therapeutic approaches that combine improved enzyme replacement therapies, gene therapy, pharmacological adjuncts, and multidisciplinary clinical care. Continued clinical research and long-term follow-up studies are essential to establish the safety, efficacy, and accessibility of these emerging treatments.

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CONCLUSION

This systematic review examined the current evidence on emerging therapeutic strategies for Pompe disease and found that significant advancements have been made beyond conventional enzyme replacement therapy (ERT). While ERT remains the standard treatment and has improved patient survival and disease management, its limitations—including poor skeletal muscle uptake, inability to effectively address central nervous system involvement, immunogenicity, and the need for lifelong administration—have driven the development of innovative therapeutic approaches. Among these, gene therapy emerged as the most promising strategy because of its potential to provide sustained endogenous acid α-glucosidase production and reduce dependence on repeated enzyme infusions. In addition, next-generation ERT, pharmacological chaperones, substrate reduction therapy, and combination therapies demonstrated encouraging potential to improve treatment efficacy and address existing therapeutic gaps.
Overall, the findings indicate that future management of Pompe disease will likely rely on personalized and multimodal treatment strategies that combine advances in gene therapy, enzyme engineering, and supportive interventions. Although many of these therapies are still undergoing clinical evaluation, the current evidence highlights their potential to improve long-term clinical outcomes and quality of life for individuals living with Pompe disease. Continued large-scale clinical trials and long-term follow-up studies are recommended to establish the safety, efficacy, and accessibility of these emerging therapies and to support their integration into routine clinical practice.

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