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Emerging Therapies for Inborn Errors of Metabolism: Enzyme Replacement, Gene Therapy, Genome Editing

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Abstract

Inborn Errors of Metabolism (IEMs) are a heterogeneous collection of inherited genetic illnesses resulting from abnormalities in enzymes, transport proteins, or cofactors involved in important metabolic pathways. These deficiencies interfere with normal biochemical processes leading to buildup of harmful metabolites, deficiency of important metabolic products and gradual multisystem dysfunction. Vitamin supplementation, dietary modification and supportive care remain the mainstay of treatment for many metabolic disorders, but these traditional treatments do not address the underlying molecular defects. Molecular medicine has revolutionised the treatment landscape through disease-modifying methods that address the underlying genetic or enzymatic abnormality. Enzyme Replacement Therapy (ERT) has emerged as an established treatment for several lysosomal storage disorders, with a relevant positive impact on survival and quality of life. More recently, gene therapy and genome editing technologies have emerged as promising approaches to restore normal gene function or permanently fix disease-causing mutations. In addition, emerging novel therapeutic modalities for inherited metabolic diseases, such as messenger RNA (mRNA)-based therapies, pharmacological chaperones and substrate reduction therapy, are expanding the treatment options for patients. Despite the tremendous advances, there are still challenges such as immune-related adverse effects, poor tissue targeting, high cost of treatment, ethical issues and uncertainty in long-term efficacy and safety. Many of these restrictions are likely to be solved by improvements in genomic medicine, vector engineering and precision medicines. This review summarises concepts, mechanisms, clinical uses, current limits and future possibilities of enzyme replacement therapy, gene therapy and genome-editing technologies for the management of inborn errors of metabolism.

Keywords: Inborn Abnormalities of Metabolism; Enzyme Replacement Therapy; Gene Therapy; Genome Editing; CRISPR-Cas9 Lysosomal Storage Problems; Precision Medicine

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Introduction

Inborn Errors of Metabolism (IEMs) are a large and heterogeneous group of inherited genetic diseases caused by pathogenic variants in enzymes, transport proteins, receptors or cofactors required for normal metabolic function. The concept of IEMs was first introduced by Sir Archibald Garrod in 1902 after he observed alkaptonuria, a disorder he termed a “inborn error of metabolism”. His pioneering study revealed the link between inherited genetic mutations and biochemical abnormalities and laid the foundation for contemporary biochemical genetics [1].

Since Garrod’s original description, the field of inherited metabolic disorders has been greatly expanded by advances in molecular genetics, genomics and metabolomics. More than 1,500 different metabolic diseases have been identified to date, impacting almost all metabolic pathways including: amino acid metabolism, carbohydrate metabolism, lipid metabolism, mitochondrial energy production, peroxisomal function, lysosomal degradation and neurotransmitter synthesis [2]. Though individual illnesses are few, together they constitute a major cause of infant mortality, developmental retardation, neurological impairment, and chronic multisystem disease. Overall incidence is predicted to be between about 1 in 800 and 1 in 2,500 live births, depending on ethnicity, geographical area and the availability of newborn screening programmes [3].

The clinical picture of IEMs is very varied. Some illnesses manifest in the newborn period with severe metabolic crises including hypoglycaemia, hyperammonaemia, metabolic acidosis, convulsions and encephalopathy. Others are asymptomatic until adolescence or maturity. Clinical features commonly include progressive neurological deterioration, intellectual disability, cardiomyopathy, hepatomegaly, renal dysfunction, skeletal abnormalities, muscle weakness,

recurrent infections and endocrine disturbances, depending on the metabolic pathway affected [4].

Pathophysiology of IEMs is based on the disruption of normal metabolic reactions due to decreased or absent enzyme activity. This leads to accumulation of harmful metabolic intermediates and deficiency of important downstream products. These biochemical imbalances cause cellular homeostasis to be impaired, oxidative stress, inflammatory responses, and permanent tissue injury in metabolically active organs such as the brain, liver, heart, kidneys, and skeletal muscles [5].

Early diagnosis is among the most important factors of positive clinical outcomes. The broad application of expanded newborn screening by tandem mass spectrometry, as well as developments in Next-Generation Sequencing (NGS), Whole-Exome Sequencing (WES), and Whole-Genome Sequencing (WGS), have dramatically improved diagnostic accuracy and enabled treatment prior to irreversible organ damage [6], many hereditary metabolic illnesses have shown a dramatic reduction in morbidity and mortality with early treatment intervention.

In the past, the main emphasis of treatment strategies was to control metabolic abnormalities by dietary protein restriction, specialised medical formulas, supplementation of vitamins or cofactors, metabolite scavengers and supportive medical care. While these therapies continue to be essential for many metabolic illnesses, they seldom fix the underlying genetic flaw that drives disease progression [7]. Consequently, a lot of effort has been put into developing therapies that could restore normal enzyme function or correct disease-causing mutations.

Recent developments in molecular medicine have altered the therapy landscape for hereditary metabolic disorders. Enzyme Replacement Therapy (ERT) is the standard treatment for several lysosomal storage disorders as it substitutes the deficient enzymes and decreases substrate accumulation. Similarly, gene therapy has advanced from experimental studies to clinical use in selected disorders, with long term expression of functional genes after a single administration. More recently, genome editing technologies like CRISPR-Cas9, base editing, and prime editing have demonstrated a capacity to permanently repair pathogenic mutations at the source of the genome, bringing precision medicine closer to clinical reality [8].

Beyond these key therapeutic achievements, the spectrum of treatment choices is expanding with the emergence of techniques such as messenger RNA (mRNA)-based treatments, pharmacological chaperones, substrate reduction therapy and stem cell-based interventions. These innovations together reflect a paradigm shift from symptomatic management to disease modification and even curative therapy.

But there are still critical issues to be resolved before these technologies can be made generally available. However, their widespread application is still hindered by high treatment costs, limited availability in low- and middle-income countries, immune responses to biologic therapies, delivery limitations, ethical concerns regarding genome editing, and unknown long-term safety. Active research is focused on overcoming these hurdles through better vector design, improved distribution, increased editing accuracy and more economical therapeutic platforms.

Herein, we review recent developments of enzyme replacement therapy, gene therapy and genome-editing technologies for the treatment of inborn errors of metabolism, focusing on their mechanisms of action, clinical applications, limitations and future prospects in the rapidly evolving field of precision medicine.

Inborn errors of metabolism are a large group of monogenic diseases caused by mutations in genes encoding enzymes, transporters, cofactors, receptors or structural proteins that are essential for normal metabolism. These mutations affect metabolic pathways involved in the synthesis, breakdown, transport or storage of carbohydrates, amino acids, lipids, nucleotides, vitamins and energy substrates.

IEMs are traditionally classified by the metabolic route involved. The main groups include disorders of amino acid metabolism (for example phenylketonuria and maple syrup urine disease), organic acidemias, fatty acid oxidation disorders, carbohydrate metabolism disorders (for example glycogen storage diseases and galactosaemia), urea cycle disorders, lysosomal storage disorders, mitochondrial diseases, peroxisomal disorders and disorders of neurotransmitter metabolism. Each type has different biochemical problems, but all have the common trait of impaired cell metabolism with increasing tissue deterioration.

Three major mechanisms have been described for the pathogenesis of IEMs: accumulation of toxic metabolites proximal to the metabolic blockage, deficiency of essential downstream products and impaired cellular energy production. These biochemical alterations result in oxidative stress, mitochondrial dysfunction, chronic inflammation, apoptosis and organ-specific pathology. The tissues like brain, liver, myocardium, kidneys and skeletal muscles have high metabolic demands and are therefore particularly susceptible to metabolic derangements.

The advances in molecular diagnostics have greatly improved disease classification with genotype-phenotype correlations allowing prognosis, genetic counselling and personalised therapeutic strategies. Moreover, precision diagnostics have paved the way for targeted molecular therapeutics that attempt to address the underlying biochemical problem instead of just relieving symptoms.

Enzyme Replacement Therapy (ERT)

Enzyme Replacement Therapy (ERT) is one of the first successful examples of precision medicine for hereditary metabolic illnesses. It is the intravenous administration of recombinant human enzymes to replace those that are missing or functionally deficient due to inherited genetic mutations. Since its introduction in the early 1990s, ERT has transformed the therapeutic landscape of multiple lysosomal storage diseases such as Gaucher disease, Fabry disease, Pompe disease, Mucopolysaccharidoses (MPS) types I, II, IVA, VI and lysosomal acid lipase deficiency [9].

The principle of therapy with ERT is the restoration of enzyme activity in the damaged cells. Recombinant enzymes are produced in genetically engineered mammalian cell systems and administered by periodic intravenous infusion. After systemic circulation, these enzymes are bound to Mannose-6-Phosphate (M6P) receptors expressed on the surface of target cells. The enzyme-receptor complex is internalised by receptor-mediated endocytosis and transported intracellularly to lysosomes. The recombinant enzyme catalyses the degradation of accumulated substrates and restores normal lysosomal function [10].

Clinical benefits of ERT include reduction of substrate accumulation, improvement in organomegaly, improved cardiac

and pulmonary function, increased exercise tolerance, improved growth in children, and improved quality of life. Early beginning of therapy, particularly before the onset of permanent organ damage, is associated with greatly improved long-term clinical results [11].

But ERT has numerous key limitations despite these great accomplishments. Recombinant enzymes are often poorly able to pass the blood-brain barrier, limiting their use for treatment of neurological symptoms of lysosomal storage diseases. Moreover, the plasma half-life of the infused enzymes is relatively short and thus, lifelong intravenous infusions are usually needed every 1-2 weeks. In some patients, anti-drug antibodies are also developed which diminsh the therapeutic efficacy or aggravate the infusion-related adverse effects. Moreover, the high costs of manufacturing, the necessity for lifelong treatment, and dependence on specialised healthcare infrastructure mean that ERT is not available to many patients, especially in resource-poor areas.

However, it is still one of the most successful examples of targeted therapy for inherited metabolic disorders, and has dramatically improved survival, reduced disease burden and improved quality of life for thousands of patients worldwide. Current research is focused on the development of next generation enzymes with longer half-lives, more tissue penetration, enhanced transport to central nervous system and lower immunogenicity, which will increase clinical effectiveness of this crucial therapeutic method.

Gene Therapies

Gene therapy has become one of the most promising disease-modifying approaches to treat Inborn Errors of Metabolism (IEMs) Gene therapy targets the underlying genetic abnormality causing the disease, unlike traditional medicines that mostly relieve symptoms or supplement missing enzyme activity. The goal is to deliver a working copy of the damaged gene into the target cells so they produce a normal enzyme and fix the metabolic deficiency. As the majority of IEMs are the result of a mutation in a single gene, they are particularly appealing targets for gene-based treatment approaches [12].

The therapy procedure starts with the discovery of the harmful mutation using molecular diagnostic techniques, such as targeted gene sequencing, whole-exome sequencing (WES) or Whole-Genome Sequencing (WGS). Molecular diagnosis has to be accurate because treatment is directed at correcting a particular genetic abnormality. Once the mutation is identified, a normal copy of the faulty gene is produced and inserted into a delivery vehicle capable of carrying the therapeutic DNA into the desired cells [13].

The most popular delivery vehicles are still viral vectors, as they are highly efficient at transduction. Adeno-Associated Virus (AAV) vectors are especially appealing because to their excellent safety profile, minimal immunogenicity, and capability of inducing long-term gene expression in non-dividing cells, in particular hepatocytes. Since the liver is a major organ in many metabolic pathways, AAV-mediated liver-directed gene therapy is the treatment of choice for many hereditary metabolic illnesses. Lentiviral vectors are also commonly used, especially for ex vivo gene therapy, as they integrate into the host genome and ensure stable and long-term gene expression [14].

Gene therapy may be given by *in vivo* or *ex vivo* methods. *In vivo* gene therapy involves direct injection of the viral vector containing the therapeutic gene into the patient's blood stream to reach target organs such as the liver, skeletal muscle, or central nervous system. Inside the target cells, the therapeutic gene is expressed and the enzyme which was lacking is now produced on a continuing basis. In contrast, *ex vivo* gene therapy involves the removal of cells (usually haematopoietic stem cells) from the patient, modification of the cells in the laboratory, and reimplantation of the cells into the patient. This method allows for the meticulous selection of effectively repaired cells prior to transplantation and diminishes some of the dangers associated with direct *in vivo* administration [15].

Successful gene transfer restores enzyme activity and re-establishes the broken metabolic pathway, reducing the buildup of harmful intermediates and promoting synthesis of critical downstream metabolites. Consequently, patients have increased metabolic stability, fewer metabolic crises, reduced organ damage, and an improved quality of life. Early management is especially worthwhile since it can help avoid irreversible neurological and systemic consequences prior to the development of irreparable tissue damage [16].

Gene therapy is being investigated in clinical trials for a number of inherited metabolic illnesses. In Phenylketonuria (PKU), Ornithine Transcarbamylase (OTC) deficiency, Pompe disease, Methylmalonic Acidemia (MMA) and Fabry disease, promising clinical outcomes have been reported, with restoration of enzyme activity reducing disease severity and, in some cases, decreasing dependence on life-long dietary therapy or enzyme replacement therapy [17].

However, despite these optimistic developments, there are still limitations to gene therapy. Viral vector immune responses may interfere with treatment efficacy or preclude re-administration. The long-term stability of gene expression in rapidly dividing tissues is unknown. The expenses of vector fabrication and treatment are too expensive. However, the ongoing developments in vector engineering, promoter optimisation, immune regulation and manufacturing technologies are improving the safety, efficacy and accessibility of gene therapy, making it closer to standard clinical practice for inherited metabolic illnesses.

Genome editing is one of the most revolutionary advances in modern genomic medicine. This is in contrast to traditional gene therapy where an extra functional copy of the gene is added. Genome editing involves directly altering the genome of the patient by fixing, removing or changing the disease-causing mutations in the genome. This approach holds the promise of permanent genetic repair and thus a potential treatment for many hereditary metabolic illnesses.

Several genome editing platforms have been created including Zinc Finger Nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs) and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) associated proteins (CRISPR-Cas). Of these technologies, CRISPR-Cas9 has emerged as the platform of choice due to its simplicity, versatility, relatively low cost, and high editing efficiency [18].

The genome editing method starts with the molecular diagnosis to identify the mutation that causes the sickness. Researchers then create a guide RNA (gRNA) that is complementary to the target DNA sequence. The guide RNA leads the Cas9 nuclease to the exact location in the genome where the mutation is. Recognition requires a Protospacer Adjacent Motif (PAM) that allows Cas9 to bind and become active.

Cas9, after binding to the target DNA, cuts the DNA three

nucleotides upstream of the PAM region creating a double stranded break. Cellular DNA repair mechanisms then repair the break through two possible pathways: Non-Homologous End Joining (NHEJ) or Homology Directed Repair (HDR). NHEJ is a fast, yet error-prone process that commonly results in insertions or deletions that affect gene function and is hence beneficial for gene knockout techniques. By contrast, HDR uses an exogenous DNA template to accurately substitute the defective sequence with the right nucleotide sequence, and is therefore especially well-suited for correcting inherited mutations [19].

Efficient distribution of genome editing components is still a key to therapeutic effectiveness. Common viral vectors include AAVs and lentiviruses, but non-viral delivery methods are increasingly being explored, such as lipid nanoparticles, electroporation, and polymeric nanoparticles, due to the decreased risk of insertional mutagenesis and immune responses.

There are certain advantages of genome editing over the usual gene therapy. It repairs the endogenous gene directly, so physiological regulation of the gene expression is maintained and the risk of abnormal overexpression is lower. In addition, successful editing may confer a durable therapeutic benefit following a single intervention. However, its widespread clinical application is still limited by concerns of off-target mutations, incomplete editing efficiency, immune responses to Cas proteins, ethical considerations and long-term genomic stability [20].

Base editing is a next generation genome-editing technology that enables highly precise correction of single nucleotide mutations without double stranded DNA breaks. Single-base substitutions account for nearly one-third of known pathogenic human genetic variants, and base editing has attracted much attention as a safer alternative to traditional CRISPR-Cas9 systems.

Base editors combine a catalytically inactive Cas protein with a nucleotide deaminase enzyme. The editor then chemically changes one nucleotide to another at the target spot, guided by a specific RNA sequence, without changing the DNA backbone. This reduces the probability of double-stranded DNA cleavage, including chromosomal rearrangements and major insertions or deletions, substantially.

Two major classes of base editors have been established. Cytosine Base Editors (CBEs) can change a C:G base pair to a T:A Adenine Base Editors (ABEs) change adenine (A) to guanine (G), converting an A:T base pair to a G:C base pair. Collectively, these systems are capable of rectifying a large fraction of pathogenic point mutations responsible for inherited metabolic disorders [21].

Preclinical investigations in phenylketonuria, methylmalonic acidemia, tyrosinemia type I and other glycogen storage illnesses have shown exceptional results for base editing. Correction of disease-causing mutations has led to increased enzyme activity, reduced accumulation of toxic metabolites and substantially improved metabolic function in animal models.

While base editing has addressed many of the constraints of traditional CRISPR-Cas9, issues still exist. The efficacy of editing varies between tissues, distribution into target organs is technically challenging and unexpected nucleotide conversions of "bystander" nucleotides can occur during the editing window. Continued improvement of editing enzymes and delivery systems is anticipated to lead to even greater therapeutic precision and safety.

Prime editing is one of the most advanced and versatile genome-editing technologies available today. Sometimes called a "search-and-replace" type of genetic editing system, prime editing allows for the precise insertion, deletion or substitution of DNA sequences without the need for double-stranded DNA breaks or donor DNA templates.

The prime-editing system comprises three core components: a Cas9 nickase enzyme, a reverse transcriptase enzyme and a prime-editing guide RNA (pegRNA). With standard CRISPR systems, the guide RNA just tells the system what DNA sequence to target. In the case of pegRNA, it also carries the desired genetic correction. The Cas9 nickase then makes a single stranded break at the target location which allows the reverse transcriptase to replicate the repaired sequence directly into the genome.

This novel approach has a number of important advantages. Prime editing can correct nearly all small insertions, deletions and point mutations, while greatly reducing unintended insertions, deletions and chromosomal rearrangements associated with double-stranded DNA cleavage. Therefore, it has emerged as one of the most promising technologies to fix the disease-causing genes responsible for hereditary metabolic illnesses [22].

Experimental investigations have revealed that prime editing, which is still mostly in the pre-clinical stage, can successfully fix mutations in phenylketonuria, Wilson disease, ornithine transcarbamylase deficiency and glycogen storage diseases. We expect that advances in editing efficiency, delivery technology, and long-term safety evaluation will accelerate clinical translation over the next decade.

Gene Therapy and Genome Editing in the Clinic

The transition of gene therapy and genome-editing technologies from the experimental research to the clinical practice has revolutionised the management of various inherited metabolic illnesses. Preclinical investigations and clinical trials have showed promising treatment results across several disease areas.

Liver-directed AAV gene therapy has showed considerable promise in phenylketonuria where restoration of phenylalanine hydroxylase activity markedly reduces circulating phenylalanine concentrations and improves metabolic regulation. Similarly, patients with ornithine transcarbamylase deficiency have shown enhanced ammonia detoxification after gene transfer, decreasing the incidence of life-threatening episodes of hyperammonaemia.

Gene therapy to treat Pompe illness has led to restoration of acid α-glucosidase activity with improvements in heart function, skeletal muscular strength and respiratory capacity. Genome-editing approaches are also being investigated for methylmalonic acidemia, glycogen storage diseases, Wilson disease, Fabry disease, and tyrosinemia type I, in which correction of pathogenic mutations has restored enzyme activity and slowed disease progression in experimental models [23].

Early results indicate that gene therapy and genome editing could lead to reduced lifelong need on food management, enzyme replacement treatment and recurrent hospital admissions, but long-term clinical data are still few. With continued improvements in delivery methods, vector safety, and editing precision, these molecular

approaches are well-positioned to transform the treatment paradigm of inherited metabolic illnesses from symptomatic management to durable, potentially curative, precision medicine.

New Therapies for Inborn Errors of Metabolism

Enzyme replacement therapy, gene therapy, and genome editing have transformed the management of multiple inherited metabolic disorders, but many patients continue to experience disease progression due to the fact that these approaches are not universally effective or applicable. Therefore, a lot of study has been concentrated on the development of new therapeutic strategies that can overcome the limits of the current interventions. Some of the most promising techniques are messenger RNA (mRNA)-based therapy, pharmacological chaperones, Substrate Reduction Therapy (SRT), and combination therapies. These novel modalities are broadening the therapeutic horizon and steering the field towards personalised precision medicine.

More recently, messenger RNA (mRNA)-based therapy has emerged as a highly promising treatment strategy for inherited metabolic diseases. Unlike traditional gene therapy, mRNA therapies do not use viral vectors to carry DNA into the host cell but instead provide transitory genetic instructions that enable cells to produce the missing or faulty protein without the need for integration into the host genome. Therefore, mRNA therapy does not carry the risk of insertional mutagenesis associated with DNA-based gene transfer and can be administered repeatedly if necessary [24].

In mRNA therapy, synthetic mRNA encoding the functional protein is encapsulated in Lipid Nanoparticles (LNPs) to shield the mRNA from enzymatic destruction and to distribute the mRNA into target cells. Within the cell, the translational machinery produces the therapeutic protein restoring enzyme activity, correcting the metabolic defect. Many hereditary metabolic diseases are predominantly hepatic, hence hepatocyte-targeted lipid nanoparticles are the delivery technique of choice.

Several pre-clinical and early-stage clinical trials have shown promising results for diseases such as methylmalonic acidemia, propionic acidemia, ornithine transcarbamylase deficiency and glycogen storage diseases. Restoration of enzyme activity has resulted in increased metabolic stability, decreased buildup of hazardous metabolites and fewer metabolic crises. Moreover, advances in lipid nanoparticle engineering are improving tissue specificity, immunogenicity, and duration of protein expression.

But there are several drawbacks to mRNA treatment. Messenger RNA is inherently unstable and quickly degraded in cells, so repeated dosing is required to maintain therapeutic protein levels. Furthermore, systemic distribution is still difficult for organs other than liver, such as central nervous system and skeletal muscle. These limitations notwithstanding, rapid technology improvements predict that mRNA therapies will be a key component of precision medicine in the future for hereditary metabolic illnesses.

Another new treatment method is the use of pharmacological chaperones, which target diseases in which the problem is protein misfolding rather than the total absence of the enzyme. Enzymes that are the product of disease-causing mutations usually retain catalytic function but are physically unstable. This can lead to incorrect folding, premature degradation or failure of the enzyme to reach its intracellular target.

Pharmacological chaperones are tiny molecules that bind preferentially to these unstable proteins and stabilise their three-dimensional structure during their production and intracellular trafficking. These compounds promote proper folding of mutant enzymes so they can avoid destruction by the endoplasmic reticulum quality-control system and reach their functional site, where they preserve adequate enzymatic activity to improve metabolic function [25].

One of the most successful therapeutic uses is the oral pharmacologic chaperone, migalastat, licensed for selected patients with Fabry disease with treatable mutations. Migalastat binds to unstable α-galactosidase A and facilitates its transport to lysosomes where it dissociates under acidic conditions and the enzyme degrades accumulated globotriaosylceramide. Clinical studies have shown improvement in renal function, cardiac morphology and gastrointestinal symptoms without the need for lifelong intravenous enzyme replacement therapy [26].

Pharmacological chaperones are being investigated also for other hereditary metabolic disorders such as Pompe disease, Gaucher disease, phenylketonuria and other lysosomal storage disorders. However, their usefulness depends on the precise mutation involved, restricting their use to patients with mutant proteins that still possess partial catalytic activity [27].

An alternative approach is Substrate Reduction Therapy (SRT), which aims at decreased synthesis of metabolites that accumulate secondary to the enzyme deficiency. SRT does not replace the missing enzyme; rather, it reduces the metabolic load upstream, restoring balance between substrate synthesis and the remaining degradative capacity of the damaged cells.

Small-molecule inhibitors are used to block enzymes that participate in substrate production. This reduction in substrate production reduces intracellular accumulation and lysosomal storage, slowing disease progression. Many substrate reduction treatments are given orally and have better tissue penetration, including partial penetration across the blood-brain barrier, compared to enzyme replacement therapy [28].

Miglustat and eliglustat are well-known examples of substrate reduction therapy for Gaucher disease. These drugs block glucosylceramide synthase, hence lowering glycosphingolipid production, and decrease substrate buildup in macrophages. Miglustat has also shown therapeutic effects in Niemann-Pick disease type C by slowing neurological progression in selected patients.

Substrate reduction therapy is also under investigation for numerous additional inherited metabolic illnesses such as mucopolysaccharidoses, Tay–Sachs disease, Sandhoff disease and GM1 gangliosidosis. The application of substrate reduction therapy in combination with ERT or gene therapy may provide a further benefit by minimising substrate build-up and restoring [29] enzyme activity.

Inborn errors of metabolism are subject to new medicines, but their widespread use is still limited by several key scientific, clinical, ethical and socioeconomic difficulties, despite great developments in molecular therapeutics.

A major challenge is the efficient delivery of therapeutic drugs to the afflicted tissues. Many metabolic diseases involve organs protected

by biological barriers, especially the brain. Recombinant enzymes, viral vectors and lipid nanoparticles are often poorly penetrating across the blood-brain barrier, limiting therapy of neurological symptoms, which are a primary cause of disability and mortality in many hereditary metabolic disorders.

The immune responses are also big challenges. Recombinant enzymes, viral vectors, Cas proteins or newly synthesised therapeutic proteins may elicit neutralising antibodies which may reduce efficacy and impede recurrent delivery. Immunogenicity is still a major concern for gene therapy and enzyme replacement therapy.

Other problems with genome-editing technologies are off-target mutations, unintended chromosomal rearrangements, mosaicism and incomplete editing efficiency. While newer approaches like as base editing and prime editing have greatly increased precision, long term genomic safety still needs rigorous assessment through extensive clinical follow up.

The economic issues are equally essential. The manufacturing complexity of recombinant enzymes, viral vectors and personalised genomic medicines leads to extremely expensive treatment costs. Many of the therapies that are currently approved cost hundreds of thousands of dollars per year, which is beyond the reach of many patients, particularly those in low- and middle-income countries, where diagnostic infrastructure and specialised treatment centres are limited.

There are also ethical issues linked to genome-editing technologies. Germline editing, however, offers serious ethical issues over heritable genetic change, permission of future generations, and equal access to cutting-edge innovation, even as somatic genome editing for therapeutic purposes has been more widely accepted. International regulatory frameworks continue to evolve in response to these challenges

Finally, long-term clinical data for many of the developing medicines are still limited. Early clinical trials have shown promising safety and efficacy, but continued surveillance is necessary to evaluate durability of treatment, late adverse events, and lifelong clinical outcomes.

The future of management of inherited metabolic disease will depend on the integration of precision medicine, genomic diagnostics, artificial intelligence and advanced molecular therapeutics. Further progress in newborn screening with genomic sequencing, metabolomics and machine learning algorithms will enable earlier diagnosis and treatment before irreversible organ damage.

Next-generation viral vectors that target tissues better, cause less immune response and can carry more therapeutic material will make gene therapy much more effective. At the same time, progress in lipid nanoparticle technology could make mRNA treatments useful for diseases other than those affecting the liver, such as neurological and muscular ailments.

The technology for modifying genomes is growing rapidly. Base, prime, RNA and epigenome editing hold promise of greater precision with less undesired DNA damage. These technologies may someday allow for permanent repair of disease-causing mutations with a single therapeutic intervention.

Combination therapy will also be increasingly significant. The combination of enzyme replacement therapy with pharmacological chaperones, substrate reduction therapy or gene therapy may prove to have synergistic advantages by simultaneously treating several facets of disease pathophysiology. Personalised treatment algorithms based on genotype-phenotype correlations, residual enzyme activity, biomarker profiles and pharmacogenomic data will further optimise therapeutic outcomes.

AI is predicted to speed up drug discovery, find new therapeutic targets, forecast pathogenic variations, optimise vector design, and personalise treatment choices. Together, these advances will facilitate the move from generalised treatment algorithms to individualised precision medicine.

Improving worldwide access to advanced medicines is just as important. International collaboration between researchers, clinicians, governments, pharmaceutical industries, and patient advocacy organisations will be needed to reduce the cost of treatment, improve diagnostic capacity, and ensure equitable access to life-saving therapies in both developed and developing countries [30].

Conclusion

In the past 20 years, the management of inborn errors of metabolism has been transformed from symptomatic care to focused molecular interventions that can address the underlying genetic causes of disease. Enzyme replacement treatment has greatly improved lifespan and quality of life for patients with numerous lysosomal storage diseases by restoring defective enzyme activity and lowering substrate buildup. In more recent times, gene therapy has shown the ability to achieve long-term expression of therapeutic genes, while genome editing tools such as CRISPR-Cas9, base editing and prime editing provide the extraordinary potential to permanently fix harmful mutations.

New therapeutic strategies such as mRNA-based therapy, pharmacological chaperones and substrate reduction therapy, significantly widen the therapeutic horizon by offering additional options for patients not appropriate for conventional medicines or needing combination therapy. These advances mark a paradigm shift in precision medicine, where treatment is targeted to the patient's specific molecular defect.

Notwithstanding these great advancements, critical difficulties persist. Challenges to broader use of these technologies include efficient transport to target tissues, especially the central nervous system, immune-mediated problems, off-target genetic consequences, high cost of treatment, ethical considerations and limited accessibility. Meeting these challenges will require sustained investment in biomedical research, technological innovation, regulatory vigilance, and international cooperation.

The future for the management of inherited metabolic diseases is becoming ever brighter as molecular diagnostics, genome engineering, artificial intelligence and precision therapies continue to advance. Emerging medicines are not just about symptom control, but have the potential to effect enduring disease change and, in many cases, permanent genetic repair. Ongoing multidisciplinary research and equitable worldwide implementation will be crucial to harness the full promise of these transformational medicines and enhance long-term outcomes and quality of life for individuals living with inborn errors of metabolism.

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