

Gene Therapy of Haemophilia: Current Status and Future Directions

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Abstract

Gene therapy represents a paradigm shift in haemophilia management, offering the potential for sustained factor expression and freedom from prophylactic infusions. Two adeno-associated virus (AAV)-based gene therapies are now approved. Long-term follow-up data demonstrate remarkable durability, with 13-year results showing sustained reductions in annualized bleeding rates in patients with haemophilia B. Outcomes differ between haemophilia A and B: factor VIII levels in haemophilia A decline after peaking, whereas factor IX expression in haemophilia B remains more stable. Recent analyses confirm significant reductions in bleeding rates and treatment requirements, along with well-characterized safety profiles. Liver toxicity remains the primary safety concern, with transaminase elevations typically responding to corticosteroids. Rare adverse events include one reported case of inhibitor development and very few thrombotic events. Reported malignancies to date have not been associated with gene therapy. Current limitations include eligibility restrictions due to preexisting neutralizing antibodies, immune responses to AAV capsids, and variable patient outcomes. These challenges may contribute to slower adoption despite regulatory approval. Emerging approaches such as CRISPR-Cas9 gene editing, high-active factor variants, and novel delivery systems are under investigation. Key implementation issues include outcome-based reimbursement, hub-and-spoke treatment models, and ensuring equitable global access.

Keywords

- ▶ haemophilia
- ▶ adeno-associated virus
- ▶ gene therapy
- ▶ factor VIII
- ▶ factor IX
- ▶ future directions

Introduction: The Clinical Burden of Haemophilia

Haemophilia constitutes a group of X-linked recessive bleeding disorders resulting from mutations in genes encoding essential coagulation factors. Haemophilia A arises from factor VIII (FVIII) deficiency, whereas haemophilia B stems from factor IX (FIX) deficiency.¹ With a combined global prevalence estimated at approximately 1.1 million affected individuals, haemophilia A accounts for roughly 80 to 85% of cases (prevalence ~1 in 5,000 male births), whereas haemophilia B represents the remaining 15 to 20% (prevalence ~1 in 30,000 male births).² The X-linked inheritance pattern pre-

dominantly affects males, although female carriers may manifest bleeding symptoms due to skewed X-inactivation.³

Disease severity correlates directly with residual coagulation factor activity levels. Severe haemophilia, defined by factor activity below 1% of normal, manifests with spontaneous bleeding episodes, particularly haemarthroses and intramuscular haemorrhages.⁴ Moderate haemophilia (factor activity 1–5%) presents with less frequent spontaneous bleeding but prolonged haemorrhage following trauma or surgical procedures. Mild haemophilia (factor activity 5–40%) typically exhibits bleeding primarily in response to significant injury or invasive procedures. Nevertheless, considerable phenotypic heterogeneity exists within these

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categories, prompting discussions regarding incorporation of clinical bleeding frequency into severity classification schemas.⁵

Until recently, haemophilia management relied predominantly on prophylactic replacement therapy, involving regular intravenous administration of clotting factor concentrates to maintain protective plasma levels.⁶ Early initiation of prophylaxis has demonstrated superior clinical outcomes compared with on-demand treatment, including reduced joint damage and improved quality of life.⁷ Recent therapeutic innovations include extended half-life factor concentrates requiring less frequent administration, subcutaneous bispecific antibodies such as emicizumab for haemophilia A, and rebalancing agents targeting tissue factor pathway inhibitor or antithrombin.

Despite these advances, significant unmet needs persist in haemophilia care. Breakthrough bleeding episodes occur even with optimized prophylaxis, including subclinical joint haemorrhages that contribute to progressive arthropathy.⁶ Treatment burden remains substantial, requiring frequent health care facility visits or home infusions, negatively impacting adherence, particularly among adolescents and young adults.⁸ Development of neutralizing antibodies (NABs, inhibitors) against infused clotting factors complicates management in approximately 25 to 30% of severe haemophilia A and 5 to 10% of haemophilia B patients.⁹ Furthermore, global health care disparities result in inadequate access to prophylactic therapy in resource-limited settings.¹⁰ These persistent challenges underscore the compelling rationale for curative therapeutic strategies.

Rationale: Why Haemophilia Represents an Ideal Gene Therapy Target

Several characteristics make haemophilia particularly suitable for gene therapy. Both haemophilia A and B result from single-gene defects in well-characterized genes (F8 and F9, respectively), enabling targeted genetic correction strategies.¹¹ Clotting factors are synthesized primarily in hepatocytes (FIX) and liver sinusoidal endothelial cells (FVIII), providing accessible target tissues for vector-mediated transduction. Further, the therapeutic threshold for clinical benefit is remarkably low—elevating factor activity from below 1% to merely 5 to 10% can transform a severe bleeding phenotype into a mild one, dramatically reducing bleeding frequency and eliminating the need for regular prophylaxis.

Finally, treatment efficacy is readily measurable through well-established laboratory assays (factor activity levels) and clinical endpoints (annualized bleeding rates [ABRs]), facilitating objective assessment of therapeutic success. Well-characterized animal models, particularly haemophilia B dogs, have enabled extensive preclinical validation of gene therapy approaches.¹²

Adeno-associated virus (AAV) was selected as the primary vector platform because of its advantageous properties. AAV vectors exhibit broad tropism, transduce both dividing and quiescent cells, demonstrate low immunogenicity compared with other viral vectors, and persist predominantly as epi-

some, minimizing insertional mutagenesis risk.¹³ Liver-directed AAV administration enables efficient hepatocyte transduction with sustained transgene expression. The relatively compact FIX gene readily accommodates packaging within AAV's approximately 4.7 kb capacity, whereas the larger FVIII gene can be delivered as a B-domain-deleted variant (BDD-FVIII) that retains full functional activity.¹⁴

A transformative discovery for haemophilia B gene therapy was identification of the naturally occurring Factor IX Padua variant (R338L mutation), which exhibits 5- to 8-fold higher specific activity than wild-type FIX while maintaining normal plasma levels.¹⁵ Incorporation of this high-activity variant into gene therapy vectors has enabled achievement of therapeutic efficacy at lower transgene expression levels, reducing vector dose requirements and enhancing treatment durability. Similar high-activity FVIII variants are currently under investigation for haemophilia A applications.

Clinical Evidence: Adeno-Associated Virus Gene Therapy Trial Results

Haemophilia B Gene Therapy

Clinical development of AAV gene therapy has progressed more rapidly for haemophilia B than haemophilia A, reflecting several factors including the smaller FIX gene size, more stable transgene expression, and lower immunogenicity.¹⁶ FIX is naturally synthesized exclusively in hepatocytes, making liver-directed AAV gene therapy a physiologically appropriate approach that targets the natural site of FIX production.

Multiple AAV-based products have now achieved regulatory approval or advanced clinical development.

The HOPE-B trial incorporated a ≥ 6 -month lead-in phase to evaluate the natural history of anti-AAV5 NABs prior to etranacogene dezaparvovec administration.¹⁷ Among 67 adult male participants with haemophilia B, 48% (32/67) had detectable AAV5 NABs at screening with a median titer of 58 (range: 9–3,440). Critically, median intrapatient coefficient of variation (CV) of NAB titers remained stable at 25% (range: 2–154%) during the lead-in period, with no significant decline over a median observation period of 240 days. Only 2 of 67 patients (3%) seroconverted to NAB positivity during the observation period—one at 4 months and one at 8 months. These findings suggest that preexisting anti-AAV5 NAB status in untreated haemophilia B patients is relatively stable, and periodic retesting of initially seropositive candidates may identify individuals whose titers have naturally declined, potentially expanding the eligible population for AAV gene therapy.

Extended follow-up from the phase 2b trial of etranacogene dezaparvovec (originally designated AMT-061) demonstrated mean FIX activity of 45.7 IU/dL at 5 years' post-treatment, with sustained efficacy and no late-onset safety concerns.¹⁸

Fidanacogene elaparvovec (Beqvez), another AAV5-FIX-Padua product, received FDA approval in April 2024 based on the phase 3 BENEENE-2 trial.¹⁹ This study enrolled 45 adults with moderately severe or severe haemophilia B,

demonstrating mean FIX activity of 26.6% at 24 months with sustained expression through extended follow-up. The mean ABR decreased to 0.98 events per year, representing a 71% reduction from baseline, with 57.5% of patients experiencing zero treated bleeds.

However, in February 2025, Pfizer announced the global discontinuation of fidanacogene elaparvovec (Beqvez) commercialization despite regulatory approval.²⁰ This unexpected decision, occurring less than 10 months after regulatory approval, underscores the complex intersection of clinical efficacy, market dynamics, manufacturing challenges, and real-world patient/physician adoption—factors that extend beyond safety and efficacy profiles.

Long-term follow-up data provide crucial insights into durability. A landmark study reported 13-year outcomes following administration of scAAV2/8-LP1-hFIXco in 10 men with severe haemophilia B.²¹ The high-dose cohort maintained mean steady-state FIX activity of 3.1 IU/dL, sufficient to reduce bleeding episodes and minimize factor replacement requirements over more than a decade of observation. However, NABs to AAV remained positive.

Haemophilia A Gene Therapy

Gene therapy for haemophilia A faces additional technical challenges compared with haemophilia B, including the larger FVIII gene requiring B-domain deletion for AAV packaging, FVIII biosynthesis complexity, and less stable transgene expression profiles.

Valoctocogene roxaparvovec (Roctavian), an AAV5 vector encoding BDD-FVIII, received European Medicines Agency approval in August 2022 and FDA approval in June 2023 for adults with severe haemophilia A without FVIII inhibitors or anti-AAV5 antibodies. The phase 3 GENE8-1 trial enrolled 134 adult males with severe haemophilia A, administering a single dose of 6×10^{13} genome copies/kg. At year 1 post-treatment, mean FVIII activity measured 43.6 IU/dL by chromogenic assay,¹⁷ declining to 29.7 IU/dL at year 3 and 22.0 IU/dL at year 4.²² Despite declining levels, the majority of patients maintained FVIII activity sufficient to remain off prophylaxis. Over the complete 4- to 5-year follow-up period, 24 of 134 participants (17.9%) resumed prophylaxis with exogenous FVIII or emicizumab, with a median time to resumption of 165 weeks. Of those who did resume prophylaxis, most had FVIII activity levels < 5 IU/dL proximal to resumption. Mean ABR decreased from 4.8 at baseline to 0.8 at 1 year (84% reduction), and this benefit was maintained at 4 to 5 years. Notably, mean annualized FVIII infusion rate decreased from 135.9 infusions/year to 2.0 infusions/year (nearly 99% reduction). No participants developed FVIII inhibitors or thromboembolic events across the 4- to 5-year observation period.

The observed decline in FVIII activity over time represents a significant challenge for haemophilia A gene therapy. Multiple hypotheses have been proposed, including immune-mediated clearance of transduced hepatocytes, cellular stress induced by BDD-FVIII expression, and loss of episomal vector genomes during hepatocyte turnover.²³ Current research focuses on optimizing immunosuppression protocols, developing hyperactive FVIII variants analogous to

FIX-Padua, and investigating alternative vector systems to address this limitation.

Safety Considerations and Adverse Event Management

Hepatotoxicity and Immune Responses

The most common and clinically significant adverse event following AAV gene therapy is elevation of liver transaminases (alanine aminotransferase [ALT]/aspartate transaminase), occurring in approximately 40 to 90% of treated patients, typically manifesting 4 to 8 weeks' post-infusion.¹¹ This hepatotoxicity is hypothesized to result from cytotoxic T lymphocyte responses against AAV capsid antigens presented on transduced hepatocytes, triggering immune-mediated cell destruction.¹¹ When transaminase levels rise, transgene expression often declines, suggesting that transduced cells are being lost.

Current management protocols employ corticosteroid immunosuppression, typically initiating prednisolone upon detection of ALT elevation to suppress T-cell responses and preserve transgene expression.^{24,25} Optimal immunosuppression strategies remain under investigation.²⁶ Recent clinical practice guidance recommends prompt corticosteroid initiation following confirmed ALT elevation, with treatment duration and tapering schedules individualized based on transaminase trends and factor activity levels. Prophylactic immunosuppression has been proposed but requires careful risk–benefit assessment given potential complications of prolonged corticosteroid exposure.

Critically, hepatotoxicity evaluation must exclude alternative etiologies including viral hepatitis, drug-induced liver injury, alcohol consumption, and rhabdomyolysis before attributing transaminase elevation to gene therapy-related immune responses.^{24,25} This necessitates comprehensive hepatological assessment and underscores the importance of multidisciplinary care teams.

To date, across all haemophilia AAV gene therapy trials, no cases of chronic or irreversible hepatotoxicity directly attributable to AAV vectors have been reported. While transient ALT elevations occur in approximately 50% of treated patients (incidence: 0.50, 95% confidence interval: 0.25–0.69),²⁷ these elevations are typically managed with immunosuppressive therapy using corticosteroids and generally resolve to baseline within weeks to months. One case of autoimmune hepatitis was reported during third-year follow-up in a patient with significant comorbidities (prior hepatitis C infection and hepatic steatohepatitis,²⁸ although causality attribution remains complex in such cases. Grade 1 to 2 adverse events predominated in most studies, with only a subset requiring prolonged corticosteroid therapy. This favorable long-term hepatic safety profile provides reassurance regarding the safety of liver-directed AAV approaches, although continued surveillance remains essential given limited post-follow-up data.

Vector Integration and Malignancy Risk

While AAV vectors predominantly persist as episomes, low-frequency integration into host chromosomes has been

documented, occurring at rates of 1 in 750 to 1 in 20,000 integration events per transduced cell.²⁹ Although integration raises theoretical concerns regarding insertional mutagenesis and oncogenesis, extensive preclinical and clinical data to date provide reassurance. One case of hepatocellular carcinoma was reported in a patient treated with etranacogene dezaparvovec; however, comprehensive genomic analysis revealed less than 0.03% vector integration within the tumor, with no insertions near oncogenes.³⁰ The patient's prior hepatitis B and C virus infections represented more plausible etiological factors. Nevertheless, long-term surveillance protocols include 6-month liver ultrasound examinations as recommended for populations at elevated hepatocellular carcinoma risk.

Pre-existing Neutralizing Antibodies

Pre-existing immunity to AAV capsids, resulting from natural environmental exposure, represents a significant eligibility barrier for gene therapy.³¹ NAbs against common AAV serotypes are prevalent in the general population, with seroprevalence estimates ranging from 30 to 60% depending on serotype and geographic region.

High-titer NABs can prevent hepatocyte transduction, resulting in treatment failure. Consequently, clinical trials typically exclude patients exceeding defined anti-AAV antibody thresholds. However, the HOPE-B trial demonstrated efficacy in patients with low-to-moderate anti-AAV5 antibody titers, suggesting that stringent seronegativity may not always be mandatory.^{32,33} Ongoing research explores immunomodulation strategies, alternative vector serotypes with reduced seroprevalence, and engineered capsids capable of evading NABs.

The Klamroth et al. natural history study examined anti-AAV5 NAB dynamics in 67 haemophilia B participants during the HOPE-B lead-in phase. Baseline seroprevalence of anti-AAV5 NABs was 48% (32/67) and NAB titers remained remarkably stable over ≥ 6 -month observation (median inpatient CV: 25%).³⁴ Anti-AAV5 NABs showed high correlation with IgG anti-AAV5 binding antibodies (median $r = 0.96$). Only 2 of 67 patients (3%) seroconverted to NAB positivity, supporting that natural exposure-related NAB changes are infrequent in untreated adults. NAB status was more common in older participants (75% in ≥ 60 years vs. 40% in 31–40 years, $p = 0.0065$). These data suggest that retesting initially seropositive patients who have not received prior gene therapy may identify individuals whose antibody titers have naturally declined, potentially expanding the candidate population for AAV-based gene therapy while maintaining safety standards.

The Multidisciplinary Care Pathway and the Role of Hub and Spoke Centres

Successful implementation of haemophilia gene therapy requires comprehensive, coordinated care delivered through multidisciplinary teams. Major guideline documents provide complementary frameworks for safe and effective gene therapy delivery.^{35,36}

The World Federation of Hemophilia (WFH) Guidelines³⁵ represent the first chapter of the WFH's transition to a living guideline model, allowing timely updates as new evidence emerges. Developed with input from clinical experts, people with haemophilia, and caregivers, the guidelines address five key domains:

- Site preparedness—ensuring haemophilia treatment centres have the education, infrastructure, and communication plans needed for integrated care.
- Shared decision-making—supporting people with haemophilia in understanding the risks, benefits, and limitations of AAV gene therapy, as well as required behaviour modifications and long-term follow-up.
- Eligibility, suitability, and screening—applying clinical, diagnostic, and psychosocial criteria to determine eligible candidates.
- Infusion day—guidance on preparation, monitoring during infusion, and post-infusion observation.
- Post-infusion care—monitoring treatment efficacy and safety.

The International Society on Thrombosis and Haemostasis (ISTH) comprehensive care pathway complements the WFH guidelines by providing detailed operational guidance based on current guideline documents and Summary of Product Characteristics.³⁶ This pathway emphasizes the practical implementation aspects of gene therapy delivery, including standardized patient education materials, counselling checklists, eligibility criteria documentation, and coordinated follow-up protocols.

The publications emphasize the critical importance of hepatology integration, particularly given the liver-directed nature of AAV gene therapy and the common occurrence of transaminase elevations requiring immunosuppression. A multidisciplinary treatment team is essential for comprehensive gene therapy management, with core members including haematologists with haemophilia expertise, hepatologists for liver assessment and immunosuppression management, specialized haemophilia nurses for patient education and monitoring coordination, laboratory specialists for factor activity and antibody testing, and psychologists or social workers for psychosocial assessment and support.³⁷ Extended team members may include pharmacists, infectious disease specialists, geneticists, and regulatory/quality assurance personnel.

The hub-and-spoke model has emerged as the internationally recommended framework for gene therapy delivery, balancing the need to concentrate expertise and resources with equitable patient access.^{38,39} Under this model, expert “hub” centres prescribe and administer gene therapy, while “spoke” centres manage pre- and post-treatment patient care through close collaboration with hubs for treatment decisions and co-management of adverse events.

According to the recently published European Association for Haemophilia and Allied Disorders (EAHAD) qualification criteria,⁴⁰ hub centres must be certified as highest-level haemophilia centres (e.g., European Haemophilia Comprehensive Care Centre (EHCCC) accredited by EAHAD,⁴¹ with

demonstrated experience in gene therapy clinical trials and/or documented training programs. They require outpatient gene therapy capability with access to intensive care units, 24-hour on-call service, comprehensive multidisciplinary teams (including haemophilia nurse specialists, gene therapy liaison nurses, psychologists, physiotherapists, and hepatologists), and facilities for safe administration including bio-isolators for Advanced Therapy Medicinal Product (ATMPs). Hub centres are responsible for procurement, storage, prescription, and administration of gene therapy medicinal products, managing immunosuppression, facilitating specialist consultations, running regional multidisciplinary team meetings, attending national panel meetings, and overseeing data reporting for long-term follow-up registries.

Spoke centres must be certified haemophilia centres with access to hepatologists, 24-hour call availability, and appropriate diagnostic capabilities with results available within 6 hours. They assess patient eligibility for gene therapy through systematic screening, conduct pre-treatment education and counselling, coordinate treatment decisions with hubs, manage routine post-treatment monitoring including dual-methodology factor level assessment (one-stage and chromogenic assays), and conduct regular liver imaging every 3 to 6 months. Both centre types must have standardized operating procedures for managing adverse events, immunosuppression, infusion reactions, and liver surveillance. Shared care between hub and spoke centres is implemented when adverse events arise, with regional multidisciplinary teams comprising both centre types including designated hepatologists, haematologists, nurses, physiotherapists, psychologists, and other specialists as needed.

Future Directions and Emerging Technologies

Despite promising advances, AAV-based gene therapy for haemophilia is limited by unpredictable patient responses, immunological barriers, durability concerns, and follow-up complexities.⁴² Many patients display variable, sometimes suboptimal coagulation factor levels after therapy. Preexisting NABs and liver enzymes can exclude candidates or compromise efficacy. Even when factor expression is initially robust, it often wanes over time with uncertain long-term stability beyond a decade. Safety remains a priority, as transient liver enzyme elevations are frequent, and rigorous long-term surveillance is essential due to unknown risks. Additionally, only specific patient groups—usually adults without inhibitors—are currently eligible, leaving other populations without gene therapy access.

Alternative Vector Systems

To address the limitations of AAV-based approaches, alternative vector systems are being investigated.⁴³ Lentiviral vector-based ex vivo gene therapy represents a promising alternative approach, particularly for haemophilia A. This strategy involves transduction of autologous haematopoietic stem cells (HSCs) with lentiviral vectors encoding FVIII, followed by myeloablative conditioning and stem cell rein-

fusion.⁴⁴ A recent phase 1 trial from India reported sustained FVIII expression ranging from 1.7 to 39.9 IU/dL over 9 to 27 months following transplantation of HSCs transduced with a lentiviral vector containing a novel FVIII variant (ET3) under control of a myeloid-specific CD68 promoter. All five treated patients achieved zero ABRs. This approach offers several theoretical advantages including applicability to patients with anti-AAV antibodies, suitability for paediatric populations (as integrated transgenes replicate with dividing cells), and potential for treatment of female patients. Nonetheless, myeloablative conditioning carries significant morbidity, and long-term integration site safety requires extensive follow-up.

Enhanced Factor Variants and Vector Engineering

Development of hyperactive FVIII variants analogous to FIX-Padua represents an active area of investigation.⁴⁵ Such variants could enable therapeutic efficacy at lower expression levels, reducing cellular stress and enhancing durability. The coagulation FVIII biological basis has been extensively characterized, revealing opportunities for engineering enhanced variants with improved specific activity, stability, and reduced immunogenicity.⁴⁶ Simultaneously, vector engineering efforts focus on developing novel AAV capsids with reduced immunogenicity, enhanced hepatocyte tropism, and ability to evade pre-existing NABs.

Genome Editing Technologies

CRISPR-Cas9-mediated genome editing could represent a paradigm-shifting approach enabling precise correction of haemophilia-causing mutations at their genomic loci, rather than delivering additional transgene copies.⁴³ Pre-clinical studies have demonstrated successful in vivo correction of FIX mutations in mouse models, with correction rates of approximately 0.5 to 5% proving sufficient for phenotypic rescue.⁴⁷

Human clinical trials of genome editing for haemophilia B have now been initiated (NCT06379789), utilizing lipid nanoparticle delivery of CRISPR components to achieve site-specific FIX gene insertion. If successful, genome editing could provide permanent, stable factor expression unaffected by hepatocyte turnover or immune responses against vector capsids.

Expansion to Paediatric Populations

Current approved gene therapies are restricted to adult patients, based on concerns regarding vector genome dilution during hepatocyte proliferation associated with liver growth, as well as ethical considerations regarding informed consent for an experimental one-time therapy with uncertain long-term effects.⁴² Early intervention could prevent joint damage accumulation and optimize quality of life.

The fundamental challenge is that normal liver growth from childhood to adulthood involves significant hepatocyte proliferation and tissue expansion. Since AAV vectors persist primarily as episomal DNA rather than integrating into the host genome, cell division during liver growth would progressively dilute the vector copy number per cell, leading to

declining factor expression over time. This vector dilution effect would be most pronounced in younger children experiencing rapid somatic growth.

Real-World Evidence and Long-Term Registries

As gene therapy transitions from controlled clinical trials to broader clinical implementation, real-world evidence generation becomes paramount. The WFH has established a global gene therapy registry (GTR) to capture long-term safety and efficacy data in diverse patient populations.⁴⁸ The WFH GTR is a prospective, observational, and longitudinal registry designed to collect long-term data on people with haemophilia who receive gene therapy, with primary objectives of determining long-term safety, efficacy, durability, and quality of life outcomes.

To facilitate systematic data collection and ensure capture of the most critical parameters, the ISTH has defined a Gene Therapy Minimum Data Set (GT-MDS) that should be collected on a national basis at specific time points for each patient treated with gene therapy products.⁴⁹ The GT-MDS was developed to ensure capturing the most relevant safety and efficacy parameters recently cited by the European regulatory authorities. The concept of assembling a minimum data set identifies a subset of critical and essential topics that should always be included, rather than creating an entirely new comprehensive dataset.

Such registries will be essential for detecting rare late adverse events, characterizing long-term durability across heterogeneous patient populations, and informing clinical practice guidelines.

Conclusion

Gene therapy for haemophilia has evolved from experimental concept to clinical reality, with AV-based products now approved for adult patients with severe haemophilia A or severe to moderate-severe haemophilia B. These therapies offer transformative benefits including sustained endogenous factor production from a single administration, dramatic reductions in bleeding rates, elimination or substantial reduction of factor replacement requirements, and profound improvements in quality of life. However, significant challenges remain, including immune-mediated hepatotoxicity requiring immunosuppression, declining transgene expression (particularly for haemophilia A), exclusion of patients with pre-existing anti-AAV antibodies (for haemophilia A), uncertainty regarding long-term durability, and substantial cost barriers limiting global accessibility.

Successful implementation requires multidisciplinary care that integrates haematology and hepatology expertise, comprehensive pre-treatment evaluation, intensive post-treatment monitoring, and long-term surveillance. Ongoing research into alternative vector systems, genome editing technologies, enhanced factor variants, and optimized immunosuppression strategies promises to address current limitations and expand the population of eligible patients. As the field matures, development of standardized care protocols, establishment of long-term safety registries, and

implementation of equitable access strategies will be essential to realize gene therapy's potential to fundamentally transform the lives of persons with haemophilia worldwide.

While gene therapy may not yet represent a definitive "cure" for all patients, it unquestionably constitutes a revolutionary advance that has redefined the therapeutic landscape for inherited bleeding disorders and established a roadmap for treatment of other monogenic diseases.

Author Contributions

W.M. wrote the article.

Conflict of Interest

W.M.: Bayer, Biomarin, Biotest, CSL Behring, Chugai, FreeLine, LFB, Novo Nordisk, Octapharma, Pfizer, Regeneron, Roche, Sanofi, sobi, Takeda/Shire, uniQure.

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