Journal Pre-proof

Overcoming Access Barriers in European CAR-T Therapy: The Role of Decentralized Manufacturing and the EASYGEN Framework

D. Narres , A.R. Scheiwe , R. Kuhlen , C. Zech , P. Müller , C. Rische , V. Längst , C. Wegener , L. Schmidt , P. Bothwell , K. Thompson , K. Mestermann , C. Sanges , D. Krones , M. Müller , A. Dünkel , M. Hudecek , U. Koehl , A. Hendel , D. Kashanin , V. Williams , J. Schueler , N. Bolaños , L. McNamara , T. Rintala , A. Sureda , A. Gandjour , T.D. Ahrens , P. Mennig , E.C. Groen , B. Glass , A. Vosen , J. Busch-Casler , M. Radic , A. Teichert , R. Hoffmann , T. Brzoska , C. Pietralla , J.O. Brunner , T. Kagerbauer , C. Zündorf , G.S. Baillie , N. Phanthaphol , F. Prósper , J.R. Rodriguez Madoz , C. Carames , S. Steppan

PII: S1465-3249(26)00900-X
DOI: https://doi.org/10.1016/j.jcyt.2026.102939
Reference: JCYT 102939

To appear in: *Cytotherapy*

Received date: 1 April 2026
Accepted date: 16 June 2026

Please cite this article as: D. Narres , A.R. Scheiwe , R. Kuhlen , C. Zech , P. Müller , C. Rische , V. Längst , C. Wegener , L. Schmidt , P. Bothwell , K. Thompson , K. Mestermann , C. Sanges , D. Krones , M. Müller , A. Dünkel , M. Hudecek , U. Koehl , A. Hendel , D. Kashanin , V. Williams , J. Schueler , N. Bolaños , L. McNamara , T. Rintala , A. Sureda , A. Gandjour , T.D. Ahrens , P. Mennig , E.C. Groen , B. Glass , A. Vosen , J. Busch-Casler , M. Radic , A. Teichert , R. Hoffmann , T. Brzoska , C. Pietralla , J.O. Brunner , T. Kagerbauer , C. Zündorf , G.S. Baillie , N. Phanthaphol , F. Prósper , J.R. Rodriguez Madoz , C. Carames , S. Steppan , Overcoming Access Barriers in European CAR-T Therapy: The Role of Decentralized Manufacturing and the EASYGEN Framework, *Cytotherapy* (2026), doi: https://doi.org/10.1016/j.jcyt.2026.102939

Overcoming Access Barriers in European CAR-T Therapy: The Role of Decentralized Manufacturing and the EASYGEN Framework

Narres* D[1], Scheiwe* AR[1], Kuhlen R[1], Zech C[1], Müller P[1], Rische C[1], Längst V[1], Wegener C[2], Schmidt L[2], Bothwell P[2], Thompson K[2], Mestermann K[3], Sanges C[3], Krones D[3], Müller M[3], Dünkel A[3], Hudecek M[3], Koehl U[3], Hendel A[4], Kashanin[5] D, Williams V[5], Schueler J[6], Bolaños N[7], McNamara L[7], Rintala T[7], Sureda A[7], Gandjour A[8], Ahrens TD[9], Mennig P[9], Groen EC[9], Glass B[10], Vosen A[11], Busch-Casler J[11], Radic M[11], Teichert A,[11] Hoffmann R[12], Brzoska T[13], Pietralla C[14], Brunner JO[14], Kagerbauer T[15], Zündorf C[15], Baillie GS[16], Phanthaphol, N[16], Prósper F[17], Rodriguez Madoz J R[18], Carames C[19], Steppan S[1]

Affiliations:

* Equal first author contribution
[1] Fresenius SE & Co. KGaA, Bad Homburg, Germany
[2] Fresenius Kabi, Germany/USA
[3] Fraunhofer Institute for Cell Therapy and Immunology IZI, Leipzig, Germany
[4]Institute of Nanotechnology and Advanced Materials, The Mina and Everard Goodman Faculty of Life Sciences, Bar-Ilan University, Safed, Israel
[5] Cellix Limited, Dublin, Ireland
[6] Charles River Laboratories Germany GmbH, Freiburg, Germany
[7] European Society for Blood and Marrow Transplantation, Barcelona, Spain
[8]Frankfurt School of Finance & Management, Germany
[9] Fraunhofer Institute for Experimental Software Engineering IESE, Kaiserslautern, Germany
[10] Helios Hospital Berlin-Buch GmbH, Berlin, Germany
[11] Helmholtz-Zentrum Dresden-Rossendorf (HZDR), Dresden, Germany
[12] Philips Intellectual Property & Standards, Eindhoven, The Netherlands
[13] Pro-Liance Global Solutions GmbH, Münster, Germany
[14] Technical University of Denmark (DTU), Kongens Lyngby (Copenhagen Area), Denmark
[15] TQ Therapeutics GmbH, Munich, Germany
[16] School of Cardiovascular and Metabolic Health, University of Glasgow, UK
[17] Hematology and Cell Therapy Department. Clinica Universidad de Navarra. Cancer Center Clinica Universidad de Navarra (CCUN). Centro de Investigacion Biomedica en Red de Cancer (CIBERONC). IdiSNA. Pamplona, Spain
[18] Hemato-Oncology Program. Cima Universidad de Navarra. Cancer Center Clinica Universidad de Navarra (CCUN). Centro de Investigacion Biomedica en Red de Cancer (CIBERONC). IdiSNA. Pamplona, Spain
[19] Quirónsalud Healthcare Network, Madrid, Spain

Correspondence: Dominik.Narres@fresenius.com, Fresenius SE & Co. KGaA, Germany

Abstract

Chimeric antigen receptor T-cell (CAR-T) therapies have revolutionized the treatment of refractory B-cell malignancies, with seven approved therapies in major jurisdictions and rapid label expansion toward earlier lines of treatment. Nevertheless, patient access remains limited by multiple bottlenecks, including shortages of lentiviral vectors, manufacturing capacity constraints, and economic factors, such as prolonged production timelines, high treatment costs and associated reimbursement challenges, and long travel distances for patients to specialized CAR-T treatment centers. Recent advances in non-viral gene delivery, automated bioprocessing, and *in vivo* T-cell engineering promise to compress production timelines and reduce costs, thereby enabling broader indications, including solid cancers and autoimmune diseases.

This review provides an overview of autologous manufacturing and delivery bottlenecks across Europe, outlines rapid manufacturing technologies and decentralized production models, and analyzes the regulatory and scientific frameworks that govern the implementation of advanced therapy medicinal products (ATMPs). In addition, it surveys non-viral and *in vivo* CAR-T therapy approaches and summarizes the contributions of pan-European consortia dedicated to harmonizing clinical translation, automation, and real-world data integration.

The EASYGEN "EASY workflow integration for GENe therapy" consortium (Grant-ID: 101194710), funded under the Innovative Health Initiative (IHI) Call 7.2 ("User-centric technologies and optimized hospital workflows for a sustainable healthcare workforce"), aims to operationalize these advances by building a modular platform for CAR-T and gene-modified immune-cell manufacturing. EASYGEN unites industrial, clinical, and academic partners to propose a scalable, decentralized point-of-care CAR-T manufacturing solution, implementing next-generation technologies such as non-viral gene transfer at the point-of-care (PoC) with interoperable data standards across multiple European sites. The consortium aims to provide a blueprint for equitable advanced therapy production and regulatory integration, while also easing hospital workflows and reducing the burden on healthcare staff by minimizing administrative complexity and coordinating inclusive data harmonization efforts within hospitals.

Beyond operational efficiency, the consortium aims to highlight how reduced vein-to-vein time, decentralized production, and improved hospital workflows may translate into fewer patients deteriorating or becoming ineligible during waiting periods.

Keywords

CAR-T; CAR-T decentralized manufacturing; European consortia; non-viral gene delivery; EASYGEN; access gap; point-of-care

Introduction

Manufacturing limitations of current CAR-T workflows

CAR-T cell therapy exemplifies the promise of personalized immuno-oncology, yet simultaneously exposes structural weaknesses in manufacturing, logistics, regulatory complexity, and health-system readiness. Since the first marketing authorizations in Europe in 2018[1], real-world adoption has diverged markedly between European countries. In 2023, European health system analyses indicated that only 11%- 30% of eligible patients in the five largest EU markets received treatment despite full reimbursement, as shown in Table 1[2].

These findings highlight a widening gap between clinical eligibility and real-world access as CAR-T indications expand, underscoring that regulatory approval and reimbursement alone are insufficient to ensure equitable delivery across European health systems.

These disparities reflect multifactorial and nationally variable barriers, including delayed referrals, limited certified centers, complex regulatory and operational requirements for program launch, budget-impact negotiations, and long vein-to-vein times that cumulatively restrict throughput and increase patient fall-off[2]. Despite regulatory approval and nominal funding, operational constraints remain decisive determinants of access to CAR-T cell therapy.

Challenges and limitations in manufacturing capacity describe the following systemic mismatch:

Manufacturing slot scarcity, limited healthcare capacity, shortages of specialized clinical staff, heterogeneous site certification and requirements, non-standardized communication and referral processes, and delayed reimbursement approvals collectively prolong the time to treatment, resulting in a dilemma of medical urgency outpacing fragmented system capacity, thereby delaying treatment initiation despite clinical eligibility[3].

Clinical and ethical implications for patients

Comparative evaluations demonstrate that vein-to-vein times exceeding 40 days are associated with significantly lower overall survival relative to manufacturing cycles below 28 days[4]. Deteriorating clinical conditions that cause performance status to decline can render patients ineligible for therapies that they were initially eligible for.

From a patient perspective, prolonged vein-to-vein times are not merely operational delays but represent periods of clinical uncertainty, psychological distress, repeated hospitalizations, and risk of disease progression that may ultimately preclude treatment eligibility.

These repeated hospitalizations also place a substantial burden on hospital systems, tying up inpatient capacity, increasing clinical staff workload, and driving up costs for payors through prolonged admissions, interim treatments, and unplanned care. Real-world analyses have shown that a substantial proportion of patients clinically deteriorate or die while awaiting CAR-T manufacture, underscoring that access delays directly translate into lost therapeutic opportunity[4,5] .

Current approaches to addressing manufacturing constraints

National strategies in Europe to reduce inequities include center expansion and streamlined referral pathways in France, decentralized manufacturing pilots in Spain, and registry-linked reimbursement frameworks in Italy, whereas Germany has adopted outcome-based reimbursement models with a primary focus on cost control[6].

However, from a patient-access perspective, the gap between regulatory approval and effective service delivery continues to cause significant delays, geographic inequities, and attrition along the treatment pathway, with direct consequences for disease control and treatment eligibility. For patients, these systemic barriers translate into long travel distances to specialized centers, complex referral pathways, and treatment delays that increase the risk of disease progression during critical care windows.

Expanding production capabilities, digitalized quality management, and harmonized data infrastructures are therefore essential to realize the full therapeutic potential of CAR-T cells and future advanced therapies[6,7].

EASYGEN is a European multi-stakeholder initiative focused on advancing scalable, high-quality, and patient-centered CAR-T manufacturing by integrating production processes across hospital environments. Drawing on operational experience across European health systems, EASYGEN brings together clinical, manufacturing, and health system perspectives to examine how manufacturing design, process standardization, and system coordination influence real-world access to CAR-T therapies.

The objective of this perspective paper is to describe the current European CAR-T manufacturing landscape, analyze emerging manufacturing and delivery models, and identify opportunities for standardization that may reduce time-to-treatment, mitigate patient attrition, defined here as the proportion of clinically eligible patients who are unable to receive CAR-T therapy due to disease progression, clinical deterioration, or system-level delays prior to infusion, and improve equity of access. This perspective synthesizes published evidence, real-world analyses, and cross-country experience to inform future manufacturing strategies for CAR-T and other advanced therapies.

Current European CAR-T manufacturing landscape

Overview of CAR-T manufacturing pathways & delivery frameworks in Europe

In Europe, commercially authorized products are typically manufactured in a centralized, industrial manner, in which vein-to-vein coordination from collection and manufacturing through distribution plays a defining operational role. This pathway sits within the EU's ATMP regulatory framework, with European Medicines Agency (EMA) guidance and ATMP-specific GMP expectations supporting a risk-based approach to complex manufacturing scenarios.

Additionally, the delivery framework is reinforced by quality systems and accreditation standards for centers - most notably the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the Foundation for the Accreditation of Cellular Therapy (FACT).

Some countries, on the other hand, also operate national “hospital exemption” routes for certain custom-made ATMP uses under defined conditions, creating an additional access pathway alongside centrally authorized products.

Manufacturing constraints and delivery bottlenecks in Europe

Manufacturing capacity remains a principal rate-limiting step in CAR-T deployment. Although commercial production has expanded since initial licensure, limitations persist in viral vector manufacturing, batch scheduling, and skilled workforce availability[8]. Lentiviral and retroviral vectors are complex biologics requiring multi-step plasmid production, transient transfection, and rigorous quality control. Global shortages of viral vectors and critical upstream raw materials have repeatedly disrupted supply chains[9]. Conventional CAR-T manufacturing relies on viral vectors for gene delivery, which limits the size and complexity of the genetic cargo that can be introduced. Autologous CAR-T manufacturing also involves sequential, time-intensive processing steps. A single autologous CAR-T product typically requires 7 - 14 days of *ex vivo* culture followed by 7 - 14 days of release testing, during which the patient’s disease may progress, or the patient may even die before the product is ready (Figure 1A)[10,11]. These manufacturing timelines directly shape clinical scheduling and treatment feasibility.

Logistical challenges between manufacturing and care delivery

Scalability across certified facilities remains uneven. Qualified good-manufacturing-practice (GMP) cleanrooms and experienced operators are concentrated in only a limited number of tertiary hospitals[2,12]. Geographic concentration leads to inequitable access and logistical bottlenecks, particularly in regions lacking domestic manufacturing nodes[2,12].

Heterogeneity in approval timelines and data collection

Beyond technical constraints, economic and regulatory heterogeneity compound these challenges[13]. Temporary hospital-based reimbursement mechanisms and country-specific managed-entry agreements generate uncertainty for both centers and payers[14]. Health-technology-assessment (HTA) timelines vary widely, with lags exceeding 12 months between EMA authorization and national listing in some jurisdictions[15].

To address data fragmentation, coordinated registry networks have emerged under the European Society for Blood and Marrow Transplantation (EBMT) and allied coalitions, linking hospital, payer, and pharmacovigilance datasets[16,17]. Yet

interoperability gaps and divergent definitions of outcomes limit cross-country comparability. As a result, real-world evidence, essential for value-based contracting and post-authorization monitoring, remains partial[18].

System-level bottlenecks - manufacturing throughput, workforce distribution, reimbursement heterogeneity, and data silos - continue to impede equitable CAR-T access throughout Europe.

Operational levers and process innovation

The transition from manual, open manufacturing to automated, decentralized manufacturing represents paradigm shifts for cell therapies. Conventional CAR-T processes involve sequential unit operations, such as leukapheresis collection and logistics, enrichment, activation, transduction, expansion, harvesting, and quality testing, often performed manually in open systems in GMP-certified laboratories to ensure safety. Each step introduces contamination risk and variability, limiting reproducibility and scalability. Figure 1A depicts the current CAR-T manufacturing process[19,20]. Figure 1B, by contrast, shows the process as envisioned by the EASYGEN consortium.

Emerging platforms integrate these operations into single modules, enabling end-to-end production in contained environments[21]. Such systems support PoC manufacturing in hospital cleanrooms, eliminating long-distance cryo-shipment and potentially shortening vein-to-vein intervals to as little as a few days[12]. Several decentralized manufacturing approaches have already entered clinical evaluation and provide important operational insights. Academic programs such as ARI-0001 and MB-CART19.1 demonstrated the feasibility of point-of-care CAR-T manufacturing using automated closed-system platforms such as CliniMACS Prodigy®. Similarly, the CellPoint/Galapagos decentralized manufacturing strategy utilized the Cocoon® platform to establish distributed near-patient manufacturing networks across multiple European sites in studies including ATALANTA-1, EUPLAGIA-1, and PAPILIO-1. These initiatives demonstrated several potential advantages of decentralized manufacturing, including reduced vein-to-vein time, minimized cryoshipment requirements, increased scheduling flexibility, and improved local manufacturing autonomy. In addition, modular industrial systems permit scale-out manufacturing through parallelized bioreactor units and digital process control[22,23]. For a comprehensive list of rapid and/or automated CAR-T manufacturing platforms identified by literature search, refer to Table 2.

However, these real-world programs also highlighted important limitations and implementation challenges. Distributed manufacturing requires harmonization of GMP standards across sites, standardized release testing and product comparability frameworks, robust digital interoperability, and coordinated pharmacovigilance oversight. In addition, decentralized manufacturing remains resource-intensive, requiring specialized workforce training, local cleanroom

infrastructure, and sustainable economic models that support geographically distributed production networks.

Importantly, the functional operability of these automated platforms is increasingly supported by positive outcomes in centralized manufacturing, where closed, end-to-end systems have demonstrated robustness, reproducibility, and regulatory acceptance in the production of approved CAR-T therapies[24,25]. Large-scale industrial deployments further indicate that modular, digitally controlled platforms can support parallelized manufacturing across multiple programs[24]. In parallel, components of these systems are being evaluated in clinical studies for decentralized manufacturing[26], suggesting that automation concepts validated in centralized settings may be transferable to hospital-based workflows.

Besides automating manufacturing, reducing the duration of key steps is another operational lever. Platforms like T-Charge, NEX-T, and FasT CAR-T explore eliminating *ex vivo* expansion to preserve the stemness of CAR-T cells, thereby achieving higher potency while eliminating days of manufacturing time. Emerging data show that short-expansion or no-expansion CAR-T cells achieve superior persistence and anti-tumor activity in animal models and early clinical studies, by preserving stem-like phenotypes. The reduction of *ex vivo* cell expansion maintains the stemness of the CAR-T cells, which achieved a higher potency after infusion [27-30].

Despite technical promises, widespread implementation faces barriers related to infrastructure and training. The installation of closed systems, e.g., CliniMACS Prodigy®, Cocoon®, or Quantum® cell expansion systems, demands validation procedures [12,24,31,32]. Smaller centers often lack resources for GMP certification or the informatics capacity for digital quality-by-design (QbD) integration[33]. Furthermore, existing regulatory pathways for distributed manufacturing remain under-defined, creating uncertainty over release authority and pharmacovigilance responsibilities[34,35].

Digitalization and data infrastructure

Digitalization in CAR-T manufacturing extends beyond automated hardware platforms and requires robust data infrastructure, interoperable IT systems, and digitally trained personnel to ensure traceability, compliance, and scalability.

European initiatives dedicated to CAR-T standardization have begun to address these issues by defining reference process templates and operator training curricula, and by harmonizing regulatory guidance[36]. As automation matures, integration with non-viral gene transfer and *in vivo* approaches will define the next phase of manufacturing innovation.

Emerging models and technological approaches

Non-Viral gene-transfer approaches and other gene-editing tools for CAR-T manufacturing

To overcome scalability issues and genetic cargo restrictions in viral gene editing methods, research has focused on *in vivo* CAR-T strategies and non-viral gene-transfer systems that bypass *ex vivo* cell manipulation and expansion (refer to supplementary Tables S1 and S2 for an overview of ongoing clinical trials)[37-39].

Transposon-based systems, such as Sleeping Beauty, TcBuster, and piggyBac, permit stable and semi-random genomic integration using plasmid DNA delivered by electroporation, eliminating the need for viral vector production[39,40]. Bioprocess and economic analyses suggest that replacing lentiviral or retroviral vectors with transposon/plasmid platforms can reduce vector-related manufacturing costs by roughly 60–80%, depending on scale and process assumptions[41].

Several first-in-human trials, e.g., the CARAMBA trial employing Sleeping Beauty-engineered CAR-T cells targeting SLAMF7, have demonstrated feasibility with response rates comparable to viral approaches and lower vector-related toxicity[42]. However, electroporation can compromise viability and transposition efficiency, necessitating optimization of cell activation and transposase expression[38,43].

At the same time, the genomic safety profile of transposon-based delivery systems requires careful consideration. Preclinical trials suggest that Sleeping Beauty transposase has a close-to-random integration profile in activated T cells[44], reducing but not eliminating the theoretical risk of insertional mutagenesis. So far, no genotoxicity (malignant transformation due to insertion), as described for the Piggyback system[45], has been observed in clinical trials using SB Transposase[46]. However, clinical experience is limited, and genomic safety must be demonstrated in ongoing long-term studies. In addition, ongoing research is developing transposase variants with better-defined half-lives or switchable approaches, which could enhance system safety and may be incorporated into EASYGEN in the future.

Beyond integrating approaches, transiently expressed, non-integrating gene-transfer systems - most prominently mRNA-based delivery - have gained substantial clinical validation in non-oncology settings, e.g., autoimmune disease, demonstrating scalable, GMP-compatible manufacturing and favorable safety profiles. While transient CAR expression is generally insufficient for durable anti-tumor responses in oncology, mRNA-based platforms are being explored for rapid prototyping, functional screening, and short-lived immunomodulation (e.g., Descartes-08, a BCMA-targeted non-viral CAR-T currently in Phase 3 for autoimmune indications; see Supplementary Table S2). These approaches may serve as enabling tools for next-generation CAR design, combination strategies, or *in vivo* reprogramming concepts[47].

Other gene-editing tools, such as CRISPR–Cas9 and TALEN, enable precise & targeted knock-in at safe-harbor loci, supporting both autologous and allogeneic "off-the-shelf" constructs[38]. These technologies facilitate multiplex engineering for immune evasion or logic-gated activation while maintaining defined genomic integration. Ongoing clinical studies have shown promising early safety, with low off-target rates and durable in vivo persistence, as well as reduced risks of graft-versus-host disease and host immune rejection, when considering CRISPR-engineered immunotherapy[48].

Allogeneic CAR-T approaches

Emerging allogeneic ("off-the-shelf") CAR-T approaches aim to address the limitations of autologous manufacturing by enabling scalable, pre-manufactured cell products derived from healthy donors. Allogeneic platforms aim to enable a shorter time to treatment, since CAR-T cells can be manufactured in batches at an industrial scale with more predictable product quality. This simplifies logistics and lowers costs across European healthcare systems[41]. However, key challenges remain, including limited *in vivo* persistence, immune-mediated clearance, and the need for intensified lymphodepletion[49]. For a complete list of ongoing allogenic CAR-T trials, see supplementary Table S3.

In vivo CAR-T approaches

Parallel advances in *in vivo* CAR-T generation aim to deliver vectors to express CAR constructs directly to lymphocytes within the patient using targeted lipid nanoparticles (LNPs), DNA nanoparticles, or engineered viral envelopes[50-52]. Preclinical data suggest that *in vivo* transfection or transduction of circulating T-cells can yield sufficient CAR expression to mediate tumor clearance without leukapheresis or *ex vivo* expansion[53-56]. Early-phase clinical and translational studies are beginning to apply *in vivo* CAR or CAR-like strategies in hematologic malignancies and immune-mediated diseases[57-59]. While translatability remains nascent, these innovations collectively mark a transition toward programmable immune engineering with simplified logistics and reduced dependence on infrastructure. For a list of ongoing in-human trials using *in vivo* approaches, refer to the supplemental data.

At the same time, alongside these ongoing technological innovations, collaborative efforts at the European level have also intensified.

Across Europe, multiple collaborative initiatives have emerged to address complementary barriers limiting broader CAR-T implementation, including manufacturing scalability, regulatory harmonization, data interoperability, toxicity prediction, reimbursement frameworks, and real-world evidence generation. Rather than functioning as isolated research programs, these consortia collectively reflect a broader transition toward integrated, system-level approaches to deploying advanced therapies. Importantly, their combined experience highlights

that the future feasibility of decentralized CAR-T manufacturing depends not only on technological innovation but equally on harmonized regulatory oversight, interoperable digital infrastructure, workforce readiness, and sustainable health-system integration. Within this evolving ecosystem, EASYGEN builds specifically on prior European efforts by focusing on rapid, non-viral, point-of-care manufacturing workflows and their integration into routine hospital operations.

T2EVOLVE was a public–private research consortium funded under the Innovative Medicines Initiative (IMI2) with an EU contribution of approximately €8.7 million and a total budget of around €19 million, running from 2021 to 2025 and coordinated by the University Hospital Würzburg; the project focused on standardizing and accelerating the development, safety assessment, and clinical translation of CAR- and TCR-engineered T-cell therapies by establishing predictive tools, shared methodologies, and regulatory guidance. Meanwhile, it has transitioned to an association to enable further collaboration to generate impact in the area of CAR-T cell therapy[60].

The GoCART Coalition is a European industry–academia collaboration supported through EU Horizon programs, coordinated by an academic–industrial steering group, and aims to enable modular, automated, and decentralized manufacturing of CAR-T therapies at or near the PoC. The initiative addresses critical bottlenecks related to manufacturing speed, cost, and scalability[61].

AIDPATH (Artificial Intelligence-Driven Production of Advanced Therapies for Personalized Healthcare) was funded under the EU Horizon 2020 program from 2021 to 2024 and coordinated by a European academic consortium including Fraunhofer institutes; it focused on integrating artificial intelligence, automation, and digital process control into decentralized manufacturing workflows for advanced cell therapies to improve robustness, reproducibility, and access[62].

JOIN4ATMP is a Horizon Europe Coordination and Support Action funded by the European Union with approximately €3 million for the period 2024 to 2026 and coordinated by Charité – Universitätsmedizin Berlin; its objective is to map and connect European ATMP activities and to identify regulatory, clinical, organizational, and economic barriers, translating these insights into actionable recommendations to improve patient access[63].

The IHI joint undertaking “EASY workflow integration for GENe therapy” EASYGEN (2025–2030) complements and extends earlier consortia such as T2EVOLVE and CARAMBA by focusing explicitly on the next generation of viral and non-viral gene-transfer platforms. Its objectives include developing GMP-compatible non-viral delivery methods, validating integrated automation lines at the PoC, and establishing shared regulatory and data frameworks across participating countries. Collectively, EASYGEN represents a cornerstone European effort to overcome the technological and regulatory barriers that have

constrained CAR-T scalability, while strengthening Europe's capacity for equitable and sustainable advanced-therapy manufacturing[64].

A major bottleneck in personalized cell therapy manufacturing is the large-scale isolation of defined target cell populations. Immunoaffinity-based cell selection using reversible binding reagents enables traceless, highly specific isolation within a closed and GMP-compliant process, while allowing integration of downstream steps such as controlled activation and gene modification[65].

EASYGEN directly addresses CAR-T manufacturing challenges by integrating rapid T-cell selection, non-viral gene transfer via transposon technology, minimized activation, and the absence of *ex vivo* expansion steps, thereby enabling shorter PoC bioprocessing. With this, EASYGEN proposes a forward-looking manufacturing paradigm to reduce core processing time from several weeks to less than 24 hours. This target is a design objective of the EASYGEN approach rather than an established clinically validated end-to-end outcome and is being tested within the EASYGEN work packages. The total turnaround will also depend on the quality release duration.

Limiting *ex vivo* manipulation is essential to preserve naïve and stem-like T-cell populations, which are critical determinants of robust *in vivo* expansion and antitumor efficacy, as previously described[39,40].

By integrating cell selection, activation, and gene modification into a single continuous workflow of approximately six hours and deliberately avoiding *ex vivo* expansion, this approach is designed to shift cellular proliferation to the *in vivo* setting, thereby preserving T-cell stemness and enabling effective post-infusion expansion (Figure 1B).

At the same time, reliance on non-viral gene transfer and minimized *ex vivo* activation may involve trade-offs in transgene delivery efficiency, product consistency, and functional potency. These parameters, as well as overall process integration, scale-up, and implementation of rapid quality control strategies, will require further process optimization, investigated throughout the EASYGEN project, and will ultimately determine achievable clinical vein-to-vein timelines. Several technical questions also remain open, including control of contaminating cell populations during selection, the risk of unintended gene modification in non-target cells, transgene delivery efficiency in minimally activated T cells, post-electroporation viability, product shelf life after formulation, and the definition of clinically relevant dosing strategies.

In addition, a fresh-in/fresh-out approach may shorten logistics and avoid cryopreservation, but it also compresses clinical scheduling. Standard lymphodepletion regimens administered several days before infusion may not align with a <24-hour workflow, and the limited shelf life of fresh-formulated

products reduces flexibility for rescheduling, underscoring the need for adapted treatment pathways.

Quality risks, safety, and quality control considerations for EASYGEN

A clinically achievable vein-to-vein timeline will therefore depend not only on accelerated manufacturing, but also on the development of integrated, fit-for-purpose quality control and release strategies.

The new POC rapid CAR T manufacturing process requires a two-step procedure for end-to-process quality control (QC). At the time point of harvesting, validated QC for purity, impurity, and viability of the rapidly manufactured CAR T cells for final release can be performed in the same way as conventional CAR T cells produced in a two-week process, as recently described[66]. In contrast, CAR expression/detection, as well as safety release testing such as sterility, endotoxin, and mycoplasma testing, require up to 14 days when performed in the classical validated way. As a result, these values are not available until days after the CAR T-cell administration. For both, new and fast QC must be established during process optimization and validation. Regarding transduction efficacy, orthogonal assays that are not reliant on surface CAR expression will be established and validated. For rapid sterility testing, new cytometry assays using fluorescently labeled microorganisms as well as 16S/18S amplicon sequencing can be performed within hours, as currently developed by Thermofisher, CharlesRiver, Qiagen, bioMérieux and others. Where selected quality attributes cannot be fully confirmed prior to infusion, implementation will need to be coupled to predefined post-infusion monitoring and risk-mitigation strategies to ensure patient safety. In addition, retention samples of the final product may provide an important safeguard by enabling retrospective testing in the event of unexpected clinical outcomes.

Finally, in the long run, the QC assays should be integrated into an automated platform that includes inline sensors, machine learning, digital concepts, and the corresponding software architecture, enabling remote oversight and real-time review of critical process parameters, as well as early intervention when predefined controls are not met.

A further prerequisite for broader point-of-care implementation will be stepwise process validation focused on sterility assurance and contamination control, with the longer-term aim of determining whether robust closed-system performance can justify progressive reduction of surrounding cleanroom requirements.

Accordingly, the EASYGEN concept should be understood as a forward-looking manufacturing objective whose clinical implementation will require further technical, operational, and regulatory validation.

Manufacturing equity and access

Persistent disparities in European access reveal that regulatory approval alone is insufficient for equitable delivery. Empirical analyses of registry and reimbursement data demonstrate strong correlations between manufacturing turnaround and patient survival[2,4,6,16,31].

Increasingly, challenges in CAR-T deployment should be interpreted through a health-system readiness lens. Readiness encompasses not only reimbursement and regulatory approval, but also workforce capacity, referral coordination, data infrastructure, manufacturing proximity, and institutional experience.

Decentralized, automated production, enabled by closed systems and standardized analytics, offers a pragmatic mechanism to reduce geographic inequity while maintaining compliance.

Clinical experience from ARI-0001, MB-CART19.1 TranspoCART19, and CellPoint/Galapagos programs suggests that local manufacturing may reduce logistical delays, improve treatment accessibility for geographically distant patients, and decrease dependency on centralized manufacturing capacity. These models may also reduce the need for prolonged bridging therapy and repeated hospitalizations during manufacturing wait times. Nevertheless, the scalability and sustainability of decentralized manufacturing remain incompletely resolved. Existing programs illustrate that regulatory harmonization, inter-site comparability, workforce availability, and distributed quality oversight represent major barriers to broader implementation.

From this perspective, decentralized and point-of-care manufacturing models represent not merely technological innovation but potential system-readiness interventions capable of reducing structural barriers that currently prevent eligible patients from reaching treatment.

However, decentralized models challenge existing regulatory assumptions about product release and pharmacovigilance oversight[35,67]. A unified European framework for distributed ATMP manufacturing would reduce these uncertainties while ensuring harmonization of quality.

Patient-centered access

A patient-centered perspective reframes manufacturing innovation as a determinant of timely access, continuity of care, and treatment feasibility. Delays in referral, production, and reimbursement disproportionately affect patients with aggressive disease, those living far from certified centers, and individuals with limited social support. Initiatives such as EASYGEN offer an opportunity to embed patient experience considerations, such as travel burden, caregiver availability, and tolerance for prolonged uncertainty, into manufacturing and deployment models, aligning technological innovation with real-world patient needs.

Regulatory science and real-world data

The EU's ATMP Regulation 1394/2007 predates many recent bioprocessing innovations, creating a misalignment between regulatory expectations and modern manufacturing realities[68]. Initiatives such as adaptive licensing, risk-based GMP, and the hospital-exemption pathway have introduced flexibility but vary markedly across Member States[68,69]. Integrating digital process data and real-world outcomes into regulatory assessment – as envisaged in recent work on digital health and real-world evidence – could enable more dynamic, lifecycle-based oversight analogous to continuous manufacturing paradigms in small molecule production[70]. Collaborative registry infrastructures - particularly those developed by the European Society for Blood and Marrow Transplantation (EBMT) within the GoCART coalition - provide a foundation for such evidence ecosystems, though interoperability and data privacy compliance remain ongoing challenges[16,71]. Within this context, the IMI-funded T2EVOLVE consortium contributed to the development of regulatory-relevant data frameworks, including the CORE CAR-T dataset, and advanced efforts to harmonize national CAR-T registries by defining common data elements across manufacturing, clinical, and long-term follow-up domains. In addition, T2EVOLVE led a pan-European patient-reported outcomes (PRO) initiative, demonstrating the feasibility and value of systematically capturing multidimensional patient experience data across countries and care settings. This work highlighted persistent physical, mental, social, and financial burdens following CAR-T therapy and underscored the importance of integrating PROs alongside clinical endpoints in real-world evidence generation, regulatory evaluation, and health technology assessment.[72]

Regulatory feasibility for models such as EASYGEN will depend on the evolving European framework for decentralized ATMP manufacturing. Recent EU reform efforts and the 2025 EMA concept paper on revision of GMP Part IV suggest increasing recognition of automated, closed, and potentially decentralized manufacturing platforms, but feasibility will still require robust process controls, clear release responsibilities, site-to-site consistency, and integrated pharmacovigilance and traceability across centers. Under hospital-exemption pathways, additional complexity arises from heterogeneous national implementation, although ongoing reforms point toward stricter quality expectations and greater transparency.[73]

The incorporation of patient-reported outcomes (PROs) and experience measures into registry infrastructures would further strengthen the real-world evidence ecosystem. PROs capturing symptom burden, functional recovery, and quality of life post-CAR-T treatments could complement clinical endpoints and support more holistic regulatory and HTA decision-making.

Technological convergence and future directions

The evolution of CAR-T therapy is currently defined by a "technological convergence," in which the boundaries among biology, digital modeling, and medical devices are permanently blurred. Central to this shift is the deployment of automated bio-processors that function as “digital twins.” By generating high-dimensional, real-time datasets, these systems facilitate advanced process modeling and predictive release testing. This is not merely a technical upgrade but a clinical necessity for decentralized models: where traditional, multi-week ex vivo expansion is omitted, patient safety must be guaranteed through closed-system CAR-T engineering and sensor-based, automated quality monitoring rather than longitudinal observation[74,75]. In parallel, the emergence of in vivo CAR-T platforms represents a fundamental paradigm shift, migrating cell production from a controlled laboratory environment directly into the patient’s systemic circulation. This transition redefines regulatory frameworks, as the intervention begins to operate as a hybrid entity: a medical device (the targeted delivery vector) that generates a medicinal product (the CAR-T cell) in situ.

The future of CAR-T therapy lies in a convergent Point-of-Care ecosystem that bridges the gap between biological complexity and clinical accessibility. By evolving automated bio-processors into "digital twins" capable of predictive release testing, the field can transition from reactive testing to real-time quality assurance, moving the aspirational <24-hour vein-to-vein timeline toward a validated reality. Addressing inherent genotoxicity and regulatory risks through high-fidelity, non-viral precision engineering—such as Sleeping Beauty transposon systems—will be critical to ensure the safety and metabolic fitness of non-expanded products. Ultimately, implementing fully closed-system manufacturing will allow CAR-T production to safely bypass traditional clean rooms. This shift necessitates a new "multilingual" professional profile that integrates cell biology, bioinformatics, and systems engineering to manage the next generation of decentralized therapeutic networks at the hospital bedside.

Ethical and societal considerations

Accelerated & personalized production raises complex ethical issues concerning patient prioritization, data ownership, and equitable distribution. The introduction of *in vivo* delivery may shift risk profiles toward systemic exposure and germline editing concerns, requiring proactive ethical review and transparent patient communication[77]. Policymakers and consortia must therefore embed ethics-by-

design principles into translational pipelines, ensuring societal legitimacy alongside technical progress[5,78].

Beyond ethical considerations, manufacturing innovation also has important implications for long-term affordability and payment sustainability. Reduced reliance on viral vectors, shortened production cycles, and more decentralized manufacturing models have the potential to alleviate key cost drivers that currently constrain payer readiness. In turn, these structural changes may enable greater adoption of outcomes-based or staged payment models, allowing health systems to better manage short-term budget impact while maintaining patient access to high-value therapies. In summary, the current phase of CAR-T evolution is characterized more by manufacturing and regulatory transformation than by incremental biological improvement. Sustained collaboration among consortia, regulators, and clinicians will determine whether these innovations translate into durable patient benefit and sustainable health-system integration.

Leveraging the EASYGEN Consortium to Address Systemic Gaps

The EASYGEN consortium is organized into dedicated work packages spanning process management, stakeholder engagement, regulatory strategy, device optimization with embedded digital Quality-by-Design elements, next-generation CAR-T treatment, and PoC deployment, as illustrated in the consortium work-package architecture depicted in Figure 1C. Within the framework of the IHI joint undertaking, co-funded by the European Union, the consortium develops and validates an end-to-end manufacturing approach that links academic GMP facilities, experts in process optimization, industrial manufacturing technology providers, and clinical centers across these work packages. By embedding regulatory and health-technology assessment from inception, EASYGEN aims to transform CAR-T manufacturing from an engineering solution into a translatable framework for future PoC ATMP production across Europe[37].

From an equity perspective, rapid PoC manufacturing models have the potential to mitigate geographic disparities by reducing reliance on centralized CAR-T production facilities. Shorter manufacturing timelines may also decrease the need for intensive bridging therapies and prolonged inpatient monitoring, thereby lowering indirect costs borne by patients and families while simultaneously reducing overall hospital resource utilization, including inpatient bed occupancy, intensive monitoring capacity, and associated staffing requirements.[79,80].

This strategy greatly reduces processing time by several days and helps circumvent capacity constraints in centralized facilities[81]. In this context, the EASYGEN work contributes to hospital workflow optimization by exploring the integration of rapid point-of-care CAR-T manufacturing into existing clinical pathways, reducing logistical complexity, coordination, and documentation demands.

Conclusion

Advances in automation, non-viral gene delivery, and *in vivo* engineering collectively redefine feasibility, cost structures, and the potential for more equitable access.

European consortia have laid the groundwork for regulatory harmonization and shared infrastructure. Still, sustained policy commitment and investment in digital competencies are required to translate these advances into routine clinical access. Patients and advocacy groups stress that innovation must be measured not only by scientific breakthroughs but by tangible improvements in access, reduced geographic disparities, and the ability of health systems to deliver therapies when they are needed most.

Importantly, decentralized manufacturing should not be viewed as a hypothetical future concept, but rather as an evolving clinical reality already explored through multiple academic and industrial CAR-T programs. Existing decentralized manufacturing initiatives have demonstrated meaningful opportunities to improve manufacturing agility and patient accessibility, while also revealing substantial regulatory, logistical, and economic complexities that must be addressed before widespread implementation is achievable.

Despite substantial technological progress, significant gaps remain in the delivery of CAR-T therapies across Europe, particularly regarding manufacturing capacity, geographic accessibility, production timelines, and the resulting inequities in patient access. Ultimately, the success of initiatives such as EASYGEN should therefore be measured not only by manufacturing speed or technical feasibility, but by their ability to address these persistent barriers and ensure that eligible patients can access CAR-T therapies in a timely, equitable, and sustainable manner, with outcomes that matter to patients, caregivers, and health systems alike. While reduced vein-to-vein times are expected to improve patient access and reduce attrition, the extent to which rapid manufacturing approaches translate into durable clinical outcomes and sustainable healthcare, as well as their scalability and cost-effectiveness, requires prospective evaluation.

Positioned at the intersection of science, engineering, and health-system policy, the EASYGEN framework aims to address key gaps in manufacturing and access outlined in this analysis, illustrating how collaborative innovation can enable the next generation of patient-centered cell therapies.

Acknowledgements

The authors acknowledge support from the EASYGEN - “EASY workflow integration for GENe therapy” consortium (Grant-ID: 101194710), funded under the Innovative Health Initiative (IHI) Call 7.2: “User-centric technologies and optimized hospital workflows for a sustainable healthcare workforce.” This support contributed to the development and execution of the research presented in this review.

Conflict of interest:

The authors declare that several contributors are members of the EASYGEN consortium, which is referenced and discussed within this work. This relationship constitutes a potential conflict of interest. All such affiliations have been fully disclosed. The authors confirm that the research and its interpretation have been conducted independently and in accordance with principles of scientific integrity.

References

1. Ali S, Kjeken R, Niederlaender C, et al. The European Medicines Agency Review of Kymriah (Tisagenlecleucel) for the Treatment of Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma. *The Oncologist*. 2020;25(2):e321-e327.
2. Achieving CAR T-cell Therapy Health System Readiness IQVIA Institute for human data science; 2025.
3. Sureda A, Adam SE, Yang S, et al. Logistical challenges of CAR T-cell therapy in non-Hodgkin lymphoma: a survey of healthcare professionals. *Future Oncol*. 2024;20(36):2855-2868.
4. Locke FL, Siddiqi T, Jacobson CA, et al. Impact of vein-to-vein time in patients with R/R LBCL treated with axicabtagene ciloleucel. *Blood Adv*. 2025;9(11):2663-2676.
5. Chen CI, Bell JAH. Ethical Prioritization of Patients to CAR T-Cell Therapies: Tool Development and Process. *Blood*. 2022;140(Supplement 1):2406-2407.
6. Canales Albendea M, Canonico PL, Cartron G, et al. Comparative analysis of CAR T-cell therapy access for DLBCL patients: associated challenges and solutions in the four largest EU countries. *Front Med (Lausanne)*. 2023;10:1128295.
7. European Commission DG Health and Food Safety and European Medicines Agency Action Plan on ATMPs; 2025:6.
8. Dunbar CE, High KA, Joung JK, Kohn DB, Ozawa K, Sadelain M. Gene therapy comes of age. *Science*. 2018;359(6372).
9. Milone MC, O'Doherty U. Clinical use of lentiviral vectors. *Leukemia*. 2018;32(7):1529-1541.
10. Yang J, He J, Zhang X, et al. Next-day manufacture of a novel anti-CD19 CAR-T therapy for B-cell acute lymphoblastic leukemia: first-in-human clinical study. *Blood Cancer Journal*. 2022;12(7):104.
11. Vadgama S, Pasquini MC, Maziarz RT, et al. "Don't keep me waiting": estimating the impact of reduced vein-to-vein time on lifetime US 3L+ LBCL patient outcomes. *Blood Advances*. 2024;8(13):3519-3527.
12. Shah M, Krull A, Odonnell L, de Lima MJ, Bezerra E. Promises and challenges of a decentralized CAR T-cell manufacturing model. *Frontiers in Transplantation*. 2023;Volume 2
13. S S KD, Joga R, Srivastava S, et al. Regulatory landscape and challenges in CAR-T cell therapy development in the US, EU, Japan, and India. *European Journal of Pharmaceutics and Biopharmaceutics*. 2024;201:114361.
14. Iglesias-López C, Agustí A, Vallano A, Obach M. Financing and Reimbursement of Approved Advanced Therapies in Several European Countries. *Value in Health*. 2023;26(6):841-853.
15. Mumford A, Roberts G, Mumford J, Coyle S, Gibson J, Edmonds T. HTA117 A Comparison of Health Technology Appraisal (HTA) Timelines and Requirements for Orphan Technologies in 10 European Countries. *Value in Health*. 2023;26(12):S341.
16. EBMT CAR-T Data Collection Initiative. Vol. 2025: European Society for Blood and Marrow Transplantation.

17. Chabannon C, Ruggeri A, Montoto S, et al. Celebrating the registration of 9.000 patients treated with CAR T cells in the EBMT registry: Collection of real-world data in the context of hematopoietic cellular therapies. *Best Pract Res Clin Haematol*. 2024;37(2):101557.
18. Ahmed N, Wesson W, Lutfi F, et al. Optimizing the post-CAR T monitoring period in recipients of axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel. *Blood Advances*. 2024;8(20):5346-5354.
19. Melocchi A, Schmittlein B, Sadhu S, et al. Automated manufacturing of cell therapies. *J Control Release*. 2025;381:113561.
20. Dias J, Garcia J, Agliardi G, Roddie C. CAR-T cell manufacturing landscape—Lessons from the past decade and considerations for early clinical development. *Molecular Therapy Methods & Clinical Development*. 2024;32(2).
21. Wang Q, Zhou L, Tan L, et al. A 3-in-1 integrated automated platform for rapid CAR-T cell manufacturing: activation, transduction, and expansion in a hollow-fiber system. *Cytotherapy*. 2025;27(8):1001-1012.
22. Cellares Services. Vol. 2025: Cellares.
23. Scale Your Impact Introducing IRO, the new standard in CGT manufacturing technology. Vol. 2025: Oribiotech.
24. Abou-El-Enein M, Elsallab M, Feldman SA, et al. Scalable Manufacturing of CAR T cells for Cancer Immunotherapy. *Blood Cancer Discov*. 2021;2(5):408-422.
25. Lock D, Monjezi R, Brandes C, et al. Automated, scaled, transposon-based production of CAR T cells. *J Immunother Cancer*. 2022;10(9).
26. Del Bufalo F, Becilli M, Rosignoli C, et al. Point-of-care fresh CAR T cells for pediatric or young adult BCP-ALL that is relapsed/refractory or in very-high-risk first relapse. *Blood Advances*. 2025;9(19):5091-5102.
27. Dickinson MJ, Barba P, Jäger U, et al. A Novel Autologous CAR-T Therapy, YTB323, with Preserved T-cell Stemness Shows Enhanced CAR T-cell Efficacy in Preclinical and Early Clinical Development. *Cancer Discov*. 2023;13(9):1982-1997.
28. Ghassemi S, Nunez-Cruz S, O'Connor RS, et al. Reducing Ex Vivo Culture Improves the Antileukemic Activity of Chimeric Antigen Receptor (CAR) T Cells. *Cancer Immunol Res*. 2018;6(9):1100-1109.
29. Ghassemi S, Durgin JS, Nunez-Cruz S, et al. Rapid manufacturing of non-activated potent CAR T cells. *Nat Biomed Eng*. 2022;6(2):118-128.
30. Ravi G, Richard S, Kumar S, et al. Phase 1 clinical trial of B-Cell Maturation Antigen (BCMA) NEX-T® Chimeric Antigen Receptor (CAR) T cell therapy CC-98633/BMS-986354 in participants with triple-class exposed multiple myeloma. *Leukemia*. 2025;39(4):816-826.
31. Locke FL, Hu Z-H, Siddiqi T, et al. Real-World Impact of Time from Leukapheresis to Infusion (Vein-to-Vein Time) in Patients with Relapsed or Refractory (r/r) Large B-Cell Lymphoma (LBCL) Treated with Axicabtagene Ciloleucel. *Blood*. 2022;140:7512-7515.
32. Fernández L, Fernández A, Mirones I, et al. GMP-Compliant Manufacturing of NKG2D CAR Memory T Cells Using CliniMACS Prodigy. *Front Immunol*. 2019;10:2361.
33. Erkens F. AIDPATH - Modular Approach to AI-Enabled CAR-T Cell Manufacturing; 2022.
34. McGrath E, Machalik P. The Regulatory Framework for CAR-T Cells in Europe: Current Status and Foreseeable Changes AND Centre Qualification by Competent Authorities and Manufacturers. In: Kröger N, Gribben J, Chabannon C, Yakoub-Agha I, Einsele H, eds. The EBMT/EHA CAR-T Cell Handbook. Cham: Springer International Publishing; 2022:191-198.

35. Chowdhury N. Common market but divergent regulatory practices: exploring European regulation and the effect on regulatory uncertainty in the marketing authorization of medical products. *Journal of European Integration*. 2013;35(6):635-652.
36. van Sinderen N, Dolva J, Riillo C, et al. Operational burden and fragmented implementation in CAR T-cell therapy: Insights from a multinational survey by the GoCART Coalition and the JACIE Quality Managers Committee. *Hemasphere*. 2025;9(10):e70243.
37. Chen Y, Xin Q, Qiu J, et al. In vivo CAR-T cell engineering: concept, research progress, potential challenges and enhancement strategies. *Experimental Hematology & Oncology*. 2025;14(1):133.
38. Irving M, Lanitis E, Migliorini D, Ivics Z, Guedan S. Choosing the Right Tool for Genetic Engineering: Clinical Lessons from Chimeric Antigen Receptor-T Cells. *Hum Gene Ther*. 2021;32(19-20):1044-1058.
39. Skeate JG, Pomeroy EJ, Slipek NJ, et al. Evolution of the clinical-stage hyperactive TcBuster transposase as a platform for robust non-viral production of adoptive cellular therapies. *Molecular Therapy*. 2024;32(6):1817-1834.
40. Yagyu S, Nakazawa Y. piggyBac-transposon-mediated CAR-T cells for the treatment of hematological and solid malignancies. *International Journal of Clinical Oncology*. 2023;28(6):736-747.
41. Abdo L, Batista-Silva LR, Bonamino MH. Cost-effective strategies for CAR-T cell therapy manufacturing. *Mol Ther Oncol*. 2025;33(2):200980.
42. Prommersberger S, Reiser M, Beckmann J, et al. CARAMBA: a first-in-human clinical trial with SLAMF7 CAR-T cells prepared by virus-free Sleeping Beauty gene transfer to treat multiple myeloma. *Gene Therapy*. 2021;28(9):560-571.
43. Izsvák Z, Hackett PB, Cooper LJ, Ivics Z. Translating Sleeping Beauty transposition into cellular therapies: victories and challenges. *Bioessays*. 2010;32(9):756-767.
44. Monjezi R, Miskey C, Gogishvili T, et al. Enhanced CAR T-cell engineering using non-viral Sleeping Beauty transposition from minicircle vectors. *Leukemia*. 2017;31(1):186-194.
45. Schambach A, Morgan M, Fehse B. Two cases of T cell lymphoma following Piggybac-mediated CAR T cell therapy. *Mol Ther*. 2021;29(9):2631-2633.
46. Kebriaei P, Singh H, Huls MH, et al. Phase I trials using Sleeping Beauty to generate CD19-specific CAR T cells. *The Journal of Clinical Investigation*. 2016;126(9):3363-3376.
47. Kitte R, Serfling R, Blache U, et al. Optimal Chimeric Antigen Receptor (CAR)-mRNA for Transient CAR T Cell Generation. *Int J Mol Sci*. 2025;26(3).
48. Ottaviano G, Georgiadis C, Gkazi SA, et al. Phase 1 clinical trial of CRISPR-engineered CAR19 universal T cells for treatment of children with refractory B cell leukemia. *Sci Transl Med*. 2022;14(668):eabq3010.
49. Lv Z, Luo F, Chu Y. Strategies for overcoming bottlenecks in allogeneic CAR-T cell therapy. *Front Immunol*. 2023;14:1199145.
50. Hunter TL. In vivo CAR T cell generation to treat cancer and autoimmune disease. *Science*. 2025;388.
51. Smith TT, Stephan SB, Moffett HF, et al. In situ programming of leukaemia-specific T cells using synthetic DNA nanocarriers. *Nat Nanotechnol*. 2017;12(8):813-820.
52. Hamilton JR, Chen E, Perez BS, et al. In vivo human T cell engineering with enveloped delivery vehicles. *Nature Biotechnology*. 2024;42(11):1684-1692.
53. Bimbo JF, van Diest E, Murphy DE, et al. T cell-specific non-viral DNA delivery and in vivo CAR-T generation using targeted lipid nanoparticles. *J Immunother Cancer*. 2025;13(7).

54. Short L, Holt RA, Cullis PR, Evgin L. Direct *in vivo* CAR T cell engineering. *Trends in Pharmacological Sciences*. 2024;45(5):406-418.
55. Bui TA, Mei H, Sang R, Ortega DG, Deng W. Advancements and challenges in developing *in vivo* CAR T cell therapies for cancer treatment. *eBioMedicine*. 2024;106.
56. Michels KR, Sheih A, Hernandez SA, et al. Preclinical proof of concept for VivoVec, a lentiviral-based platform for in vivo CAR T-cell engineering. *J Immunother Cancer*. 2023;11(3).
57. Chahin N, Sahagian G, Feinberg MH, et al. Durability of Response to B-Cell Maturation Antigen-Directed mRNA Cell Therapy in Myasthenia Gravis. *Ann Clin Transl Neurol*. 2025;12(11):2358-2366.
58. A First-in-Human, Phase 1, Single-Center, Open-Label, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of CPTX2309 by Intravenous Administration in Healthy Volunteers; 2025.
59. A Phase I Clinical Study of BCMA Chimeric Antigen Receptor T Cell（SYS6020）Injection in Refractory Active Systemic Lupus Erythematosus Patients; 2024.
60. T2EVOLVE (Grant agreement ID: 945393): European Commission; 2021.
61. GoCART COALITION. 2021.
62. AIDPATH (Grant agreement ID: 101016909): European Commission; 2021.
63. JOIN4ATMP (Grant agreement ID: 101137206): European Commission; 2024.
64. EASYGEN (Grant agreement ID: 101194710): European Commission; 2025.
65. Radisch S, Poltorak MP, Wagner M, et al. Next generation automated traceless cell chromatography platform for GMP-compliant cell isolation and activation. *Sci Rep*. 2022;12(1):6572.
66. Aleksandrova K, Leise J, Priesner C, et al. Automated manufacturing and characterization of clinical grade autologous CD20 CAR T cells for the treatment of patients with stage III/IV melanoma. *Front Immunol*. 2024;15:1328368.
67. Elsallab M, Maus MV. Expanding access to CAR T cell therapies through local manufacturing. *Nature Biotechnology*. 2023;41(12):1698-1708.
68. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 1394/2007. European Union: EUR-Lex; 2007:17.
69. Cuende N, Ciccocioppo R, Forte M, et al. Patient access to and ethical considerations of the application of the European Union hospital exemption rule for advanced therapy medicinal products. *Cytotherapy*. 2022;24(7):686-690.
70. Mahadik S, Sen P, Shah EJ. Harnessing digital health technologies and real-world evidence to enhance clinical research and patient outcomes. *DIGITAL HEALTH*. 2025;11:20552076251362097.
71. Chabannon C, Ruggeri A, Montoto S, et al. Celebrating the registration of 9.000 patients treated with CAR T cells in the EBMT registry: Collection of real-world data in the context of hematopoietic cellular therapies. *Best Practice & Research Clinical Haematology*. 2024;37(2):101557.
72. Pennings ERA, Spanjaart AM, Thielen FW, et al. Patient-reported outcomes in patients with hematologic malignancies treated with CAR T-cell therapy in Europe. *Blood Adv*. 2025;9(24):6380-6393.
73. Agency EM. Concept paper on the revision of Part IV Guidelines on

Good Manufacturing Practice specific to Advanced Therapy Medicinal Products 2025.
74. Aghamiri SS, Amin R. The Potential Use of Digital Twin Technology for Advancing CAR-T Cell Therapy. *Current Issues in Molecular Biology*. 2025;47(5):321.

75. Egan JR, Marí-Buyé N, Benítez-Cano EV, et al. A digital shadow of CAR T cell expansion in a perfusion bioreactor: Informing optimal harvest times for autologous cell therapy. *Biotechnology Progress*. 2025;41.
76. . !!! INVALID CITATION !!! 12,75,76.
77. Youssef E, Weddle K, Zimmerman L, Palmer D. Pharmacovigilance in Cell and Gene Therapy: Evolving Challenges in Risk Management and Long-Term Follow-Up. *Drug Safety*. 2025.
78. Bell JAH, Jeffries GA, Chen CI. Mitigating inequity: ethically prioritizing patients for CAR T-cell therapy. *Blood*. 2023;142(15):1263-1270.
79. Shah M, Krull A, Odonnell L, de Lima MJ, Bezerra E. Promises and challenges of a decentralized CAR T-cell manufacturing model. *Frontiers in Transplantation*. 2023;Volume 2 - 2023.
80. Luanpitpong S, Klaihmon P, Janan M, et al. Point-of-care manufacturing of anti-CD19 CAR-T cells using a closed production platform: Experiences of an academic in Thailand. *Molecular Therapy Oncology*. 2024;32(4).
81. Agliardi G, Dias J, Rampotas A, Garcia J, Roddie C. Accelerating and optimising CAR T-cell manufacture to deliver better patient products. *The Lancet Haematology*. 2025;12(1):e57-e67.
82. Bristol Myers Squibb and Cellares Announce a $380M Worldwide Capacity Reservation and Supply Agreement for the Manufacture of CAR T Cell Therapies to Bring the Promise of Cell Therapy to More Patients, Faster: Businesswire A Berkshire Hathaway Company; 2024.
83. Hankey KG, Luetkens T, Avila S, et al. Eight-Day Point of Care CAR T-Cell Manufacturing on Clinimacs Prodigy from Healthy Donors As a Proof-of-Concept Study. *Blood*. 2021;138(Supplement 1):2851-2851.
84. Castella M, Caballero-Baños M, Ortiz-Maldonado V, et al. Point-Of-Care CAR T-Cell Production (ARI-0001) Using a Closed Semi-automatic Bioreactor: Experience From an Academic Phase I Clinical Trial. *Frontiers in Immunology*. 2020;Volume 11.
85. Anguille S, Kuipers I, Saevels K, et al. Initial Clinical Results of Atalanta-1, a Phase I/II Trial of Point-of-Care Manufactured GLPG5102 (19CP02) in RR NHL. *Blood*. 2022;140(Supplement 1):10323-10324.
86. ARCE therapeutics DashCAR®.
87. FasTCAR Our Next-day Manufacturing Autologous Platform. Vol. 2025: GRACELL A member of the AstraZeneca Group.
88. Anaya D, Kwong B, Park S, et al. DEVELOPMENT OF INGENUI-T, A RAPID AUTOLOGOUS CHIMERIC ANTIGEN RECEPTOR (CAR)-T MANUFACTURING SOLUTION USING WHOLE BLOOD, FOR TREATMENT OF AUTOIMMUNE DISEASE. *Cytotherapy*. 2024;26(6, Supplement):S9.
89. Kyverna therapeutics
90. Henckels MMLaKA. Full speed ahead: how rapid CAR-T manufacturing can shape the cell therapy landscape. *Cell & Gene Therapy Insights 2025*.
91. Flinn IW, Jaeger U, Shah NN, et al. A First-in-Human Study of YTB323, a Novel, Autologous CD19-Directed CAR-T Cell Therapy Manufactured Using the Novel T-Charge TM platform, for the Treatment of Patients (Pts) with Relapsed/Refractory (r/r) Diffuse Large B-Cell Lymphoma (DLBCL). *Blood*. 2021;138(Supplement 1):740-740.
92. Engels B, Zhu X, Yang J, et al. Preservation of T-Cell Stemness with a Novel Expansionless CAR-T Manufacturing Process, Which Reduces Manufacturing Time to Less Than Two Days, Drives Enhanced CAR-T Cell Efficacy. *Blood*. 2021;138(Supplement 1):2848-2848.
93. Bu D, Bennett P, Barton N, et al. Identification and Development of PHE885: A Novel and Highly Potent Fully Human Anti-BCMA CAR-T Manufactured with a Novel T-

Charge TM Platform for the Treatment of Multiple Myeloma. *Blood*. 2021;138(Supplement 1):2770-2770.
94. Galapagos. Galapagos Announces Intention to Wind Down Cell Therapy Business as Part of the Company's Ongoing Transformation; 2025.

Tables and figures

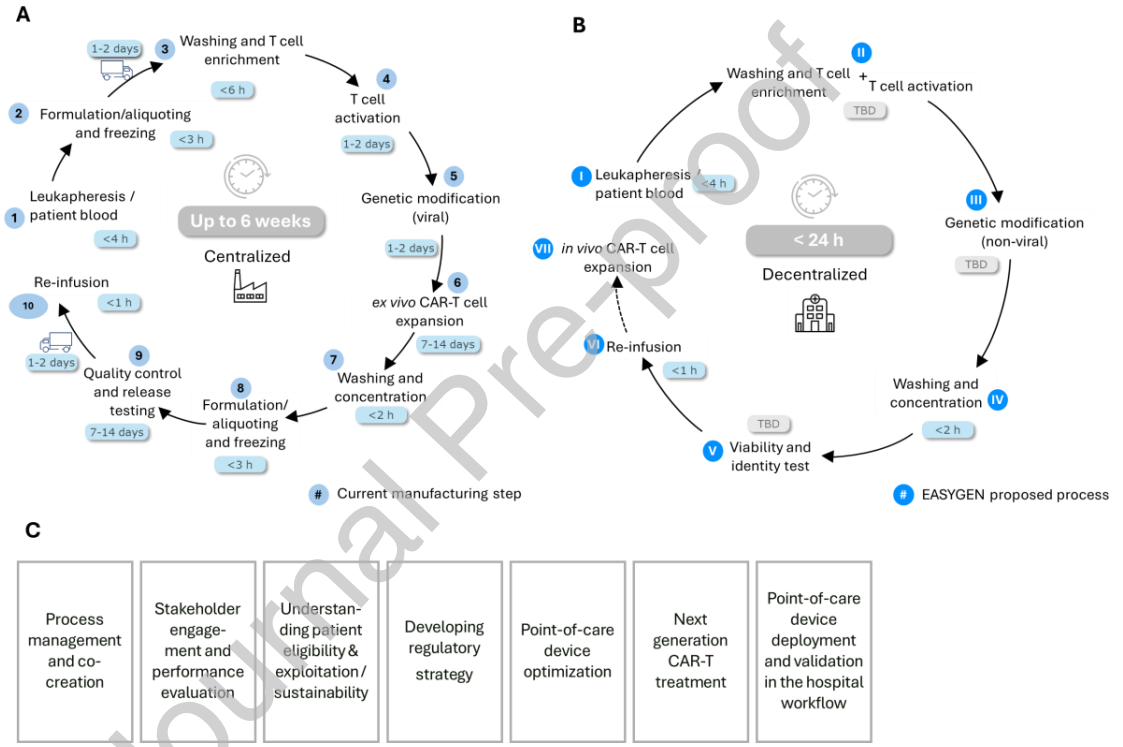

Fig. 1 Centralized (A) versus decentralized EASYGEN (B) CAR-T manufacturing. Conventional centralized workflows typically require ~6 weeks vein-to-vein due to transport, cryopreservation, prolonged *ex vivo* expansion, and extensive quality control. In contrast, EASYGEN aims to achieve a forward-looking <24-hour core-processing pathway by enabling point-of-care, closed and automated processing, including rapid T-cell enrichment, non-viral gene transfer via flow electroporation, elimination of prolonged *ex vivo* expansion through *in vivo* CAR-T expansion, and streamlined quality testing approaches, which are subject to implementation and validation of rapid/risk-adapted QC and release strategies.(C) EASYGEN work-package architecture. The diagram illustrates the collaborative structure of the EASYGEN consortium, comprising 10 work packages (7 displayed). Own illustrations.

Tables

Table 1
Selected access metrics for CAR-T therapies in Europe. Own visualization, data extracted from the 2025 report by the IQVIA Institute for Human Data Science[2]

Country	Estimated % of eligible patients treated in 2023*	Average vein-to-vein time (days)	Number of certified treatment centers (as of June 2024)
France	~30%	~32	37
Italy	~11%	~32	34
Spain	~18%	~36	33
Germany	~17%	~26	45
United Kingdom	~15%	~26	26

Table 2
Overview of major manufacturing platforms with ongoing clinical trials advancing rapid, point-of-care (PoC), or autologous CAR-T cell manufacturing, identified by literature analysis and clinicaltrial.gov

Platform/ device	Vendor	Modality & advertised *ex vivo* duration	Key capabilities	Maturity/ status	Example clinical programs (compound names; target; indication)
Cell Shuttle®	Cellares Inc. California, US	Fully integrated, high-throughput automation; end-to-end cell processing[82]	Fully automated, high-throughput CAR-T manufacturing with scalable multi-shuttle design[82]	Global capacity and supply agreements with pharma; Phase ½ Studies[82]	NCT06121297 (CABA-201; CD19; SLE) NCT06154252 (CABA-201; CD19; IIM) NCT06328777 (CABA-201; CD19; SSc)
CliniMACS® Prodigy	Miltenyi Biotec B.V. & Co. KG Bergisch Gladbach, GER	PoC, closed, "fresh-in/ fresh-out" feasible; no cryopreservation required[57]. 8 day processing time is feasible[83],	Closed, automated end-to-end CAR-T manufacturing in a single integrated device[57]	Used in academic PoC programs in EU/ US; peer-reviewed case series; ongoing randomized and comparative trials[84]	NCT04792489 (MB-CART2019.1; CD19, CD20; DLBCL) NCT05641428 (ARI-0001 CAR T-cells; CD19 ;LBCL) NCT04778579 (ARI-0001 CAR T-cells; CD19 ;ALL) NCT06189157 (MB-CART19.1; CD19; SLE) NCT03434769 (CAR-T cells;CD19 ; NHL) NCT03765177(CLIC-1901;CD19 ; ALL, NHL) NCT07053800 (Obe-cel; CD19; SLE) NCT04844866 (MB-CART2019.1; CD19; DLBCL) NCT06508931 (MB-CART2019.1; CD19; B-cell neoplasm) NCT07288879 (MB-CART2019.1; CD19; DLBCL) NCT06708845 (zamto-cel; CD19, CD20, Autoimmune diseases) NCT07178431 (MB-CART2019.1; CD19; MS) NCT06347718 (anti-CD19 CAR T cell therapy; CD19; B cell mediated autoimmune disease) NCT06189157 (MB-CART19.1; CD19; SLE) NCT06424340 (MB-dNPM1-TCR.1; dNPM1; AML)
Cocoon® platform (decentralized/ near-patient automation)	Lonza Group AG Basel, CH	Automated, closed single-use cassette bioreactor; 1 device per patient slot; reported 7-day vein-to-vein in PoC setting[85]	Modular, automated and decentralized CAR-T manufacturing with near-patient capability[85]	Clinical feasibility and PoC use with academic/biotech partners; multi-site programs	NCT06561425*[1] (GLPG5101; CD19; NHL) EUCT 2022-500782-27-00*[1] (GLPG5301; BCMA, MM)
DashCAR®	ARCE therapeutics Tapei, TW	Manufacturing process requires 24-72 hours.[86]	Strong efficacy and safety profile; rapid manufacturing enabling timely treatment[86]	Phase 1/2 clinical development (IND cleared; ongoing)	NCT06680752 (ARD 103; CLL-1; AML, MDS)

FasTCAR® process	AstraZeneca PLC Cambridge, UK (Gracell Biotechnologies, acquired 2023)	"Next-day" autologous CAR-T; ~24 h[87]	Ultra-fast CAR-T manufacturing enabling next-day dosing with simplified process steps[87]	FDA IND cleared for early-line MM in the US; multiple trials in China and the US	NCT06530849 (GC012F; CD19, BCMA; SLE) NCT06235229 (GC012F; CD19; MM) NCT05850234 (GC012F; CD19, BCMA; MM) NCT06897930 (AZD0120; CD19, BCMA; SLE) NCT07295847 (AZD0120; CD19, BCMA; SSc, IIM, D2T RA)
Ingenui-T	Kyverna Therapeutics CA, US	Autologous CAR-T; ~3 day manufacturing time *ex vivo*[88]	No leukapheresis (whole blood input); reduced vein-to-vein time; designed for autoimmune indications[89]	Early-mid clinical development in autoimmune diseases (Phase1/2)	NCT06588491 (Anti-CD19 CAR T-Cell Therapy; CD19; SPS) NCT06384976 (Anti-CD19 CAR T-Cell Therapy; CD19: MS) NCT06193889 (KYV-101; CD19; MG)
Nex-T	Bristol Myers Squibb NY, US	Autologous CAR-T; ~5-6 day manufacturing[90]	Minimal ex vivo expansion to preserve less differentiated T cells; improve consistency;[30]	Clinical-stage platform supporting next-generation CAR-T programs; early clinical trials ongoing	NCT07015983 (CC-97540; CD19; SLE) NCT07335562 (BMS-986353; CD19; Breakfree-SSc) NCT06220201 (CC-97540; CD19; RMS, PMS, MG) NCT05869955 (CC-97540; CD19; SLE, IIM, SSc, RA),
T-Charge®	Novartis AG Basel, CH	Rapid *ex vivo* expansion; <48 h total; ~24 h culture in some reports	Rapid CAR-T manufacturing preserving T-cell stemness and reducing vein-to-vein time	Phase 1/2 programs in hematology and autoimmunity; as of 2021[91-93]	NCT03960840 (YTB323; CD19; CLL, DLBCL, ALL, LBCL); NCT06675864 (YTB323; CD19; PMS) NCT06868290 (Rapcabtagene Autoleucel; CD19; GPA, MPA) NCT06581198 (Rapcabtagene Autoleucel; CD19; SLE, LN) NCT06665256 (Rapcabtagene Autoleuce; CD19; IIM) NCT06655896 (Rapcabtagene Autoleucel; CD19; dcSSc) NCT05172596*(PHE885; BCMA; MM) NCT04318327*(PHE885; BCMA; MM)

SLE: Systemic Lupus Erythematosus
IIM: Idiopathic Inflammatory Myopathy
SSc: Systemic Sclerosis
DLBCL: Diffuse Large B-Cell Lymphoma
LBCL: Large B-Cell Lymphoma
ALL: Acute Lymphoblastic Leukemia
NHL: Non-Hodgkin Lymphoma
MS: Multiple Sclerosis
AML: Acute Myeloid Leukemia
MM: Multiple Myeloma
MDS: Myelodysplastic Syndrome
D2T RA: Difficult to treat rheumatoid arthritis
SPS: Stiff Person Syndrome
MG: Myasthenia Gravis
RMS: relapsing forms of multiple sclerosis

PMS: Progressive Multiple Sclerosis
RA: Rheumatoid Arthritis
CLL: Chronic Lymphocytic Leukemia
GPA: active Granulomatosis with Polyangiitis
MPA: Microscopic Polyangiitis
LN: Lupus Nephritis
dcSSc: diffuse cutaneous systemic sclerosis
*Discontinued
*[1]Galapagos announced its exit from the cell therapy field in October 2025[94]