



Overcoming access barriers in European CAR-T therapy: the role of decentralized manufacturing and the EASYGEN framework

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A B S T R A C T

Background: 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 nonviral 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.

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Methods: 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 nonviral 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.

Results: 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 nonviral 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.

Conclusions: 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.

Key Words: access gap, CAR-T, CAR-T decentralized manufacturing, EASYGEN, European consortia, nonviral gene delivery, 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, nonstandardized 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 [18].

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 [19]. 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 [19,20].

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 [21].

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 [21,22].

EASYGEN is a European multistakeholder 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

Table 1
Selected access metrics for CAR-T therapies in Europe.

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

Own visualization, data extracted from the 2025 report by the IQVIA Institute for Human Data Science [2].

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 and 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 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 [23]. Lentiviral and retroviral vectors are complex biologics requiring multistep plasmid production, transient transfection, and rigorous quality control. Global shortages of viral vectors and critical upstream raw materials have repeatedly disrupted supply chains [24]. 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) [25,26]. 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

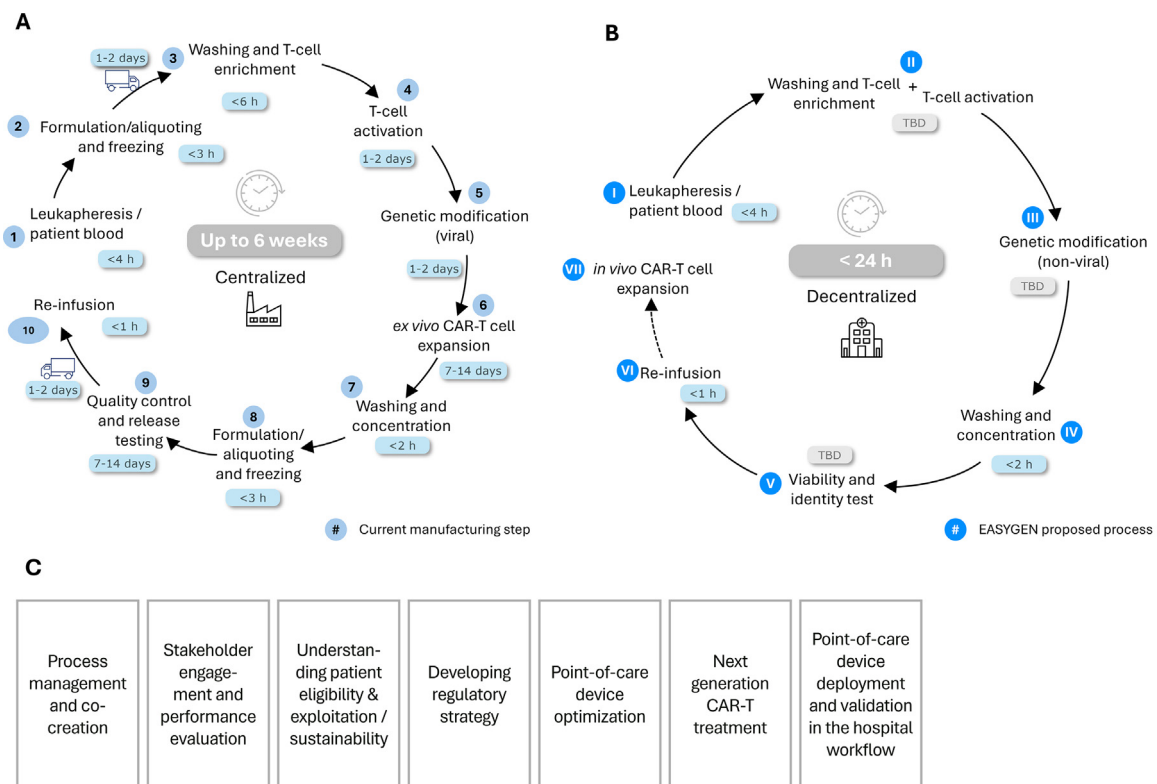


Fig. 1. Centralized (A) versus decentralized (B) CAR-T manufacturing. (A) Conventional centralized workflows typically require ~6 weeks vein-to-vein due to transport, cryopreservation, prolonged *ex vivo* expansion, and extensive quality control. (B) A decentralized CAR-T manufacturing approach in EASYGEN aims to achieve a forward-looking <24-hour core-processing pathway. This shall be achieved by enabling point-of-care, closed and automated processing, including rapid T-cell enrichment, nonviral gene transfer via flow electroporation, replacement of prolonged *ex vivo* expansion via *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.

hospitals [2,27]. Geographic concentration leads to inequitable access and logistical bottlenecks, particularly in regions lacking domestic manufacturing nodes [2,27].

Heterogeneity in approval timelines and data collection

Beyond technical constraints, economic and regulatory heterogeneity compound these challenges [28]. Temporary hospital-based reimbursement mechanisms and country-specific managed-entry agreements generate uncertainty for both centers and payers [29]. Health-technology-assessment (HTA) timelines vary widely, with lags exceeding 12 months between EMA authorization and national listing in some jurisdictions [30].

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 [31,32]. Yet interoperability gaps and divergent definitions of outcomes limit cross-country comparability. As a result, real-world evidence, essential for value-based contracting and postauthorization monitoring, remains partial [33].

System-level bottlenecks such as 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 [34,35]. 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 [36]. 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 [27]. 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 PAPILO-1. These initiatives demonstrated several potential advantages of decentralized manufacturing, including reduced vein-to-vein time, minimized cryo-shipment 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 [37,38]. 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 [39,40]. Large-scale industrial deployments further indicate that modular, digitally controlled platforms can support parallelized manufacturing across multiple programs [39]. In parallel, components of these systems are being evaluated in clinical studies for decentralized manufacturing [41], 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 FasTCAR® 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 [13,42–44].

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 [27,39,45,46]. Smaller centers often lack resources for GMP certification or the informatics capacity for digital quality-by-design (QbD) integration [47]. Furthermore, existing regulatory pathways for distributed manufacturing remain under-defined, creating uncertainty over release authority and pharmacovigilance responsibilities [48,49].

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 [50]. As automation matures, integration with nonviral gene transfer and *in vivo* approaches will define the next phase of manufacturing innovation.

Emerging models and technological approaches

Nonviral 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 nonviral 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) [51–53].

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 [53,54]. 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 [55].

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 [56]. However,

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 accessing clinicaltrial.gov.

Platform/ device	Vendor	Modality and 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 [3]	Fully automated, high-throughput CAR-T manufacturing with scalable multishuttle design [3]	Global capacity and supply agreements with pharma; Phase 1/2 Studies [3]	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 [4]. 8 day processing time is feasible [5].	Closed, automated end-to-end CAR-T manufacturing in a single integrated device [4]	Used in academic PoC programs in EU/US; peer-reviewed case series; ongoing randomized and comparative trials [6]	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) NCT06561425 (GLPG5101; CD19; NHL) ^b EUCT 2022-500782-27-00 (GLPG5301; BCMA, MM) ^b
Cocoon® platform (decentralized/ near-patient automation)	Octane Medical Group, Kingston, Ontario, CA	Automated, closed single-use cassette bioreactor; one device per patient slot; reported 7-day vein-to-vein in PoC setting [7]	Modular, automated and decentralized CAR-T manufacturing with near-patient capability [7]	Clinical feasibility and PoC use with academic/biotech partners; multisite programs	NCT06680752 (ARD 103; CLL-1; AML, MDS)
DashCAR®	ARCE therapeutics Tapei, TW	Manufacturing process requires 24–72 hours [8]	Strong efficacy and safety profile; rapid manufacturing enabling timely treatment [8]	Phase 1/2 clinical development (IND cleared; ongoing)	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) NCT06588491 (Anti-CD19 CAR T-Cell Therapy; CD19; SPS) NCT06384976 (Anti-CD19 CAR T-Cell Therapy; CD19; MS) NCT06193889 (KYV-101; CD19; MG)
FasTCAR® process	AstraZeneca PLC Cambridge, UK (Gracell Biotechnologies, acquired 2023)	"Next-day" autologous CAR-T; ~24 h [9]	Ultra-fast CAR-T manufacturing enabling next-day dosing with simplified process steps [9]	FDA IND cleared for early-line MM in the US; multiple trials in China and the US	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), 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 Autoleucel; CD19; IIM) NCT06655896 (Rapcabtagene Autoleucel; CD19; dcSSc) NCT05172596 (PHE885; BCMA; MM) ^a NCT04318327 (PHE885; BCMA; MM) ^a
Ingenui-T	Kyverna Therapeutics CA, US	Autologous CAR-T; ~3 day manufacturing time ex vivo [10]	No leukapheresis (whole blood input) required; reduced vein-to-vein time; designed for autoimmune indications [11]	Early-mid clinical development in autoimmune diseases (Phase 1/2)	
NEX-T®	Bristol Myers Squibb NY, US	Autologous CAR-T; ~5–6 day manufacturing [12]	Minimal ex vivo expansion to preserve less differentiated T cells; improve consistency; [13]	Clinical-stage platform supporting next-generation CAR-T programs; early clinical trials ongoing	
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 [14–16]	

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.

aDiscontinued

bGalapagos announced its exit from the cell therapy field in October 2025 [17].

electroporation can compromise viability and transposition efficiency, necessitating optimization of cell activation and transposase expression [52,57].

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 [58], 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 [59], has been observed in clinical trials using SB Transposase [60]. 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, nonintegrating gene-transfer systems – most prominently mRNA-based delivery – have gained substantial clinical validation in nononcology 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 nonviral 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 [61].

Other gene-editing tools, such as CRISPR–Cas9 and TALEN, enable precise and targeted knock-in at safe-harbor loci, supporting both autologous and allogeneic “off-the-shelf” constructs [52]. 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 [62].

Allogeneic CAR-T approaches

Emerging allogeneic (“off-the-shelf”) CAR-T approaches aim to address the limitations of autologous manufacturing by enabling scalable, premanufactured 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 [55]. However, key challenges remain, including limited *in vivo* persistence, immune-mediated clearance, and the need for intensified lymphodepletion [63]. For a complete list of ongoing allogeneic 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 [64–66]. 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 [67–70]. Early-phase clinical and translational studies are beginning to apply *in vivo* CAR or CAR-like strategies in hematologic malignancies and immune-mediated diseases [4,71,72]. 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, nonviral, 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 [73].

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 [74].

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 [75].

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 [76].

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 nonviral gene-transfer platforms. Its objectives include developing GMP-compatible nonviral 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 [77].

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 [78].

EASYGEN directly addresses CAR-T manufacturing challenges by integrating rapid T-cell selection, nonviral 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 [53,54].

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 postinfusion expansion (Figure 1B).

At the same time, reliance on nonviral 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 nontarget cells, transgene delivery efficiency in minimally activated T cells, postelectroporation 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 [79]. 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 [2,19,21,31,45].

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 [49,80]. 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 bio-processing innovations, creating a misalignment between regulatory expectations and modern manufacturing realities [81]. Initiatives such as adaptive licensing, risk-based GMP, and the hospital-exemption pathway have introduced flexibility but vary markedly across Member States [81,82]. 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 [83]. 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 [31,84]. 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 [85].

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 [86].

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, multiweek 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 [87,88]. 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, nonviral precision engineering—such as Sleeping Beauty transposon systems—will be critical to ensure the safety and metabolic fitness of nonexpanded 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 and 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 [89]. Policymakers and consortia must therefore embed ethics-by-design principles into translational pipelines, ensuring societal legitimacy alongside technical progress [20,90].

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 [51].

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 [91,92].

This strategy greatly reduces processing time by several days and helps circumvent capacity constraints in centralized facilities [93]. 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, nonviral 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.

Author Contributions

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Declaration of competing 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.

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Supplementary materials

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