

Cost of decentralized CAR T-cell production in an academic nonprofit setting

Tao Ran¹ | Stefan B. Eichmüller²  | Patrick Schmidt^{2,3} | Michael Schlander^{1,4}

¹Division of Health Economics, German Cancer Research Center (DKFZ), Heidelberg, Germany

²Research Group GMP & T Cell Therapy, German Cancer Research Center (DKFZ), Heidelberg, Germany

³Department of Medical Oncology, National Center for Tumor Diseases (NCT) and University Hospital Heidelberg, Heidelberg, Germany

⁴Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

Correspondence

Stefan B. Eichmüller and Michael Schlander, DKFZ, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany.

Email: s.eichmueller@dkfz.de (S. E.) and

Email: m.schlander@dkfz.de (M. S.)

Open access funding enabled and organized by Projekt DEAL.

Abstract

Chimeric antigen receptor (CAR) T-cell therapy is a promising immunotherapy with high acquisition costs, and it has raised concerns about affordability and sustainability in many countries. Furthermore, the current centralized production paradigm for the T cells is less than satisfactory. Therefore, several countries are exploring alternative T-cell production modes. Our study is based on the T-cell production experience in a nonprofit setting in Germany. We first identified the work steps and main activities in the production process. Then we determined the fixed costs and variable costs. Main cost components included personnel and technician salaries, expenditure on equipment, a clean room, as well as production materials. All costs were calculated in 2018 euros and converted into U.S. dollars. For a clean room with one machine for closed and automated manufacturing installed, annual fixed costs summed up to approximately €438 098 (\$584 131). The variable cost per production was roughly €34 798 (\$46 397). At the maximum capacity of one machine, total cost per product would be close to €60 000 (\$78 849). As shown in the scenario analysis, if three machines were to be installed in the clean room, per production cost could be as low as €45 000 (roughly \$59 905). If a cheaper alternative to lentivirus was used, per production total cost could be further reduced to approximately €33 000 (roughly \$44 309). Decentralized T-cell production might be a less costly and more efficient alternative to the current centralized production mode that requires a high acquisition cost.

KEYWORDS

CAR-T cell therapy, costs, good manufacturing practice, price, T-cell production

1 | INTRODUCTION

Cancer immunotherapy is a method to treat cancer patients by generating or augmenting their immune response against tumor cells.^{1,2} Chimeric antigen receptor (CAR) T-cell therapy is an innovative type of adoptive cellular therapy that generates a robust immune-mediated antitumor response through the ex vivo manipulation of T cells.¹ In 2017, the United States (US) Food and Drug Administration approved two CAR-T therapies (Kymriah and Yescarta) with orphan drug

Abbreviations: ATMP, advanced therapeutic medicinal product; B-ALL, B-cell acute lymphoblastic leukemia; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; DLBCL, diffuse large B cell lymphoma; DKFZ, German Cancer Research Center (Deutsches Krebsforschungszentrum); GMP, good manufacturing practice; SOPs, standard operation procedures.

[Correction added on 10-July-2020, after first online publication: Projekt Deal funding statement has been added.]

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designation, followed by similar approvals from the European Commission in 2018. The two therapies are to treat relapsed or refractory B-cell Acute Lymphoblastic Leukemia (for patients up to age 25, Kymriah only) and Non-Hodgkin Lymphoma including diffuse large B-cell Lymphoma (for patients over 18). However, the list prices of these drugs are fairly high. For instance, in the US, the list price for Kymriah is \$475 000, and for Yescarta \$375 000; in Germany, Kymriah has been reported to be €320 000 per patient.³

Various stakeholders have raised concerns about the cost of CAR-T therapy, given the increasingly heavier burden placed by highly-priced cancer drugs on society.⁴⁻⁶ Its high price, along with its non-trivial associated clinical costs of hospitalization, causes much struggle in payers to allocate adequate hospital reimbursement, which can lead to treatment delay.⁷ Also, patients in different countries may encounter restricted access or refused coverage by payers,⁴ or suffer financial toxicity in the US.^{6,8} Moreover, many have expressed that this therapy with the current high price would become unaffordable in the future,^{5,9-11} because of its potential to treat more cancer types.^{1,10,12} Unsurprisingly, immediately upon its first marketing authorization, a question was raised about the production cost of this therapy.¹⁰

Additionally, questions have been raised on the process-related efficiency of the current centralized production of the CAR-T therapy.¹³⁻¹⁷ As a response, researchers proposed “on-site” production of CAR-T cells, an alternative made possible by recent technological improvement in production automation.^{13,18-20} Compared to the centralized mode, decentralized “in-house” production does not require shipping and handling of the leukapheresis product, which saves time and money. Furthermore, several labor-intensive production work steps are handled by machines. Previous studies have explored the estimation of the production cost using economic modeling based on hypothetical data.^{17,21} However, to date, no real-world production cost data have been made available.

Our study aims to estimate the “on-site” production costs of CAR-T cells in an academic nonprofit setting based on data collected at a single site in Germany. Possible scale-up scenarios are explored. This is the first study that has used real-world data to calculate the cost of decentralized production, a potentially less costly manufacturing paradigm. It may provide useful information to manufacturers or providers who consider adopting the decentralized production paradigm.

2 | METHODS

Our analysis was based on the T-cell production process at the Research Group Good Manufacturing Practice (GMP) and T-Cell Therapy at the German Cancer Research Center in Heidelberg, Germany, in 2018. Our production strictly followed the quality specifications to reach the standard clinical grade. Until recently, we have successfully generated CAR T-cell products consisting of 8×10^8 to 5.5×10^9 cells with yielding transduction rates of 30.9% to 98.9%. We calculated the costs by identifying the major components and main activities in the production process as applied in validation runs.

What's new?

Chimeric antigen receptor (CAR) T cell therapy is a promising therapeutic strategy for certain types of malignancies. However, high acquisition costs of commercial products, currently manufactured in a centralized mode, is controversial. Here, the authors examined the cost of an alternative method of T-cell production in Germany. Based on maximum capacity of one machine for automated manufacturing, fixed costs were \$584 131, with total cost per product about \$78 849. With use of three machines or use of a less-expensive viral vector, costs dropped significantly. The analyses suggest that decentralized CAR T-cell production in a non-profit setting would be relatively cost-efficient.

2.1 | Cell production process

In general, cell production includes cell collection, washing, selection, T-cell activation, transduction, expansion, bead removal and harvest,^{22,23} as seen in Figure 1. Current automation technology enables machineries to handle the core steps, which saves labor and time. CliniMACS Prodigy was used for our calculation, although alternative devices also exist,

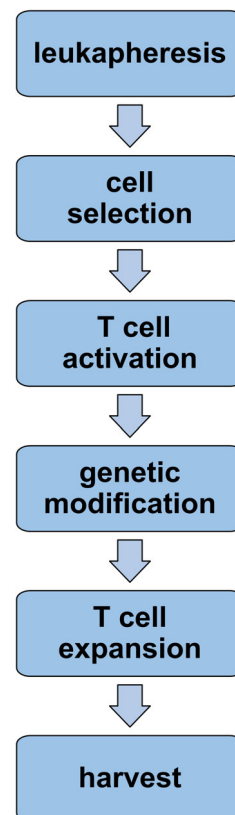


FIGURE 1 Flowchart of the production process [Color figure can be viewed at wileyonlinelibrary.com]

including ambr 250, Aastrom Replicell System, Robotized Cell Processing Expert System, Lonza Cocoon, "Kotozujuri", Select Systems, Quantum Cell Expansion System, Fully Automated Smart Cell Factory and Auto-stem Stemcell Factory.¹⁷ A closed and automated manufacturing platform can include steps from selection to harvest in a single-use, closed tubing system.^{19,23} As a result, expanded T cells, with beads removed, are ready to be harvested as personalized final product after 12 to 14 days. Although the core steps can be carried out by machines, highly skilled and knowledgeable personnel and continuously trained technicians are still needed to maintain the compliant GMP condition. In the case of the DKFZ, a head of production, a qualified person and a head of quality control (different from the head of production) were responsible for the production process. Further, two experienced technicians were involved in the production process. Additionally, a clean room was utilized for the production, to minimize the risk of potential batch loss due to infection.¹⁸

2.2 | Cost calculation method

Our cost calculation first identified the work steps of the process, including leukapheresis, cell production using a closed manufacturing system, harvesting and optional cryopreservation,¹⁹ as well as the key production activities and related working hours. The main activities of the two technicians included setting up the T-cell transduction process in the machine using all of the consumables (following "standard operation procedures" or SOPs generated by the machine software), checking the process once per day, and changing the media and waste bag(s) once per production. Extra hours were spent on preparing for the production on the first day, and on harvesting T cells on the last day, respectively. Prior to and during the production, the head of

production prepared protocols and SOPs, supervised and monitored the production. The qualified person oversaw the production and release of the products, and the head of the quality control maintained the overall and specific quality. In addition, external labs were utilized for sterile control and specimen tests.

Second, we determined fixed and variable costs. On a yearly basis, fixed costs mainly included expenditure on purchasing and maintenance of various equipment such as the closed manufacturing system, liquid nitrogen tank, freezers and fridges and on the clean room, as well as the salaries of the key personnel and technicians (including annual trainings). All devices were assumed to have zero salvage value and zero depreciation rate, according to the accounting practice at DKFZ. The value of the machinery was evenly distributed over each year of its life time, without considering value-added tax. For key personnel and technicians, gross salary, including paid vacations and other benefits rates for public service (Arbeitgeberbrutto) were used. Variable costs included expenditure on consumables (eg, media, cytokines, beads, buffer and plastic ware) for each production, human serum albumin and lentivirus. Note that consumables such as wafers, syringes and caules were purchased for the whole year and were therefore included in the fixed cost. Additional costs of contamination controls and measuring endotoxin levels carried out by external labs were also included in the calculation. All costs were calculated in 2018 euros and converted into 2018 US dollars using Purchasing Parity Power data from the World Bank.

3 | RESULTS

Yearly fixed costs of the main components are listed in Table 1. Since only one machine for closed manufacturing was used, total fixed cost

TABLE 1 Annual fixed costs

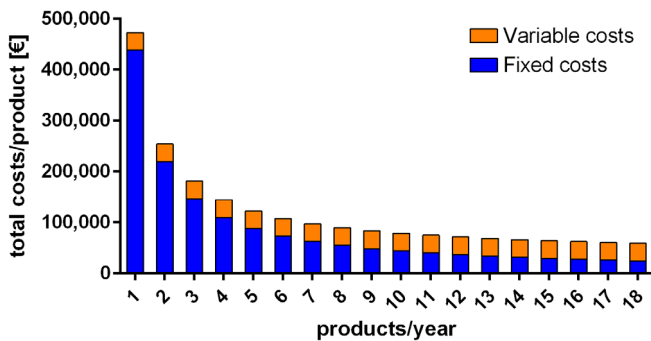
Category	Cost (euro)	Cost (dollar)	Percentage
Clean room (grade B)	€70 000	\$93 333	16.0%
Devices	€29 482	\$39 309	6.7%
Consumables (fixed yearly)	€500	\$667	0.1%
Responsible personnel	€196 390	\$261 853	44.8%
Experienced technicians	€129 400	\$172 533	29.5%
Training (yearly)	€4000	\$5333	0.9%
Maintenance and monitoring	€8326	\$11 101	1.9%
Sum	€438 098	\$584 131	100.0%

Category	Cost (euro)	Cost (dollar)	Percentage
Production materials (variable)	€32 300	\$43 067	92.8%
External tests and sterile control	€353	\$471	1.0%
Leukapheresis	€2145	\$2860	6.2%
Sum	€34 798	\$46 397	100.0%

TABLE 2 Variable cost per production

TABLE 3 Per production costs

Products	Fixed cost	Variable cost	Total cost/product	Fixed cost share	Variable cost share	Closed manufacturing systems
1	\$584 131	\$46 397	\$630 528	92.6%	7.4%	1
2	\$292 065	\$46 397	\$338 462	86.3%	13.7%	1
10	\$58 413	\$46 397	\$104 810	55.7%	44.3%	1
18	\$32 452	\$46 397	\$78 849	41.2%	58.8%	1
19	\$38 391	\$46 397	\$84 788	45.3%	54.7%	2
36	\$20 261	\$46 397	\$66 658	30.4%	69.6%	2
37	\$25 567	\$46 397	\$71 964	35.5%	64.5%	3
54	\$13 508	\$46 397	\$59 905	22.5%	77.5%	3

**FIGURE 2** Per product fixed and variable cost [Color figure can be viewed at wileyonlinelibrary.com]

of production was \$584 131. The main cost drivers were the annual salaries of the responsible personnel and experienced technicians, as illustrated in Figure S1.

Per production variable costs are listed in Table 2. \$46 397 were needed for one product, with variable cost components consisting of production materials (main cost driver), tests, and leukapheresis. Figure S2 illustrates the share of each component in the variable cost. Production materials were composed of lentivirus (\$866 666/batch or \$28 889/production), consumables (media, cytokines, beads, buffer and plastic ware, with a total cost of \$13 333/production), and human serum albumin (\$400/production), as shown in Figure S3.

Total per production costs (as the summation of fixed cost and variable cost) are presented in Table 3. Given the personalized nature of the product, one closed manufacturing system can only handle one product at a time, leading to its maximum capacity of 18 products per year, with a total cost per product of approximately \$78 849. The maximum capacity estimation included consideration of the individual production cycle length (roughly 2 weeks), paid holidays of the technicians (6 weeks), clean room shut down for maintenance (1 month) and other types of maintenance (2 weeks). Typically, if more products are made, annual fixed cost is divided among more products, thus yielding a lower fixed cost per production. Therefore, as shown in Figure 2, it would be expected that total cost per production in our case

TABLE 4 Costs per product using plasmid-based transfection systems

Products	Fixed cost	Variable cost	Total cost	Fixed cost share	Variable cost share
1	\$605 464	\$26 397	\$631 861	95.8%	4.2%
18	\$33 637	\$26 397	\$60 035	56.0%	44.0%
54	\$17 912	\$26 397	\$44 309	40.4%	59.6%

should decrease rapidly, because of this decline in fixed cost per production.

3.1 | Scenario analysis

3.1.1 | Scenario 1

At its maximum capacity, a clean room of roughly 20 m² (215 square feet) can hold three closed manufacturing devices, which could lead to a lower cost per production as presented in the lower sections of Table 3. If more devices were to be added, the cost of devices, responsible personnel, experienced technicians and maintenance would also increase. However, the cost of the responsible personnel and experienced technicians would not be proportionally multiplied. Specifically, for two machines that make 36 products in a clean room, only three personnel and 2.5 technicians would be needed, resulting in per production cost of \$66 658. For three machines making 54 products, 4 personnel and 3 technicians would be needed, resulting in per production cost of roughly \$59 905.

3.1.2 | Scenario 2

A cheaper substitute for transfection with lentiviral vectors are plasmid based integration vectors such as transposons and CRISPR/CAS9,^{24,25} which have been tested successfully by us for the generation of CAR-transfected T cells. Plasmids cost \$9333/production (1/3 of the cost of lentivirus), with the requirement for an additional machine (electroporator, at a yearly cost of \$10 667) for the three

closed manufacturing devices. Per production costs using plasmids are listed in Table 4. Compared to lentivirus, using plasmids would lower the variable cost by almost 45%, leading to per product cost of \$44 309 at the maximum capacity of making 54 products.

4 | DISCUSSION

Our cost estimation of the maximum capacity of 18 products per year per machine was based on our experience in Germany, which can be quite conservative. Institutions in other countries have made 24 products per year per machine with two machines running, which can potentially lower the cost further. Nevertheless, even in our case, per production cost was associated with substantial economies of scale, that is, it went down fairly quickly when more T-cell products were made. This would particularly be the case if more closed manufacturing devices were to be installed in the clean room, mainly because of the reduction in per product fixed cost as production scales up. Moreover, we used clean room of grade B (ISO 5). Fixed cost would be lowered further if a clean room with a grade level of C (ISO 7)²¹ was used, which is possible for all steps using a closed system. Additionally, plasmid vectors, a cheaper alternative to lentivirus, have different levels of quality. If plasmids of regular quality were used with a cost of approximately \$40 000 per batch (instead of the best quality ones of \$280 000 in Scenario 2), per production cost would be as low as \$33 333, assuming the quality of T-cell products remain the same. Certainly, a larger clean room with more devices installed could potentially lower the costs further.

While our analysis is based on our local experience in Heidelberg, we do not believe the situation would differ much at other sites in Germany, even if local variance in unit costs might result in minor differences in costs. It should be noted, that regulatory issues for the production of ATMPs are based on EU regulations, which are then transferred to local legislation in all EU countries. Even outside EU, these regulations are quite similar. Following these rules is mandatory and results in similar quality requirements for consumables and equipment, for clean rooms, and the demand for a proper quality management system.

In addition to cost reduction, producing T cells within or close to clinical facility would also save time and associated clinical costs. The time period of 12 to 14 days for a closed and automated manufacturing system to produce T cells is much shorter than the 3 to 4 weeks currently required by the centralized manufacturing mode.^{13,14} This difference is likely due to the fact that neither cryopreservation nor shipping of T cells is needed in the decentralized production mode, which is actually preferred, as the quality of T cells suffer substantially from freezing and thawing. In contrast, in centralized production, both the leukapheresate and the final products are frozen, shipped and thawed again. While waiting for the centralized T-cell product to be ready, patients usually need to receive bridging chemotherapy for disease control.¹⁴ Shortening the production time and thus patients' waiting time would avoid some or all costs of the bridging chemotherapy, and would also reduce potential expenditure on hospital stays

and lodging involved in the waiting period. This would add to the cost advantage of decentralized over centralized production.

4.1 | Limitations

Our study has several limitations. First, our estimation was based on the experience of a nonprofit organization. Sunk costs such as personnel's effort on protocol writing, administrative paperwork for facility and device setup, and GMP certification were not considered. Similarly, research and development costs and clinical site onboarding were excluded. Therefore, our results cannot be generalized to the commercial setting, where additional costs would need to be incurred in regulatory affairs and intellectual property management,^{11,15,18} and a return on investment would be expected.¹⁷ Validation runs have to be added as sunk costs and can be calculated as three additional products. Additionally, the scale-up pattern in a commercial setting would be different,²⁶ likely requiring high start-up costs to build new clean rooms.²¹ On the other hand, the production mode in a commercial setting would aim for profit maximization or cost minimization, which can be potentially more efficient than our case. Nevertheless, our results should be generalizable to other nonprofit organizations (including academic university hospitals) that adopted similar production processes. In fact, research conducted in the U.S. also showed that "on-site" production using CliniMACS Prodigy was cost-saving compared to centralized production.²⁰

We assumed that the machineries were used for their full life time, whether that be for 10 years or 20 years, which might not reflect the practice in other institutions. Depending on the practice of different countries or institutions, some machineries could be replaced by newer generations within the first few years, while others could be used for longer than 20 years. Furthermore, we did not include the cost due to production failure in our estimation, because the failure rate is relatively low according to the literature, ranging from 0% to 5%²⁷⁻²⁹ and to our own experience. If we included the cost due to production failure in our calculation, the maximum increase (assuming 5% failure rate) in cost per product would be 3% to 4% at the maximum production capacity. Additionally, the lentivirus used in our study was sold in batches, with the cost of \$866 667 per batch of 30 products. Also, pre-release testing cost for contamination may be higher in other countries.

As mentioned before, we have used the CliniMacs Prodigy for our calculation, but alternative devices do exist. To clarify, we do not intend to endorse the use of one particular system over another. Besides the production systems mentioned earlier, CAR-TXpress filed the patent application for its automated technology,²¹ aiming to improve efficiency and reduce manufacturing costs. Certainly, regulatory and other hurdles exist regarding decentralization,^{30,31} although several manufacturers expressed preference to "in-house" manufacturing, in terms of cost reduction, flexibility and efficiency.³² Potential solutions to the challenges in automated production and commercialization have been discussed in other studies.^{33,34}

Our estimation did not include clinical costs for patient screenings, bridging chemotherapy, lymphodepleting chemotherapy, toxicity

management and follow-up costs.¹⁴ In particular, the costs of toxicity management (such as cytokine release syndrome, or CRS, and neurotoxicity) can be substantial for severe CRS or neurotoxicity.^{35,36} Conservative estimation of the clinical costs in the U.S. (from a payer's perspective) ranged from 10% to 50% of the drug price.³⁶⁻³⁸

4.2 | Acquisition costs

The high acquisition cost of CAR-T therapy has been subject to intense discussion.^{5,6,39} On the one hand, this therapy seems to offer high added value, given its innovative nature,^{1,2} and its potential for cure.^{2,40} Moreover, it has been designated as an orphan drug, which often tend to have a high price tag. On the other hand, there is concern on budget impact, since this innovative mechanism for treating rare hematologic malignancies has the potential to be applied to many more cancers.^{1,10,12} Despite the 1-month-performance guarantee in the U.S.⁴¹ and the risk-sharing agreement with the German sickness funds (details of which have been treated as “commercial in confidence” information) offered by the manufacturer of Kymriah, CAR-T therapies currently rank among the most expensive pharmaceutical products. Yet, overall budget impact, as the product of cost per patient and patient numbers, appeared manageable in most jurisdictions to date, because of the small patient population.⁴² Nevertheless, the patient population can increase rapidly given its potential to treat more cancers. Moreover, while an inverse relationship has been found between prevalence and official prices of orphan medicinal products,⁴³ this has not been confirmed for cancer drugs.⁴⁴ As a consequence, the outlook concerning the sustainability of spending on new cancer drugs might well be more troublesome compared to that on non-oncological orphan drugs.⁴⁵

Some proposals, such as annuity-based payment mechanisms,⁴⁶ cannot solve the issue, as they merely shift costs over prolonged time periods. Also, the 1-month-performance guarantee offered by the manufacturer essentially only makes the average price of Tisagenlecleucel similar to its competitor who has no money-back guarantee, given approximately 20% of the patients might fail in the first month.⁴¹

Against this background, more recently developed “in-house” production mode may offer another option to bring down the cost. As illustrated earlier, production costs can go down with increasing volume because of economies of scale. Moreover, potentially cheaper substitutes for expensive lentivirus might further drive the cost down. Hopefully, this will translate into more bearable acquisition costs, either as the result of increased competition (eg, via the availability of decentralized manufacturing processes as an alternative) or by outright price regulation (with reimbursement decreasing with growing volume), or by a combination of both.

It is worth noting that the added value of CAR-T therapy might yet to be fully justified,⁸ as only few studies have been published with long-term follow-up, which indicate effectiveness but are single arm,

Phase 1 or 2 trials.⁴⁷⁻⁵⁰ Several studies have provided some evidence of CAR-T being cost-effective compared to the existing therapies at higher thresholds,^{36,37,51} although it should be noted that its comparators were of high price as well.^{3,51,52}

Although a novel, promising therapy, the centralized production paradigm of CAR-T cells in a commercial setting is less than satisfactory, particularly in light of its high price tag. “On-site” production in an academic, nonprofit institution using automated machineries might be an alternative mode to improve efficiency, primarily by lowering production and overall cost. Our study contributes to our understanding of the costs of T-cell production by providing fixed and variable cost information on this newer production paradigm. The cost information might also inform policy makers in developing future pricing and reimbursement mechanisms. Future research is needed to calculate the costs in a commercialized setting, and to consider the associated clinical costs.

ACKNOWLEDGEMENTS

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

In addition to his primary employment with the DKFZ, M. S. is Chairman & Scientific Director of the nonprofit Institute for Innovation & Valuation in Health Care (InnoVal-HC) in Wiesbaden/Germany, which accepts funding under an unrestricted educational grants policy only. In the context of his involvement with noncancer-related projects at InnoVal-HC, he has received travel expenses and honoraria for lectures and presentations. The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon reasonable request.

ORCID

Stefan B. Eichmüller  <https://orcid.org/0000-0002-3497-6904>

REFERENCES

1. Khalil DN, Smith EL, Brentjens RJ, Wolchok JD. The future of cancer treatment: immunomodulation, CARs and combination immunotherapy. *Nat Rev Clin Oncol*. 2016;13:394.
2. June CH, Sadelain M. Chimeric antigen receptor therapy. *N Engl J Med*. 2018;379:64-73.
3. Bach PB, Giralt SA, Saltz LB. FDA approval of Tisagenlecleucel: promise and complexities of a \$475000 cancer drug. *JAMA*. 2017;318:1861-1862.
4. Danzon PM. Drug pricing and value in oncology. *Recent Results Cancer Res*. 2019;213:153-167.
5. Prasad V, de Jesus K, Mailankody S. The high price of anticancer drugs: origins, implications, barriers, solutions. *Nat Rev Clin Oncol*. 2017;14:381-390.
6. Tran G, Zafar SY. Financial toxicity and implications for cancer care in the era of molecular and immune therapies. *Ann Transl Med*. 2018; 6:166.
7. Leech AA, Dusetzina SB. Cost-effective but unaffordable: the CAR-T conundrum. *J Natl Cancer Inst*. 2018;111:2018-2019.

8. Jain T, Litzow MR. No free rides: management of toxicities of novel immunotherapies in ALL, including financial. *Blood Adv.* 2018;2:3393-3403.
9. Dranitsaris G, Zhu X, Adunlin G, Vincent MD. Cost effectiveness vs. affordability in the age of immuno-oncology cancer drugs. *Expert Rev Pharmacoecon Outcomes Res.* 2018;18:351-357.
10. Prasad V. Immunotherapy: Tisagenlecleucel—the first approved CAR-T-cell therapy: implications for payers and policy makers. *Nat Rev Clin Oncol.* 2018;15:11-12.
11. Xie F. Highly priced gene therapies: a wake-up call for early Price regulation. *Pharmacoeconomics.* 2018;36:883-888.
12. Kakarla S, Gottschalk S. CAR T cells for solid tumors: armed and ready to go? *Cancer J.* 2014;20:151-155.
13. Köhl U, Arsenieva S, Holzinger A, Abken H. CAR T cells in trials: recent achievements and challenges that remain in the production of modified T cells for clinical applications. *Hum Gene Ther.* 2018;29:559-568.
14. Buechner J, Kersten MJ, Fuchs M, Salmon F, Jager U. Chimeric antigen receptor-T cell therapy: practical considerations for implementation in Europe. *Hema.* 2018;2:e18.
15. Harrison RP, Rafiq QA, Medcalf N. Centralised versus decentralised manufacturing and the delivery of healthcare products: a United Kingdom exemplar. *Cytotherapy.* 2018;20:873-890.
16. Harrison RP, Ruck S, Rafiq QA, Medcalf N. Decentralised manufacturing of cell and gene therapy products: learning from other healthcare sectors. *Biotechnol Adv.* 2018;36:345-357.
17. Harrison RP, Zylberberg E, Ellison S, Levine BL. Chimeric antigen receptor-T cell therapy manufacturing: modelling the effect of off-shore production on aggregate cost of goods. *Cytotherapy.* 2019;21:224-233.
18. Harrison RP, Ruck S, Medcalf N, Rafiq QA. Decentralized manufacturing of cell and gene therapies: overcoming challenges and identifying opportunities. *Cytotherapy.* 2017;19:1140-1151.
19. Mock U, Nickolay L, Philip B, et al. Automated manufacturing of chimeric antigen receptor T cells for adoptive immunotherapy using CliniMACS prodigy. *Cytotherapy.* 2016;18:1002-1011.
20. Zhu F, Shah N, Xu H, et al. Closed-system manufacturing of CD19 and dual-targeted CD20/19 chimeric antigen receptor T cells using the CliniMACS prodigy device at an academic medical center. *Cytotherapy.* 2018;20:394-406.
21. Lopes AG, Sinclair A, Frohlich B. Cost analysis of cell therapy manufacture: autologous cell therapies. *BioProcess Int.* 2018;16:S3-S8.
22. Gee AP. GMP CAR-T cell production. *Best Pract Res Clin Haematol.* 2018;31:126-134.
23. Wang X, Riviere I. Clinical manufacturing of CAR T cells: foundation of a promising therapy. *Mol Ther Oncolytics.* 2016;3:16015.
24. Monjezi R, Miskey C, Gogishvili T, et al. Enhanced CAR T-cell engineering using non-viral sleeping beauty transposition from minicircle vectors. *Leukemia.* 2017;31:186-194.
25. Salas-McKee J, Kong W, Gladney WL, et al. CRISPR/Cas9-based genome editing in the era of CAR T cell immunotherapy. *Hum Vaccin Immunother.* 2019;15:1126-1132.
26. Dai X, Mei Y, Nie J, Bai Z. Scaling up the manufacturing process of adoptive T cell immunotherapy. *Biotechnol J.* 2019;14:e1800239.
27. Jacoby E, Bielora B, Avigdor A, et al. Locally produced CD19 CAR T cells leading to clinical remissions in medullary and extramedullary relapsed acute lymphoblastic leukemia. *Am J Hematol.* 2018;93:1485-1492.
28. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and Young adults with B-cell lymphoblastic leukemia. *N Engl J Med.* 2018;378:439-448.
29. Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. *N Engl J Med.* 2019;380:1726-1737.
30. Trainor N, Pietak A, Smith T. Rethinking clinical delivery of adult stem cell therapies. *Nat Biotechnol.* 2014;32:729-735.
31. Krackhardt AM, Anliker B, Hildebrandt M, et al. Clinical translation and regulatory aspects of CAR/TCR-based adoptive cell therapies—the German cancer consortium approach. *Cancer Immunol Immunother.* 2018;67:513-523.
32. DeArment A. In-house CAR-T manufacturing preferable to outsourcing, execs say. In: Medcity News 2018. <https://medcitynews.com/2018/09/in-house-car-t-manufacturing-preferable-to-outsourcing-exec-say/>.
33. Kaiser AD, Assenmacher M, Schroder B, et al. Towards a commercial process for the manufacture of genetically modified T cells for therapy. *Cancer Gene Ther.* 2015;22:72-78.
34. Piscopo NJ, Mueller KP, Das A, et al. Bioengineering solutions for manufacturing challenges in CAR T cells. *Biotechnol J.* 2018;13:1700095.
35. Siddiqi T, Garcia J, Dehner C, et al. Estimation of the resource utilization and costs of cytokine release syndrome observed in the transcend-NHL clinical trial: a micro-costing study. *Am Soc Hematol.* 2018;132:319.
36. Whittington MD, McQueen RB, Ollendorf DA, et al. Long-term survival and value of chimeric antigen receptor T-cell therapy for pediatric patients with relapsed or refractory leukemia. *JAMA Pediatr.* 2018;172:1161-1168.
37. Lin JK, Lerman BJ, Barnes JI, et al. Cost effectiveness of chimeric antigen receptor T-cell therapy in relapsed or refractory pediatric B-cell acute lymphoblastic leukemia. *J Clin Oncol.* 2018;36:JCO2018790642.
38. Hettle R, Corbett M, Hinde S, et al. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. *Health Technol Assess.* 2017;21:1-204.
39. Danzon PM, Taylor E. Drug pricing and value in oncology. *Oncologist.* 2010;15(Suppl 1):24-31.
40. Hinrichs CS, Rosenberg SA. Exploiting the curative potential of adoptive T-cell therapy for cancer. *Immunol Rev.* 2014;257:56-71.
41. Dolgin E. Bringing down the cost of cancer treatment. *Nature.* 2018;555:S26-S29.
42. Schlander M, Dintsios CM, Gandjour A. Budgetary impact and cost drivers of drugs for rare and Ultrarare diseases. *Value Health.* 2018;21:525-531.
43. Medic G, Korchagina D, Young KE, et al. Do payers value rarity? An analysis of the relationship between disease rarity and orphan drug prices in Europe. *J Mark Access Health Policy.* 2017;5:1299665.
44. Korchagina D, Jaroslowski S, Jadot G, Toumi M. Orphan drugs in oncology recent results. *Cancer Res.* 2019;213:109-142.
45. Schlander M, Adarkwah CC, Gandjour A. Budget impact analysis of drugs for ultra-orphan non-oncological diseases in Europe. *Expert Rev Pharmacoecon Outcomes Res.* 2015;15:171-179.
46. Ollendorf D. Pricing models & strategies to make CAR-T therapy affordable. *Cell and Gene Therapy Insights.* 2018;4(4):363-368. <http://dx.doi.org/10.18609/cgti.2018.033>.
47. Park JH, Riviere I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N Engl J Med.* 2018;378:449-459.
48. Hirayama AV, Gauthier J, Hay KA, et al. High rate of durable complete remission in follicular lymphoma after CD19 CAR-T cell immunotherapy. *Blood.* 2019;134:636-640.
49. Ma F, Ho JY, Du H, et al. Evidence of long-lasting anti-CD19 activity of engrafted CD19 chimeric antigen receptor-modified T cells in a phase I study targeting pediatrics with acute lymphoblastic leukemia. *Hematol Oncol.* 2019;37:601-608.
50. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med.* 2020;382:1331-1342.
51. Sarkar RR, Gloude NJ, Schiff D, Murphy JD. Cost-effectiveness of chimeric antigen receptor T-cell therapy in pediatric relapsed/refractory B-cell acute lymphoblastic leukemia. *J Natl Cancer Inst.* 2018;111:711-726.

52. Bach PB. National Coverage Analysis of CAR-T therapies—policy, evidence, and payment. *N Engl J Med*. 2018;379:1396-1398.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Ran T, Eichmüller SB, Schmidt P, Schlander M. Cost of decentralized CAR T-cell production in an academic nonprofit setting. *Int. J. Cancer*. 2020;147:3438–3445. <https://doi.org/10.1002/ijc.33156>