

Although, in general, PET is the technique of choice for molecular imaging, MRI spectroscopy provides a non-invasive alternative (ie, not using ionising radiation) to study certain metabolites and monitor changes within tissues in conjunction with treatment. MRI spectroscopy offers a range of opportunities for pharmacodynamic studies in early clinical trials. ¹H-MRI spectroscopy can also be used to study tumours based on choline-containing compounds, which are abundant in cell membranes. Monitoring variability in the amount of choline within a tissue reflects tumour cellularity changes in response to treatments in prostate, breast, and brain tumours.

MRI also presents a higher spatial anatomical resolution than PET scans. Tumours are spatially heterogeneous and evolve over time in response to treatment selective pressures. Whole-body MRI is feasible in relatively short times (30–40 min for whole-body MRI scan, including anatomical and functional sequences), and it is easy to implement at most MRI units. Accounting for this higher spatial resolution and with the advent of novel computational analysis tools, whole-body MRI allows for the evaluation of intra-patient and intra-tumour heterogeneity. In a clinical trial of the PARP inhibitor, olaparib, in metastatic prostate cancer, diffusion-weighted

MRI guided the identification of relapse foci within bone metastases, revealing emerging mutations as mechanisms of resistance. Together, these features could aid drug development, assess intra-patient differential responses, and guide biopsies for studying resistance mechanisms and identify putative predictive biomarkers for more efficient clinical trials.

Finally, MRI does not use ionising radiation so, unlike CT or PET scans, it is an ideal assay for clinical trials in paediatric tumours or specific populations with contraindications to radiotherapy, such as pregnant women.

In summary, multi-parametric MRI offers the opportunity for early and accurate imaging compared with standard PET imaging in some settings. However, we can use different MRI and PET techniques as tools for precision medicine depending on the tumour type and the mechanism of action of the tested drug. One technique might present advantages over the other as a predictive biomarker or response endpoint in clinical trials. Advances in both MRI and PET can accelerate drug development by tailoring imaging assessment in clinical trials to tumour type and drug mechanism of action. In the future, hybrid PET–MRI imaging will open new horizons in imaging by using a combination of molecular, functional, and anatomical information.



Digital Oncology

Medical crowdfunding to access CAR T-cell therapy

School of Public Policy, Georgia Institute of Technology, Atlanta, Georgia 30332-0345, USA (LDS, SOO, ADL)
aaron.levine@pubpolicy.gatech.edu

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For more on the **costs of CAR T-cell therapies** see *JAMA Oncol* 2018; 4: 994–96

For more on **side effects associated with CAR T-cell therapy** see *Cell Gene Ther Insights* 2018; 4: 295–307

For more on **crowdfunding for medical treatment** see *JAMA* 2017; 317: 1623–24 and *Soc Sci Med* 2017; 187: 233–42

US Food and Drug Administration (FDA) approval of two chimeric antigen receptor T (CAR T) cell therapies—tisagenlecleucel and axicabtagene ciloleucel—in 2017 offered new therapeutic options to paediatric patients with relapsed or refractory acute lymphoblastic leukaemia and adult patients with relapsed or refractory diffuse large B-cell lymphoma. These therapies, which have now been approved by regulatory bodies around the world, provide hope to patients who have few other available options, but these therapies raise important ethical concerns. These concerns are driven by the extraordinarily high costs of these therapies—either US\$475 000 for paediatric patients with acute lymphoblastic leukaemia or \$373 000 for adult patients with diffuse large B-cell lymphoma, for the drug product alone in the USA—and the associated costs and their serious side-effects. CAR T-cell therapies were developed and approved at a time when patients were increasingly turning to crowdfunding to raise funds to pay for medical expenses and gain access to established or unproven medical interventions, yet little is known about patients' use of crowdfunding to access CAR T-cell therapy. We sought to understand whether and why patients were using crowdfunding to raise money to access CAR T-cell

therapies, either during clinical development or after regulatory approval.

We systematically searched GoFundMe, the most popular crowdfunding website, for English-language campaigns related to CAR T-cell therapy. We searched three times over a 15-day period between Oct 21, 2018, and Nov 3, 2018, using keyword searches for “CAR-T”, “cancer”, and “chimeric,” and the trade names for the first two CAR T-cell therapies: “Yescarta” and “Kymriah”. We reviewed each search result to assess if the campaign met our inclusion criteria (ie, the campaign sought to raise funds for a specific patient or group of patients to receive CAR T-cell therapy). We found 143 distinct campaigns and coded each campaign to identify key characteristics. Objective measures (ie, goal amount, amount raised, number of donations, number of Facebook shares, campaign state date, patient diagnosis, patient sex, and patient age <18 years) were assessed by a single coder, while more subjective measures (ie, reasons for campaign, explanation of CAR T-cell therapy, link to learn more about therapy, discussion of risks, and discussion of success rates) were independently assessed by two coders. Disagreements were discussed and resolved by consensus. Monetary values were converted to US dollars using exchange rates determined on Nov 3, 2018.

The 143 campaigns aimed to raise \$8.81M in total and successfully raised \$1.90M from 36 182 donations. The average campaign aimed for \$61 622 and raised \$13 259 from 253 donations, while the median campaign aimed for \$10 000 and raised \$4356 from 39 donations. The three largest campaigns raised \$589 520, \$235 449, and \$126 582, respectively, accounting for over half of the total funds raised. This skewed distribution was also visible in the sharing of campaigns on social media, with the average campaign shared on Facebook 665 times and the median campaign shared 261 times. The three most widely shared campaigns were shared more than 5000 times each and made up 39.5% (37 600 of 95 117) of the total Facebook shares among the full set of 143 campaigns. These three campaigns were the most successful in terms of total funds raised. The oldest campaigns started in 2014, early in the clinical development of CAR T-cell therapy, and the number of campaigns increased over time, especially after FDA approval of the first two CAR T-cell therapies (figure).

Not surprisingly, given the approved indications for tisagenlecleucel and axicabtagene ciloleucel, the most common diagnoses (among campaigns where the patient's diagnosis was clearly specified) were diffuse large B-cell lymphoma (51 [36%]) and acute lymphoblastic leukaemia (44 [31%]). The third most common was multiple myeloma (12 [8%]), a condition for which no approved CAR T-cell therapies exist but multiple CAR T-cell clinical trials are underway. A smaller number of campaigns focused on CAR T-cell therapy for other experimental indications (eg, glioblastoma).

Patient demographics were coded when readily available on the campaign site. Most campaigns sought to raise funds for a male patient (87 [61%]) and 37 (26%) campaigns aimed to raise funds to support care for a minor (<18 years of age).

Patients used crowdfunding to fund both direct medical and indirect non-medical costs associated with CAR T-cell therapies. The most common reason for crowdfunding was to support medical expenses (71 [49%]), but this was a broad category that included contributions to the cost of the CAR T-cell treatment itself and pretreatment and post-treatment care. In many campaigns, fundraising targeted indirect expenses, such as travel costs (63 [44%]), housing and living expenses (60 [42%]), or replacement of lost wages (42 [29%]).

Because crowdfunding can shape public understanding of medical therapies, we coded several variables related to how campaigns described CAR T-cell therapy. 35 [24%] campaigns included an explanation of how CAR T-cell therapy works and 12 (8%) campaigns provided a link for readers to learn more about these therapies. Neither the serious risks (20 [14%]) associated with CAR T-cell therapy nor the success rates (16 [11%]) seen in early clinical studies were mentioned frequently.

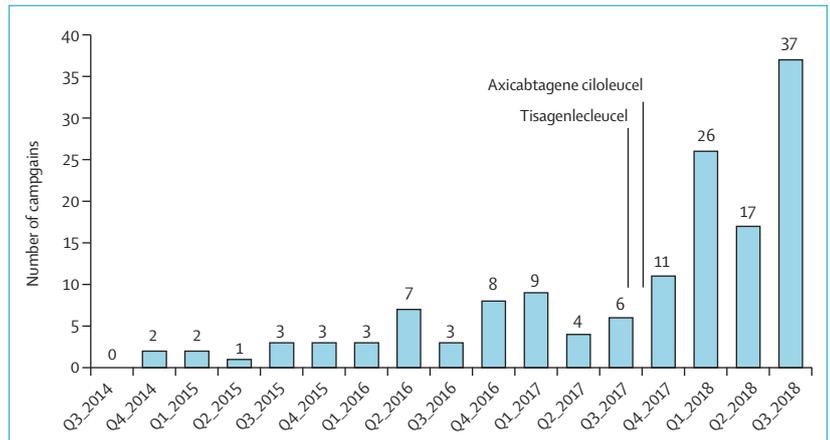


Figure: Number of CAR T-cell therapy crowdfunding campaigns on GoFundMe, 2014–18
Campaigns are grouped according to their start dates. Vertical lines show the US FDA approval dates for the first two CAR T-cell therapies: tisagenlecleucel on Aug 30, 2017, and axicabtagene ciloleucel on Oct 18, 2017.

These results, which find that only a small number of campaigns provide information about how CAR T-cell therapy works, or describe its risks or benefits, suggest that, although crowdfunding might raise awareness of CAR T-cell therapy to some extent, it is not likely a source of detailed information about the therapy.

Crowdfunding data have several limitations (eg, uncertainty about the actual use of funds, campaigns that were taken down before the study period) but can offer insight into patient experiences and perspectives. The need for many patients to crowdfund for CAR T-cell therapy raises questions about access to these therapies that are directly relevant to clinical researchers developing novel personalised therapies as well as clinicians treating patients with CART-cell therapies today. The results also corroborate growing concerns within oncology about the financial toxicity of cancer care. This growing literature shows that even well-insured patients can suffer serious financial harm as a result of a cancer diagnosis due to the high cost of cancer drugs (and associated co-pays and co-insurance) along with a host of ancillary medical and non-medical costs. Our results strongly suggest that crowdfunding is one approach patients with cancer use to help manage the financial burdens of cancer care.

Many of the campaigns we analysed, including nearly all campaigns that started before the FDA approved tisagenlecleucel in August, 2017 and campaigns for patients seeking treatment for multiple myeloma or other conditions for which no CAR T-cell therapies are currently approved, aimed to raise funds to support participation in clinical trials. Patient crowdfunding to access CAR T-cell therapy clinical trials reinforces existing concerns about fairly managing access to clinical trials for promising breakthrough innovative treatments and raises questions about whether clinical trial slots are disproportionately available to the wealthy, well connected, or social media

For more on crowdfunding for alternative therapies see *JAMA* 2018; **320**: 1705–06 and *Lancet Oncol* 2019; **20**: 28–29
For more on CAR T-cell therapy approaches for multiple myeloma see *Leuk Lymphoma* 2018; **59**: 2056–67
For more on the financial toxicity of cancer care see *CA Cancer J Clin* 2018; **68**: 153–65
For more on concerns on clinical trials access see *J Med Ethics* 2017; **43**: 391–400

savvy. It also raises concerns about the representativeness of study populations and calls for greater attention to the obligations of clinical trial sponsors to increase participation. Actions to support equitable access to these trials (eg, subsidising travel and housing, publicising resources available from patient organisations) are strongly justified both on grounds of justice and beneficence. Sponsors should, on ethical grounds, strive to cover required non-medical costs for research participants. Clinical researchers should also share resources (eg, subsidised short-term housing, support from patient advocacy groups) that make participation in clinical trials more affordable and support equitable access to clinical research.

Patient crowdfunding to support indirect costs associated with accessing approved CAR T-cell therapies raises questions about patient access and the potential

for CAR T-cell therapies to exacerbate existing health disparities. Clinicians considering CAR T-cell therapies should ensure their patients are aware of the potential indirect costs associated with these treatment options and informed about resources to help address these costs.

Indirect costs associated with CAR T-cell therapy appear to motivate many of the crowdfunding campaigns we analysed. These costs are driven, in part, by the limited number of hospitals that administer these therapies and the requirement that patients stay near the site of administration for an extended period after treatment. Minimising geographical restrictions on access and reducing side-effects so that patients can receive treatment and follow-up care near their homes will be important if CART-cell therapies are to reach their full potential.

Linda D Ho, Sarah O Oso, Aaron D Levine