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Protocol for the avatar acceptability study: a multiperspective cross-sectional study evaluating the acceptability of using patient-derived xenografts to guide personalised cancer care in Australia and New Zealand

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ABSTRACT

Introduction Patient-derived xenografts (PDXs) have the potential to transform personalised cancer care, however, little is known about the acceptability of using PDXs to guide treatment decision-making. Given that patient and community preferences can influence satisfaction with care as well as the success of new technologies, we will evaluate the acceptability of PDXs in individuals affected by cancer and community comparisons.

Methods and analysis This comparative cross-sectional study will recruit 323 individuals affected by cancer (cancer survivors (of childhood or adult cancer) and parents of childhood cancer survivors) and 323 community comparisons (adults and parents). We will collect data via structured interviews and questionnaires. To determine the acceptability of PDXs, we will assess five domains: willingness to use PDXs when/if diagnosed with cancer, perceived advantages and disadvantages of PDXs, maximum acceptable out-of-pocket costs per patient, maximum acceptable turnaround time to receive results and maximum acceptable number of mice sacrificed per patient. The primary endpoint will be participants' decisional balance ratio (calculated as participants' advantages ratings divided by perceived disadvantages ratings).

Ethics and dissemination The study protocol has been approved by the South Eastern Sydney Local Health District Human Research Ethics Committee (HREC:12/173) and UNSW Sydney (HC15773). The results will be disseminated in peer-reviewed journals and at scientific conferences. A lay summary will be published on the Behavioural Sciences Unit website.

Strengths and limitations of this study

- This study is the first to assess the acceptability of using patient-derived xenografts (PDXs) to guide cancer-related treatment decision-making.
- This comparative cross-sectional study builds on in-depth qualitative interviews which informed the development of our structured interviews/questionnaires, increasing the relevance of the questions to participants.
- We will invite four groups of participants across Australia and New Zealand, including cancer survivors (who have had childhood or adult cancer), parents of childhood cancer survivors, community comparisons who have no cancer history and community parents who do not have a child with cancer. This breadth of participants strengthens the study's generalisability.
- The study may recruit a biased sample of individuals who are more interested in health research and will not have representation from non-English-speaking participants.
- While this study will provide invaluable data about the acceptability of PDXs, participants' anticipated response to PDXs may not reflect their actual response if faced with a current cancer diagnosis.

INTRODUCTION

Patient-derived xenografts (PDXs) have the potential to transform personalised cancer care by using in vivo animal models to predict individual patient's responses to chemotherapeutic agents.[1] PDXs are created by directly engrafting cancerous tissue from an individual patient into immunodeficient mice.[2 3] Following tumour engraftment, the tumour can be extracted and implanted into more mice, creating a cohort of mice carrying tumours reflective of the original patient's.[1] It is then possible to use these live tumour samples to test the effectiveness of different (randomly assigned) therapies on the patient's specific tumour.[2 4] Should one

or more therapies prove effective in the mice, these can be ranked and recommended for use as targeted therapies for the patient.[2 5]

Mouse (murine) models have been used for decades in preclinical cancer research.[3 4] However, the use of PDXs to guide clinical decision-making in 'real time' for current patients is new. Personalised PDX models have now been trialled in childhood[6–10] and adult[11–14] cancers. Preliminary data are promising, demonstrating good concordance in drug response between the engrafted and the original tumour.[3 15–17] Early evidence suggests that PDXs have the potential to facilitate the choice of the optimal therapy for patients, potentially improving their prognosis,[3] reducing exposure to toxic and costly side effects of ineffective therapies[4] and ideally, leading to faster recovery.[4] Given these encouraging findings, multiple personalised medicine programmes are now using PDXs to generate individualised treatment recommendations for patients, for example, the Breast Cancer Genome Guided Therapy Study,[18] the 'Cancer Avatar Project' for melanoma and high-grade breast, ovarian, lung, liver and ovarian cancer,[19] and the Zero Childhood Cancer project for high-risk paediatric tumours.[20] Each programme has a budget in the millions.[18–20]

It is important to consider the limitations of this highly experimental and costly addition to in vitro and genetic testing-based precision medicine platforms. First and foremost is the chance that engraftment can be unsuccessful.[21] Engraftment success depends on various factors, including the tumour type, the strain of the recipient mice and the site of transplantation.[2 11 17] There may also be inconsistent results when mouse tumours do not mirror the original tumour[22] or do not behave as expected (eg, not metastasising).[3 17 21] This is particularly problematic across successive generations of PDXs, potentially producing results that are difficult to interpret.[22] Tumour graft latency—the time from implantation to the growth of a progressing xenograft tumour—can range from several weeks to months.[17 23] This delay may mean that some patients will not receive PDX-informed treatment recommendations until after their cancer has changed or become terminal.[11 16]

There is an increasing expectation for patients to be involved in treatment decisions, which research suggests can improve satisfaction with care.[17] Patients will therefore play a critical role in PDX development by joining PDX-based clinical trials, participating in precision medicine programmes and making treatment decisions based on PDX results.[11 24] Yet, patients commonly face multiple complex treatment decisions at a time of high distress.[25 26] Within the context of childhood cancer, decision-making about PDXs will be further complicated by the fact that parents must consent on behalf of their child.[27]Patient and parent distress may undermine the capacity to make fully informed treatment decisions and may increase their risk of having unrealistic expectations (ie, holding therapeutic misconceptions).[25 27] Personalised PDXs have clearly already captured the public imagination, with phrases such as 'mouse avatars', 'surrogate patients', 'stand-ins for real people' and 'mini-me's' appearing in popular media.[17 28] Patients have also published poetry about their PDXs,[29] highlighting the potential for personalised PDXs to leave a lasting impression on patients.

Successful implementation of new technologies into practice is dependent on the consideration of patients' preferences, including their acceptance and willingness to pay.[30 31] Despite the fact that personalised PDX models are at the cusp of implementation into cancer clinics, there has not been a study to evaluate the acceptability of the use of PDXs to guide cancer clinical care. We will therefore assess acceptability among those who have been affected by cancer (specifically, cancer survivors and parents of childhood cancer survivors) and those who have not been affected by cancer (community comparisons who may in the future face a cancer diagnosis themselves). We will assess five domains:

1. Willingness to use: We will examine how willing participants perceive they would be to consent to using PDXs to guide their treatment decision-making after a cancer diagnosis.
2. Perceived advantages and disadvantages of PDXs: We will ask participants to rate seven possible advantages and seven possible disadvantages of PDXs. We will examine whether participants' perceived advantages outweigh disadvantages by calculating a decisional balance ratio (the primary endpoint for the study).
3. Maximum acceptable cost: We will examine participants' reported maximum acceptable out-of-pocket cost per patient (ie, willingness to pay).
4. Maximum turnaround time: We will examine participants' reported maximum acceptable turnaround time for waiting to receive PDX results (ie, willingness to wait).
5. Maximum number of mice: We will examine participants' reported maximum acceptable number of mice sacrificed per patient.

Objectives

This comparative cross-sectional study aims to assess PDX acceptability to individuals affected by cancer across the entire age spectrum and the general community. We will also compare PDX acceptability between individuals affected by cancer and community comparisons and identify key sociodemographic factors which influence PDX acceptability. We hypothesise that most individuals affected by cancer and community comparisons will find PDXs acceptable and will report being willing to use PDXs to guide treatment decisions if faced with cancer. Given the salience of the cancer experience, we hypothesise that individuals affected by cancer (ie, cancer survivors and survivors' parents) will report being willing to pay more, wait longer and sacrifice more mice, than community participants. We expect that individuals considering cancer in a child and those with higher personal incomes will report a higher willingness to pay for PDXs.

Table 1 Participants' seven most commonly endorsed advantages and disadvantages of personalised patient-derived xenografts, identified in our pilot study

Advantages	Disadvantages
1. The mouse avatars might improve treatment selection, which may improve the patients' chance of surviving.	1. The results might not be the same in the patient as they are in the mice, so the treatment chosen might not work on the patient.
2. The avatars could guide treatment selection to reduce the patients' chances of developing side effects from their treatment.	2. The scientists may be unable to find any effective treatment using this technology.
3. To help future research about how best to treat cancer.	3. The treatment recommended from the avatar testing may be unavailable or too expensive to use.
4. To help doctors choose the right drug more quickly, which might avoid having to try several other drugs on the patient before finding the best one.	4. The testing will involve harming animals.
5. To provide reassurance that doctors have done everything they can to make the best possible treatment selection.	5. The patient might be recommended a treatment which is different to the most common treatment used for their type of cancer, or the treatment may not be compatible with any existing treatment that we know is effective.
6. The patient might recover faster if the right drug is chosen earlier.	6. It would take some time to get the results from the mouse avatars, which might mean you might not choose the right treatment straight away.
7. The results from the avatars might help make the patient and their family feel more confident about the outcome of the treatment.	7. It might be difficult to change treatments if the patient has already started on another treatment plan.

METHODS AND ANALYSIS

Study design

We followed two statements in developing this manuscript: the Strengthening the Reporting of Observational studies in Epidemiology statement[32] and the Standard Protocol Items for Clinical Trials statement.[33] This study will use a cross-sectional observational design to evaluate the acceptability of using PDXs to guide treatment decision-making in cancer care.

This study is based on the findings of a pilot (completed in 2016) in which we conducted 24 telephone interviews with childhood cancer survivors (n=16) and parents (n=8). The interviews contained open-ended questions to elicit survivors' and parents' perceived advantages and disadvantages of using PDXs. From these, we identified the seven most commonly endorsed advantages and seven most commonly endorsed disadvantages, of PDXs (see table 1). These 14 advantages and disadvantages will now be evaluated by participants in this large-scale avatar acceptability study.

Setting

The avatar acceptability study will be conducted in Australia and New Zealand. We will collect data from paediatric and adult hospitals across Australia and New Zealand, as well as through online research panels.

Participants

We will recruit four groups of participants:

1. Cancer survivors, who were diagnosed with cancer at least 6 months prior to study participation, are no longer on active treatment, are in remission and are currently aged over 16 years.
2. Parents of childhood cancer survivors who meet the above criteria, but are aged less than 16 years. They are herein referred to as 'survivors' parents'.
3. Community comparisons herein referred to as 'community adults', who have no history of cancer, no children with a history of cancer and are aged over 16 years.
4. Parent community comparisons herein referred to as 'community parents', who have no children with a history of cancer and have at least one child aged under 16 years.

Exclusion criteria for this study include: (1) any individual affected by cancer identified as unsuitable to participate by their treating oncologist (due to psychological or medical concerns) and (2) any participant who is unable to read and write English.

Recruitment

We will identify eligible childhood cancer survivors and parents of survivors through the electronic databases of all 11 paediatric oncology hospitals across Australia/New Zealand. Participant information will be extracted including name, address, phone number, diagnosis, date of diagnosis, date of birth and vital status (ie, 'alive'/'deceased'). Eligible participants will be invited via post. We will send childhood cancer survivors (and survivors' parents) an invitation package containing a personalised invitation letter, information sheet and questionnaire to collect sociodemographic and clinical

data. Participants will be able to opt-in for a telephone interview (indicated at the end of the questionnaire). We will contact participants who opt-in by telephone to arrange an interview at a time convenient for them. Potential participants who do not respond within 2 weeks after the initial mail-out will be followed up by telephone (up to two times) and thereafter will be assumed as lost to contact.

We will invite survivors of adult cancer and community comparisons through two online research panels. Survivors of adult cancer will receive an invitation through two voluntary registers of individuals affected by cancer, including 'Pathfinder' and 'Register 4'. Further information about Pathfinder is available at https://pathfinderregister.com.au/ and additional information about Register 4 can be found here: https://www.register4.org.au/. Community adults and community parents will be invited through PureProfile, an organisation which holds a register of individuals interested in participating in research, largely comprising respondents to Australia Post's surveys. We will email participants registered with Pathfinder, Register 4 and PureProfile a link to the online questionnaire. They will first complete a series of screening questions to assess their eligibility for the study.

Data collection

We will collect childhood cancer survivors' and survivors' parents' clinical and demographic data through questionnaires. We will elicit childhood cancer survivors' and parents' perceived acceptability of PDXs through a structured telephone interview, conducted by trained researchers with no previous relationship with participants. We chose an interview format for data collection for childhood cancer survivors and parents because email addresses are not available through treating hospitals and we have conducted successful telephone-based research with this population previously.[34] We will digitally audio record and transcribe all transcripts verbatim, with the permission of participants.

We chose an online survey format for adult cancer survivors and community participants to enable us to reach a larger representative sample. As per PureProfile procedure, eligible community participants will receive ~$A5 for participation. We will remove duplicate cases (indicated, eg, by duplicate IP addresses and survey data).

Outcomes

The primary endpoint of this study is to evaluate the acceptability of PDXs to cancer survivors, survivors' parents, community adults and community parents, as assessed by the decisional balance ratio. A secondary endpoint is to examine whether there are any differences in the acceptability of PDXs between cancer survivors and community adults, and between survivors' parents and community parents. We will also assess any sociodemographic factors which may influence acceptability.

Measures

Given that there are no available tools to assess the primary research question for this study, we have purposively designed the study measures, using in-depth data collected in our pilot. Before asking any questions, we will briefly describe PDXs to participants (see online supplementary files 1 and 2). To check participants' understanding, we will ask interview participants to describe their understanding in their own words, providing an opportunity to correct misunderstandings. In the online surveys, we will invite participants to indicate how well they understood the PDX description and assess their understanding with a 'True or False' question about PDXs. We will analyse data from any participants who demonstrate that they do not understand the key elements of the PDX process separately from those who indicate that they do understand PDXs. We will not exclude participants who do not understand PDXs because patients who do not understand new medical advances often still need to make a decision about whether they would like to use these advances in their care.

We will index PDX acceptability across five domains:

1. Willingness to use PDXs: We will assess participants' perceived willingness to use a PDX if facing a cancer diagnosis in themselves or in their child (survivors' parents and community parents only). Participants will be invited to rate their willingness to use PDXs both before, and after, discussion of the advantages and disadvantages (table 1) to assess any changes after deliberation. Willingness will be measured on a scale of 1='not at all willing' to 7='very willing'.
2. Perceived advantages and disadvantages: We will ask participants to rate the perceived importance of seven advantages and seven disadvantages of PDXs listed in table 1, measured on a scale of 1='not at all important' to 7='very important'. We will use these scores to calculate a decisional balance ratio (mean advantages score divided by mean disadvantages score), which is the primary endpoint for the study.
3. Maximum out-of-pocket costs: We will assess participants' willingness to pay by gradually increasing a suggested out-of-pocket cost until participants indicate that they are not willing to pay that amount, on a scale ranging from $A100 to $A50 000.
4. Maximum length of time willing to wait for results: We will assess maximum acceptable wait time to receive results by increasing a suggested wait time to participants until participants indicate that they are not willing to wait that long, on a scale from 2 weeks to 1 year.
5. Maximum acceptable number of mice per patient: We will assess the maximum acceptable number of mice per patient by increasing a suggested number of mice until participants indicate that they are not willing to sacrifice that number, on a scale from 10 to 1000.

Data analysis

For data analysis, we will group participants into one of four categories: cancer survivors (survivors of childhood

or adult cancer) to be compared with community adults, and parents of childhood cancer survivors to be compared with community parents. We will use participant ratings of PDX advantages and disadvantages to create a decisional balance ratio, calculating the individual's mean advantages ratings divided by their mean disadvantages ratings. This approach assesses whether participants' perceived advantages outweigh the perceived disadvantages. Similar approaches have been used in other studies, for example, the decisional balance ratio created by Tercyak *et al*.[35] Any values above 1 will indicate that participants perceive that the advantages of PDXs outweigh the disadvantages (ie, PDXs are 'acceptable'), while values below 1 will indicate that the disadvantages outweigh the advantages (ie, PDXs are 'not acceptable'). A value of 1 will represent 'decisional equivalence', that is, that neither the advantages nor the disadvantages outweigh the other. For this data analysis, participants with decisional equivalence will be grouped into the 'not acceptable' category to create a binary endpoint. If participants indicate that they do not understand the PDX description, we will conduct a subgroup analysis of the data from this group to examine their acceptance and willingness to use PDXs. We anticipate this number to be low (~2%) based on our pilot data. The exact statistical tests for this analysis will therefore depend on the final number of participants who indicate that they do not understand the description.

We will use SPSS V.24.0 for all statistical analyses.[36] Results will be considered statistically significant when $p<0.05$ (two tailed), appropriately adjusted for multiple testing using a Bonferroni correction. We will use independent samples t-tests and a 2×2 repeated measures analysis of variance to examine differences between cancer survivors and community adults, and between survivors' parents and community parents. We will conduct exploratory regressions to explore factors influencing five outcomes: willingness to use, decisional balance ratio, willingness to pay, willingness to wait and maximum acceptable number of mice. The regressions will test the influence of key sociodemographic factors including: the target patient (ie, considering PDX for themselves or for their child), sex, income and education. We will check all data for skew and will check ordinal data treated continuously for linearity using the univariate residuals. We will ensure data quality by conducting careful data cleaning, including checking ranges for all variables and double coding 10% of all data. Data analysis will use listwise deletion (ie, participants with missing item responses will be excluded from analyses including that item). We will check the consistency of data collected by telephone interview by checking adherence to the structured interview schedule alongside data collection. Data with more than 15% deviation from the standardised interview schedule will be excluded from analysis.

Sample size

For the primary analysis, we will calculate a binary measure of acceptability for each participant ('acceptable' will include decisional balance ratios greater than 1, 'not acceptable' will include decisional balance scores equal to or less than, 1). We will use this binary measure to estimate the prevalence of PDX acceptability in each sample. A minimum sample size of 323 in individuals affected by cancer plus 323 community comparisons will allow us to produce estimates of the prevalence in each group with 95% CIs that each has a margin of error of no more than 5%.[37] This assumes that the true prevalence is approximately 70%, based on the qualitative interviews we conducted in our pilot.

Patient and public involvement

This programme of work has been carefully designed by our multidisciplinary team of researchers, and oncology and allied health professionals. Childhood cancer survivors and parents also guided the study design. Our key research questions and our list of pros and cons are based on the results of our pilot study, which involved survivors and parents, to maximise the relevance of the advantages and disadvantages of PDXs to patients and the public. The protocol development was also informed by our Scientific and Consumer Advisory Committees, which include families affected by cancer and health professionals with an interest in cancer survivorship care. We will maintain regular meetings with both Committees during the conduct of the study. We will disseminate the results of our study via letters, study newsletters and our webpage.

ETHICS AND DISSEMINATION

Data management

We will use an electronic database to organise study data and for data analyses. Electronic data will be password protected and kept at the Kids Cancer Centre, Sydney Children's Hospital, on a secure server, which is backed up daily. Hard copy data that contain participant identifiers will be filed in a lockable filing cabinet at the Kids Cancer Centre under the responsibility of the principal investigator, data custodian and other research staff. Access to the database and passwords will be restricted to the principal investigator, study coordinator and study research assistants. Stored data include: participant files, study protocol, signed consent forms, questionnaires, ethics correspondence and approvals, other regulatory documentation, and other documents pertaining to the conduct of the study. We will remove patient identifiers for data analysis and related study documents will only contain a unique participant ID. Only research staff will have access to linkable information which will be kept confidential by law. A data monitoring committee will not be needed because the study poses minimal risk to participants and focuses on behavioural issues.[38]

After completion of the research, we will store study-related records for all patients in a secure storage facility for at least 5 years from the date of publication, in accordance with the Australian Code for the Responsible Conduct of Research.[39]

Any amendments, where necessary, will be submitted for review and approval prior to implementation. Study status will be reported annually, as required. A final study notification will be forwarded at completion of the study or in the event of early termination to the relevant ethics committees. Participants will be informed that they are free to withdraw from the study at any time, without affecting their right to medical care. Participation is voluntary, and those who wish to revoke their consent will be able to do so at any time without consequence to their treatment or relationship with their treating team or the research team. Their data collected as part of the study will be removed from the study and destroyed.

Adverse events

This study is of low risk and we do not anticipate any adverse events to occur. However, it is possible that participating in the study may lead to anxiety or distress. Any evidence of this, as expressed directly during an interview or as indicated in questionnaire comments will be addressed directly and as soon as possible by a clinical psychologist from the research team. All adverse events will be monitored and reported to the ethics committees. Progress addressing adverse events will be recorded until their resolution.

End of study

The study recruitment will end when 323 individuals affected by cancer (including survivors and survivors' parents) and 323 community participants (including community adults and community parents) are recruited.

Study oversight

The Behavioural Sciences Unit research team at the Kids Cancer Centre, Sydney Children's Hospital will be responsible for all aspects of the study including the design, ongoing management, ethical conduct, statistical analysis and dissemination of the results.

Dissemination

All data collected from participants will be de-identified and summarised (eg, mean±SD) for dissemination. The results will be disseminated in peer-reviewed journals and at scientific conferences. A lay summary will be published on the Behavioural Sciences Unit website: http://www.behavioural sciencesunit.org/. No participant names or other identifying information will appear in any publications stemming from this research.

Study status

Study recruitment was initiated in January 2016 and is expected to be completed in early 2018.

DISCUSSION

Individualised treatment may soon serve as standard care in oncology.[28] PDXs offer a new form of patient-tailored medicine, bridging the gap between in vitro studies and human trials.[16] This is the first study which aims to determine the acceptability of using PDXs to guide cancer-related treatment decision-making. Key strengths include the involvement of multiple stakeholders across two countries, including parents, child and adult cancer survivors (who best understand the stakes involved), as well as community comparisons (who may be affected by cancer in future). This multiperspective approach will enhance the generalisability of our findings. This study is also strengthened by the in-depth pilot data which we used to inform data collection. The results of this study will guide consent consultations for future patients and will form the foundation for further studies relating to the cost-effectiveness of PDXs. Effective delivery of PDX-based clinical trials and precision medicine programmes of the future will require a coordinated effort between clinicians, and laboratory and behavioural scientists. This study is an important step in encouraging coordination between these complementary disciplines to bring about successful translation of PDXs into clinical care.

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Contributors CEW is leading the project coordination and conceived the project. She developed the protocol and wrote the first and final drafts of the manuscript. ELD will contribute to data entry and lead data analysis. JEF will conduct interviews and contribute to data analysis and interpretation. CS helped to design the protocol, write the first and final drafts of the manuscript and will lead participant recruitment, data collection and data entry. VFQ will perform data entry and analysis and review manuscript drafts. KFT, AFP, GMM and RBL helped to design the study and write the first and final drafts of the manuscript. GG will assist with participant recruitment and data collection and will review manuscript drafts. RJC helped to conceive the project, develop the protocol and write the manuscript. All authors provided feedback on drafts of this article and read and approved the final manuscript.

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Competing interests None declared.

Patient consent Not required.

Ethics approval This study has been approved by the South Eastern Sydney Local Health District (SESLHD) Human Research Ethics Committee (HREC, 12/173) and UNSW Sydney (HC15773).

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