Research Paper

The Avatar Acceptability Study: Survivor, Parent and Community Willingness to Use Patient-Derived Xenografts to Personalize Cancer Care

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ABSTRACT

Background: Using patient-derived xenografts (PDXs) to assess chemosensitivity to anti-cancer agents in real-time may improve cancer care by enabling individualized clinical decision-making. However, it is unknown whether this new approach will be met with acceptance by patients, family and community.

Methods: We used a cross-sectional structured survey to investigate PDX acceptability with 1550 individuals across Australia and New Zealand (648 survivors of adult and childhood cancer, versus 650 community comparisons; and 48 parents of childhood cancer survivors versus 204 community parents). We identified factors influencing willingness-to-use PDXs, willingness-to-pay, maximum acceptable wait-time, and maximum acceptable number of mice used per patient.

Findings: PDXs were highly acceptable: ~80% of those affected by cancer felt the potential advantages of PDXs outweighed the disadvantages (community participants: 68%). Survivors’ and survivors’ parents’ most highly endorsed advantage was ‘increased chance of survival’. Harm to animals’ was the least endorsed disadvantage for all groups. Cancer survivors were more willing to use PDXs than community comparisons [p < .001]. Survivors and survivors’ parents were willing to pay more [p < .001; p = .004 respectively], wait longer for results [p = .03; p = .01], and use more mice [p = .01; p < .001] than community comparisons. Male survivors and survivors’ parents were willing to pay more [p < .001; p = .001 respectively]. Male survivors with higher incomes found PDXs more acceptable [p = .002] and were willing to pay more [p < .001] than female survivors. Mothers found PDXs more acceptable [p = .04] but were less willing to wait [p = .02] than fathers.

Interpretation: We found significant attitudinal support for PDX-guided cancer care. Willingness-to-pay and maximum acceptable number of mice align well with likely future usage. Maximum acceptable wait-times were lower than is currently achievable, highlighting an important area for future patient education until technology has caught up.

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1. Introduction

Patient-derived xenografts (PDXs) can be created by engrafting an individual patient’s tumor into immune-deficient mice [1,2]. Once the tumor has engrafted, the tumor is extracted and implanted into secondary recipient mice, creating further cohorts of mice with tumors which closely mirror the patient’s original tumor. These PDXs (or ‘mouse avatars’) can then be used for drug efficacy studies by randomly assigning
Evidence before this study

Using patient-derived xenografts (PDXs) to guide treatment decision-making within personalized medicine programs may represent a significant advance in cancer care. However, patient and community preferences can shape the success of newly developed technologies. PDX models are nearing implementation into personalized medicine programs worldwide, warranting this timely evaluation of their acceptability and likely future uptake in personalized cancer care.

Added value of this study

This is the first study to evaluate the acceptability of PDXs to guide treatment decision-making in cancer care. This study of 1,550 individuals affected by cancer and community comparisons comprehensively assesses: perceived advantages/disadvantages of PDXs, willingness to use PDXs if diagnosed with cancer, maximum acceptable out-of-pocket costs/patient, maximum acceptable time to receive PDX results and treatment recommendations, and maximum acceptable number of mice used per patient. Our study compares the perspectives of cancer survivors with community comparisons (who may face a future cancer diagnosis), strengthening the study’s generalizability. It also investigates the perspectives of parents considering PDXs for their child.

Implications of all the available evidence

Our results show high willingness-to-use PDXs, indicating a likely high uptake of PDXs in future practice, particularly for children with cancer. Participants’ willingness-to-pay and maximum acceptable number of mice align well with planned PDX models. However, current wait times appear too long for participants, who preferred potentially unachievable maximum wait times in current models. This emphasizes the need to educate potential patients appropriately upon enrolment into PDX-guided personalized medicine programs to manage their expectations. Our results will inform the successful implementation of PDX models, and similar technologies, and guide the future of patient involvement in cancer treatment decision-making.
telephone interviews with 16 cancer survivors (9 female) and 8 parents of survivors (5 mothers). We used these interviews to identify participants’ seven most commonly endorsed advantages and seven most endorsed disadvantages of PDXs (Supplementary Table 1). The main study used the themes arising from the pilot for a comprehensive quantitative assessment. The Institutional Review Boards of 11 Australian and New Zealand hospitals and UNSW Sydney provided ethical approval. We recruited participants from January 2016–April 2018.

2.2. Participants (Table 1)

2.2.1. Individuals affected by cancer

1) Cancer survivors: Eligible survivors included survivors of childhood and adult cancer, diagnosed at least 6 months prior to study participation who had completed cancer treatment and were aged 16 or older.

2) Parents of childhood cancer survivors (“survivors’ parents”): Parents of childhood cancer survivors who were aged <16 years.

2.2.2. Individuals not affected by cancer (community comparisons)

3) ‘Community adults’: Community members with no history of cancer, no children with cancer and currently aged 16 or older.

4) ‘Community parents’: Parents with no history of cancer, no children with cancer and at least one child aged under 16.

2.2.3. Exclusions

We excluded individuals with insufficient English and those considered unsuitable by their medical team (e.g. severe cognitive impairment).

2.3. Recruitment

Aligning with the protocol [19], we aimed to recruit a minimum of 323 individuals affected by cancer and 323 community comparisons. We matched the community comparison groups to the groups affected by cancer (by age and sex). We recruited survivors of adult cancers and community comparisons through three voluntary online research panels (Register4 and PathFinder for adult cancer survivors, PureProfile for community comparisons). The panels have national coverage and reach a demographically diverse participant group. We emailed panel members an invitation to complete screening questions before directing eligible participants to an online survey. Community comparisons received ~AUS$5. We prevented responses from duplicate IP addresses.

There is no similar online panel for childhood cancer survivors and pediatric hospitals do not routinely collect email addresses, so we posted study invitations to childhood cancer survivors and childhood cancer survivors’ parents. Childhood cancer survivors/survivors’ parents provided demographic data via a paper questionnaire and then completed a structured telephone interview with trained interviewers with no previous relationship with participants. We digitally recorded and transcribed interviews verbatim.

2.4. Measures

Participants self-reported their: sex, education, postcode, parental status and income. Individuals affected by cancer reported their (or their child’s): cancer diagnosis and time since diagnosis (in years). We briefly described PDXs to all participants (Supplementary Table 2) and then asked participants to indicate how well they understood the description [1 = ‘not at all’, to 5 = ‘completely’].

We then assessed participants’ willingness-to-use a PDX if facing a cancer diagnosis in themselves (survivors, community adults), or in their child (survivors’ parents, community parents) [1 = ‘not at all willing’, to 7 = ‘very willing’].

We asked participants to rate the seven advantages and seven disadvantages identified in the pilot study [1 = ‘not at all important’, to 7 = ‘very important’], and then re-assessed willingness-to-use.

We assessed willingness-to-pay by gradually increasing a suggested out-of-pocket cost until participants indicated that they were not willing to pay that amount [from AUS$100 to AUS$50,000; NZD$110 to NZD$55,000; equivalent to approximately USD$75 to USD$38,000].

We assessed maximum acceptable wait-time to receive results/recommendations by increasing wait-time from two weeks to one year.

We assessed maximum acceptable number of mice/patient by first asking participants whether the number of mice would influence their decision. If participants answered yes, they then indicated how many mice would be acceptable, with response options increasing from 10 to 1000 mice until participants indicated that they would be unwilling to use that number.

2.5. Statistical analysis

The primary outcome was decisional balance score. Similar to Tercyk et al. [20], we created a decisional balance score for each participant by calculating the individual’s mean advantages ratings divided by their mean disadvantages ratings. Values above one indicated a leaning towards the advantages, suggesting that PDXs were considered “acceptable”. Values below one indicated a leaning towards the disadvantages, and that PDXs were “not acceptable”. A value of one represented decisional equivalence, that is, neither the advantages nor the disadvantages outweighed the other. For this study we categorized a decisional balance score of one as “not acceptable”.

We excluded a random selection of 135 community adults under the age of 43, and a further 95 male community adults under the age of 43 to match the cancer and community groups. We used independent and paired samples t-tests and a 2 × 2 repeated measures analysis of variance (ANOVA) to examine between and within group differences in the cancer and community groups. We computed exploratory regressions to explore sociodemographic factors (sex, income, education and rurality) influencing four outcomes: decisional balance, willingness-to-pay, maximum acceptable wait-time, and maximum acceptable number of mice. We produced bivariate correlations between outcome variables and influencing factors first, and then included correlations with p ≤ .02 in the final regression models. We performed bootstrapping on all final regression models. Given the differences in timing and type of treatment patients typically receive across cancer diagnoses (e.g., chemotherapy for hematological cancers, surgery for solid tumors), we also conducted a secondary analysis investigating differences between hematological and solid cancers for the four main

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Individuals affected by cancer</th>
<th>Community comparisons</th>
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<tbody>
<tr>
<td>Adults considering PDX for self</td>
<td>Survivors of adult and childhood cancer</td>
<td>versus</td>
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<tr>
<td>Parents considering PDX for their child</td>
<td>Parents of childhood cancer survivors ['survivors' parents']</td>
<td>Community adults</td>
</tr>
<tr>
<td></td>
<td>versus</td>
<td>Community parents</td>
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</table>

Abbreviations: PDX: patient-derived xenografts.
outcome variables. Significant differences were determined using Welch’s t-test, given the large difference in sample size across these two diagnosis groups [21]. We planned a-priori to analyze data from participants who indicated that they did not understand PDXs separately [19]. Regressions that included income as a variable excluded participants who chose not to report their income (Table 2). We have provided a denominator (i.e., the number of participants who provided a response) for each reported statistic, to highlight any missing data. We provided a denominator (i.e., the number of participants who provided a response) for each reported statistic, to highlight any missing data. We provided a denominator (i.e., the number of participants who provided a response) for each reported statistic, to highlight any missing data. We used SPSS25.0 and considered results significantly different to those who did not. We used SPSS25.0 and considered results significantly different to those who did not.

### 3. Results

1550 individuals participated [1298 in the adult groups (648 survivors versus 650 community comparisons) and 252 in the parent groups (48 parents of childhood cancer survivors versus 204 community parents)]. See Table 2 for demographic/clinical characteristics.

The groups were well matched: there were no significant sex, age, income, or rurality differences between survivors and community comparisons. A higher percentage of survivors had post-school qualifications compared with community participants, so we included education in all regression models. There were no significant sociodemographic differences between survivors’ parents and community parents. One adult survivor, eight community adults, and one community parent indicated that they did not understand PDXs. The groups were too small to conduct separate analyses, so we excluded these participants from final analyses.

#### RQ1. Perceived advantages and disadvantages of PDXs and decisional balance

Survivors and community comparisons rated the potential advantages of PDXs (cancer: M = 6.37, SD = 0.95; community: M = 5.91, SD = 1.39) significantly higher than potential disadvantages (cancer: M = 4.81, SD = 1.34; community: M = 4.96, SD = 1.29; F = 839.66, p < .001), however, the magnitude of this difference was significantly larger for survivors (F = 56.41, p < .001).

Eighty-three percent of survivors (535 out of 648) and 68% of community adults (444/650) had a decisional balance greater than one (Fig. 1). Decisional balance was significantly higher in survivors...
Given the unequal sample sizes between parent groups, we conducted separate paired t-tests to compare within group differences in perceived advantages and disadvantages for the parent samples separately. Survivors’ parents and community parents rated the potential advantages of PDXs significantly higher than potential disadvantages (cancer: MD = 2.57, t(46), p < .001; community: MD = 0.76, t(203) = 8.07, p < .001).

Eighty-nine percent of survivors’ parents (42/47) and 68% of community parents (138/204) had a decisional balance greater than one (Fig.1). Decisional balance was significantly higher in survivors’ parents than in community participants [MD = 0.96, 95%CI [0.53, 1.40], t(50.30) = 4.45, p < .001] (Supplementary Fig. 1). Survivors’ parents, mothers, and those with higher income were more likely to indicate a higher decisional balance score.

When considering the seven listed advantages/disadvantages of PDXs, the most important perceived advantage varied across groups (survivors and survivors’ parents: ‘improving survival chances’, community adults: ‘faster recovery’, community parents: ‘avoiding other drugs’) (Supplementary Table 1). Survivors, community adults and community parents endorsed ‘recommended treatments being unavailable/too expensive’, as the most important disadvantage. The least endorsed advantage across all groups was ‘reassurance doctors tried everything’ and the least endorsed disadvantage was ‘PDXs harm animals’.

**RQ2.** Willingness-to-use PDXs, before and after consideration of advantages/disadvantages

Cancer survivors indicated a higher willingness-to-use PDXs than community comparisons, when averaged across before (cancer: M = 6.03, SD = 1.46; community: M = 5.47, SD = 1.77) and after (cancer: M = 5.85, SD = 1.36, community: M = 5.31, SD = 1.69; F = 43.21, p < .001) consideration of the advantages and disadvantages of PDXs. A main effect of time-point (i.e., comparing before and after scores, averaged across group) suggested that participants’ willingness-to-use PDXs decreased after consideration of the advantages and disadvantages (F = 38.07, p < .001), with the magnitude of this decrease similar for survivor and community participants (F = 38.38, p = .54).

In the parent groups, community parents’ willingness-to-use decreased after consideration of the advantages and disadvantages of PDXs (MD = 0.25, t(203) = 4.76, p < .001), whereas, survivors’ parents ratings did not significantly change (MD = 0.11, t(46) = 1.22, p = .23).

**RQ3.** Willingness-to-pay for PDXs

Seven percent of survivors (36/542) reported being willing to pay the maximum proposed amount (AUD$50,000/NZD$55,000), while 2% of community adults (11/520) were willing to pay the maximum (Fig. 2). Survivors were willing to pay more than community participants (t(1060) = 9.04, p < .001). Survivors, men, and participants with higher incomes, were more likely to indicate a higher willingness-to-pay (Table 3).

Thirty-eight percent of survivors’ parents (14/37) reported being willing to pay the maximum, while 15% of community parents (23/156) were willing to pay the maximum (Fig. 2). Survivors’ parents were willing to pay more than community parents (t(49.90) = 3.05, p = .004). Survivors’ parents with higher incomes were more likely to indicate a higher willingness-to-pay (Table 3).

**RQ4.** Maximum acceptable wait-time for results/recommendations from PDXs

Two percent of survivors (11/603) reported being willing to wait the maximum time (one year), while 0.5% of community adults (3/584) reported being willing to wait that long. Survivors reported a willingness to wait longer than community participants (t(1185) = 2.43, p = .02). Fig. 3. Survivors, men, those of older age, and those with post-school

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### Table 3

<table>
<thead>
<tr>
<th>Survival and Community Adults</th>
<th>$\beta^b$ [95%CI]</th>
<th>t</th>
<th>p</th>
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<tbody>
<tr>
<td>Decisional balance $R^2 = .05$</td>
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<tr>
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<td>0.95</td>
<td>.36</td>
</tr>
<tr>
<td>Sex &amp;</td>
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<td>.006</td>
</tr>
<tr>
<td>Age &amp;</td>
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<td>2.65</td>
<td>.01</td>
</tr>
<tr>
<td>Income &amp;</td>
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<td>2.99</td>
<td>.001</td>
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<tr>
<td>Willingness to pay $R^2 = .15$</td>
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<td>.001</td>
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<td>.045</td>
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<td>Sex &amp;</td>
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<td>.002</td>
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<tr>
<td>Age &amp;</td>
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<td>-1.96</td>
<td>.06</td>
</tr>
<tr>
<td>Income &amp;</td>
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<td>6.10</td>
<td>.001</td>
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<tr>
<td>Willingness to wait $R^2 = .04$</td>
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<tr>
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<td>2.14</td>
<td>.03</td>
</tr>
<tr>
<td>Education &amp;</td>
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<td>.01</td>
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<tr>
<td>Sex &amp;</td>
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<tr>
<td>Number of mice R $R^2 = .03$</td>
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<tr>
<td>Group &amp;</td>
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<td>.003</td>
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<tr>
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<td>.56</td>
</tr>
<tr>
<td>Age &amp;</td>
<td>-0.01 [-0.02, 0.003]</td>
<td>-1.99</td>
<td>.10</td>
</tr>
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*We used bootstrapping methods for all regression models.

Unstandardized regression coefficients reported.

Coded as 0 = community participants, 1 = survivors.

Coded as 0 = males, 1 = females.

Coded as 0 = community parent, 1 = survivors’ parents.
education were more likely to indicate a higher maximum wait-time (Table 3).

Among survivors' parents, 16% (7/43) were willing to wait the maximum time (one year), compared with 2% (3/180) of community parents. Survivors' parents were willing to wait longer than community parents ($t(51.36) = 2.94$, $p = .01$), Fig. 3. Survivors' parents, fathers, and those with post-school education were more likely to indicate a higher maximum wait-time (Table 3).

RQ5. Maximum acceptable number of mice/patient.

Nine percent of survivors (19/217) endorsed a willingness-to-use up to 1000 mice, while 5% (11/219) of community participants (who indicated the number of mice would influence their decision) were willing to use up to 1000 mice (Fig. 4). Survivors were willing to use more mice per patient than community comparisons ($t(420) = 3.06$, $p = .002$). The regression indicated that survivors accepted a higher number of mice (Table 3).

Fifty-nine percent of survivors' parents (16/27) endorsed a willingness-to-use up to 1000 mice, while 11% (8/71) of community parents (who indicated that the number of mice would influence their decision) were willing to use up to 1000 mice. Survivors' parents were willing to use many more mice per patient than community parents ($t(37.59) = 4.12$, $p < .001$), Fig. 4. Survivors' parents, and those with post-school qualifications, accepted a higher number of mice, Table 3.

3.1. Secondary research question: Acceptability of PDX by cancer type

In the survivor group, average decisional balance, maximum acceptable wait-time and maximum acceptable number of mice did not differ between those diagnosed with hematological cancer versus solid tumors (MD = 0.22, $-0.01, 1.08$; $p = .19, 0.96, 0.21$ respectively). Survivors diagnosed with hematological cancers were willing to pay more for PDXs compared with survivors diagnosed with solid tumors ($t(28.45) = 2.86$, $p = .01$). There were no significant differences in decisional balance, willingness to pay, acceptable wait-time, or acceptable number of mice across children's cancer diagnoses among survivors' parents (MD = 0.34, $-0.35, -0.58, 0.20$; $p = .43, 0.73, 0.15, 0.77$ respectively).
4. Discussion

Most cancer survivors, parents of childhood cancer survivors, and the general community favor the use of PDXs in future cancer therapeutic strategies. Participants reported a high willingness-to-use and a perception that PDX advantages outweighed disadvantages, suggesting likely high consent rates when PDXs are implemented into personalized cancer care. Reflecting the salience of the cancer experience, those affected by cancer were more willing to use PDXs and were willing to pay more, wait longer, and use more mice, than community participants. Reflecting the notion that the ‘stakes are higher’ when considering cancer in a child, parents reported being willing to pay large sums and use many mice, for their child. Other sociodemographic factors appeared important too. Males found PDXs more acceptable, and were willing to pay more than females, while mothers found PDXs more acceptable but were willing to wait less time, than fathers. Participants with higher incomes found PDXs more acceptable and were willing to pay more. Willingness-to-pay and maximum acceptable number of mice appeared largely in line with the likely PDX services of the future [2,11], although many participants’ maximum acceptable wait-times were lower than is currently achievable [11].

PDX efficacy data, while promising, is not yet robust [2,11]. Our description of PDXs did not state that PDXs were effective, yet many participants endorsed ‘potential improved survival’ as their most important perceived advantage (particularly survivors and survivors’ parents). Potential health benefit is a key motivator for many patients and parents considering enrolling in research [22]. While willingness-to-use did decline somewhat after consideration of the advantages and disadvantages of PDXs, willingness-to-use remained high, especially in those affected by cancer. It seems that disclosure of PDX limitations will be unlikely to dissuade families. Ensuring fully informed consent will be challenging, given the complexity of the PDX process [2], differences in PDX models across institutions [2], the often overwhelming availability of cancer information [23], and low pre-existing health literacy in some patients [24]. PDX information should follow patient education guidelines [25] to ensure that materials are easy-to-understand, while consent consultations should carefully gauge patient/parent understanding, and encourage question-asking.
Cancer is a life threatening diagnosis: it is therefore understandable that patients and parents feel impatient to receive treatment recommendations. Yet, wait-times for PDX results/recommendations are currently longer than most other tests in cancer care. Given our data showing a disconnect between participants’ maximum acceptable wait-times, and current engraftment efficiency [2], it is important that consent consultations/forms clearly highlight the likely wait-time for PDX results. Our data (reflecting other willingness-to-wait studies) [14] indicate the steepest drop in willingness-to-wait when the wait-time increases from one to three months, suggesting that patients/parents may need additional support once the wait-time exceeds one month. Our data suggesting possible sex differences in willingness-to-wait (males and fathers appeared willing to wait longer than females and mothers) also warrant further investigation. There are few health-focussed studies available comparing willingness-to-wait between males and females. One study reported equivalent willingness-to-wait in males and females waiting for care in an emergency department [26]. More generally, our findings may have been influenced by sex differences in general healthcare-seeking behaviors, with research suggesting that men might be less likely to engage in health care-seeking behaviors, including waiting longer to seek medical advice about their symptoms [27].

Many participants (particularly parents, those with higher incomes and those with hematological cancers) were willing to pay large out-of-pocket costs for PDXs. This willingness-to-pay likely reflects a perception of high worth of PDXs, as well as serving as a surrogate indicator of likelihood of adoption [14,28]. Fear of cancer recurrence, which remains prevalent even decades after treatment completion [29], may have driven survivors’ and survivors’ parents’ willingness-to-use and pay. This powerful fear likely represents a vulnerability for families desperate for a cure [13]. Given that commercial laboratories are already offering costly direct-to-consumer PDX services [3,30], this raises concerns about how PDXs will be marketed to vulnerable families, and highlights the need for careful PDX regulation [3].

The role of animals in society appears to be transforming. Animal advocacy groups often fight for a reduction in the use of research animals, yet PDXs will involve dozens of mice per patient. Despite these numbers, and the fact that PDXs form a more direct link between animals and individual patients, our finding that ‘harm to animals’ was the least endorsed disadvantage reflects an acceptance of the use of animals for potentially lifesaving purposes. Like other studies [31], we showed that acceptability dropped with the use of more animals. However, individuals affected by cancer clearly accepted the largest numbers of mice (especially survivors’ parents, most of whom indicated a willingness to use up to 1000 mice per child). This research question revealed the strongest discrepancy in views between individuals affected by cancer and community participants, which might create some discordance in future PDX implementation and funding models. It remains unclear how PDX acceptability might be shaped if increasing the number of mice used would also increase PDX efficacy.

4.1. Limitations

We recruited a large sample across two countries, plus a well-matched comparison group. However, anticipated uptake of new technologies does not always mirror actual uptake [14]. Participants’ attitudes might change to reflect a higher acceptability if individuals are currently faced with cancer. It was not possible to calculate study response rates given the different recruitment methods used for each group. Our data may not generalize to other contexts, (e.g. non-English speaking communities, non-universal healthcare systems). Breast cancer survivors and women were over-represented, which is common [32]. Recruiting survivors introduced a survival bias, creating an underrepresentation of aggressive cancers (e.g. lung cancer). A small amount of variance in our regressions was captured by our predictors, suggesting there are likely to be unmeasured variables influencing acceptability. Our different data collection methods (questionnaire versus interview) were necessary to ensure the representation of different cohorts. However, the data may have been influenced by the different data collection approaches.

4.2. Future directions

Prospective studies assessing the impact of using PDXs to guide treatment decisions in personalized medicine programs are needed. There are several technical developments in PDXs which warrant additional acceptability studies, including the use of zebrafish and tumor organoids [11]. Patient/parent willingness to undergo additional procedures to enable PDX creation (e.g. biopsies) also remains unexplored, as does the acceptability of the term ‘avatar’ to describe PDXs. Healthcare systems need to consider the cost-benefits of PDXs as they move into clinical care [2,3]. PDXs will likely improve with time, potentially warranting ongoing research of the acceptability of the more sophisticated technology.

5. Conclusions

PDXs are likely to play a key role in translational cancer care of the future, yielding personalized treatment information to guide clinical decision-making [1]. Despite being expensive and using animals to guide treatment decision-making [1,11], individuals affected by cancer, and the general community, find PDXs highly acceptable.
Declaration of interests

Kathy M. Tucker has received Honoria from AstraZeneca Australia with respect to mainstreaming BRCA genetic testing in adults. No other authors have conflicts of interest to declare.

Author’s contributions

CEW conceived and coordinated the project. She developed the protocol and wrote the manuscript. ELD contributed to data entry and lead the data analysis. JEF conducted interviews and contributed to data analysis and interpretation. CS helped to design the protocol, lead participant recruitment, conducted interviews and contributed to data entry. VFQ performed data entry and analysis and reviewed manuscript drafts. KFT, AFP, GMM and RBL helped to design the study and contributed to the manuscript development. GG assisted with participant recruitment and data collection and reviewed manuscript drafts. RJC helped to conceive the project, develop the study protocol and contributed to the manuscript. All authors provided feedback on drafts of this article and read and approved the final manuscript.

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