Author/s:
De Abreu Lourenco, R;McCarthy, MC;McMillan, LJ;Sullivan, M;Gillam, L

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Understanding decisions to participate in genomic medicine in children's cancer care: a comparison of what influences parents, health care providers and the general community.

De Abreu Lourenco, R[1*], McCarthy, M.C.[2,3,4*], McMillan, L.J.[2], Sullivan M,[3,4], Gillam, L.[5,6]

1. Centre for Health Economics Research and Evaluation, University of Technology Sydney, 1-59 Quay Street, Haymarket NSW 2000, Australia
2. Clinical Sciences, Murdoch Children's Research Institute 50 Flemington Road Parkville 3052
3. Children's Cancer Centre, Royal Children's Hospital, 50 Flemington Road, Parkville, Victoria, 3052 Australia
4. Department of Paediatrics, University of Melbourne, 50 Flemington Road, Parkville 3052 Australia
5. Melbourne School of Population and Global Health, University of Melbourne, Parkville, Victoria 3052, Australia
6. Department of Bioethics, Royal Children's Hospital, 50 Flemington Road, Parkville, Victoria, 3052 Australia

*joint first authors

Corresponding Author: Associate Professor Richard De Abreu Lourenco,

Centre for health Economics Research and Evaluation, University of Technology Sydney, Australia.

Email: Richard.DeAbreuLourenco@chere.uts.edu.au

+61 2 95144729

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Abbreviations	
HCPs	Healthcare providers
QoL	Quality of life
mWTP	Marginal willingness to pay
DCE	Discrete Choice Experiment
ANZCHOG	Australian and New Zealand Children's Haematology Oncology Group

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Abstract

Background: The emerging role of genomically-guided precision medicine in pediatric cancer care presents significant clinical, practical and ethical challenges. We investigated the factors that influence decision-making in genomic medicine from the perspective of different stakeholders in the context of difficult-to-treat childhood cancer.

Methods: Healthcare providers (HCPs), parents of childhood cancer survivors and general community members completed an online discrete choice experiment survey. Respondents considered whether to recommend (HCPs) or choose (parents/community) a genomically-guided approach to pediatric cancer treatment. Respondents completed 8 choice questions varying by: survival benefit, prognosis, likelihood of finding a target, quality of life (QoL), HCP/parent preference, need for biopsy, cost and who pays. Data were analyzed using a probability regression model, with findings expressed as relative importance, stated importance, and marginal willingness to pay (mWTP).

Results: 126 HCPs, 130 parents and 531 community members participated. The probability of recommending/choosing genomically-guided treatment increased significantly with better prognosis, survival benefit, improvements in QoL, and decision-making partner support. It decreased with increasing costs and if parents paid for treatment. HCPs were more responsive to all factors but were most influenced by survival outcomes, parents and community members by QoL. In contrast to these forced-choice preference results, HCPs stated they were most influenced by QoL and community members by survival.

Conclusion: Our findings support the primacy of QoL in genomic decision-making, with some differences across stakeholders in the other factors influencing decision-making. These findings emphasize the need for high quality information-giving and communication to support genomic medicine choices.

Introduction

Despite significant improvement in survival rates, childhood cancer remains a leading cause of death in children[1]. While some pediatric cancers are highly curable, survival rates for many others remain low, especially after disease relapse[2]. Whole genomic technology such as next generation sequencing (NGS) holds the hope that individualized analysis of a child's tumour may improve their survival through selection of novel targeted therapy (precision medicine), especially in relapsed/refractory cancers. However, the emerging precision medicine approach to treatment selection has limitations due to relatively low rates of actionable targets in many pediatric tumours[3], high rates of variants of unknown significance[4,5] and the complexities of managing additional findings that may have implications for other cancer risk or familial risk.[3-5] Moreover, if novel therapeutic drug targets are identified, their efficacy or safety in the pediatric setting may be unknown, or they may not be accessible due to cost.[3] The precision analysis of a tumor is also highly complex and may be challenging for parents and patients to understand, especially in stressful circumstances, making it difficult to provide truly informed consent.[6,7] Thus, the emerging role of precision medicine in the clinical setting presents significant clinical, practical and ethical challenges to address.[8,9]

Understanding parent and healthcare provider (HCP) preferences for genomically informed treatment is an important step in attempting to address these challenges. However, there are only a small number of studies investigating these preferences.[10-15] Broader research, examining parental decision-making about treatment options for their child with cancer, indicates parents are influenced by numerous factors including: the child's prognosis and quality of life (QoL), the impact of treatment on the family, as well as cost and funding considerations.[16,17] Several studies have highlighted how these factors influence HCPs and parents differently. For example, compared to oncologists, parents report more hope[18] and optimism[19,20] for their child's survival and may preference continuing cancer-directed therapy despite knowing cure is not possible.[21] Oncologists may not only have different views from parents on a child's prognosis but may be more influenced by different aspects of a child and family's QoL when considering treatment options.[18,21-23]

While the relative influence of these factors is not yet well understood, quantifying their influence can be used to guide clinical and ethical decision-making at the individual level, particularly given the complexities of informed consent processes and parent expectations of genomics.[15] Further, broader community views on the use of genomic medicine in childhood cancers can potentially inform healthcare priorities and decisions regarding resource allocation[24], particularly since, within a publicly funded health care system, the general community can be considered the funders.

One way to uncover the factors influencing decision-making is through the use of discrete choice experiments (DCE), applied widely in the field of health services research, including clinical genetics.[24,25] DCEs are a means of comparing alternative service models or treatment options ("profiles") described by their key characteristics ("attributes") thought to influence decision-making: e.g., survival or QoL. Systematically varying the combinations of attributes produces

different profiles, over which respondents state their preferences over repeated questions. The choices individuals make allow their preferences between attributes to be quantified.[26] Moreover, their preferences are informative in understanding what may be considered socially acceptable benchmarks for treatment participation.

We report on a DCE aimed at empirically investigating the factors influencing decision-making in genomically-guided medicine by oncology HCPs, parents of children treated for cancer and the general community. The principle aims of the study were to: (1) quantify the importance of those factors; and (2) investigate whether the three groups differ in the value and importance they place on factors (attributes) influencing decision-making in genomically-guided medicine. The DCE represents the third phase of a larger study; the first two (qualitative) phases have been reported elsewhere.[27]

Methods

Participants

Eligible HCPs: Oncology medical, nursing and allied health staff, clinical researchers and affiliated specialist staff directly involved in provision of pediatric cancer care. Recruitment was via email sent to members of the Australian and New Zealand Children's Haematology Oncology Group (ANZCHOG) and those who consented to recontact following Phase 1 of the study.[27]

Eligible Parents: (i) ≥ 18 years; (ii) had a child diagnosed with cancer ≤ 18 years who had completed treatment between 2-10 years ago; and (iii) had sufficient English and computer literacy to complete

the survey. Recruitment was via mailout to the Paediatric Integrated Cancer Service, Victoria, Australia research repository which contains contact details of parents of children who have consented to be contacted for research purposes.

Eligible Community: (i) ≥ 18 years; (ii) had not had a child treated for cancer; and (iii) had sufficient English and computer literacy to complete the survey. Recruitment was via the online panel provider, Toluna Australia (https://au.toluna.com).

Procedure

This study was approved by The Royal Children's Hospital Human Research Ethics Committee (HREC No 38050A). HCPs and community participants were provided with an online information statement that addressed the voluntary, anonymous and confidential nature of the survey. Parents (excluding any opt-outs) were telephoned by a research assistant two weeks after receiving a study information letter. Those interested were sent an email with the survey link which included an online information statement, and two reminder emails if required. Survey completion was accepted as consent.

The survey was administered online via SurveyEngine, with separate links administered to the three groups. The survey commenced in November 2018 and was completed over one week by the general community and closed in April 2019 for the HCP and parent populations to allow for sufficient recruitment.

DCE Development and Data Collection

Development of the DCE is detailed in the online supporting information. Respondents were asked whether they would recommend (for HCP) or accept (for parents/general community) a genomically-guided approach to treatment; comprising the decision to undergo treatment predicated on the chance of finding a possible treatment target. The approach described varied according to: the chance of surviving two years without genomically-guided treatment (survival prognosis), the chance of surviving two years with genomically-guided treatment (survival benefit), the chance of finding a target drug, QoL (impact on symptoms and functioning), HCP/parent preference, need for a biopsy, cost of treatment and who pays (Table 1). Each respondent completed eight forced-choice tasks (they had to state a preference to accept or recommend participation) out of a possible 64 (example in Figure 1). Respondents were also asked to state which attribute they considered to be the most important and which the least important when making their decisions.

Statistical Analysis

Analyses were conducted using Stata 16.[28] Answers to questions on stated attribute importance were summarised as within-sample frequencies. Choice question responses were analysed using a probit analysis[26] ; modelled as a binary function of the attribute levels corresponding to each choice profile, with subsequent analyses investigating the potential impact of demographic factors on choice. All attributes were modelled as categorical using effects coding (linear modelling of cost or chance attributes was not supported). With effects coding the constant coefficient is interpreted as the default probability of an HCP to recommend, or a parent/community member to accept, the proposed approach to genomically-guided treatment regardless of the levels of the attributes.[29]

Choices were analysed within samples separately (HCPs, parents and general community) and subsequently combined. A sample specific dummy variable was included to test for between group differences in the combined analysis.

The coefficients from the probit analysis were used to assess relative attribute importance, the influence of a given attribute on the choices individuals made, expressed on a scale from 0 to 1. This was calculated for each attribute as the range for its choice coefficients (difference between its highest and lowest coefficient values) as a proportion of the total range of choice coefficients across all attributes.[30]

mWTP was estimated by taking the marginal rate of substitution (or ratio) between the cost attribute and other attributes for which there was a significant choice coefficient.[31] As cost was specified as a categorical variable, the value used to estimate mWTP for a given attribute was determined using the mean across the coefficient values for cost.[31]

Results

A total of 126 HCP, completed the survey, comprising mainly nurses (30.2%), oncologists (24.6%) and allied health professionals (23.0%), with an average of 12.7 years (SD=8.8 years) in the pediatric cancer setting. A total of 266 identified eligible parents were contactable by telephone; 242 consented to participate and 130 completed the survey within the study timeframe (response rate 53.7%; 89% mothers). Of these, 44.0% had a child treated leukemia (mostly acute lymphoblastic leukaemia), 27.2% a solid organ/connective tissue cancer, 12.8% brain cancer, and 11.2% for

lymphomas. General community members comprised 532 participants. In general, a higher proportion of respondents in the parent and general community sample were younger, educated at a vocational level, and potentially of lower income (noting 11% of respondents did not disclose income) compared with the Australian population (Table 2).

Stated attribute importance

Stated attribute importance shows differences between the three groups in the factors they reported to have most and least influenced their choices to recommend or participate in a genomically-guided approach to treatment (Figure 2). HCPs and parents reported that QoL as most influential, while the general community reported survival benefit was most influential. All three groups reported that the need to have a biopsy was least influential factor (Figure 2).

Factors affecting choice

The results of the choice survey are presented graphically in Figure 3 and numerically in Supplemental Table S1. These results show, for each factor, whether that factor had a statistically significant influence on decisions about genomically-guided treatment and the direction of that influence. For example, a positive coefficient – the coefficient and its 'whiskers' sit to the right of the red line in Figure 3 - indicates that presence of that factor would increase the probability of a respondent choosing to recommend/ participate in a genomically-guided treatment.

Overall, the results show that all three samples had a default position (regardless of factors shown) to recommend/participate in a genomically-guided approach to treatment for difficult-to-treat pediatric cancers. This is evidenced by the positive and statistically significant coefficient for the constant in the model.

Factors affecting choice in each group

Across all three groups, six factors influenced choices for genomically-guided treatment in a positive direction: a 50% chance of two-year survival without treatment (prognosis survival); an additional 30% chance of surviving two years with treatment (survival benefit); the ability to spend time at home or doing usual activities (QoL functioning and symptoms); support from the other party in making the decision (i.e. parents or HCP, respectively); and having treatment funded by the national public insurer (the PBS). In addition, when the chance of finding a molecular target that could be treated reached 20%, it was influential for HCPs, but not for the other groups.

For all three groups, there was a decreased probability of choosing to recommend/participate in a genomically-guided treatment if it made only a small difference in the child's chance of two-year survival without treatment (1% compared with 10%), or in the difference in two-year survival with treatment (5% compared with 10%; observed for HCP and parent only). Increasing costs for parents had a negative influence on the probability to recommend/participate in genomically-guided treatment. The impact of parents paying was statistically significant for all groups, but the amount paid only achieved statistical significance for the general community sample and only for costs of $250,000 or above.

The influence of these factors on choices did not alter with the inclusion of demographic characteristics into the models (Supplemental Table S2).

Relative importance of factors influencing choice in each group

The results of the analysis of relative factor importance as derived from the forced-choice models are presented in Figure 4. Survival benefit most influenced choices for HCPs; QoL most influenced choices made by parents and the general community. There were differences between groups on the importance of survival prognosis (more important to the general community), finding a target (more important to HCPs), who pays (less important to HCPs) and cost of treatment (more important to the general community).

Combined analysis of choices

The results from the pooled analysis, combining all three groups, are provided in Supplemental Table S1. The same factors were influential across the whole sample as for each sub-group. The resulting choice coefficients are consistent with those from the individual sample analyses.

There was no difference identified between the general community sample and HCPs, as shown by the coefficients on the sample specific variables. However, parents were more likely overall to choose genomically-guided treatment for a child than HCPs. That is, while choice coefficients within an attribute were generally more widely spread for HCPs (showing greater responsiveness to the changes between the levels), the constant for the parent sample was almost double that of the HCP (illustrating the higher overall propensity to choose to participate in genomics) and the sample specific variable was statistically significant. This suggests that pooling of the results across the groups may not be appropriate given differences in underlying choice behaviour between HCPs and parents.

Willingness to pay (WTP)

The amount paid (cost) was statistically significant for the general community only. Thus, estimation of mWTP was restricted to the results from that sample and only for those factors with a statistically significant influence on choice. Results for mWTP are shown in Supplemental Table S3. Overall, the largest mWTP was with respect to the default willingness to accept genomic medicine (the constant). Thereafter, respondents were next willing to pay the most for changes in functioning; being able to regain usual activities compared with being in hospital most of the time had a mWTP of A$196,040. In contrast, if parents instead of the drug company were asked to pay for treatment, the largest required compensation (a negative mWTP) was A$187,871.

Discussion

Our study provides important insights into multiple factors that influence the decisions of parents, HCPs and the community, to adopt clinical care informed by genomics. While other studies have sought to understand the individual perspectives of HCPs and parents regarding genomics,[10,12,15] our research, using a DCE, is unique in seeking the participants' explicit choices about genomic medicine, including the comparative weight individuals place on the potential benefits of precision treatment, and the factors that influence their decision-making. Our results also revealed differences between stated attribute importance (as reported by respondents) and relative attribute importance (as revealed by the analysis of the forced-choice questions). For example, HCPs stated that QoL was the most important attribute influencing their choices, yet the results from the analysis of the DCE (forced-choices) showed that survival benefit was the most influential attribute. This finding highlights the importance of taking a nuanced approach to discussing all factors that may be relevant

to genomic decision-making, not simply the factors that individuals may state are important to them or factors that physicians may believe to be important.

For all groups, the gains associated with participating in genomically-guided treatment were important influencers of the choice to recommend/participate in genomic medicine. There were however differences in the weight applied to these benefits; HCPs placed more weight on gains in 2-year survival relative to other factors, while parents and the general community placed more weight on QoL. This result differs somewhat from broader research examining parent decision-making in oncology in which parents placed a higher emphasis on survival and the likelihood of cure.[18,20,23] It is possible HCPs' emphasis on survival benefit over QoL is particular to genomically-guided treatment, reflecting their understanding that targeted therapies are less likely to be associated with the toxicities of more standard treatments such as chemotherapy and radiotherapy.

HCPs were also the only group to be influenced by the increased likelihood of finding an actionable target. This finding is consistent with other studies that have found oncologists are more likely to recommend WGS with increased likelihood of finding an actionable target and where it is more likely to influence clinical treatment.[13] It is feasible that parent and community participants may have had limited understanding of the concept of an actionable target and this result potentially speaks to the importance of optimal information-giving and communication in this complex setting. Strategies for improving patient/consumer understanding and consent, such as using a specialist informed consent team, active communication and alternative decision-making processes, have been described in clinical and ethical literature and are important to consider in this context.[7,9]

All groups were more likely to choose to recommend/participate in a genomically-guided approach if it was also supported by the decisional partner (e.g., the parents for HCPs, or the converse). This is consistent with previous studies which show that HCPs strive to incorporate family preferences into their decision-making,[18,32,33] while families similarly look to HCPs to provide expertise and guidance through the decision-making process.[17,23]

Our results showed that the choice to recommend/participate in genomically-guided treatment varied depending on the child's predicted survival without genomically-guided treatment. Of note, the probability of choosing to recommend or participate did not always increase as the prognosis for survival increased. We believe that this result is consistent with other findings in this area, particularly from end-of-life decision-making.[17,22] That is, there is an apparent trade-off arising between the desire to do no harm in the face of little or no survival benefit,[34] balanced against the hope that doing something will result in a positive outcome.[10-12] Research examining parent end-of life decision-making has found that hope for a cure or a miracle is a critical factor influencing parents even while they also demonstrate their understanding that the chance of cure is remote.[22,35] A similar factor may be at play in our findings.

The primacy of QoL to parents/general community in our study may be due to the extent of information provided in the survey on that factor; this included both functional and treatment impacts. Other studies have shown parents regard functional impacts such as their child's capacity to make friends and have a social life as critical factors when weighing trade-offs between survival and QoL.[23] Parents have previously described the importance of information and open communication regarding prognosis and treatment impacts to their decision-making[17,34,36] and bereaved parents are less likely to recommend active treatment if their own child had experienced treatment-related

suffering at end-of-life.[37] This establishes an important context for our findings which were framed in the setting of difficult-to-treat pediatric cancer. Through the potential values ascribed to the prognosis attribute, our choice scenarios reflected situations of variable survival potential. Previous literature has indicated that parents of children at end-of-life are more likely to be overly optimistic and also are influenced by the desire to have more time with their child.[17] There is also evidence that parents desire to be 'good parents' which includes knowing that everything has been done for their child.[38] That bereaved parents would opt for less cancer-directed care for their child at the end-of-life, especially if their child has suffered[17,21] reflects the importance of QoL in this setting and accords with our findings on the primacy of QoL in guiding parental decision-making.

An important element in the expansion of genomic medicine is its accessibility, particularly in terms of how much and who pays for care. In our study, all groups were more likely to recommend/participate in genomically-guided treatment if it was publicly funded (via the Australian universal health care system for drugs, the PBS) but less likely where parents were asked to pay. The cost of treatment was only significant for the general community sample and only once costs reached $250,000 per treatment course. Importantly, our DCE scenario asked respondents to make decisions about participating in genomic testing while also presenting them with the implications of that testing in terms of the subsequent availability of treatment and its outcomes. Thus, our results on mWTP provide information on the potential value of test-and-treatment strategies that can be applied in future cost-benefit analyses of precision medicine.[39]

There are some limitations in our study. The HCP and parent samples were drawn from convenience samples. We noted some differences in the demographic composition of our general community sample and the general Australian population. However, in our choice models including respondent

demographics only income showed some significance, but this was not consistent across the income levels tested or groups suggesting that this result is likely to be spurious. We also note that the survey was limited to English-speaking families. Equity of access and informed consent are important issues in the delivery of personalized medicine, and this should be addressed in future studies. Our choice scenarios assumed that the likelihoods of treatment responses were known. Other studies [40] directly incorporate the impact of statistical uncertainty in a DCE on community preferences for precision medicine. This is a topic that requires further consideration in the field of difficult-to-treat pediatric cancers, particularly with respect to decisions involving participation in genomically-focused clinical trials. Finally, while our choice questions were hypothetical in nature, they provide a richness of information in understanding the factors that affect decision-making for genomic-guided treatment.

With the continued expansion of genomics in pediatric cancer care, clinicians and families are increasingly faced with difficult choices about participating in new and sometimes uncertain treatments. Our research has shown that while there is general alignment in the factors that influence their choices, some differences arise in prioritizing survival over QoL effects. These potential tensions can be addressed by establishing clear ethical frameworks to guide decision-making in difficult-to-treat pediatric cancers. We found that clinicians, parents and members of the general community were not only influenced by the characteristics of genomically-guided treatment approach but by the presence (or absence) of support of the decisional partner. The resulting ethical frameworks will thus need to address not only the type of information required to support to decisions, but importantly, who might be involved in forming those decisions.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Table 1: Attribute Descriptions and Levels

Attribute	Description shown	Levels
Recommend/ Support	Is your doctor in favour of treatment / The family is in favour of pursuing treatment	Yes No
QoL: Adverse Effects	The treatment makes the/your child	Feel sick without improving the symptoms of their cancer. Feel the same, without improving the symptoms of their cancer. Feel sick, but it improves the symptoms of their cancer. Feel better, and improves the symptoms of their cancer.
QoL: Functioning	The treatment means the/your child	Spends more time in hospital without improving their functioning. Spends some time in hospital, but has periods of improved functioning. Is able to spend more time at home, school and play. Is able to go back to their usual activities at home, school and play.

Cost	Funding for the drug treatment is provided by	Drug company The PBS The hospital The parents
Amount	Total cost of treatment is:	$25,000 $100,000 $175,000 $250,000
Benefit	The chance of the/your child surviving for two years with a targeted approach to treatment is: (as increment on prognosis)	5 in 100 10 in 100 20 in 100 30 in 100
Prognosis	The chance of the/your child surviving for two years without a targeted approach to treatment is:	1 in 100 10 in 100 25 in 100 50 in 100
Biopsy	In order to test which drug treatment is suitable for the (your) child, a fresh tumour biopsy:	Is not required (only a blood sample will be collected from your child). Is required.

Target	The chance of finding a target for which there is a drug is:	1 in 100 10 in 100 15 in 100 20 in 100

Table 2: Participants in the DCE and comparison to Australian population

	HCP	Parents	General Community	Australian Population
n (%)	n = 126	n = 130	n = 532	
Gender				
Males	24 (19)	9 (6.9)	274 (51.5)	(49.2)
Females	95 (75.4)	116 (89.2)	248 (46.6)	(50.8)[a]
Not reported	7 (5.6)	5 (3.8)	10 (1.9)	
Age				
16-24	1 (0.8)	- (0)	40 (7.5)	(15.8)
25-44	70 (55.6)	46 (35.4)	221 (41.5)	(34.8)
45-64	48 (38.1)	77 (59.2)	163 (30.6)	(29.8)
65-74	- (0)	2 (1.5)	80 (15)	(11.1)
75 or over	- (0)	- (0)	18 (3.4)	(8.5)
Not reported	7 (5.6)	5 (3.8)	10 (1.9)	
Household income per year				
Under $40,000	1 (0.8)	18 (13.8)	123 (23.1)	(22.2)
$40K-$79,999	5 (4)	25 (19.2)	152 (28.6)	(25.1)
$80,000-$149,999	39 (31)	40 (30.8)	153 (28.8)	(29.6)
Over $150,000	53 (42.1)	26 (20)	50 (9.4)	(23.3)
Unknown	21 (16.7)	16 (12.3)	44 (8.3)	
Not reported	7 (5.6)	5 (3.8)	10 (1.9)	
Educational Status				
School only	- (0)	30 (23.1)	137 (25.8)	(32.1)
University	117 (92.9)	37 (28.5)	75 (14.1)	(25.1)
Vocational	2 (1.6)	58 (44.6)	310 (58.3)	(15.7)
Not reported	7 (5.6)	5 (3.8)	10 (1.9)	(27.1)

Employment Status				
Full time	85 (67.5)	34 (26.2)	229 (43)	(42.7)
Part time	34 (27)	53 (40.8)	113 (21.2)	(19.6)
Home duties/NILF[b]	7 (5.6)	34 (26.2)	79 (14.8)	(34.3)
Unemployed	126 (100)	4 (3.1)	101 (19)	(3.3)
Not reported	7 (5.6)	5 (3.8)	10 (1.9)	
Country of Origin				
Australia	71 (56.3)	109 (83.8)	396 (74.4)	(69.5)[c]
New Zealand	13 (10.3)	2 (1.5)	5 (0.9)	
Other	35 (27.8)	14 (10.8)	121 (22.7)	(23.5)
Not reported	7 (5.6)	5 (3.8)	10 (1.9)	(6.9)

Notes: [a] Based on the proportion of Australians 15 or over in 2019. [b]NILF refers to individuals not in the labour force and applies only to the estimates of the Australian population for which the proportion reporting home duties, relative to employment, was not available; labour force data for Australian population is as at November 2018 to coincide with survey completion. [c] Proportion presented is for Oceania.

Australian data were sourced from the Australian Bureau of Statistics Online, see www.abs.gov.au.

Figure 1: Example choice question – HCP sample

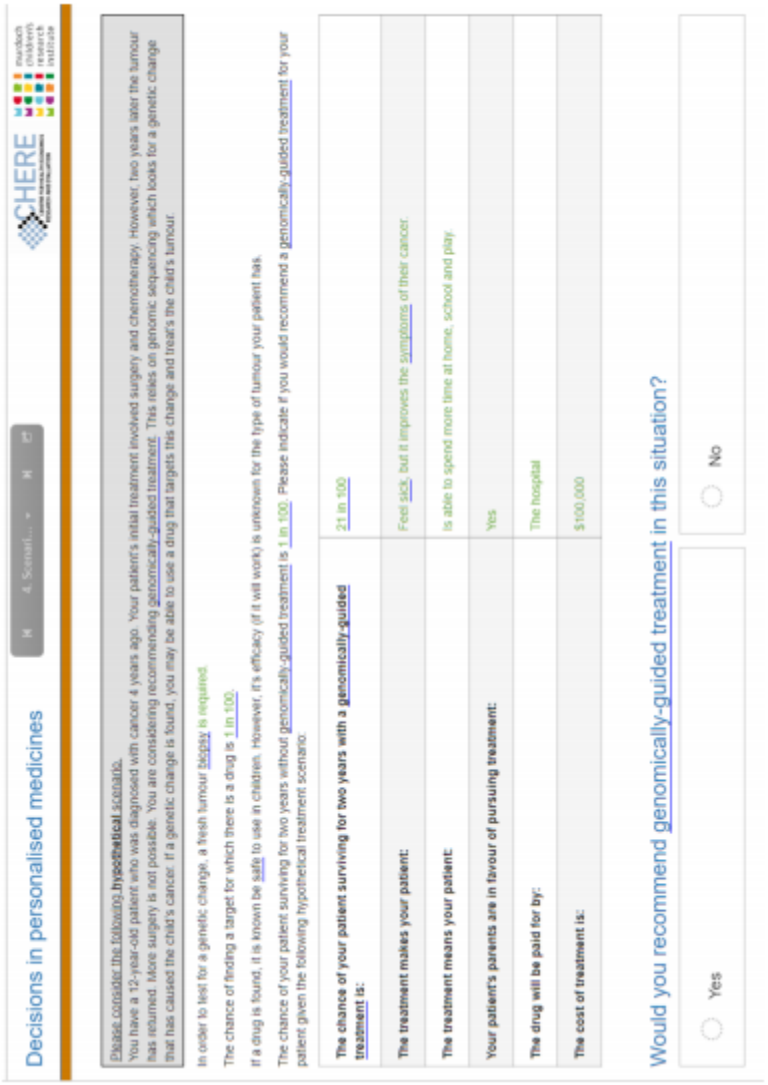
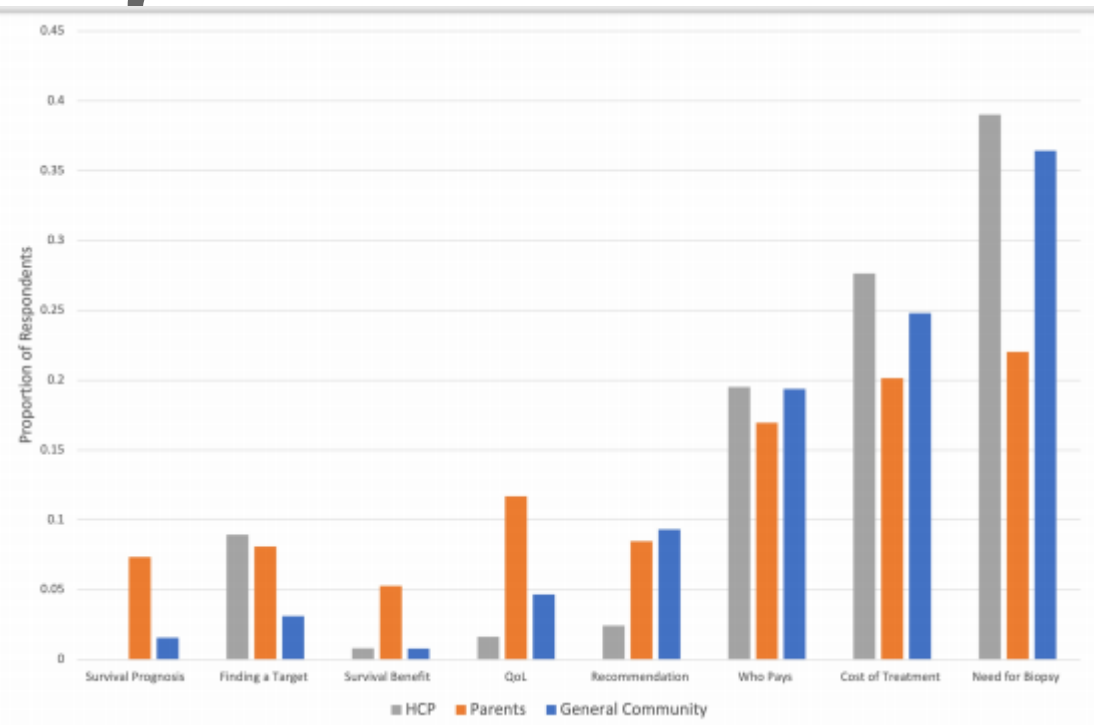


Figure 2: Stated attribute importance

a) Most important attribute

b) Least important attribute

Note: Respondents were asked to state which attribute was most important in influencing their choices and separately, the least important in influencing their choices. The attribute chosen as most important was removed from the consideration set for the least important.



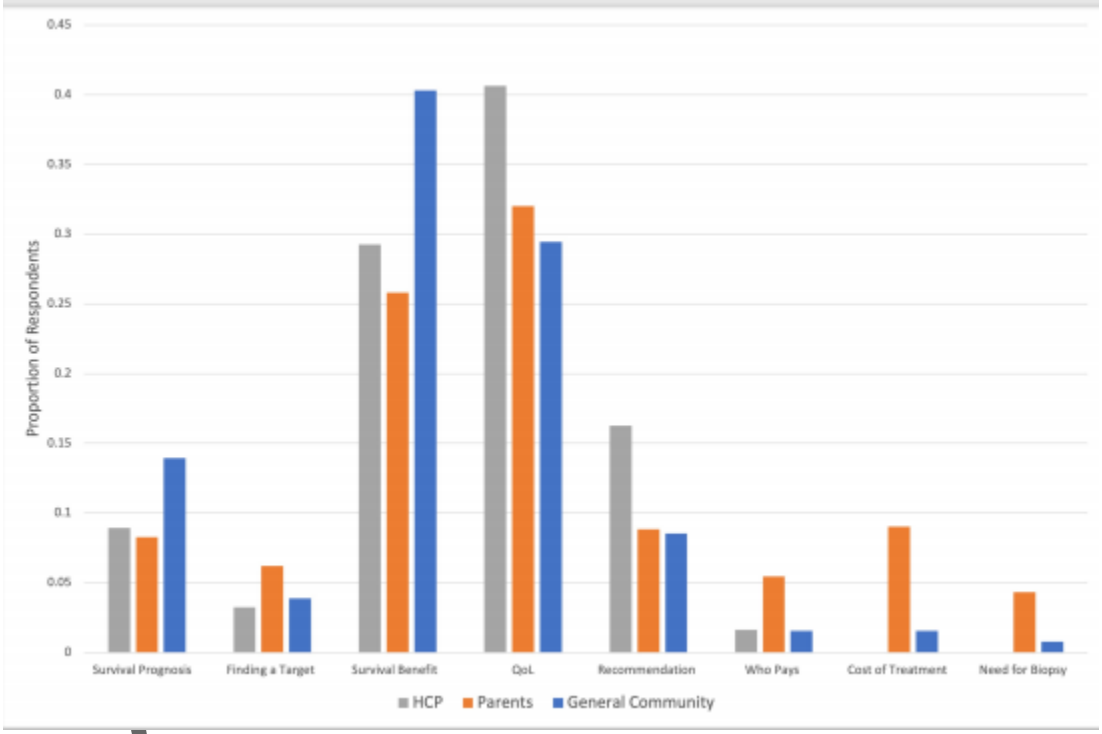


Figure 3: Choice Coefficients

Note: Graphical presentation of probit regression analysis; circles represent choice coefficient, whiskers 95% confidence intervals. Variables were effects coded and expressed as categorical variables, shown as "*Var: Base*" above. Numerical values for all choice coefficients and corresponding summary statistics are provided in the online appendix.

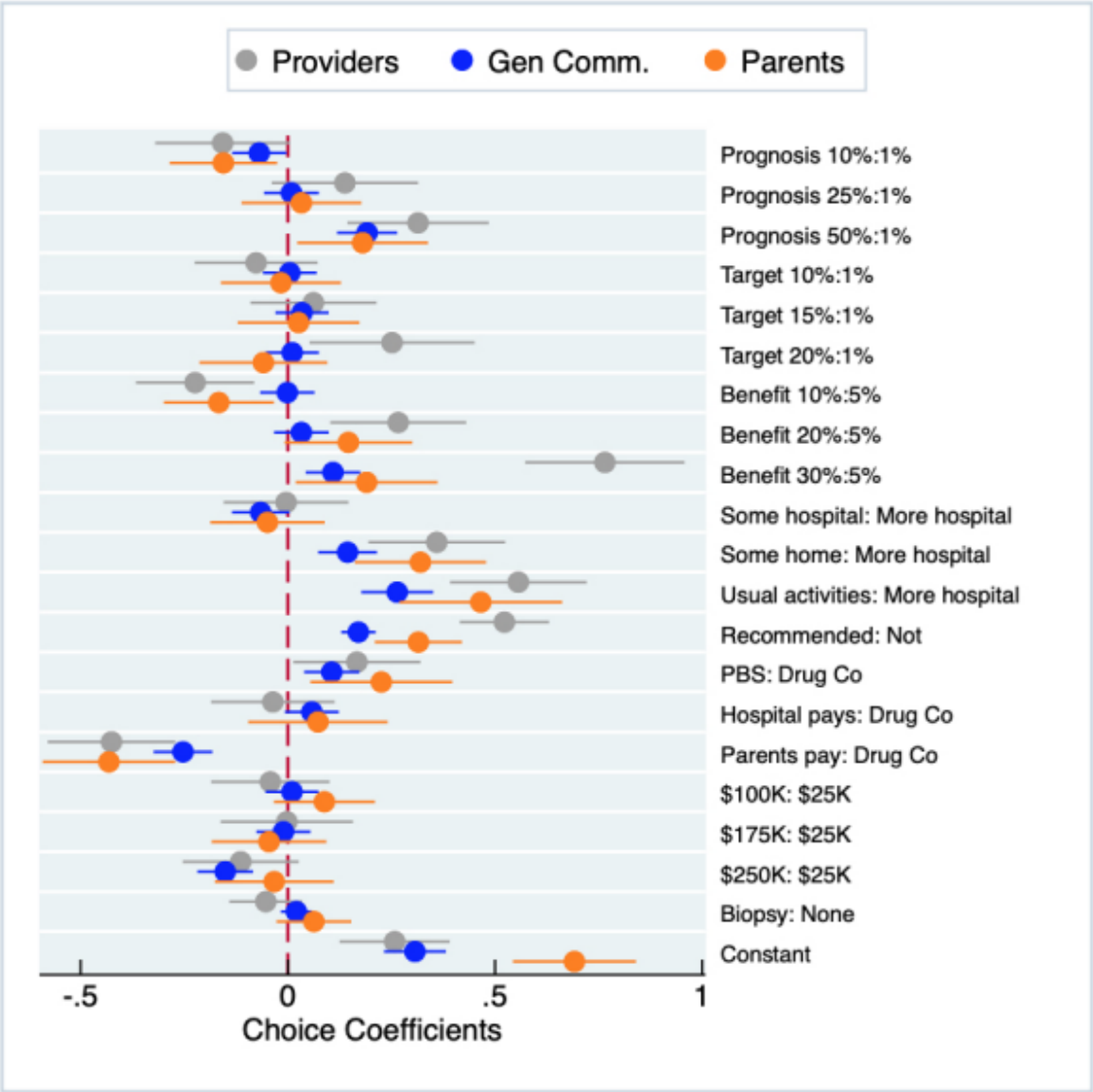


Figure 4: Relative attribute importance

Note: At the extreme, if an attribute had a score of 0 it would have no impact on choices relative to the other attributes. An attribute with a value of 0.5 would account for half of the impact on choices, relative to the other attributes.