International Microsimulation Association

RESEARCH ARTICLE

Modelling the Economic Impact of Next Generation Sequencing and Precision Medicine on Childhood Cancer Management—a Microsimulation Approach

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ABSTRACT Precision medicine is a new approach to identify the best treatment available to patients based on their genomic information. However, no economic evaluation of genome sequencing has been reported for the treatment of childhood cancers, which is critical to evaluate the feasibility of implementing patient's genome sequencing as part of a publicly funded treatment strategy. We have developed a microsimulation model, PeCanMOD, to evaluate the cost and benefit of applying the Next Generation Sequencing (NGS) in the management of childhood cancer. This paper describes the construction of PeCanMOD. We used linked datasets of children under 18 year of age, living in New South Wales (NSW), Australia, who have had cancer, as a base population. Their records were extracted from the NSW Central Cancer Registry and were linked to mortality and hospital datasets. In addition, we simulated the genomic landscape of the cancer registry population, through information obtained from 1,200 molecularly profiled paediatric cancer from the Foundation Medicine. The model simulated the number of individuals eligible for precision medicine, and the incremental cost of treatment per life year gained if precision medicine was introduced for late stage cancer patients as a final treatment option. Cost of drugs, and hospital admission were included in the model. Data on response rate and probability of survival was imputed based on the latest available evidence. Each unit record in the model was weighted using input from the Australian Institute of Health and Welfare (AIHW) to reflect total paediatric cancer population in Australia. The model demonstrates the application of microsimulation modelling to simulate the impacts of NGS and precision medicine on costs and health outcomes for childhood cancer.

JEL classification: C1, C3, I1

DOI: https://doi.org/10.34196/ijm.00230

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Author Keywords: childhood cancers, economic impacts, genomic technology, precision medicine

1. Introduction

Treatment of paediatric cancer is one of the greatest success stories of modern medicine (***Smith et al., 2014***) and the success was exemplified by the treatment of acute lymphoblastic leukaemia (ALL), one of the most common types of paediatric cancers. The disease has progressed from being incurable in

the 1950s to a current 5-year survival rate of 90% (***Cools, 2012***). Improvements in survival outcome were observed among other childhood cancers, including Wilms tumour, non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, and germ cell tumours (***Smith et al., 2014***). These improvements are largely due to identifying various subtypes of the disease and adopting risk-based treatment strategies by stratifying cancer according to various biomarkers. However, the improvement in rate of survival has been reaching a plateau for some cancer types, including Diffuse Intrinsic Pontine Glioma (DIPG) and rhabdoid tumours, with little or no improvement over decades with current approaches, and thus, new treatment approaches such as precision medicine are now needed to further improve survival rates in childhood cancers (***Forrest et al., 2018***; ***Pritchard-Jones et al., 2013***; ***Seibel et al., 2017***; ***Tran et al., 2017***). Precision medicine is an approach to patient care that allows doctors to tailor treatments according to patient's genetic makeup. Both somatic (non-hereditary) and germline (hereditary) mutations information are important in precision medicine, where the interaction between germline and somatic mutations was found to drive the development of paediatric cancer (***Sweet-Cordero and Biegel, 2019***). Survivors of childhood cancers often suffer from treatment related toxicity either during the treatment or later in life, and researchers are hoping that the effect can be ameliorated via the use of precision medicine.

Australian Institute of Health and Welfare (AIHW) reported that approximately 70% of cancer costs were attributed to hospitalisation for patients in the age group of 0-19 years (***Australian Institute of Health and Welfare, 2019a***; ***Australian Institute of Health and Welfare, 2019b***). Healthcare costs of cancer for children aged 0-19 years were about AU$290m in 2015-2016 (***Australian Institute of Health and Welfare, 2019a***; ***Australian Institute of Health and Welfare, 2019b***). Cancer was the most common cause of death from chronic disease among children, and leukaemia was reported as one of the most common childhood cancers.

Due to the advancement in medical science and genome sequencing technology, there is an increasing number of studies that have identified mutations at the genomic level unique to cancer patients, which led to potential application of genomic-guided precision medicine (***Gröbner et al., 2018***; ***Rehm, 2017***; ***Turnbull, 2018***). The increased investigative power of Next Generation Sequencing (NGS), coupled with a decreasing cost of performing sequencing, has enabled many institutions to perform Whole Exome Sequencing (WES) or Whole Genome Sequencing (WGS) on significant numbers of tumour samples (***Vis et al., 2017***). Although there is a growing effort in the field of medicine to implement precision medicine treatment for cancer patients via genome sequencing, no economic evaluation of genome sequencing has been reported for the treatment of childhood leukaemia or other childhood cancers, which is critical to evaluate the feasibility of implementing patient's genome sequencing as part of the treatment strategy. Our recent review of cost-effectiveness studies of using NGS in cancer management has found that there were only six studies reporting on the application of genome sequencing technology in cancer, suggesting more evidence is required in order to implement this approach into clinical care for childhood cancer patients (***Tan et al., 2018***). Thus, there is a need to develop a modelling approach for cost and effectiveness of precision medicine program in childhood cancer precision medicine studies. The structure of precision medicine trials is complicated especially with "basket" trials, designed to identify biomarkers that occur at either a low or unknown frequency across diseases (***Weymann et al., 2019***). Sequencing results from a "basket" trial would subsequently lead to multiple sub-treatment arms or clinical trials that treat patients with drugs targeting specific genomic variants, with only a few eligible subjects being enrolled into each sub-treatment arm. This heterogeneity of "basket" trials makes modelling them using decision trees, or Markov Chain models challenging in low frequency diseases.

We propose to create a microsimulation model, Paediatric Cancer MOD (PeCanMOD), capable of simulating costs and benefits of precision medicines. Microsimulation, traditionally used in policy for income and tax modelling, has increasingly been applied in healthcare research (***Rutter et al., 2011***; ***Schofield et al., 2018***). Application of microsimulation model in health and healthcare research include study of cost-effectiveness, mortality, disease prevalence and burden, population screening program, spatial model, disease transmission, and healthcare policy evaluation (***Schofield et al., 2018***). Our proposed model is a static microsimulation model to evaluate the cost-effectiveness of precision medicine in paediatric cancer. Microsimulation is undertaken at an individual level and can accommodate different treatments and outcomes for each individual. Thus, this modelling approach is well suited for handling heterogeneity in genetic differences and targeted therapies in precision

medicine studies. In this paper, we have described the structure of the model, and expected outputs from PeCanMOD. To our knowledge, this is the first such model of this kind applied to precision medicine and paediatric cancer.

2. Materials and methods

2.1. Base population

The model is developed with inputs from multiple datasets (***Figure 1***). The base population in the model is sourced from the New South Wales (NSW) Central Cancer Registry which contains records of people who have had cancer in NSW (***Cancer Institute, 2018***). The study cohort comprised children

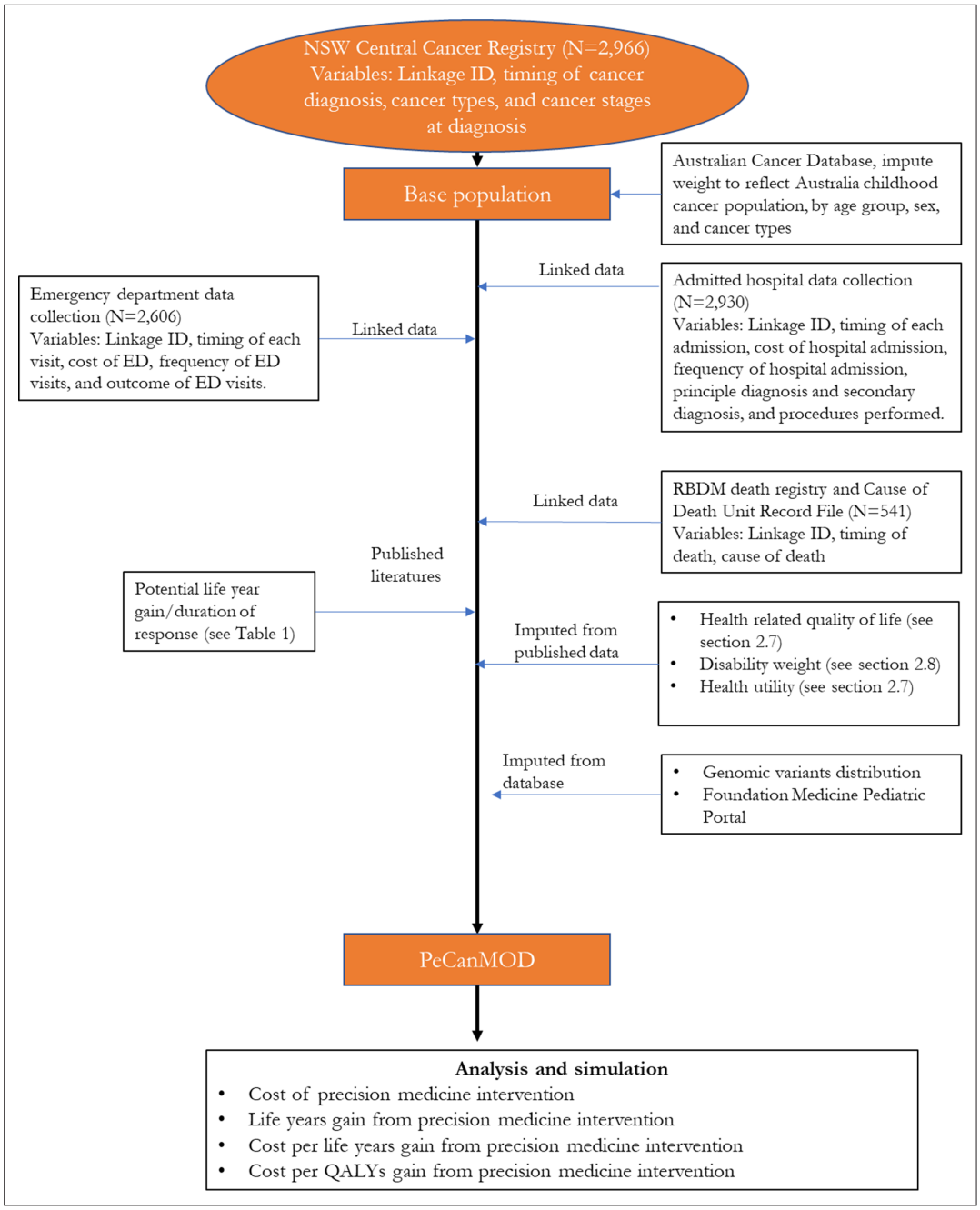

Figure 1. Structure of PeCanMOD

aged <18 years, who were registered in the NSW Central Cancer Registry as cancer patients with a date of diagnosis between 1 July 2001 and 31 December 2012.

2.1.1. Data sources

- NSW Central Cancer Registry maintains records of all cases of cancer diagnosed in NSW residents. To study paediatric cancer population, we selected data of all NSW cancer patients diagnosed with cancer under the age of 18. Key variables used in the model include linkage ID, timing of cancer diagnosis, cancer types, and cancer stages at diagnosis.
- NSW Admitted Patient Data Collection includes records for all hospital separations (discharges, transfers, and deaths) from all NSW public and private hospitals and day procedure centres. Key variables used in the model include timing of each admission, cost of hospital admission, separation outcome, frequency of hospital admission, principle diagnosis and secondary diagnosis, and procedures performed.
- NSW Emergency Department Data Collection provides information about presentations to the Emergency Departments in NSW. Key variables used in the model include timing of each visit, cost of emergency service, frequency of visits, and outcome of visits.
- Registry of Births, Deaths and Marriages, and Cause of Death Unit Record File contain information of all registered deaths in NSW and cause of death. Key variables used in the model include timing of death, and cause of death.

2.2. PeCanMOD structure

Globally, there were multiple large-scale precision medicine clinical trials designed for treating high-risk paediatric cancer (***Chang et al., 2016***; ***Harttrampf et al., 2017***; ***Khater et al., 2019***; ***Mody et al., 2015***; ***Wong et al., 2020***; ***Worst et al., 2016***). Patients who had previous treatment failure, experiencing cancer relapsed, or were diagnosed with high-risk cancer (less than 30% 5-year survival rate) were the major participants in these precision medicine studies.

To reflect the current practice, the model assumed that individuals who were eventually decreased due to their illness would be simulated to have been eligible for precision medicines in our simulation prior to their death. These individuals were assumed to be high risk patients, who were unlikely to be cured with the current treatment regime. We identified these individuals from the NSW Central Cancer Registry by linking the dataset to other administrative datasets. Each individual in the NSW Central Cancer Registry dataset was assigned a unique identifier by the Centre for Health Record Linkage (***Centre for Health Record Linkage, 2018***), and data for these individuals were extracted from the other administrative datasets such as the NSW Registry of Births, Deaths, Marriages, and NSW Cause of Death Unit Record File. Records were then linked based on the unique identifier for each patient. The NSW Registry of Births, Deaths, and Marriages death registrations and the NSW Cause of Death Unit Record File records date of death, and cause of death (***Figure 1***).

2.3. Imputation of genomic variants

Understanding the prevalence of genomic variants responsible for cancer development is critical to estimate the effectiveness of a precision medicine programme (***Subbiah et al., 2018***). We imputed genomic variants responsible for cancers using published data from the Foundation Medicine Pediatric Portal (***Chmielecki et al., 2016***; ***Chmielecki et al., 2017***). The dataset consists of the molecular profiles of over 1200 paediatric tumours sequenced by the Foundation Medicine. We estimated the prevalence of genomic variants in each cancer type from this dataset. Imputation of having specific genomic variant was carried out based on the distribution of genomic variants in each cancer type (55 categories) and allocated using Monte Carlo simulation method to the matched cancer type. We have considered other data sources (***Gröbner et al., 2018***; ***Ma et al., 2018***; ***Rusch et al., 2018***), but none were as comprehensive as the Foundation Medicine dataset in terms of cancer types (***Table 2***).

2.4. Simulation

To model genomic variants, we assigned a random value between 0 to 1 drawn from a uniform distribution to individuals in the cancer registry. Controlling for cancer types, if the value falls between the

Table 1. Characteristics of childhood cancer population in NSW Central Cancer Registry and selected individuals used in the model.

Total childhood cancer population from NSW Central Cancer Registry (2001-2012)			Selected individuals for simulation model‡		
	N	%		N	%
Sex			Sex		
Male	1639	55.26	Male	303	56.01
Female	1327	44.74	Female	238	43.99
Age at diagnosis			Age at diagnosis		
0-4	1117	37.66	0-4	193	35.67
5-9	528	17.8	5-9	99	18.3
10-14	632	21.31	10-14	119	22
15-17	689	23.23	15-17	130	24.03
Cancer types			Cancer types		
-Acute lymphoblastic leukaemia	712	23.78	Brain	159	29.39
-Brain	342	11.42	Acute lymphoblastic leukaemia	92	17.01
-Hodgkin's disease	210	7.01	Bone	54	9.98
-Non-Hodgkin's lymphoma	186	6.21	Acute myeloid leukaemia	42	7.76
-Bone	177	5.91	Connective tissue, peripheral nerves	38	7.02
-Acute myeloid leukaemia	168	5.61	Other endocrine glands	33	6.1
-Connective tissue, peripheral nerves	148	4.94	Non-Hodgkin's Lymphoma	22	4.07
-Kidney	134	4.48	All other cancer types†	101	18.6
-Other endocrine glands	113	3.77			
-Melanoma of skin	106	3.54			
-Colon	70	2.34			
-Thyroid	68	2.27			
-Testis	67	2.24			
-Central nervous system	67	2.24			
-Ill-defined and unspecified site	60	2			
-Eye	59	1.97			
-Other lymphatic, hematopoietic	49	1.64			
-Liver	41	1.37			
-Ovary	41	1.37			
-Other myeloid leukaemia	27	0.9			
-Other thoracic organs	20	0.67			
-All other cancer types†	129	4.31			
Year of diagnosis			Year of diagnosis		
2001*	144	4.86	2001*	34	6.28
2002	261	8.80	2002	60	11.09
2003	249	8.40	2003	58	10.72
2004	259	8.73	2004	45	8.32

Continued

Table 1. Continued

Total childhood cancer population from NSW Central Cancer Registry (2001-2012)			Selected individuals for simulation model‡		
2005	241	8.13	2005	52	9.61
2006	261	8.80	2006	41	7.58
2007	229	7.72	2007	45	8.32
2008	226	7.62	2008	40	7.39
2009	256	8.63	2009	46	8.5
2010	270	9.10	2010	40	7.39
2011	277	9.34	2011	32	5.91
2012	293	9.88	2012	48	8.87

*2001 data started from 1st of July.
†Including cancer types with equal or less than 20 records.
‡Selected individuals were those who were eventually deceased due to their illness.

upper and lower bounds for a gene, then the individual would be assigned the associated gene in this simulation. The simulation process was repeated 1,000 times.

The treatment protocol was mostly based on one of the largest paediatric cancer precision medicine trials, NCI-COG Pediatric MATCH (MATCH) (***Table 3***) (***Allen et al., 2017***). Due to limited evidence of the effectiveness of precision medicine as well as limited understanding of the distribution of actionable variants within the patient population, we have made several assumptions in our current model, and the model will be updated as results from the precision medicine trials become available. Treatment response rate and survival duration used in this model were sourced from clinical trials results on adult cancers (***Tables 4 and 5***) as there were no reported outcomes of these medications for childhood cancer cohort. It is possible that children's response to these medicines may be different to their adult counterpart's (***Joseph et al., 2015***). A one-way sensitivity analysis on response rate and duration of response will be conducted to estimate resulting cost and effectiveness in best- and worst-case scenarios (range of input parameters are described in ***Tables 4–6***). Method for sensitivity analysis is described in 2.10.

The model simulated the number of individuals eligible for precision medicine, and the cost of treatment per life year gained if precision medicine was introduced to late stage cancer patients as final treatment options (***Figure 2***). The probability of responding to precision medicine for each genomic variant and duration of response were estimated based on published literature or reports from the U.S. Food and Drug Administration (***Table 4***). They were used to estimate the incremental life years that would have been gained for each individual in our base population if they had had one of the 10 targeted therapies from the MATCH trial for their specific simulated genomic variant, with the assumption that the patients died if they failed to respond, and that if they did respond, the patients would only survive as long as the duration of response (***Table 5***).

2.5. Cost of Next-Generation Sequencing (NGS)

The model assumes that each patient receives Whole-Genome Sequencing (WGS) at a cost of AU$4,926 per cancer patient (range: AU$2,991-AU$45,333) (reported costs were inflated to 2019 values by the consumer price index in origin country, and converted to Australian dollars using Purchasing Power

Table 2. Comparison of reference datasets for genomic variants distribution imputation.

Datasets	% of base file matched with reference dataset (by cancer types)
Foundation Medicine Pediatric Portal	73
Grobner et al.	57
Rusch et al.	24
Ma et al.	10

Table 3. Genomic variants eligible for precision medicine and the corresponding drugs.

Drugs	Genomic variants eligible for precision medicine
Larotrectinib	NTRK1,NTRK2,NTRK3
Erdafitinib	FGFR1,FGFR2,FGFR3,FGFR4
Tazemetostat	EZH2 gain of function,EZH2,BRG1,INI1,SMARCA4 inactivation,SMARCB1 inactivation
Samotolisib	TSC1,TSC2
Selumetinib Sulfate	BRAF,GNA11,GNAQ,HRAS,KRAS,NF1,NRAS
Ensartinib	ALK fusion protein, ALK gene mutation, ALK gene translocation,ROS1 fusion positive,ROS1 gene mutation,ROS1 gene translocation
Vemurafenib	BRAF v600x
Olaparib	Deleterious ATM, Deleterious BRCA1, Deleterious BRCA2, Deleterious RAD51C, Deleterious RAD51D
Palbociclib	RB1
Ulixertinib	ARAF,BRAF,GNA11,GNAQ,HRAS,KRAS,MAP2K1,MAPK1,NF1,NRAS

Parities) (***Table 6***) (***Gordon et al., 2020***; ***Schwarze et al., 2020***; ***Schwarze et al., 2018***; ***Weymann et al., 2017***) . Note that the cost of WGS included all steps in the sequencing pathway, including the costs of bioinformatic analysis and returning results. We also model the cost and effectiveness if each patient receives targeted multi-gene panel sequencing versus WGS. The cost of targeted multi-gene panel sequencing is assumed to be AU$1,433 (range: AU$437-AU$10,178) per sample (***Gordon et al., 2020***; ***Hamblin et al., 2017***; ***van Amerongen et al., 2016***; ***Yu et al., 2018***).

2.6. Cost of drugs and managing toxicity

For the base case, the cost of hospital admission for precision medicine was assumed to be the same as the cost of hospital admission for chemotherapy less the direct cost relating to pharmacy, and was estimated based on Australian Refined Diagnosis Related Groups version 8.0 (AR-DRGs). AR-DRGs is a classification system to classify patient hospital admissions by connecting the number and type of patients treated in a hospital (known as hospital casemix) to the resources required by the hospital. For drugs that do not require inpatient care, we will refer to outpatient service cost for chemotherapy administration. Costs of managing toxicity or adverse events from treatment were assumed to be AU$5,890 per month per person (based on our (unpublished) analysis of the NSW Admitted Patient Data Collection linked to the NSW Central Cancer Registry) (***Table 6***).

The costs of drugs in the model are based on published costs from the Pharmaceutical Benefits Scheme (***Pharmaceutical BenefitsScheme, 2019a***; ***Pharmaceutical BenefitsScheme, 2019b***; ***Pharmaceutical BenefitsScheme, 2019c***), or online materials (***Herper, 2018***; ***Pagliarulo, 2019***), or imputed as the mean of available costs (e.g. Tazemetostat, Samotolisib, Selumetinib Sulfate, Ensartinib, and Ulixertinib) (***Table 6***).

All costs were presented in 2019 Australian dollars. For costs not originally reported in Australian dollars or in 2019 cost base, we inflated the reported costs to 2019 by the consumer price index in origin country and converted to Australian dollars using Purchasing Power Parities.

2.7. Health utility

Health Related Quality of Life (HRQoL) measures the impact of health states on patient's quality of life. In the context of cost-utility analysis, HRQoL is summarised into utility values ranging between

Table 4. Model inputs-- response rate to drugs.

Drugs	Mean response rate	Distribution[§]	Source/note
Larotrectinib	0.73	Binomial (55,0.73)	(Food and Drug Administration, 2018)
Erdafitinib	0.322	Binomial (87,0.322)	(Food and Drug Administration, 2019)
Tazemetostat*	0.38 or 0.05	Binomial(21,0.38) or Binomial(43,0.05)	(Italiano et al., 2018)
Samotolisib	0.34	Binomial (47,0.34)	(Bendell et al., 2018)
Selumetinib Sulfate	0.17	Binomial (36,0.17)	(Jain et al., 2014)
Ensartinib	0.69	Binomial (13,0.69)	(Horn et al., 2017)
Vemurafenib†	range (0.17-0.769)		(Hyman et al., 2015)
Olaparib	0.53	Binomial (92,0.53)	(Golan et al., 2019)
Palbociclib‡	0.5	Triangular (0.25, 0.5, 0.75)	n.a.
Ulixertinib	0.14	Binomial (101,0.14)	(Sullivan et al., 2018)

*Depending on cancer types (for blood cancers, response rate was assumed to be 0.38, and 0.05 for solid cancers).

†response rate varies by cancer types.

‡There is no data available for Palbociclib, so we assumed 0.5 response rate with a triangular distribution of ±0.25.

§Binomial (N,p), triangular (a, c, b).

0 (death) and 1 (perfect health). Utility measurements allow for comparison of health outcomes across diseases as well as comparison between various health care interventions. In PeCanMOD, we impute utility based on cancer type, treatment phase, health outcome, age, and gender from published literature. A review by ***Tarride et al. (2010)*** has summarised the health utilities measured for Acute Lymphoblastic Leukaemia patients during treatment (range: 0.81-0.91), and survivors of various cancers . ***Yeh et al. (2016)*** measured and reported that health utility among childhood cancer survivors is significantly poorer than health utility for the general population. In addition, a systematic review and meta-analysis of child health utilities by ***Kwon et al. (2018)*** reported utilities for a wide range of health conditions, including cancers.

Table 5. Model inputs-- duration of response.

Drugs	Mean duration of response	Weibull (shape, scale)	Source/note
Larotrectinib	6 months	(2.45,10.45)	(Food and Drug Administration, 2018)
Erdafitinib	5.4 months	(1.86,6.58)	(Food and Drug Administration, 2019)
Tazemetostat	12.4 months	(1.8,19.7)	(Italiano et al., 2018)
Samotolisib	6 months	(1.55,7.6)	(Bendell et al., 2018)
Selumetinib Sulfate	2 months	(1.3,2.65)	(Jain et al., 2014)
Ensartinib	5.8 months	(1.57,7.3)	(Horn et al., 2017)
Vemurafenib*	range (3-13 months)	(1.81,8.57)	(Hyman et al., 2015)
Olaparib	6 months	(1.95,21.73)	(Golan et al., 2019)
Palbociclib	9.5 months	(1.53,12.06)	(McShane et al., 2018)
Ulixertinib	6.6 months	(1.73,8.16)	(Sullivan et al., 2018)

*Duration of response varies by cancer types.

Table 6. Model inputs, including costs of medicine, drug admission at hospital, toxicity management, and sequencing.

Drugs	Mean monthly cost (US$)	Mean monthly cost (AU$)	Source/note
Larotrectinib	11,000 (range: 8,250-13,750)	15,629 (range:11,722-19,536)	(Herper, 2018)
Erdafitinib	16,380 (range: 12,285-20,475)	23,273 (range: 17,455-29,091)	(Pagliarulo, 2019)
Tazemetostat	N/A	11,658 (range: 8,744-14,573)	Average of drug prices of Larotrectinib, Erdafitinib, Vemurafenib, Olaparib, and Palbociclib
Samotolisib	N/A	11,658 (range: 8,744-14,573)	Average of drug prices of Larotrectinib, Erdafitinib, Vemurafenib, Olaparib, and Palbociclib
Selumetinib Sulfate	N/A	11,658 (range: 8,744-14,573)	Average of drug prices of Larotrectinib, Erdafitinib, Vemurafenib, Olaparib, and Palbociclib
Ensartinib	N/A	11,658 (range: 8,744-14,573)	Average of drug prices of Larotrectinib, Erdafitinib, Vemurafenib, Olaparib, and Palbociclib
Vemurafenib	N/A	8,189 (range: 6,142-10,236)	(Pharmaceutical BenefitsScheme, 2019c)
Olaparib	N/A	6,961 (range: 5,221-8,701)	(Pharmaceutical BenefitsScheme, 2019a)
Palbociclib	N/A	4,239 (range: 3,179-5,299)	(Pharmaceutical BenefitsScheme, 2019b)
Ulixertinib	N/A	11,658 (range: 8,744-14,573)	Average of drug prices of Larotrectinib, Erdafitinib, Vemurafenib, Olaparib, and Palbociclib
Hospital care	Mean monthly cost per person (US$)	Mean monthly cost per person (AU$)	
Admission for drug treatment	N/A	901 (range: 676-1,126)	AR-DRGs
Managing toxicity/adverse drug events	N/A	5,230 (range: 3,923-6,538)	
Sequencing	Mean cost per service (USD)	Mean cost per service (AUD)	
Whole-genome sequencing	3,347 (range: 2,032-30,805)	4,926 (range: 2,991-45,333)	(Gordon et al., 2020; Schwarze et al., 2020; Schwarze et al., 2018; Weymann et al., 2017)
Targeted multi-gene panel sequencing	1,236 (range: 525-6916)	1,433 (range: 773-10,178)	(Gordon et al., 2020; Hamblin et al., 2017an van Amerongen et al., 2016; Yu et al., 2018)

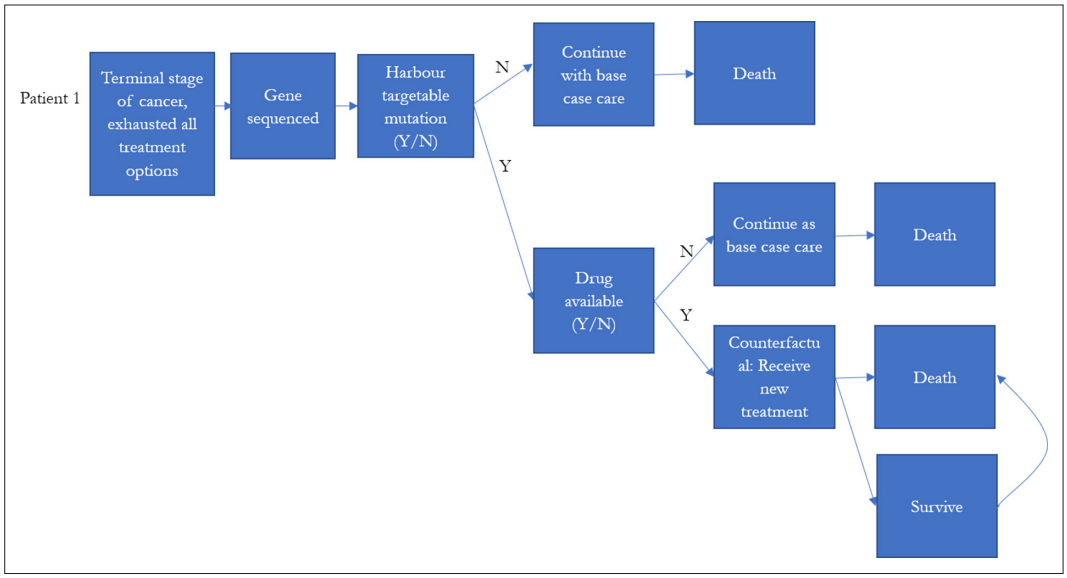

Figure 2. Model schematic of decision tree for testing and initial treatment.

2.8. Disability adjusted life years (DALYs)

Health utility data is scarce for most childhood cancers, especially during the treatment phase. To model health outcomes we used Disability-Adjusted Life Year (DALY). DALYs is a standard metric used to describe burden of disease. This value is calculated using the Years of Life Lost (YLL) and the Years Lived With Disability (YLD). The Global Burden of Disease Study (***Global Burden of Disease Collaborative Network, 2018***) reported the DALY burden due to childhood cancers (***GBD 2017 Childhood Cancer Collaborators, 2019***). We attributed DALYs based on patients' response to precision medicine during the microsimulation. The model will first determine YLD with estimated duration of response to precision medicine and corresponding disability weight for treatment phase and cancer types. As we assumed that once patient will only survive as long as the duration of response, we will determine YLL based on the life expectancy at the counterfactual age at death.

2.9. Budget impact analysis

The model assigns a multiplier to individuals to reflect the number of childhood cancer patients within the Australian population. The Australian Institute of Health and Welfare (AIHW) published childhood cancer incidence between 1982-2015 (***Australian Institute of Health and Welfare, 2019a***; ***Australian Institute of Health and Welfare, 2019a***), and the multipliers are assigned to the total costs incurred by each individual in the NSW Central Cancer Registry, by age group at diagnosis, cancer types, sex, and year of diagnosis.

2.10. Sensitivity and uncertainty analysis

We perform one-way sensitivity analysis to determine the parameters that have the biggest influence on the model outcome. This is achieved by changing one parameter at a time while keeping other parameters constant. The parameters of interest are varied between plausible extremes (input values range are described in ***Tables 4–6***). Model outcome (incremental costs per life year gained) for each scenario is then compared against base case to identify the parameters that significantly affect model outcome.

We also conduct probabilistic sensitivity analysis to explore the robustness of model results on all model parameters such as costs of drugs and response rate to precision medicine using Monte Carlo simulation. We assumed lognormal distributions for cost of drugs and sequencing, binomial distributions for the response rates to drugs, and Weibull distributions for the duration of response.

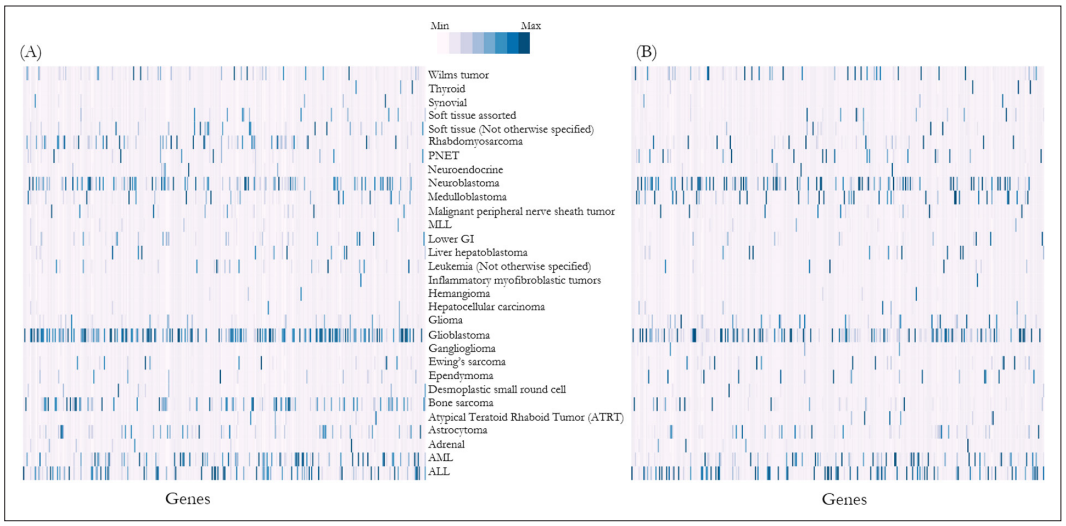

Figure 3. Heat map shows frequency of mutations (normalised and represented as Z-scores) in each gene in (**A**) reference population, i.e. Foundation Medicine dataset, and (**B**) NSW Central Cancer Registry population simulation output.

Note: Each column along the horizontal axis represents a gene responsible for cancers. Distribution of genomic variants were significantly correlated between the reference population and NSW Central Cancer Registry simulation output (ρ=0.73, p<0.01) (details list of genes is described in Appendix 1).

2.11. Weighting

The PeCanMOD assigns weights to individuals to reflect an estimate of childhood cancers within the Australian population. The Australian Institute of Health and Welfare published national annual cancer incidence by cancer types and sex via its Australian Cancer Database (***Australian Institute of Health and Welfare, 2019a***; ***Australian Institute of Health and Welfare, 2019a***). Person weight was assigned to each individual in the NSW Central Cancer Registry, controlling for year of diagnosis, sex and cancer types.

2.12. Validation

We carried out internal validation including debugging via code walk through to ensure that the model does not have obvious construction and syntax errors. We also compared model output against external data where available. Model input and output are assessed by paediatric medical oncologist (authors TOB, and TT) for face validity.

To validate whether the imputed genomic variants distribution is comparable with the Foundation Medicine Pediatric Portal data, we performed Spearman's rank correlation coefficient analysis and demonstrated that the distribution of genomic variants was significantly correlated between the reference population and NSW Central Cancer Registry simulation output (ρ=0.73, p<0.01) (***Figure 3***).

2.13. Ethics approval and consent to participate

Human Research Ethics approval has been obtained from the NSW Population & Health Services Research Ethics Committee (HREC/17/CIPHS/7). We have sought permission to waive consent from NSW Ministry of Health under the Health Records and Information Privacy Act 2002 (NSW).

3. Discussion

This paper described the development of a microsimulation model PeCanMOD developed to simulate costs and potential benefits from receiving precision medicine as the last treatment resort for childhood cancer patients. Application of microsimulation model to evaluate cost-effectiveness of intervention in adult cancers was not uncommon, for example, ***Petelin et al. (2019)*** modelled cost-effectiveness in a subset of breast and ovarian cancers or Bongers et al modelled cost-effectiveness in non-small-cell lung cancer (***Bongers et al., 2016***; ***Petelin et al., 2019***). Introduction of precision

medicine into children is more recent than for adults. Therefore, there is no microsimulation model for precision medicine in children cancer. Our aim is to fill this knowledge gap through the development of PeCanMOD. The model can be applied in evaluating the cost-effectiveness of multi-drug precision medicine program, and the model output can report the cost-effectiveness of individual drug candidate, and the impact of introducing drug candidate on government's budget, by taking into account of prevalence of target genomic variants in population of interest.

This study has some limitations. The NSW Admitted Hospital Data Collection dataset is limited to hospital admissions occurred in NSW. Therefore, treatments occurred beyond NSW hospital were not captured. We were unable to account for migration events after patients were diagnosed with cancer as this information were not available in the linked datasets. However, we expect only a very few cases of migration as only ~1.2% of the records did not have matching hospital admission records. The mortality data in our dataset was also limited to only patients that died in NSW due to cancer. Patients died outside of NSW were not recorded in our dataset. In a recent report by NSW Cancer Institute, retrospectively matching NSW Central Cancer Registry data to the National Death Index resulted in 0.16% additional death records (***NSW Cancer Institute, 2020***). Therefore, we do not expect this limitation to have material impact on the process of identifying patients eligible for precision medicine in our model.

In our model, the treatment protocol is largely based on NCI-COG Pediatric MATCH study. Due to limited evidence of the effectiveness of precision medicine as well as limited understanding of the distribution of actionable variants within the patient population, we have made several assumptions in our current model. To reflect current practice, we modelled that only patients with high-risk cancer or those that have experienced treatment failure to be eligible for precision medicine. However, it is possible that with improvement in technology and clinical implementation, precision medicine can be administered as soon as patients are diagnosed with cancers, and not limited to patients that experiencing treatment failure. The current assumption might introduce heavier weight into certain cancer types as individuals were selected for inclusion in the model based on survival outcomes (post-hoc), which is not feasible in reality.

Due to limited data availability, the model used results from adult trials to simulate drug efficacy in children. In optimal scenario, children are likely to react to medicine just as well as adults, however, it is also possible that they may metabolize certain medicines differently to adults resulting in severe adverse drug reactions and toxicity (***Contopoulos-Ioannidis et al., 2010***). Extrapolation of the therapeutic benefit from adults to children need to be treated with cautions (***Janiaud et al., 2015***). Therefore, this model will be continuously updated with new input parameters when relevant clinical trials data are reported.

We were not able to control for other variables, such as sex and age, as these data was not recorded in the Foundation Medicine dataset. Age and sex were significantly associated with cancer risk in this cohort (***Stjernfelt et al., 2020***), and controlling for age, sex, as well as cancer types, will greatly improve the impute estimates. Furthermore, the Foundation Medicine dataset was not designed to reflect the cancer prevalence in population, with emphasis on cancer types with low 5-year survival. We have imputed genomic variants onto Australian population based on US data, which may not be reflective of genomic diversity of Australian population as disease associated variant might differ across populations (***Altshuler et al., 2015***; ***Corona et al., 2013***). However, we were unable to ascertain this without evidence from cross-population comparison of the distribution of pathogenic variants responsible for childhood cancer.

Apart from being required to have the appropriate genomic variants, patients also have to meet several other requirements, such as performance status (general well-being of the patients), in order to be eligible for precision medicine trials. In this model, we have simply assumed that all patients having the targetable genomic variants would also meet other eligibility criteria for precision medicine trials. As more clinical trials data becomes available, the model will be updated so that it remains current. As NCI-COG Pediatric MATCH have not yet published their clinical findings, we have used published drug responses in other settings (e.g. adult cancers) as our guide for response rate and survival. Key parameters, including the genomic landscape of paediatric cancer and the effectiveness of precision medicine, are influential in modelled outcomes. With increasingly widespread implementation of genomic sequencing, we will also assume that the cost of genomic analysis will decrease. At present, economic models for precision medicine suffer from the lack of "real world" clinical trial data inputs for the model (***Terkola et al., 2017***). The design of this model allows flexibility in modelling

other treatment protocols, as well as determining the minimum effectiveness or maximum costs of treatment required to achieve cost-effective care. There are several paediatric oncology precision medicine trials ongoing, and health outcome results from these studies are highly anticipated.

However, it is also noteworthy that the majority of ongoing precision medicine clinical trials do not have a matching control population, therefore, modelling the cost-effectiveness of precision medicine programme would rely on counterfactual simulation *in silica*.

Furthermore, as highlighted in this modelling exercise, understanding the genomic landscape of paediatric cancer patients is crucial in determining the proportion of eligible participants for precision medicine. We believe that a registry created for cancer patients and linking details of the patients' genomic information would be very useful for future economic evaluation.

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Acknowledgement

We thank the Cancer Institute NSW, and the NSW Ministry of Health for access to the health data, the NSW Registry of Births Deaths and Marriages for providing access to mortality data, and the NSW Centre for Health Record Linkage for conducting record linkage. The Cause of Death Unit Record File (Cause of Death Unit Record File) is provided by the NSW Registry of Births, Deaths, and Marriages, NSW Coroner and the National Coronial Information System.

Funding

No specific funding for this article is reported.

Conflict of Interest

No competing interests reported.

Data and Code Availability

The data underlying the model are confidential. However, the authors are happy to discuss the methods used in model development. The code is not available due to the confidential nature of the data underlying the study. However, the authors are happy to discuss the approach taken to model development.

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Appendix 1:

List of genes corresponding to horizontal label in ***Figure 2*** (from left to right).

ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	APC	APCDD1	AR	ARAF	ARHGAP26	ARID1A	ARID1B	ARID2	ASXL1	ATM	ATR	ATRX	AURKA
AURKB	AXIN1	BAP1	BARD1	BCL10	BCL11B	BCL2	BCL2A1	BCL2L2	BCL6	BCL7A	BCOR	BCORL1	BRAF	BRCA1	BRCA2	BRD4	BRIP1	C17orf39
CARD11	CASP8	CBFB	CBL	CCND1	CCND2	CCND3	CCNE1	CCT6B	CD22	CD274	CD36	CDC73	CDH1	CDH2	CDH20	CDK12	CDK4	CDK6
CDKN1B	CDKN2A	CDKN2B	CDKN2C	CEBPA	CHD2	CHEK2	CHUK	CIC	CIITA	CKS1B	CPS1	CRBN	CREBBP	CRKL	CRLF2	CSF3R	CTCF	CTNNA1
CTNNB1	CUX1	CYLD	DAXX	DDR2	DDX3X	DICER1	DIS3	DNMT3A	DOT1L	EED	EGFR	ELP2	EP300	EPHA3	EPHA5	EPHA7	EPHB1	EPHB4
EPHB6	ERBB2	ERBB3	ERBB4	ERG	ESR1	ETS1	ETV1	ETV6	EWSR1	EZH2	FAM123B	FAM46C	FANCA	FANCI	FANCM	FAS	FAT1	FAT3
FBXO11	FBXW7	FGF10	FGF14	FGF19	FGF23	FGF3	FGF4	FGF6	FGFR1	FGFR2	FGFR3	FGFR4	FLCN	FLT1	FLT3	FLT4	FOXO1	FOXP1
FUBP1	FUS	GABRA6	GATA1	GATA2	GATA3	GATA4	GLI1	GNAS	GRIN2A	GRM3	H3F3A	HDAC4	HEY1	HGF	HIST1H1D	HIST1H2AM	HLA	HLA.A
HNF1A	HOXA9	HRAS	ICK	IDH1	IDH2	IGF1	IGF1R	IGF2R	IGH	IKBKE	IKZF1	IKZF2	IKZF3	IL7R	IRF2	IRF8	IRS2	JAK1
JAK2	JAK3	JUN	KDM4C	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KEL	KIT	KRAS	LRP1B	LRRK2	LZTR1	MAGI2	MALT1	MAP2K1	MAP2K4
MAP3K1	MAP3K13	MAP3K14	MAP3K6	MAP3K7	MAPK1	MCL1	MDM2	MDM4	MED12	MEF2C	MEN1	MET	MKI67	MLH1	MLL	MLL2	MLL3	MLLT10
MPL	MRE11A	MSH2	MSH3	MSH6	MTOR	MUTYH	MYC	MYCL1	MYCN	MYH11	MYST3	NCOR1	NCOR2	NF1	NF2	NFE2L2	NFKBIA	NKX2.1
NOD1	NOTCH1	NOTCH2	NOTCH3	NOTCH4	NPM1	NRAS	NSD1	NTRK1	NTRK3	NUP214	NUP98	PALB2	PARK2	PASK	PAX3	PAX5	PBRM1	PBX1
PDCD11	PDCD1LG2	PDGFB	PDGFRA	PDGFRB	PHF6	PIK3C2B	PIK3C2G	PIK3CA	PIK3CG	PIK3R1	PIK3R2	PLAG1	PLCG2	PMS2	POLE	POT1	PPP2R1A	PRDM1
PREX2	PRKCI	PRKDC	PTCH1	PTEN	PTPN11	PTPN6	PTPRD	PTPRO	RAD50	RAD51	RAD51C	RAD54L	RAF1	RANBP2	RARA	RB1	REL	RET
RICTOR	RNF213	RNF43	ROS1	RPTOR	RUNX1	RUNX1T1	SDHA	SDHD	SETBP1	SETD2	SF3B1	SH2B3	SLIT2	SMAD4	SMARCA4	SMARCB1	SMARCD1	SOX10
SOX2	SPEN	SPTA1	SRC	SRSF2	SS18	STAG2	STAT4	STAT6	STK11	SUFU	SUZ12	TAF1	TAL1	TBL1XR1	TBX3	TCF3	TERT	TET2
TLL2	TMEM30A	TNFRSF11A	TNKS	TNKS2	TP53	TRRAP	TSC1	TSC2	TSHR	TYK2	U2AF1	VHL	WHSC1	WT1	XPO1	XRCC2	ZMYM3	ZNF217
ZNF703	ZRSR2																	

Appendix 2:

Data linkage methodology

Centre for Health Record Linkage performed the linkage of NSW Cancer Registry, admitted patient data, emergency department data, and Registry of Births, Deaths and Marriages and Cause of Death Unit Record File. Identifying information (name, address, date of birth and sex) for each dataset is included in the Master Linkage Key (MLK) using probabilistic record linkage methods and ChoiceMaker software (***Borthwick et al., 2003***). At the completion of the linkage process, each record in the MLK was assigned a record identification number and a MLK person ID to allow linked records for the same individual to be identified and extracted.

Once the linkages were completed, the Centre for Health Record Linkage created a Project Person Number (PPN) (also known as linkage ID in the manuscript) for each person identified in the linkage, and assigned this PPN to the corresponding datasets.

Data linkage outcome:

Datasets	% records linked
NSW Central Cancer Registry (base population)	100
NSW Admitted Patient Data Collection	98.8
NSW Emergency Department Data Collection	87.8
Registry of Births, Deaths and Marriages Deaths registry	18.3
Cause of Death Unit Record File	17.7