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# Preimplantation genetic diagnosis for retinoblastoma survivors: a cost-effectiveness study

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**Abstract** This study aimed to investigate the cost-effectiveness of preimplantation genetic diagnosis (PGD) for the reproductive choices of patients with heritable retinoblastoma. The study modelled the costs of three cycles of in-vitro fertilization (IVF) and PGD across all uptake rates of PGD, number of children affected with retinoblastoma at each uptake rate and the estimated quality-adjusted life years (QALYs) gained. Cost-effectiveness analysis was conducted from the Australian public healthcare perspective. The intervention was the use of three cycles (one fresh and two frozen) of IVF and PGD with the aim of live births unaffected by the retinoblastoma phenotype. Compared with the standard care pathway (i.e. natural pregnancy), IVF and PGD resulted in a cost-saving to 18 years of age of AUD$2,747,294 for a base case of 100 couples with an uptake rate of 50%. IVF and PGD resulted in fewer affected ($n$=56) and unaffected ($n$=78) live births compared with standard care (71 affected and 83 unaffected live births), and an additional 0.03 QALYs per live birth. This modelling suggests that the use of IVF and PGD to achieve an unaffected child for patients with

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heritable retinoblastoma resulted in an overall cost-saving. There was an increase in QALYs per baby across all uptake rates. However, in total, fewer babies were born following the IVF and PGD pathway.

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**KEYWORDS:** cost-effectiveness, assisted reproductive technology, in-vitro fertilization, preimplantation genetic diagnosis, retinoblastoma, autosomal-dominant disease

## Introduction

Retinoblastoma is the most common intraocular neoplasm in childhood (Asnaghi et al., 2018), with an incidence rate of one per 15–20,000 live births (Belson et al., 2019; Kivela, 2009). The disease or its treatment can be blinding, and without treatment, it is fatal (Chantada, 2015) with the potential for metastatic progression (Asnaghi et al., 2018). Single or multiple tumours can arise in the developing retinal cells of one or both eyes at any time during the gestation period (Paquette et al., 2012) until approximately 5 years of age. A germline mutation can arise *de novo* in an individual or be inherited from either parent in an autosomal-dominant inheritance pattern (Cavenee et al., 1986; Vogel, 1979). Germline *RB1* mutations are associated with increased risk of the development of second, primary cancers throughout the survivor's lifetime (MacCarthy et al., 2013).

Treatment of retinoblastoma depends on the stage of disease at diagnosis, and can include one or a combination of treatments to achieve disease control (Jenkinson, 2015). With early diagnosis and access to treatment, retinoblastoma is the most survivable paediatric cancer, with 5-year survival rates >90% (Kaatsch, 2010).

Prior to discovery of the *RB1* gene, all infants at risk of harbouring a familial mutation were screened under general anaesthetic at regular intervals until 5 years of age. Genetic testing has since transformed the treatment landscape for at-risk offspring, removing the need for intensive and invasive screening in those found not to have inherited a familial mutation (Noorani et al., 1996; Richter et al., 2003). Moreover, genetic testing provides survivors with family planning options for implantation of unaffected embryos (Backenroth et al., 2018).

### IVF and PGD for people with vision impairment

Preimplantation genetic testing is a well-established option for families at risk of having children with monogenic conditions, and can be used to provide reproductive choices for families with various other monogenic conditions (Backenroth et al., 2018; Schofield et al., 2017; Stark et al., 2019). In the context of assisted reproductive technology (ART), preimplantation genetic diagnosis (PGD) involves obtaining a cellular biopsy of an embryo to evaluate the genetic composition, allowing the selection of a genetically unaffected embryo for transfer (Dhanjal et al., 2007). In principle, the use of PGD during in-vitro fertilization (IVF) should reduce the risk of termination of pregnancy. PGD also reduces the risk of recurrence of a genetic condition such as retinoblastoma (Yahalom et al., 2018).

IVF and PGD have associated emotional and psychological costs (Malina and Pooley, 2017). However, the use of PGD can help carrier parents to avoid the psychological impacts associated with passing on a known genetic disorder to their biological child (Beard et al., 2016; Ormondroyd et al., 2018). PGD is a costly intervention that may be prohibitive for prospective parents hoping to reduce their chance of passing on a known genetic disease. Although most ART treatments performed in Australia are subsidized through the universal healthcare insurance system, the cost of PGD for genetic disorders is not publicly funded and is borne out-of-pocket by patients (Lee et al., 2019). This contrasts with other countries, such as the UK, where PGD is funded through the National Health Service (NHS) to mitigate the financial burden associated with these procedures (NHS Commissioning Board, 2013).

The quality of life of retinoblastoma survivors is often reduced, particularly for social and emotional aspects (Batra et al., 2016), and especially for children (aged ≤18 years) receiving treatment (Belson et al., 2019; Zhang et al., 2018). Given that treatment is often expensive and healthcare resources are limited, it is important to determine if a treatment is cost-effective (Schofield et al., 2018; Stark et al., 2019); however, to the authors' knowledge, there has been no evaluation of the cost-effectiveness of using IVF and PGD in relation to retinoblastoma. The aim of this study was to evaluate the cost-effectiveness of IVF and PGD for retinoblastoma with a known *RB1* mutation within the Australian healthcare system.

## Materials and methods

### Data sources

#### Model inputs: treatment costs of retinoblastoma

Costs used in the model were divided into two main categories: healthcare costs associated with treating retinoblastoma, and direct costs related to prevention strategies (i.e. IVF and PGD).

Medical costs for the treatment and surveillance of 12 *RB1*-mutation-positive offspring born to parents with a germline mutation were collected from the Royal Children's Hospital, Victoria, Australia, for the period between July 2002 and July 2017. For these 12 patients, 11 developed retinoblastoma; one patient was an unaffected carrier and was excluded from the analysis. Patient age at commencement of treatment ranged from birth to 4.9 months. The number and total cost of visits were obtained to estimate costs per year for each patient. Visits included the number of emergency encounters, number of inpatient encounters and number of outpatient encounters. The treatment costs

of allied health, emergency, medical, nursing, pathology, pharmacy, imaging, theatre, intensive care and other costs were obtained from the treating centre. To estimate mean cost per year, data were used from the 11 patients with the retinoblastoma phenotype, excluding the single child who was an unaffected carrier. All babies of retinoblastoma survivors are tested using a single gene panel; retinoblastoma-negative babies receive no further monitoring, while retinoblastoma-positive babies receive an examination under anaesthesia every 3 months. Data were collected on the number of years of treatment each patient had received (range 2–15 years). The total costs were then divided by years of treatment to estimate costs per year (mean $13,892; maximum $38,816). To estimate the total cost for patients with retinoblastoma to 18 years of age, mean cost per year was multiplied by 18, giving hospital costs of $250,056 from diagnosis to 18 years of age. These costs are conservative as they only include costs at the main treatment centre and exclude local community or general practitioner visits, and because patients will continue to require ongoing medical surveillance throughout their lives and the costs in this analysis cease at 18 years of age. Further, as 11 patients had the phenotype out of 12 patients with the genotype, it was estimated that the penetrance rate was 96%. The model assumed that parents with a genotype-positive, phenotype-negative child would have no further children, based on previously published choices of parents with retinoblastoma (Dommering et al., 2012), and treatment costs were not included for genotype-positive, phenotype-negative children. All costs are reported in 2019 Australian dollars (AUD$).

### Model inputs: IVF and PGD costs

Costs of IVF and PGD were based on publically available data from major IVF providers on the health and medical costs of IVF, using IVF cost data from www.TheFertilityCentre.com.au, www.IVF.com.au and www.MonashIVF.com to account for price variation. Costs were presented from the healthcare perspective, with out-of-pocket costs presented separately. Additional costs outside of IVF clinics for specialist visits, drugs, anaesthesia, day surgery, and medical benefits scheme and expanded costs were included (Pham et al., 2018). PGD costs included genetic screening, validation fees and feasibility testing (for single gene disorders). Freezing embryos, with up to 6 months of storage, and day surgery costs were also included. The decision tree illustrates modelling of the standard care pathway (i.e natural pregnancy) and the IVF and PGD pathway (Figure 1). For the purpose of the model, standard care was taken to be 0% uptake of IVF and PGD, where all pregnancies were natural. The IVF and PGD pathway occurs when couples first attempt IVF and PGD, and the couples who do not achieve a baby through IVF proceed to a natural pregnancy.

### Model inputs: effectiveness, quality of life and utility

Health-related quality of life of patients was estimated in three age groups using PedSQL4.0 estimates for children with retinoblastoma from previously published literature from paediatric patients (Zhang et al., 2018). The PedSQL scores were mapped on to a Child Health Utility-9 Dimension score using an algorithm based on Australian adolescents (Mpundu-Kaambwa et al., 2017). Quality of life was determined for each of three life periods, converted to utilities for each period, and summed to obtain utility from birth to 18 years of age. The utilities were used to derive the additional quality-adjusted life years (QALYs) with IVF and PGD. The three life periods were:

- from the year of diagnosis and period of most intense treatment (<24 months) until 7 years of age;
- from 8 to 12 years of age; and
- from 13 to 18 years of age.

A QALY is used to assess quality-of-life benefits in economic evaluations, and states of health are assigned a 'utility' or value between 1 (full health) and 0 (death). The amount of time, in years, that a person spends in each health state is multiplied by the utility to estimate the QALYs. For this analysis, the cost difference and QALY difference were modelled for 100 hypothetical couples for the standard care pathway and the IVF and PGD pathway, also calculating the different numbers of affected and unaffected babies (Figure 2). Using quality-of-life data from previously reported values for patients with retinoblastoma, there were reductions in utility of 0.06, 0.03 and 0.03 per child for 5–7, 8–12 and 13–18 years of age, respectively (Zhang et al., 2018), which were used to model utility for retinoblastoma survivors.

### Base case

The base case in this analysis was 50% uptake of IVF and PGD for 100 couples, each aiming for two babies. A study of retinal diseases showed that from the patients' perspective, 52% of couples supported PGD (Willis et al., 2013). Attitudes to PGD for retinal disease may be generally different from those of parents of children with blindness, with parents with retinal disease reported to have higher accepance rates for the use of genetic testing (Potrata et al., 2014).

## Results

### Medical costs

The mean number of emergency encounters, number of inpatient encounters and number of outpatient encounters for patients with the retinoblastoma phenotype was 5.2, 40.5 and 34.3 visits per patient, with a maximum number of 79 inpatient encounters and 109 outpatient encounters for a patient 15 years after diagnosis. The mean cost for treating retinoblastoma from diagnosis to 18 years of age, for all medical costs including allied health, was AUD$250,056. Out-of-pocket costs and healthcare costs for IVF were AUD $5,648.03 and AUD $6982.82, respectively. PGD costs were AUD$5470. One fresh and two frozen cycles were used in this analysis to achieve an unaffected baby.

A base case of 100 couples, each aiming for two babies, with a 50% uptake rate of IVF and PGD led to 56 affected babies and 78 unaffected babies, compared with 71 affected and 83 unaffected babies with the standard care pathway. An uptake rate of 50% resulted in mean QALYs per baby of 17.86 for the IVF and PGD pathway, compared with mean QALYs per baby of 17.83 over 18 years for the standard care pathway; a difference of 0.03 QALYs per baby. However, in total, fewer babies were

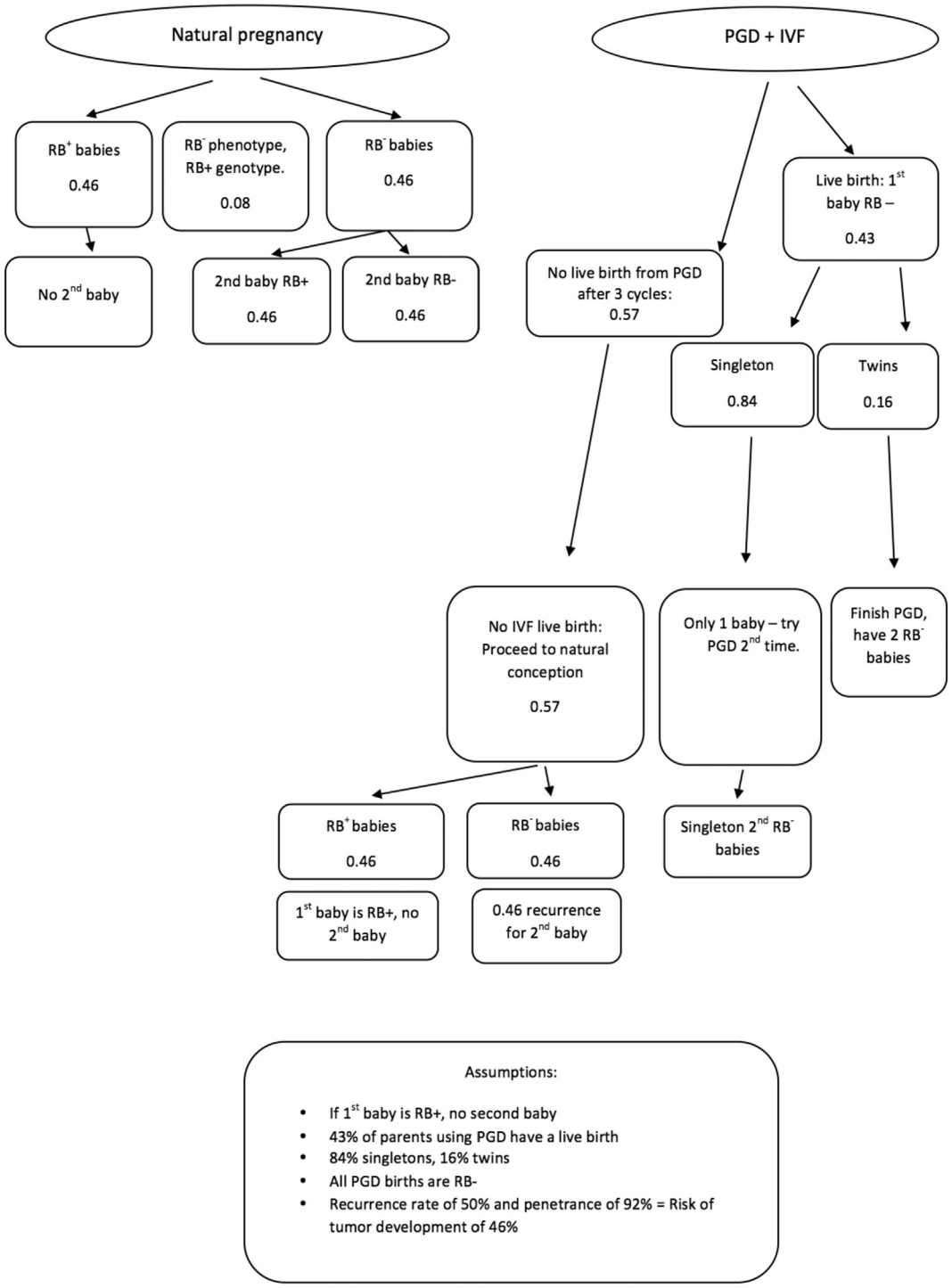


**Figure 1** Decision tree for 100 couples using standard care or in-vitro fertilization (IVF) and preimplantation genetic diagnosis (PGD), and the number of babies which result. Babies are either retinoblastoma positive or negative (RB+, RB-); if the first baby is RB+, the model assumes that the couple will choose not to have a second baby. In addition, the model assumes that 43% of parents using PGD have a live birth, 84% of PGD births are singletons and 16% are twins, and all PGD births are unaffected. Note that the recurrence rate of 50% with a penetrance rate of 92% gives a risk of tumour development of 46% (see Table 1 for more information), so not all probabilities total 1.Figure 1

born via the IVF and PGD pathway, resulting in fewer total QALYs (2393.24 for the IVF and PGD pathway versus 2745.58 for the standard care pathway). The cost of the IVF and PGD pathway was $14,295,354 for 100 couples, each aiming for two babies, and $17,747,847 for the standard care pathway, resulting in an overall cost-saving of $3,452,493 with the IVF and PGD pathway (Figure 2). It is noteworthy that all uptake rates using the IVF and PGD pathway resulted in cost-savings

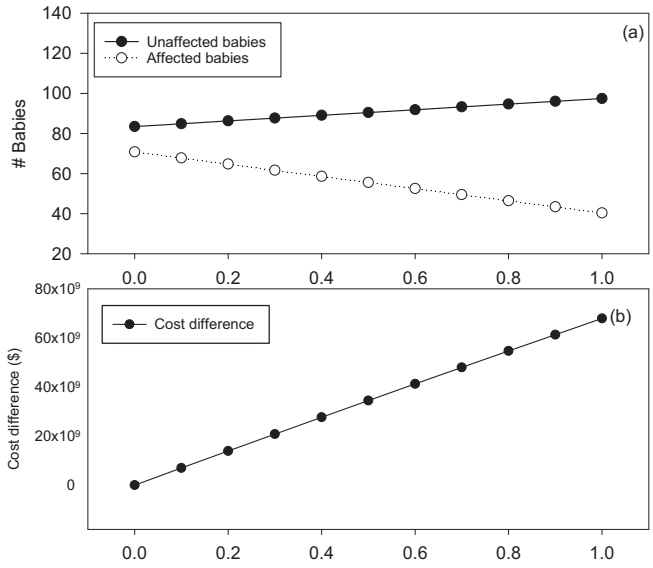


**Figure 2** Impact of preimplantation genetic diagnosis (PGD) uptake rate on: (a) total number of babies in the intervention [in-vitro fertilization (IVF) and PGD] and standard care pathways; and (b) cost difference. Panel (a) shows the number of affected and unaffected babies from 100 couples, each aiming to have two children, varying according to PGD uptake rate. The model assumes that if a couple's first baby has the retinoblastoma phenotype, they will choose to avoid a further pregnancy. Panel (b) shows the increase in cost-savings per uptake rate for 100 couples, each aiming to have two children; assumptions are described in the Materials and methods section. The uptake rate is the proportion of couples who elect to use IVF and PGD instead of having a natural pregnancy, from 0 to 1.0. The cost difference is intervention costs minus standard care costs for each uptake rate, meaning savings in each case (note: this is the reverse of the incremental cost-effectiveness ratio, where the cost difference is negative). The total cost is the sum of costs of all retinoblastoma-positive babies plus costs of IVF and PGD per uptake rate.Figure 2

and an increase in QALYs per baby, and impacted on the total number of children born.

### Sensitivity analysis

A sensitivity analysis was conducted on the impact of uptake rates from 0% to 100% for IVF and PGD for 100 couples, based on the difference between standard care and the invention: the cost of IVF and PGD. For the standard care pathway, there were 71 retinoblastoma-affected babies and 83 unaffected babies (for all couples). As the uptake rate of IVF and PGD increased, the proportion (and cost) of affected babies decreased, and the cost of IVF also increased. The sensitivity analysis showed that the cost-saving increased from $0 to $6,793,517 as the uptake of IVF and PGD increased from 0 to 100% of couples (Figure 2). An additional sensitivity analysis was conducted to test the impact of aiming for one instead of two children. The estimated costs of the IVF and PGD pathway were $9345,304 for 100 couples for a 50% uptake rate, and $11,512,696 for the standard care pathway. This suggests that IVF and PGD gives an estimated saving of $2,167,392 for one baby (Figure 2). A one-way sensitivity analysis on changing the input parameters (and their baseline) – (i) cost of disease (AUD$250,056), (ii) percentage success rate for couples having a baby by IVF (43%), (iii) cost of IVF and PGD (AUD$12,631), and (iv) number of cycles required to obtain a live birth using PGD (2.94) – was conducted. These variables were selected as they are likely to vary. The sensitivity analysis showed that the cost of disease and success rate of IVF had a greater impact on cost-savings than the cost of IVF and PGD (Figure 3).

At 10% uptake for IVF and PGD, assuming that couples are aiming for two babies, there were 68 retinoblastoma-affected babies and 80 unaffected babies. This is a decrease in both retinoblastoma-affected babies (from 71 babies) and unaffected babies (from 83 babies) compared with standard care. At 50% uptake of IVF and PGD, there were 56 affected babies and 78 unaffected babies. The cost-saving was $699,366 at 10% uptake of IVF and PGD and $3,452,354 at 50% uptake of IVF and PGD for 100 couples aiming for two babies.

## Discussion

When one parent is a carrier of a heritable *RB1* mutation, this analysis showed that the IVF and PGD pathway resulted in higher average QALYs per baby and is a cost-saving option for couples aiming to have one or two children compared with the standard care pathway. There were, however, fewer total QALYs in the IVF and PGD pathway compared with the standard care pathway due to fewer babies being born via the IVF and PGD pathway. The use of average QALYs per baby may be an appropriate outcome measure if the preference of prospective parents is not to pass on the condition to their future children and they wish to avoid the use of prenatal testing (Dommering et al., 2004). As uptake rates of IVF and PGD rise, the savings increase. Nonetheless, due to the high cost of retinoblastoma, the IVF and PGD pathway resulted in a cost-saving even at a low uptake rate (10%).

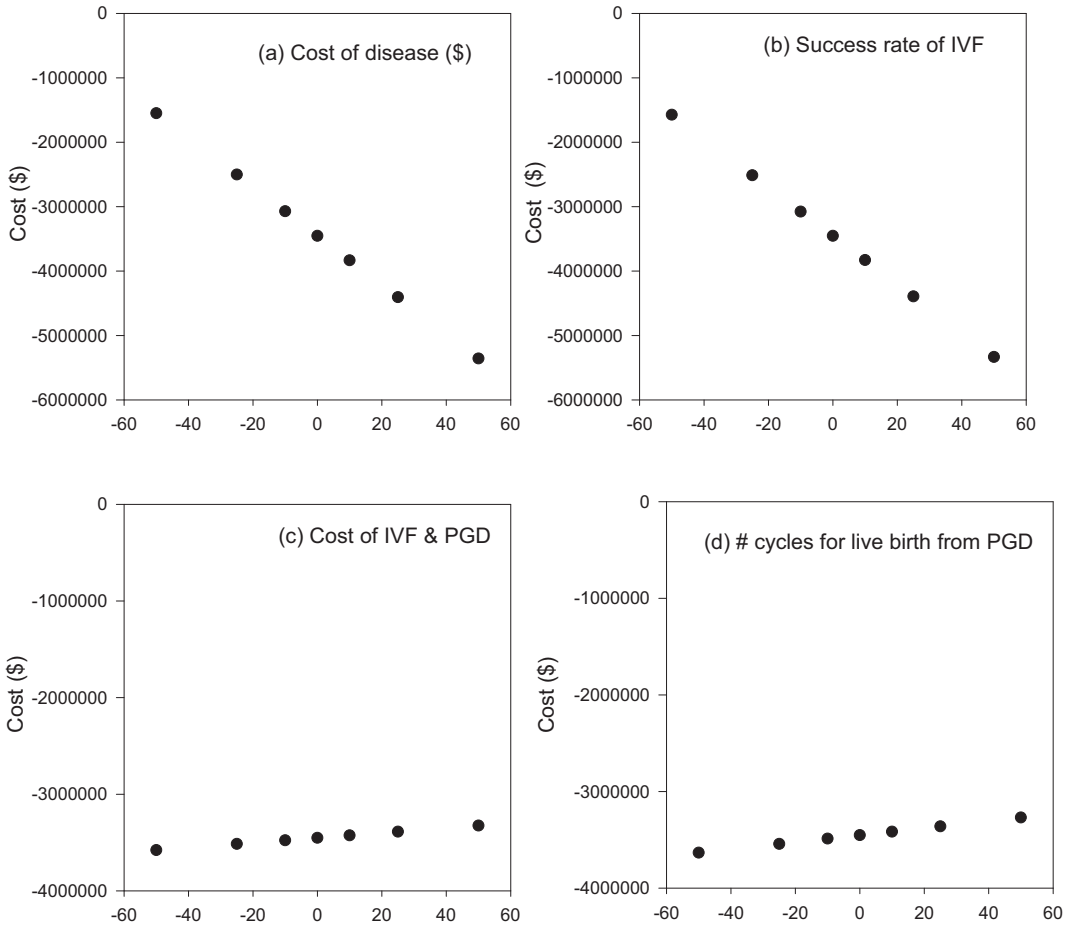


**Figure 3** Sensitivity analysis on the effect of changing the input parameters by +/- 25% or 10% on cost difference (AUD$), while holding all other variables constant. Input parameters tested were: (a) disease costs (AUD$), (b) success rate of in-vitro fertilization (IVF), (c) costs of IVF and preimplantation genetic diagnosis (PGD), and (d) number of cycles required to obtain a live birth from PGD. Figure 3

Currently, the UK NHS subsidizes up to three cycles of PGD for at-risk retinoblastoma survivors (NHS Commissioning Board, 2013). However, PGD for retinoblastoma is not currently subsidized in Australia, and PGD is cost-prohibitive for some families (Darbari et al., 2018). This analysis suggests that using IVF and PGD for retinoblastoma is cost-saving compared with the costs of treatment and surveillance of a patient with retinoblastoma, and more unaffected children will be born. The study cost estimate of IVF and PGD of $12,631 for three cycles (one fresh and two frozen) for out-of-pocket and healthcare costs combined was comparable with estimates from an Australian study (Pham et al., 2018).

A limitation of this study is that medical costs were only modelled up to 18 years of age. Given that retinoblastoma survivors with an *RB1* mutation are at risk of developing second, primary tumours throughout their lifetime (Kleinerman et al., 2019), with associated high treatment costs (Dimaras et al., 2015), these results are likely to be conservative. Additionally, this study did not include the cost of non-medical and other indirect costs, such as travel time and costs, and lost productivity. Further, this model made a number of assumptions, such as the number of cycles required to achieve a baby. However, to use the most accurate assumptions available, probabilities were obtained from previously published studies (Table 1). IVF and PGD have associated emotional and psychological costs (Malina and Pooley, 2017). Further, the psychological, emotional and physical costs of IVF and PGD were not included in this analysis. However, the use of PGD can help carrier parents avoid the psychological impacts associated with passing on a known genetic disorder to their biological child (Beard et al., 2016; Ormondroyd et al., 2018). It is worth noting that increases in quality of life (and QALYs) when PGD is used, compared with not using PGD, are due to the fact that the number of unaffected children is higher than the number of affected children. Consistent with previous literature, this study used a utility decrement of 0.07 for infertility of the parent of a child not born; however, in the present study, all parents had at least one child (either affected or unaffected) (Scotland et al., 2011). (See Table 2.)

These results suggest that using IVF and PGD for adult survivors with a heritable mutation is a cost-saving strategy to reduce the recurrence of retinoblastoma. Previous studies have shown that ART provides benefits for families with a range of heritable conditions, and in the case of molecular

**Table 1** Model parameters and sources used.

| Parameter | Comment | Variable | Source |
|---|---|---|---|
| Total medical costs from age at diagnosis to 18 years of age | Including emergency, allied health, medical, pathology, nursing, pharmacy, imaging and theatre | AUD $250,056 | Clinician observation |
| Retinoblastoma assumptions: statistical likelihood of children born with retinoblastoma per couple | Autosomal-dominant | 50% | Dimaras et al. (2015) |
| PGD assumptions | Proportion of live births from PGD | 43% | Girardet et al. (2018) |
| | Number of PGD cycles to achieve unaffected baby | 2.94 (34% of cycles) | Girardet et al. (2018) |
| IVF assumptions | Rate of twins | 14% | Girardet et al. (2018) |
| Quality of life of retinoblastoma survivors versus controls | 5–7 years<br>8–12 years<br>13–18 years | 83 versus 89<br>82 versus 85<br>83 versus 86 | Zhang et al. (2018) |

PGD, preimplantation genetic diagnosis; IVF, in-vitro-fertilization.
Dimaras, H., Corson, T.W., Cobrinik, D., White, A., Zhao, J., Munier, F.L., et al., 2015. Retinoblastoma. Nat. Rev. Dis. Primers 1, 15021.
Girardet, A., Ishmukhametova, A., Viart, V., Plaza, S., Saguet, F., Verriere, G., et al., 2018. Thirteen years' experience of 893 PGD cycles for monogenic disorders in a publicly funded, nationally regulated regional hospital service. Reprod. Biomed Online 36, 154–163.
Zhang, L., Gao, T., Shen, Y., 2018. Quality of life in children with retinoblastoma after enucleation in China. Pediatr. Blood Cancer 65, e27024.

diagnosis for suspected childhood syndromes, also has increased cost-effectiveness (Schofield et al., 2017; Stark et al., 2019). If government funding was available to fund IVF and PGD for non-fertility purposes such as retinoblastoma, there would be significant savings, particularly in terms of a reduction in hospital costs. In recent years, there has been increasing use of IVF and PGD, meaning it is timely to determine the cost-effectiveness of IVF and PGD for retinoblastoma and monogenic inherited eye diseases (Hlavatá et al., 2016). Subsidies for PGD vary by country; for example, in Australia, there is public funding for IVF for fertility issues but not for PGD, whereas in the UK, PGD is funded for three cycles under the NHS (NHS Commissioning Board, 2013). Given that cost is a commonly reported barrier to PGD uptake (Darbari et al., 2018), the absence of subsidies for PGD means that there are socio-economic inequalities for the opportunity to have a child unaffected by retinoblastoma. PGD may be used on a suite of other

**Table 2** In-vitro fertilization (IVF) and preimplantation genetic diagnosis (PGD) costs for fresh and frozen cycles, and PGD costs separately.

| IVF and PGD item | Item number (MBS, PBS)[a] | Healthcare costs (AUD$)[a] | Out-of-pocket costs (AUD$) |
|---|---|---|---|
| Fresh transfer cycle (no ICSI), includes hospital, anaesthetic and bed fees | 13200, 13209, 13212, 13203, 13215 | 3110.95 | 2769.07 |
| Frozen cycle, includes transfer of frozen embryos, preparation of frozen embryos | 13209, 13218, 13215 | 742.10 | 1439.48 |
| Specialists, drugs and anaesthesia, 104.<br>drugs: Follitropin alpha, x 5; Cetrorelix x 10, Choriogonadotropin Alfa: 6433N, 9599F, 6182J,<br>anaesthesia | MBS17610, 20943, 23031 | 2387.67 | |
| Total for 1 x fresh cycle and 2 x frozen cycles [following Giradet et al. (2018)] | | 6982.82 | 5648.03 |
| PGD: preimplantation genetic screening amplification fee, validation fee, screening fee (per embryo, capped at AUD$2720)<br>(source: MonashIVF.com) | | 0 | 5470 |

MBS, medical benefits scheme; PBS, pharmaceutical benefits scheme; ICSI, intracytoplasmic sperm injection.
[a]Healthcare costs include PBS and Medicare, the Australian universal healthcare scheme.
[b]The model assumes that one fresh cycle and two frozen cycles are required, on average, for each unaffected live birth. MBS and PBS item numbers are listed. These costs assume that ICSI is not used, and that local anaesthetic is used during egg retrieval and embryo transfer procedures. Government benefits and out-of-pocket costs are listed separately.
Girardet, A., Ishmukhametova, A., Viart, V., Plaza, S., Saguet, F., Verriere, G., et al., 2018. Thirteen years' experience of 893 PGD cycles for monogenic disorders in a publicly funded, nationally regulated regional hospital service. Reprod. Biomed Online 36, 154–163.

monogenic conditions, including genetic eye conditions and other conditions such as cystic fibrosis (Backenroth et al., 2018; Dolan et al., 2017; Girardet et al., 2018; Hlavatá et al., 2016). Thus, if PGD was made more affordable, families with other conditions would have improved affordable reproductive choices.

## Conclusion

This study conducted an economic evaluation of use of the IVF and PGD pathway compared with natural pregnancy for couples with a germline retinoblastoma mutation. The analysis showed that even at low uptake rates, where only of 10% couples used IVF and PGD, there was a cost-saving of AUD$699,366, increasing to AUD$3,452,354 for an uptake rate of 50% and AUD$6,793,517 for an uptake rate of 100% for 100 couples. Further, the number of babies born without the familial *RB1* mutation increased as the uptake rate increased. For all uptake rates of IVF and PGD, and for families aiming for one or two children, quality of life improved and there was always a cost-saving.

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