

1 Preimplantation genetic testing for BRCA gene mutation carriers: a cost  
2 effectiveness analysis

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19 Running title: IFV/PGT-M for BRCA gene mutation carriers

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## 23 **Abstract**

24 **Objective:** Gynecologic oncologists should be aware of the option of conception  
25 through IVF/PGT-M for families with high BRCA related morbidity or mortality. Our  
26 objective was to investigate the cost-effectiveness of preimplantation genetic testing  
27 for selection and transfer of BRCA negative embryo in BRCA mutation carriers  
28 compared to natural conception.

29 **Design:** Markovian process decision analysis model comparing two strategies,  
30 conception through IVF/PGT-M and BRCA negative embryo transfer and natural  
31 conception with a 50% chance of BRCA positive newborn.

32 **Setting:** Not applicable

33 **Population:** Theoretical couple, with either one parent carrying a BRCA germ line  
34 mutation.

35 **Intervention:** None

36 **Methods:** Costs of two strategies were compared using quality adjusted life years  
37 (QALYs'). All costs were discounted at 3%.

38 **Main outcome measure:** Incremental cost effectiveness ratio (ICER) compared to  
39 willingness to pay threshold was used for cost-effectiveness analysis.

40 **Results:** IVF/ PGT-M is cost-effective with an ICER of 150,219 new Israeli Shekels,  
41 per QALY gained (equivalent to 44,480 USD), at a 3% discount rate.

42 **Conclusion:** IVF/ PGT-M and BRCA negative embryo transfer compared to natural  
43 conception among BRCA positive parents is cost effective and should be considered  
44 for selected couples with high BRCA mutation related morbidity.

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47 **Keyword:** IVF, PGT-M, BRCA, cost-effectiveness

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49 Tweetable abstract: IVF/PGT-M compared to natural conception for BRCA gene

50 carriers is cost effective in Israel

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## 65 Introduction

66 BRCA mutation carriers have an estimated 80% life time risk of breast cancer, up to  
67 40% life time risk of ovarian cancer, as well as increased risk of other malignancies  
68 including gastro-intestinal, pancreatic and prostate cancer <sup>1</sup>. In some family clusters,  
69 high disease burden is noticed with several generations effected at young ages,  
70 causing significant physical and psychological morbidity <sup>2,3</sup>. Previous studies have  
71 shown that population based BRCA screening is cost effective and can be used as a  
72 screening tool that allows very effective risk reduction strategies for BRCA carriers <sup>4-</sup>  
73 <sup>6</sup>. Another possible strategy that may prevent passing on the BRCA gene to next  
74 generations is selection of BRCA negative embryos using in-vitro fertilization (IVF)  
75 and preimplantation genetic testing for monogenic/single gene disorders (PGT-M).  
76 PGT-M enables selection of unaffected embryos for embryo transfer and may be  
77 used for prevention of single gene disorders, such as BRCA gene mutations, in  
78 offspring <sup>7,8</sup>. The Ethics committee opinion of the European Society of Human  
79 Reproduction and Embryology stated that PGT-M for adult-onset conditions is  
80 ethically justifiable when the conditions are serious and when there are no known  
81 interventions for the conditions, or the available interventions are either inadequately  
82 effective or are perceived to be significantly burdensome <sup>9</sup>. Indeed, delivering a  
83 BRCA negative newborn would prevent the need for life long cancer surveillance for  
84 BRCA positive patients along with the medical, psychological and financial burden  
85 associated, and may be a suitable solution for some BRCA positive families.

86 The aim of our study was to investigate whether IVF/ PGT-M for BRCA negative  
87 embryo selection among BRCA positive parents as opposed to natural conception  
88 with a 50% chance of a BRCA positive fetus, due to dominant gene inheritance,  
89 would be a cost effective strategy.

## 90 **Methods**

91 The target population for our research are potential BRCA positive parents (mother  
92 or father). Costs of IVF/PGT-M, with BRCA negative embryo selection and transfer  
93 versus natural conception with a 50% chance of BRCA positive newborn, were  
94 compared using a Markovian process decision analysis model (Figure 1). The model  
95 assumed that all women in the IVF/ PGT-M arm would undergo ovarian stimulation  
96 and ovum pick. After intracytoplasmic sperm injection (ICSI), fertilization and embryo  
97 biopsy, a BRCA negative embryo would be selected for embryo transfer. In the  
98 natural conception arm, women would conceive naturally, without any manipulation,  
99 and assume a 50% chance of bearing a BRCA positive newborn, as BRCA is a  
100 dominant gene. BRCA negative newborns would assume to have the general  
101 populations' life-time-risk of breast and ovarian cancer. At age 40, BRCA positive  
102 females would be offered risk reduction salpingo-oophorectomy (RRSO) for ovarian  
103 cancer prevention <sup>10</sup>. Management of breast cancer risk for BRCA positive females  
104 would include screening with yearly breast MRI/ultrasound or risk reduction  
105 mastectomy (RRM) for breast cancer prevention <sup>10</sup>. Costs of these two strategies  
106 were compared using quality-adjusted life years (QALYs), which reflect both quality  
107 and quantity of life lived. Incremental cost effectiveness ratio (ICER) was used for  
108 cost-effectiveness analysis, compared to a willingness to pay threshold.

### 109 **IVF/PGT-M arm**

110 In this arm, all couples with either one BRCA positive parent were assumed to  
111 undergo ovarian stimulation, ovum pick-up and ICSI. After fertilization, embryos  
112 would be biopsied and only BRCA negative embryos would be transferred. All  
113 women were assumed to have IVF before age 35, where IVF success rates are

optimal <sup>11</sup>, as the knowledge of BRCA carrier state among afflicted families would to be known at an early age. The following steps were assumed in the IVF/ PGT-M arm, probabilities were taken from the ESHRE PGD consortium data collection regarding success of IVF/ PGT-M cycles preformed for single, autosomal dominant gene disorders <sup>8</sup>: (1) ovarian stimulation and ovum pick-up, on average, 13 oocytes are retrieved per IVF cycle among patients <35 years, undergoing IVF/PGD for dominant, single gene disorders, (2) insemination with ICSI, 82% of oocytes are successfully inseminated, (3) fertilization, 76% of inseminated oocytes are fertilized, (4) embryo biopsy, 79% of embryos are successfully biopsied.

Accordingly, per cycle start, out of 13 oocytes retrieved, 6.4 embryos will be available for biopsy, half of which, 3.20 embryos, will be BRCA negative embryos, available for transfer. The first embryo will be used for fresh embryo transfer, the remaining embryos will be frozen for future frozen thawed embryo transfer cycles.

The overall live birth rate per embryo transfer for couples undergoing IVF/ PGT-M for genetic disorders reaches 45.8% <sup>12</sup>. The model assumed that after the first fresh embryo transfer, 54.2% of couples who fail would have a second thawed embryo transfer, while 29% of couples who will fail the second transfer, will have a third, thawed embryo transfer. Therefore, 3 available healthy, non BRCA mutated embryos, with a 45.8% live birth rate per embryo transfer would result in an overall 84% chance of a live, BRCA negative baby, from one cycle of fresh embryo transfer and two more cycles of thawed embryo transfers. The remaining 16% of couples who failed the IVF/ PGT-M path would go back to the natural conception arm.

#### **Natural conception arm**

In this arm, couples are assumed to conceive naturally. As BRCA is a dominant gene, these couples would have a 50% chance of bearing a BRCA positive fetus, of those, 50% would be females, positive for BRCA gene mutations with respective increased risk of breast and ovarian cancer. As the chances of other BRCA related malignancies among male mutation carriers are much lower than among female mutation carriers these were not included in our model. BRCA negative newborns were assumed to have the natural populations' breast and ovarian cancer risk.

#### **Model costs**

In vitro fertilization, PGT-M and embryo transfer, as well as BRCA screening and other treatment related costs including, RRSO, RRM and breast and ovarian cancer treatment costs were received from the Israeli ministry of health 2020 pricing list according to specified codes with conservative assumptions of health resources utilities. Elaborate costs used in the model, from payer perspective, are shown in supplementary Table 1, 2, 3, 4 and 5 for, ovarian cancer treatment, breast cancer treatment, IVF/PGT-M, BRCA positive patients follow-up and total costs, respectively. All costs were discounted at 3%.

#### **Probabilities**

Model probabilities are presented in Table 1. The probability of being at the end of each arm of the Markovian model was calculated by multiplying the probabilities of events along the arms' path. Stage distribution and Kaplan Meir survival curves for each stage were used to calculate mortality rates of subjects who developed breast cancer or ovarian cancer, based on the Surveillance, Epidemiology and End Results program data base (SEER) <sup>13,14</sup>. Survival curves were extrapolated by fitting Weibull distribution using the Nelder-Mead Algorithm.

## 161 **Quality adjusted life years and incremental cost effectiveness ratio**

162 Value of health benefits for each strategy (IVF/ PGT-M versus natural conception)  
 163 were calculated using quality adjusted life years (QALY's). QALY's are calculated by  
 164 multiplying the utility value associated with a given state of health by the number of  
 165 years lived in that state, where QALY of one reflects one year lived in perfect health  
 166 and QALY of zero represents death state. The incremental cost effectiveness ratio  
 167 was then calculated by using the formula: (average cost IVF/ PGT-M – average cost  
 168 natural conception) / (average QALY IVF/ PGT-M – average QALY natural  
 169 conception). The incremental cost effectiveness ration (ICER) calculated, enabled to  
 170 determine whether offering IVF/ PGT-M to BRCA positive families is cost effective or  
 171 not, compared to willingness to pay threshold. An intervention was defined as cost  
 172 effective if the ICER per QALY is between 1-3 times per capita gross national  
 173 product (GNP). GNP in Israel is estimated at 42,160 USD, equivalent to 142,500  
 174 new Israeli Shekels (NIS) <sup>15</sup>. Interventions below 1 GNP per capita are considered  
 175 very cost effective <sup>16</sup>.

## 176 **Sensitivity analysis**

177 One-way sensitivity analysis was conducted with all variables to evaluate model  
 178 uncertainties. In addition, a probabilistic sensitivity analysis (Monte Carlo simulation)  
 179 was conducted with all variables, using 100 trials, each included 10,000 couples.

## 180 **Ethical approval statement**

181 As this work is a theoretical, mathematical model, not involving any human or animal  
 182 subjects in any form, after consultation with our local IRB (TLV) at the Tel-Aviv  
 183 medical center, it was exempt from the need of IRB approval

## 184 **Results**



Delivering a BRCA negative newborn after IVF/ PGT-M, compared to natural conception, is cost effective according to our model, with an ICER of 150,219 NIS per QALY gained, at a 3% discount rate compared to a willingness to pay threshold of 1-3 times Israeli GNP per capita, equivalent to 44,480 USD (Table 2).

## **Sensitivity analysis**

In order to assess the effect of each parameter on the ICERS, a sensitivity analysis was conducted. Results are shown on a tornado diagram (Figure 2). The most influential parameter that effects the ICER was found to be the discount rate, set at 3% in our model. As the money spent on IFV/ PGT-M is used at present, while screening strategies for BRCA carriers, risk reduction surgeries as well as breast and ovarian cancer treatments start many years later (beginning at age 30 years), discounting makes costs of future spending much lower than current values. Reducing the discount rate to zero resulted in a negative ICER of -19,658 NIS, meaning that IVF/ PGT-M would be cost saving and not just cost effective.

Probabilistic sensitivity analysis (Monte Carlo simulation) was conducted with all variables, using 100 trials, each included 10,000 couples. At a willingness to pay threshold of 340,000 NIS (which are equivalent to 100,000 USD), in over 85% of simulations iterations IVF/ PGT-M compared to natural conception is cost effective (Acceptability curve, which shows the results of probabilistic sensitivity analysis and presents the relative cost-effectiveness as a function of the ICER, willingness to pay threshold, is shown in Supplementary Figure 1)

## **Discussion**

### **Main findings**

208 In this cost effectiveness analysis, we found that at current pricing, with a 3%  
209 discount rate, IVF/ PGT-M for BRCA negative embryo selection is cost effective  
210 compared to natural conception, with an ICER of 150,219 NIS per QALY gained.  
211 This ICER is just short of being very cost effective, compared to a WTP threshold of  
212 one GNP per capita in Israel.

### 213 **Strengths and limitations**

214 Our work has several limitations. As correlation between BRCA gene mutation and  
215 other malignancies, such as prostate, gastrointestinal and pancreatic cancer is much  
216 weaker we decided not to include these in our model. The number of uncertainties  
217 that would arise in a model that would include many more malignancies would be, in  
218 our opinion, too large, making our theoretical model much weaker. Another major  
219 limitation that would need to be addressed as IVF and PGT-M technologies improve,  
220 making it more readily available for widespread use is the ethical justification of  
221 putting couples through a potentially dangerous medical procedure in order to avoid  
222 potential disease that would develop many years later such as ovarian cancer that is  
223 highly preventable with RRSO and breast cancer that is both preventable and highly  
224 curable for patients under tight follow-up. From a practical standpoint, the prevalence  
225 of BRCA in Israel, particularly among Jews of Askenazi origin, is as high as 2.5%,  
226 and offering IVF/ PGT-M on a large population scale might not be a feasible option.  
227 Saving this procedure to selected families with high disease burden or extreme  
228 cancer anxiety would be a more practical approach.

229 Our work has several advantages. In our model, IVF/ PGT-M strategy was found to  
230 be cost effective compared to natural conception. When calculating the costs of  
231 breast and ovarian cancer treatment, we assumed a very conservative use of health

resource utilities. In addition, costs involved with male BRCA related malignancies were not included in our calculations, (mainly because the probabilities of these malignancies are much smaller). Had we taken these risks into consideration in our model, cost-effectiveness would likely to increase considerably. Another important point that underestimates the advantage of having IVF/ PGT-M, and would make this strategy more cost effective, is the elimination of the 50% chance of passing on the BRCA gene to second generations in the IVF/ PGT-M arm. In the natural conception arm, BRCA positive newborns would themselves have a 50% chance of passing the BRCA mutated gene to their offspring with the costs involved. Our model included the most up-to-date recommendations for breast and ovarian cancer treatments including the use of poly ADP ribose polymerase (PARP) –inhibitors for the first line treatment of ovarian cancer, that was only recently approved for use in Israel, in BRCA positive patients. These are highly costly drugs that add considerably to cancer treatment costs. Most up-to-date data regarding the effect of RRSO on breast cancer risk was also included in our model. Previous data estimated a 50% reduction in risk of breast cancer as a result of RRSO. Newer data that used RRSO as a time dependent covariate did not find such an effect and in fact found no influence of RRSO on breast cancer risk <sup>22–24</sup>. A possible strategy that would further increase success rates of IVF/PGT-M, for couples who failed to produce a BRCA negative embryo would be to transfer a male embryo, regardless of its' BRCA status. Using a male BRCA positive embryo for transfer would not prevent passing on the BRCA gene to the next generation, but would eliminate the risk of ovarian cancer, keep the chance of breast cancer (male breast cancer) very low while increasing the number of embryos available for transfer.

## **Interpretation**

Advances in PGT-M can prevent passing of single gene disorders such as BRCA mutations to future generations by selecting a BRCA negative embryo. The prevalence of BRCA gene mutations reaches as high as 2.5% among Jews of Ashkenazi ancestry <sup>17</sup> and although offering IVF/ PGT-M on a large population scale may not be feasible, this technology can be an extremely useful solution for families with very high BRCA related morbidity or mortality. These families carry a heavy medical as well as psychological burden with a life-long fear of cancer as well as fear of passing this cancer potential to their descendants. Our model shows that IVF/PGT-M is a cost effective option that may be offered to selected patients. This option should be kept in mind of gynecologists, gynecologic oncologists, oncologist and any other physician involved with medical care of BRCA positive patients.

The sensitivity analysis showed that the most important factor impacting the ICER in our model is the discount rate. This is caused because the costs involved in IVF/ PGT-M are assumed to be spent at present while the money saved by preventing the birth of a BRCA positive offspring will only be seen within 30-40 years when screening and risk reduction surgeries will be implemented. Thus, the long projection period makes the yearly discount a very influential factor in the model. Reducing the discount rate to zero resulted in a negative ICER (-19,658 NIS), making IVF/PGT-M cost saving. In a similar work, only recently published by Lipton et-al, a more conservative discount rate of 1.5% was assumed <sup>18</sup>. In this work, that was done on Canadian data, IVF/PGT-M was found to be cost effective for both BRCA1 and BRCA2 mutation carriers with an ICER of 14,242 USD and 12,893 USD, respectively. In our model the base line discount rate assumed was 3%, one that is used more frequently in cost effectiveness analysis in the United States and in most European countries <sup>19</sup>.

282 The probability that a BRCA carrier would undergo RRSO also had a significant  
283 influence on the ICER calculated (tornado diagram, figure 2). The probability  
284 estimated in our model was 65%, based on previous data <sup>20,21</sup>, raising this probability  
285 would make the ICER significantly more cost effective. Presuming that IFV/PGT-M  
286 would be offered to families with high disease burden, we believe that the uptake of  
287 both RRSO and RM would be much higher among these families, making IFV/PGT-  
288 M even more cost effective.

## 289 **Conclusions**

290 IVF/PGT-M for BRCA positive parents versus natural conception at current pricing,  
291 with a 3% discount rate, is cost effective and should be offered to selected couples.  
292 Discount rate is the most influential parameter that effects the ICER.

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295 of interests

296 **Contribution to Authorship:** All authors contributed substantially to planning and  
297 caring out this work. NM, ML, DG, YC and IL were involved in conceptualization,  
298 and study design. NM and ML were involved in methodology and project  
299 administration. NM, DG, YC, TS, SPH and IL were involved in investigation and data  
300 analysis. NM, ML, SPH were involved in writing the original draft. All authors were  
301 involved in reviewing and editing the final article version.

302 **IRB:** As this work is a theoretical, mathematical/financial model, not involving any  
303 human or animal subjects in any form, after consultation with our local IRB at the  
304 Tel-Aviv medical center, it was exempt from the need of IRB approval.

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Table 1: Probabilities used in model

Table 2: Cost effectiveness analysis

Figure 1: Markovian decision analysis model, IFV/PGD for BRCA mutation carriers  
versus natural conception

Figure 2: Tornado diagram, sensitivity analysis of influence of model parameters on  
incremental cost effectiveness ratio