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The most efficient and effective *BRCA1/2* testing strategy in epithelial ovarian cancer: Tumor-First or Germline-First?

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HIGHLIGHTS

- An efficient strategy for genetic testing in epithelial ovarian cancer is highly desired.
- We compared costs and effects of two strategies: Tumor-First and Germline-First.
- Average testing costs per patient are much lower with the Tumor-First strategy.
- In a likely scenario, more patients and relatives with a germline *BRCA1/2* PV are identified with the Tumor-First strategy.

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ABSTRACT

Objective. Genetic testing in epithelial ovarian cancer (OC) is essential to identify a hereditary cause like a germline *BRCA1/2* pathogenic variant (PV). An efficient strategy for genetic testing in OC is highly desired. We evaluated costs and effects of two strategies; (i) Tumor-First strategy, using a tumor DNA test as prescreen to germline testing, and (ii) Germline-First strategy, referring all patients to the clinical geneticist for germline testing.

Methods. Tumor-First and Germline-First were compared in two scenarios; using real-world uptake of testing and setting implementation to 100%. Decision analytic models were built to analyze genetic testing costs (including counseling) per OC patient and per family as well as *BRCA1/2* detection probabilities. With a Markov model, the life years gained among female relatives with a germline *BRCA1/2* PV was investigated.

Results. Focusing on real-world uptake, with the Tumor-First strategy more OC patients and relatives with a germline *BRCA1/2* PV are detected (70% versus 49%), at lower genetic testing costs (€1898 versus €2502 per patient, and €2511 versus €2930 per family). Thereby, female relatives with a germline *BRCA1/2* PV can live on average 0.54 life years longer with Tumor-First compared to Germline-First. Focusing on 100% uptake, the genetic testing costs per OC patient are substantially lower in the Tumor-First strategy (€2257 versus €4986).

Conclusions. The Tumor-First strategy in OC patients is more effective in identifying germline *BRCA1/2* PV at lower genetic testing costs per patient and per family. Optimal implementation of Tumor-First can further improve detection of heredity in OC patients.

Abbreviations: OC, epithelial ovarian cancer; PV, pathogenic variant; BC, breast carcinoma; PARP, poly-ADP ribose polymerase; RRSO, risk-reducing salphingo-oophorectomy; RRM, (bilateral) risk-reducing mastectomy.

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1. Introduction

A considerable proportion, around 10 to 15%, of women with epithelial ovarian cancer (OC) have a hereditary cause of this disease. These women have a germline pathogenic variant (PV) in one of the OC risk genes, predominantly *BRCA1* and *BRCA2* [1–3]. Recognizing heredity may both guide treatment choices with PARP inhibitors [4,5] and prevent advanced cancers in relatives when they opt for OC risk-reducing surgery and for breast carcinoma (BC) surveillance or risk-reducing surgery [6]. Recent guidelines state that all OC patients are eligible for germline testing [7,8]. Generally, a referral to a clinical geneticist for counseling precedes germline testing. However, uptake of referral and germline testing appears low and consequently heredity may remain unrecognized [9].

Recently, experts have proposed and introduced the Tumor-First strategy for OC patients. Tumor-First means that OC tumor DNA of all newly diagnosed patients is systematically examined for the presence of PV in OC risk genes, which may be somatic or derived from the germline [1,10,11]. This tumor DNA test is a prescreen and solely those OC patients with a PV in tumor DNA (<20%) are referred to the clinical geneticist for counseling and germline testing. This allows genetic counseling to be targeted at those at high hereditary risk. Besides that, the Tumor-First test informs on the effectiveness of OC treatment with PARP inhibitors as these are more effective in patients that have a either a germline (hereditary) or a somatic (non-hereditary) *BRCA1/2* PV which are both detected by the tumor DNA test [4,5]. Validation of the tumor DNA test for this purpose has been presented in several previous articles [10,11].

The Tumor-First strategy has shown a high implementation rate (over 70%) in the first years and the strategy was appreciated by both gynecologists and patients [1]. However, the costs and effects of the Tumor-First strategy have not been specified yet. The question remains what is the most efficient (i.e. cost-effective) strategy, Tumor-First or Germline-First (referring all OC patients to the clinical geneticist)? The aim of this study is to evaluate costs and effects of the Tumor-First strategy compared to the Germline-First strategy in a Dutch healthcare system using decision analytic modelling from a healthcare perspective.

2. Methods

We have built decision analytic models to compare two *BRCA1/2* testing strategies for OC patients, namely (i) Tumor-First strategy, using a tumor DNA test as prescreen to germline testing, and (ii) Germline-First strategy, referring all patients to the clinical geneticist for germline testing with subsequent tumor testing to detect somatic variants for PARP inhibitor effectiveness. We aimed to analyze costs and effects in both a realistic situation and a situation in which implementation of testing would be optimal (100%). Therefore, we used two scenarios in our models: (i) a likely scenario using real-world uptake data in both strategies, and (ii) an optimistic (headroom) scenario exploring the maximum net benefit. Main outcomes consisted of the average costs of genetic testing (including germline test counseling) per OC patient and per family of an OC patient, the proportion of germline *BRCA1/2* PV identified and life years saved in female relatives with a germline *BRCA1/2* PV. Our study design and main outcomes are summarized in Fig. 1. Analyses are based on the situation in the Netherlands and were performed from a healthcare payer perspective using costs in Euros (€), at 2022 indexed prices. The analyses were performed in Microsoft Excel (2016).

2.1. Modelling costs per OC patient and BRCA1/2 PV detection probabilities

To analyze the average genetic testing costs per OC patient and the probabilities of detecting germline and somatic *BRCA1/2* PV, we have built decision trees that depict the detailed probabilities of events and associated costs in both strategies. The decision tree of the likely scenario is shown in Fig. 2 and the decision tree of the optimistic scenario is provided in Fig. S1. A complete overview of input parameters is provided in Table S1. The proportion of germline *BRCA1/2* PV was set at 0.10 and the proportion of somatic *BRCA1/2* PV at 0.08 based on two recent empirical Dutch studies who were rather similar in their results [1,10].

The costs in the model represent an average of the 2022 healthcare costs that the eight Dutch clinical genetic centers openly display on their websites. These are costs that hospitals charge uninsured patients and we use these here to approximate the amount healthcare insurers imburse the hospitals as this is not openly available for all indications. Healthcare insurers reimburse providers based on cost packages for specific healthcare services, either based on diagnosis and treatment combinations (DBC) or other healthcare services.

We approximate molecular analysis of tumor tissue to cost €1607, germline panel testing €1829, targeted germline testing €579, and clinical genetics counseling €1736. The details and healthcare service codes are provided in Table S1. Assumptions were made that (i) the Tumor-First strategy allows for targeted germline testing based on the detected PV in the tumor and (ii) that hospitals in the Netherlands are provided the opportunity to claim costs for tumor DNA testing at the price equivalent to germline testing because it replaces the germline test for the majority of patients.

Uptake probabilities were used in the likely scenario (Fig. 2). Uptake probabilities were obtained from two regional studies in the Netherlands that both evaluated regional uptake of testing from 2016 to 2017 [1,12]. Vos et al. present uptake probabilities of Tumor-First [1], and Bokkers et al. present uptake of germline testing when referring all patients to the clinical geneticist (before their intervention) [12]. Uptake of tumor testing following germline testing in the Germline-First strategy was assumed to be 0.5 as this varies over time due to changes in the treatment of OC with PARP inhibitors. We incorporated a probability of false negative tumor DNA test results based on the spectrum of germline PV and known limitations of the NGS and MLPA tests used in the Dutch laboratories.

To aid interpretability of our results, in addition to our main outcomes (Fig. 1), we also used these decision trees to calculate the costs to detect one patient with a germline *BRCA1/2* PV. We calculated this by multiplying the average costs by the number of patients needed to test to detect one germline *BRCA1/2* PV.

2.2. Modelling costs per family of an OC patient

The average genetic testing costs per family of an OC patient include genetic testing of the OC patient and cascade testing of relatives (both male and female) in case a germline *BRCA1/2* PV was identified. To calculate this we used the following formula: $c1 + (p1 * p2 * (c2 + c3) * n1)$. Where c1 represents the average costs for genetic testing per OC patient (€), p1 indicates the probability that a germline *BRCA1/2* PV is identified (%), p2 indicates the probability that an individual has a germline *BRCA1/2* PV (%), c2 represents the costs of genetic counseling of a relative (€), c3 represents the costs for a germline tests (€), and n1 represents the number of relatives tested per index OC patient.

Average costs for genetic testing per OC patient and the probability that a germline *BRCA1/2* PV is identified are results of the patient decision tree. The costs of genetic counseling of a relative was estimated to be €1668 and germline testing €579. According to consensus-based expert opinion and a Dutch study [13], on average four family members (females and males) are tested per OC patient but with major variation among families.

To aid interpretability of our results, we also calculated the costs to detect one relative with a germline *BRCA1/2* PV. This includes the counseling and testing costs multiplied by the number of relatives needed to test to detect one PV (minimum two and maximum four) in addition to the costs to detect one index patient divided by the number of relatives tested per index patient.

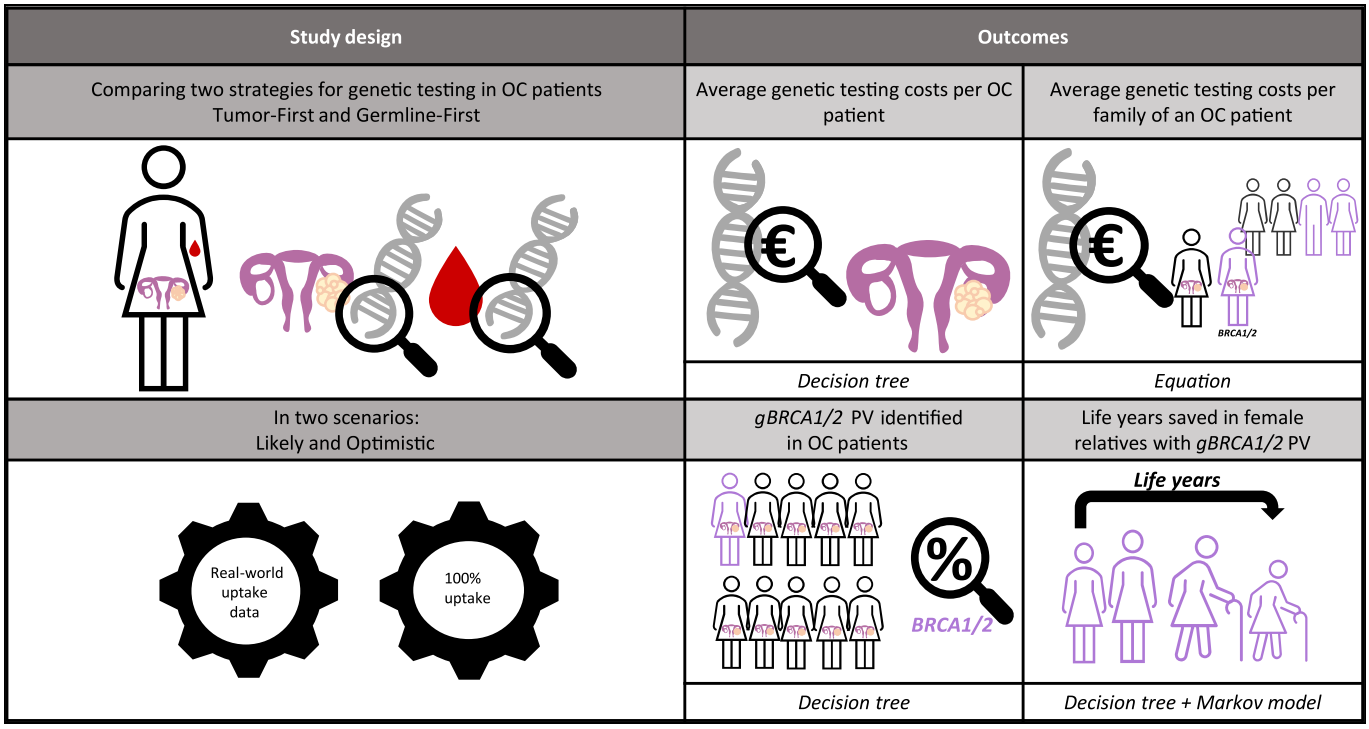

Fig. 1. Overview of study design and main outcomes.
Abbreviations: OC – epithelial ovarian cancer, PV – pathogenic variant, *gBRCA1/2* – germline *BRCA1/2*.

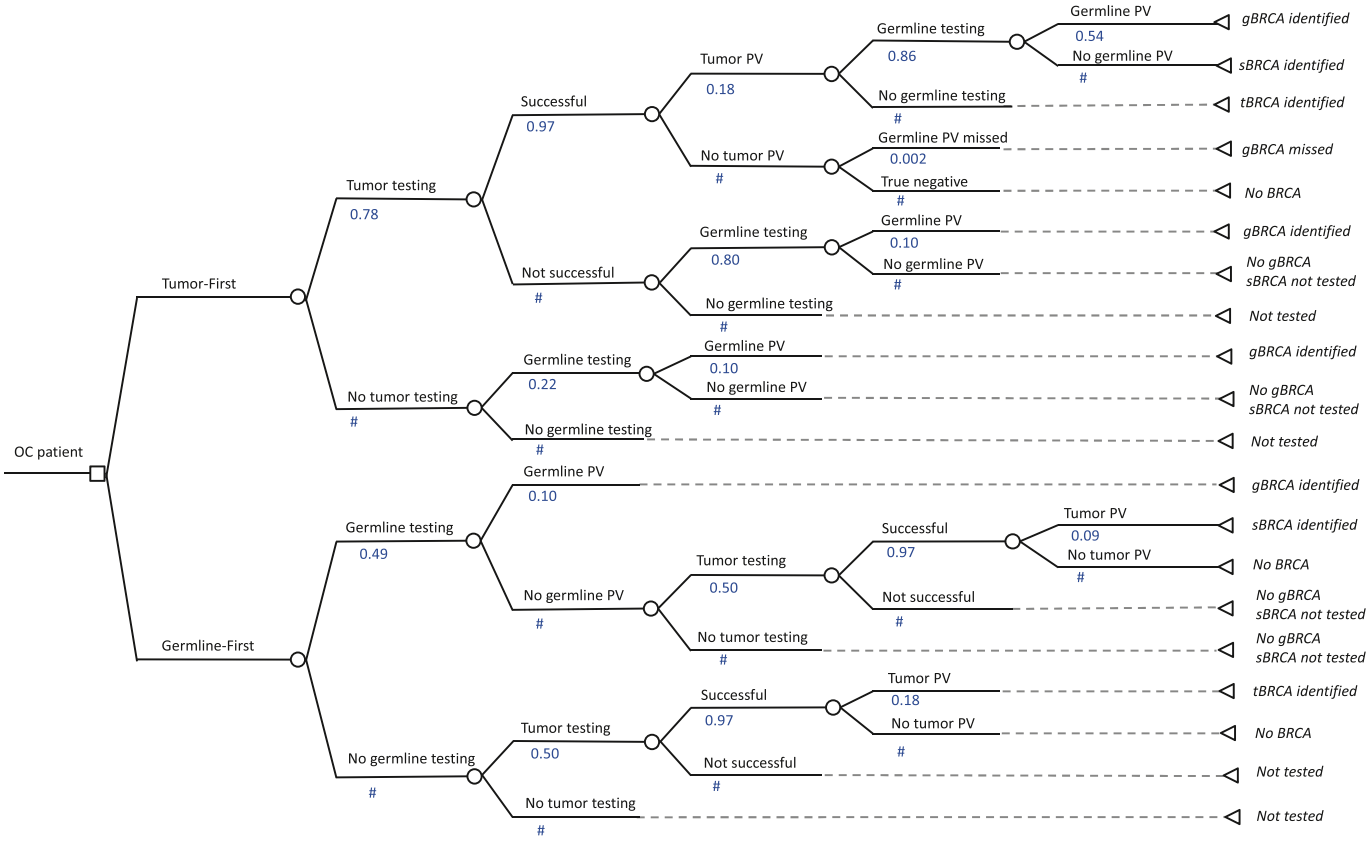

Fig. 2. Decision tree comparing genetic testing strategies for epithelial ovarian cancer patients in a likely scenario (Tumor-First versus Germline-First). Numbers indicate the probability (# means the complementary probability). The optimistic scenario is provided in Fig. S1.
Abbreviations: OC – epithelial ovarian cancer, PV – pathogenic variant, *gBRCA* – germline *BRCA1/2* pathogenic variant, *sBRCA* – somatic *BRCA1/2* pathogenic variant, *tBRCA* – tumor *BRCA1/2* pathogenic variant (either germline or somatic).

2.3. Modelling life years saved in female relatives with a BRCA1/2 PV

In a likely scenario, the higher uptake of testing in the Tumor-First strategy can prolong lives in female relatives with a germline *BRCA1/2* PV due to the ability to choose for risk-reducing surgeries. To analyze these life years saved, we developed a decision tree combined with a Markov model, as illustrated in Fig. 3. The modelled population consisted of female relatives with a germline *BRCA1/2* PV. Uptake of germline testing in relatives was considered optimal (100%).

In the decision tree, relatives could undergo risk reducing surgeries. Input probabilities on risk-reducing salphingo-oophorectomy (RRSO) and bilateral risk-reducing mastectomy (RRM) were both obtained from recent Dutch studies [14,15]. As the uptake of RRSO was extremely high, we considered the probability for a patient to undergo RRM without RRSO neglectable. Therefore, the decision tree ends with three groups of relatives that were included as Markov model starting states: healthy with both RRSO and RRM, healthy with RRSO without RRM, and healthy without both RRM and RRSO.

In the Markov model, healthy women could develop OC or BC and stay in these health states up to five years after which they were considered cured. Age-related risks for OC and BC were obtained from Kuchenbaecker et al. [16], and an average of *BRCA1* and *BRCA2* was calculated (52% *BRCA1*, and 48% *BRCA2* [1]). We assumed that RRSO reduces the risk of OC to zero and does not affect BC risk [17], and that RRM reduces the risk of BC to zero. Yearly mortality rates of OC and BC were obtained from the Netherlands Cancer Registry [18], and age-related mortality rates were obtained from Statistics Netherlands [19].

A hypothetical cohort of one thousand female relatives were modelled at a starting age of 38. This starting age was set at 38 based on the average age of one sister of an OC patient (age 58 [1]), one daughter and one sisters' daughter (both age 28 [20]). We assumed that relatives had undergone risk-reducing surgery before the start of modelling (age 38). The cycle length of the model was 1 year, and female relatives were modelled lifelong (maximum till the age of 100). We use current (undiscounted) genetic testing costs to calculate effects in the future discounted at 1.5% [21].

2.4. Dealing with uncertainty – deterministic and probabilistic sensitivity analyses

Sensitivity analyses were performed to investigate the sensitivity of the outcomes to uncertainty in the input parameters. Deterministic sensitivity analyses were performed either because (i) an individual parameter is rather uncertain or because (ii) parameters show large

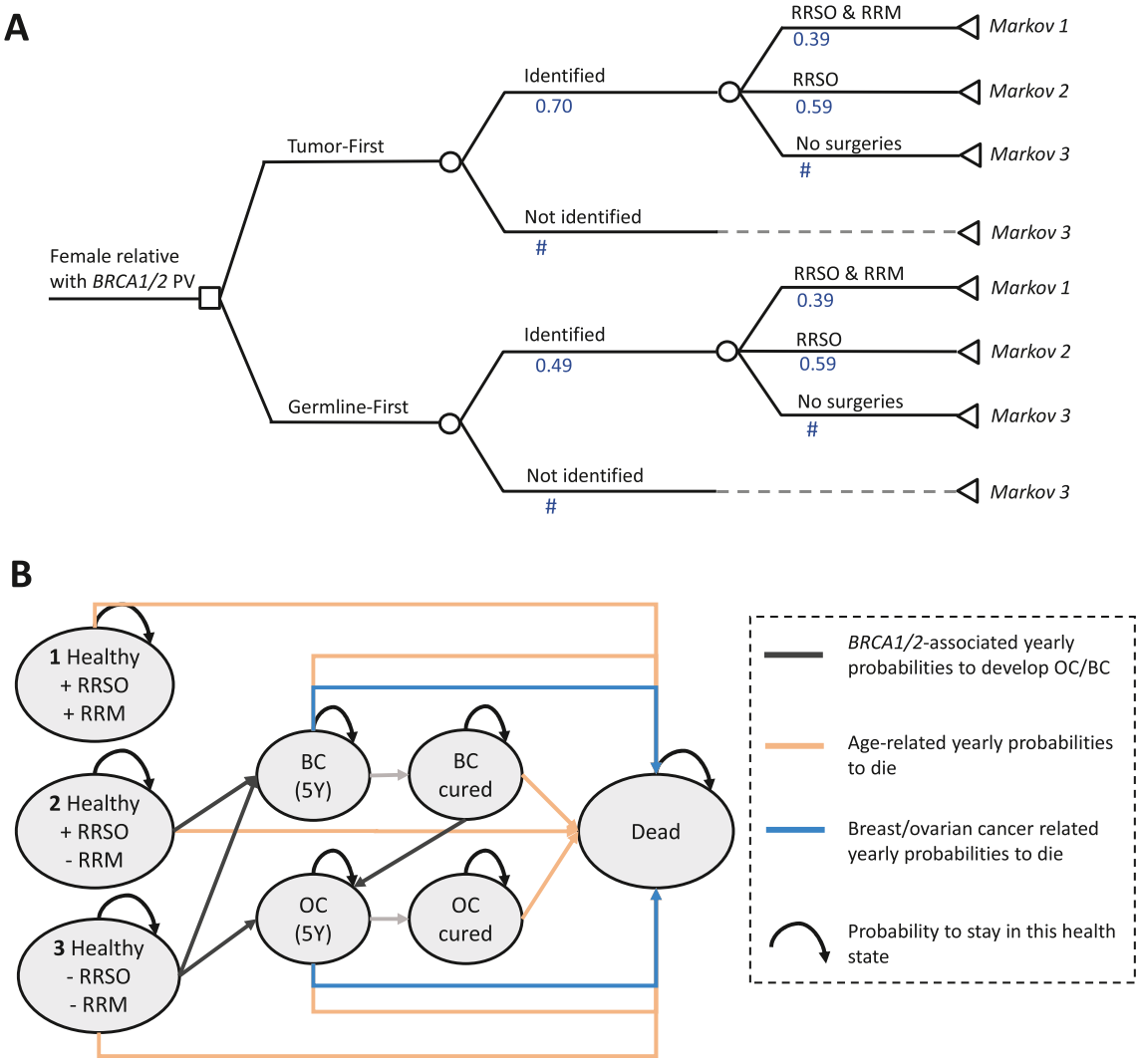

Fig. 3. Female relatives of OC patients with a germline PV in *BRCA1/2* are modelled in a decision tree (A, Tumor-First versus Germline-First) for being identified and their choices on risk reducing surgeries and subsequently enter a Markov model to investigate life years saved (B). Numbers indicate the probability (# means the complementary probability).
Abbreviations: RRSO – risk reducing salphingo-oophorectomy, RRM – risk reducing mastectomy (bilateral), OC – epithelial ovarian cancer, BC – breast carcinoma, 5Y – five years.

variation among countries. We performed deterministic sensitivity analyses varying the: proportion of germline and somatic *BRCA1/2* PV, the counseling costs, the uptake of tumor testing in the Germline-First strategy, the number of relatives tested per index patient with a germline *BRCA1/2* PV, the uptake of germline testing in relatives, the uptake of RRSO, the discount rate, and the starting age of relatives in the Markov model.

However, as all input parameters have their parametric uncertainty (i.e. standard error), we also performed a probabilistic sensitivity analysis using random sampling from all parameter's a priori distributions and simulating them 10,000 times (Monte Carlo simulation). We assigned beta distributions to probabilities, gamma distributions to costs, and log-normal distribution to cancer risks.

3. Results

3.1. Costs: average genetic testing costs per OC patient and per family

In the likely scenario, the average genetic testing costs per OC patient are slightly lower with Tumor-First compared to Germline-First (€1898 compared to €2502), as calculated by our decision analytic model and presented in Table 1. This likely scenario includes that more patients receive testing with Tumor-First. In the optimistic scenario, in case uptake of tumor and germline testing would be 100% for both strategies, the average genetic testing costs per OC patient are much lower with the Tumor-First strategy compared to the Germline-First strategy (€2257 compared to €4986).

This difference in costs is impacted by varying input parameters such as the proportion of germline *BRCA1/2* PV (from 0.0 till 0.2) and the genetic counseling costs (from €0 till €2000), as illustrated in Fig. S2 A & B. Increasing the proportion of germline *BRCA1/2* PV and decreasing the counseling costs reduce the difference in average genetic testing costs between the two strategies. However, the difference in costs remains substantial even at low counseling costs of €100 and a high proportion of 0.2 germline *BRCA1/2* PV (respectively €1423 and €2339).

Deterministic sensitivity analysis varying the uptake of tumor testing in the Germline-First strategy (to detect somatic variants for treatment option with PARP inhibitors) is shown in Fig. S2D (Likely scenario). Increasing this uptake increases the average genetic costs in the Germline-First strategy but not in the Tumor-First strategy. In case uptake of tumor testing in the Germline-First strategy is zero, the average genetic testing costs are slightly higher in the Tumor-First strategy (€1898 compared to €1753). However, the optimistic (headroom) scenario indicates that genetic testing costs are considerably lower in the Tumor-First strategy when comparing it to Germline-First without tumor testing (€2257 compared to €3565).

The costs per average family including an OC patient and testing of four relatives at risk are displayed in Table 1. In the likely scenario, the costs per family are slightly lower for the Tumor-First strategy compared to the Germline-First strategy, namely €2511 compared to €2930. This difference is larger in the headroom scenario, €3110 for Tumor-First compared to €5856 for Germline-First. Increasing the number of relatives tested per index patient with a germline *BRCA1/2* PV increases the genetic testing costs per family, as illustrated in Fig. 4. In the likely scenario, the steeper slope of the Tumor-First strategy illustrates the greater proportion of OC patients with a germline *BRCA1/2* PV identified.

Table 1
Cost outcomes.

Outcome costs	Average genetic testing costs per OC patient (€)		Average genetic testing costs per family of an OC patient (€)	
	Likely	*Optimistic*	*Likely*	*Optimistic*
Tumor-First	1898	2257	2511	3110
Germline-First	2502	4986	2930	5856
Increment	−604	−2728	−419	−2745

Abbreviations: OC – epithelial ovarian cancer, PV – pathogenic variant.

The parametric uncertainty in the individual cost outcomes is presented in Table S2, i.e. a mean and 95% confidence interval resulting from probabilistic sensitivity analysis. Following our results, when comparing Tumor-First to Germline-First, the costs to detect one index patient with a germline *BRCA1/2* PV and the costs to detect one relative with a germline *BRCA1/2* PV are lower in Tumor-First (respectively €27,733 lower and €6933 lower), as displayed in Table S3. The costs to detect one relative with a germline *BRCA1/2* PV become more similar as more relatives are tested as illustrated in Fig. S3.

3.2. Effects: proportion BRCA1/2 PV identified and life years saved

Focusing on effects, our decision analytic models illustrate that, in a likely scenario, improved uptake of testing in the Tumor-First strategy leads to more patients with a germline *BRCA1/2* PV being identified, as displayed in Table 2. Where 49% of OC patients with a germline *BRCA1/2* PV was identified with the Germline-First strategy, with the Tumor-First strategy 70% was identified. In the optimistic scenario, with uptake of testing 100% for both strategies, 100% of patients with a germline *BRCA1/2* PV were identified with the Germline-First strategy, compared to 98% with the Tumor-First strategy.

In the likely scenario, the difference in uptake of testing between Tumor-First and Germline-First also affects relatives of OC patients. Substantially, more OC patients with a germline *BRCA1/2* PV are identified in the Tumor-First strategy, and thus more first- and second degree relatives with a *BRCA1/2* PV are identified. Thereby, a cohort of female relatives with a germline *BRCA1/2* PV lives on average 0.54 life years longer with Tumor-First compared to Germline-First as calculated by our Markov model with a discount rate of 1.5%. This average of 0.54 life years originates from the 2.5 discounted life years saved in 21% of relatives that were identified with Tumor-First but not with Germline-First, and no life years saved in all other relatives. Undiscounted, identifying relatives with germline *BRCA1/2* PV saves 4.1 life years, so Tumor-First compared to Germline-First testing saves on average 0.87 undiscounted life years.

This maximum average number of discounted life years saved (0.54) decreases in case uptake of germline testing in relatives decreases as illustrated in Table S4. Additionally, the life years saved decrease in case the starting population is of an older age compared to the base case scenario aged 38. A cohort aged 58 lives on average 0.36 life years longer with Tumor-First compared to Germline-First, and a cohort aged 68 on average 0.12 life years longer. Also, the number of life years saved with Tumor-First reduce in case the uptake of RRSO is lower than the base case scenario (0.98). Female relatives live on average 0.44 life years longer with Tumor-First compared to Germline-First when uptake of RRSO is 0.8 and 0.33 life years longer when uptake of RRSO is 0.60.

With Tumor-First life years are saved because 21% extra relatives with a germline *BRCA1/2* PV are identified due to the higher uptake of testing. More life years are saved in case the difference in germline *BRCA1/2* PV detected between the two strategies increases, as presented in Table S4. For example, increasing the difference in germline *BRCA1/2* PV detected to 35%, for example by further increasing the uptake of Tumor-First testing, would save on average 0.89 life years. The parametric uncertainty in the effect outcomes are presented in Table S5, showing a mean and 95% confidence interval.

4. Discussion

Our health economic evaluation demonstrates that the Tumor-First strategy ensures that more patients and relatives with a germline *BRCA1/2* PV are detected compared to the Germline-First strategy with referral of all OC patients to the clinical geneticist (70% versus 49%),

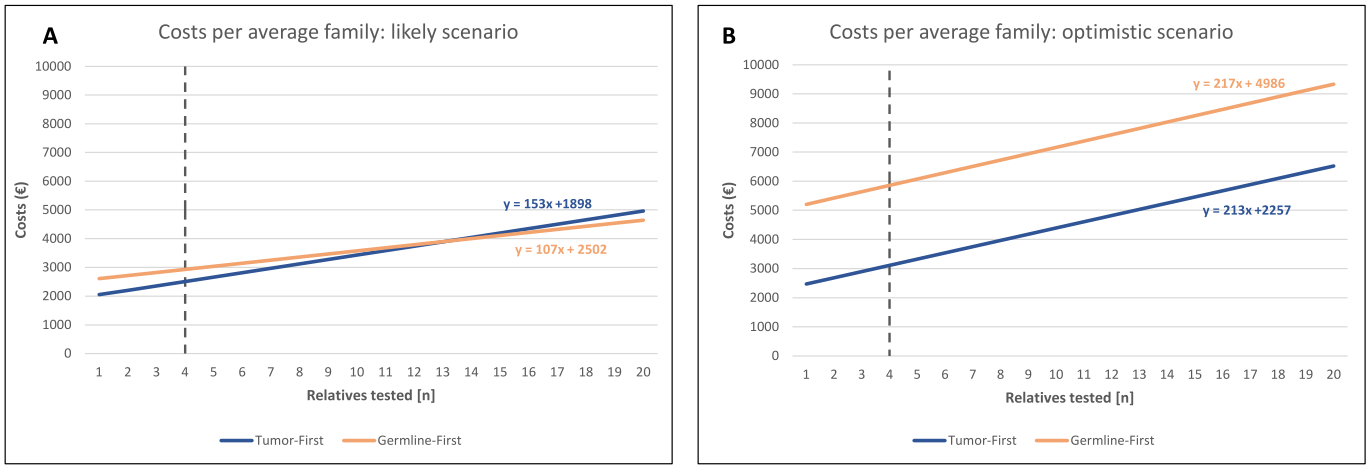

Fig. 4. Average costs per family including OC patient and cascade testing of relatives, depending on the number of relatives tested per index patient in a likely scenario (A) and optimistic scenario (B).

and at lower genetic testing costs (€1898 versus €2502 per patient, and €2511 versus €2930 per average family). Due to the improved detection of heredity, a cohort of female relatives with a germline *BRCA1/2* PV can live on average 0.54 life years longer with Tumor-First compared to Germline-First. In an optimistic scenario, in case uptake of testing would be 100% for both strategies, the average genetic testing costs per OC patient are substantially lower with the Tumor-First strategy compared to the Germline-First strategy (€2257 versus €4986). It is crucial to commit time and effort into further increasing the uptake of genetic testing with the Tumor-First strategy to identify more patients and relatives with a germline *BRCA1/2* at lower genetic testing costs.

Other cost-effectiveness analyses of *BRCA1/2* testing strategies have predominantly focused on comparing germline testing to no testing (usual care) [22,23]. Here, we considered germline testing of all patients with OC to be usual care and compared this to the Tumor-First strategy, which is a similar approach to a recent study by Kwon et al. [24]. In contrast to the latter study [24], the genetic testing costs were our main outcome and we did not incorporate treatment costs. We demonstrated that the Tumor-First strategy saves testing costs. By using the tumor DNA test as prescreen, >80% of OC patients are not referred to the clinical geneticist preventing genetic counseling and germline testing costs. Thereby, the Tumor-First strategy is more efficient and it does not only save costs, but also time and for most patients the potential emotional burden of visiting a clinical geneticist.

A strong point of our study is that our results are based on expert opinion, data from peer-reviewed literature and, in contrast to the study of Kwon et al. [24], we did incorporate real-world uptake of testing. Comparing two different regions within the Netherlands during the same time period, testing rates were higher with the Tumor-First strategy compared to the Germline-First strategy [1,12]. A systematic review including international data revealed even lower uptake (30%) of testing with the Germline-First strategy [25]. This low uptake may be caused by the intensive OC treatment in which a referral to the clinical geneticists is delayed to a later phase in the care pathway. With the Tumor-First strategy, the pathologists systematically requests a tumor DNA test once histologically diagnosing OC and the gynecologists is given extra incentive to refer in case of an aberrant tumor DNA test. This is more user-friendly for professionals which could explain the improved uptake of testing.

Due to this improved uptake of testing, a cohort of female relatives with a germline *BRCA1/2* PV can live on average 0.54 life years longer with Tumor-First compared to Germline-First (0.87 undiscounted life years). Identifying relatives with a germline *BRCA1/2* PV saves 4.1 undiscounted life years according to our model. More life years will be saved in individuals with a *BRCA1* PV compared to those with a *BRCA2* PV because of the higher OC risks. Norum et al. have demonstrated that RRSO compared to no intervention saves 9.5 undiscounted life years in women with a *BRCA1* PV [26]. Additionally, Petelin et al. have shown that their regional cancer prevention program saves on average 6.1 and 4.4 undiscounted life years in individuals with a germline *BRCA1* or *BRCA2* PV, respectively [27]. We might have underestimated the life years saved as we have used general OC and BC survival data (and not *BRCA1/2* specific), and as our Markov model is a rather straightforward presentation of reality that does not include the risk of contralateral BC [16], the possible minimal impact of RRSO on BC risk [28], and breast cancer surveillance [29]. In contrasts, not including the small residual cancer risk after risk-reducing surgeries [30,31] might have overestimated the life years saved. Notably, we investigated female relatives but life years can also be saved in male relatives as males with a *BRCA2* PV can benefit from prostate cancer surveillance [32,33].

Importantly, further increasing the uptake of genetic testing with the Tumor-First strategy can save even more life years in relatives, i.e. the 70% of OC patients with a germline *BRCA1/2* PV identified with Tumor-First leaves room for improvement. Noticeably, life years would also be saved by increasing the uptake of genetic testing with the Germline-First strategy or by focusing on alternative strategies

Table 2
Effect outcomes.

Outcome effects	Germline *BRCA1/2* PV identified (%)		Life years in saved in female relatives with germline *BRCA1/2* PV (y)	
	Likely	*Optimistic*	*Likely*	*Optimistic*
Tumor-First	70	98	29.63	n/a
Germline-First	49	100	29.09	n/a
Increment	21	−2	0.54	n/a

Abbreviations: OC – epithelial ovarian cancer, PV – pathogenic variant, n/a – not applicable.

such as mainstreaming [12,34]. However, the Tumor-First strategy is more efficient as the tumor DNA test simultaneously guides medical oncologists in treatment choices. PARP inhibitors are more effective in patients that have a either a germline (hereditary) or a somatic (non-hereditary) *BRCA1/2* PV which are both detected by the tumor DNA test [4,5]. The cost-effectiveness analysis by Kwon et al. calculated the incremental costs per progression free life year gained due to eligibility for PARP inhibitor treatment, and concluded that the Germline-First strategy is not cost-effective [24]. Here, we did not incorporate this in our models as the local treatment indications for PARP inhibitors are highly subjective to changes due to new scientific evidence [35–37]. We did gather the expert opinion of twelve experienced medical oncologists from the Netherlands. They indicated that they value the tumor DNA test result and use the result for the prediction of the effectiveness of PARP inhibitors (unpublished data).

Given the results of our analysis, and the additional advantages of the Tumor-First strategy, we consider it essential to further work toward full implementation of the Tumor-First strategy. In 2020, a nationwide implementation study of the Tumor-First strategy has been started in the Netherlands [38]. All involved professional disciplines support national implementation as emerged during multidisciplinary focus group discussions [39]. In order not to miss heredity in OC patients, it is of crucial importance that the quality of the tumor DNA test equals that of a germline test (that is most often done in DNA from blood). Validation of the tumor DNA test specifically for this purpose is essential to implement the Tumor-First workflow, and agreements in this regard are advised [10,11]. In the Netherlands, besides testing for *BRCA1/2*, the gene panel has been broadened and currently also includes other OC risk genes like *RAD51C*, *RAD51D*, *BRIP1* and *PALB2*. In the future, the test is to be expected to also include determination of homologous recombination deficiency profiles in absence of PV in OC risk genes.

To conclude, when comparing two strategies for genetic testing in OC patients, Tumor-First and Germline-First, the average costs for genetic testing are substantially lower with the Tumor-First strategy. Additionally, uptake of genetic testing is higher with the Tumor-First strategy identifying more OC patients and relatives with a germline *BRCA1/2* PV and saving life years in these relatives. Implementation of Tumor-First can efficiently improve the detection of heredity in OC.

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CRediT authorship contribution statement

Vera M. Witjes: Conceptualization, Methodology, Writing – original draft. **Marjolijn J.L. Ligtenberg:** Conceptualization, Writing – review & editing. **Janet R. Vos:** Methodology, Writing – review & editing. **Jozé C.C. Braspenning:** Writing – review & editing. **Margreet G.E.M. Ausems:** Writing – review & editing. **Marian J.E. Mourits:** Writing – review & editing. **Joanne A. de Hullu:** Writing – review & editing. **Eddy M.M. Adang:** Methodology, Writing – review & editing. **Nicoline Hoogerbrugge:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Data availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

Vera M. Witjes, Marjolijn J.L. Ligtenberg, Janet R. Vos, Jozé C.C. Braspenning, Marian J.E. Mourits, Joanne A. de Hullu, Eddy M.M. Adang, and Nicoline Hoogerbrugge declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2023.04.029.

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