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Mainstream germline genetic testing for patients with epithelial ovarian cancer leads to higher testing rates and a reduction in genetics-related healthcare costs from a healthcare payer perspective

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HIGHLIGHTS

- With mainstream genetic testing, genetic testing is offered more often after diagnosis to patients with ovarian cancer.
- Genetics-related healthcare costs per patient can be significantly reduced with a mainstream genetic testing pathway.
- High morbidity and mortality might be a barrier for offering germline genetic testing to patients with ovarian cancer.
- Around 10% of patients with epithelial ovarian cancer decline germline genetic testing.

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ABSTRACT

Objective. Germline genetic testing is increasingly offered to patients with epithelial ovarian cancer by non-genetic healthcare professionals, so called mainstream genetic testing. The aim of this study was to evaluate the effect of implementing a mainstream genetic testing pathway on the percentage of newly diagnosed patients with epithelial ovarian cancer to whom genetic testing was offered and the genetics-related healthcare costs.

Methods. The possible care pathways for genetic counseling and testing and their associated costs were mapped. Patient files from all newly diagnosed patients with epithelial ovarian cancer before (March 2016 – September 2017) and after (April 2018 – December 2019) implementing our mainstream genetic testing pathway were analyzed. Based on this analysis, the percentage of newly diagnosed patients to whom genetic testing was offered was assessed and genetics-related healthcare costs were calculated using a healthcare payer perspective based on a Diagnosis-Related Group financing approach.

Results. Within six months after diagnosis, genetic testing was offered to 56% of patients before and to 70% of patients after implementation of our mainstream genetic testing pathway ($p = 0.005$). Genetics-related healthcare costs decreased from €3.511,29 per patient before implementation to €2.418,41 per patient after implementation of our mainstream genetic testing pathway (31% reduction, $p = 0.000$).

Conclusion. This study shows that mainstream genetic testing leads to a significantly higher proportion of newly diagnosed patients with epithelial ovarian cancer being offered germline genetic testing. In addition, it significantly reduces genetics-related healthcare costs per patient.

1. Introduction

All patients with epithelial ovarian cancer (EOC) are eligible for genetic testing [1–3]. Over the last few years, more genes have been

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identified as cancer predisposition genes for EOC [4], and treatment with Poly Adenosine Diphosphate-Ribose Polymerase (PARP) inhibitors for patients carrying a pathogenic variant in a *BRCA1* or *BRCA2* gene has proven to be effective for both first line treatment and in recurrent disease [5].

Despite the importance of genetic testing, referral rates for patients with EOC have remained low [6]. Therefore, different initiatives have been taken to increase the number of patients who are offered genetic testing [7]. Mainstream genetic testing is one of these initiatives. With mainstream genetic testing, non-genetic healthcare professionals (HCPs) incorporate germline genetic testing into their routine care, offering pre-test counseling and requesting the genetic test themselves [8]. Mainstream genetic testing pathways, predominantly for EOC, have been implemented around the world and have shown positive experiences amongst HCPs and patients [9,10].

Although low referral rates were the main drivers to implement mainstream genetic testing, there is limited research on the impact of such a care pathway on the proportion of eligible patients who are offered genetic testing before and after implementation. Only one study has evaluated how many of the patients presenting at the gynecology department were actually offered genetic testing before and after implementing a physician-coordinated genetic testing pathway [11].

For mainstream genetic testing pathways to become sustainable as standard care, healthcare costs of these pathways should be considered as well. So far, the costs of a mainstream genetic testing pathway have only been evaluated by George et al. in the UK [8], who showed a significant cost reduction. The healthcare costs and care pathways differ between countries. Therefore, it is important to evaluate the impact of mainstream genetic testing on healthcare costs in other countries and healthcare systems. In the Netherlands, the healthcare system is a variation on a Diagnosis-Related Group (DRG) system, in which there are predefined rates for healthcare costs [12–14].

We have recently implemented a mainstream genetic testing pathway for patients with EOC in which gynecologic oncologists and nurse specialists perform pre-test counseling and request germline genetic testing themselves [15]. We have shown that this new care pathway is acceptable to these non-genetic HCPs and that it is feasible for them to incorporate these tasks into their daily practice. The aim of this study was to evaluate the impact of our mainstream genetic testing pathway on the proportion of newly diagnosed patients with EOC to whom germline genetic testing was offered and genetics-related healthcare costs using a healthcare payer perspective by comparing a period before and after implementation of this new care pathway.

2. Material and methods

2.1. Study design and data collection

This study was part of a multi-center, prospective, observational study on the acceptability and feasibility of the implementation of a mainstream genetic testing pathway for patients with EOC. We have previously developed and implemented sequentially a mainstream genetic testing pathway in the four hospitals in the central region of the Netherlands, consisting of one academic and three non-academic teaching hospitals. Details of the development and protocol of this pathway are available elsewhere [15].

Non-genetic HCPs (i.e., gynecologic oncologists, gynecologists with a subspecialty training in oncology and nurse specialists) were first required to complete a concise accredited online training module consisting of four short films with a duration of approximately 30 min in total. Only trained non-genetic HCPs received the necessary forms to perform pre-test counseling and order the germline genetic test themselves. Genetic testing for the entire region was coordinated and performed at the University Medical Center Utrecht. Post-test counseling with a genetic HCP (i.e., clinical geneticist or genetic counselor) was offered to those patients carrying a (likely) pathogenic variant or variant of unknown significance in a cancer predisposition gene or with a relevant personal or family history requiring further evaluation by a genetics team. If required by the patient or the non-genetic HCP, patients could also be referred to the genetics department for pre-test genetic counseling performed by a genetic HCP.

The Netherlands Comprehensive Cancer Organisation (IKNL) provided data on all newly diagnosed patients with EOC who were diagnosed or treated in the participating hospitals between March 2016 and December 2019. Subsequently, we consulted the electronic patient files of the gynecology departments of the local hospitals of these patients to evaluate the time of diagnosis. The time of diagnosis was based on the date of the histology report, and if absent, the date of the cytology report. We also evaluated if a genetic test had been offered and at what time. The time of offering the genetic test was based on the date of referral to the genetics department or the date that pre-test counseling was offered by the non-genetic HCP. When no genetic test had been offered and/or performed, we reviewed these files to identify any reasons for this. In addition we evaluated the electronic patient files of the genetics department of the University Medical Center Utrecht, which were available for all patients who accepted genetic testing or were referred to the genetics department but did not opt for genetic testing. From these patient files, we ascertained whether patients received pre-test counseling and genetic testing, and if not, any reasons for this. In addition, for deceased patients, we reviewed if a genetic test had been offered through a family member. We evaluated the gynecology and genetics files between January 2021 and March 2021. In addition, in March 2022 we evaluated if a genetic file was present for all patients who had not been offered genetic testing previously. If present, we only checked if a genetic test had been performed since we first evaluated these patient files. All data were stored in the Electronic Data Capturing tool 'Castor EDC' [16].

For both assessing the number of newly diagnosed patients to whom genetic testing was offered and calculating the genetics-related healthcare costs, we only selected patients to whom genetic testing had been offered within six months after diagnosis. We excluded patients who had been offered genetic testing before their EOC diagnosis (e.g., genetic testing because of a family or personal history of breast cancer or predictive testing because of a known pathogenic variant in a cancer predisposition gene in the family). We considered six months a reasonable time period to be offered genetic testing, as most treatments are completed within six months after diagnosis. We evaluated a time period before (March 2016 – September 2017) and after implementing our new mainstream genetic testing pathway (April 2018 – December 2019). Depending on the start date for each hospital, the period after implementing our mainstreaming pathway varied between hospitals (for the Academic hospital from April 2018 to December 2019, and for the three non-academic teaching hospitals from August 2018, March 2019, and July 2019 respectively to December 2019). We selected a period of at least six months before implementing our mainstream genetic testing pathway to ensure there was no overlap of patients between the two time periods.

2.2. Percentage of patients to whom genetic testing was offered

For each patient, we evaluated whether a germline genetic test had been offered (i.e., referral to the genetics department or pre-test counseling by a non-genetic HCP) within six months after diagnosis, and whether a genetic test had been performed. If no genetic test had been offered and/or performed, we checked the files for possible reasons.

2.3. Cost analysis

In the Netherlands, a basic health insurance package is mandatory for all citizens. Citizens pay a premium for this basic package to insurers which is dependent on their income. All genetic care is covered by this

basic health package. Insurers reimburse hospitals based on predefined rates for healthcare costs in so called Diagnosis Treatment Combinations (DBCs), which is a variation on the Diagnosis-Related Group (DRG) system [12–14]. A DBC covers a full package of costs for a diagnosis-treatment combination, including diagnostics, consultation costs, HCPs' salary, and other possible costs for services provided during the hospital stay. A DBC reflects the average costs for the care provided. More than one DBC may apply to a patient. These costs are partly based on fixed national rates, determined by the Dutch ministry of Health and partly on agreements made between healthcare providers and health insurers [13].

The genetic care can be divided into different DBC packages. For patients with cancer who are eligible for diagnostic genetic counseling and testing, these packages can be divided into a simple and complex trajectory. Patients who refrain from diagnostic genetic testing after pre-test counseling fall into the simple trajectory unless there is a need for psychosocial support at the genetics department. Patients who, after pre-test counseling, opt for a genetic test fall into the complex trajectory. The DBCs do not include the costs of a genetic test.

First we mapped the possible care pathways for genetic counseling and testing and their associated costs (Fig. 1). Before the implementation of our mainstream genetic testing pathway, pre-test counseling was only offered at the genetics department. After implementing our mainstream genetic testing pathway, non-genetic HCPs could perform pre-test counseling themselves at the gynecology department, but the option to refer for pre-test counseling at the genetics department remained. Based on electronic health records, we determined the number of patients in each care pathway in the two time periods and calculated the genetics-related healthcare costs per patient (i.e., costs for simple or complex trajectory and, if applicable, costs for germline panel genetic testing). We calculated the average costs per patient based on the total claimed costs for all patients who received at least pre-test counseling at the genetics department or completed genetic testing at the gynecology department. We used the most recent national prices to best determine the impact on the current healthcare costs. National prices for 2021 were set at €543,02 for a simple trajectory, €1713,27 for a complex trajectory and €1831,00 for germline panel genetic testing [17].

2.4. Ethics approval and consent to participate

This study was reviewed by the Medical Review Ethics Committee (MREC) of the UMC Utrecht in March 2018 and the Medical Research Involving Human Subjects Act (WMO) did not apply to our study.

2.5. Statistical analyses

Descriptive statistics were used to describe the number and percentages of patients in all care pathways. The proportion of patients to whom genetic testing was offered before and after implementation of our mainstream genetic testing pathway was compared using the Pearson Chi-square test. Genetics-related healthcare costs between the two time periods were compared using the Mann-Whitney *U* test. A *p*-value <0.05 was considered as statistically significant. Statistical analyses were performed using IBM SPSS statistics 26.0.0.1.

3. Results

3.1. Percentage of newly diagnosed patients to whom genetic testing was offered and reasons for not offering genetic testing

3.1.1. Before the implementation of our mainstream genetic testing pathway

We identified 183 patients who were newly diagnosed with EOC between March 2016 and September 2017 and to whom no genetic testing was offered before this diagnosis (Fig. 2). At time of checking the patient files, 102/183 patients (56%) were offered genetic testing within six months after diagnosis, of whom 91/102 patients (89%) received pre-test counseling with a genetic HCP, and 90/91 patients (99%) completed genetic testing. The other 11/102 patients (11%) declined referral or cancelled their appointment after referral to the genetics department.

The remaining 81/183 patients (44%) were not offered genetic testing within six months after diagnosis, In total, 24/81 patients (29%) were offered a genetic test at least six months after diagnosis and for 3/81 patients (4%) family members were referred to a genetics department, because the patient was too sick to attend the genetics department or had died. The remaining 54/81 patients (67%) were not offered genetic testing. For the majority of these patients, we could not find a possible reason for this. However, we did notice that 40/54 patients (74%) had died and 19/40 patients (48%) had died within six months after diagnosis.

3.1.2. After the implementation of our mainstream genetic testing pathway

We identified 162 patients who were newly diagnosed with EOC between April 2018 and December 2019 and who had not been offered genetic testing prior to their EOC diagnosis (Fig. 3). Genetic testing was offered to 114/162 patients (70%) within six months after diagnosis ($p = 0.005$ in comparison to 56% before implementation), of whom 19/114 patients (17%) were referred to the genetics department and 95/114 patients (83%) were offered genetic testing by a non-genetic HCP of the gynecology department. In total, 17/19 patients (89%) referred to the genetics department received pre-test counseling and 17/17 patients (100%) completed genetic testing. The other 2/19 patients (11%) declined referral or cancelled their appointment after referral. In the mainstreaming pathway, 90/95 patients (95%) who were offered genetic testing accepted the genetic test, and 88/90 patients (98%) completed genetic testing. The other 5/95 patients (5%) declined genetic testing.

The remaining 48/162 patients (30%) were not offered genetic testing within six months after diagnosis at time of checking the patient files. In total, 11/48 patients (23%) were offered a genetic test at least six months after diagnosis, and for 5/48 patients (10%) family members were referred to a genetics department. The remaining 32/48 patients (67%) had not been offered genetic testing. Again, for the majority of these patients, we could not find a possible reason for this, but 20/32 of these patients (63%) had died, 11/20 (55%) had died within six months after diagnosis.

3.2. Genetics-related healthcare costs

3.2.1. Period before the implementation of our mainstream genetic testing pathway

In total, 90 patients received pre-test counseling, genetic testing and post-test counseling by a genetic HCP (Fig. 2). The genetics-related costs for these patients included the costs for both the complex trajectory and the genetic test. One patient received pre-test counseling only, because the patient elected not to proceed with genetic testing. The genetics-related costs for this patient only included the costs of the simple trajectory. Based on these costs, the genetics-related healthcare costs before implementing our mainstream genetic testing pathway were €3.511,29 per patient.

3.2.2. Period after the implementation of our mainstream genetic testing pathway

In total, 69 patients received pre-test counseling and testing by a non-genetic HCP and did not require additional counseling at the genetics department (Fig. 3). For these patients, the healthcare costs only included the costs of the genetic test. In addition, 19 patients received pre-test counseling and testing by a non-genetic HCP bud did require additional counseling at the genetics department. Therefore, the costs for these patients included both the costs of the complex trajectory

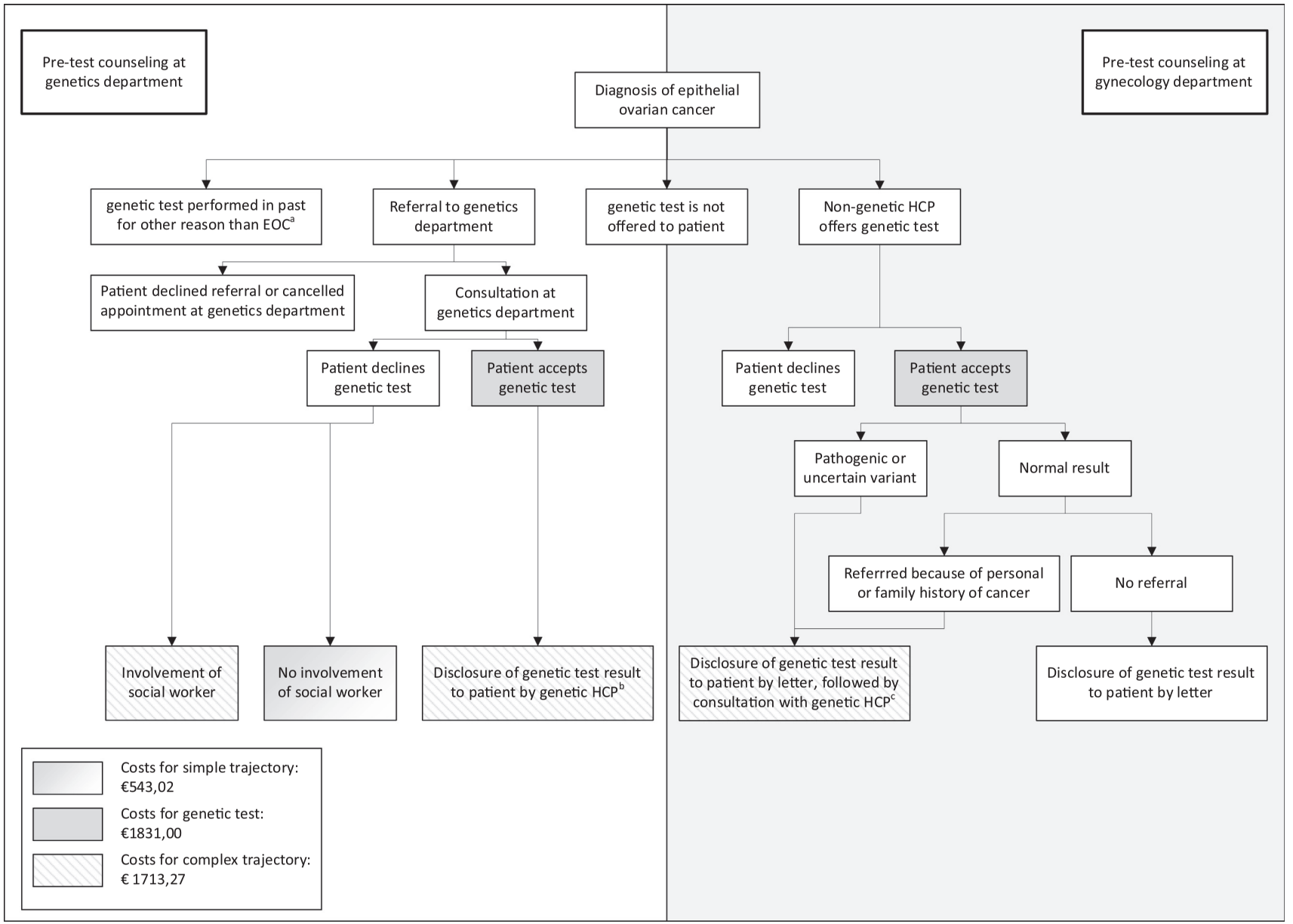

Fig. 1. Pathways for genetic testing with pre-test counseling by a genetic HCP and non-genetic HCP. Note: These pathways are not in chronological order. Before April 2018 all patients with epithelial ovarian cancer had to be referred for pre-test counseling and testing at a genetics department (left side of this figure). After implementing our mainstream genetic testing pathway, there was still an option to refer patients to the genetics department, but trained non-genetic HCPs also had the option to offer pre-test counseling themselves at the gynecology department (right side of this figure). [a] Genetic testing could have been offered before the ovarian cancer diagnosis because of a family or personal history of breast cancer or predictive testing because of a known pathogenic variant in a cancer predisposition gene in the family. [b] At the University Medical Center Utrecht, the majority of genetic test results were disclosed during a telephone consultation. Patients who carried a pathogenic variant or variant of unknown significance were subsequently invited for in-person post-test counseling at the genetics department. [c] Patients were invited for in-person post-test counseling at the genetics department.

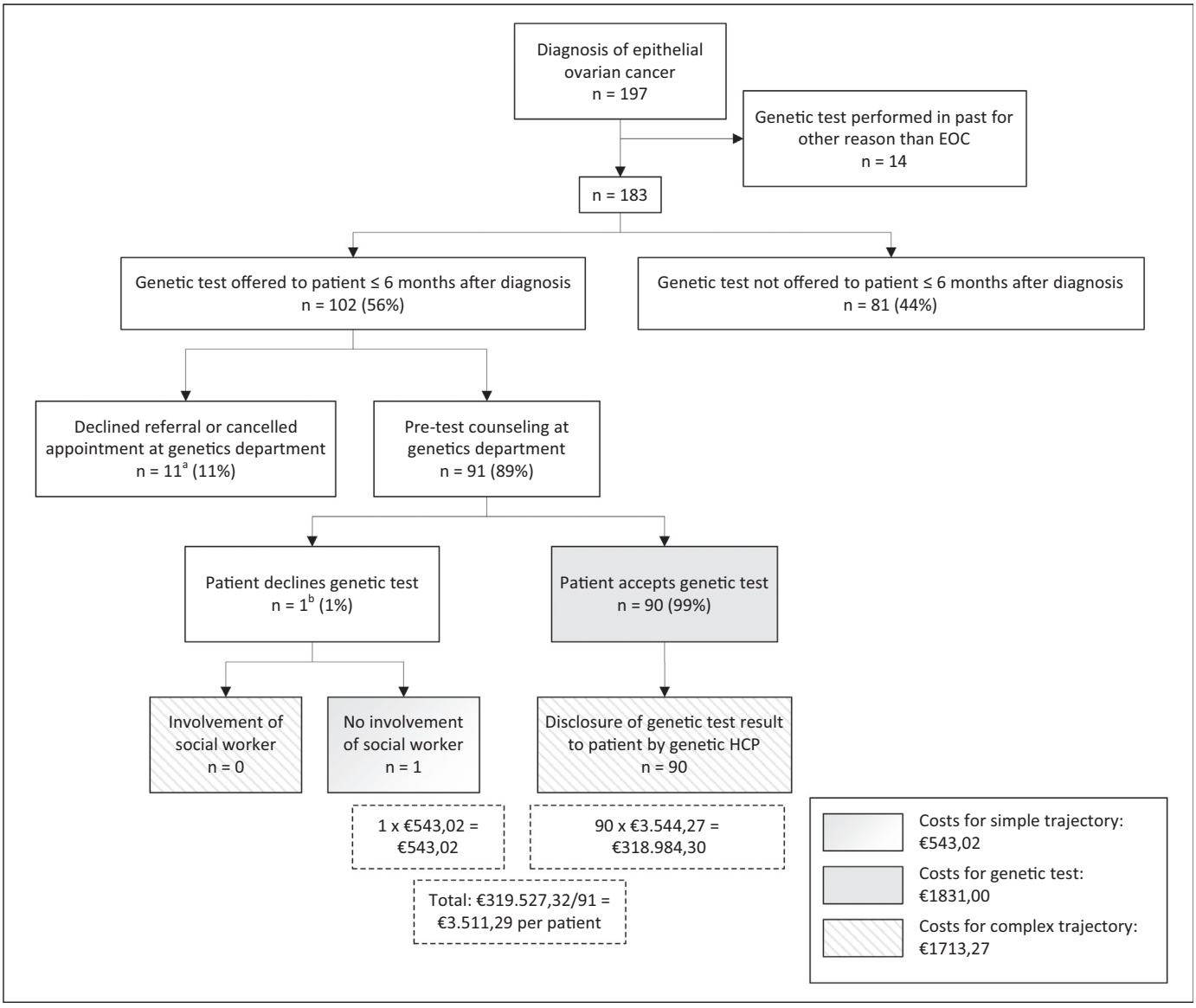

Fig. 2. Percentage of newly diagnosed patients to whom genetic testing was offered and genetics-related healthcare costs before the implementation of our mainstream genetic testing pathway. EOC: epithelial ovarian cancer. HCP: healthcare professional. [a] Three of these patients initially declined referral for genetic testing but accepted genetic testing at a later stage via our mainstream genetic testing pathway. One patient died shortly after referral. [b] Patient declined genetic testing because she 'had too much on her mind' at time of pre-test counseling.

and the costs of the genetic test. For 17 patients, pre-test counseling, genetics testing and post-test counseling were performed by a genetic HCP. For these patients, the costs for both the complex trajectory and the genetic test were included. Based on these costs, the genetics-related healthcare costs after implementing our mainstream genetic testing pathway were €2.418,41 per patient, which is a 31% reduction ($p = 0.000$) compared to healthcare costs per patient before implementation of our mainstream genetic testing pathway.

4. Discussion

This study evaluated both the proportion of patients with newly diagnosed EOC to whom germline genetic testing was offered and genetics-related healthcare costs in a period before and after implementing a mainstream genetic testing pathway. After implementing our mainstream genetic testing pathway, the proportion of newly diagnosed patients who were offered genetic testing increased from 56% to 70% and genetics-related healthcare costs per patients decreased by 31%.

Low referral rates for germline genetic testing is one of the main reasons to start with mainstream genetic testing. Previous studies have focused mainly on the number of patients who accepted genetic testing after being offered genetic testing. In our study these rates were between 95% and 100%. This is comparable to previous studies showing testing rates between 80% and 100% after pre-test counseling [8,18,19]. In addition, Yoon et al. showed that these testing rates were comparable between a mainstream and standard genetic testing pathway [18]. Powell showed that a significantly higher number of patients completed genetic testing in a mainstream genetic testing pathway (100%) in comparison to patients in a standard genetic testing pathway (85.2%) [20]. Flaum et al. showed that the number of genetic tests increased after implementing their mainstream genetic testing pathway [21]. However, eligibility criteria for genetic testing were stricter before implementing their mainstream genetic testing pathway, which makes it difficult to assess the actual impact of this pathway. To evaluate the effect of mainstream genetic testing, testing rates should be compared with the number of patients eligible for genetic testing. Only one other study evaluated how many patients, who presented at their

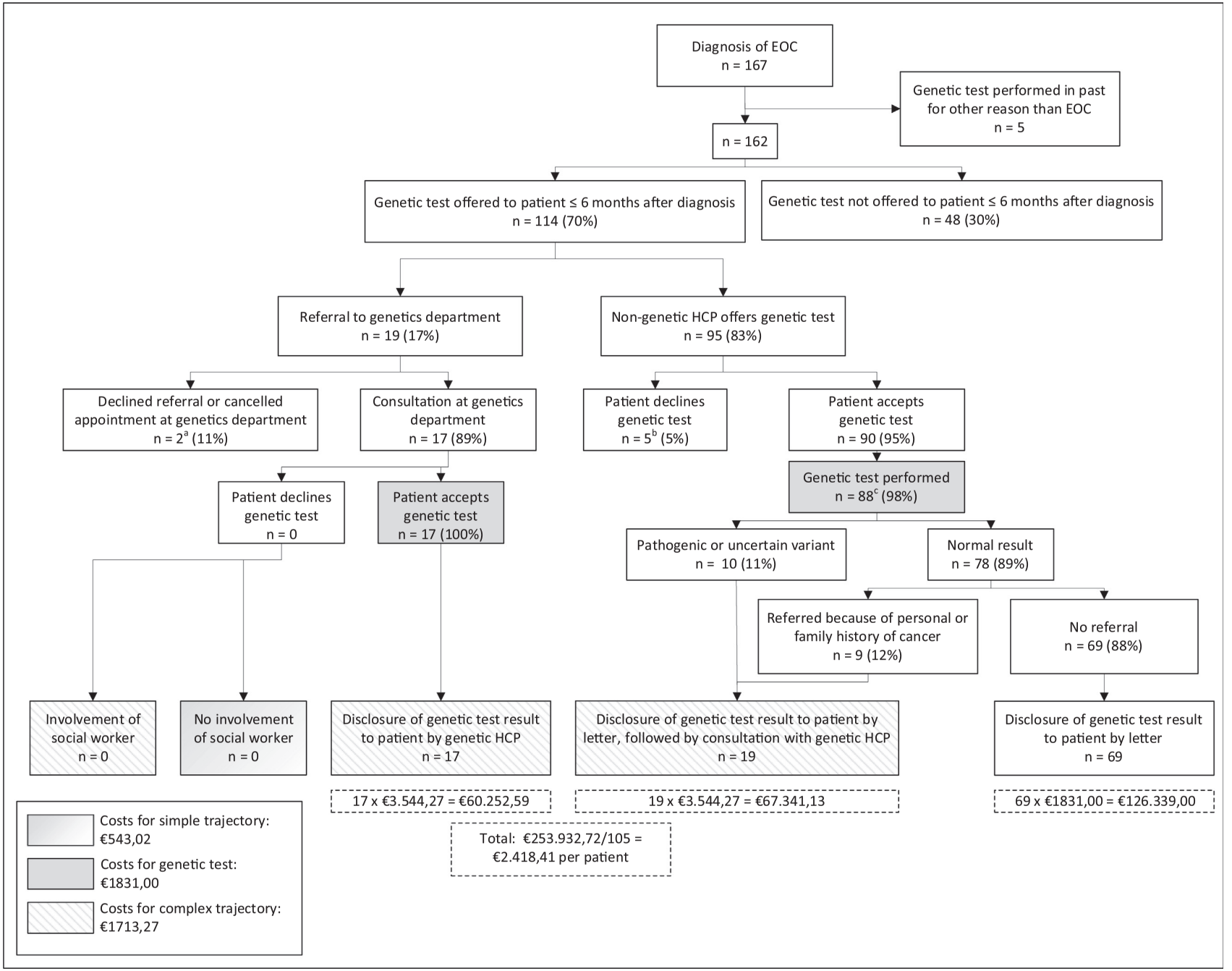

Fig. 3. Percentage of newly diagnosed patients to whom genetic testing was offered and genetics-related healthcare costs after implementation of our mainstream genetic testing pathway. EOC: epithelial ovarian cancer. HCP: healthcare professional. [a] For both patients it was not the right time to discuss genetic testing. Both patients indicated that they would contact the genetics department in a later stage, but omitted to do so. [b] Three patients needed time to think before making a decision about genetic testing, and genetic testing was not addressed a second time, for one patient her children considered genetic testing unnecessary, for one patient it is unclear if this patient declined genetic testing or if testing was not performed for another reason [c] Two patients accepted genetic testing, but for unclear reasons these tests were never performed.

gynecology clinic, were offered genetic testing in the same clinic before and after implementing a mainstream genetic testing pathway [11]. In this study, a physician-coordinated genetic testing pathway was implemented, in which the number of patients recommended to have genetic counseling and testing had increased to 87% after implementing this pathway. It is difficult to attribute this increase to the effect of mainstream genetic testing, as multiple interventions were used in this study to increase the rates of recommendation and acceptance of genetic testing (i.e., integrating genetic counselors within the gynecologic oncology department and assisted genetic counseling referral).

After implementation of our mainstream genetic testing pathway, still 30% of newly diagnosed patients had not been offered genetic testing within six months after diagnosis. A large proportion of these patients (63%) had died, 55% of whom died within six months of the diagnosis. A reason for not offering genetic testing to all patients might be the high morbidity and mortality amongst patients with EOC [4]. For newly diagnosed patients there is much to discuss during a consultation and genetic testing is usually not a first priority. It is possible that non-genetic HCPs simply do not get around to perform pre-test counseling. This is in line with our previous findings, where non-genetic HCPs reported that their main reasons for not discussing genetic testing was that the patient was too ill or there was no appropriate moment during the consultation to discuss genetic testing [15]. Moreover, it is notable that after implementation of our mainstreaming pathway a substantial proportion of patients (23%) who had not been offered genetic testing within six months after diagnosis were offered genetic testing at a later stage. However, by postponing to discuss the genetic test there is a greater chance that this will be forgotten or that the patient will have died. Because genetic testing is beneficial not only to patients but also to family members, it is important that family members be informed about genetic testing when the patient has died. Family members should then be referred to a genetics department for pre-test counseling and testing.

Incorporating a tumor-first approach into our workflow might increase the testing rates even further [22]. Tumor material is almost always obtained, at least for diagnostic purposes, and tumor material can be evaluated for genetic alterations at the same time as establishing the diagnosis. However, it remains important to incorporate an informed consent procedure for all of these patients, as patients may not opt for genetic testing. In this study, approximately 11% of patients declined an appointment at the genetics department for pre-test counseling after referral. This is comparable with the data in the studies of Bednar et al. [11] and McGee et al. [23]. For daily practice, it is important to realize that between 5% and 11% of patients with EOC decline germline genetic testing. Therefore, we plea to implement a pre-test counseling procedure when considering tumor and germline genetic testing.

For a new care pathway to be sustainable, it is important to consider the impact on healthcare costs as well. We showed a reduction in genetics-related healthcare costs per patient of 31% in a DRG system. George et al. reported that their mainstream pathway led to an approximate 13-fold reduction in resource requirement, resulting in a cost reduction of approximately £2.6 M per year [8]. However, these costs are based on the estimated number of genetics appointments and associated costs, instead of the actual number of genetics appointments. For this estimation, they only considered patients with a pathogenic variant who would need an additional appointment at the genetics department after mainstream genetic testing. They did not take into account patients that might need additional counseling at the genetics department because of a personal or family history of cancer.

In both our study and the study performed by George et al. costs were based on the costs of counseling at the genetics departments. However, implementing a mainstream genetic testing pathway causes a shift in range of duties between non-genetic and genetic HCPs. Performing pre-test counseling and requesting the genetic test themselves increases the workload of non-genetic HCPs. So far, the costs for pre-test counseling have only been incorporated into the DBCs for genetic care performed by genetic counselors. The DBCs used by non-genetic HCPs for the care they provide do not include their additional time investment to perform pre-test counseling, which is around 10 min for the majority of non-genetic HCPs based on our previous research [15]. Non-genetic HCPs cannot use the DBCs for genetic care because these are based on the time investment and salary of genetic HCPs. It is important in the future that DBCs be adjusted to account for the time and resources that non-genetic HCPs spend on pre-test counseling and requesting genetic testing. Incorporating this additional time investment into these DBCs would increase the billable rates for the care provided by these non-genetic HCPs, and therefore also cause a shift in costs between the DBCs used by the genetics and gynecology department. That said, previous research has shown that the increase in workload is limited and not comparable to the pre-test counseling offered at a genetics department [9]. Therefore, we expect the reduction in healthcare costs to remain significant even if the slight increase in workload is incorporated into the billable care for EOC patients. The overall impact on healthcare costs also depends on the effects, e.g., the cancers that could have been prevented in patients and family members due to the timely identification of a pathogenic variant in a cancer predisposition gene. Previous studies have shown that it is cost-effective to offer genetic testing to all patients with EOC [24,25].

A major strength of this study is that all data are based on the actual number of newly diagnosed patients with EOC provided by the comprehensive cancer registration, and that we were able to review the medical files of all these patients.

This study also has limitations. We evaluated two different time periods to assess the impact of our mainstream genetic testing pathway on testing rates. With the increasing utility of PARP inhibitors, the rise in our testing rates may be biased. In addition, the percentage of patients that was offered a genetic test and declined was based on the information from the patient records. We do not know if non-genetic HCPs always documented in their patient files when a patient declined referral to a genetics department or did not opt for a germline genetic test after pre-test counseling. Therefore, the number of patients that was offered a genetic test and also the number of patients that declined referral might be an underestimation. However, given the high mortality in our study group, we consider it more plausible that an appropriate time to discuss a genetic test could not be found and that indeed no genetic test was offered to these patients. More details about the diagnoses might help support this assumption. Therefore, it is a limitation that we did not include more information about the diagnoses, e.g., histology or stage. Another limitation of our study is that the healthcare costs were based on a healthcare payer perspective, and therefore do not reflect the actual costs.

In conclusion, mainstream genetic testing increases testing rates amongst newly diagnosed patients with EOC, and significantly reduces genetics-related healthcare costs using a healthcare payer perspective. This study shows that mainstream genetic testing may be sustainable for the routine care of patients with EOC.

CRediT authorship contribution statement

K. Bokkers: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization, Project administration. **G.W.J. Frederix:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **M.E. Velthuizen:** Formal analysis, Investigation, Data curation, Writing – review & editing. **M. van der Aa:** Resources, Writing – review & editing. **C.G. Gerestein:** Resources, Writing – review & editing. **E.B.L. van Dorst:** Resources, Writing – review & editing. **J.G. Lange:** Resources, Writing – review & editing. **J.A. Louwers:** Resources, Writing – review & editing. **W. Koole:** Writing – review & editing. **R.P. Zweemer:** Conceptualization, Methodology, Writing – review & editing, Supervision. **M.G.E.M. Ausems:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

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Declaration of Competing Interest

AstraZeneca sponsored the training module that was developed as part of this project, and was not involved in the development of its content.

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