BRCA testing in women with high-grade serous ovarian cancer: gynecologic oncologist-initiated testing compared with genetics referral

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HIGHLIGHTS

- Uptake of genetic testing increased from 50.9% to 86.2% with introduction of the gynecologic oncologist-initiated genetic testing protocol.
- A reduction of 128 days to obtain mutation status is observed between gynecologic oncologist-initiated versus traditional genetic testing.
- This may allow timely access to maintenance Parp-inhibitors and family counseling.

ABSTRACT

Objective Up to 15% of patients with high-grade serous ovarian, tubal, or peritoneal carcinoma harbor a mutation in *BRCA* genes. Early notion of mutation status may facilitate counseling, predict prognosis, and increase access to Parp-inhibitors. The aim of this study was to examine the rate of germline genetic testing in a retrospective cohort of women with high-grade serous ovarian, tubal, or peritoneal carcinoma to determine if a new pilot project of gynecologic oncologist-initiated genetic testing improved the rate of testing, after 1 year of implementation.

Methods Gynecologic oncology-initiated genetic testing was implemented at a single university hospital center with input and collaboration from gynecological oncologists, nurses, and genetic counselors. All patients diagnosed with high-grade serous ovarian, tubal, or peritoneal carcinoma after August 2017 were offered gynecologic oncologist-initiated genetic testing for a panel of 13 hereditary breast and ovarian cancer susceptibility genes. Data from this group was then compared with a historic cohort of patients who received traditional genetic counseling between January 2014 and August 2017 (control group). Patients that had genetic testing through a clinical trial were excluded. The primary outcome was the uptake of genetic testing in both groups. Secondary outcomes included difference in time from diagnosis to genetic result between both cohorts. Data was analyzed using SPSS 25.0 and medians (ranges) were reported.

Results A total of 152 women with high-grade serous ovarian, tubal, or peritoneal carcinoma were included in this study. Between January 2014 to July 2017 there were 108 patients with high-grade serous ovarian, tubal, or peritoneal carcinoma, among which 50.9% (n=54) underwent genetic testing following referral to genetics. The prevalence of *BRCA* pathogenic variants was 25.9% (14/54): 9.2% (5/54) in *BRCA1* and 16.7% (9/54) in *BRCA2*. The median time from diagnosis to genetics referral was 53 days (range; 3–751), and median time from diagnosis to test result disclosure was 186 days (range;

15–938). After 1 year of implementation of the gynecologic oncologist-initiated genetic testing model, among 44 women diagnosed with high-grade serous ovarian, tubal, or peritoneal carcinoma, 86.2% underwent genetic testing. The median time from diagnosis to result disclosure decreased to 58 days, representing a reduction of 128 days, or 4.27 months ($P<0.001$). Reasons for non-testing included refusal, death, and follow-up at another hospital. The prevalence of germline *BRCA1/2* pathogenic variants was 21% (8/38).

Conclusion Gynecologic oncologist-initiated genetic testing at the time of high-grade serous ovarian, tubal, or peritoneal carcinoma diagnosis leads to increased uptake and decreased delays in testing compared with referral for traditional genetic counseling.

INTRODUCTION

High-grade serous carcinoma of the ovary, fallopian tube, or peritoneum is the leading cause of gynecologic cancer-related deaths in women.¹ Approximately 15% of unselected cases are caused by germline mutations in the *BRCA1* and *BRCA2* genes.² Germline mutations in more recently identified ovarian cancer predisposition genes such as *RAD51C*, *RAD51D*, and *BRIP1* are also seen in about 3% of women with ovarian cancer undergoing multi-gene panel testing.³ Identifying patients with germline *BRCA* mutations has implications for the use of novel therapeutics such as poly(ADP-ribose) polymerase inhibitor (PARPi).⁴ It also has implications for surveillance and risk reduction of other cancers for the patient and her family.^{4,5}

Germline *BRCA* testing is available throughout Canada. However, uptake is variable and remains low for high-grade serous ovarian, tubal, or peritoneal carcinoma, varying from 20% to 32% between 1997 to 2015.⁶ Reasons for low uptake include

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administrative errors, physician lack of awareness, or non-belief in the utility of genetic testing in high-grade serous ovarian, tubal, or peritoneal carcinoma and patient unawareness or refusal.⁶ In Canada, there is no federally governed or funded system for genetic testing. Rather, it is province-specific. In Quebec, the test was previously only obtainable at the request of a geneticist after genetic counseling and consent by the patient. In this process, there were risks of patients not being tested due to lack of physician referral, administrative delays, or progression of disease.

A position statement released by the Society of Gynecologic Oncology of Canada in 2017 titled “No woman left behind” set as an objective that all women with high-grade serous ovarian, tubal, or peritoneal carcinoma should undergo *BRCA* testing. In addition, the *BRCA* Testing to Treatment Consortium was initiated to lay out a framework and strategy to increase genetic testing in breast and ovarian cancers in Canada.⁷ Given recent approvals of PARPi as maintenance therapy for high-grade serous ovarian, tubal, or peritoneal carcinoma, the demand for genetic testing has increased, and there is greater urgency in obtaining genetic test results for the purposes of treatment. For these reasons, the traditional referral system for genetic testing is no longer sustainable with current resources. A proposed fast-tracked alternative care model has been successfully implemented in other centers across Canada, the United Kingdom, and other European countries.⁸ Other strategies such as educational videos, information kits, opt-out programs, and direct pathology-mediated referrals have been proposed as alternatives to referral-based ascertainment and traditional pre-test genetic counseling.⁷

Our objective was to determine the feasibility of a gynecologic oncologist-initiated genetic testing model at a single, high-volume academic center. We compared the rate of genetic testing for high-grade serous ovarian, tubal, or peritoneal carcinoma patients via the traditional genetics referral-based program from April 2014 to July 2017, to that of the gynecologic oncologist-initiated genetic testing model, after 1 year of implementation (August 2017 to August 2018). Secondary outcomes included wait times in obtaining results. The present study reports on the results of the first year of a gynecologic oncologist-initiated genetic testing pilot project.

METHODS

After institutional review board approval, we performed a retrospective case-series study of all patients diagnosed with high-grade serous ovarian, tubal, or peritoneal carcinoma and treated at the McGill University Health Centre, Montreal, Quebec, between January 2014 and August 2018. Exclusion criteria included: any histology other than high-grade serous ovarian, tubal or peritoneal carcinoma, ovarian metastasis from another primary, and genetic testing in the context of a clinical trial.

In the genetic referral cohort from January 2014 to July 2017, patients with high-grade serous ovarian, tubal, or peritoneal carcinoma were initially referred to medical genetics at the physician's discretion and based on risk factors including age, family history, or prior history of breast or ovarian cancer. Institutional guidelines for genetics referral of all women with high-grade serous ovarian, tubal, or peritoneal carcinoma were only implemented at our hospital in August 2015. Different panels of gene tests were

ordered over this period due to the rapidly changing testing environment at the time: the only constant being *BRCA1* and *BRCA2*. Therefore, the primary focus of this study was on *BRCA1/2* germline mutation rates as these are the only two genes approved for PARPi for ovarian cancer. During this time period, some patients obtained genetic testing following enrollment in a clinical trial and were excluded in the present study.

As of August 2017, genetic testing was offered to all patients with newly diagnosed high-grade serous ovarian, tubal, or peritoneal carcinoma under the gynecologic oncologist-initiated genetic testing initiative. The timeframe for the genetics referral cohort was estimated based on a similar number of high-grade serous ovarian, tubal, or peritoneal carcinoma cases per year as compared with the gynecologic oncologist-initiated genetic testing cohort (25–40 cases). Consecutive patients diagnosed and treated with high-grade serous ovarian, tubal, or peritoneal carcinoma at our institution were included in this cohort. A core team comprised of a gynecologic oncologist, genetic counselor, and nurse worked together to develop a pathway for gynecologic oncologist-initiated genetic testing. An algorithm was developed to outline the pathway, which included a checklist to ensure consistency of information provided to patients at the time of consent. A patient education pamphlet explaining the rationale for genetic testing, an overview of the testing process, and potential results was developed and is provided to patients at the time of consent and testing. Result disclosure was done by the genetics team, by telephone for negative results and in person for positive results for a pathogenic or likely pathogenic variant and for variants of uncertain significance, if deemed necessary.

The gynecologic oncologist-initiated genetic testing protocol consisted of next generation sequencing of a customized panel of 13°C susceptibility genes (*BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, *TP53*, *BRIP1*, *RAD51C*, *RAD51D*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*). Whole blood was sent to a commercial laboratory (Invitae, San Francisco, California). Results were reported back via a shared genetic testing portal accessible to both the medical genetics service and the gynecologic oncology team. Test results were also scanned directly into the patient's electronic health record. Genetic counselors were responsible for disclosing results to patients and organizing an in-person counseling visit, when indicated.

For the genetics referral cohort, data collected included age at diagnosis, date of surgery, whether genetic testing was performed (yes/no), date of referral to genetics, date of initial genetics appointment, date of testing, date of reported results, and results of genetic testing. Reasons for patients not being tested were noted, if known. Using this data, we calculated the timeframe to genetic testing from date of surgery. We report crude numbers and percentages for the proportion of women with high-grade serous ovarian, tubal, or peritoneal carcinoma undergoing genetic testing in the genetics referral cohort as well as the number of germline mutations identified in this group. This was then compared with the outcomes for women tested prospectively via the gynecologic oncologist-initiated genetic testing model during the 1-year pilot project.

Data was analyzed using SPSS 25.0. We report medians for a non-gaussian distribution.

Table 1 Mutation prevalence and delays in obtaining results between the genetics referral cohort and the gynecologic oncologist-initiated testing cohort

	Genetics referral cohort (January 2014–July 2017)	Gynecologic oncologist- initiated genetic testing (August 2017–August 2018)	Significance
Patients with HGSC	108	44	
Patients undergoing genetic testing, n (%)	54 (50%)	38 (86.3%)	
Prevalence of germline <i>BRCA</i> mutations, n (%)	14 (25.9%)	8 (21.1%)	
<i>BRCA1</i>	5 (9.2%)	5 (13.1%)	
<i>BRCA2</i>	9 (16.7%)	3 (7.8%)	
Median time from diagnosis to genetics consult	53 days (range 3–751 days)		
Median time from diagnosis to genetic testing	154 days (range 4–848 days)	40 days (range 8–175 days)	P<0.01
Median delay between testing and result	28.5 days (range 7–271 days)	8 days (range 8–48 days)	P=0.002
Median time from diagnosis to result		58 days (range 19–175 days)	P<0.01

186 days (range 15–938 days)

P-values obtained with the Mann–Whitney *U* test for medians

*HGSC :high-grade serous ovarian, tubal, or peritoneal carcinoma, BRCA: BReast CAncer gene

RESULTS

From January 2014 to July 2017, 108 women were diagnosed and treated for high-grade serous ovarian, tubal, or peritoneal carcinoma at our institution. Among these, 54 women (50%) underwent germline genetic testing via referral for traditional genetic counseling. Those tested in the context of a clinical trial were excluded. The prevalence of germline *BRCA* mutations in this group was 25.9% (14/54): 9.2% (5/54) in *BRCA1* and 16.7% (9/54) in *BRCA2* (table 1). The median time from initial diagnosis (either diagnostic biopsy or primary debulking surgery) to genetics referral was 53 days (range; 3–751) and the time from diagnosis to genetic testing was 154 days (range; 4–848) (table 1). The median delay from testing to disclosure of genetic test results was 28.5 days (range; 7–271). The median time from initial diagnosis to results disclosure was therefore 186 days (range; 15–938).

During the first year of implementation of the gynecologic oncologist-initiated genetic testing model (August 2017 to August 2018), there were 44 newly diagnosed cases of high-grade serous ovarian, tubal, or peritoneal carcinoma at our center. Among these, 86.2% (38/44) underwent genetic testing through this protocol. Reasons for non-testing included refusal (n=1), death shortly following diagnosis (n=2), and care transferred to another hospital prior to testing (n=1), and two other. The prevalence of *BRCA1* or *BRCA2* mutations was 21.1% (8/38): 13.1% (5/38) in *BRCA1*, 7.8% (3/38) in *BRCA2*. The median time from diagnosis (either biopsy date or primary surgery) to genetic testing was 40 days (range; 8–175, P<0.01) and median time from obtaining a result from the date of initial surgery was 58 days (range; 19–175, P=0.02). The time between testing to result was a median of 16 days (range; 8–48). This implies a reduction of 128 days from time of diagnosis to result disclosure after implementation of the gynecologic oncologist-initiated genetic testing protocol (P<0.01).

DISCUSSION

Both the Gynecologic Oncology Society of Canada and the National Comprehensive Cancer Network now recommend genetic counseling and germline *BRCA1/2* testing for all women with high-grade serous ovarian, tubal, or peritoneal carcinoma.⁹ Prior to this recommendation, only 20% of women diagnosed with high-grade serous ovarian, tubal, or peritoneal carcinoma in Canada had undergone genetic testing between 1997 and 2011.^{6,10} Understandably, the recommendation of universal *BRCA1/2* testing for all women with high-grade serous ovarian, tubal, or peritoneal carcinoma significantly increased the demand for *BRCA* testing and the urgency in obtaining results for the purposes of treatment, which became unsustainable with the currently available medical genetics resources.⁷ With multidisciplinary collaboration between Medical Genetics and Gynecologic Oncology, we developed a model for gynecologic oncologist-initiated genetic testing to improve accessibility, streamline care, and re-orient already scarce genetic counseling resources to the test disclosure process. After a 1-year pilot project, our results suggest that gynecologic oncologist-initiated genetic testing is feasible, improves testing rates, expedites the genetic testing process, and significantly reduces time to obtaining a result as compared with the traditional genetics referral-based model.

The introduction of PARPi was the key motivator in the rapid development of a gynecologic oncologist-initiated testing model in order to facilitate an increased number of women being tested and eliminate certain barriers to genetic testing compared with the traditional cohort. In the first year of implementation, gynecologic oncologist-initiated genetic testing led to an 86.2% testing rate and a reduction of 128 days from time of diagnosis to disclosure of genetic test results. Reasons for non-testing in our model included death, refusal, and follow-up at another center. Conversely, reasons

Original research

typically cited for low genetic testing rates among patients referred for traditional genetic counseling may be more procedural in nature and include referral processing issues, physician lack of knowledge or belief in new guidelines, and patient unawareness or refusal.⁶ Within the gynecologic oncologist-initiated genetic testing protocol, the rapid identification of high-grade serous ovarian, tubal, or peritoneal carcinoma patients harboring *BRCA* germline mutations can serve to guide treatment decisions and facilitate more timely genetic counseling and cascade testing of at-risk family members.

Gynecologic oncologist-initiated genetic testing has already been implemented in several parts of Europe, and other centers in Canada with similar favorable results to our center. In the United Kingdom, the “Mainstreaming Cancer Genetics programme” led to genetic testing rates of 100% for the 207 women with high-grade serous carcinoma included, of whom 16% had a *BRCA* pathogenic variant and were subsequently referred to genetics within 3 weeks.⁸ The pathway led to a four-fold reduction in time and 13-fold reduction in resources, thus proving to be efficient and cost-effective. Knowledge of *BRCA* status was useful in 132/207 women as some were entered in PARPI trials and others benefitted from enhanced breast cancer screening. In Canada, a survey by the *BRCA* Testing to Treatment Consortium found that the turn-around time to results with referral to genetics was 8 months, which is consistent with wait times previously experienced in our centre.⁷ The ENGAGE trial (Evaluating a Streamlined Onco-genetic *BRCA* Testing and Counseling Model Among Patients With Ovarian Cancer) in Europe and the US had similar findings with decreased turnaround times of 9.1 months after oncologist-initiated *BRCA* testing.¹¹ Collectively, these studies show that alternative models of care can be successfully employed to increase the uptake of genetic testing within certain patient populations without requiring traditional in-person pre-test counseling by a genetics professional.

We reported a higher prevalence of *BRCA* pathogenic variants (25.9%) between 2014 and 2017 than traditionally reported in the literature (10%–15%).³ Not surprisingly, gynecological oncologists were more likely to refer women with high-grade serous ovarian, tubal, or peritoneal carcinoma who may have had a higher index of suspicion for harboring a *BRCA1/BRCA2* mutation (younger age at diagnosis, family history of cancer, Ashkenazi Jewish descent) as compared with women outside these groups and thus having a higher pre-test probability. As a result, the genetics referral cohort may be enriched for higher risk patients which likely explains the higher prevalence of germline *BRCA1/BRCA2* mutations in this group. After 1 year of implementation of the gynecologic oncologist-initiated genetic testing protocol in an unselected group of women with high-grade serous ovarian, tubal, or peritoneal carcinoma, pathogenic variant rates (21.1%) were similar to that reported in the literature.

All patients found to have a pathogenic variant in any of the genes tested were subsequently seen by a genetic counselor. Bypassing traditional pre-test genetic counseling in patients that would ultimately test negative reduced the strain on the genetics department and allowed for more efficient use of the genetic counselors' time to see higher risk patients.⁸ The gynecologic oncologist-initiated genetic testing model also led to increased collaboration between the gynecologic oncology team and genetic counselors. Although not directly evaluated in our study, gynecologic oncologist-initiated genetic testing has been shown to increase patient satisfaction. In

one study, strategies that use alternative means to traditional pre-test genetic counseling and expedite results had increased patient (99%) and clinician (80%) satisfaction, with referral to genetics reserved for more complex cases and family members of affected individuals.¹¹ In the United Kingdom Mainstreaming Cancer Genetics Programme, most women were satisfied with this service and none asked to have a pre-testing genetic counseling appointment. In the DNA direct model, most patients chose this model as compared with referral to a genetic counselor (59%); among these, all (100%) proceeded to testing and most felt satisfied.¹⁰

It is increasingly accepted that all women with high-grade serous ovarian, tubal, or peritoneal carcinoma should be offered germline genetic testing for relevant ovarian cancer susceptibility genes, including *BRCA1* and *BRCA2*. The debate up to this point has been how to best achieve this goal. Models proposed include gynecologic oncologist-initiated genetic testing, the presence of a medical geneticist at tumor boards and clinics to flag relevant cases for referral, pathology-mediated referrals, and “peri-diagnostic tumor testing”.⁷ However, logistical issues inherent in somatic testing include the need for an altered informed consent process, increased test costs (as each person has two DNA samples analyzed), false positives, and technical issues related to formalin fixation, making a rapid access germline test more accessible and feasible, as described in our model.⁶

Limitations of the current study include its small sample size, analysis of trends at two different time points, as well as potential selection bias in the genetics referral cohort. Future directions include an evaluation of patient satisfaction and quality of life in a prospective cohort of patients undergoing testing via the gynecologic oncologist-initiated genetic testing protocol at our institution.

CONCLUSION

Gynecologic oncologist-initiated genetic testing leads to increased testing rates and decreased time from diagnosis to test result disclosure as compared with the traditional genetics referral-based model. This facilitates rapid treatment-based decisions, more timely identification of relatives who can benefit from increased surveillance and risk reduction opportunities, and more efficient use of genetic counselor resources.

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