Ovarian cancer is the seventh most common malignancy among New Zealand females and the fourth leading cause of female cancer death in this country. The association between ovarian cancer risk and germline pathogenic variants in BRCA1 and BRCA2 genes has been recognised for nearly two decades. Several population level studies have shown that germline BRCA pathogenic variants account for 11.6–16.6% of invasive ovarian carcinomas and are even more likely to be identified in women with high-grade serous tumour histology. The lifetime population risk of developing an epithelial ovarian, fallopian or primary peritoneal carcinoma is 1.3%; rising to 44% risk for women with a germline BRCA1 pathogenic variant and 17% for those with a BRCA2 pathogenic variant by age 80.

Determining BRCA pathogenic variant status is increasingly advantageous. Genetic testing of patients enables targeted cascade testing of breast and ovarian cancer-free family members. There is currently no effective screening for ovarian cancer, but procedures such as bilateral salpingo-oophorectomy (RRBSO) may reduce risk of HGSC and play a role in the reduction of risk of breast cancer. However it should be noted that recent studies, including a Cochrane...
systematic review, question the quality and reliability of this evidence due to analysis bias and study design.10,11 These recent studies suggested the role of RRBSCO in increasing overall survival and lower HGSC and breast cancer mortality for BRCA1 and BRCA2 pathogenic variant carriers is of very low certainty.10

In women with ovarian cancer, BRCA pathogenic variants are associated with improved progression-free and overall survival compared to pathogenic variant negative patients.12 In addition, a new therapy – poly-(ADP)-ribose polymerase (PARP) inhibitor – is becoming established internationally as an effective maintenance therapy in women with recurrent ovarian cancer.13,14 While PARP inhibitor targeted therapy is not funded in New Zealand, knowledge of a patient's BRCA status can influence clinical decision-making.

New Zealand testing guidelines recommend BRCA pathogenic variant testing for women under 70, or women over 70 with a positive family history of breast or ovarian cancer, or for whom there is limited information available from recorded genealogy.15 However, guidelines internationally are shifting towards universal referrals.16 Despite this shift, international studies are showing referral rates of only 23.1% to 51.7%.17,18

To date there has been no published data exploring New Zealand referral patterns. The multi-centre retrospective audit detailed here examines this country's rate of referrals to genetic services for counselling and subsequent testing for women with high-grade serous ovarian cancer diagnosed in 2015–2016. This baseline data will allow identification of areas where referral rates can be improved and also provide comparison data for future studies.

Methods

Study design
A multi-centre retrospective audit.

Data source
This study was approved by the New Zealand Northern Health and Disability Ethics Committee (Approval Number 17/NTA/181, 11 October 2017). Eligible cases were identified from the Christchurch, Dunedin, Wellington and Auckland Gynaecologic Oncology Multi-Disciplinary Tumour Board Meetings (MDM) 2015–2016 databases. Patients who met the eligibility criteria were cross-referenced against the records of each centre's local genetic services database. Clinical data including demographics of the patients (domicile DHB, ethnicity) and tumour information were collected from the MDM database. Further information including who made the referral, patient attendance for counselling, time between each stage of the referral and testing process, family and personal history of breast or ovarian cancer, and current status were collected from each participating hospital’s clinical database, electronic medical records and genetic service database. This data was gathered at each locality and de-identified prior to central collation.

Study cohort and eligibility criteria

Outcomes

The primary outcome for this audit was to establish the proportion of eligible women with high-grade serous cancer of the ovary, fallopian tube or peritoneum discussed at the gynaecological oncology MDMs who were referred for genetic counselling and BRCA pathogenic variant testing.

Secondary outcomes were to determine which specialties were making the referrals, the timeliness of the referrals, genetic reviews and reporting of results, the proportion of women who underwent BRCA pathogenic variant testing and of those, how many had a germline BRCA pathogenic variant. The study also began to explore reasons why some women were not referred to genetics services or a decision was made not to proceed with testing.

Statistical analysis
The results were largely descriptive, however a Chi-square analysis was used to investigate any differences in referral rate by year, by referral centre and between Māori vs non-Māori.

Results

Study cohort
This audit identified 245 women referred to the MDMs with high-grade serous cancer of the ovary, fallopian tube or peritoneum.
Of this group, 32 were excluded due to failure to meet inclusion criteria, ie, were over 70 without a family or personal history of ovarian or breast cancer. Seven women were excluded due to having previously undergone BRCA pathogenic variant testing prior to their diagnosis, and one woman was excluded due to missing date of birth. Thus, 205 women were eligible for referral to genetic counselling and consideration for BRCA testing during the two-year study period. Table 1 shows the demographics of the eligible population.

### Primary outcome

Over a two-year period, 143 of the 205 (70%) eligible patients were referred for genetic counselling. Sixty-two (30%) were not referred. The proportion referred vs not referred or not known did not change between 2015 and 2016 (69% vs 71%, Pearson $X^2=0.07$ $P=0.80$). There was also no difference in proportion of Māori vs non-Māori referred 13/20, (65%) compared to 130/185 (70%) (Pearson $X^2(1)=0.04$ $P=0.84$). There was no difference between the referral rates from each centre. These ranged from 68% to 75% (Pearson $X^2(3)=0.32$, $Pr=0.96$). However, when considering the patient’s domicile district health board, referral rates ranged from 27% to 100%. There was no clear explanation for this difference as there was no consistent trend in patient characteristics or number of cases from low referring DHBs that made them stand out from other DHBs.

Figure 1 demonstrates the results at each stage of the referral process.

<table>
<thead>
<tr>
<th>Table 1: Eligible population demographics in numbers and percentages.</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Number (n=205)</td>
</tr>
<tr>
<td>Mean age at diagnosis</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
</tr>
<tr>
<td>NZ European</td>
</tr>
<tr>
<td>NZ Māori</td>
</tr>
<tr>
<td>Pacific Island</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td><strong>Site of primary</strong></td>
</tr>
<tr>
<td>Ovary</td>
</tr>
<tr>
<td>Fallopian tube</td>
</tr>
<tr>
<td>Primary peritoneal</td>
</tr>
<tr>
<td>Mullerian (unknown) or 2 origins</td>
</tr>
<tr>
<td><strong>FIGO stage at diagnosis</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Personal history of breast or ovarian cancer</strong></td>
</tr>
<tr>
<td>14</td>
</tr>
<tr>
<td><strong>Family history of breast or ovarian cancer</strong></td>
</tr>
<tr>
<td>79</td>
</tr>
</tbody>
</table>
Figure 1: Flow chart of results of women eligible for referral for BRCA pathogenic variant testing.

**Total not referred (n=62)**
- >70 yo and no personal/family history (n=74)
- >70 yo and personal/family history (n=5)
- ≤ 70yo (n=33)

**Women referred to genetic services (n=143)**

**Currently waitlisted (n=1)**
- Did not attend (n=10)
  - No current family members at risk (n=1)
  - Unable to be contacted (n=1)
  - No review but DNA stored (n=2)
  - No further information (n=6)

**Attended a genetics review appointment (n=132)**
- More appropriate relative chosen (n=1)
- Declined testing (n=1)
- DNA stored but not tested (n=1)
- No recommendation (n=1)

**Recommended for BRCA testing (n=128)**
- Died before testing (n=2)
- No samples received (n=4)
- Results still pending (n=2)

**Results Available (n=120)**
Characteristics of those not referred

Referrals were not made for 62/205 (30%). Of this group, 24/62 (39%) were over 70 years and had no personal or family history of breast or ovarian cancer. Five (8%) were over 70 years but had a family history (n=3), personal history (breast cancer) (n=1), or limited information was available from recorded genealogy (n=1). There was no record of why they were not referred. The remaining 33/62 (53%) were 70 years or under. Of these, three declined and two were seen privately. There was no record why a referral was not made for the remaining 28.

Attendance and recommendation of review

Of the 143 women who were referred, one is currently on the waitlist for genetic review while 10 (7%) did not attend their appointments. Reasons for non-attendance included not having any family members at risk (n=1), unable to be contacted (n=1) or not wanting genetic review but choosing to store DNA for future use (n=2). There was no information available for the other six women.

The other 132/143 (92%) attended a genetics review appointment. A more appropriate relative was chosen to undergo BRCA testing for one woman. No recommendation was found for one woman. One woman declined testing and one woman chose to have her DNA stored but not tested. Overall 128/143 (90%) were recommended to receive BRCA testing.

Two women died before testing was performed and their DNA remains stored. Therefore, 126/143 (88%) underwent genetic testing. The laboratory did not receive DNA samples for four women. Two underwent testing but the results were still pending during the data collection phase of the study. Thus results were available for 120/126 (95%) who underwent testing.

Results of the test

Of the 128 women recommended for BRCA testing, 120 received results (94%). Of these, 19/120 (16%) tested positive for a germline BRCA pathogenic variant. The majority of pathogenic variants (13/19, 68%) were in the BRCA2 gene, compared to the BRCA1 gene (6/19, 32%). In addition, nine women (8%) were found to have a variant of unknown significance in either BRCA1 or BRCA2. However, the majority tested (92/120 [77%]) had a negative or uninformative result.

The majority of women diagnosed with a germline pathogenic variant in BRCA1 or BRCA2 were under 70 years of age (16/19, 84%). Thirteen had a positive family or personal breast or ovarian cancer history (13/19, 68%). The three with a germline pathogenic variant in BRCA1 or BRCA2 who were over 70 all had positive family histories. Table 2 demonstrates the demographics of women who have been tested and have results for BRCA pathogenic variant testing.

Who made referrals?

Medical oncologists made the majority of referrals (91/143 [64%]), followed by gynaecological oncologists (35/143 [24%]). General practitioners referred 3/143 (2%) while 14/143 (10%) came from other healthcare professionals such as genetic counsellors and oncology clinical nurse specialists.

Timeliness of referral and process of genetic testing

Where dates were reported, the average time between diagnosis and referral was 2.6 months (SD 3.4, range 0–22 months).

### Table 2: Demographic data based on results of test for BRCA pathogenic variant.

<table>
<thead>
<tr>
<th>Result</th>
<th>Number of women</th>
<th>Mean age (range)</th>
<th>Family history</th>
<th>Personal history</th>
<th>Family or personal history n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>6</td>
<td>51 (42–66)</td>
<td>3</td>
<td>1</td>
<td>4 (67%)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>13</td>
<td>63 (42–88)</td>
<td>9</td>
<td>2</td>
<td>9 (69%)</td>
</tr>
<tr>
<td>VUS 1 or 2</td>
<td>9</td>
<td>64 (49–75)</td>
<td>5</td>
<td>2</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Negative (uninformative)</td>
<td>92</td>
<td>62 (39–83)</td>
<td>52</td>
<td>7</td>
<td>57 (62%)</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>62 (39–88)</td>
<td>69</td>
<td>12</td>
<td>75 (63%)</td>
</tr>
</tbody>
</table>
took on average 3.4 months (SD 2.7, range 0.2–19.6 months) between referral and review by genetic services and on average 7.4 months (SD 3.7, range 1.3–21.5 months) between referral and results being available for the patient. There was an average of 3.8 months (SD 2.7, range 0.8–15.4 months) between review and results, assuming the date of review correlates with the date of blood sample collection.

Discussion

The BRCA status of women with ovarian cancer is becoming increasingly important in guiding oncological management and giving unaffected pathogenic variant carriers the opportunity to reduce their risk of developing breast or ovarian cancers in the future.

This study showed the nationwide referral rate for women discussed at the central gynaecological oncology MDMs with a high-grade serous cancer of the ovaries, fallopian tubes or peritoneum diagnosed in 2015–2016 was 70%. This rate is higher than that of an Australian study, which showed an overall referral rate of 40.6% over a two-year period, and 51.7% over a one-year period (during which time there was a genetics team member present at the weekly MDM). The New Zealand referral rate was also higher than the 23% reported in a Canadian study of women diagnosed with invasive serous ovarian cancer between 2002 and 2009. However, it is of concern that 30% of eligible women were not referred to this important health service. A recent US study showed disparities in the referral rate for genetic assessment for women with ovarian cancer with 61% of Caucasians, compared to 40% Asians, 38% Latinos and 33% of African-Americans referred. However, our study found no statistical difference in referral rates for indigenous Māori compared to non-Māori (65% vs 70%).

No statistical difference was observed between the centres in which MDMs were held. Referral rates ranged from 68% to 75%. This suggests that the barriers to referral are not centre-specific. There was a significant range of referral rates based on patients’ domicile DHB (27–100%). The reasons for this remain unclear at this time.

The majority of referrals (64%) were made by medical oncologists, followed by gynaecological oncologists (24%). With no protocol for referral in place, there is risk that some women may be referred multiple times while others are missed. International trials investigating different strategies suggest having a single specialty in charge of referral, or having a specialised online referral form. Highlighting the need for referral on histopathology reports may reduce the numbers of multiple or missed referrals.

Our results suggest that the referrals that are being made are appropriate, with 128 (90%) of those referred offered BRCA testing. It appears there is significant interest among patients for testing as 98% (126/128) of those recommended undertook the tests. This is a positive outcome when compared to an uptake of 75% reported by Cohen et al. While not a component of this study, previous research has shown that the main motivation for testing is the potential benefit for family members, while the main concern is the effect of testing on insurance policies. In New Zealand, insurers cannot make applicants take genetic tests, however they do require the results of these tests be disclosed when applying for life or health insurance. Pathogenic variants in genes, such as BRCA1 and BRCA2, may increase premiums or set exclusions on policies. As genetic tests become cheaper and more common, insurance may be further impacted.

Each step in the process of referral was approximately three months with time from diagnosis to referral (2.6 months), referral to review (3.4 months) and review to results (3.8 months). This is significantly shorter than the >3 years median time between patients’ initial gynaecological visit and the genetic counselling referral reported in Meyer et al. However, a Norwegian study showed a median time of 34 days between diagnosis and blood sampling (review) and overall time of 52 days (1.4 months) between diagnosis and receiving initial results.

The observed BRCA pathogenic variant rate in those with known results (16%) is similar to those seen in a range of overseas
Of note, 68% of patients had pathogenic variants in their germline BRCA2 gene compared to 32% with pathogenic variants in their BRCA1 gene. This is in contrast to current literature, which suggests BRCA1 pathogenic variants are more likely. Even when the seven women excluded from the current study because of prior testing are included, the New Zealand ratios still differ to those reported in the international studies with 14/25 (56%) BRCA2 pathogenic variants found compared to 11/25 (44%) of BRCA1.

Of those who tested positive, 32% (6/19), had no family history of breast or ovarian cancer. This finding is largely consistent with the Australian Ovarian Cancer study's finding of 44%. These results thus suggest testing should be performed regardless of family history. However, current resourcing means those over 70 in this situation are unlikely to be tested.

International developments include focusing on increasing the number of women tested. Innovations include having geneticists attend clinic days for counselling sessions and training oncologists to provide BRCA counselling and pathogenic variant testing to shorten the referral and review components of testing.

In a ‘Mainstreaming’ model, patients suitable for genetic testing are identified at MDM meetings, with testing ordered by the treating physician after abbreviated pre-testing counselling. A number of overseas centres have adopted this approach. Auckland City Hospital is reportedly planning to shift to this model in the near future.

However, while routine testing would increase the number of women with known pathogenic variants, it could create new issues with the potential for the system to be overwhelmed with lower-risk women, leading to delayed results for those at higher risk. While shifting pre-counselling to oncologists or having no pre-test counselling would relieve the burden on genetic services, there are concerns women might not be adequately prepared for the implications of the results for either themselves or their families. As the diagnostic phase is already a sensitive and emotional time, discussions regarding BRCA testing must be done with care and consideration.

**Recommendations**

International studies argue for improving rates of referral and testing. Further studies are required in order to determine how best to achieve this in New Zealand. This retrospective audit of MDM databases and medical records gives baseline data but does not give an understanding of how local practices have evolved. Further exploration of the reasons behind regional variations, including the wide range of referral rates noted in this study, would be a useful contribution to understanding current practice. Some of this research would need to be done with individual DHBs.

Once the factors impacting on current practice are understood, a further study is recommended to consider New Zealand-appropriate strategies to enhance referral and testing rates. This could include an evaluation of the success of strategies used overseas, an examination of the potential for building on existing national initiatives such as the New Zealand Familial Gastrointestinal Cancer Service, and a report on the impact of New Zealand’s health insurance provision and blend of private and public healthcare on any alternatives under consideration.

It is recommended that establishing national standards for referrals and testing should be examined as one potential strategy. Areas of practice identified in this study that could usefully be addressed through national standards include the establishment of a systematic approach to referrals and the setting of standards for timeframes, including those between diagnosis, testing and receiving results.

Finally, it is recommended that further study be conducted to determine the ways in which counselling services can be most responsive to changing needs of patients and physicians.

**Limitations**

A significant limitation of this study is the retrospective design and reliance on databases. This inherently leads to issues pertaining to data collection and entry such as ascertainment bias. However, having access to the MDM database, Genetic Services database and patient electronic...
medical records enabled a level of corroboration. Data collection was confined to the women presented at MDMs. While every woman with a gynaecological cancer should be presented to an MDM, it is possible some were not including those who may not have wanted treatment or follow up, or passed away in the interim. Data collection was limited by the availability of electronic medical records for a number of patients. These patients were typically from DHBs outside of the main centres where data could not be accessed off-site, or were women seen in private practice. Despite these limitations, the findings are useful for establishing baseline data and determining the need for future services.

Conclusion

This study has shown that New Zealand has a relatively high rate of referral for women with high-grade serous ovarian cancer to genetic services for germline BRCA testing. However, there remains a significant portion of the population who are missing out on referral. Through identification of barriers and implementation of strategies to improve systems, referral rates may increase further. Germline BRCA pathogenic variant testing is increasingly important to the identification of pathogenic variant carriers so that best practice care can be offered to patients with ovarian cancer and their families.

Competing interests:
Nil.

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