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BRCA1/2 germline testing in non-mucinous epithelial ovarian carcinoma: changing international practice and implications for service provision

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Ovarian carcinoma is the fourth most common cancer for women in Republic of Ireland, with an average of 361 cases per year.¹ The association with germline mutations in *BRCA1/2* genes in non-mucinous ovarian cancer risk is well established.² Determining the *BRCA* status of ovarian cancer patients has important prognostic and therapeutic implications for individual patients.³ The frequency of *BRCA1/2* germline mutations in non-mucinous ovarian carcinoma is estimated at 14–15%,² with previous studies finding a higher rate of 16.6% in serous ovarian carcinoma and 17.1% in high-grade serous carcinoma.³ Family history has been shown not to be sufficiently accurate to predict mutation status.^{2,3} In Ireland, as in most European countries, and the United States, the current recommendation is that patients with a family history of breast/ovarian cancer should be offered full mutation screening of the *BRCA1/2* genes as appropriate following the assessment by a clinical genetics service.⁴

The landscape of germline mutation status testing is rapidly evolving. *BRCA1/2* genes were merely discovered in the early 1990 s, however in 2016, the genes are known to have important prognostic and therapeutic implications, most notably with Inhibitors of poly (ADP-ribose) polymerase (PARP inhibitors), such as olaparib showing antitumour activity in cancer associated with the *BRCA1/2* mutation.⁵ The NCCN guidelines have been updated to recommend PARP inhibitors in patients with germline *BRCA1/2* mutations.⁶ In some health-care systems, for example, in Austria⁷ and in Ontario, Canada,⁸ *BRCA1/2* germline mutation testing is offered for all non-mucinous or serous epithelial carcinoma.

Hoberg-Vetti *et al.*,⁹ in *EJHG* September 2015, detailed the high acceptability of germline mutation status testing to patients, and

further recommended germline *BRCA1/2* testing in all patients with epithelial ovarian cancer owing to the high prevalence of pathogenic *BRCA1/2* variants in this group.

As a result, we anticipate germline mutation status testing in serous epithelial ovarian carcinoma will soon be recommended as routine internationally, and attempted to quantify the impact such a recommendation may bear on Irish oncology and genetic services.

A SINGLE CENTRE EXPERIENCE OF BRCA1/2 GERMLINE MUTATION TESTING IN OVARIAN CARCINOMA

In a large Irish tertiary referral centre, Cork University Hospital, over a 12-month period, January–December 2014, we identified patients with ovarian cancer, excluding cases of borderline, germ cell and sarcomatoid tumours. A total of 71 patients were identified, all females with a mean age of 58 years (range; 22–85 years). Seventy-six per cent of patients (54/71) had non-mucinous epithelial ovarian carcinoma and 24% (17/71) of patients had non-epithelial/mucinous ovarian carcinomas. Fourteen per cent (10/71) were investigated for germline *BRCA1/2* mutations and 50% of these cases are confirmed positive for germline *BRCA1/2* mutations.

Therefore, with the current recommendation of family history as the gateway to entry to the genetic testing pathway, we have a high positive test rate (50%); that is, family history tends to correctly identify those most likely to carry *BRCA1/2* germline mutations. However, were all non-mucinous epithelial tumours eligible for testing, 45 more patients in our centre would have been tested, and with a 14% positive test rate, this may have identified a further six to seven patients with germline mutations of the *BRCA1/2* genes.

NATIONAL AND INTERNATIONAL IMPLICATIONS

If these data were extrapolated to apply to all cases in Ireland, of 361 cases (the yearly average), this may result in a further 274 cases eligible for testing per year, with ~38 more patients identified with *BRCA1/2* mutations per year in Ireland.

In Ireland, as would be the case in many European countries, this has great implications for genetic service provision. Not only will increased resources for laboratory testing be required, but greater resources will be required to ensure training of expertise in genetics and genetic counselling, especially with regard to interpretation of variance of uncertain significance.

Alternative models for genetic counselling are rapidly being developed, such as telephone counselling,¹⁰ and we recommend that patients with ovarian carcinoma are included in newer pathways to allow for easier access to genetic information and psychological support.

In summary, we anticipate a surge in demand for genetics services, including genetic counselling, in the coming years and advise that health-care systems address this anticipated demand in resource planning.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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