BJOG: 2017-OG-18871: Germline & somatic genetic testing in ovarian cancer patients

Dhivya Chandrasekaran, [1,2] *Ranjit Manchanda[1,2,3]

[1]Barts Cancer Institute, Charterhouse Square, QMUL, London, UK, [2]Department of Gynaecological Oncology, St Bartholomew's Hospital, London, UK, [3]Gynaecological Cancer Research Centre, Women's Cancer, University College London, UK

***Corresponding Author**

Dr Ranjit Manchanda

Consultant Gynaecological Oncologist, Clinical Senior Lecturer

Barts Cancer Institute, Centre for Experimental Cancer Medicine

Charterhouse Square

London EC1M 6BQ

Email- r.manchanda@qmul.ac.uk

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Genetic testing for germline-*BRCA1/BRCA2* mutations in epithelial ovarian cancer (EOC) was commissioned by NHS-England in 2015 following the drop in *BRCA*-testing threshold to 10% carrier probability. EOC *BRCA*-carriers can benefit from targeted therapy such as poly-ADP-ribose-polymerase inhibitors (PARP-i) which improve survival in recurrent disease. Additionally, downstream predictive/cascade-testing enables unaffected at-risk mutation carriers to access opportunities of screening and chemoprevention (selective-estrogen-receptor-modulators) for breast cancer (BC), or surgical prevention (risk-reducing mastectomy and/or risk-reducing salpingo-oophorectomy) to reduce their BC and/or ovarian cancer (OC) risks. Unaffected women can also benefit from lifestyle and reproductive advice incorporating breast-feeding, contraception and informed reproductive decision-making, including preimplantation genetic-diagnosis. In this BJOG issue, Rust et al report on the Scottish *BRCA*-testing experience in unselected EOC *(Rust BJOG; 2018)*. Their findings are reassuring, in line with the established literature and reconfirm the importance of offering genetic-testing to all women (irrespective of age) with non-mucinous high-grade EOC. Although they tested women with low-grade disease too, *BRCA*-mutations are not associated with low-grade EOC and these women can be excluded. The 13% mutation rate in their prevalent sub-group highlights the importance of testing all women under follow-up too. Unselected *BRCA*-testing in high-grade EOC is cost-effective *(Eccleston ValueHealth.2017;20(4):567-576)* and identifies 50% additional carriers compared to earlier family-history/clinical-criteria based testing *(George, SciRep.2016;6:29506, Rust BJOG;2018)*. This offers a precision-medicine approach to reduce the burden of *BRCA*-associated cancers in the population. A number of delivery models founded on local solutions/contexts have been used to successfully implement this strategy with high uptake and patient acceptability: traditional Clinical-Genetics model (e.g. West-Scotland, Guys-Hospital), Mainstreaming (Medical-oncology driven: e.g. Royal-Marsden, East-Scotland), Genetics Co-ordinated (e.g. Cambridge/East-of-England) and Cancer-MDT coordinated (Surgical/Medical/Clinical-oncology driven: e.g. Barts-Health).

Newer intermediate-risk OC genes (*RAD51C/RAD51D/BRIP1*) are associated with OC-risks of 5.8%-11%. RRSO is cost-effective and now recommended for women at >5% OC-risk thus providing clinical utility for testing *RAD51C/RAD51D/BRIP1* mutations too *(Manchanda, J Med Genet:2016;53(9):591-9)*. Additionally these mutations affect the homologous recombination repair pathway leading to a functional "BRCA-ness" tumour and are likely to respond to PARP-i *(Mirza NEng JMed 2016;375:2154-64)*. Although the authors undertook *RAD51C/RAD51D* testing, this was in part restricted to women with strong family-history, which may be suboptimal at identifying carriers. Somatic *BRCA*-mutations

occur in around 7% of EOC. These women also benefit from PARP-i in terms of improved survival following recurrence. The introduction of Olaparib/Rucaparib into clinical practice and availability of other PARP-i trials, suggests clinical utility in offering somatic *BRCA*-testing too, although its cost-effectiveness needs confirmation. Robust concordance data for germline and somatic mutation testing are currently lacking and need establishing. We recommend germline *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* panel-testing and somatic-*BRCA1/BRCA2* testing for all high-grade EOC. The satisfaction/regret, quality-of-life and cost-effectiveness with this approach is being evaluated in the SIGNPOsT study (ISRCTN-16988857). Future therapeutic/technological developments including homologous recombination deficiency assays and stratified medicine approaches will warrant testing to be undertaken soon after diagnosis to deliver a personalised targeted precision-medicine strategy for OC therapy. Given the limited awareness and small proportion of at-risk carriers identified in the population to date, this will also provide much needed impetus for earlier identification of unaffected carriers and consequent OC/BC prevention.

Disclosure of Interests

RM declares research funding from The Eve Appeal, CRUK and Barts and the London Charity into population based risk stratification, targeted ovarian cancer prevention, and genetic testing in ovarian cancer outside this submitted work.

Funding

The commentary is not funded by any charity or grant.