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Running Title: Genetic testing in ovarian cancer patients
Genetic testing for germline-\textit{BRCA1/BRCA2} mutations in epithelial ovarian cancer (EOC) was commissioned by NHS-England in 2015 following the drop in \textit{BRCA}-testing threshold to 10\% carrier probability. EOC \textit{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 \textit{BRCA}-testing experience in unselected EOC \textit{(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, \textit{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 \textit{BRCA}-testing in high-grade EOC is cost-effective \textit{(Eccleston ValueHealth.2017;20(4):567-576)} and identifies 50\% additional carriers compared to earlier family-history/clinical-criteria based testing \textit{(George, SciRep.2016;6:29506, Rust BJOG;2018)}. This offers a precision-medicine approach to reduce the burden of \textit{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 \textit{(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 \textit{RAD51C/RAD51D/BRIP1} mutations too \textit{(Manchanda, J Med Genet:2016;53(9):591-9)}. Additionally these mutations affect the homologous recombination repair pathway leading to a functional “\textit{BRCA}-ness” tumour and are likely to respond to PARP-i \textit{(Mirza NEng JMed 2016;375:2154-64)}. Although the authors undertook \textit{RAD51C/RAD51D} testing, this was in part restricted to women with strong family-history, which may be suboptimal at identifying carriers. Somatic \textit{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 \textit{BRCA1/BRCA2/RAD51C/RAD51D/BRIP1} panel-testing and somatic-\textit{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

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