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INTRODUCTION

BRCA to the future: towards best testing practice in the era of personalised healthcare

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The year 2014 marked the twentieth anniversary of the discovery of the breast cancer susceptibility gene, *BRCA1*.[1,2] Since this discovery, our understanding of pathogenic *BRCA* variants and the associated increase in lifetime cancer risks has advanced significantly.[3,4] National guidelines have been developed to help clinicians identify patients with an increased risk of pathogenic *BRCA* mutations, and genetic counselling for risk assessment is now a routine practice.[5,6] The evolution of genetic counselling models has placed increasing importance on the use of multidisciplinary health-care teams, including medical geneticists, genetic counsellors, gynaecologists, surgeons, radiotherapists, medical oncologists and all other professionals involved in a patient's management. There has also been a surge of technological advances and new strategies allowing for the rapid turnaround of *BRCA1* and *BRCA2* mutation testing. In addition, evaluation of *BRCA* and other BRCA-like deleterious mutations as potentially actionable tumour targets are underway, such as the development of poly(ADP)-ribose polymerase (PARP) inhibitors in classes four or five *BRCA* mutation-positive cancers.[7–9] The present supplement contains review articles based on presentations from a scientific symposium focused on the evolving *BRCA* testing landscape (*BRCA* to the future: towards best testing practice in the era of personalised healthcare) held at the European Human Genetics Conference in Milan, June 2014.

In the first review, Professor Dominique Stoppa-Lyonnet discusses the biological effects and clinical implications of pathogenic *BRCA* mutations. BRCA1 and BRCA2 have key roles in the repair of DNA double-strand breaks via the mechanism of homologous recombination (HR) and ensure genome stability.[10–13] Germline deleterious mutations in *BRCA1* or *BRCA2* are associated with elevated risk of developing breast and/or ovarian cancer, sometimes with a genotype–phenotype correlation.[3,4,14] *BRCA* pathogenic mutation-positive ovarian or breast cancers are susceptible to inhibitors of additional DNA damage repair pathways, such as PARP inhibitors.[7–9] As the presence of actionable *BRCA* mutations in patients with breast and/or ovarian cancer becomes increasingly important in clinical management decisions, there is increasing support to expand the screening criteria for *BRCA* mutation testing, including testing for pathogenic mutations in other HR-deficiency genes.

In his review on *BRCA* testing, Dr Andrew Wallace covers the challenges of *BRCA* testing from the perspective of a diagnostic laboratory. Demand for *BRCA* testing is steadily increasing, placing a strain on diagnostics laboratories, particularly in those offering rapid genetic testing at the point of diagnosis. Increasingly, diagnostic laboratories are adopting next-generation sequencing (NGS) technology for *BRCA* testing, which offers the potential of fast, scalable, cost-efficient and comprehensive sequencing.[15–19] However, the choice and complexity surrounding NGS means that adopting this technology into the diagnostic laboratory requires many considerations, such as selection of an NGS platform, enrichment methods, sequencing chemistries, analytical procedures and techniques for somatic and germline mutation discovery. Interpreting *BRCA* test results can also be a complex process, involving the assessment of variants of unknown clinical significance, ensuring laboratory results are consistent and clearly reported, and understanding the role of passenger somatic mutations. *BRCA* testing of formalin-fixed paraffin-embedded tumour samples also presents a number of additional challenges to the diagnostics laboratory, including limited quantity and quality of extracted DNA, and artefactual sequence alterations.[20–23]

Genetic counselling is integral to the *BRCA* testing process. In the final review, Professor Nicoline Hoogerbrugge and Dr Marjolijn Jongmans examine best practices for genetic counselling and *BRCA* testing, exploring the challenges facing current practice and looking at adapted models of genetic counselling. Current practice in many countries requires face-to-face counselling with a qualified genetics counsellor both prior to, and following, *BRCA* testing.[5,6] As demand for genetic testing increases, new approaches for delivering genetic counselling may be necessary. It is possible that future *BRCA* testing and counselling models will incorporate different elements from these new approaches in order to optimise workflow in the era of personalised care. Examples include conserving germline *BRCA* testing and associated genetic counselling to those patients with a positive tumour pathogenic *BRCA* mutation result, enabling trained oncologists and medical specialists/staff, in addition to genetic counsellors, to manage pre-test genetic consultations with patients[24] and accounting for patient preferences regarding counselling and information such as telephone consultations with additional educational resources for selected patients.[25]

I greatly appreciate the collaboration of Professor Stoppa-Lyonnet, Dr Andrew Wallace, Professor Nicoline Hoogerbrugge and Dr Marjolijn Jongmans for an engaging symposium and subsequent review articles. We hope that this supplement provides you with a comprehensive update on the practical, prognostic and clinical implications of the evolving *BRCA* testing landscape.

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CONFLICT OF INTEREST

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