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BJOG ON THE CASE

BJOG PERSPECTIVES

Prenatal diagnosis and pre-implantation genetic diagnosis for cancer susceptibility conditions

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Multi-gene panel testing has led to identification of individuals with pathogenic variants in cancer susceptibility genes.[1]

For a minority of these syndromes, risks are well-established and discussion regarding options of pre-implantation genetic diagnosis (PGD) and prenatal diagnosis (PND) has been advocated by healthcare professionals, legal bodies and the public.

The UK Human Fertilisation and Embryology Authority granted the first PGD licence for a cancer susceptibility condition for familial adenomatous polyposis (FAP) in 2004, acknowledging that, although surveillance and surgical options are available, the impact on quality of life and morbidity associated with these interventions is significant.

This led to a public consultation in 2006 on PGD for later-onset cancer susceptibility conditions, hereditary breast and ovarian cancer associated with BRCA1 and BRCA2 pathogenic variants and Lynch syndrome caused by pathogenic mismatch repair gene variants. The decision was made to license PGD for these conditions, although this was not without controversy.

It was argued that PND and PGD should be reserved for 'high-penetrance' conditions associated with limited life expectancy and absence of treatment options. However, most cancer susceptibility conditions demonstrate reduced penetrance[2] and risk-reduction measures are often available, albeit associated with life-changing impacts on physical and emotional well-being.

Although management of hereditary cancer conditions has significantly improved, the psychological burden associated with them should not be underestimated. Couples wishing to pursue PND or PGD often have far-reaching personal and familial experiences motivating their decision and express a sense of obligation to prevent a repetition of such experiences in future generations.[3]

Recently, the situation has been complicated by identification of individuals with germline variants from tumour next generation sequencing panels, undertaken to guide cancer therapy.[4] Patients ascertained by this route may not have a familial high-risk picture for cancer, despite carrying a gene variant classically associated with high penetrance. It is unknown whether cancer risk for these individuals equates to that evidenced for patients ascertained due to a high-risk family history. Furthermore, variants considered to be 'moderate' penetrance may be found in high-risk families, leading to debate over the extent of their contribution to the familial cancer susceptibility.

Collectively, these issues raise the question of which conditions or gene variants justify discussion of reproductive diagnostic tests with couples in the setting of hereditary cancer.

Factors which differ between countries, for example, legal aspects of termination, PGD licensing requirements, resource and infrastructure to facilitate reproductive techniques, may also influence or constrain a clinician's decision to discuss PND or PGD with their patients.

International guidance in this area is lacking leading to disparity in access to PND and PGD for couples. The ethical debate and inequity is particularly pertinent for moderate-penetrance genes, those with differing risks according to gender and those associated with dominant and recessive conditions.

There is a rapidly growing need for clarity in this complex field. Patients, clinicians and the public need confidence that robust, equitable and ethical pathways are in place for the important minority of couples who wish to access PND or PGD in the context of hereditary cancer susceptibility.

Disclosure of interests

Professor Kilby was a chief investigator for the PAGE Study funded by the Wellcome Trust and Department of Health. He is presently the Fetal Medicine lead for the GLH of West Midlands, Oxfordshire and Wessex. He is a member of the Fetal Genomics Group of the British Society of Genetic Medicine and he represents the RCOG on the Joint Committee of Royal Colleges on Genetics and Genomics. He is a Vice-Chair and a member of the RCOG Genomics 'taskforce'. Completed disclosure of interests form available to view online as supporting information.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article. ■

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