The importance of genetic counselling in genome-wide sequencing

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Genome-wide sequencing (GWS) is the most sensitive test available for detecting pathogenic genetic variants. In line with guidelines in North America and Europe, best clinical practice requires GWS to be implemented as a holistic clinical service that includes both pre-test and post-test genetic counselling.

Genome-wide sequencing (GWS) of exomes or whole genomes can identify a specific inherited or de novo genetic cause in half of patients with serious but nonspecific conditions, such as intellectual disability or epileptic encephalopathy[1]. GWS is not a perfect genetic test, but it provides a substantial improvement in diagnostic sensitivity compared with cytogenetic analysis and chromosomal microarray analysis, the previous clinical standards for genome-wide testing for genetic causes of disease.

The greatest strength of diagnostic GWS — its ability to recognize single-nucleotide variants and small or large copy number variants anywhere in the genome, regardless of the particular genes or regions involved — also creates the biggest problems associated with using it as a clinical test. Each of us has 4–5 million nucleotides that differ from the human reference genome. Thus, interpretation of GWS data involves identifying one or two pathogenic variants from an enormous pool of mostly benign variants that are unlikely to be related to the patient's disease. This inherently difficult problem, which often takes us to (or beyond) the limit of our current knowledge of genome biology, distinguishes GWS from most other clinical tests, including targeted genetic tests.

Compared with traditional single gene or chromosomal genetic counselling, diagnostic GWS often raises complex 'genomic counselling' issues for clinicians who order the test and for patients and their families, resulting in the need for personalized support[2]. These issues include, among others, unclassified variants, variants of uncertain significance (VUS), secondary findings (which can result in the disclosure of multiple and unanticipated disorders) and challenges associated with a rare disease diagnosis. Furthermore, up to 5% of patients undergoing GWS will have more than one genetic diagnosis identified that contributes to their clinical phenotype.

Importantly, obtaining explicit consent for diagnostic GWS from a patient is not genetic counselling. Genetic counselling is a supportive, educational, unbiased and non-directive communication process. Pre-test genetic counselling for GWS should involve obtaining a detailed family history and explanation of the method of testing used, its risks and benefits, and its potential to deliver uncertain, undefined, difficult to interpret or partial results; the possibility of secondary findings; implications for other family members, including the potential need for testing relatives; and potential privacy and insurance implications of making a genetic diagnosis. In addition, the process should provide emotional support to patients and families facing a possible genetic diagnosis; guide them in making informed decisions that are consistent with their own values; help families to make effective use of the testing results; and reduce the likelihood of adverse outcomes when results are returned that differ from the families' expectations. Patients should understand that they have the option to decline GWS before providing informed consent.

Guidelines in the USA, Canada and Europe consider genetic counselling to be a necessary component of clinical GWS testing[3]. Patients undergoing genetic testing who receive pre-test and/or post-test genetic counselling show greater knowledge, a better understanding of the results, improved decision-making, decreased distress and greater satisfaction with the testing process than patients who do not receive counselling[4,5]. Genetic counselling is typically provided by genetic health-care professionals (that is, genetic counsellors or clinical geneticists), but it may also be provided by other clinicians with specialized training. As genomic testing has become more commonplace, more nongenetic health-care professionals are ordering genomic testing, often without genetic counselling. Reasons for this omission include lack of training or time, issues around reimbursement of the health-care provider and limited access to genetic counsellors. Most family physicians do not feel knowledgeable about available genetic testing, and nongenetic health-care providers may not follow recommended guidelines when it comes to genomic testing — including not taking a family history, failing to discuss the types of results that can be generated, ordering testing without offering genetic counselling and ordering inappropriate tests. In a large US population-based

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study of women newly diagnosed with breast cancer, only 40% of all high-risk women and 62% of high-risk women undergoing genetic testing received genetic counselling[6]. It is important for providers to identify and refer at-risk patients to genetic counsellors or specialist physicians when indicated. The integration of genetic counsellors into laboratories can improve selection of the most appropriate genomic test for each patient and create economic efficiencies.

Ultimately, lack of appropriate genetic counselling can result in patient harm. VUS are frequently reported by clinical laboratories, and the uncertainty associated with them may complicate medical management, cascade testing and prenatal diagnosis, and create psychosocial challenges for families. VUS are often difficult for clinicians to explain to patients. In one example widely reported in the US media, the misinterpretation and subsequent mishandling of a VUS in *MLH1* by members of a patient's health-care team (that did not include a genetic counsellor) resulted in her undergoing unnecessary surgical procedures (bilateral mastectomy and hysterectomy) and pursuing a US$1.8 million medical malpractice lawsuit against the health-care providers. This patient was not offered genetic counselling, which would have likely included breast cancer risk assessment based on family history alone.

Generally, a VUS should not be used in clinical decision-making, but clinical findings and family histories should also be taken into account; a physician may consider a VUS to be actionable because of the clinical circumstances in some patients. In addition, some VUS may subsequently be reclassified as disease-causing, either because the patient's disease evolves over time or the phenotypic spectrum associated with such variants is clarified in the medical literature. Similarly, variants initially classified as disease-causing may later be reclassified as being of uncertain significance or benign. These reclassifications may have an important impact on families and health-care providers. Variant reclassification can build trust between a genetic counsellor and patient by demonstrating that the case is being managed with ongoing care, but the uncertainty associated with a VUS can create psychosocial challenges. Families may recall and interpret these results in a variety of ways that can make medical decision-making challenging, particularly in disorders with reduced penetrance.

Secondary or incidental findings are much more likely to be identified with GWS than with single-gene or small panel tests. Policies for return of secondary findings to patients or families differ among jurisdictions[3] and also may differ for children and competent adults. Guidelines in the USA require deliberate investigation of 59 disease-associated genes for all patients undergoing GWS who do not 'opt out', while Canadian and European approaches avoid intentional analysis of disease-associated genes unless they may be related to the indication for testing. Determining a family's preferences for receiving secondary findings and informing them of classes of secondary findings that are always, or never, returned per laboratory or jurisdictional policy are important components of pre-test genetic counselling. Similarly, appropriate recommendations for management of secondary findings that are returned to patients are a key aspect of post-test counselling.

Clinical implementation of GWS is putting increased pressure on an already strained resource owing to the current shortage of genetic counsellors. Genetic counsellors typically hold a Master's degree and have specific expertise to help patients navigate the complexities of the genomic testing process. They are in demand in many specialty areas, including laboratory medicine, prenatal diagnosis, cancer and the neonatal intensive care unit (owing to rapid GWS). Maximizing the efficiency of genetic counsellors through their integration into novel clinical service models and innovative methods of delivery (such as online decision aids, videoconferencing and telehealth) is underway. However, the lack of professional recognition in many jurisdictions results in counsellors restricting their practice to tertiary health-care settings, which limits access to this service. This is particularly relevant to families in remote regions and to underserved and under-represented communities.

Genetic counselling for families considering GWS helps to prepare them for the unexpected. Most patients and physicians think of diagnoses as black or white; genetic counselling is valuable in preparing families when a diagnosis is grey. Genetic counselling is essential when using a test that may probe the limits of our clinical and scientific knowledge. Perhaps most importantly, offering GWS without pre-test and post-test genetic counselling wastes much of the test's diagnostic potential and risks losing the trust of patients, physicians and insurers.

1. Wright, C. F., FitzPatrick, D. R. & Firth, H. V. Paediatric genomics: diagnosing rare disease in children. *Nat. Rev. Genet.* **19**, 253–268 (2018).
2. Patch, P. & Middleton, A. Genetic counselling in the era of genomic medicine. *Br. Med. Bull.* **126**, 27–36 (2018).
3. Knoppers, B., Zawati, M. & Senecal, K. Return of genetic testing results in the era of whole-genome sequencing. *Nat. Rev. Genet.* **16**, 553–559 (2015).
4. Christie, J. et al. Cognitive and psychological impact of BRCA genetic counseling in before and after definitive surgery breast cancer patients. *Ann. Surg. Oncol.* **19**, 4003–4011 (2012).
5. Armstrong, J. et al. Utilization and outcomes of BRCA genetic testing and counseling in a national commercially insured population. *JAMA Oncol.* **1**, 1251–1260 (2015).
6. Kurian, A. W. et al. Genetic testing and counseling among patients with newly diagnosed breast cancer. *JAMA* **317**, 531–534 (2017).

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A.M.E. contributed to all aspects of the article. J.M.F. made substantial contributions to discussions of the content and reviewed and/or edited the manuscript before submission.

Competing interests
The authors declare no competing interests.