CGG/ERN GENTURIS/ICARE Monthly Journal Round-Up – May & June 2024

Bigger picture

30 years on since the identity of the *BRCA1* gene was revealed (and 29 years since *BRCA2*), William Foulkes reflects on how clinically important these cancer genetics discoveries were and celebrates the identification of *BRCA1* in a commentary piece in *Nature Reviews Genetics*. Foulkes considers the developments that soon followed identification of the two genes, including identification of founder pathogenic variants, the important link to ovarian cancer risk and the doors this has opened to risk management, subsequent identification of the *PALB2* gene, and development or specific therapies for *BRCA1/2*-related cancers. Foulkes also discusses the hot topic of polygenic risk scores (PRS), both in individuals with pathogenic variants in moderate risk breast cancer genes, as well as at the population level. Finally, Foulkes considers how our understanding on the penetrance of these genes may shift as testing is offered more widely and depending on the context in which the pathogenic variant is identified, and suggests where the future of genetic testing could be going.

In the clinic

Carrier testing for partners of MUTYH variant carriers: UK Cancer Genetics Group recommendations. McVeigh *et al.* (2024). *Journal of Medical Genetics*; doi: 10.1136/jmg-2024-109910.

- Genetic testing for individuals with a personal or family history of polyposis or early-onset colorectal cancer frequently identifies heterozygous carriers of *MUTYH* variants, which in isolation do not explain the phenotype. Heterozygous *MUTYH* variants are also being identified through commercial pan-cancer gene panels, as incidental findings through WGS, tumour testing or direct-to-consumer testing.
- The carrier frequency of common founder *MUTYH* variants in White Europeans is higher than the 1 in 70 frequency threshold for carrier testing in partners of known carriers, however, the frequency of *MUTYH* variants in non-European populations is not well established.
- *MUTYH* variants are much more likely to be identified incidentally than other, more highly penetrant recessive disorders and the phenotype is adult onset, which presents unique challenges to *MUTYH* carrier testing.
- The potential workload of cascade testing in relatives of heterozygous *MUTYH* carriers in the absence of proven cost-effectiveness needs due consideration.
- The UK Cancer Genetics Group (UKCGG) aimed to establish current practice in *MUTYH* partner carrier testing and cascade testing in order to standardise the approach across the UK and Ireland. They surveyed lead genetic counsellors, cancer genetic consultant leads and clinical scientists in each regional genetics service.
- The survey showed variability in approaches across regions (see paper for figures).
- It was agreed, in order to standardise practice across GLHs, that:
    - Carrier testing for *MUTYH* should be prioritised for partners of patients with MAP.

- Full gene sequencing should be undertaken.
- Testing should be offered irrespective of the ethnicity of the partner, given that the carrier frequency in populations outside of white Europeans is not well established.
- Full *MUTYH* gene testing may be offered directly to children of patients with MAP in the event that their other parent is not available for carrier testing.
- Carrier testing should not routinely be offered to partners of heterozygous *MUTYH* carriers in the absence of consanguinity or a personal or family history of polyposis or colorectal cancer, particularly if reproductive decision-making would not be influenced.

Joint ABS-UKCGG-CanGene-CanVar consensus regarding the use of CanRisk in clinical practice.
Tsoulaki *et al.* (2024). *British Journal of Cancer*; doi: 10.1038/s41416-024-02733-4.

- Workshop held between UKCGG, the Association of Breast Surgery (ABS) and the CanGene-CanVar programme to establish best practice guidelines for clinical application of CanRisk.
- A pre-workshop survey was sent out to gauge current use of CanRisk. The themes arising from the survey were used to create proposed statements for best practice across five topics:
  - Utilisation of BC risk assessment tools
  - Providing information to patients from CanRisk
  - Use of CanRisk for breast surveillance recommendations and appropriate timing
  - Use of CanRisk for genetic testing eligibility
  - CanRisk model inputs.
- Consensus was reached in the following areas:

  Assessment input
  - It is important to explain that the risk assessment could alter depending on accuracy and extent of the information input into the model and/or changes in understanding of how these factors influence risk.
  - Best practice for CanRisk model inputs – three generation family tree, affected and unaffected relatives, genetic test results (patient and family members) and, where available, any additional information.

  Genetic testing
  - It is appropriate to round up to the nearest whole number for determining genetic test eligibility (but not in the situation of breast surveillance recommendations).

  Breast surveillance
  - CanRisk is the preferred method to make breast surveillance recommendations for women unaffected with BC and relevant family history (where no known monogenic cause). This should be done close to the age at which screening would commence.
  - Personalised risk assessment is warranted for women unaffected with BC who have a LP/P variant in a moderate risk BC gene similar to unaffected women with relevant family history and no known monogenic cause
    - Although this statement was supported, some felt an assessment would not result in a change of practice so may not be the best use of clinical time.

  Bilateral RRM
  - Best practice to use CanRisk for 5/10 year and lifetime BC risks for affected and unaffected women considering RRM as part of broader consultation and shared decision making.

Contralateral BC risk

- CanRisk assessment is limited in this situation as it does not include assessment of treatment, prognosis of primary tumour and other competing risks, and data on CBC risk for BC predisposition genes other than BRCA1 and BRCA2 is limited. Therefore it should not be used in isolation.

Counselling and ethics

The experience of receiving a letter from a cancer genetics clinic about a risk for hereditary cancer. Öfverhold *et al.* (2024). *European Journal of Human Genetics*; DOI: https://doi.org/10.1038/s41431-024-01551-9

- Clinical practice in many parts of Europe, the United States and Australia has a family-mediated model for disclosure of genetic test results, meaning that healthcare professionals counsel patients on the importance of informing their relatives of genetic findings
- The complexities of this are increasing given the different routes through which genetic diagnoses are made
- Some meta-analyses show that about 70% of relatives are informed about hereditary cancer risk after a family-mediated model is used with a proband
- The attitudes of at-risk relatives are not well known
- In this study, 14 at-risk relatives who had received a letter from a cancer genetics clinics were interviewed. There results were analysed in two sections: “actions and reactions when receiving the letter” and “an important message to hold and to handle for oneself and others”
- Actions and reactions when receiving the letter:
  - All found the letters easy to understand, and they had complete contact information
  - Varying degrees of knowledge prior to receiving
  - Many patients reached out to the clinic that had sent the letter in a few days or weeks
  - Those who waited longer felt their delay was due to other priorities such as the birth of a child or caring for a relative
  - Many expressed a need for genetic counselling before telling their own relatives
- An important message to hold and to handle for oneself and others: Six subthemes were identified:
  - “It felt important, worrying or even frightening”: Participants who had not known a letter was coming felt confused, worried, and fearful, describing this as an “unsolicited message”. Those who had prior knowledge wanted to take action straight away.
  - “I want access and understanding when contacting healthcare”: Most commented on positive experiences with finding information about who to contact. They all felt their queries should be answered promptly and speaking to a genetic counsellor was mostly positive but sometimes concerning
  - “A personal notice from relatives is welcomed and the right thing to do”: Participants who received letters without prior knowledge expressed disappointment and anger. Those who had prior knowledge appreciated this, even if the contact was only brief. The general attitude was that it was caring, or even “correct” to personally notify relatives before sending a healthcare letter.

  - "Disclosure is a family matter": All participants talked about responsibility of disclosing to their relatives, and there was a general sense of duty.
  - "Healthcare should support the family but guard the right of the individual": All participants assumed that the proband in the family received support in sending out the letter. All participants thought that the healthcare professional should contact relatives directly if there were issues with disclosure.
  - "An unsolicited letter can safeguard autonomy but may do harm": Repeated theme that healthcare professionals should contact relatives directly if needer to protect autonomy. Participants believed they had a right know about their risk. However, some concerns were raised about breach of privacy and the possibility of doing harm if the letter was received during a difficult time.
- This study draws on real-life experience from participants who have very recently reached out to genetics services. However, there remains a lack of knowledge about those who do not choose to reach out for more information
- Direct disclosure of genetic information remains an ethical concern, but the authors argue that direct contact with relatives should be implemented into ethical frameworks for use in appropriate circumstances.

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