CGG/ERN GENTURIS/ICARE Monthly Journal Round-Up – February 2023

In the clinic

Germline predisposition to haematological malignancies: Best practice consensus guidelines from the UK Cancer Genetics Group (UKCGG), CanGene-CanVar and the NHS England Haematological Oncology Working Group. Speight *et al.* (2023). *British Journal of Haematology*; doi: 10.1111/bjh.18675.

- WGS and large somatic gene panels in haematological malignancies are identifying an increasing number of individuals with either potential or confirmed germline predisposition to haematological malignancy.
- Establishing pathways for appropriate germline confirmation with the possibility of cascade predictive testing in family members is a relatively new area of expanding clinical and laboratory work.
- The UKCGG, CanGene-CanVar and the NHS England Haematological Oncology Working Group held a 2-day workshop to establish consensus guidelines on clinical and laboratory pathways.
- The workshop focussed on the management of germline pathogenic variants in *DDX41*, *CEBPA*, *RUNX1*, *ANKRD26*, *ETV6* and *GATA2*.
    - The genes were chosen as the focus of the meeting based on the organising committee's experience in clinical practice and existence of research evidence.
- Extensive review of the literature and clinical characteristics, genetics and prevalence of established inherited predisposition to haematological malignancy syndromes generated a background document that was sent to delegates prior to the meeting.
- Delegates were also sent a scoping survey to assess current practice and ideas on best practice pathways. Response themes were used to create key questions to be addressed in the meeting.
    - 42% response rate (including responses from all GLHs in England, Scotland and Wales).
- Attendees (106 on day 1, 93 on day 2) came from a broad range of specialties across the UK, including patient support group representatives, clinical cancer geneticists, genetic counsellors, paediatric and adult haematologists and clinical scientists.
- A number of related polls were conducted, with proposed statements for best practice in different scenarios.
    - Consensus was reached when ≥80% respondents selected 'Agree/Strongly Agree' or 'Yes' in response to the statement posed.
    - Time was allocated for whole group discussion around each polling question for feedback, discussion and debate, which helped inform any consensus reached.
- **Somatic reporting**

  - Consensus reached that a statement on the report suggesting possible germline origin of a variant should be considered for any variant where a confirmed germline finding would have potential clinical significance, especially if the variant allele frequency is >30%.
- **Confirmatory/predictive germline testing process**
  - Consensus reached that best practice would be to undertake diagnostic germline confirmatory testing in the proband prior to offering cascade germline testing to relatives, although this may not be feasible in all situations.
- **Sample selection**
  - Fibroblast-derived DNA from a skin biopsy was shown to be the most common sample type used in both routine and time-sensitive situations.
  - Consensus reached that this is best practice/first option in list of possible sample types.
  - Practice does and will continue to depend on the clinical situation.
- **Patient information**
  - Consensus reached that it is appropriate to inform patients of the possibility of finding a germline genetic variant when arranging genetic testing of patients with a known haematological disorder.
  - One patient representative wrote: 'Us patients want to know what you might find. Whether or not we want to know what you *did* find is a separate issue, but if you are doing any test on a patient, you must tell them what it might show'.
- **Referral to clinical genetics**
  - Consensus reached that it is preferable that the Haematology team arrange confirmatory testing of a likely pathogenic/pathogenic variant of potential germline origin in time sensitive situations.
  - Strong consensus that a referral to Clinical Genetics for genetic counselling is appropriate for all identified carriers and relatives as part of offering predictive testing, regardless of age or whether the relative is a potential bone marrow transplant donor.
- **Age of predictive testing**
  - Best practice considered to be assessment on a case-by-case basis.
  - Regarding *DDX41*, delegates felt it would rarely be appropriate to consider predictive testing before adulthood.
- **Management of carriers**
  - Consensus reached that all identified carriers of germline variants who develop a blood phenotype be referred to Haematology for monitoring and follow-up.
  - A minority of centres are currently offering screening to heterozygous carriers of *CEBPA, ANKRD26, ETV6, GATA2, DDX41* and *RUNX1*.
  - No consensus reached on whether to offer screening to heterozygous carriers with no blood phenotype or what the type or frequency of screening should involve.

- Key recommendations:
  - There should be close liaison between somatic and germline teams for variant interpretation.
  - There is a need for MDT working to provide the best patient care.
  - Prospective data should be collected to inform future best practice.
- Gene-specific guidance is required for the management of carriers and more evidence regarding the utility of screening in this patient group is needed.
- Unique challenges arose related to donor selection for those patients requiring allogenic transplant when potential related donors carry/are at risk of inheriting a constitutional variant predisposing to haematological malignancy.

Management of patients with germline predisposition to haematological malignancies considered for allogeneic blood and marrow transplantation: Best practice consensus guidelines from the UK Clinical Genetics Group (UKCGG), CanGene-CanVar, NHS England Genomic Laboratory Hub (GLH) Haematological Malignancies Working Group and the British Society of Blood and Marrow Transplantation and cellular therapy (BSBMTCT). Clark *et al.* (2023). *British Journal of Haematology*; doi.org/10.1111/bjh.18682.

- Following on from the consensus meeting outlined in the above publication, a specific workshop was arranged to discuss the impact of germline predisposition to haematological malignancies on specific issues related to allogeneic BMT and reach consensus on management of these issues, particularly in relation to the testing and selection of related donors.
- The organising committee included representation from four national collaborative groups; the British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT), UKCGG, CanGene-CanVar research programme (CGCV) and the NHS England GLH Haematological Malignancies Working Group.
- Invitations to the workshop were sent to attendees of the previous consensus meeting, as well as additional key stakeholders and clinicians with specialist expertise in bone marrow transplantation.
  - No patient representatives participated in this meeting.
- The organising committee generated statements upon which to gather consensus based on their expertise.
  - Consensus agreement was set at a threshold of ≥80% of at least 40 respondents selecting ‘agree’/‘strongly agree’.
  - Statements were debated and rephrased in real time in order to reach consensus if possible.
  - Of 82 participants, 66 participated in the in-meeting polling.
- Recommendations:
  - Patients requiring BMT should be assessed for a potential heritable cause for their phenotype
  - **Timescales** - For patients being considered for BMT, there is an urgency to identify genetic variation. Where germline status in a patient has already been confirmed, testing of potential related donors for the variant may occur simultaneously with tissue typing. In urgent situations, germline testing of

potential donors can proceed in parallel with confirmatory testing in the patient.

- Where there are concerns about possible or confirmed heritable risk, search and testing of unrelated volunteer donor (VUD) should happen in parallel with evaluation of related donors to allow donor options to be assessed without delay
- **Donor selection** - While every effort should normally be made to avoid using a carrier family member as a donor there may be situations where this is unavoidable, or uncertainty remains, for instance if a potential familial donor declines site-specific testing for the familial variant, or if the variant identified in the proband is of uncertain significance.
- Where all related matched donors are either carriers or decline testing, careful assessment of risks and benefits of an unrelated donor versus a carrier family member/untested family member requires discussion at a MDT meeting with access to expert opinion and consideration on a gene-specific basis.
- **Genetic counselling -** Dedicated, skilled genetic counselling in this area remains the 'gold standard' and this should become an essential component of future integrated haematological oncology service design.
- **Considering VUS** - When a Class 3 VUS is identified then further assessment of clinical status and family history is warranted to inform MDT discussions
- If MDT decision is made to test for VUS in relatives to inform transplant options then relatives should be offered genetic counselling to ensure they understand the uncertainty and outcomes of testing.
- **Awareness and resources** - Need for education and guidance for HCPs working in transplant on the clinical significance of these genes.

Counselling and ethics

Population-based BRCA1/2 testing programmes are highly acceptable in the Jewish community: results of the JeneScreen Study. Tiller *et al.* (2022). *J Med Genet*; http://dx.doi.org/10.1136/jmedgenet-2022-108519.

- Three Jewish founder *BRCA* pathogenic variants (PV) account for >90% of PVs in Ashkenazi Jewish people. However, family-history based genetic testing strategies miss >50% of those carrying these PVs in this community
- This may be because family history information is lacking due to factors such as family dispersal and the impact of the Holocaust
- The JeneScreen project was set up to offer founder PV testing in Sydney and Melbourne. This was for people with at least one Jewish grandparent, with no previous genetic testing history or personal cancer diagnosis in the year prior
- Participants completed questionnaires after receiving information about the project and 2 weeks after receiving their results

- 594 participants returned a sample and received results. 0.8% were found to carry a founder PV. 504 participants completed questionnaires
- Data collection focused on the following areas: knowledge, decisional conflict, anxiety and test-related stress, decisional regret, risk perception and satisfaction
- Data was either collected through online or face-to-face education. Differences in these methods are also explored in this paper
- Knowledge scores were significantly lower in those educated to year 10 or below compared to those with higher education levels
- There was no significant difference in decisional conflict between those found to carry a founder PV, and those who did not. Those with a higher level of education had less decisional conflict
- Anxiety did not significant rise after the test results were received. However, test-related distress significantly increased in those found to have a PV
- There was no significant difference in post-decision regret between those found to carry a PV and those who did not
- The results significantly changed risk perceptions for those from low risk family histories but did not change perceptions of those at high risk
- 93.2% of participants were satisfied or very satisfied with the JeneScreen programme. There was no significant difference between those with or without a founder PV
- Read about a similar NHS BRCA screening programme recently introduced in England: https://jewishbrca.org/

Exploring the role of a multidisciplinary hereditary gynecologic oncology clinic in epithelial ovarian cancer risk-reducing surgical decision-making practices: A mixed-methods study.
Casalino *et al.* (2023). *Journal of Genetic Counseling*; 00: 1-16. DOI: 10.1002/jgc4.1684

- The Hereditary Gynecology Clinic (HGC), a provincial program in Winnipeg, Canada, is an interdisciplinary team of gynaecological oncologists (GOs), menopause specialists, and registered nurses.
- A mixed-methods study design was used to explore the decision-making processes of individuals with pathogenic variants in *BRCA1* or *BRCA2* who have been recommended (or who completed) risk-reducing salpingo-oophorectomy (RRSO) and how experiences with healthcare providers at the HGC influenced this decision.
- 43 people completed a survey and 15 participated in an in-depth interview
    - Majority of survey participants had already had RRSO or had already decided they would undergo RRSO in the future (28/43, 65%). 13 (30%) were undecided and 2 (5%) were firmly decided against RRSO
    - Of the interview participants, 10 (67%) had not had RRSO and 8 (53%) were pre-menopausal at time of interview

- Factors including participant age (<50 or ≥50 years of age), menstrual status (pre- or post-menopause), and previous breast cancer diagnosis impacted one or more of the following: cancer-related worry, decisional conflict, satisfaction with decision.
    - Individuals <50 and pre-menopausal individuals felt more decisional conflict, less satisfaction with RRSO decision, and more cancer-related worry.
    - Differences in scores were not statistically significant between individuals with vs without children, between those with vs without FH of HGSOC, or between those who did or did not consult with a gynaecologist/GO. Some of these findings were somewhat inconsistent with the qualitative interviews.
    - Individuals with a previous BC diagnosis had less cancer-related worry than those without a previous BC diagnosis.
    - Mean scores evaluating the HGC's impact on decisional outcomes and preparedness for decision-making about RRSO were not significant. The authors suggest that patients appear to be utilising the HGC when they are ready to undergo RRSO, and so the HGC plays a supportive role rather than helping with decision-making itself.
- Four themes emerged from the interviews:
    - **Personal contextual factors -** *Such as age, menopausal status, marital status, family history of cancer, beliefs, values, and previous experiences with risk-reducing surgery and the healthcare system*
    - **Practical implications of RRSO -** *Risk of other health conditions, side effects of RRSO (menopause; uncertain impacts on mood, identity, breast cancer risk)*
    - **Emotional implications of RRSO -** *Cancer-related worry, sense of control, impact on gender identity and self-image*
    - **Coping strategies and networks -** *Gathering information, sharing information with others, family support networks, support networks with BRCA-positive individuals*
- The authors describe how individuals in this study "*perceived their HGSOC risk through a personalised lens"*, and how this lens "*contributes to how the practical and emotional implications of being BRCA-positive, as well as the need for RRSO, are interpreted"*.
- They suggest that the individual's ultimate decision of whether or not to pursue RRSO depends on what they believe will provide them with the most control over their perceived cancer risk and associated implications.
- Importantly, decision-making regarding RRSO changes with time, and so may be revisited over time as circumstances and contextual factors change.
- Based on the interview outcomes, the authors present a thematic framework consolidating the various influences on decision-making and linking these to the emotional and practical implications of RRSO. They also describe strategies for improving support, decisional outcomes, and the overall experiences of individuals who are *BRCA*-positive attending the HGC.

Monthly Journal Round-Up brought to you by:

Izzy Turbin, Principal Genetic Counsellor, Addenbrooke's Hospital, Cambridge
Nancy Whish, STP Trainee Genetic Counsellor, Addenbrooke's Hospital, Cambridge
Alice Coulson, Genetic Counsellor, GOSH, London

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