CGG/ERN GENTURIS/ICARE Monthly Journal Round-Up – November & December 2023

In the clinic

The English National Lynch Syndrome transformation project: an NHS Genomic Medicine Service Alliance (GMSA) programme. Monahan et al. 2023. *BMJ Oncology.* doi:10.1136/bmjonc-2023-000124

- GMSA National LS Transformation Project - A project led by led by North Thames and South East GMSAs to embed robust Lynch syndrome testing pathways.
- Prior to the project - Evidence of variation and low testing levels in eligible patients.
- Aims of the project include:
  - Providing leadership and expertise to drive awareness, provide training, facilitate pathway improvements and support the reduction in testing variation and overall compliance with testing guidelines.
  - Support local audit programmes.
  - Creation and maintenance of a national Lynch registry and access to the national Bowel Screening Programme for LS patients.
- Key performance indicators include:
  - A 50% increase on testing across each step of the testing pathway.
  - Appointment of an LS champion in each colorectal (CRC) and endometrial cancer (EC) MDT.
  - Qualitative baseline survey of perceptions of testing level, barriers and solutions by each LS Champion.
  - Standardisation of reporting for pathology.
  - Identification of all diagnosed LS patients by each GMSA.
  - Development of online training modules and national training workshops for members of the CRC or EC MDTs, primary care and pathologists.
- A survey of LS champions about local testing practices, barriers to delivery and potential solutions to improve pathways was conducted and some key findings listed below.
  - 126 responses (59 from CRC MDTs and 67 from EC MDTs; 70.7% response rate)
  - There were reported differences in the clinician responsible for actioning genetic referral. 64.2% of respondents believing that the responsibility for following up results was with another member of the team rather than themselves.
  - 25.4% were not aware if the index tumour MMR test was IHC or MSI in their institution. 27.8% offered both IHC and MSI.
  - Results of MMR testing were reportedly discussed at 56% of CRC and 62% of EC MDT meetings.
  - 45.2% stated that patients would be referred to clinical genetics prior to the point of eligibility for genetic testing.
  - Referral for genetic testing was often performed in an ad hoc way without a consistent approach (88%).
  - 32% reported they would like to be 'upskilled' to offer genetic testing locally without external referral.

  - ‘Universal testing’ for LS in 71% of CRC MDTs and 66% of EC MDTs (in accordance with NICE guideline recommendations). Universal testing offered in some case in 17% of CRC or EC MDTs. 12% reported that the recommended universal testing is never offered.
  - The main barriers to delivery were reported to be local resource including funding, awareness of regional service commissioning structures, and time pressure.
- This survey data shows there is lack of clarity on whose responsibility this is, and there is much room for improvement in discussing test results at MDT, the understanding of genetic testing pathways and referral to clinical genetics.
- To effectively embed a robust mainstream approach to LS testing, there needs to be adequate resources for training clinical staff, identification of bottlenecks in local services, management of variation and ensuring the pathways are sustainable.
- The National Disease Registration Service (NDRS) is developing a nationally coordinated measurement of variation in performance, and will report on long-term project impact in 2026.

Co-design of patient information leaflets for germline predisposition to cancer: recommendations for clinical practice from the UK Cancer Genetics Group (UKCGG), Cancer Research UK (CRUK) funded CanGene-CanVar Programme and the Association of Genetic Nurse Counsellors (AGNC). Kohut K, Speight B, Young J et al. 2023. *Journal of Medical Genetics*. doi: 10.1136/jmg-2023-109440

- Services usually create their own patient information leaflets (PIL) which leads to duplication of effort and variability in the formatting, content, signposting and patient input.
- A two-day meeting aimed to: Make recommendations on the co-design of PIL for germline cancer susceptibility genetic testing; Provide consistency across the UK of high-quality information given to patients; Minimise duplication of effort through formation of a national collaboration and working groups; Create a list of trusted, up-to-date patient resources for signposting.
- Meetings were attended by multidisciplinary clinicians and experts from across the UK, as well as patients, charities and peer support groups.
- The paper summarises some of the key issues in the use and development of PILs.
  - Feedback from patients about whether they use PILs is not typically sought.
    When it is sought, there is a range of feedback from patients… “Nice to be involved in your own care”, “[receiving a leaflet is] something I would have found useful”, “didn’t feel very personal to me”.
  - Increasing demand on services leaves little time for the robust development and updating of PILs.
  - Our knowledge of these genes and cancer risks is rapidly evolving which makes it challenging to keep PILs accurate and up to date.
  - There is a lack of standard guidance for PIL development in clinical genetics.
  - Many PILs contain complex terminology resulting in a high reading level, with limited use of visual presentation of cancer risks and communication about uncertainty.
- Over the 2 days, Lynch syndrome and germline predisposition to haematological malignancies were chosen as exemplar conditions to be the focus for the development of co-designed PILs.

- It was discussed that PIL provided at time of diagnosis testing may not need to be extensively detailed, so patients could have a shorter PIL, which can be replaced by a longer and more specific PIL if a GPV was found.
- There was discussion about the importance of using visual aids with numbers, pictures and graphics to communicate risk.
- Key recommendations:
    - PIL should be offered to patients, alongside their personalised clinic letter, during the genetic testing process.
    - PIL should be as inclusive as possible. Attention should be paid to the readability of leaflets, with inclusion of visuals and aiming for the national average reading age of 9-11 years.
    - PIL should include date of creation and next review.
    - PIL should signpost to relevant charities.
    - Patients with lived experience should be invited to co-design and evaluate PIL.
- Formation of a national collaboration and working groups to develop and update PIL will improve equity of care and reduce duplication of effort, and these recommendations will improve the quality, usefulness and consistency of the information offered to patients regarding genetic testing.

New Macmillan online resource about breast cancer susceptibility genes

- May be useful to circulate to mainstreaming clinicians in your region and to individuals undergoing training to offer genomic testing for breast cancer patients
- www.macmillan.org.uk/healthcare-professionals/innovation-in-cancer-care/genomics-toolkit/breast/breast-cancer-susceptibility-genes

Counselling and ethics

Pregnancy After Breast Cancer in Young BRCA Carriers: An International Hospital-Based Cohort Study. Lambertini et al. 2023. *JAMA.* doi: 10.1001/jama.2023.25463.

- This study investigated cumulative incidence of pregnancy and disease-free survival in young women with breast cancer (BC) and a germline *BRCA* variant, given concerns about the hormone surge during pregnancy potentially increasing recurrence risk and possible negative foetal effects of women's exposure to anticancer therapies.
- This was a hospital based retrospective cohort study across 78 centres worldwide.
- 4732 *BRCA* carriers: Women diagnosed with invasive BC at 40 or under, with germline PVs in *BRCA1* or *BRCA2.*
- The study found that 1 in 5 patients conceived within 10 years after BC diagnosis.
- The cumulative incidence of pregnancy at 10 years: Overall = 22%; Hormone-receptor positive = 18%; Hormone receptor negative = 26%
- Median time of BC diagnosis to conception was 3.5 years.
    - Significantly longer (4.3 years) for women with hormone-receptor positive BC, compared to hormone-receptor negative (3.2 years).
- Figures for women with hormone-receptor positive BC are as such presumably due to exposure to endocrine therapy. Incidence of pregnancy in these women is predicted to

increase based on early results of the POSITIVE trial showing the safety of temporary interruption of endocrine therapy (18 to 30 months in) to attempt pregnancy.

- This study suggests pregnancy may have a slight protective association in *BRCA1* carriers, as analysis showed it appeared to be associated with lower rates of events such as recurrence, metastases, new invasive BC or death.
- Analysis of *BRCA2* carriers identified a possible association between pregnancy and adverse disease-free survival outcomes. This may be due to *BRCA2* carriers being more likely to develop hormone-receptor positive cancer. This said, analysis found no statistical significance and the study suggests there is no detrimental impact of pregnancy in patients with hormone-receptor positive BC.
- 80% of pregnancies occurred spontaneously, despite receipt of prior chemotherapy in over 90% of patients. However, women diagnosed during reproductive years should be offered fertility preservation strategies, which may be particularly relevant for women considering PGT-M.
- There was no significant difference in disease-free survival observed between patients with or without a pregnancy after breast cancer. The study concluded that pregnancy after BC was not associated with adverse maternal prognosis or foetal outcomes.
- Observed differences between *BRCA1* and *BRCA2* carriers warrant further investigation and could influence the respective counselling of these women.

Breast and colorectal cancer risks among over 6,000 CHEK2 pathogenic variant carriers: A comparison of missense versus truncating variants. Mundt *et al.* (2023). *Cancer Genetics*; 278: 84-90. https://doi.org/10.1016/j.cancergen.2023.10.002.

- This study compares cancer associations with truncating and missense pathogenic variants in *CHEK2* across breast and (non-polyposis) colorectal cancer.
- Retrospective analysis of 705,797 patients receiving multigene panel testing between 2013 and 2020. Individuals with a single truncating or missense *CHEK2* PV were evaluated against individuals with no detected PV or those with a VUS.
- Odds ratios (ORs) and 95% confidence intervals (CIs) calculated for cancer risk after adjusting for age at diagnosis, cancer history, and ancestry.
- 6255 *CHEK2* PVs (4505 truncating PVs and 1750 missense PVs).
- *CHEK2* PVs were associated with an increased risk of ductal invasive breast cancer and ductal carcinoma in situ (DCIS), with no statistically significant difference when truncating PVs and missense PVs were evaluated separately.
- All *CHEK2* PVs assessed conferred little to no risk of colorectal cancer.

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