CGG/ERN GENTURIS/ICARE Monthly Journal Round-Up – August 2022

In the clinic

A digital pathway for genetic testing in UK NHS patients with cancer: BRCA-DIRECT randomised study internal pilot. Torr *et al*. 2022. *J Med Genet.* doi:10.1136/ jmedgenet-2022-108655

- Rapid, digital pathway supported by a genetics specialist hotline (staffed by a genetic counsellor, oncogenetics specialist nurse or clinical geneticist), for delivery of germline testing of *BRCA1/BRCA2/PALB2* (BRCA-testing), integrated into routine UK NHS breast cancer care
    - Aims to be patient-centred, 'light-touch' for clinicians, and integrated into NHS clinical, laboratory and informatics systems
    - DNA sampling via saliva – completed in clinic or at home with postal return
    - See the paper for more information about the digital platform, pre-test information, consent and return or results
- The pathway was piloted as part of the large BRCA-DIRECT study in 130 unselected patients with breast cancer (invasive breast cancer or high-grade DCIS)
- Preliminary data was gathered from a randomised comparison of delivery of pretest information digitally (fully digital pathway) or via telephone consultation with a genetics professional (partially digital pathway).
- Uptake of genetic testing was 98.4%, and good satisfaction was reported for both the fully and partially digital pathways (evaluated using a 15-item study-specific survey, conducted 7 days post-receipt of result) – see figure 3 in the paper for comparison between patient reported satisfaction for digital and telephone pretest information
- Both pathways had similar outcomes for patient knowledge score (evaluated using questionnaire comprising 14 'true' or 'false' statements at baseline and 7 days after consent) and anxiety (evaluated using Spielberger State-Trait Anxiety Inventory for Adults at baseline, 7 days after consent, and 7 and 28 days after results)
- <5% of patients contacted the genetics specialist hotline (further patients contacted the hotline with 'administrative' calls)
- Overall median time for testing of samples (from consent to availability of results) was 27.6 days, and time-to-results (time from receipt of sample to return of results) was 38.4 days
- Survey sent to HCPs showed that the majority agreed (to varying extents) that all aspects of the digital pathway were equivalent (or superior) to standard-of-care
- The pilot data offer a preliminary demonstration of feasibility and acceptability of a fully digital pathway for BRCA-testing

- The full powered study will evaluate non-inferiority of the fully digital pathway, with detailed quantitative assessment of outcomes and operational economic analyses.

Risk of Peritoneal Carcinomatosis After Risk-Reducing Salpingo-Oophorectomy: A Systematic Review and Individual Patient Data Meta-Analysis. Steenbeek *et al*. 2022. *J Clin Oncol.* https://doi.org/10.1200/JCO.21.02016

- Women with *BRCA1/2* pathogenic variants (PV) are at high lifetime risk of developing epithelial ovarian cancer (EOC). Timely risk reducing salpingo-oophorectomy (RRSO) is recommended for *BRCA1/2*-PV carriers. Despite EOC risk reduction of up to 96%, a risk of developing peritoneal carcinomatosis (PC) persists after RRSO, although risk factors are unknown.
- Previous studies have shown that PC might derive from the fallopian tube epithelium and not the pelvic peritoneum, suggesting noninvasive serous tubal intra-epithelial carcinoma (STIC) as a precursor for high-grade serous carcinoma.
- In this study, the authors analyzed the risk of PC in women who presented with serous tubal intraepithelial carcinoma at RRSO. Aggregated data from 4754 women and individual patient data from 3121 woman were included in this systematic review and meta-analysis, of whom 122 and 115 had STIC at RRSO, respectively.
- Considering the women with STIC at RRSO, median age at RRSO was 52 years (range 36-77) ($p < 0.001$), 70.4% harbored a *BRCA1*-PV and 25.2% a *BRCA2*-PV. Main characteristics of STIC were: median size 1.5 mm (range 0.1-8.0), 87.4% located in the fimbriated end, 77.0% unifocal and 90.0% unilateral.
- Fifteen (13%) of the women with STIC at RRSO developed PC during a median follow-up of 52.5 months (range 2-246), with the interval from surgery to PC diagnosis being 48.0 months (range 18-118).
- After the diagnosis of STIC, 28 women underwent surgery and 11 had chemotherapy, none of whom developed PC. The authors consider the data insufficient for clinical recommendations.
- The results showed an increased risk of PC in *BRCA1/2*-PV carriers with STIC identified at RRSO.
    - The presence of STIC at RRSO was associated with higher age at time of surgery ($p < 0.01$) and harboring a *BRCA1*-PV ($p = 0.016$); however when STIC was found, age at RRSO timing was not associated with the risk of developing PC.
    - The hazard ratio (HR) for developing PC in women with STIC is 33.9 (95% CI, 15.6-73.9; $p < 0.001$) compared with women without STIC.
    - The cumulative risk of developing PC after RRSO at 5 or 10 years is, respectively, 10.5% (95% CI, 6.2-17.2) and 27.5% (95% CI, 15.6-43.9) for women with STIC, compared with 0.3% (95% CI, 0.2-0.6) and 0.9% (95% CI, 0.6-1.4) for women without STIC.
- Although age at RRSO does not influence the risk of developing PC when STIC is found, the risk of STIC presence increases with age, and the recommendation should remain to undergo RRSO within the current guideline age (35-40 years for *BRCA1*-PV and 40-45 years for *BRCA2*-PV carriers).

- The authors discuss that although the association between STIC and PC remains unclear, it is hypothesized that STIC could be part of a process that results in an invasive cancer, rather than the primary source of a neoplasm itself. Based on the literature, the authors consider less likely that PC derives from missed invasive carcinomas at RRSO.
- The authors conclude that *BRCA1/2*-PV carriers with STIC at RRSO have an increased risk of developing PC, which increases over time. For this reason, pathology reports should follow a structural assessment to minimize the chance of missing STIC. If STIC is found, staging surgery following RRSO should be considered, but the role of chemotherapy or PARP inhibitors in this setting is unclear.
- Future investigation should be directed at better understanding STIC characteristics, PC etiology and clinical management after STIC diagnosis.
- Also see the editorial from Kelly-Anne Phillips and Michael L. Friedlander: https://doi.org/10.1200/JCO.22.00325

Counselling and ethics

Influence of family history on penetrance of hereditary cancers in a population setting. Jackson *et al*. 2022 (preprint). *medRxiv.* https://doi.org/10.1101/2022.07.08.22277415

- Through analysis of 454,712 UK Biobank participants with exome sequence and clinical data, the study team identified participants with a self-reported family history of breast or colorectal cancer and a P/LP variant in the major genes associated with hereditary breast cancer or Lynch syndrome, and calculated survival to cancer diagnosis.
- Women with a pathogenic *BRCA1/2* variant had an increased risk of breast cancer that was significantly higher in those with a first-degree family history than those without (1.5/1.9-times higher)
- Penetrance to age 60 was also higher in those with a family history vs those without (i.e. more likely to develop cancer earlier)
- A similar pattern was seen in Lynch syndrome – individuals with a pathogenic *MLH1, MSH2* or *MSH6* variant had an increased risk of bowel cancer that was significantly higher in those with a family history than those without (2.1/1.9/1.9-time higher)
- Penetrance to age 60 was also higher for carriers of a pathogenic *MLH1* or *MSH2* variant in those with a family history vs those without
- The authors acknowledge the limitation that the older cohort in the UK Biobank is likely to be confounded by survival bias i.e. individuals with the most severe early-onset disease will not appear as they would have died prior to recruitment, and also that the UK Biobank is not a representative cohort due to recognised recruitment biases

- The authors conclude that individuals with pathogenic cancer syndrome variants are at significantly less elevated risk of cancer in the absence of family history, and so invasive follow-up may be unwarranted

Monthly Journal Round-Up brought to you by:

Izzy Turbin, Genetic Counsellor, Addenbrooke's Hospital, Cambridge
Fátima Vaz, Senior Graduate Assistant of Medical Oncology, Instituto Português de Oncologia de Lisboa, ERN GENTURIS Affiliated Partner
Dr Carolina Pereira, Instituto Português de Oncologia de Lisboa, ERN GENTURIS Affiliated Partner

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