CGG/ERN GENTURIS/ICARE Monthly Journal Round-Up – November 2021

Bigger picture

The recent study by Yadav and colleagues into germline pathogenic variants in cancer predisposition genes among women with invasive lobular carcinoma of the breast has established that pathogenic variants in *ATM, BRCA2, CDH1, CHEK2* and *PALB2* are associated with an increased risk of invasive lobular carcinoma (ILC). In contrast, the study shows that pathogenic variants in *BRCA1* are not associated with ILC.

The authors show that there are similar overall pathogenic variant frequencies for ILC and infiltrating ductal carcinoma (IDC), and therefore suggest that cancer histology should not influence the decision to proceed with testing. They suggest multigene panel testing may be appropriate for women with ILC, but that *CDH1* should be specifically discussed in light of its low prevalence and gastric cancer risk.

While *CDH1* pathogenic variants were not observed commonly (20 (0.5%) ILCs from the clinical testing cohort and 7 (0.2%) ILCs from the population-based cohort), they were associated with high risks of ILC (OR = 15.74). The authors suggest this high risk may justify risk-reducing mastectomy even in the absence of a family history of breast cancer. Of note, of the 20 women with *CDH1* pathogenic variants in the clinical testing cohort, only 50% had either a personal (1 of 20) or family history (9 of 20) of gastric cancer.

Pathogenic variants in *CHEK2, BRCA2,* and *ATM* were observed in more than 1% of ILCs in the cohort of women undergoing clinical testing, while only *CHEK2* and *BRCA2* pathogenic variants were found in more than 1% of ILCs in the population-based cohort. In case-control analysis, *BRCA2* pathogenic variants were associated with high risks of ILC (OR = 4.94), while *CHEK2, ATM,* and *PALB2* pathogenic variants were associated with moderate risks (OR = 2-4).

Translational science

Lessons learned from drug trials in neurofibromatosis: A systematic review. Dhaenens *et al*. (2021). *European Journal of Medical Genetics.* https://doi.org/10.1016/j.ejmg.2021.104281

- Neurofibromatosis (NF) is the umbrella term for Neurofibromatosis type I (NF1), Neurofibromatosis Type II (NF2) and schwannomatosis (SWN). These are hereditary disorders that predispose to benign and malignant tumor formation and a variety of other manifestations.
- EU-PEARL is a European collaborative project that aims to develop platform trials for NF.

- The aim of this systematic review was to create an overview of clinical drug trials performed in NF over the last ten years. This information could be used to identify learning points which can guide the development of the platform trials.
- This systematic review included publications of drug trials performed in NF patients, which could be either observational or clinical trials. Systematic reviews, secondary analyses and studies reporting n < 10 patients were excluded.
- After abstract screening and full-text review, 42 full-text publications were included. Of these publications, 31 described trials in NF1, 11 in NF2, but none in SWN.
    - Most trials within the NF1 population focused on the manifestation groups benign peripheral nerve sheath tumors (32%), neurodevelopmental manifestations (26%) and low grade glioma (23%). All studies in NF2 focused on the tumor manifestation vestibular schwannomas.
    - Single-arm trials were the most common in both NF1 (58%) and NF2 (55%). All studies were limited to phase I and II trials.
    - Most trials were single-country (85%) and generally included 5 participating centers or less.
    - Primary endpoints were mainly functional; Patient reported outcome measures (PROMs) were only used in 10% of all trials as primary endpoint.
    - The majority of NF1 trials included only children and young adults into their study population (71%). Included patient populations were small (68% including 50 patients or less), with high drop-out rates of more than 20% in two-thirds of NF1 trials. In NF2, population numbers were even smaller, with 82% of the trials including 10 to 25 patients.
- The authors conclude that there has been a lack of studies on underrepresented manifestations like cutaneous manifestations and high-grade gliomas in NF1, tumor manifestations other than vestibular schwannoma in NF2, and schwannomatosis. They also identify a need for more trials for adult NF1 patients and the use of PROMs as primary endpoints.
- Innovative trial designs such as platform trials with more efficient use of participants and the possibility of testing multiple interventions simultaneously could be a solution for some of these problems.

Multi-omics analysis identifies therapeutic vulnerabilities in triple-negative breast cancer subtypes. Lehmann *et al.* (2021). *Nature Communications*. https://doi.org/10.1038/s41467-021-26502-6

- Triple-negative breast cancer (TNBC) is a collection of biologically diverse cancers characterized by distinct transcriptional patterns, biology, and immune composition. TNBCs subtypes include two basal-like (BL1, BL2), a mesenchymal (M) and a luminal androgen receptor (LAR) subtype.
    - The authors conducted a detailed analysis of mutation, copy number, transcriptomic, epigenetic, proteomic, and phospho-proteomic patterns and then they moved on to describe the genomic landscape of TNBC subtypes using samples from The Cancer Genome Atlas (TCGA) and Clinical Proteomic Tumor Analysis Consortium (CPTAC).

  - They demonstrate that mesenchymal subtype tumors display high mutation loads, genomic instability, and absence of immune cells, low PD-L1 expression, decreased global DNA methylation, and transcriptional repression of antigen presentation genes.
  - They also prove that major histocompatibility complex I (MHC-I) is transcriptionally suppressed by H3K27me3 modifications by the polycomb repressor complex 2 (PRC2).
  - Then, with the use of pharmacological inhibitors of PRC2 subunits they observed that EZH2 or EED restores MHC-I expression and enhances chemotherapy efficacy in murine tumor models, providing a rationale for using PRC2 inhibitors in PD-L1 negative mesenchymal tumors.
- Overall, this study identifies a potential mechanism of immune escape and provides further understand the biology of TNBC subtypes. TNBC cell line and animal models identify genetic and pharmacological vulnerabilities and identify potential therapeutic strategies for TNBC patients.

In the clinic

A prospective prostate cancer screening programme for men with pathogenic variants in mismatch repair genes (IMPACT): initial results from an international prospective study. Bancroft *et al*. (2021). *Lancet Oncol.* https://doi.org/10.1016/ S1470-2045(21)00522-2

- The IMPACT study is prospectively assessing prostate-specific antigen (PSA) screening in men with germline MMR pathogenic variants.
- Men aged 40-69 years without a previous prostate cancer diagnosis and with a known germline pathogenic variant in the *MLH1, MSH2,* or *MSH6* gene, and age-matched male controls who tested negative for a familial PV, underwent a baseline PSA screening.
- Men who had a PSA level higher than 3.0 ng/mL were offered a transrectal, ultrasound-guided, prostate biopsy and a histopathological analysis was done.
- Between September 2012 and March 2020, 828 men were recruited (644 carriers [204 carriers of *MLH1*, 305 carriers of *MSH2*, and 135 carriers of *MSH6*] and 184 non-carrier controls [65 non-carriers of *MLH1*, 75 non-carriers of *MSH2*, and 43 non-carriers of *MSH6*]). 134 non-carriers from the *BRCA1* and *BRCA2* cohort of the IMPACT study were included (and screened for PVs in the MMR genes) to boost the non-carrier control groups.
- Within the first screening round, 56 (6%) men had a PSA concentration of >3.0 ng/mL and 35 (4%) biopsies were done. 18 (51%) of the biopsies indicated the presence of cancer.
- Overall incidence of prostate cancer was 1.9%.
  - Incidence among *MSH2* carriers was 4.3% vs 0.5% in *MSH2* non-carrier controls
  - Incidence among *MSH6* carriers was 3.0% vs 0% in *MSH6* non-carrier controls
  - None were detected among the *MLH1* carriers or non-carrier controls
- The overall positive predictive value of biopsy using a PSA threshold of 3·0 ng/mL was 51.4%, and the overall positive predictive value of a PSA threshold of 3·0 ng/mL was 32·1%.
- *MSH2* carriers were diagnosed at a non-significantly younger age and had more clinically significant disease at diagnosis compared with non-carriers
- Findings support the use of targeted PSA screening in men with *MSH2* and *MSH6* PVs to identify those with clinically significant prostate cancer. Further annual screening rounds will need to confirm these findings.

- Authors suggest that testing for MMR variants will likely become routine practice at prostate cancer diagnosis over the coming years
- The study is also looking at multiple secondary endpoints which require the full 5 years of PSA screening to be completed and will be reported as part of future analyses

Clinical value of a screening tool for tumor predisposition syndromes in childhood cancer patients (TuPS): a prospective, observational, multi-center study. Postema *et al*. (2021). *Familial Cancer*. https://doi.org/10.1007/s10689-021-00237-1

- This study is a continuation of a previous study performed by same authors who had developed a screening tool to increase diagnostic accuracy and clinical efficiency of identifying tumor predisposition syndromes (TPSs) in children with cancer.
- Here the authors report on the value of this tool in clinical practice.
- TuPS is a prospective, observational, multi-center study including children newly diagnosed with cancer from 2016 to 2019 in the Netherlands.
- The screening tool consists of a checklist, 2D and 3D photographic series and digital assessment of these by a clinical geneticist.
- If a TPS was suspected, the patient was assessed positive and referred for routine genetic consultation.
- Primary aim was to assess the clinical value of this new screening tool.
- Of the 363 included patients, 57% (208/363) were assessed positive. In 15% of patients (32/208), the 2D photographic series with (n = 12) or without (n = 20) 3D photographs were decisive in the positive assessment. In 2% (4/208) of positive assessed patients, a TPS was diagnosed, and in an additional 2% (4/208) a germline variant of uncertain significance was found.
- Thirty-five negatively assessed patients were evaluated through routine genetic consultation as controls, in none a TPS was detected.
- Using the screening tool, 57% of the patients were assessed as suspected for having a TPS. No false negative results were identified in the negative control group in the clinical care setting.

Counselling and ethics

Uptake and timing of bilateral and contralateral risk-reducing mastectomy in women with Li–Fraumeni syndrome. Siegel *et al.* (2021). *Breast Cancer Research and Treatment;* https://doi.org/10.1007/s10549-021-06410-5

- The purpose of this study was to evaluate risk-reducing mastectomy (RRM) uptake in a cohort of women with LFS.
- Women (n = 205) with LFS enrolled in NCI's LFS study reported lifetime cancer diagnoses and mastectomies and completed questionnaires regarding reproductive history, cancer worry and risk perceptions. A subset of women participating in an annual cancer screening study received counselling regarding RRM.
- The results of this study showed that 65% (n = 71) of women diagnosed with presumed unilateral breast cancer (n = 109) underwent contralateral RRM over their lifetime.
- Nearly half (49%, n = 25) of the women who did not complete contralateral RRM within one year of their breast cancer diagnosis (n = 51) developed contralateral breast cancer (median

interval = 6 years). Only 18.5% (n = 15) of women without breast cancer history (n = 81) underwent bilateral RRM.

- Median age at bilateral RRM of 39 years was sub-optimal for breast cancer risk reduction.
- Contralateral RRM was associated with early genetic diagnosis, participation in the screening study, and fewer prior cancers.
- Bilateral RRM uptake was associated with having had children, having breastfed, and high cancer worry.
- This study led the authors to conclude that the frequency of contralateral breast cancer necessitates active discussion of benefits of contralateral RRM and counselling regarding bilateral RRM should be tailored to the early age at risk of breast cancer onset in LFS.
- The authors also suggest that there is a need for research into the survival and long-term benefits of RRM in LFS.

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