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

Bigger picture

The American College of Medical Genetics and Genomics (ACMG) have issued an updated policy statement (v3) regarding the genes in which incidental variants detected as part of Whole Exome/Genome sequencing for unrelated indications should be reported. The members of a Secondary Findings Working Group (SFWG) comprised biochemical, molecular and cytogenetics laboratory directors, genetic counsellors, clinical geneticists, cardiologists and pharmacogenomics expert, as well as a patient representative. The SFWG meets monthly, to vote on inclusion or exclusion or relevant genes/phenotypes. The group review the genes and phenotypes on the preceding policy statement list to determine their continued (or not) appropriateness for inclusion on the updated list. They also reviewed gene-phenotype pairs scored as highly actionable by the ClinGen actionability working group, and considered genes for review after consulting the French Society of Predictive and Personalised Medicine on Hereditary Cancer Genes and the eMERGE network.

The SFWG broke into subgroups to determine final list of genes for consideration of full review. After discussion at the wider group, a motion to include/exclude the gene from v.3 of the list was made and seconded – prompting a vote on the final decision subject to ramification by the ACMG Board of Directors. The cancer subgroup prioritized 13 new genes for consideration related to seven hereditary cancer phenotypes. Relevant, recent literature on phenotype, penetrance, and actionability was curated from a gene-focused search of Pubmed, GeneReviews and OMIM, as well as input from the subgroup members. Technical considerations of sequencing the genes were reviewed with relevant expert SFWG members. Genes that were recommended for addition to the SF v3.0 list include *PALB2*, *TMEM127, MAX,* while variants that were considered but not listed included (among others) *SDHA* – due to poor analytic specificity; *EPCAM* and *GREM1* – because of difficulty in deletion/duplication analysis; *BRIP1, RAD51C* and *RAD51D* – because of incomplete penetrance and issues with risk management; *BAP1, DICER1, POLE, POLD1* – because of uncertainty regarding penetrance and phenotype. The process of reviewing genes for inclusion on this list is dynamic – and the SFWG will continue to review this list of actionable genes, and new nominations (via ACMG website) on an ongoing basis.

Translational science

Re: ERCC3, a new ovarian cancer susceptibility gene? Soukupova *et al*. (2021). *Letter to the editor, European Journal of Cancer*; 150: 278-280. https://doi.org/10.1016/j.ejca.2021.03.014

- The authors in this letter highlight an old study from Stradella *et al*. 2020, which suggested *ERCC3* as a new gene predisposing the hereditary breast (BC) and ovarian (OC) cancer.
- The study from Stradella *et al*. performed *ERCC3* screening by multigene-panel analysis in 1311 unrelated patients after regional consensus for genetic testing in hereditary cancer was carried out. They also used 453 Spanish cancer-free individuals and 51,343 GnomAD non-Finnish, non-cancer European individuals as control populations.
- They identified 13 patients with heterozygous *ERCC3* truncating variants (0.99%). Five of them also carried a mutation in a high- /moderate-penetrance HBOC gene (*BRCA1, BRCA2, CHEK2*, and *TP53*) being Multilocus Inherited Neoplasia Alleles syndrome (MINAS) patients.
- The authors found an almost statistically significant association of truncating *ERCC3* variants with BC (odds ratio [OR] = 2.25, confidence interval [CI] = 0.6–5.93, P = 0.11), and observed for the first time a significant association with ovarian cancer (OR = 4.74, CI = 1–14.34, P = 0.028), that holds even after removing MINAS cases.
- To conclude, the authors suggested that this is the largest HBOC series comprehensively analysed for *ERCC3* mutations, and the first study identifying *ERCC3* as a cancer risk for Ovarian Cancer and confirm the association of *ERCC3* truncating mutations with breast cancer.

Nuclear PTEN and p53 suppress stress-induced liver cancer through distinct mechanisms. Kato *et al.* (2021). *Biochemical and Biophysical Research Communications*; 549: 83-90. https://doi.org/10.1016/j.bbrc.2021.02.093

- The authors here explore the in vivo relationship between p53 and PTEN which is currently unknown even though it is well established that both genes are implicated in DNA repair, cell cycle progression, and genome maintenance and are found highly mutated in a wide variety of cancer types.
- The authors here analysed the liver of mice in which nuclear PTEN and p53 are individually or simultaneously depleted.
- They showed that nuclear PTEN deficiency upregulates p53 expression upon oxidative stress.
- They also showed that the loss of p53 potentiates stress-induced accumulation of PTEN in the nucleus.
- Next, they examined oxidative stress-induced DNA damage in hepatocytes, and found that nuclear PTEN loss aggravated the damage while p53 loss did not under oxidative stress.
- They observed that mice lacking nuclear PTEN had increased hepatocellular carcinoma under oxidative stress, while mice lacking p53 in hepatocytes had accelerated hepatocellular carcinoma and intrahepatic cholangiocarcinoma and through further analysis they reached to the conclusion that the formation of cholangiocarcinoma appears to involve the transformation of hepatocytes into cholangiocarcinoma.

- Lastly, they used double KO mice for the two genes and showed that the simultaneous loss of nuclear PTEN and p53 exacerbated both types of liver cancers.
- Overall this work shows that nuclear PTEN and p53 suppress liver cancers through distinct mechanisms and raises questions about the importance of uncovering the molecular mechanisms underlying the new role of p53 in the suppression of liver cancers in future studies using our mouse models.

In the clinic

Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Menon *et al*. (2021). *The Lancet.* https://doi.org/10.1016/S0140-6736(21)00731-5

- This month, Prof Usha Menon and colleagues published the long-awaited long term results of the UKCTOCS randomised control trial, examining the role of different screening approaches in women aged 50-74 years at population level risk of ovarian cancer. The total number of women recruited to the study was an impressive 202638, of whom 202562 were ultimately included in the analysis.
- Women were randomised in a 1:1:2 ratio to multimodal screening (CA125 pattern as per ROCA calculation and Transvaginal ultrasound (with interval based on result)); annual TVUS; and no screening. Clinical data was prospectively collected by linking women using their NHS number to National Cancer and Death Registration data and Hospital Episode Statistics records. The primary outcome was death from tubal/ovarian cancer (including epithelial, non-epithelial & borderline subtypes) up to June 30 2020.
- Over the study period, 2055 women were diagnosed with tubal/ovarian cancer over the study period – including 522/50625 (1%) in the MMS arm, 517/50623 (1%) in the USS arm and 1016/101314 (1%) in the "no screening" group. When comparing MMS to no screening, there was a 24.5% reduction in Stage IV disease, but this did not translate to a reduction in deaths. 1206 died of their disease – 296 (0.6%) in the MMS group, 291 (0.6%) in the USS group and 619 (0.6%) in the no screening group.
- Although this is a negative study, these results are useful, and the authors emphasise that the primary outcome of screening trials should be cancer mortality. Given that USS/MSS screening was not associated with a reduction in deaths from tubal/ovarian cancer, screening of this nature in women at population risk cannot be recommended.

Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer. Tutt *et al*. (2021). *NEJM.* doi:10.1056/NEJMoa2105215

- PARP inhibitors target cancers with defects in homologous recombination repair by synthetic lethality
- Phase 3, double-blind, randomised trial involving patients with HER2 negative early breast cancer with *BRCA1* or *BRCA2* germline pathogenic/likely pathogenic variants and high risk clinicopathological factors who had received local treatment and neo-adjuvant or adjuvant chemotherapy

- Patients (n=1836) randomly assigned in a 1:1 ratio to 1 year or oral olaparib or placebo
- Primary end point: invasive disease-free survival
- At median follow-up of 2.5 years, the 3-year invasive disease-free survival was 85.9% in olaparib group and 77.1% in the placebo group
    - 3-year distant disease-free survival was 87.5% in olaparib group and 80.4% in placebo group
- Olaparib was associated with fewer deaths than placebo (59 vs 86), however the between-group difference was not significant at an interim-analysis boundary of a P value of <0.01
- 52 weeks of adjuvant olaparib after completion of local treatment and neoadjuvant or adjuvant chemotherapy was associated with significantly longer survival free of invasive or distant disease than was placebo
- Olaparib had limited effects on global patient-reported quality of life
- Longer blinded f/u is required to assess the effect of olaparib on overall survival
- The trial provides evidence that germline *BRCA1* and *BRCA2* sequencing is an important biomarker for the selection of systemic therapy in early breast cancer

Effect of Aspirin on Cancer Incidence and Mortality in Older Adults. McNeil *et al*. (2021). *JNCI Journal of the National Cancer Institute.* doi: 10.1093/jnci/djaa114

- ASPirin in Reducing Events in the Elderly (ASPREE), a randomised, double-blind, placebo-controlled trial of daily low-dose aspirin (100mg) in older adults, showed an increase in all-cause mortality, primarily due to cancer
- 19114 Australian and US community-dwelling participants aged 70 years and older without cardiovascular disease, dementia, or physical disability were randomly assigned to aspirin or placebo group and followed for a median of 4.7 years.
- 981 cancer events occurred in the aspirin and 952 in the placebo groups. There was no statistically significant difference between groups for all incident cancers, haematological cancer, or all solid cancers, including by specific tumour type.
- However, aspirin was associated with an increased risk of incident cancer that had metastasized or was stage 4 at diagnosis, and with higher risk of death for cancers that presented at stages 3 or 4, regardless of whether the cancer was localised or metastatic at presentation
- In older adults, aspirin treatment had an adverse effect on later stages of cancer evolution. These findings suggest that in older persons, aspirin may accelerate the progression of cancer.
    - Possible explanations include that aspirin may suppress anti-tumour inflammatory or immune responses critical to controlling later stage growth and spread
    - Thus, suggest caution with aspirin use in this age group, however results of the study do not specifically address whether aspirin use initiated at a younger age should be discontinued after ages 65 to 70 years

Counselling and ethics

Helping young children understand inherited cancer predisposition syndromes using bibliotherapy. Schlub *et al.* (2021). *Journal of Genetic Counseling*; 00: 1-14. https://doi.org/10.1002/jgc4.1396

Introduction

- Parents are often tasked with communicating information about genetic conditions to their children who may already be affected, at risk or who have an affected relative. There are often dilemmas faced in knowing what, how and when to tell their children. There is also a healthcare burden for the parent who may also have the same condition
- Families with Li-Fraumeni syndrome (LFS) and hereditary pheochromocytoma and paraganglioma syndrome (HPPS) can face these challenges as onset or surveillance can begin in childhood.
- Bibliotherapy is a psycho-educational strategy, using books and stories to help people understand and adapt to new information. Typically involves the reading and discussion of a storybook between caregiver and child. Books have been shown to create a space for emotional healing and development of insight as well as identify difficult emotions
- This study aimed to develop a bibliotherapy tool for children aged between 5 and 10 years in families with LFS or HPPS, and to gather insight about parents' experiences of using this to support communication with their at-risk children

Materials, Methods and Results

- The story "Emily Goes to the Doctor" is about a six-and-a-half year old girl whose mother has symptoms of LFS/HPPS. Her siblings have had a genetic test and the story follows Emily having her test, and follows her journey learning about the condition and associated screening. There are also problems and solutions which are introduced and Emily has a wider character, meaning she is not defined just by her condition
- Telephone interviews with 12 parents were used to understand how they had found using the book with their children
- Overall, the book received positive feedback about appearance, tone, length and readability for age group, but there were differing opinions on age-appropriateness
- Parents also provided requests for changes based on their experience
- Three thematic areas emerged from interviews: Innate parental wisdom in communicating about LFS/HPPS, bibliotherapy and the experience of the child and bibliotherapy as an extra tool for parents

Discussion

- The five bibliotherapuetic stages were facilitated in "Emily Goes to the Doctor" and children maintained attention and personally identified with some aspects of the story
- Helped parents find age-appropriate language and recreated a shared ritual of reading together – the process was not distressing for parent or child
- Helped parents identify any misunderstandings or concerns
- Bibliotherapy could be an affordable and accessible intervention for genetic counsellors

Association of Salpingectomy with Delayed Oophorectomy Versus Salpingo-oophorectomy with Quality of Life in *BRCA1/2* Pathogenic Variant Carriers: A Non-randomised Controlled Trial. Steenbeek *et al*. (2021). *JAMA Oncology.* doi:10.1001/jamaoncol.2021.1590

- Multicentre non-randomised controlled preference trial (TUBA study) comparing menopause-related quality of life after risk-reducing salpingectomy (RRS) with delayed oophorectomy with RRSO in carriers of *BRCA1/2* PVs (n = 577)
- Patients at the clinical genetics or gynaecology department (in all Dutch university hospitals) between the ages of 25 and 40 years (*BRCA1*) or 25 to 45 years (*BRCA2*) who were pre-menopausal, had completed childbearing, and were undergoing no current treatment for cancer were eligible.
- Primary outcome was menopause-related QoL as assessed by the Greene Climacteric Scale (GCS; 21 symptoms rated on a 4-point Likert scale), with a higher scale sum (range 0-63) representing more climacteric symptoms
- Secondary outcomes: health-related QoL, sexual functioning and distress, cancer worry, decisional regret, and surgical outcomes
- At time of analysis, 394 patients had undergone RRS and 154 had undergone RRSO
- Without HRT, the adjusted mean increase from the baseline score on the GCS was 6.7 points higher during 1 year after RRSO than after RRS
    - After RRSO with HRT, the difference was 3.6 points compared with RRS
- Impaired sexual functioning was present in 53 of 148 women (35.8%) in the RRSO group at baseline, increasing over 3 months (61 of 138 [44.2%]) and 1 year (65 of 117 [55.6%]). In the RRS group, corresponding findings were impaired sexual functioning in 121 of 388 women (31.2%) at baseline, 103 of 373 (27.6%) at 3 months, and 85 of 301 (28.2%) at 1 year.
- Women in the RRS group experiencing less increase in sexual distress compared to RRSO group (without HRT), and difference became more pronounced over time
- Decline in cancer worry was similar in both groups, and both groups had low levels of decisional conflict and/or decisional regret
- Study suggests that patients have better menopause-related QoL after RRS than after RRSO, regardless of HRT
- International f/u study is currently evaluating the oncologic safety of RRS

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