CGG/ERN GENTURIS/ICARE Monthly Journal Round-Up – January 2024

Translational science & In the clinic

Sebaceous carcinoma epidemiology, associated malignancies and Lynch/Muir-Torre syndrome screening in England from 2008 to 2018. Cook *et al.* (2023). *Journal of the American Academy of Dermatology*; 89(6): 1129-1135.

- Sebaceous carcinomas (SC) may be associated with Muir-Torre syndrome (MTS), an allelic variant of Lynch syndrome (LS), however there is limited data on the mismatch repair (MMR) status of SC.
- Previously it has been estimated that 18.8% to 33.3% of patients with sebaceous tumors have LS, but MMR screening of SC samples to aid detection of LS is currently not standard practice in England
- A review by Owen *et al.* (2019; *Lancet Oncology*) did not recommend universal IHC testing for MMR deficiency in SC tumours as they reported a much lower sensitivity and specificity for detecting LS using this strategy, compared with colorectal cancers. However, Cook *et al*. argue that the data sets used to calculate sensitivity and specificity were incomplete, and that next generation sequencing assays are becoming increasingly sensitive and can also detect MSI.
- This retrospective cohort study of SC patients in the National Cancer Registration and Analysis Service in England looked at the population level frequency of MMR screening in SC.
- Of the 1077 cases studies, MMR immunohistochemistry screening was performed in only 20% of SC tumours, and of these, 32% (70/220) were MMR deficient.
    - Patients with dMMR SC were younger (median age 67y) compared with patients with pMMR SC (median age 78y)
    - The most common dMMR patterns were loss of MSH2 and MSH6 (74.3%), followed by MLH1 and PMS2 (21.4%), MSH6 alone (2.9%), and PMS2 alone (1.4%)
- Of the 1077 patients, 19% (210/1077) developed at least one other recognised LS-associated cancer, and in total, 274 LS-associated cancers were diagnosed across 210 patients
- 29% of the LS-associated cancers occurred after the diagnosis of SC
- When separating extraocular and periocular SC, extraocular SC tumours were associated with significantly increased rates of colorectal and upper urinary tract cancers. Periocular SC were not associated with significantly increased rates of MTS/LS-associated cancers.
    - Extraocular SC also had a higher frequency of being dMMR compared to periocular SC (39% compared with 11%).
- 56 of the patients were shown to have had germline DNA MMR testing, 25 of whom had previously had MMR IHC testing of their tumour.
    - In 54% (30/56), germline testing identified pathogenic variants in an MMR gene
    - 50% of the patients with dMMR tumours (12/24) were found to have germline pathogenic vairants

Universal testing of cutaneous sebaceous carcinoma: a missed opportunity in Lynch syndrome detection. Rajan *et al.* (2024). *Lancet Oncology*; 25(1): E1-E2. https://doi.org/10.1016/S1470-2045(23)00595-8

- This correspondence is in response to the above paper by Cook *et al*.
- The group identified the following barriers to Lynch syndrome testing in sebaceous carcinoma:
    - Clinical scores such as the Mayo score, which captures variables such as age and family history, have restricted benefit in the context of rare cancers, as clinicians are not always aware to apply such guidance.
    - Cost-effectiveness; the authors argue this is not a barrier given the small number of people with SC in the UK (approx. 100 cases/year), and that precendent for cost and clinical eddectiveness has already been set in NICE guidance by the recommendation of testing 42,000 colorectal and 9000 endometrial cancers each year.
    - Absence of awareness of cutaneous LS manifestations
- The solution proposed is to mandate reflex LS diagnostic testing of SC, either through IHC for MMR proteins or MSI studies, followed by linked-up systematic constitutional testing for MMR deficient SC.

Counselling and ethics

Assessment of the psychosocial impact of pancreatic cancer surveillance in high-risk individuals. Anez-Bruzal *et al.* (2023). *Cancers*; 16(1), 86; https://doi.org/10.3390/cancers16010086

- If pancreatic cancer is detected at a localised stage where resection is possible, the 5 year survival rate is 42%, however for locally advanced/metastatic disease, the 5 year survival rate is 15%
- Magnetic cholangiopancreatography (MRCP) and endoscopic ultrasound have demonstrated utility in detecting precursor lesions and pancreatic cancer at earlier stages
- A pre/post screening survey design was used, and 100 participants were recruited who were deemed to be at higher risk of developing pancreatic and were having surveillance through Penn Medicine's Pancreatic Cancer Risk Management programme. Most participants had a germline pathogenic variant associated with an increased risk of pancreatic cancer
- Average age of participants was 59 years old, and 71% of participants were female
- 95 participants had no concerning findings on screening, 1 was diagnosed with a pancreatic cancer and 4 had lesions that were found to be benign after further screening
- 97% of participants identified early detection as one of their motivations for undergoing surveillance, and a reduced sense of fear and feelings of control were also motivations. 79% stated that contributing to scientific research was a motivation for them
- In the 7 days prior to surveillance, there were infrequent negative emotions (such as unhappiness or depression) and after surveillance there were feelings of reassurance, relaxation and hopefulness
- 53% decrease in levels of distress reported following receipt of surveillance results which was sustained at 4-6 weeks post-surveillance
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- Individuals with a family history of pancreatic cancer perceived a greater benefit from screening than those without a family history
- Authors acknowledged that there are cohorts who will benefit from additional counselling about surveillance before choosing to go ahead
- The study enrolled from a single site and the majority of participants represented a single demographic (non-Hispanic White females). Further studies in diverse groups needed

Families' experiences accessing care after genomic sequencing in the pediatric cancer context: "It's just been a big juggle". Vuocolo *et al.* (2024). *Journal of Genetic Counselling*; 00, 1–14. https://doi.org/10.1002/jgc4.1858

- Genomic testing in the paediatric oncology setting may detect cancer predisposition syndromes (CPS) which may have implications for CPS-related follow-up care for the child and their family members.
- In this study, semi-structured interviews were conducted with 20 patient families from the Texas KidsCanSeq (KCS) Study to explore their experience of learning about a cancer predisposition syndrome (CPS) diagnosis and following up on recommended care.
- Alterations had been identified in the following CPS genes: *BRCA1, CDKN2A, DDX41, DICER1, FAP, LZTR1, MSH6, NF1, NF2, PTEN, RB1* x3*, RET, SDHB, SDHD, TP53* x3, and *WT1.*
- In 9 of the 20 families, a parent had a confirmed molecular and/or clinical diagnosis of the same syndrome, and in four families at least one additional child had the familial variant.
- The authors identified a variety of barriers and/or facilitators, including:
    - Difficulty differentiating which follow-up care recommendations were made for their child's current cancer treatment vs the CPS
    - Organisational factors: Travel time and distance affected ease of access to follow-up care. In contrast, co-ordination of care to streamline multiple appointments with different providers helped facilitate CPS care. Some patients reported clinician knowledge of the gene or being able to access genetic testing or specialised care could be a challenge.
    - Financial factors: Financial assistance and insurance were facilitators, while costs and lack of insurance were barriers, particularly for patients who lose coverage during transitions from paediatric to adult care, and for adult family members who had no coverage.
    - Beliefs and perceptions: Perception of risk as being less important to them as a family member, feeling overwhelmed with the patient's current cancer care
    - Social factors: Competing life priorities made accessing follow-up care more difficult, while community support alleviated this. Health literacy also impacted patients' perceived ability to retain information.
- The authors suggest introduction of cancer care/hereditary cancer navigators and integrating longitudinal genetic counselling into hereditary cancer centres may help to improve coordination of cancer treatment and CPS-related care, as well as adherence to surveillance protocols as children get older. They also suggest developing travel plans, creating transition plans for children reaching adulthood, and facilitating cascade testing.

Monthly Journal Round-Up brought to you by:

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