CGG/ERN GENTURIS/ICARE Monthly Journal Round-Up – June 2023

Translational science

Molecular Profile of MSH6-Associated Colorectal Carcinomas Shows Distinct Features From Other Lynch Syndrome–Associated Colorectal Carcinomas. Helderman *et al.* (2023). *Gastroenterology*; 1-4. https://doi.org/10.1053/j.gastro.2023.03.198

- At the Leiden University Medical Center (LUMC, The Netherlands), researcher-in-training Noah Helderman, who works at the Department of Clinical Genetics under the supervision of Dr. Maartje Nielsen and in collaboration with Dr. Tom van Wezel and Prof. dr. Dr. Hans Moreau of the Department of Pathology, studied and described the molecular profile of 106 colorectal tumors from Lynch Syndrome (LS) patients - with focus on the *MSH6* tumors – using NGS (part WES and part cancer hotspot panel).
- Compared to other LS colorectal tumors, *MSH6*-associated colorectal tumors displayed an abundance of MMR-deficiency signature-associated point mutations, but contained fewer MMR-deficiency signature-associated insertion/deletion variants. These findings introduce the hypothesis that *MSH6*-associated CRCs are less sensitive to immunotherapies and frameshift peptide-neoantigen-based vaccines as compared to other LS subgroups, as microsatellite instability (accumulation of insertion/deletion variants) is one of the biological biomarkers for immunotherapy response. Future research in which, among other things, the immune response in these tumors is mapped is therefore of great importance.
- Another relevant finding involved the lower frequency of *CTNNB1* variants in *MSH6*-associated colorectal tumors versus *MLH1*-associated colorectal tumors. It is believed that *CTNNB1* variants are responsible for an invasive growth pattern, hypothetically leading to the development of post-colonoscopy tumors. The relatively low abundance of *CTNNB1* variants in *MSH6*-associated colorectal tumors could therefore explain the relatively low (15%) prevalence of post-colonoscopy tumors in *MSH6* variant carriers. The prevalence of post-colonoscopy tumors in carriers of *MLH1/MSH2* variants is around 45%. This suggests that surveillance intervals, as previously proposed for *PMS2* carriers (post-colonoscopy tumor incidence of 0%), may be extended for *MSH6* carriers.

In the clinic

ERN GENTURIS tumour surveillance guidelines for individuals with neurofibromatosis type 1. Carton *et al.* (2023). *EClinicalMedicine*; doi: 10.1016/j.eclinm.2022.101818.

- Members of the European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS) conducted a comprehensive literature review to develop guidelines on tumour surveillance in neurofibromatosis type 1 (NF1) patients.
- Aims to integrate evidence, information from patient representatives and expert opinion into information that will assist healthcare professionals.
- The guidelines proposed are not prescriptive and may be adapted to the local healthcare system.

- Guideline recommendations on surveillance protocol, including type, age and interval of surveillance, and the grade of recommendation (strong: expert consensus and consistent evidence; moderate: expert consensus with inconsistent evidence; and weak: expert majority decision without consistent evidence), are included for:
    - Optic pathway glioma
    - Brain or spine glioma
    - Cutaneous neurofibroma
    - Plexiform neurofibroma
    - Orbital & Periorbital Plexiform neurofibroma
    - Malignant peripheral nerve sheath tumour + Atypical neurofibromateous neoplasm of uncertain biologic potential
    - Juvenile myelomonocytic leukaemia
    - Breast cancer
    - Phaeochromocytoma and paraganglioma
    - Glomus tumours of the digits
    - Gastrointestinal stromal tumour
- Guidelines on breast screening recommend annual MRI between age 30-50 years, or mammography if MRI is not available, followed by national breast screening from age 50, in line with the general population.
- NF1 has a major impact on the quality of life and mental health of the patient and their family, and as such it is strongly advised to have a psychologist as part of the MDT to support them with decision making and any negative effects on their wellbeing.
- Gaps in knowledge and a range of further research needs were identified, including the course of some NF1 manifestations, evaluation on the impact of psychological support on patients and the expected effects of increased screening on outcome.

Following this, on the 5/6/23, the UKCGG released a statement on recommendations for breast surveillance in patients with NF1.

- Women with NF1 are offered moderate risk breast screening.
- Level of increase BC risk in NF1 patients, reported in several studies, falls within the moderate risk category as defined by NICE guideline CG164.
- Moderate risk breast screening comprises annual mammography between 40-49 years of age, followed by entry into the National Breast Screening programme at age 50.
- If there is additional family history of breast cancer then an individualised assessment could move them into the high risk category.

Counselling and ethics

A survey of genetic and palliative care health professionals' views of integrating genetics into palliative care. White *et al.* (2023). *European Journal of Human Genetics*; DOI: https://doi.org/10.1038/s41431-023-01409-6

- In a palliative setting, the main clinical benefit of genetic counselling is for relatives, rather than the patient themselves. Providing patients with this care can encourage DNA storage or genetic testing, and to manage future disease risk for families.

- Palliative patients can also experience personal or psychological benefits to genetics care such as addressing concerns, making meaning from their illness or providing reassurance that family members will be cared for.
- A quantitative survey was designed to assess genetic and palliative care health professionals' attitudes towards integrating genetics care into palliative care services. This was carried out in Australia.
- Key areas such as frequency of genetic activity, previous training, barriers, resources and tools were assessed.
- 73 completed responses were received (response rate of 6%)
- Palliative health professionals only occasionally performed exercises such as taking a family history and making a risk assessment, and rarely requested genetic testing or DNA storage. Almost all had not received genetic risk assessment training.
- The most frequently selected perceived barrier was palliative care health professionals' lack of knowledge on genetic testing and DNA storage.
- Suggested facilitators included developing referral templates and fostering closer working relationships.
- The majority of participants agreed that palliative patients may experience positive emotional benefits from genetic counselling and testing, and that this would be important for relatives.
- Genetics health professionals indicated that those with palliative care needs were under-referred to Genetics services.
- Mainstream models may disrupt pathways between genetics and palliative services as there is misunderstanding of the roles of each team.
- This study identifies some of the barriers and facilitators to support the integration of genetics into the routine care of people with palliative needs.

Summary of the experiences, knowledge, medical management, and family communication of monoallelic MUTYH carriers. McKenna *et al.* (2022). *Journal of Genetic Counseling*; doi: 10.1002/jgc4.1641.

- Pathogenic/likely pathogenic *MUTYH* variants are one of the most common findings on multigene cancer panels.
- 1-2% of the population are monoallelic *MUTYH* carriers.
- This study aims to understand the patient experience and understanding of these results, and whether they influence medical management or familial communication.
- 49 monoallelic *MUTYH* carriers, recruited from the Prospective Registry of Multiplex Testing (PROMPT), completed a cross-sectional self-report survey on:
    - sociodemographic characteristics
    - medical and family history
    - experiences with *MUTYH* genetic testing
    - genetics and *MUTYH* knowledge
    - perceived cancer risk
    - familial communication
- The National Comprehensive Cancer Network (NCCN) provides the only recommendation to date to address monoallelic *MUTYH*-associated risk, recommending earlier and more frequent screening only for carriers with a family history of CRC in a first degree relative.

- 61% reported satisfaction with how their healthcare provider managed their genetic result.
    - The information was given to participants from a range of healthcare professionals.
    - Of those given their results by a genetic counsellor, 69% were satisfied with their healthcare provider's knowledge and management.
    - 39% reportedly being unsatisfied with their healthcare provider's knowledge and management highlights the need for better clinician education on the management of these patients such that they can give clear information to patients.
- 65% reported that they'd been recommended colonoscopy based on the result.
    - 63% of these individuals had no personal or family history of CRC.
    - 24% of participants had their testing in 2016 or earlier, of note because in 2016 the NCCN recommended earlier colonoscopies for monoallelic *MUTYH* carriers, which was subsequently reversed in 2017.
    - This study cannot deduce how these recommendations were made by healthcare providers, but indicates an area for further research and clear guidance, so that only necessary screening occurs.
- Most participants showed good understanding of *MUTYH* variants; that they are associated with increased risk of colon cancer and colon polyps, and that monoallelic and biallelic carriers have different cancer risks. However, less than half seemed to understand that only biallelic carriers have polyposis.
- The majority (98%) of participants reported their genetic test results with at least some of their relatives, but only 13% of eligible relatives reportedly underwent cascade testing.
    - To the participants with biological children, most shared information with the other birth parent, but only a small number pursued genetic testing.
    - Healthcare providers offering additional resources for family members on how to proceed with genetic testing if they are interested limits the chance of relatives not pursuing cascade testing due to lack of information on how to do so.
- This data is limited by its small cohort, the majority of whom were white females, but highlights areas of improvement in the clinical care of these patients, such as clinician education and communication, and the need for clear surveillance guidance.

Monthly Journal Round-Up brought to you by:

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