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

Translational science

Early Cancer Detection in Li-Fraumeni Syndrome with Cell-Free DNA. Wong *et al.* (2023). *Cancer Discovery*; doi: 10.1158/2159-8290.CD-23-0456.

- This study provides proof-of-principle for a liquid biopsy assay for the early detection of cancer in Li-Fraumeni Syndrome (LFS) patients.
    - The assay integrates a targeted gene panel, shallow whole genome and cell-free methylated DNA immunoprecipitation sequencing.
- 193 blood samples from 89 LFS patients. The TP53 carriers were classified into 3 groups:
    - 42 "LFS Healthy" – TP53 carriers who have never had cancer
    - 21 "LFS Past Cancer"
    - 26 "LFS Active Cancer"
- Targeted sequencing
    - Variant calling identified somatic TP53 variants in 41.9% of cancer positive samples.
    - Combined with shallow WGS, this resulted in a detection rate of 62.5%.
    - This suggests relying on targeted sets of genomic alterations is not sufficiently sensitive.
- Fragment size analysis
    - TP53 carriers exhibit shorter fragments of cfDNA.
    - Fragmentation of cfDNA correlated to the individuals' clinical cancer status. Baseline fragmentation differs between individuals due to genetic and lifestyle factors, so sensitivity could be increased by establishing patient-specific baselines and detection thresholds through their routine bloodwork.
- cfDNA methylation
    - Explored a pan-cancer approach using a universal cancer marker set. Pan-cancer associated methylation detected 65.2% of late-stage cancers and 42.9% of early-stage cancers.
    - The study built a breast-cancer specific methylation classifier and found 24 differentially methylated regions in individuals with active breast cancer, compared to individuals with active non-breast cancer and healthy controls.
    - Using this breast cancer signature, 57 LFS samples scored positive for cancer, 18 of which were actually cancer positive, 12 of which were breast cancer. Results suggest there may be some cancer-type crossover.
- Multi-modal analysis
    - Combined analysis detected a cancer-associated signal in 81.6% of LFS patients with active cancer (about a 32-56% improvement over each individual analysis), increasing to almost 92% in those with late-stage cancers.
- The study also compared ctDNA analysis within phenoconverters (16 individuals that transitioned from cancer negative to positive, positive to negative or developed multiple cancers during the study period) and found multi-modal analysis of cfDNA outperformed or was contemporary with current clinical screening modalities.

    - Cancer-associated signal was detected for 35.6% of clinically cancer-free patients, wherein the participant subsequently developed a cancer or suspicious finding on imaging follow-up.
    - Cancer-associated signal was also detected for 30.1% of clinically cancer-free patients with no subsequent clinical finding. However, combining ctDNA analysis with imaging surveillance may help increase sensitivity and decrease rate of false positives for both methods.
- Individually, each investigation was able to detect cancer-associated signals, but often lacked sensitivity. Combined analysis increased detection rate in patients with an active cancer diagnosis over uni-modal models. This method was able to detect cancer-associated signal in carriers prior to diagnosis with conventional screening.
- Overall positive predictive value = 67.6% (54.2% in clinically cancer-free patients)
- Overall negative predictive value = 96.5% (95.4% in clinically cancer-free patients)
- The results suggest multimodal liquid biopsy is beneficial and complementary to management of LFS patients.
- It would be interesting to assess the effect of liquid biopsy on the psychosocial impact of current surveillance programs.

Germline EGFR Mutations and Familial Lung Cancer. Oxnard *et al.* (2023). *Journal of Clinical Oncology.* doi: 10.1200/JCO.23.01372.

- This prospective study aimed to characterise the clinical phenotype of patients and families with germline *EGFR* pathogenic variants.
- 141 participants enrolled.
- In confirmed or obligate carriers of a germline *EGFR* pathogenic variant (PV; n=90), 55% were affected with lung cancer, with 52% diagnosed by age 60 years.
    - More than half were never smokers.
- Among *EGFR* -PV carriers, 25% had lung nodules.
    - Including a 28-year-old with >10 nodules.
- Penetrance of germline PVs was variable within and among kindreds.
    - High in one family carrying germline *EGFR* R776H.
- *EGFR* T790M
    - 58% of carriers of this variant were from the US South.
    - Shared genomic segment analysis of the 46 participants carrying this variant identified a cluster of 41 distantly related individuals with clear evidence of a shared 4.1Mb haplotype surrounding the variant, suggesting a shared ancestor 223-279 years ago.
- Somatic genotyping of 37 participants with lung cancer and a germline PV showed 35 (95%) had an *EGFR* comutation.
    - Tumour NGS (n=19) showed *EGFR* was the most commonly mutated gene (89%), excluding the known germline PV, followed by *TP53* (47%).
    - 14 patients with lung cancer and germline *EGFR* T790M received treatment with osimertinib, a next generation *EGFR* inhibitor with potent activity against *EGFR* T790M, without any excess toxicity. The study suggests this agent could be studied as a potential cancer interception strategy for patients with *EGFR* T790M and growing lung nodules.

In the clinic

Prevalence and significance of DDX41 gene variants in the general population. Kovilakam *et al.* (2023). *Blood*. doi: 10.1182/blood.2023020209

- Germline *DDX41* variants are linked to myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML).
- This study looked at the frequency and significance of different *DDX41* variants in over 450,000 UK Biobank participants.
    - Identified 452 novel nonsynonymous DNA variants in ~3500 individuals.
- Germline pathogenic variants in *DDX41* are relatively common in the general population (~1 in 429).
    - This may need to be considered when selecting donors for stem cell transplantation.
- P.M1? (Start loss variant) and p.D140Gfs*2 were relatively common (n=218 and n=258, respectively) but only present in participants of European ancestry, as were several other variants at lower frequency.
- 55 non-synonymous variants were unique to participants of non-European ancestry.
- 1,059 individuals had pathogenic germline DDX41 variants, of which 34 developed MDS/AML.
    - 7 of 218 had start-lost variants, 22 of 584 had truncating variants, and 5 of 257 had missense variants.
    - Absolute risk of MDS/AML in *DDX41*-GPV carriers was 3.21%.
- Significant associations of *DDX41* PVs with MDS, AML and family history of leukaemia were found.
    - No association with lymphoma, myeloproliferative neoplasms, or other cancers were found.
- No increased prevalence of clonal haematopoiesis (when haematopoietic stem cells start making blood cells with the same genetic mutation).
    - Unlike sporadic MDS/AML, *DDX41*-mutant MDS/AML does not commonly evolve from pre-existing clonal haematopoiesis, but follows a distinct evolutionary path.
- The study found no increase in somatic mutations in *DDX41*-GPV cases of AML compared to sporadic AML, and thus ruled out genomic instability as a driver of leukemogenesis in *DDX41*-mutant AML.
- *DDX41*-GPV carriers with higher mean cell volume and somatic *DDX41* mutations in blood DNA are at higher risk of progression to MDS/AML and should be monitored.
    - The study proposes that *DDX41*-GPV carriers after age ~40 with a rise in MCV should have further investigations, and routine monitoring for *DDX41* somatic mutations should be considered.

Counselling and ethics

The right not to know: Non-disclosure of primary genetic test results and genetic counselors' response. Murphy *et al.* (2023). *Journal of Genetic Counseling*; 00, 1-13. https://doi.org/10.1002/jgc4.1797

- Some patients who choose to go ahead with genetic testing later indicate that they do not wish for their results to be disclosed to them, despite careful pre-test genetic counselling about the implications of the test and the results
- Bioethical frameworks can be used to help clinicians approach these scenarios, such as the core principles of autonomy, non-maleficence, beneficence and justice
- A patient's ability to deny receiving relevant health information is known as "the right not to know" (RNTK) and creates tension between the core principles. This leads to debates around when, and to what extent, RNTK should be used in healthcare
- RNTK is a key bioethical consideration in clinical genetics practice, and is more ethically complicated when the results are medically actionable whether these are primary or secondary findings
- This study aimed to describe cases where patients requested non-disclosure of primary findings, or disclosure to another person, and how genetic counsellors responded to this
- 11 genetic counsellors took part in interviews about their experiences of non-disclosure and the most common request was that results were disclosed to another person. The majority of the cases discussed related to cancer genetic testing
- In around half of cases, requests to disclose the result to another person were granted. In the other half of cases, patients were encouraged to reconsider testing or joint disclosure was offered
- For those who request that the result was disclosed to no-one, the responses varied widely. Some convinced patients to receive their results, some put the result in an envelope or waited for the patient to come back to them. In only one case, the results were not disclosed at all
- Factors that influenced genetic counsellors to grant a patient's disclosure request included: poor prognosis, negative genetic results and the relationship with the patient/family. Factors influencing genetic counsellors to not accept the disclosure request included having positive results, having a negative relationship with the patient, or having concerns about the legality of the situation
- Five themes emerged from the interview content: clinician understanding of patients' requests, the role of prognosis/medical actionability, relationships, legality and availability of electronic patient medical records
- More work is needed to establish whether there should be standard practice in these scenarios, and to understand why non-disclosure situations appear to be more common in cancer genetic counselling
- The authors note that there are limitations to this study due to sample size, self-selection bias and all participants being female and based in the USA

Monthly Journal Round-Up brought to you by:

Izzy Turbin, Principal Genetic Counsellor, Addenbrooke's Hospital, Cambridge
Nancy Whish, STP Trainee Genetic Counsellor, Addenbrooke's Hospital, Cambridge
Alice Coulson, Genetic Counsellor, GOSH, London

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