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

In the clinic

Update of penetrance estimates in Birt-Hogg-Dubé syndrome. Bruinsma *et al.* (2023). *Journal of Medical Genetics*; 60:317-326. doi: 10.1136/jmg-2022-109104.

- Burt-Hogg-Dubé (BHD) syndrome is caused by autosomal dominantly inherited variants in the FLCN gene. BHD patients are at increased risk of fibrofolliculomas, pulmonary cysts, pneumothorax and renal cell carcinoma, with some debate about whether colonic polyps should also be included in this list.
- This review pooled pedigree data from studies that recruited families carrying FLCN variants (pathogenic or likely pathogenic) and conducted segregation analysis to estimate the cumulative risk of each manifestation for carriers of FLCN pathogenic variants.
- 204 families informative for at least one manifestation.
    - 1076 individuals informative for renal tumours.
        - 138 FLCN carriers had been diagnosed with renal tumour (median age of diagnosis was 50 years old).
    - 763 individuals informative for lung manifestations.
    - 767 individuals informative for skin involvement.
    - 221 individuals informative for polyps.
- By age 70 years, risk of each manifestation in FLCN variant carriers were found to be:
    - Renal tumours – 19% for males, 21% for females
    - Lung involvement – 87% for males, 82% for females
        - Average age of diagnosis 39 years old.
    - Skin lesions – 87% for males, 78% for females
    - Colonic polyps – 21% for males, 32% for females
        - Similar to estimates of the prevalence of colonic polyps in the general population.
- There was variable expression and severity of these manifestations.
- These penetrance estimates are important for the genetic counselling and clinical management of patients with BHD syndrome. Rather than research that reports the proportion of their study population with these manifestations, this review gives cumulative risk estimates which are less affected by age distribution of the study sample and are more clinically useful.
- The current analysis does not provide evidence that colonic polyps should be added to the diagnostic criteria, but further research is needed on this issue, and clinicians should be alert to these possible manifestations.

Utility of polygenic risk scores in UK cancer screening: a modelling analysis. Huntley *et al.* (2023). *The Lancet Oncology*; doi.org/10.1016/S1470-2045(23)00156-0.

- PRS scores might enable more efficient targeting of cancer screening and enable extension into new age ranges and disease types.

- This study presents an overview of the performance of PRS tools and the benefits and harms of PRS-stratified cancer screening for 8 cancers.

	Estimated percentage of cases captured by PRS-defined high-risk quintile (20%) of the population	Maximum potential annual deaths averted by extending UK screening programmes to PRS-defined high risk quintile (Including aged 40-49 for BC, aged 50-59 for prostate and aged 60-69 for colorectal cancers).	Maximum potential annual deaths averted by unstratified screening of the full population aged 48–49 years for breast cancer, 58–59 years for colorectal cancer, and 68–69 years for prostate cancer.
Breast	37%	102	80
Prostate	46%	188	155
Colorectal	34%	158	95
Pancreatic	29%		
Ovarian	26%		
Renal	22%		
Lung	26%		
Testicular	47%		

- The paper presents breast, colorectal and prostate cancers as being the most plausible for using PRS stratification (due to stronger PRS predictiveness than other cancers and there being established cancer screening tools) despite only modest potential efficacy gain for hypothetical PRS-stratified screening.
- A modest number of deaths could be averted by introduction of PRS-stratified screening as opposed to screening an equivalent sized group at the upper end of the respective age range.
- These maximum numbers are estimated under favourable assumptions (full population uptake for PRS profiling and subsequent cancer screening) and would be substantially attenuated by incomplete population uptake of PRS profiling and cancer screening, interval cancers, non-European ancestry, and other factors.
- Other favourable assumptions and methods which limit this analysis include:
    - That all cancers that are expected to occur within the screening interval are present at the time of screening.
    - Use of real-world screening tools that are superior to those currently implemented in the UK.
- Lifetime risk in high-risk groups for less common cancers such as pancreatic, renal and ovarian were elevated but still modest.
    - For example, estimated lifetime ovarian cancer risk in the PRS-defined top 1% of high risk females was 3.5% which would not meet the 5% threshold for prophylactic salpingo-oophorectomy.
- Restriction of smaller, high-risk quantiles increases the enrichment for cancer but also increases the absolute numbers of cancers missed in the PRS-defined low-risk group. This

would lead to a substantial proportion of incident cases being excluded from PRS-stratified screening programmes because they arise in individuals assigned as low-risk by PRS.
- There is potential harm to the population in being assigned as high or low risk. Also, PRS stratification does not attenuate the challenges and limitations of cancer screening programmes.
- PRS-tools are significantly derived from GWASs with participants of predominantly western European ancestry. Therefore, proposed PRS-based screening programmes will not equivalently serve non-European populations and existing inequalities in screening participation could be exacerbated.
- More research is needed to understand the real-world clinical impact, costs and harms of screening in this way.

Counselling and ethics

Pilot study of a culturally sensitive intervention to promote genetic counselling for breast cancer risk. Henderson *et al.* (2022). *BMC Health Services Research*; 22: 826. https://doi.org/10.1186/s12913-022-08193-x

- Despite benefits of genetic counselling and testing, uptake in cancer genetics services can be low. The underrepresentation of ethnically and socioeconomically diverse populations in genomics is well-characterised
- Decision aids can be useful in promoting positive health behaviour change and informed decision-making. Little work has been done to understand decision-making processes in ethnic minority women, or to develop culturally tailored decision aids
- A culturally sensitive, narrative decision aid was developed to promote uptake of genetic counselling among Black women at risk for a hereditary breast cancer syndrome. This was developed through semi-structured interviews and story circles with Black women, along with one-to-one interviews. It is a six minute video which tells the story of a Black woman who is referred for genetic counselling
- 30 participants viewed the video, and completed pre and post survey questionnaires. The questionnaires assessed intentions, knowledge, perceived normative beliefs, barriers, self-efficacy, attitudes, and environmental complaints
- 50% of participants indicated that they were extremely likely to attend a genetic counselling appointment, compared with 70% after viewing the video. 50% of participants felt watching the video had changed their mind on genetic counselling
- Before watching the video, 77% of participants believed they family would be interested in learning about genetic counselling. This increased to 94% after watching. The proportion of people who believed they had barriers to attending an appointment decreased after watching the video
- As this study took place in America women expressed worry about the cost of medical care and that they may not know how much an appointment would cost.
- Most participants enjoyed watching the video and felt they could relate to the characters. Changes were suggested such as giving more details about the personal benefits and limitations of genetic counselling
- The authors note that there are some limitations to this study. This includes small sample size, and uncertainty around whether this intervention would have the same effect for those from different ethnicities.

Psychological impact of risk-stratified screening as part of the NHS Breast Screening Programme: multi-site non-randomised comparison of BC-Predict versus usual screening. French *et al.* (2023). *British Journal of Cancer;* 128:1548-1558. doi.org/10.1038/s41416-023-02156-7.

- Offering risk stratified screening can provide women at high risk of BC with additional screening, but there is concern that it could also increase harms such as anxiety and cancer worry.
- This study aimed to assess whether there were difference in self-reported harms and benefits between women offered risk stratified breast cancer screening (BC-Predict) compared to those offered standard screening as per the NHS Breast Screening Programme.
- Part of the larger PROCAS2 study.
- 5901 women invited to participate and offered BC-predict or NHSBSP. 662 consented to the study. Women who chose BC-predict received a 10 year risk estimate:
    - High – 8%
    - Above average – 5-7.99%
    - Average – 2-4.99%
    - Below average - <2%
- Questionnaires were given at baseline, 3 months and 6 month and collected data on state anxiety, breast cancer worry, knowledge of and attitudes towards screening, satisfaction with the information and demographic and clinical information.
- Women who accepted the offer of BC-Predict did not significantly differ from those who declined this offer on variables including age and state anxiety, however they were from less deprived areas, had higher screening knowledge, lower risk perceptions and less worry about cancer.
- Women's' risk perceptions and cancer worry changed in line with the risk estimates they were provided.
- Baseline levels of anxiety and cancer worry were the strongest predictor of psychological response.
- Women who took up BC-Predict screening and were categorised as high risk reported higher risk perceptions and cancer worry than other women, but this did not reach clinical levels.
- It has been previously suggested that risk stratification of screening would lead to increased understanding of screening but this study did not find evidence to support this; BC-Predict participants did not report increased cancer screening knowledge.
- This study concludes that risk stratified screening is unlikely to produce psychological harms in the women it is offered to.

Monthly Journal Round-Up brought to you by:

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