**Assessment of a Polygenic Risk Score in Screening for Prostate Cancer,** McHugh et al. (2025), *The New England Journal of Medicine,* 392 (14), 1406- 1417, doi: 10.1056/NEJMoa2407934

Screening by prostate-specific antigen (PSA) has been to have a high false-positive rate. GWAS have identified common germline variants, which can be used to calculate a polygenic risk score (PRS) associated with prostate cancer risk.

**Methods**

- BARCODE1 study (March-July 2019) calculated polygenic risk scores (PRS) for 6393 participants (aged 55-69). Participants were recruited through primary care in the UK.
- The PRS was derived from 130 variants known to be associated with an increased risk of prostate cancer.

**Results**

- Out of the 6,393 participants who were genotyped, 745 had a PRS in the 90$^{th}$ percentile or above
- 62.8% of those who had a PRS in the 90$^{th}$ percentile or above, underwent MRI and biopsy
- The mean age of participants was 61.2 years and 20.9% reported a family history of prostate cancer
- In 40% (187) of participants who underwent an MRI and biopsy, prostate cancer was detected. Of the participants diagnosed with prostate cancer, 55.1% had a cancer classified with a Gleeson score of at least 7 (intermediate or higher), warranting clinical management. 71.8% of these patients would have had a missed diagnosis with the standard diagnostic pathway.
- Of the cancers detected by biopsy, 21.4% of participants had a cancer that was classified as unfavourable intermediate or, high or very high risk, warranting radical treatment. 42.5% would have had a missed diagnosis with the standard criteria.
- Of the 187 participants diagnosed with prostate cancer following a biopsy and MRI, 100 had either a high PSA level or a lesion with a PI-RADS score of 3 or higher. Only 30 met both thresholds for PSA levels and lesion score, therefore, meeting the standard criteria for biopsy
- The PRS was compared to the 10-year risk calculated based on age and family history of the prostate cancer. Almost all participants with PRS in the 90$^{th}$ percentile or above had a 10-year-risk above 3.8%. Others with a 1 year-risk above the threshold of 3.5-4% but lower PRS, had a FH of prostate cancer. This shows that PRS supplements risk stratification and does not replace known risk factors.

**Conclusion**

- The study showed the use of PRS in detection of prostate cancer, including those warranting clinical management in 55.1% of participants or radical treatment in 21.4%.

- Around 42.5% of participants would have had a missed diagnosis if they followed the standard pathway. Further research is needed into the recommended age of PRS, replication gin non-European ancestry groups and evaluating the economic effects.

**Cytogenetic Signatures Favouring Metastatic Organotropism in Colorectal Cancer,** Golas et al. (2025), *Nature Communications,* 16, doi*:* 10.1038/s41467-025-58413-1

**Background**

- Colorectal cancer (CRC) accounts for ~10% of cancer-related deaths globally, with metastasis driving mortality. This study investigates metastatic organotropism—the pattern of CRC spreading to specific organs such as liver, lung and brain.
- Cytogenetic events such as chromosomal imbalances (CI) in CRCs favours site specific metastatic colonization of cancer cells. These site enriched CI patterns can serve as biomarkers for metastatic potential in precision oncology.
- Evidence suggests that metastasis is not just governed by passive mechanical forces but rather involves an active modulation of the secondary site microenvironment by cancer cells. This leads to formation of permissive metastatic niche which promotes tumour cell survival.
- However, the genetic determinants of metastatic organotropism in CRC remain poorly defined, particularly in the context of chromosomal imbalances.

**Methods**

- This study integrated data from three cohorts: CRCTropism (n=314 tumours), MSK MetTropism (n=3,548 tumours), and TCGA (used for transcriptomic and proteomic validation).
- CRCTropism analysed using high resolution DNA copy number profiling, allowing precise mapping of chromosomal gains and losses. MSK MetTropism performed gene level CNV detection and mutational analysis using NGS and TCGA cohort provided RNA-seq and RPPA data to assess downstream gene expression and protein level effects of identified genomic changes.
- Site-specific enrichment of genetic alterations were visualized using ternary plots (organotrophic maps), which showed the relative frequency of each CI in metastases to different organs.

**Results**

- As a result, chromosomal arm aneuploidies were found to be a major source of DNA copy number aberrations. Brain metastases exhibited the highest burden of chromosomal imbalances with seven specific brain organotrophic CIs which includes +12p (*KRAS*), -3q, and +5q. Whereas, lung metastases had the lowest number of chromosomal arm aneuploidies and focal CIs and showed no exclusive site-specific CNVs.
- This study found enrichment of concurrent *KRAS* mutation and amplification specifically in brain metastases. +12p amplification, encoding *KRAS* alteration was present in 50% of brain metastases, compared to 19% and 17% in liver and lung metastases. These tumours displayed significant upregulation of glycolysis and cell cycle promoting.
- Brain metastases tumours also exhibited higher winter hypoxia scores which is indicative of enhanced adaption to oxygen-deprived environment that is brain.
- Additional co-amplifications of *MDM2* and *CDK4*, both located on chromosome 12, were also more frequent in brain metastases.
- Deletions in DNA repair genes *MLH1* and *BRCA1*, also enriched in brain metastases, were associated with altered gene expression profiles. CRCs with *MLH1* and *BRCA1* deletion

showed upregulation of developmental *HOX* genes, a pattern not explained by CNV but likely driven by transcriptional or epigenetic reprogramming.

- Oncogenetic tree modelling for CRC demonstrated that common alterations like +13q, +20q, and -18q were typically early events in tumour evolution, shared across all metastatic sites.

**Conclusion**

- This study provides evidence that cytogenetic evolution underlies metastatic organotropism in colorectal cancer. The discovery of KRAS mutation combined with amplification as a hallmark of brain metastasis is particularly notable. While *KRAS* mutations are well-characterized drivers in CRC, the amplification of mutant *KRAS* adds a new dimension to tumour aggressiveness and adaptability, particularly under metabolic and hypoxic stress in brain.
- These findings align with prior knowledge of the brain as a metabolically restrictive environment, suggesting that only tumours with enhanced glycolytic capacity and survival mechanisms can successfully colonize it.
- This study found upregulation of glycolysis and cell cycle pathways occurs despite impaired ATR signalling in CRCs with *KRAS* mutation and amplification. This delicate balance between DNA damage and repair capacity may drive the evolution of more aggressive cancer phenotypes.
- The recurrent co-amplification of *MDM2* and *CDK4* may further promote unchecked proliferation and p53 pathway evasion in these aggressive tumours.
- Upregulation of *HOX* genes in MLH1- and BRCA1-deleted CRCs suggests a reversion to developmental programs that enhances cellular plasticity, independent of apparent gene dosage effect which may contribute to the aggressive behaviour of CRC.
- These cytogenetic signatures serve as biomarkers to predict metastatic potential and destination, enabling tailored surveillance and early intervention. Moreover, tumours harbouring KRAS amplifications might represent a distinct therapeutic subclass, possibly responsive to combination strategies targeting metabolism, cell cycle, and MAPK signalling.
- The findings support a punctuated model, where early common alterations set the stage, but organ-specific traits are acquired later, potentially during the metastatic transition. This has implications for the timing of intervention and the window of opportunity for interception.
- This study emphasizes the need for integrated cytogenetic profiling in advanced cancer diagnostics and underscores the potential of CNV-driven biomarkers in personalized oncology.

**Germline Pathogenic DROSHA Variants Are Linked to Pineoblastoma and Wilms Tumour Predisposition,** Fiorica et al. (2025), Clinical Cancer Research, 31 (8), pp. 1491-1503, doi: 10.1158/1078-0432.CCR-24-2785.

**Background**

- DROSHA, DICER1 and DGCR8 play an important role in miRNA processing and mutations in these genes are associated with multiple cancers, including Pineoblastoma and Wilm's Tumour.
- Germline Pathogenic Variants (GPVs) in DICER1 and DGCR8 have previously been reported to increase tumour risk. However, no such association has been identified between DROSHA GPVs and tumour predisposition.
- This study presented 9 patients from 8 families with Pineoblastoma or Wilms tumour and their germline and tumour DNA was analysed. The study aimed to identify the association between DROSHA GPVs and increased predisposition to Pineoblastoma and Wilm's tumour.
- The study further investigated the impact of DROSHA GPVs on paediatric and adult-onset cancers in large datasets and estimated the population prevalence and penetrance of germline DROSHA loss of function variants by analysing germline data from large databases like The Cancer Genome Atlas (TCGA), Childhood Cancer Survivor Study (CCSS), St Jude PeCan Portal, UK Biobank, OpenPedCan and Geisinger DiscovEHR.

**Results**

- In eight out of the nine probands, a somatic second DROSHA loss of function variant was observed in the tumour and no patient had any additional GPVs in DICER1 or DGCR8 or any other gene associated with Pineoblastoma or Wilms tumour predisposition (Results summarised in Table 1). Biallelic inactivation of DROSHA was confirmed in families 1, 3, 4, 6, 7 and 8 based on the occurrence of an acquired somatic loss of heterozygosity or loss of function DROSHA variant in trans to germline variants.
- These results, along with previous studies, indicate that GPVs in DROSHA are associated with a novel autosomal dominant cancer predisposition to Pineoblastoma and Wilms tumour, which phenocopies DICER-1 tumour-related predisposition. This observation is supported by the fact that Pineoblastoma in most of the patients in the cohort were confirmed to be PB-miRNA1 subtype via methylation or chromosomal data.
- Further, various Paediatric and adult tumour datasets were investigated to identify additional DROSHA GPVs. No additional germline loss of function DROSHA variants were identified in CCSS and St Jude PeCan portal (overlap could not be excluded). Additionally, they investigated the association between DROSHA GPVs and adult-onset cancer risk but no significant loss of heterozygosity or acquired somatic DROSHA mutation was observed in the tumour DNA for adult patients in the TCGA cohort.
- Analysis of large-scale germline databases highlighted the rarity of DROSHA GPVs in the human population and suggested that DROSHA is not a common driver of adult-onset cancers.

Table 1: Summary of results for the nine patients from eight families with Pineoblastoma and Wilms tumour

| Family | No. of Probands | Diagnosis | Age at Dx | Germline DROSHA Variant | Somatic Second Hit | Biallelic Inactivation | Subtype | Family History |
|---|---|---|---|---|---|---|---|---|
| 1 | 2 | Pineoblastoma | 6 | DROSHA c. 811C>T (p. Arg271Ter, nonsense) | DROSHA c. 795C>G (p. Tyr265Ter, nonsense) | Yes (in trans) | Not specified | 1st cousins; both mothers unaffected |
| | | Pineoblastoma | 5 | DROSHA c. 811C>T (p. Arg271Ter, nonsense) | Not available | Could not be confirmed | Not specified | |
| 2 | 1 | Pineoblastoma | 8 | DROSHA c. 2883-1G>A (splice acceptor) | DROSHA c. 2683-1G>T (splice acceptor); chr5 loss (tetraploid) | Suggestive | PB-miRNA1 | Paternal cousin with medulloblastoma |
| 3 | 1 | Pineoblastoma | 7 | DROSHA c. 403_409delinsC CACTT (p. Ala135Leufs*9, frameshift) | Same variant with LOH (VAF = 0.81) | Yes | PB-miRNA1 | None reported |
| 4 | 1 | Pineoblastoma | 11 | DROSHA c. 3261+1G>C (splice donor) | Same variant with LOH (VAF = 1.00) | Yes | PB-miRNA1 | Not available |
| 5 | 1 | Pineoblastoma | 15 | DROSHA c. 3548del (p. Asn1183Ilefs*8, frameshift) | DROSHA c. 1869del (p. Phe623Leufs*3, frameshift) | Likely (phase unknown) | PB-miRNA1 | Uterine/ovarian and pancreatic cancers |
| 6 | 1 | Wilms tumour (bilateral) | 3 | 1.29 Mb deletion of 5p13.3 including DROSHA | DROSHA c. 147_148delinsA T (p.Gln50Ter, nonsense; VAF = 0.8) | Yes | Not specified | Maternal ATM variant; grandmother with BC; asymptomatic father with 5p13.3 deletion |
| 7 | 1 | Pineoblastoma | 21 | DROSHA c. 2436_2439del (p. Asp814Asnfs*19, frameshift) | Copy-neutral LOH | Yes | Not specified | Mother had Ewing sarcoma and carried same 4bp deletion |
| 8 | 1 | Pineoblastoma | 8 | DROSHA c. 2988C>A (p. Glu1033Ter, nonsense) | Whole-gene deletion | Yes | PB-miRNA1 | None reported |

**Conclusion**

- Results of this study could have potential prognostic importance as miRNA altered subtypes of Pineoblastoma have a significantly better prognosis compared to other subtypes.
- Further research is imperative to develop clinical guidelines and recommendations and therefore genetic testing for DROSHA GPVs is recommended for all patients diagnosed with Pineoblastoma, especially those whose methylation profile indicate PB-miRNA1 or PB-miRNA2 subtypes.
- Genetic counselling and testing recommended for first-degree relatives and close neurological follow up advised up to the age of 21 for individuals with DROSHA GPVs. Considering the limited availability of data, further research is required to define surveillance recommendations for carriers of DROSHA with or without Pineoblastoma in first-degree relatives. It is also advisable to include DROSHA in hereditary Wilms tumour panels.

**Natural history of medullary thyroid carcinoma in MEN 2 patients carrying a variant at codon 804 in the RET proto-oncogene: A study by the French Neuroendocrine Tumor Group (GTE),** Suteau et al. (2025). Annales d'Endocrinologie; 86 (2), doi: 10.1016/j.ando.2025.101705.

- **Background:** RET variants at codon 804 are part of the low to moderate risk group in the American Thyroid Association (ATA) classification system, with recommendation for risk-reducing thyroidectomy beyond the age of five. However, there is much variation in the aggressiveness of thyroid cancers in individuals carrying these variants.

- **Aim:** The study objective was to report on a large cohort of French carriers of a pathogenic variant at codon position 804 in the RET proto-oncogene.

- **Methods:** Patients from 12 university hospitals with a RET 804 variant were recruited in a retrospective non-interventional French national study, from the French GTE-ENDOCAN-RENATEN database. Incidence and severity (TNM stage and calcitonin levels) of medullary thyroid carcinoma (MTC), phenotype-genotype correlation and clinical outcome were assessed.

- **Results:** 322 patients were studied. Index cases (n = 65) had a median age at diagnosis of57 years (range: 46–66), and relatives (n = 257) a median age of 37 years (range: 18–51). Median first calcitonin measurement was 240 ng/L (range: 79–1344) in index cases, and 6.7 ng/L (range: 0–22) in relatives. In index cases, the pathogenic variant c.2410G>A (p.Val804Met) in RET was more frequent (80%of cases) than c.2410G>C or c.2410G>T (p.Val804Leu). MTC was multifocal, node-positive and metastatic in 64%, 51% and 20% of cases respectively. TNM stage, preoperative calcitonin level and male gender were predictive of persistent disease (defined by postoperative calcitonin > 5 ng/L) ($P < 0.001$). Ten-year disease-free survival (DFS) was 61%. In total, 113 relatives were operated on: 62% with MTC and 34%with isolated C-cell hyperplasia (CCH); the youngest patients were aged 20 for MTC and 4 years for CCH. Ten-year DFS was 90%.

- **Conclusions:** RET pathogenic variants affecting codon 804 mainly led to low aggressiveness disease, with late presentation and prolonged DFS. The authors suggest surgery in relatives if calcitonin values are above 6 ng/L, instead of 10 ng/L. Long-term surveillance is recommended to be mandatory, since recurrence remains possible several years after surgery.

- **Reflections for practice:**

    - This paper adds to the growing evidence around the presentation of MTC and age-related penetrance in carriers of RET codon 804 pathogenic variants.
    - Incidental findings of variants at this codon have increased in the UK in recent years primarily as a result of the 100,000 Genomes Project and Whole Genome Sequencing testing methodologies.
    - Assessing the ideal timing for risk-reducing thyroidectomies is a challenge for multi-disciplinary teams caring for children and adults with RET codon 804 variants, particularly when identified as an incidental finding with no background family history of MEN2-related tumours.

- Hopefully the increasing evidence base for these and other low to moderate RET variants will inform national and international consensus recommendations around risk-reducing surgery and tumour surveillance.

**From science to sensory art: an inclusive pedagogical tool for the UK blind, low-vision and diverse-needs community to increase cervical cancer awareness,** Arunthavalingam et al. (2025), *Immunology and Cell Biology*, 103 (4), p. 341-349, doi: 10.1111/imcb.70010

Complex concepts, such as HPV and cervical cancer, is largely inaccessible to blind, low-vision and diverse-needs (BLVDN) communities. One way to bridge the gap is through tactile art, increasing understanding and accessibility.

**Methods**

- University students in Cambridge paired with artists to recreate a sensory model of the HPV developing into cervical cancer. This formed part of the Sensory Science Cambridge exhibition at the Cambridge Festival in March 2024
- A diorama was created to increase the understanding of the development of cervical cancer in BLVDN communities. This was a multi-panel artwork to show; normal, uninfected cervical cells, disease progression from low-grade to high-grade, cervical cancer and metastasis

**Results**

- The artwork improved participant understanding, indicating that the use of braille, explanatory panels and verbal descriptions can facilitate understanding of complex concepts
- By using familiar materials and yellow colour scheme increased accessibility for those with low vision
- By developing different resources for the public, can increase awareness and scientific literacy. It is important for individuals to understand the disease, risk factors and available preventative measures.
- According to RNIB, about 7% registered blind or partially sighted people can be read braille. Therefore, by incorporating a multi-sensory approach with verbal explanations ensures everyone is included.

**Conclusion**

- By working with schools and charities, further resources can be created that may also incorporate high quality braille, interactive buttons, other technologies.

**Monthly Journal Round-Up brought to you by:**


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