COMMENT

# The European Journal of Human Genetics is turning 30: a selection of major cancer genetics papers published by the Journal

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## INTRODUCTION

Genetic susceptibility to cancer has been a strong point of the European Journal of Human Genetics from the beginning. With the generalization of next-generation and exome sequencing, the identification of new cancer-predisposing genes, the advent of personalized oncology, and the increase in referrals to cancer genetics clinics, it is more than ever a hot topic. Here is a selection of four major cancer genetics papers published by the journal in the past few years, in no particular order.

## MAINSTREAMING GERMLINE *BRCA1/2* TESTING IN NON-MUCINOUS EPITHELIAL OVARIAN CANCER IN THE NORTH WEST OF ENGLAND. FLAUM N. ET AL., 2020 [1]

In the field of genetic susceptibility to breast and ovarian cancer, pioneers come from the United Kingdom. Forecasting the advent of PARP-inhibitors for the treatment of *BRCA1/2*-associated cancer, specialists at the Royal Marsden in London were among the first to develop mainstreaming pathways for *BRCA1/2* germline testing [2, 3]. Mainstreaming allows trained oncologists and surgeons to prescribe rapidly germline analysis to breast and ovarian cancer susceptibility genes, bypassing the need for systematic referral to already-overburdened cancer geneticists. As a result, more pathogenic variant (PV) carriers are identified. They can then benefit from personalized treatment with PARP-inhibitors and personalized long-term management. At-risk relatives are then offered genetic testing, this time through dedicated cancer genetics clinics.

In this article, teams from Manchester reported the benefits of mainstreaming in women with non-mucinous epithelial ovarian cancer [1]. After its introduction, the monthly rate of newly identified *BRCA1/2* PV carriers increased 2.7 fold. The vast majority of PV carriers (35/39) had been referred to cancer genetics clinics. In addition, 31 first-degree relatives had undergone presymptomatic testing at the time of writing, albeit the rate of uptake was lower than with standard genetics-led germline testing.

This article focused specifically on ovarian cancer cases. Solid evidence has now emerged of the benefit of PARP-inhibitors in breast and pancreatic cancer associated with germline *BRCA1/2* PV [4–6]. The number of patients eligible for germline testing is increasing dramatically as a result. It would be unrealistic to expect cancer genetics services to see all these patients. Mainstreaming does seem the best and only way forward, not only in the United Kingdom, but also in other European countries, and beyond.

## ACQUIRED SOMATIC MMR DEFICIENCY IS A MAJOR CAUSE OF MSI TUMOUR IN PATIENTS SUSPECTED FOR "LYNCH-LIKE SYNDROME" INCLUDING YOUNG PATIENTS. LEFOL C. ET AL., 2021 [7]

As a clinical cancer geneticist I have always felt a bit uncomfortable returning a Lynch-like result to a patient. Indeed, there are no data supporting specific surveillance recommendations, not only for the patient but also for first-degree relatives. Thanks to studies such as this one, this diagnosis is becoming rarer.

Lynch-like implies that the patient has unrecognized Lynch syndrome. It usually required that:

- The patient had been diagnosed with a cancer belonging to the Lynch syndrome spectrum, mainly colorectal or endometrial
- The cancer was mismatch-repair deficient (MMRd), i.e. it was characterized by loss of MMR protein expression and/or microsatellite instability, with no *MLH1* promoter hypermethylation in case of MLH1 expression loss
- No germline PV or likely pathogenic variant (LPV) had been identified in the MMR genes (*MLH1, EPCAM-MSH2, MSH6, PMS2*)

Lefol et al. showed that purely somatic double hits in the MMR genes explained 72/113 (63.7%) of MMRd cancers in the absence of germline PV, in a series of colorectal, endometrial, duodenal and sebaceous carcinomas [7]. Remarkably, these observations were made regardless of age at diagnosis. There was therefore a clear explanation to the MMRd, and it did not include a germline event. The Lynch-like label therefore no longer applied. In other words, they could reasonably be considered non-Lynch, sparing index cases and first-degree relatives intensive multi-organ cancer screening, and sometimes risk-reducing surgery. A study from the United States published around the same time drew comparable

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conclusions 8]; double somatic hits were found in 88% of colorectal MMRd cancers whith no MMR germline PV.

Admittedly, a minority of cases still remain Lynch-like. The jury is still out whether they should be managed like bona fide Lynch cases, or according their family history. Nevertheless, the increasing availability and sensitivity of tumour sequencing suggests their number will decrease event further in the future. This is reassuring, as it means less uncertainty for clinical cancer geneticists and for patients.

### VARIANTS IN MEMBERS OF THE CADHERIN-CATENIN COMPLEX, *CDH1* AND *CTNND1*, CAUSE BLEPHAROCHEILODONTIC SYNDROME. KIEVIT A. ET AL., 2018 [9]

Strictly speaking, this may not be primarily a cancer genetics paper. It is however of utmost relevance to cancer geneticists. PV in *CDH1*, the gene coding for the E-cadherin adhesion protein, cause the Hereditary Diffuse Gastric Cancer syndrome (HDGC). HDGC patients have an increased risk of gastric cancer of the diffuse type and of female lobular breast cancer [10]. Prophylactic total gastrectomy, alternatively endoscopic surveillance, and breast cancer screening using MRI are recommended. An excess of non-syndromic orofacial clefts is also observed.

In this paper, the authors confirmed the association of *CDH1* with the rare blepharocheilodontic syndrome (BCDS), only a few months after the original paper [9, 11]. Cleft lip and palate, eyelid abnormalities, hypertelorism, sparse hair and dental abnormalities characterize BCDS. Twelve cases with eight distinct variants were reported. Interestingly, most variants were missense, and thus differed from the classic truncating HDGC variants. They altered highly-conserved amino acids in the extracellular domain, destabilizing as a result interactions with $Ca^{2+}$ ions. Others were splicing variants leading to an exon 7 deletion. These specificities of BCDS-associated *CDH1* variants, added to zebrafish experiments showing severe developmental defects, raised for the first time the hypothesis of a genotype-phenotype correlation.

If there is a genotype-phenotype correlation, it is likely to be only partial. Medical geneticists managing *CDH1*-associated BCDS patients should therefore discuss with their cancer genetics colleagues cancer screening in adults cases. In parallel, cancer geneticists should be aware of a potential risk of malformative syndromes in their *CDH1* families, especially if the causing variant is located in the extracellular domain.

### THE WIDE SPECTRUM OF *POT1* GENE VARIANTS CORRELATES WITH MULTIPLE CANCER TYPES. CALVETE O. ET AL., 2017 [12]

Until recently, cancer geneticists did not collaborate with cardiologists and cardiovascular surgeons, simply because there was no opportunity to do so. With the involvement of *POT1* (Protection of telomeres 1) in cardiac sarcoma susceptibility, things are about to change. In 2017, Calvete *et al*. identified *POT1* LPV/PV in four patients with cardiac sarcoma, either sporadic ($n = 3$) or with a family history suggestive of Li-Fraumeni syndrome but who had tested negative for *TP53* germline testing (Li-Fraumeni-like) [12]. These observations confirmed those of a previous study, where three Li-Fraumeni-like families with cardiac angiosarcoma carried a *POT1* missense variant, with solid evidence for pathogenicity [13]. Interestingly *POT1* LPV/PV were also observed in breast angiosarcoma cases [12, 13].

Cardiac angiosarcomas are rare and aggressive tumours of endothelial origin [14]. In this paper, only two of the four cardiac sarcomas were proven angiosarcomas. The precise type of the other two was not documented. Regardless of an association between *POT1* and cardiac sarcomas in general, of more specifically cardiac angiosarcomas, regular cardiac surveillance seems warranted in LPV/PV carrier, with magnetic resonance imaging and/or echography. When sarcoma is suspected, cases should then be referred to cardiovascular surgeons. Collaboration goes both ways; cardiologists and cardiovascular surgeons should also refer their sarcoma cases to cancer genetics for expert assessment and *POT1* germline testing.

Major advances have been made regarding *POT1* in the past few years. We now know that LPV/PV also increase the risk of melanoma, glioma, and lymphoid - perhaps myeloid—neoplasms [15–17]. Adding cardiac sarcoma to the spectrum makes *POT1*-associated cancer genetic susceptibility even more fascinating. It also shows the importance of a truly multidisciplinary approach to carrier management.

## CONCLUSION

I hope you have enjoyed this selection of cancer genetics papers published by the European Journal of Human Genetics. You might have noticed it was a truly European selection, as authors came from the United Kingdom, France, the Netherlands, and Spain, reflecting the role of European centres, alongside their North-American and Asian counterparts, in the success of the Journal. As a member of the editorial board, I can only look forward to your future submissions. Exciting years lie ahead in the fascinating and ever-expanding field of genetic susceptibility to cancer.

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## COMPETING INTERESTS

I have received honoraria from AstraZenca and MSD (Merck and Co.), the manufacturers of the PARP-inhibitor olaparib.

## ADDITIONAL INFORMATION

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