

## FAMILIAL CANCER CLINICAL UNIT

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### OVERVIEW

The SARS-CoV2 pandemic created an unprecedented situation affecting all human activities and it forced alliances between healthcare workers, academics, scientists, and administrative and government entities around the world, to accelerate our knowledge about the disease and the search for efficient treatments and immunisation. COVID-19 exhibits great clinical and, possibly, populational heterogeneity, in which our genes probably play an important role.

In April 2020, our Unit, together with the Genotyping Unit, set out to identify prognostic markers that could help to stratify the population and allow us to identify *a priori* those subjects who will have a more severe course of Covid-19, in order to focus preventive resources on them and prioritise future immunisation. Since the beginning of the pandemic, various

national and international projects and initiatives have been launched with similar objectives. The *COVID-19 Host Genetics Initiative* (<https://www.covid19hg.org/>) is an international consortium that integrates more than 150 participants. Together with other groups from Spain, we are participating in exploring the role of host genetic factors in the severity of the disease. At the national level, the *ScourGe* consortium was created, made up of more than 70 clinical, research and biobank groups. We are currently analysing the genome of more than 10,000 individuals with different clinical forms of Covid-19.

The goal is to ultimately gather genomic data from many thousands of individuals from different populations to try to identify clinically relevant markers in a disease like Covid-19, whose genetic bases will be difficult to unravel.

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### CLINICAL, DIAGNOSTIC AND RESEARCH HIGHLIGHTS

Since the summer of 2020, the Unit has expanded with 3 new people joining from the Human Genetics Group: Ana Osorio, Alicia Barroso and Victoria Fernández, all 3 involved in the research and diagnosis of hereditary forms of breast cancer. This is the most important change since the Unit's creation and represents a huge reinforcement for our diagnostic and research activity.

Clinical and diagnostic activity during 2020 was also disrupted by the Covid pandemic. For several months the Consultancy in the Fuenlabrada University Hospital had to remain closed. Even so, throughout the year we saw a total of 365 patients (32.1% decrease over 2019). Also, because of the pandemic, the number of genetic studies carried out decreased from over 572 performed in 2019 to 344 during 2020 (39.8% decrease).

Laura Pena left the Unit in November 2019. However, she defended her doctoral thesis in January of 2020. In her work — “Clinical and genetic characterisation of 145 Spanish patients diagnosed with PTEN hamartoma tumour syndrome” —, she characterised the disease in a wide series of Spanish patients, at both genetic and clinical levels, reviewing the patients' features, comparing them with other studied populations, and assessing the usefulness of the diagnostic criteria. The second objective of the work was to look for other genetic factors that could be involved in the phenotype of patients with PHTS who do not harbour *PTEN* mutations. The results of this work were used to formulate several recommendations: for the diagnosis, the selection of the most useful clinical features to drive genetic testing; and for the follow-up, obesity check-ups and anticipation of cancer screenings. Overall, this

work contributes to accelerate and improve the diagnosis and management of PHTS patients.

During 2020 we continued our work on early-onset colorectal cancer (EOCRC). Our goal is to build partnerships with patients, clinicians, and researchers. The increase in EORC incidence, its global dimension, and the many aspects distinguishing it from colorectal cancer that develops at older ages, make it necessary to bring attention to this problem and understand the causes of this striking increase. In June we launched the 2<sup>nd</sup> International Symposium on EOCRC in collaboration with Fight Colorectal Cancer (Fight CRC), a leading patient-empowerment and advocacy organisation in the United States. This collaboration was established based on the priorities that emerged from the 1<sup>st</sup> EOCRC Working Group held in Denver, CO (USA) in February 2019, to align research priorities in exploring the causation and aetiology of sporadic EOCRC and to support their ongoing work in convening a workgroup of now over 100 active participants. A result of these efforts has been the implementation of the Spanish EOCRC Group and the European Study of EOCRC Group (see in publications list Perea *et al.*, 2020). We believe that these initiatives will help to better develop the fight against EOCRC. ■

### ► PUBLICATIONS

- Fachal L *et al.* (incl. Osorio A) (2020). Fine-mapping of 150 breast cancer risk regions identifies 191 likely target genes. *Nat Genet* 52, 56-73.
- Silvestri V *et al.* (incl. Osorio A) (2020). Characterization of the cancer spectrum in men with germline BRCA1 and BRCA2 pathogenic variants: results from the consortium of investigators of modifiers of BRCA1/2 (CIMBA). *JAMA Oncol* 6, 1218-1230.
- Yang X *et al.* (incl. Osorio A) (2020). Ovarian and breast cancer risks associated with pathogenic variants in RAD51C and RAD51D. *J Natl Cancer Inst* 112, 1242-1250.
- Figlioli G *et al.* (incl. Urioste M, Osorio A) (2020). The spectrum of *FANCM* protein truncating variants in European breast cancer cases. *Cancers (Basel)*, 12, 292.
- Perea J, García JL, García-Olmo D, Urioste M, González-Sarmiento R; on behalf of the Spanish EOCRC group and the European study of EOCRC group (EUREOC) (2020). Comment on: clinicopathological

features and oncological outcomes of patients with young-onset rectal cancer. *Br J Surg* 107, e277.

- Tapial S, García JL, Corchete LA, Holowatyj A, Perez J, Rueda D, Urioste M, González-Sarmiento R, Perea J (2020). Copy neutral loss of heterozygosity (cn-LOH) patterns in synchronous colorectal cancer. *Eur J Hum Genet*. PMID: 33268847.
- Carreño M, Pena-Couso L, Mercadillo F, Perea J, Urioste M (2020). Investigation on the role of PALB2 gene in CDH1-negative patients with hereditary diffuse gastric

cancer. *Clin Transl Gastroenterol*. PMID: 33512806.

### ► Book chapter

- Osorio A, Urioste M (2020). *Principales alteraciones genéticas y síndromes hereditarios*. In: “*Guía OncoSur de Cáncer de Mama*”. E.M. Ciruelos, M.J. Echarrí, y Pernaut C (coordinators). *Fundación OncoSur. Arán Ediciones*, S.L. Madrid. ISBN: 978-84-18116-06-3.