CRC is the third most frequent type of cancer and the third cause of cancer-related deaths in most developed countries. Age is the main risk factor. The median age at diagnosis is 68 years in men and 72 in women. Since the mid-2000's, CRC global incidence and mortality in the USA and Europe have been decreasing at an annual rate of 2–3% for both sexes. This decrease is probably related to the extended use of the faecal occult blood test and colonoscopy, which facilitates the removal of precursor lesions, and to the increased awareness among the general population of the preventive and risk factors.

Recent epidemiological studies indicate that CRC incidence in people under 50 is increasing, which is the opposite situation for individuals over 50 years of age. The greater increase was observed in the age range of 40 to 49 years, in which the incidence changed from 18.2 cases population in 1992, to a rate of 26.5 per 100,000 in 2015. This caught the attention of researchers and the general media. Several causal hypotheses were contemplated – new exogenous factors, epigenetic modifications, low-penetrance gene variants and their interactions – and there is a proposal to launch a research agenda to advance knowledge about the aetiologial factors and diagnostic methods of early-onset CRC (EOCRC).

Since 2010 the Familial Cancer Clinical Unit (FCCU), together with the Surgery Department of the Fundación Jiménez Díaz University Hospital and the Institute for Biomedical Research of Salamanca, has been committed to investigating EOCRC. The aim is to: (i) accelerate research to address unanswered questions about the causes of the increase in EOCRC; and (ii) increase the adoption of evidenced-based practices to improve the clinical and familial boundary between early-onset colorectal cancer (EOCRC) and other forms of colorectal cancer. Our clinical and diagnostic activities in 2019 can be summarised as: 538 patients visited our consultancy at HUF (600% increase over 2018); and 572 genetic diagnostic studies were performed in the FCCU laboratory (12.59% increase). Among these studies, we identified 17 cases of CRC in individuals younger than 45, of whom were patients younger than 30 (14 and 28 years old). The FCCU also focuses its research efforts on less frequent cancer predisposition syndromes. One of these is the PTEN hamartoma tumour syndrome (PHTS), in which the high clinical heterogeneity is a major obstacle to establishing an early diagnosis. We studied this pathology at the clinical and molecular level in the largest series of Spanish patients with PHTS (145 probands). Our findings are consistent with the syndrome descriptions in other populations, with few exceptions such as a higher proportion of carriers of mutations in PTEN exon 1 who apparently have an increased risk of developing renal cancer. We discussed the usefulness of the different diagnostic criteria proposed to date and made recommendations based on our results (FIGURE).

Noteworthy is that we highlight a novel risk for patients with PHTS, namely the development of cancer at young ages, for which we suggest to anticipate cancer screening in these individuals. Moreover, we demonstrated that the presentation of cancer types within the PHTS spectrum criterion alone is not sufficient to refer patients for PTEN screening, at least as a first measure. In collaboration with the groups of Dr Pulido (Haberes) and Dr Cid (UMC), we functionally demonstrated the deleterious effect of several PTEN variants of unknown significance. However, about half of our PHTS patients could not be explained by alterations in PTEN, and therefore we also focused our efforts on the search for other genes possibly involved in this disease, using a gene panel (including PIK3/AKT/mTOR pathway genes) and whole exome sequencing. Future directions will focus on unravelling the relevance of these findings. Our study continues to contribute to a better definition of PHTS and to accelerate its diagnosis.