The Human Cancer Genetics Programme (HCGP) is a translational research programme working on areas related to genetics, genomics, pharmacogenetics, molecular cytogenetics, and the environmental bases of human cancer.

The Programme’s interests focus on: (1) identifying new genetic and non-genetic factors related to cancer predisposition and risk in order to guide risk-stratified screening strategies towards personalised cancer prevention and treatment; and (2) understanding the molecular mechanisms involved in cancer to facilitate the development of targeted therapies and early diagnostics.

In 2023, HCGP was composed of 2 Research Groups: Hereditary Endocrine Cancer (HECG) and Genetic and Molecular Epidemiology (GMEG); and 3 Units: Human Genotyping-CEGEN, Molecular Cytogenetics, and the Familial Cancer Clinical Unit. In addition, the Programme includes a Familial Cancer Consultancy at the Hospital Universitario de Fuenlabrada to evaluate families with cancer and provide genetic counselling.

The Programme works in close collaboration with the clinical community to foster cooperation in genetic diagnosis and research, and to promote training and education. In 2023, there were 1,145 visits at the Familial Cancer Consultancy (579 new cases and 566 patients receiving results), and the HCGP performed 2,128 genetic diagnoses and carried out 2,102 cytogenetic studies. In terms of research, the Programme’s members participated in collaborative studies involving a network of more than 30 hospitals from our National Health System, not only to conduct collaborative studies but also to facilitate clinical translation. The Programme also offers professionals and students from different national and international research centres the opportunity to join, either as visitors or for training visits consisting of short-term stays of 1 to 3 months. Three national and 7 international visitors, and 4 medical residents from different Spanish hospitals were hosted in 2023. In terms of education, 5 Bachelor’s, 2 Master’s, and 16 PhD students worked on their research projects.

The Programme has established research collaborations with national and international groups; this is well demonstrated by its publication record as well as the key roles held by several of the Programme’s members in consortia and international projects. In 2023, for example, GMEG members, led by Núria Malats, in collaboration with C. Van Eijck from Erasmus Medical Centre, Rotterdam, undertook a study, published in GUT, that showed that pancreatic cancer in women is more sensitive to gemcitabine-based neoadjuvant chemoradiotherapy, resulting in longer survival after resection compared to men.

Especially noteworthy is the contribution of several of the HCGP’s group members to IMPaCT, an initiative of the Instituto de Salud Carlos III to Promote Precision Medicine in our country. Milestones and major achievements of the HCGP in 2023 include the following:

- GMEG was awarded an Innovative Health Initiative European project on liquid biopsy and cancer minimal residual disease.
- GMEG contributed to the bladder cancer field through the identification of new genetic susceptibility variants revealing new biological and translational insights.
- Mercedes Robledo led an international study published in *Nature Communications*. Focusing on metastatic pheochromocytoma, it was the first to identify differences in the tumour microenvironment dependent on the driver gene, which is of potential relevance for the treatment of patients with this disease.
- Sandra Rodriguez-Perales and Raul Torres-Ruiz generated a human genome editing-based MLL::AF4 ALL model recapitulating key cellular and molecular leukemogenic features (work published in *Blood*).

One of the main strategic initiatives of the CNIO at present is the consolidation of a new Cancer Genomics Programme. HCGP groups will become part of the new Programme. I am confident that, under this new strategic action, the Programme will continue to grow and further develop research in the field of cancer genomics.

Maria A Blasco, Director
OVERVIEW

Our Group is mainly interested in identifying genetic risk factors involved in endocrine tumour susceptibility. Through a comprehensive analysis of tumour genomic features, we have been able to propose diagnostic and prognostic markers to identify altered pathways that could be therapeutically targeted, and to identify new major susceptibility genes.

We are also interested in defining markers associated with differences in anticancer drug response and toxicity. We are applying targeted and whole-exome next-generation sequencing to a large series of clinically well-characterised patients. The aim is to identify new therapeutic approaches to personalise cancer treatment. These efforts will collectively improve the diagnosis, prognosis, and treatment of patients.

“We showed the utility of immunological parameters with prognostic value in PPGL, showed that DLST mutations remodel cellular succinyloma — being a promising therapeutic target — and defined novel RCC drug response predictive markers.”
DLST mutations in pheochromocytoma and paraganglioma (PPGL) cause protein hyposuccinylation and metabolic remodeling

PPGLs are the most heritable tumours. One of the most recently identified PPGL susceptibility genes is DLST, a component of the OGDH complex that catalyses the conversion of alpha-ketoglutarate to succinyl-CoA in the tricarboxylic acid (TCA) cycle. In addition, DLST plays an underutilized role in protein succinylation, a post-translational modification (PTM) that causes changes in protein structure and function. Accordingly, this PTM has been implicated in the development of several diseases, including cancer. Through an in-depth molecular characterisation of DLST-mutated PPGLs, we explored the underlying mechanisms of tumorigenesis, focusing on the role of succinylation. We found a dramatic decline in succinylation levels in the absence of DLST. Moreover, DLST mutations found in PPGLs remodel the cellular succinylnome and cause a transcriptional shift from oxidative phosphorylation to a hypoxic cellular state. We concluded that global protein succinylation decreases strongly in DLST-deficient tumours (mPPGL). Genomic profiling of a large cohort of metastatic renal cell carcinoma (mRCC) revealed that high mutational load, a hypoxic cellular state, and tumour hyposuccinylation are associated with poor survival outcomes in patients with non-metastatic and metastatic mPPGLs. In conclusion, DLST mutations may serve as predictors of antiangiogenic drug responses. These findings have clinical implications for patients with metastatic renal cell carcinoma.

**Novel predictive biomarkers for renal cancer therapy**

Targeted therapy has improved the survival of patients with metastatic renal cell carcinoma (RCC). However, the large inter-patient variability in drug response stresses the urgent need to define novel predictive biomarkers. Here we provide two examples:

1. **DLST mutations in pheochromocytoma**

   DLST was the only shared mutated gene in 3 chromophobe RCC patients with an aggressive clinical course. This highlights the potential of DLST mutations as a potential novel marker of sensitivity to antiangiogenic drug treatment.

2. **Increased drug sensitivity in mutant cells**

   Using cell line models. Prognostic analyses and immunofluorescence assays demonstrated a p62-mediated deregulation of autophagy in USP9X-depleted cells that has a synergistic effect with mTOR inhibitors. Thus, we defined USP9X as a potential novel marker of sensitivity to mTOR inhibitors and a target for immunotherapy.

**Gene expression in renal cancer**


The scope of the research carried out by the Genetic and Molecular Epidemiology Group (GMEG) ranges from the identification of aetiological agents and genetic pathways to the translation of the findings into the clinical and public health domains, focusing on bladder, pancreatic, and breast cancers.

We employ a wide variety of biomarkers, including omics data, to better characterise exposures, genetic susceptibility patterns, and cancer outcomes. While omics data provide a unique opportunity in this regard, their integration with non-omics data poses important challenges, and GMEG explores this methodological field in epidemiologic studies.

The strategic goals of the Group are to:

- Identify non-genetic and genetic factors, as well as their interactions, associated with cancer development and progression, and with its molecular/omics subphenotypes.
- Develop and apply statistical/informatics tools to model the risk and course of patients with cancer by integrating epidemiological and clinical data with omics information.
- Assess clinical and public health strategies for cancer control using newly developed biomarkers and algorithms.

“Epidemiological studies aim to analyse the causal relationship between an exposure and an outcome. We have applied causal inference approaches to assess bias generated by factors that may distort the real effect of the exposure.”
In 2023, GMEG contributed to the pancreatic cancer (PC) field by undertaking a study that showed that PDAC tumours of women are more sensitive to gemcitabine-based neoadjuvant chemoradiotherapy (nCRT), resulting in longer survival after nCRT compared with men. The tumour microenvironment (TME) of women contained fewer protumoural macrophages after nCRT, highlighting the importance of considering sex disparities for PDAC treatment. GMEG also contributed to showing that GATA4 and GATA6 expression was significantly decreased in metastases and negatively correlated with basal markers. On bladder cancer (BC), GMEG conducted a study to characterise the muscle-invasive bladder cancer (MIBC) microenvironment by analysing the tumour-infiltrating B- and T-cell repertoire according to the taxonomic molecular subtypes. We used RNAseq data from 396 MIBC samples included in TCGA. We found different patterns of tumour-infiltrating immunity among the different MIBC subtypes. In addition, we observed that the Ba/Sq and Stroma-rich tumours were more clonally expanded than the Luminal subtypes (FIGURE 1). We also found that higher TCR diversity and richness were significantly associated with better survival in the Stroma-rich and Ba/Sq subtypes. Importantly, GMEG contributed to an international meta-analysis of genome-wide genotyping data led by the NC1 (USA) to identify new susceptibility variants for bladder cancer, summing up 24 independent BC susceptibility markers at genome-wide significance. Combined with smoking, they may inform screening interventions for BC. Also in collaboration with the NC1, we demonstrated that smoking and BK polyoma virus infection contribute to bladder tumorigenesis through distinct molecular mechanisms involving different FGFR3 and PIK3CA mutations. Finally, we identified a predictive signature for response to neoadjuvant chemotherapy in MIBC patients that integrates the expression of 3 genes with clinicopathological characteristics and taxonomic subtypes.

Combining it with Mendelian randomisation (MRinCMA) to address the limitations resulting from fitting strong assumptions on confounding bias (FIGURE 2). We applied the new approach to analyse the causal effect of obesity and diabetes on pancreatic cancer, considering each factor as potential mediator. By applying MRinCMA, we did not find any evidence of causality of obesity or diabetes on pancreatic cancer. With this new methodology, researchers would be able to address CMA hypotheses by appropriately accounting for the confounding bias assumption, regardless of the conditions used in their studies in different settings. Furthermore, we performed a benchmarking analysis of 5 tools for microbe sequence detection using transcriptomics data (Kraerner, MetaPhlAnAN2, PathSeq, DRAC, and Pandora). To this end, we built a synthetic database mimicking real-world structure with tuned conditions accounting for microbe species prevalence, base calling quality, and sequence length. Results from this study supported the use of KRAERN for routine microbiome profiling based on its competitive sensitivity and runtime performance. Nonetheless, we strongly endorse to complement it by combining with MetaPhlAn2 for thorough taxonomic analyses.

Translational activities

GMEG actively supports several clinical trials on immunotherapy in BC at the methodological level. We continue to support the Spanish Familial Pancreatic Cancer Registry (PanGen-PAM) and the European Registry of PC (PancreOS) under the umbrella of Pancreatic Cancer Europe (PCE). We chair the Spanish Alliance for Pancreatic Cancer Research (ALAPANCC) to accelerate the translation of research results into the clinical and public health domains. We lead the Research Work Stream of the PCE multistakeholder platform, and we have advanced in increasing awareness about PC. We also contributed to the European Alliance for Personalised Medicine (EAFPMM) series of expert interviews to ascertain the current state of the uptake of advanced molecular diagnostics/NGS for quick and efficient genetic profiles of tumour cells across member states.

**RESEARCH HIGHLIGHTS**

**PUBLICATIONS**

- de Villareal J, Jang GH, Costello E, Gallimore S, Pilarsky C, Schlitter AM, Martinez Gut. PMID: 37709493. (*

**RESEARCH FINDINGS**

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Methodological contributions

We further applied causal inference approaches such as mediation analysis (CMA), which consider the mediation effect of a third variable, and proposed an extension of CMA, combining it with Mendelian randomisation (MRinCMA) to address the limitations resulting from fitting strong assumptions on confounding bias (FIGURE 2). We applied the new approach to analyse the causal effect of obesity and diabetes on pancreatic cancer, considering each factor as potential mediator. By applying MRinCMA, we did not find any evidence of causality of obesity or diabetes on pancreatic cancer. With this new methodology, researchers would be able to address CMA hypotheses by appropriately accounting for the confounding bias assumption, regardless of the conditions used in their studies in different settings. Furthermore, we performed a benchmarking analysis of 5 tools for microbe sequence detection using transcriptomics data (Kraerner, MetaPhlAnAN2, PathSeq, DRAC, and Pandora). To this end, we built a synthetic database mimicking real-world structure with tuned conditions accounting for microbe species prevalence, base calling quality, and sequence length. Results from this study supported the use of KRAERN for routine microbiome profiling based on its competitive sensitivity and runtime performance. Nonetheless, we strongly endorse to complement it by combining with MetaPhlAn2 for thorough taxonomic analyses.

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**HUMAN CANCER GENETICS PROGRAMME | GENETIC AND MOLECULAR EPIDEMIOLOGY GROUP**

**FIGURE 1**

BSI clonal expansion and diversification by microinvasive bladder cancer subtypes. (A) Clonal expansion by using the Gini Index (Y axis) and clonal diversification displayed by Gini Vertex (X axis). (B) clonal repertoire from samples representing one Ba/Sq (black) and one Lum (green).

**FIGURE 2**

Causal diagram. (A) Causal mediation analysis (CMA) graph. (B) Mendelian randomisation (MR) analysis with instrumental variables (IVs). (D) Structural equation model (SEM), where directed arrows represent causal effect, bidirectional arrows indicate a correlation between variables.
The Molecular Cytogenetics and Genome Editing Unit is dedicated to understanding the role of chromosomal rearrangements in cancer progression and identifying new therapeutic targets. These rearrangements, which alter the structure of chromosomes, are frequent and recognised characteristics of cancer. By using a combination of CRISPR/Cas9 and cytogenetic technologies, the Unit creates models that mimic chromosomal and genetic alterations found in cancer. The aim is to enhance our understanding of cancer-causing mechanisms, which could lead to the development of innovative cancer treatments. The Unit also provides researchers at the CNIO and other institutions with the latest models of innovative cancer treatments. We are comparing OGM to standard techniques like karyotyping and fluorescent in situ hybridisation using various tumour samples. OGM is a promising complementary approach to cytogenetic techniques for cancer cell characterisation, offering a cost-effective analysis and identification of complex cytogenetic rearrangements.

**RESEARCH HIGHLIGHTS**

Around 20% of human cancers have specific fusion oncogenes (FOs), which are unique diagnostic and therapeutic targets due to their tumour-specific expression. Conventional diagnostic techniques like qRT-PCR, FISH, or NGS are routine but require specialised machinery and personnel, are expensive, time-consuming, and involve multiple steps. Many current treatments are non-selective, leading to severe side effects. We have applied the RNA-targeting Cas13 system for selective cleavage of FO transcripts. Unlike the CRISPR/Cas9 method, RNA targeting with Cas13 results in reversible and temporally controllable alterations without DNA modification. Compared to shRNAs, the Cas13 method has high knockdown efficiency and no off-target effects, offering unique advantages for therapeutic purposes. Diagnostic methods based on Cas13 provide rapid RNA detection with attomolar sensitivity and single-base mismatch specificity.

Our Unit has been enhancing the Optical Genome Mapping (OGM) technique, a method that analyses ultra-long DNA molecules for high-resolution, genome-wide analysis of cytogenetic variations. We are comparing OGM to standard techniques like karyotyping and fluorescent in situ hybridisation using various tumour samples. OGM is a promising complementary approach to cytogenetic techniques for cancer cell characterisation, offering a cost-effective analysis and identification of complex cytogenetic rearrangements.

**FIGURE 1 CRISPR/Cas3 targets RNA, not DNA.** Once activated by target RNA, it cleaves nearby RNA molecules indiscriminately, known as the collateral effect. The extent of this effect is linked to the target transcript’s expression level and varies with the cell type, potentially leading to cell death.

**OVERVIEW**

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“The use of gene editing to mimic and eliminate chromosomal or gene alterations, enhancing our understanding of cancer and developing new treatment tools. We offer cutting-edge cytogenetic and CRISPR technologies.”

**Publications**

OVERVIEW

The Unit’s activity is divided into 2 main areas.

1. Genetic diagnosis in patients with suspected hereditary cancer using next-generation sequencing. 52% of our activity is dedicated to genetic diagnosis in the Familial Cancer Clinic of the University Hospital of Fuenlabrada (FCC-UHF), and 48% to providing this service to other hospitals in Madrid and the rest of Spain. 59% of the genetic diagnoses were carried out in index cases, while 41% were predictive studies in relatives to determine genetic diagnoses were carried out in index cases.

2. Research work. We participated in the identification of genetic factors and the interpretation of genetic variants of unknown significance (VUS) in the PTEN Hamartoma Tumour Syndrome (PTHS). We are involved in the IMPaCT-GENóMICA and IMPaCT-VUSCan projects, having been one of the main participants in the Spanish Hereditary Cancer Variants Database (SpadaHC).

FAMILIAL CANCER CLINICAL UNIT

Maria Currás
Clinical Unit Head
Post-Doctoral Fellow
Bruna Calsina
Graduate Student
Erik Michel Marchena (until March) (PEL, CAM)
Tumour Variants Reclassification (TVC) Unit

Plan de Empleo Joven de la Comunidad de Madrid (Youth Employment Plan, Community of Madrid)

RESEARCH HIGHLIGHTS

Clinical and diagnostic activity

1068 patients were evaluated at the FCC-UHF and 2023 genetic studies were performed at the Familial Cancer Clinical Unit (FCCU) during 2023. A total of 355 pathogenic or probable pathogenic variants were identified, allowing families and patients to benefit from appropriate clinical follow-up, early detection in unaffected patients, and/or personalised medicine. We implemented the diagnosis of MLH1 methylation in endometrial and colorectal tumours and the genetic diagnosis of healthy individuals with deceased relatives affected by cancer. In addition, we updated the genes to be studied per tumour and expanded the range of tumours in which the presence of germline mutations is excluded (including bladder and genitourinary tumours, among others).

IMPaCT-GENóMICA

This project aims to identify genetic variants that could explain cancer predisposition. The FCCU participated, among other centres in Spain, in the clinical decision-making committee to choose the most appropriate unsolved familial cases. A total of 22 families from Madrid and 169 Spanish families were recruited. Our Unit contributed 6 families with cases related to prostate (3), testicular (1), pancreatic (1), and breast (1) cancers.

We will also be involved in the analysis and integration of data for candidate variant prioritisation and functional evaluation, among other CNIO Groups and Units.

SpadaHC

SpadaHC is a database for sharing genetic variants identified in hereditary cancer genes, which currently includes data from 15 Spanish genetic diagnostic reference laboratories. The database also provides frequencies of these variants in the Spanish population and is a useful resource for research and clinical genetic laboratories to improve knowledge of the genetic basis of hereditary cancer.

The current version of the database contains 1.16M genetic variants from 4294 individuals and 14776 variant classifications. A total of 2469 variants had different pathogenicity classifications, and we participated in their homogenisation. For this purpose, we took into account the criteria of the American College of Medical Genetics and the results of our laboratory, and resolved the discrepancies in 84 clinically relevant variants. For most of the variants, a consensus on the best classification was reached to provide better clinical decision-making support.

PTEN variants

We participated in the comprehensive functional characterisation of 6 novel variants of unknown significance identified in the PTEN gene and also initiated a collaboration with the PTEN Research Foundation on premalignant lesions and vascular malformations in patients with PHTS.

‘PUBLICATIONS’


‘AWARDS AND RECOGNITION’

Bruna Calsina:

- ENAT Scientific Award, The European Network for the Study of Adrenal Tumors (ENAT).
- Award for PhD-Authored Publications, CNIO Lab day.

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HUMAN CANCER GENETICS PROGRAMME | FAMILIAL CANCER CLINICAL UNIT
Our research focuses on identifying genetic factors that influence breast cancer susceptibility and treatment efficacy and toxicity. Through our research, we aim to refine personalized risk assessment for breast cancer, pioneer innovative strategies for early detection, and improve the precision and safety of cancer treatment for patients.

Additionally, we strive to implement this information in the clinical setting. By translating our research findings into practice, we aim to improve patient outcomes by providing more individualised and effective approaches to cancer prevention, detection, and treatment.

**RESEARCH HIGHLIGHTS**

**Identification of novel breast cancer susceptibility genes by exome sequencing**

To comprehensively assess the role of rare coding variants, we conducted a meta-analysis using 3 extensive whole-exome sequencing datasets, comprising 26,368 female cases and 227,673 female controls. Significant associations between protein-truncating variants and breast cancer were discovered for 6 genes at an exome-wide significance level ($P < 2.5 	imes 10^{-6}$). ATM, BRCA1, BRCA2, CHEK2, PALB2, and MAP3K1. Additionally, associations were found for LZTR1, AT8, and BARD1 with $P < 1 	imes 10^{-4}$ (Wilcoxon et al. 2022).

**Genetic characterisation and clinical impact of 21 actionable pharmacogenes in the Spanish population**

We analysed genetic data from 3,006 Spanish individuals to determine the allele frequencies for 21 actionable pharmacogenes. Our findings show that 98% of the Spanish population carries at least 1 allele linked to a therapeutic change. We translated this genetic data into clinical recommendations, suggesting an average need for therapeutic changes in 3.31 out of 64 associated drugs (https://cvs.clínicoinforme.es/)

**Novel genetic variants associated to susceptibility to SARS-CoV-2 infection and disease severity**

We participated in the second updated genome-wide association study (GWAS) on COVID-19 severity and infection susceptibility to SARS-CoV-2 from the COVID-19 Host Genetic Initiative. A meta-analysis of up to 219,692 cases and over 3 million controls identified 51 distinct genome-wide significant loci – adding 28 loci from the previous data release (Pairo-Castineira et al. and Castro-Santos P et al. 2023).

**Identification of anthracycline-induced cardiotoxicity (AIC) genetic risk markers by intermediate molecular phenotypes (IMPs)**

AIC affects cancer patients, but we cannot predict who may suffer from this complication. We propose that levels of IMPS in the myocardium associated with histopathological damage could explain AIC susceptibility, so variants of genes encoding these IMPS could identify patients susceptible to this complication. We found genetic variants linked to these markers, and 2 genetic risk scores for paediatric and breast cancer patients were constructed (Gómez-Vecino et al. 2023).