

Supplementary Table 5: HDGC emerging research areas divided into sections based on patient groups with different genetic risk factors

Emerging Research Areas	
<i>Carriers of likely pathogenic and pathogenic variants in CDH1 or CTNNA1</i>	
Main Topic	Sub-topics
Penetrance and risk prediction analysis	<ul style="list-style-type: none"> • Establish cancer registries combining clinical, phenotypic, pathological, and molecular data. A database on the likely pathogenicity of known germline <i>CDH1</i> variants is currently under construction (contact Carla Oliveira, on behalf of the European Reference Network GENTURIS at carlaol@ipatimup.pt). • Study extended family pedigrees to understand variant-specific penetrance and variant-specific disease phenotypes • Evaluate environmental and physiological risk factors • Identify genes that modify <i>CDH1</i> mutation penetrance • Evaluate gastric cancer risk in families with no history of DGC
Genotype-phenotype correlations	<ul style="list-style-type: none"> • Understand differences and similarities between <i>CDH1</i>- and <i>CTNNA1</i>-associated disease phenotypes • Further investigate the gastric and breast cancer histological and molecular subtypes associated with <i>CDH1</i> and <i>CTNNA1</i> deleterious variants • Identification of congenital malformations or other non-cancer phenotypes • Correlation of cancer-phenotypes and non-cancer phenotypes with variant molecular type (truncating vs missense)
Somatic events and triggers of cancer development	<ul style="list-style-type: none"> • Correlation of numbers of precursor, indolent SRC foci, and aggressive SRC foci with risk of progression • Identification of the cell compartment (differentiated vs progenitor vs stem cells) where cancer initiates • Identification of genetic, epigenetic and environmental triggers of transition from intramucosal <i>foci</i> to deeper, invasive cancer • Frequency of <i>H. pylori</i> infection and associated strains
Cancer diagnosis, chemoprevention, and treatment	<ul style="list-style-type: none"> • Identification of early diagnostic biomarkers • Evaluation of the potential of gene replacement as a germline therapy • Evaluation of the potential of synthetic lethality as a chemoprevention approach
Cancer surveillance and risk reduction measures	<ul style="list-style-type: none"> • Definition of cost-effective surveillance methodologies and their periodicity • Determination of the age-range of onset for DGC and LBC to optimise the timing for risk reduction interventions • Determining patient factors in choosing surveillance vs. surgery • Assessing quality of life; psychological interventions and outcomes
Gastroenterology/Pathology	<ul style="list-style-type: none"> • Determination of whether CRC is a minor part of the <i>CDH1</i> and/or <i>CTNNA1</i> spectrum, and if yes, its histological type
Long term follow-up: Nutrition post-gastrectomy	<ul style="list-style-type: none"> • Relationship between diet, nutrition, drug absorption, changes in body composition and quality of life
Pharmacology	<ul style="list-style-type: none"> • Impact of gastrectomy on uptake of common medications including SSRIs, SERMs, and anti-inflammatories.
<i>Carriers of variants of unknown significance (VUS)</i>	
Main Topic	Sub-topics

Variants of unknown significance in <i>CDH1</i> and <i>CTNNA1</i>	<p>For missense variants, regulatory or deep intronic variants, large gene duplications, and full-gene deletions:</p> <ul style="list-style-type: none"> • Classification according to their impact on: (i) normal splicing, (ii) transcription, and (iii) protein function • Validation and standardisation of methodologies for <i>in silico</i>, <i>in vitro</i> and <i>in vivo</i> molecular analysis
<i>Families meeting HDGC genetic testing criteria but lacking clinically-relevant variants in <i>CDH1</i> or <i>CTNNA1</i></i>	
Main Topic	Sub-topics
Novel disease causative events	<ul style="list-style-type: none"> • Alternative loss of function mechanisms affecting <i>CDH1</i> and <i>CTNNA1</i>, such as epimutations or defects in regulatory regions • Alternative genes to <i>CDH1</i> and <i>CTNNA1</i> • Somatic mosaicism associated with <i>CDH1</i> and <i>CTNNA1</i> loss of function
Surveillance endoscopy	<ul style="list-style-type: none"> • Risk estimation and benefit of endoscopic surveillance
<i>All patient groups</i>	
Main Topic	Sub-topics
Improved endoscopic methods	<ul style="list-style-type: none"> • Confocal endoscopy • Artificial intelligence • Measurements of resistance of the gastric wall for detection of (larger) submucosal infiltrative lesions
Model systems	<ul style="list-style-type: none"> • Development of pre-clinical and clinical models to better estimate risk and inform surveillance strategies

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