3º ENCONTRO NACIONAL DE INVESTIGAÇÃO CLÍNICA & INOVAÇÃO BIOMÉDICA

21 MAIO | ISCTE LISBOA

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Infarmed Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.
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PtCRIN Portuguese Clinical Research Infrastructure Network
iscte Instituto Universitário de Lisboa

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A medicina personalizada na investigação clínica e translação para a prática

O exemplo das síndromes hereditárias ligadas a cancro

Carla Oliveira

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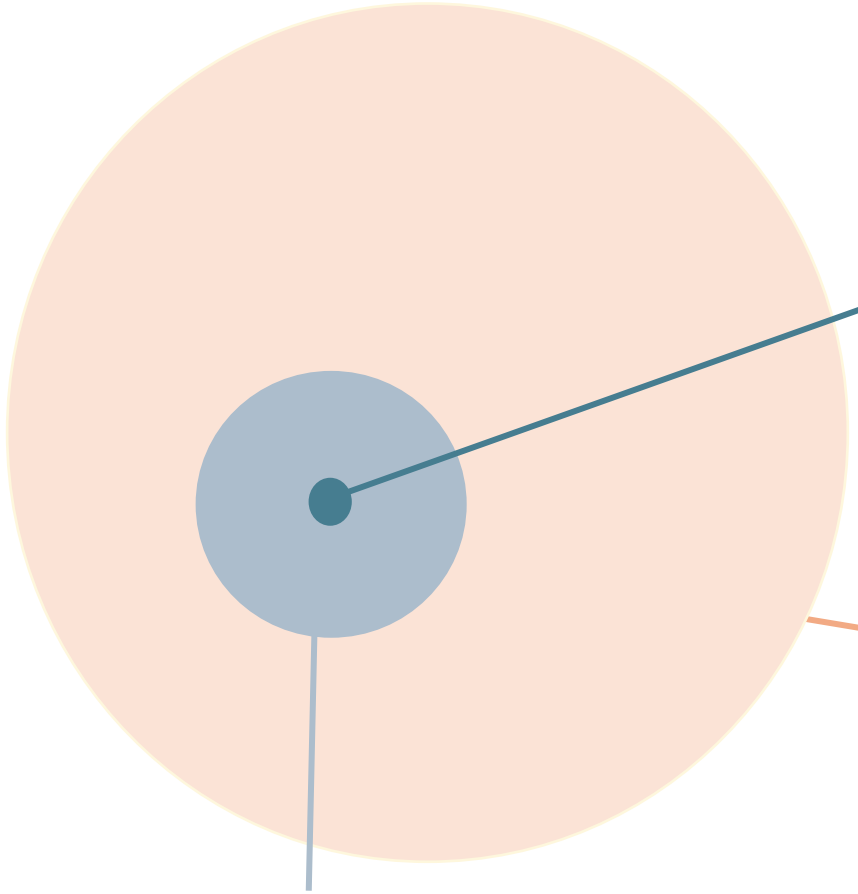
Cancer

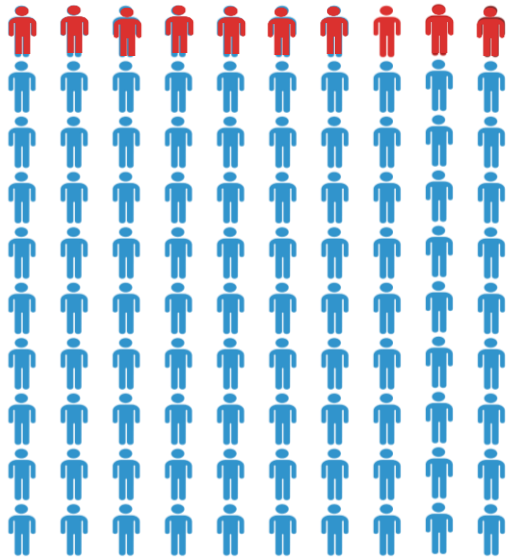


Known inherited susceptibility to cancer:
'Hereditary'
Single genes

No family history of cancer:
'Sporadic'
? multi-factorial origins
Environmental factors

Family history of cancer:
'Familial'
? multi-factorial origins

Why is this important?



<10 %

HEREDITARY

is genetically determined from birth

IDENTIFICATION OF A GENETIC CAUSE

allows spotting individuals at high cancer-risk, prior to disease development

Hereditary Cancer is the only cancer that is preventable

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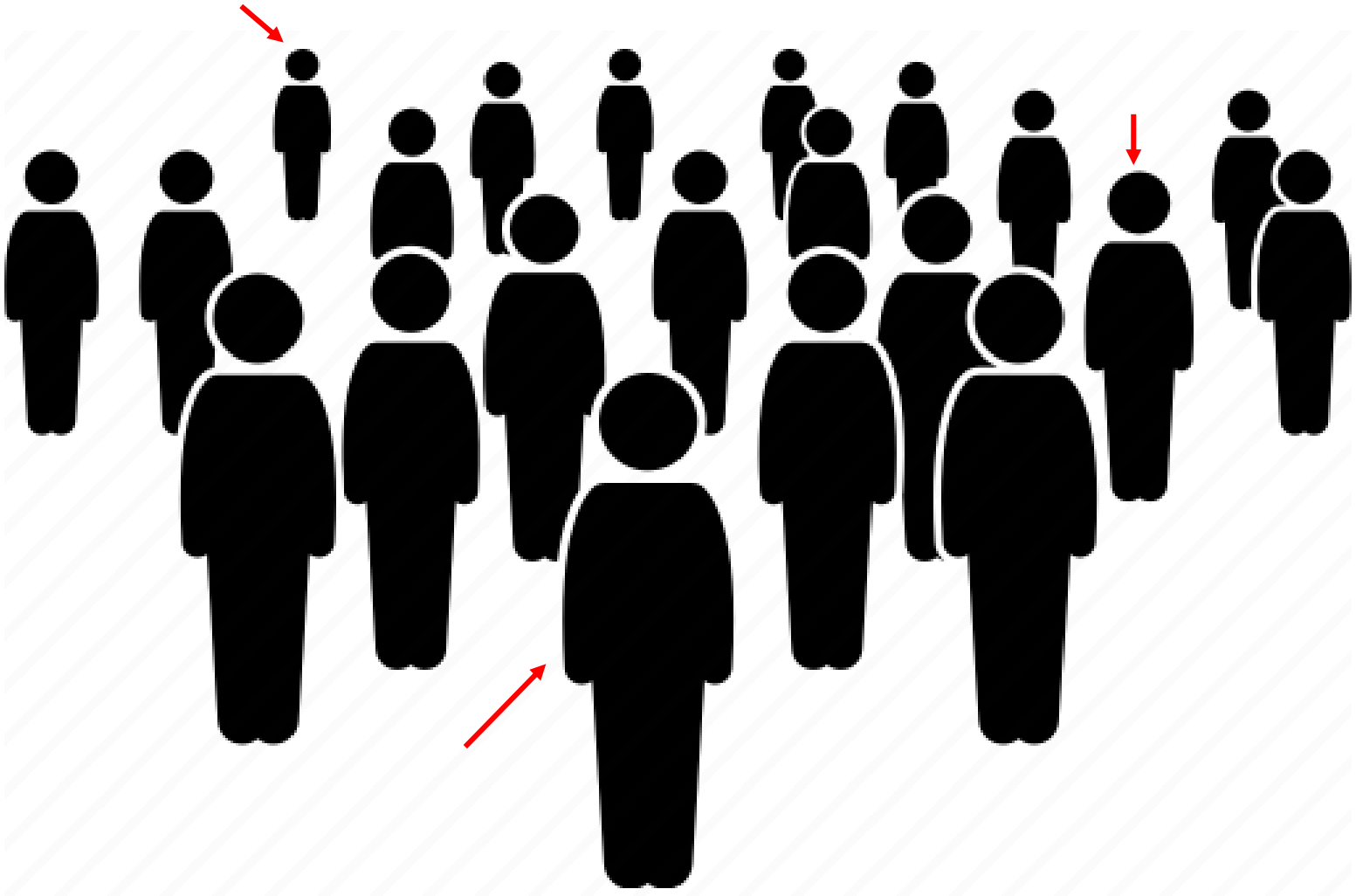
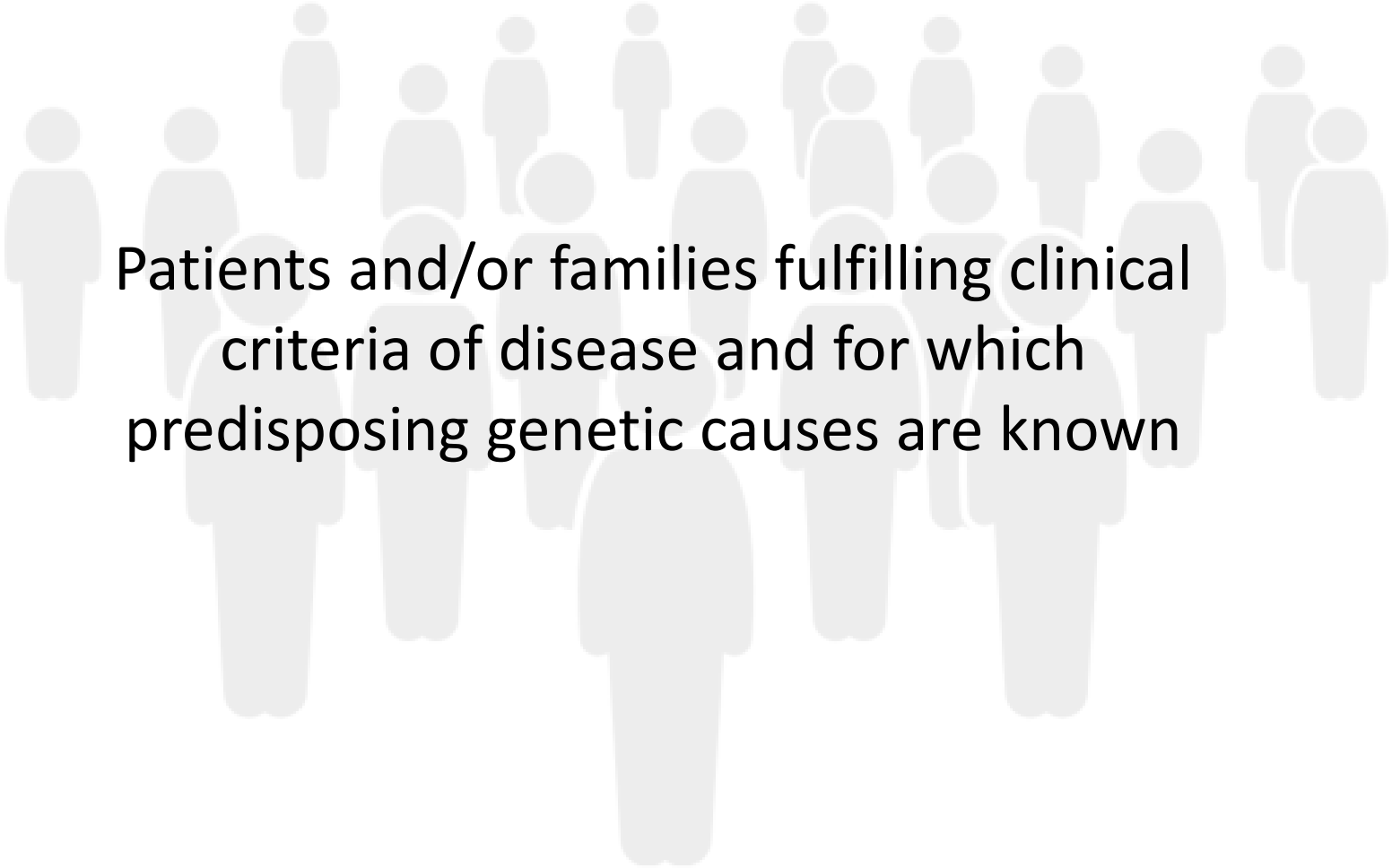
Who should be tested in a population?



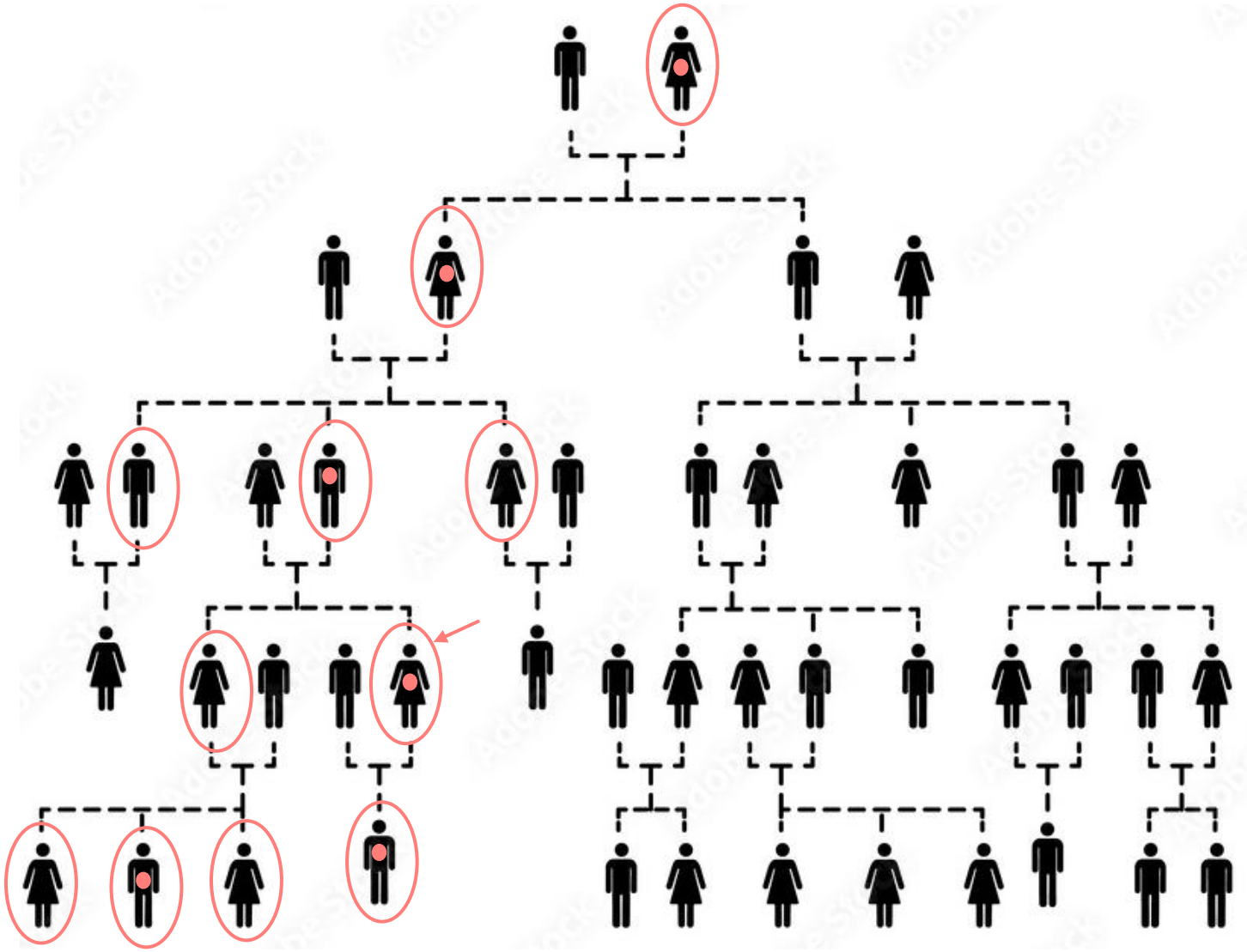
Who should be tested in a population?



Patients and/or families fulfilling clinical criteria of disease and for which predisposing genetic causes are known

Who should be tested in a family?

If a predisposing variant is found,



How does it work?

Scientific Knowledge / Guidelines / Resources are essential to:

- ***Recognize and refer*** *patients for genetic testing*
  - *Consensus clinical guidelines*
  - *Identification of individuals with high risk for inherited cancer*
  - *Interpretation of their clinical presentations and family history*
- ***Prescribe testing*** *of the gene(s) predicted to cause the inherited cancer syndrome*
- ***Clinically manage*** *patients with cancer predisposition and their families:*
  - *Providing Genetic Cancer* ***Risk Assessment***
  - *Prescribing the* ***right high-risk screening***, ***preventive care***, ***targeted treatment***

This allows pre-symptomatic and preventive testing

What are the advantages of predictive testing

- Individuals carrying a high-risk germline variant related to their disease are identified
- Relatives at risk are offered genetic testing
- Relatives that are non-carriers of the disease-risk variant are discharged
- Carriers of high-risk variants are referred for specialized care
- Organs at risk can be surveilled or removed
- Intensive surveillance increases the likelihood of finding cancer at early and treatable stages
- Targeted treatment can be offered
- Reproductive options can be offered
- Increased survival becomes a reality

Examples from our research at i3S

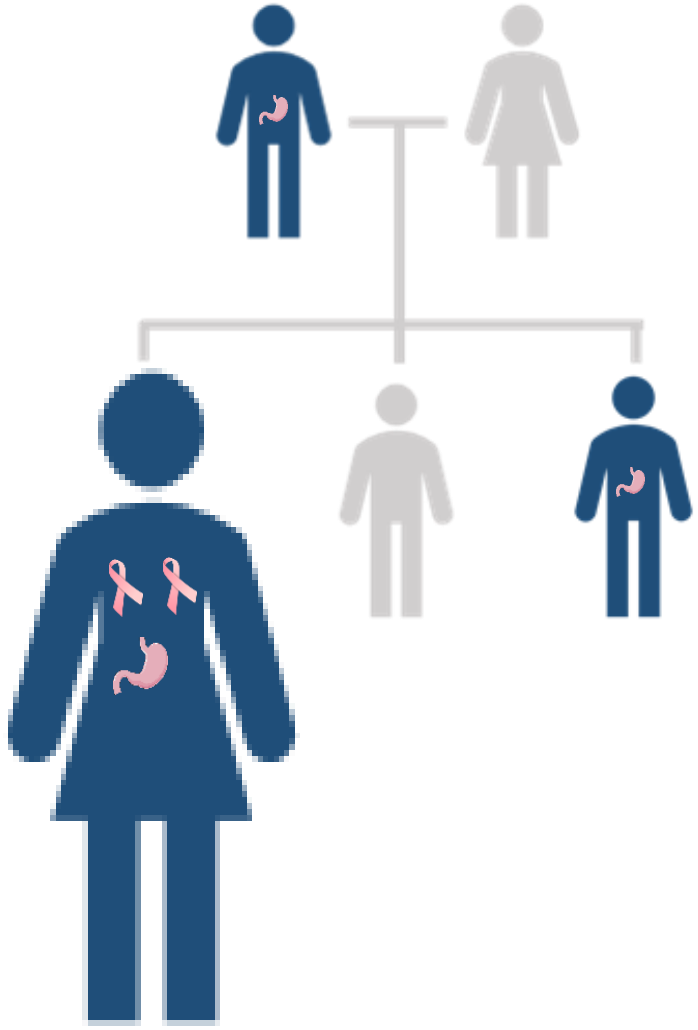
Hereditary Diffuse Gastric Cancer (HDGC)

Population incidence: ***5-10 per 100,000 births***

Target organs: ***Stomach (GC)*** *and* ***female breasts (BC)***

Mortality rate: ***High for DGC; moderate for LBC***

Causal Genes: ***CDH1 and CTNNA1***



Guilford et al, Nature Genetics 1998
Caldas & IGCLC, JMG 1999
Fitzgeral & IGCLC, JMG 2010
Van der Post & IGCLC, JMG 2015
Oliveira C et al, Lancet Oncology 2015
Blair et al, Lancet Oncology 2020
Garcia-Pelaez et al, Lancet Oncol 2023

Which is the probability for cancer development if someone is a carrier of a CDH1 variant?

Carla Oliveira
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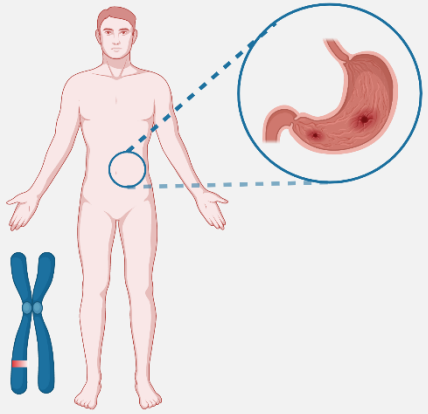
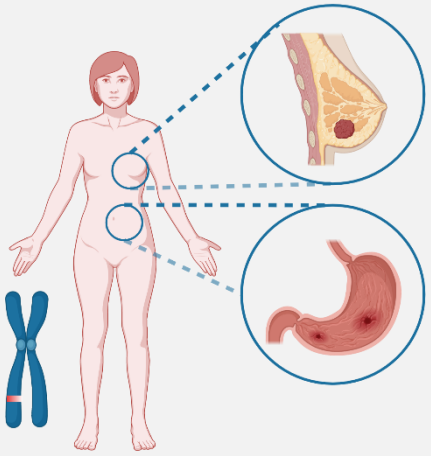
Increased risk for Stomach cancer



Increased risk for breast cancer

Increased risk for Stomach cancer



Probability of **Cancer development**

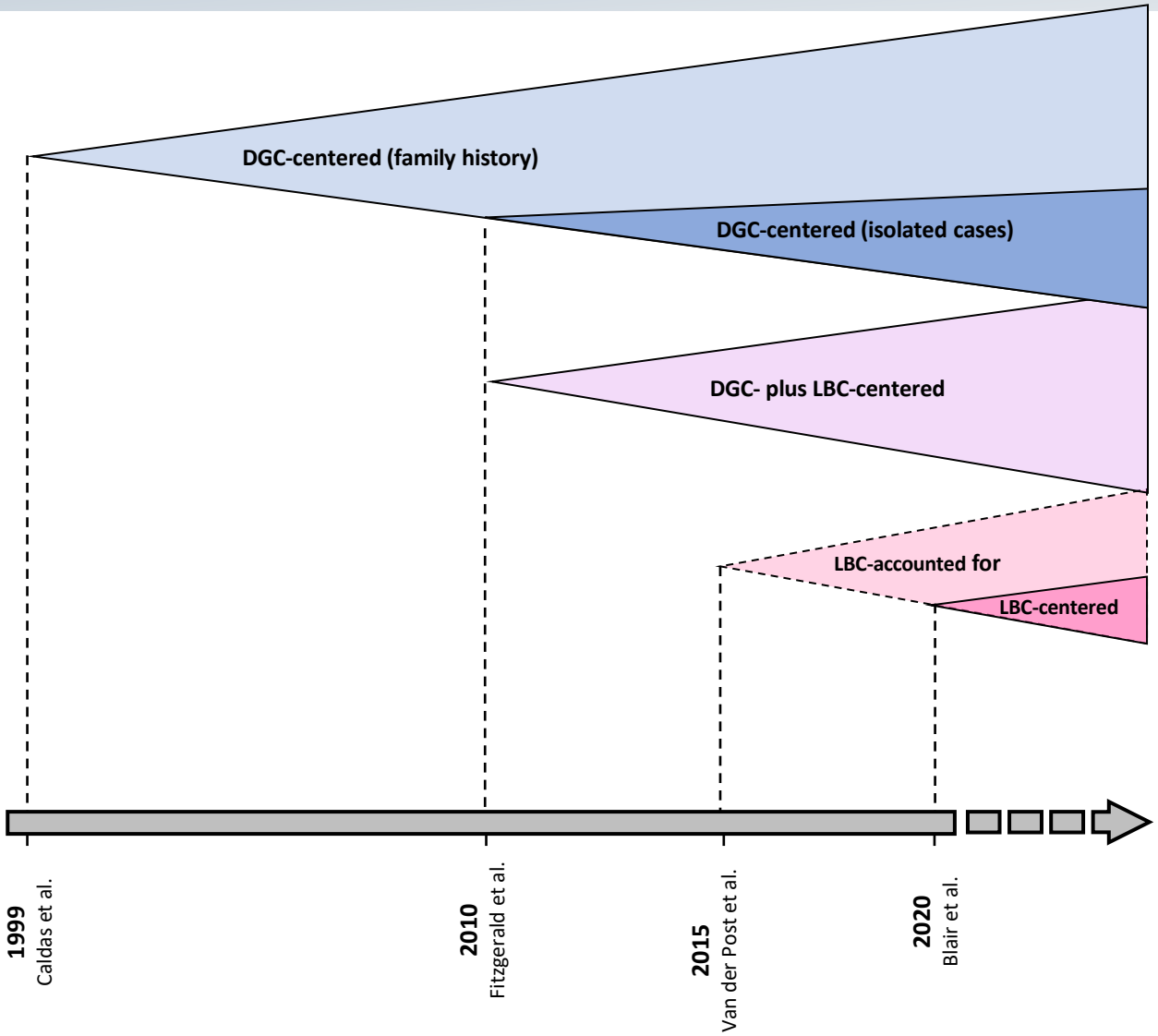
Who should be tested?

Clinical criteria for testing of *CDH1 in the germline*

Family criteria	1	**≥2 GC**, **1 DGC**
	2	**≥1 DGC** and **≥1 LBC <70** in different relatives
	3	**≥2 LBC <50** in different relatives
Individual criteria	4	Isolated **DGC <50**
	5	Isolated **DGC** (Māori ethnicity)
	6	Isolated **DGC** in CL/P individuals/families
	7	History of **DGC and LBC**, **both <70**
	8	Bilateral **LBC <70**
	9	**Gastric *in situ* signet ring cells** and/or pagetoid spread of signet ring cells **<50**

Blair & IGCLC, Lancet Oncol 2020

www.thelancet.com/oncology **Vol 21 August 2020**



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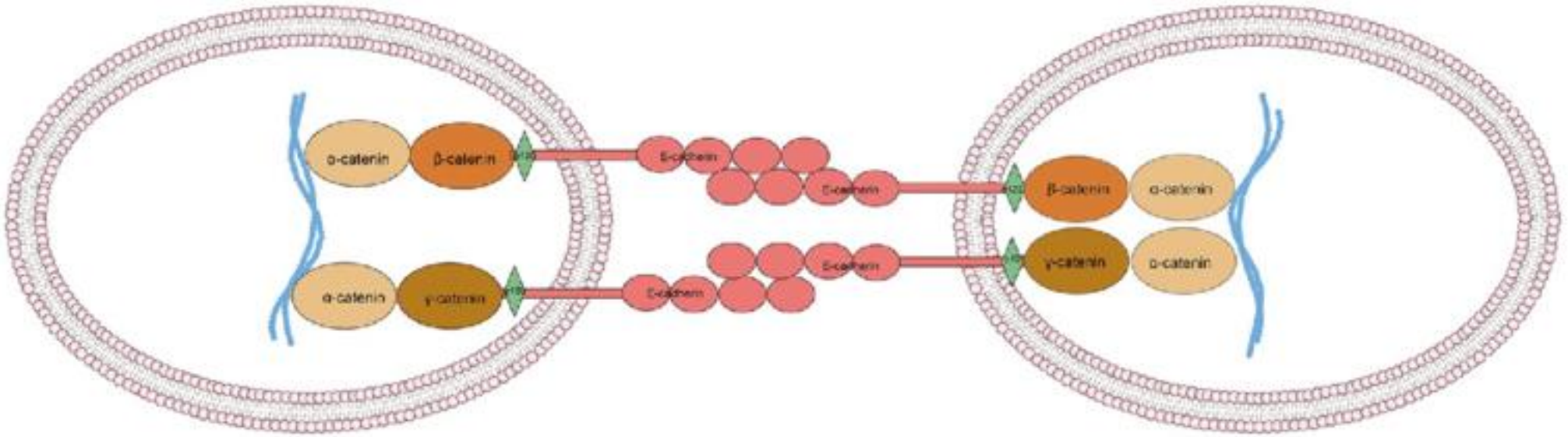
Which genes should be tested?

Which genes should be tested?



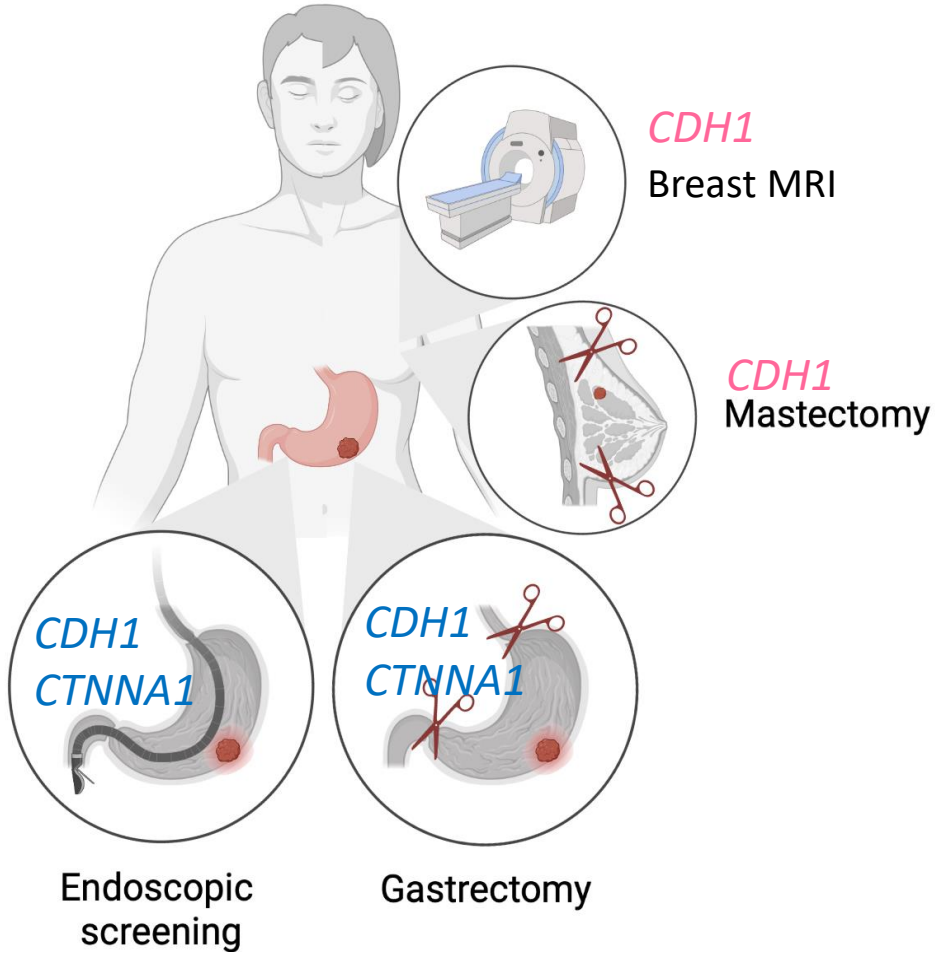
In principle, only the genes associated with the disease
CDH1 encoding E-cadherin and *CTNNA1* encoding alpha-catenin

Why is this important?

The identification of a germline variant in CDH1 and CTNNA1 has tangible consequences

Surveillance and Prophylaxis in asymptomatic carriers

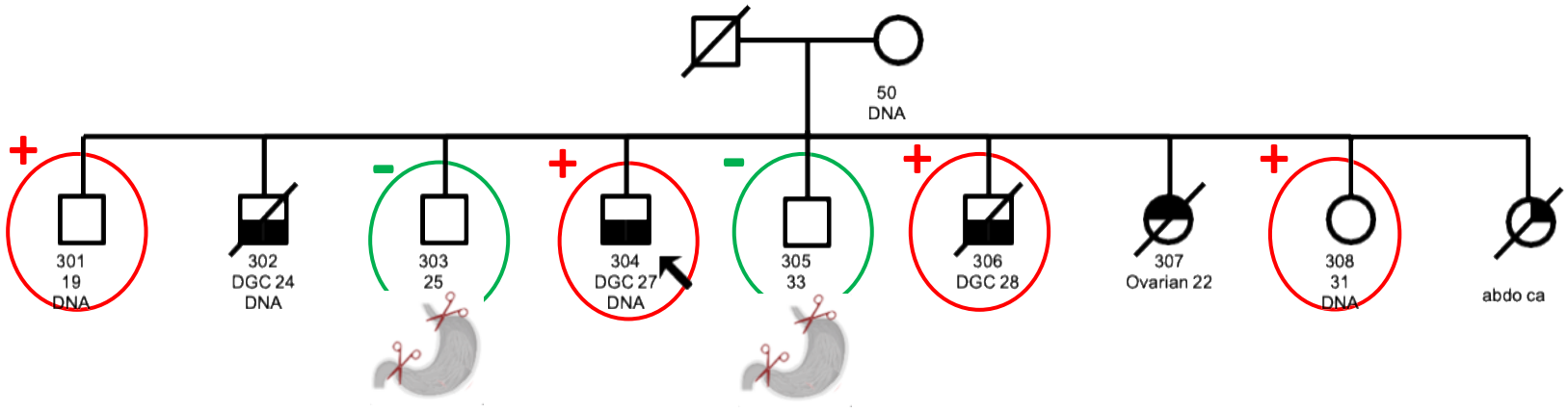
- Risk reduction gastrectomy in 20s or 30s
- Surveillance with endoscopy and multiple biopses until **early cancer lesions** are found



- Bilateral surveillance in females over 30 years with MRI and surgery to remove early lesions
- Prophylactic mastectomy in females *(if positive biopsy)*

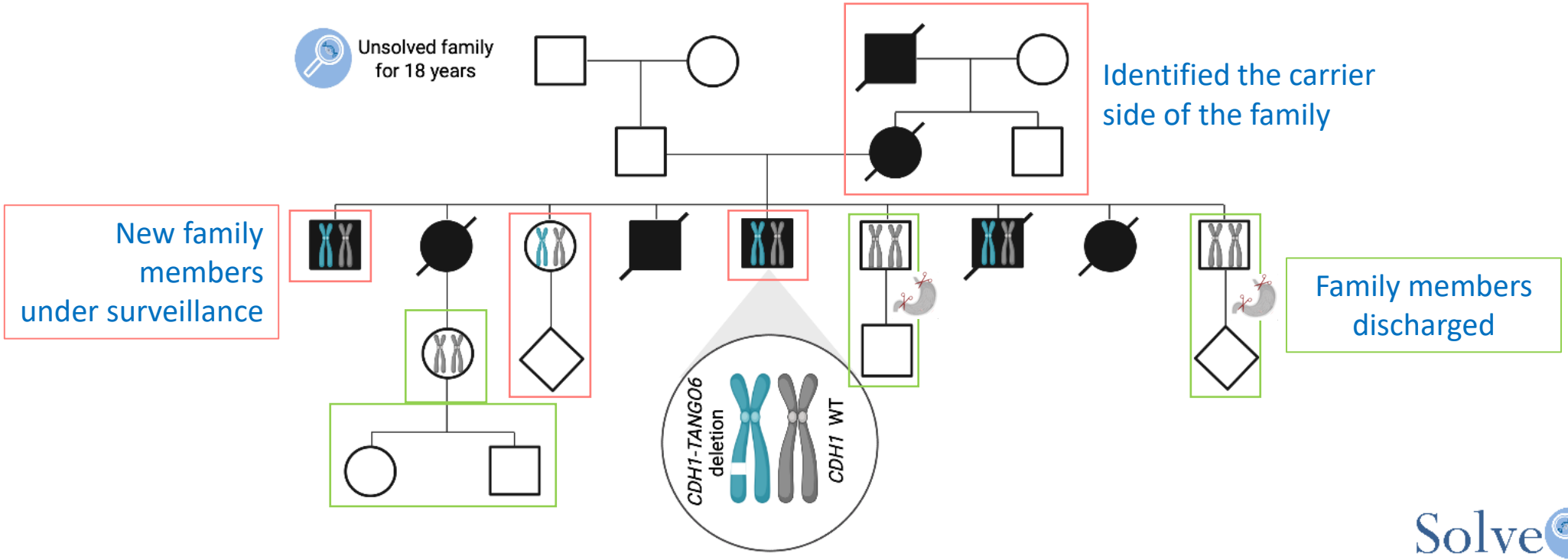
Blair et al, Lancet Oncology 2020
Garcia-Pelaez et al, Lancet Oncol 2023

The odissey of an unsolved HDGC family: **2003 -2020**



São José C et al, Gastric Cancer, 2023

The same family: 20 years later



Research: *São José C et al, Gastric Cancer, 2023*

Practice: *The family has been re-engaged and managed according to a new and clinically actionable diagnosis*

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Genotype-first approach to identify associations between *CDH1* germline variants and cancer phenotypes: a multicentre study by the European Reference Network on Genetic Tumour Risk Syndromes

José Garcia-Pelaez, Rita Barbosa-Matos, Silvana Lobo*, Alexandre Dias*, Luzia Garrido, Sérgio Castedo, Sónia Sousa, Hugo Pinheiro, Liliana Sousa, Rita Monteiro, Joaquin J Maqueda, Susana Fernandes, Fátima Carneiro, Nádia Pinto, Carolina Lemos, Carla Pinto, Manuel R Teixeira, Stefan Aretz, Svetlana Bajalica-Lagercrantz, Judith Balmaña, Ana Blatnik, Patrick R Benusiglio, Maud Blanluet, Vincent Bours, Hilde Brems, Joan Brunet, Daniele Calistri, Gabriel Capellá, Sergio Carrera, Chrystelle Colas, Karin Dahan, Robin de Putter, Camille Desseignés, Elena Domínguez-Garrido, Conceição Egas, D Gareth Evans, Damien Feret, Eleanor Fewings, Rebecca C Fitzgerald, Florence Coulet, María Garcia-Barcina, Maurizio Genuardi, Lisa Golmard, Karl Hackmann, Helen Hanson, Elke Holinski-Feder, Robert Hüneburg, Mateja Krajc, Kristina Lagerstedt-Robinson, Conxi Lázaro, Marjolijn J L Ligtenberg, Cristina Martínez-Bouzas, Sonia Merino, Geneviève Michils, Srdjan Novaković, Ana Patiño-García, Guglielmina Nadia Ranzani, Evelin Schröck, Inês Silva, Catarina Silveira, José L Soto, Isabel Spier, Verena Steinke-Lange, Gianluca Tedaldi, María-Isabel Tejada, Emma R Woodward, Marc Tischkowitz, Nicoline Hoogerbrugge, Carla Oliveira*

Lancet Oncol 2022

Published Online
November 24, 2022
https://doi.org/10.1016/S1470-2045(22)00643-X

José Pelaez

We demonstrated that:

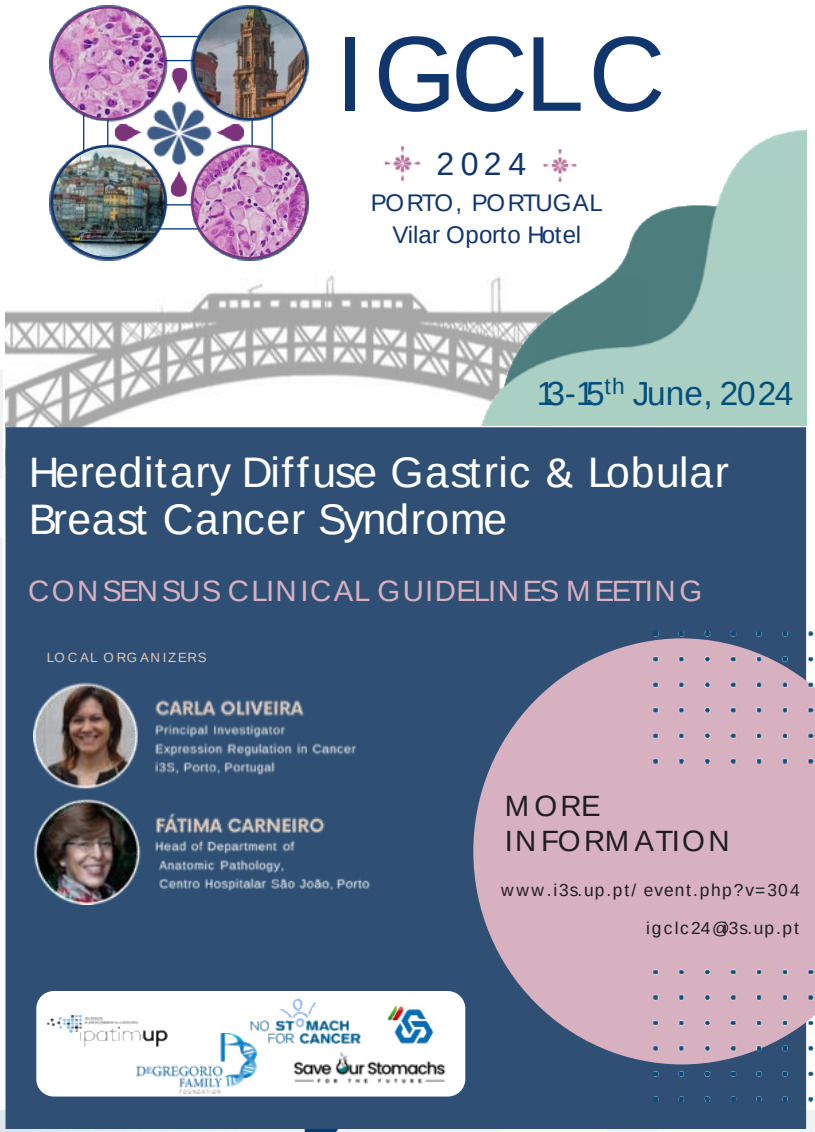
- There are specific types of *CDH1* variants that greatly increase the risk for diffuse gastric cancer and lobular breast cancer
- The current criteria to select patients for testing are clearly insufficient

3º Encontro Nacional de Investigação Clínica & Inovação Biomédica

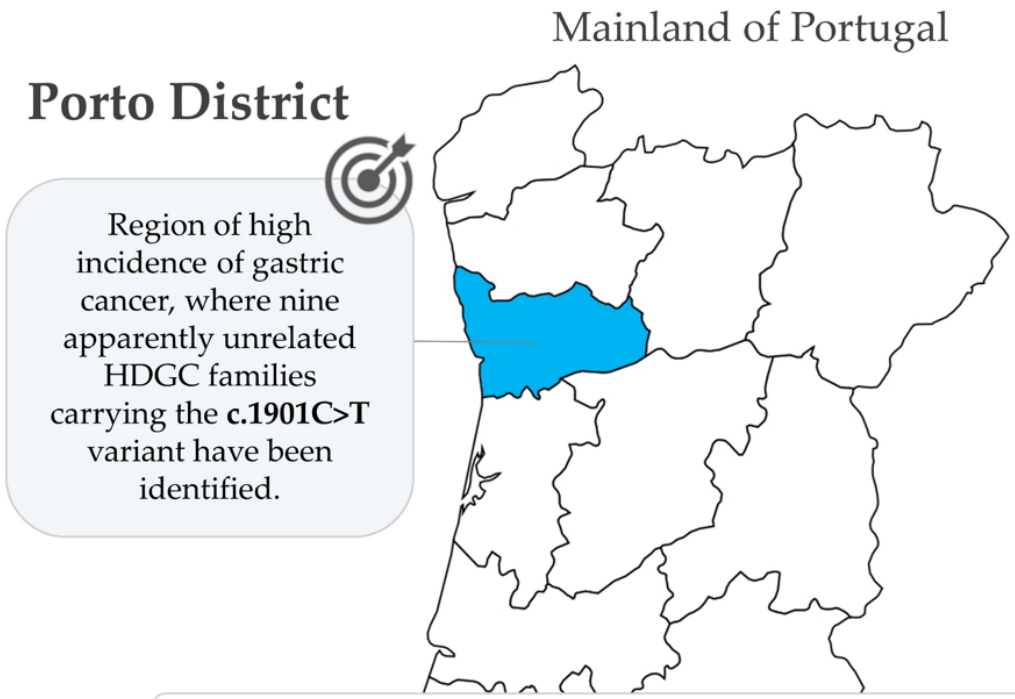
New criteria for genetic testing in HDGC families

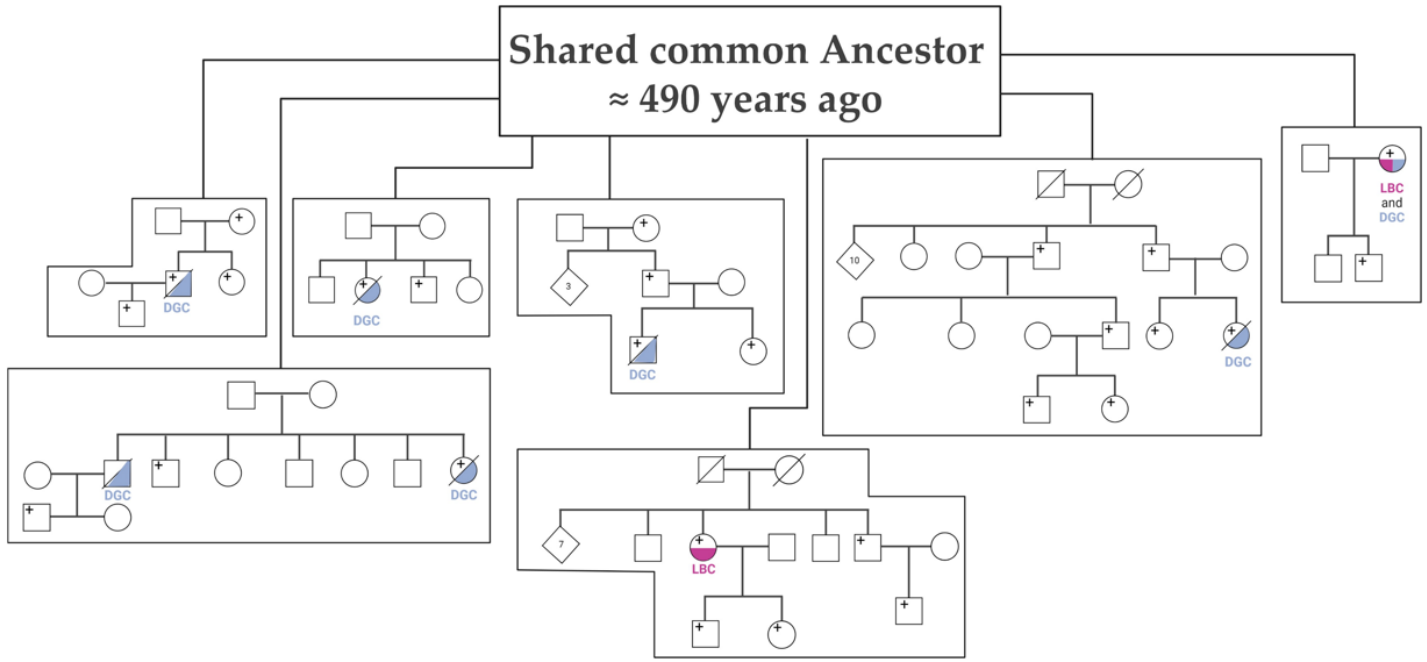
Research: *Pelaez J & ERN GENTURIS, Lancet Oncology 2023*

Practice: *The new proposed criteria for testing will be presented and discussed with the International Gastric Cancer Linkage Consortium for inclusion in Consensus Clinical Guidelines*



A Founder variant in *CDH1* in the Portuguese population





Research: *Matos R et al, Cancers, 2021*

Practice: *This is the first variant we test in families from the Porto District*

Best Use of Resources

If **1 million GC cases** are diagnosed yearly worldwide and 1% are potentially inherited…

This means that per year:

1. *We can work towards **identification of families** that **carry inherited causative genetic defects** and are **predicted to develop** GC throughout their lives.*

2. *This represents up to **10.000** GC patients per year plus their carrier relatives*

3. *If we can identify these individuals while they are asymptomatic, we can prevent disease, so we do not need to treat or cure*

Preventable

SUSTAINABLE CARE FOR RARE TUMOUR RISK SYNDROMES

https://preventable.eu/

HORIZON EUROPE

CANCER PREVENTION VS CANCER TREATMENT: THE RARE TUMOUR RISK SYNDROMES BATTLE

4.6	36	15	8
Budget (M€)	Duration (Months)	Partner Institutions	European Countries

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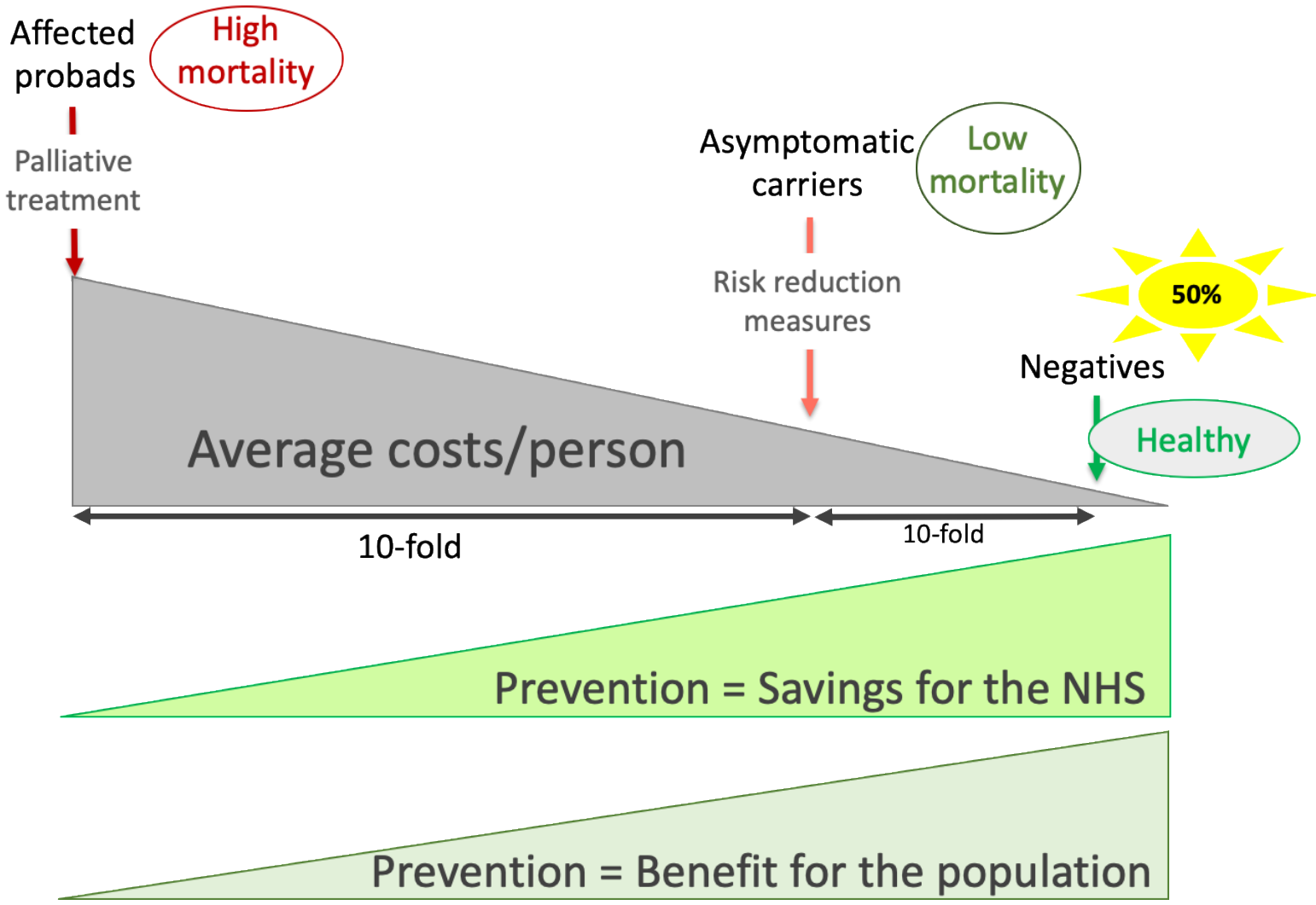
Best Use of Resources: 200 individuals from an HDGC family



Main expected outcomes of PREVENTABLE

Clinical:
Clinical care targeting patients at risk
Improved overall survival

Health Economics:
Demonstration of cost-effectiveness of surveillance and early diagnosis over treatment of advanced disease

CANCER TREATMENT
VS
CANCER PREVENTION

COST SURVEILLANCE / PROPHYLAXIS
VS
COST TREATMENT

https://preventable.eu/

Aknowledgements

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https://ec.europa.eu/health/ern_en

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M. Tischkowitz

All patients and their families

The IGCLC International Gastric Cancer Linkage Consortium

PrevenTalk 1

REGISTER NOW

Understanding and Addressing the Challenges of Rare Tumour Risk Syndromes

Uniting Science, Health Management and Policy

24 May 2024 | 16:00 – 17:00 CET

Online (zoom video conference)

https://bit.ly/PrevenTalk1

Our speakers

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Project Coordinator
PREVENTABLE

Hildegunn Vetti

Geneticist FMM
Principal Investigator
PREVENTABLE

Raquel Chantre

Healthcare Manager
APAH Portugal

Alina Senn

Policymaker
European Commission DG
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SUSTAINABLE CARE FOR RARE TUMOUR RISK SYNDROMES

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Conference

REGISTER NOW

CHARTING THE ECONOMICS OF HEREDITARY CANCER: FROM THEORY TO REAL WORLD DATA

Agenda:

- Rare Tumour Risk Syndromes (RTRS)
- Helathcare cost-Effectiveness
- PrevenTalk 2 (RTRS stakeholder outreach)
- Communication in Healthcare

3 October 2024

Rouen, France

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SUSTAINABLE CARE FOR RARE TUMOUR RISK SYNDROMES

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Muito obrigado pela vossa atenção.
Thank you for your time.