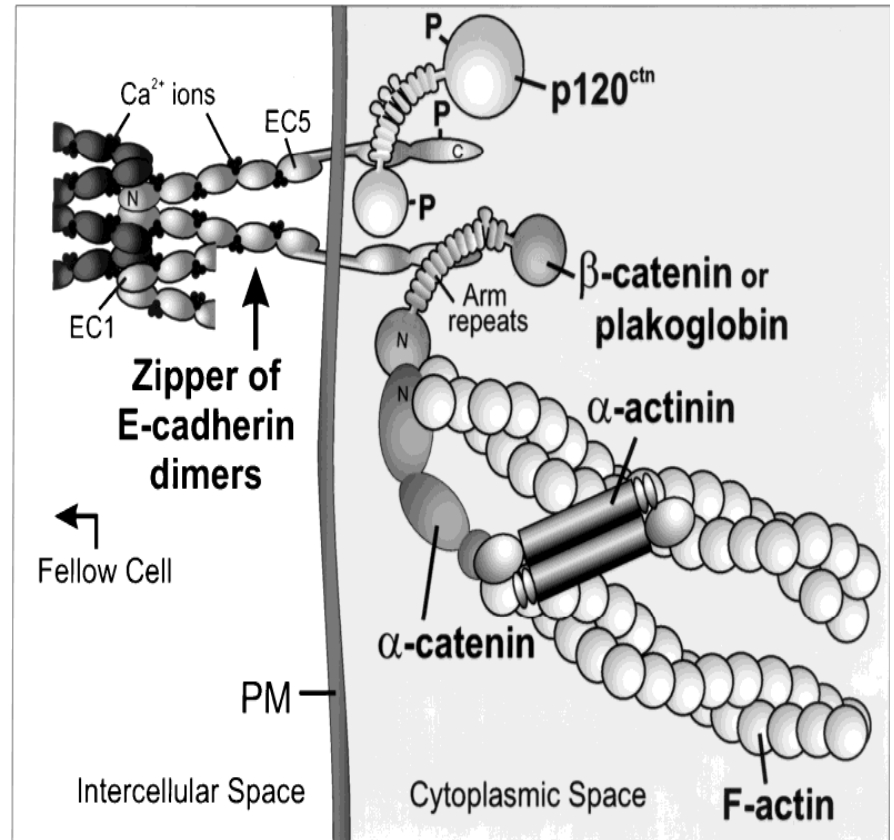
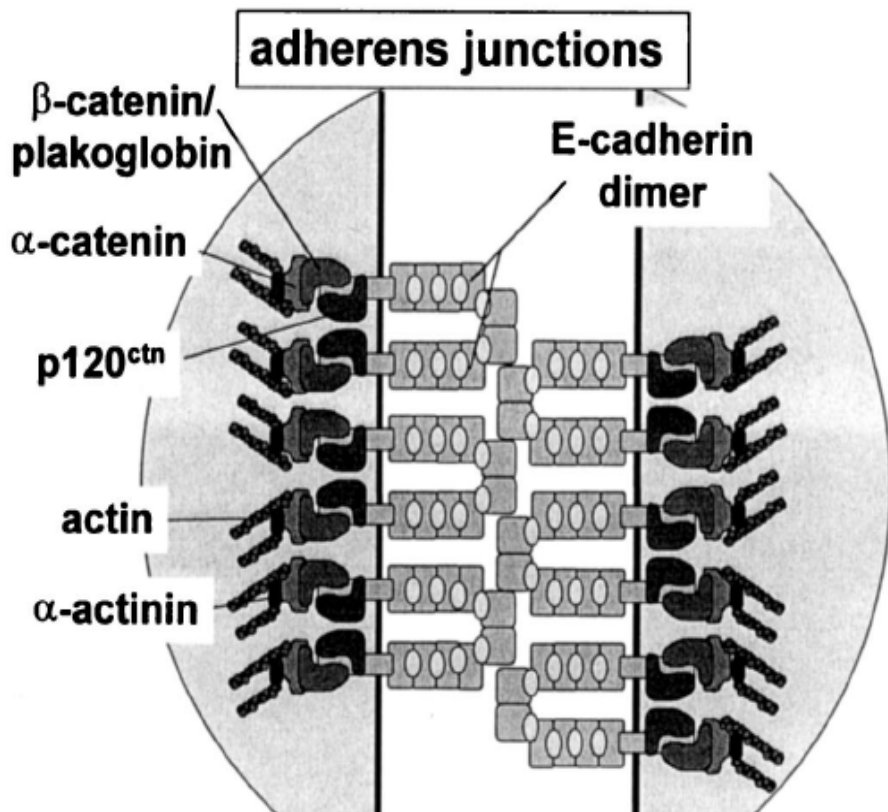


CDH1 gene mutation and related cancer spectrum

Molecular Diagnostic Lab
City of Hope National Medical Center
08/17/08

CDH1 gene

- **Position:** chr16:67328696-67426945
- **Band:** 16q22.1
- **Genomic Size:** 98.25kb
- **Exon:** 16, start codon at exon1
- **Protein:** 882aa, Epithelial-cadherin precursor (E-cadherin) (Cadherin-1)
- **Protein function:** Transmembrane glycoproteins mediating calcium-dependent cell-cell adhesion, maintain the normal architecture and formation of epithelial cells. Loss of function contributes to progression in cancer by increasing proliferation, invasion, and/or metastasis



Schematic overview of the E-cadherin–catenin–cytoskeleton complex at the plasma membrane of two neighboring cells.

Cadherins are vital in cell-cell adhesion during tissue differentiation. Cadherins are linked to the cytoskeleton by catenins. Catenins bind to the cytoplasmic tail of the cadherin. Ca²⁺ ions are essential for the correct conformation and functionality of the cadherins

Lifetime Risk of Gastric Cancer

Based on rates from 2001-2003, 0.89% of men and women born today will be diagnosed with cancer of the stomach at some time during their lifetime.

This number can also be expressed as 1 in 113 men and women will be diagnosed with cancer of the stomach during their lifetime.

Hereditary Diffuse Gastric Cancer (HDGC)

- Two or more cases of gastric cancer in a family, with at least one diffuse gastric cancer diagnosed before age 50 years
- Three or more cases of gastric cancer in a family, diagnosed at any age, with at least one documented case of diffuse gastric cancer

International Gastric Cancer Linkage Consortium (IGCLC) [Caldas et al 1999].

Guilford P et al. Nature. 1998;392:402-5

- Since 1964, 25 family members have died of gastric cancer. Majority of cases died before 40 yrs with the youngest age of death is 14
- Three mutations were identified in three different families:

1st mutation: 1008 G>T, splice donor site of exon 7, cause 7 bp insertion and generate a premature stop codon in exon 8.

2nd mutation: 2382insC frameshift mutation.

3rd mutation: 2095C>T nonsense mutation.

CDH1 mutation identified in Other races

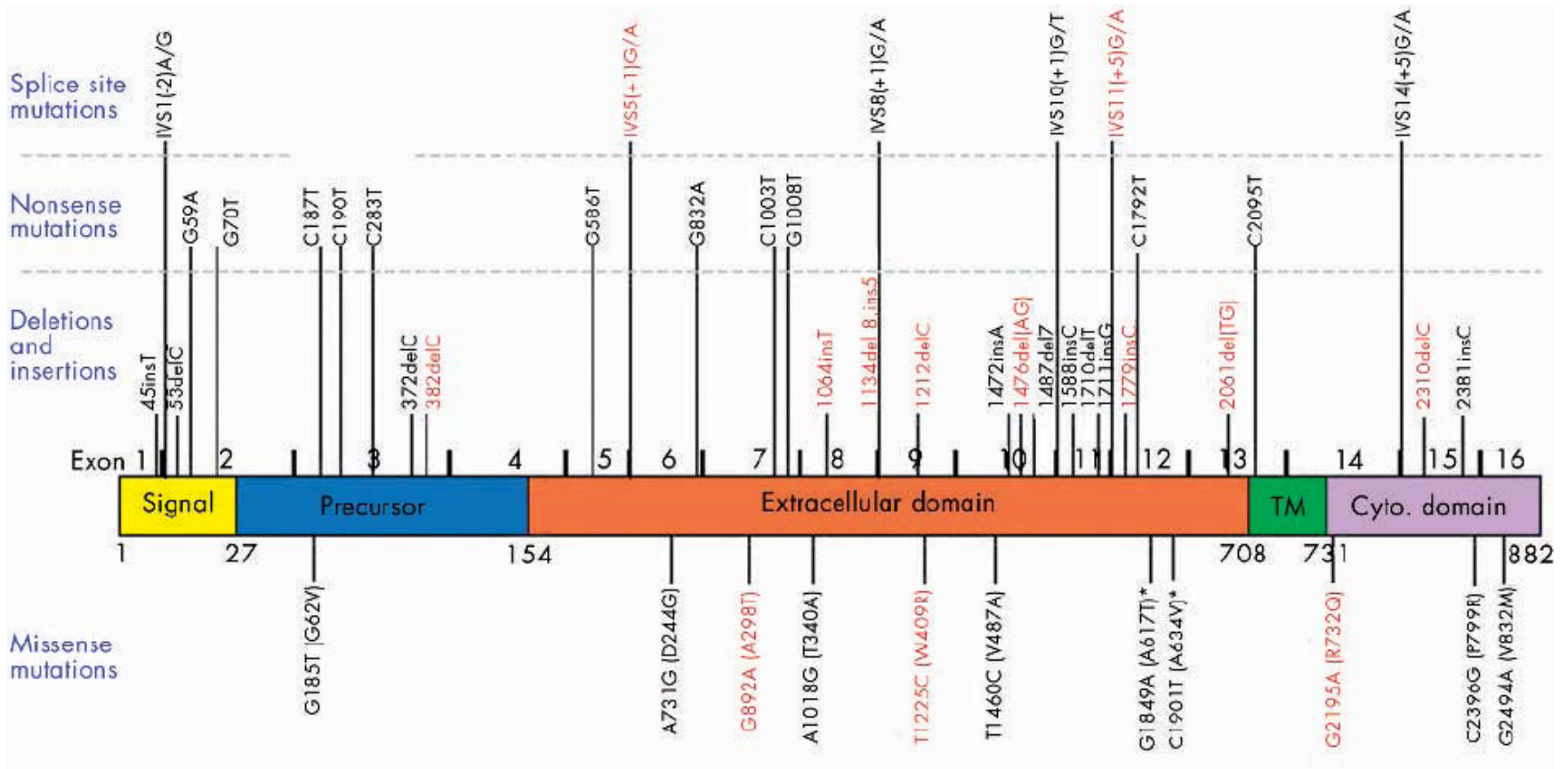
Mutations detected in USA, UK, Canada, Italian, China, Korea, Japan, Pakistan and Spanish origin

1. Gayther SA *Cancer Res* 1998; 58:4086–89
2. Oliveira C *Hum Mutat* 2002;19:510–17
3. Suriano G *Hum Mol Genet* 2003;12:575–82.
4. Keller G J *Med Genet* 2004;41:e89
5. Brooks-Wilson AR (2004) *J Med Genet* 41:508-17

Life time risk of HDGC with CDH1 mutation

- Based on data from 11 families which included at least 3 cases of DGC and at least 1 affected member had tested positive for CDH1 mutation. Families from NZ, UK, USA, Canada, Germany, France, Pakistan.
- Total 476 individuals, 80 cases of Diffuse Gastric Cancer, 7 cases of Breast Cancer, 5 cases of colon cancers, 9 other cancers were reported.
- The estimated cumulative risk of gastric cancer by age 80 years is **67%** (95% CI, 39-99) for men and **83%** for women (95% CI, 58-99). Women also have a **39-52% risk for lobular breast cancer (95% CI, 12-84)**.
- The average age of onset of hereditary diffuse gastric cancer is **38** years, with a range of **14-69** years.

Germline Mutations



More than 80 CDH1 mutations have been found to date. Two marked with an asterisk have been reported as somatic mutations in sporadic DGC. No Gross deletions/duplications, complex rearrangements, repeat variations been reported. They spread out all over CDH1 gene.

Summary of mutation in sporadic early onset gastric cancer

Study Characteristics						Findings		
Reference	Age	n	GC Incidence/Country	Histology	Methods	#GL	CPC	Other
This study	≤50	81	Low/Canada	36 DGC 41 MGC 4 SGC	PCR-SSCP	EX1/nt41delT Fs term 32	30/♂	Loss of E-cad IHC staining
Suriano 05	≤35	10	Low/North America (diverse ethnicity)	All DGC	PCR-dHPLC	EX8/nt1063delT Fs term 355	27/nos	
						EX9/ntC1285T P429S, in vitro ✓	27/nos	
Keller 04	≤45	15	High/Germany	14 DGC 1 MGC	PCR-dHPLC	EX11/nt1619insG Fs term 547	29/nos* Mom had bilateral brca	abN E-cad IHC, diffuse cytoplasmic staining
Suriano 03	≤51	66	Mix/UK 26, USA 6, Portugal 22, Italy 11, Greece 1	37 DGC, 12 IGC, 17 MGC	PCR-SSCP	EX12/ntC1901T A634V, in vitro ✓	30/♂	E-cad IHC could not be done
EOGC studies with negative findings								
Saito 99	<35	9	High/Japan	All DGC	PCR-SSCP	0/9		
Brooks-Wilson 04	<50	9	Low/US, UK, Canada	All DGC	Seq & PCR-SSCP	0/9, SNPs only		
Carvalho 04	<45	40	Mixed:Netherlands, Finland, USA	21 DGC 10 IGC 9 MGC	PCR-SSCP	0/40 3 variants		
Oliveira 04	<45	23	High/Portugal	16 DGC 2 IGC 5 GC	PCR-SSCP	0/23 SNPs only		

Total

253

5

5/253=2%

Legend: DGC = diffuse gastric cancer, MGC = mixed gastric cancer, SGC = solid gastric cancer, IGC = intestinal gastric cancer, abN = abnormal, nos = not otherwise specified, in vitro ✓ =pathogenicity proven by in vitro mutant studies, ♂ = male, brca =breast cancer.

Caveats:

- SSCP, dHPLC may miss some mutations because of limited sensitivity of techniques
- Failure of PCR in some exons
- No methods used to detect large deletion/duplications

Indications for DNA testing

Hereditary Diffuse Gastric Cancer¹⁻³

- **Two or more cases of gastric cancer in one's family with at least one diffuse gastric cancer diagnosed before age 50 years.**
- **Three or more cases of gastric cancer in one's family, diagnosed at any age, with at least one documented case of diffuse gastric cancer.**

Early onset Sporadic Gastric Cancer⁴⁻⁷

- **An individual diagnosed with diffuse gastric cancer before 45 years of age.**

Lobular Breast Cancer⁸⁻¹¹

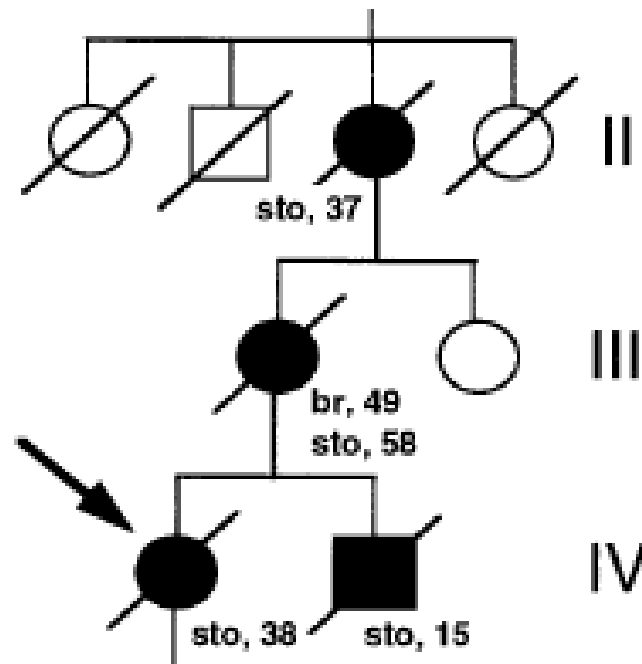
- **An individual diagnosed with both diffuse gastric cancer and lobular breast cancer (no other criteria required).**
- **One family member diagnosed with diffuse gastric cancer and another with lobular breast cancer (no other criteria required).**

Signet Ring Colon Cancer ^{9, 12, 13}

- **One family member diagnosed with diffuse gastric cancer and another with signet ring colon cancer (no other criteria required).**

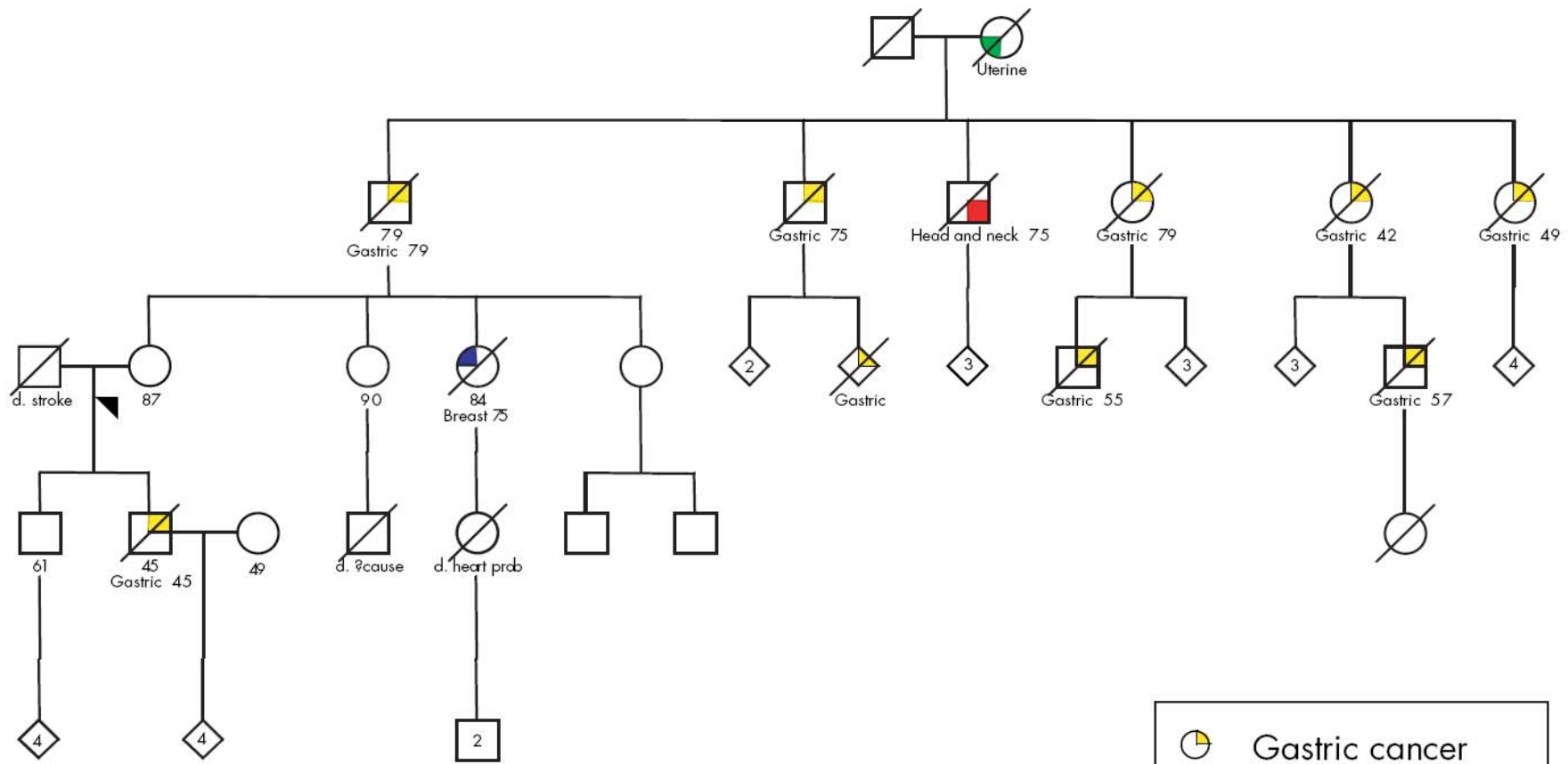
1. Guilford P et al. *Nature* 1998; 392:402–5;
2. Gayther SA. et al. *Cancer Res* 1998; 58:4086–89.
3. Oliveira C et al. *Hum Mutat* 2002; 19:510–17
4. Suriano G et al. *Hum Cancer Biol* 2005; 11:5401–09
5. Suriano G et al. *Hum Mol Genet* 2003; 12:575–82.
6. Keller G J et al. *Med Genet* 2004; 41: e89.
7. Bacani, JT. et al. *J Med Genet.* 2006; Jun 26 online.
8. Keller G et al. *Am J Pathol* 1999; 155:337–42.
9. Brooks-Wilson AR et al. *J Med Genet.* 2004; 41:508-17.
10. Oliveira C et al. *Hum Mutat* 2002;19:510–17.
11. Berx G. et al. *Breast Cancer Res* 2001; 3:289–293
12. Richards FM. et al. *Hum Mol Genet* 1999; 8:607–10.
13. Kim, HC et al. *Gut* 2000; 47 262-67

Lobular breast carcinoma: part of CDH1 mutation spectrum



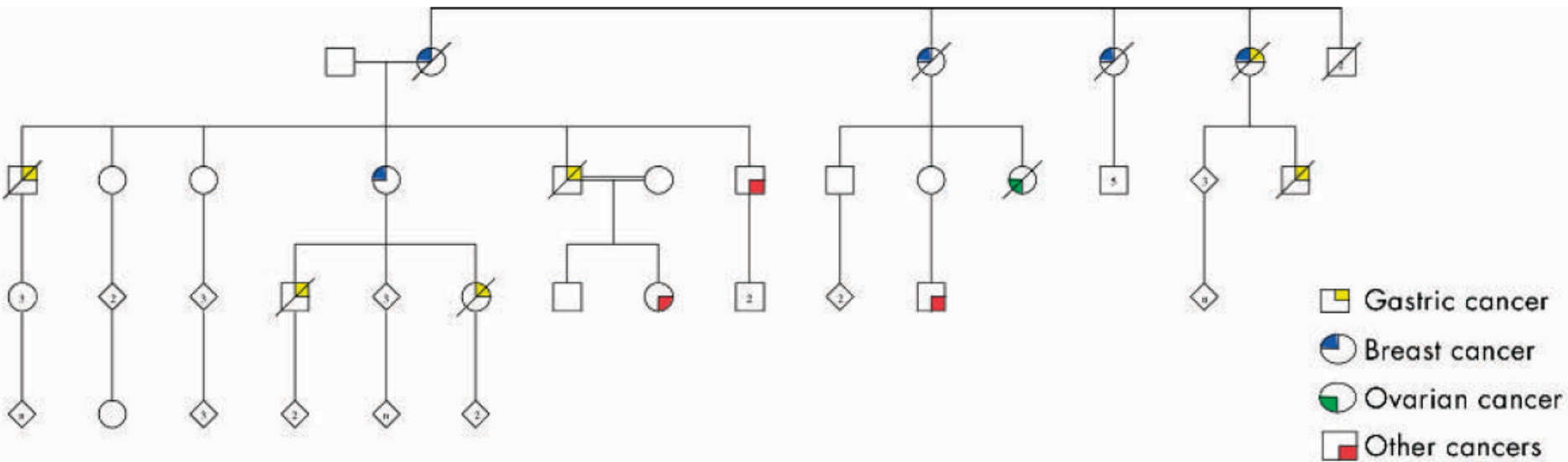
Mother of proband with both diffuse gastric cancer and lobular
breast cancer
377delC of exon 3

Keller et al *AJP* 1999, Vol. 155 (2) 339-42



One family member diagnosed with diffuse gastric cancer and another with lobular breast cancer. Mutation: 2310delC of exon 15

Brooks-Wilson, A R et al. J Med Genet 2004;41:508-517



One family member diagnosed with diffuse gastric cancer and another with lobular breast cancer. Mutation: IVS11+5 G>A

Brooks-Wilson, A R et al. J Med Genet 2004;41:508-517

CDH1 mutation and Lobular breast cancer

- In 11 HDGC families, 7 breast cancers were identified in female family members, Pharoah et al. estimated the cumulative risk for breast cancer is 39% at 80 years
- Of the 45 HDGC kindred identified, 18 families include at least 1 case of breast cancer (1-5 cases/kindred), in total, there are 32 cases of breast cancer in these 18 families.
- Increasing evidence suggests that the lobular breast cancer associate with HDGC

[Keller et al 1999 , Oliveira et al 2002 , Brooks-Wilson et al 2004]

CDH1 mutation associate with HDGC and lobular breast cancer

- E-cadherin immunostaining is complete absent in most (85%) sporadic invasive lobular breast cancer but not ductal breast cancer
- Somatic CDH1 mutation have been identified in 56% of sporadic lobular lobular breast cancer but are rare in ductal breast cancer

The E-cadherin/catenin complex: an important gatekeeper in breast cancer tumorigenesis and malignant progression

Geert Berx and Frans Van Roy

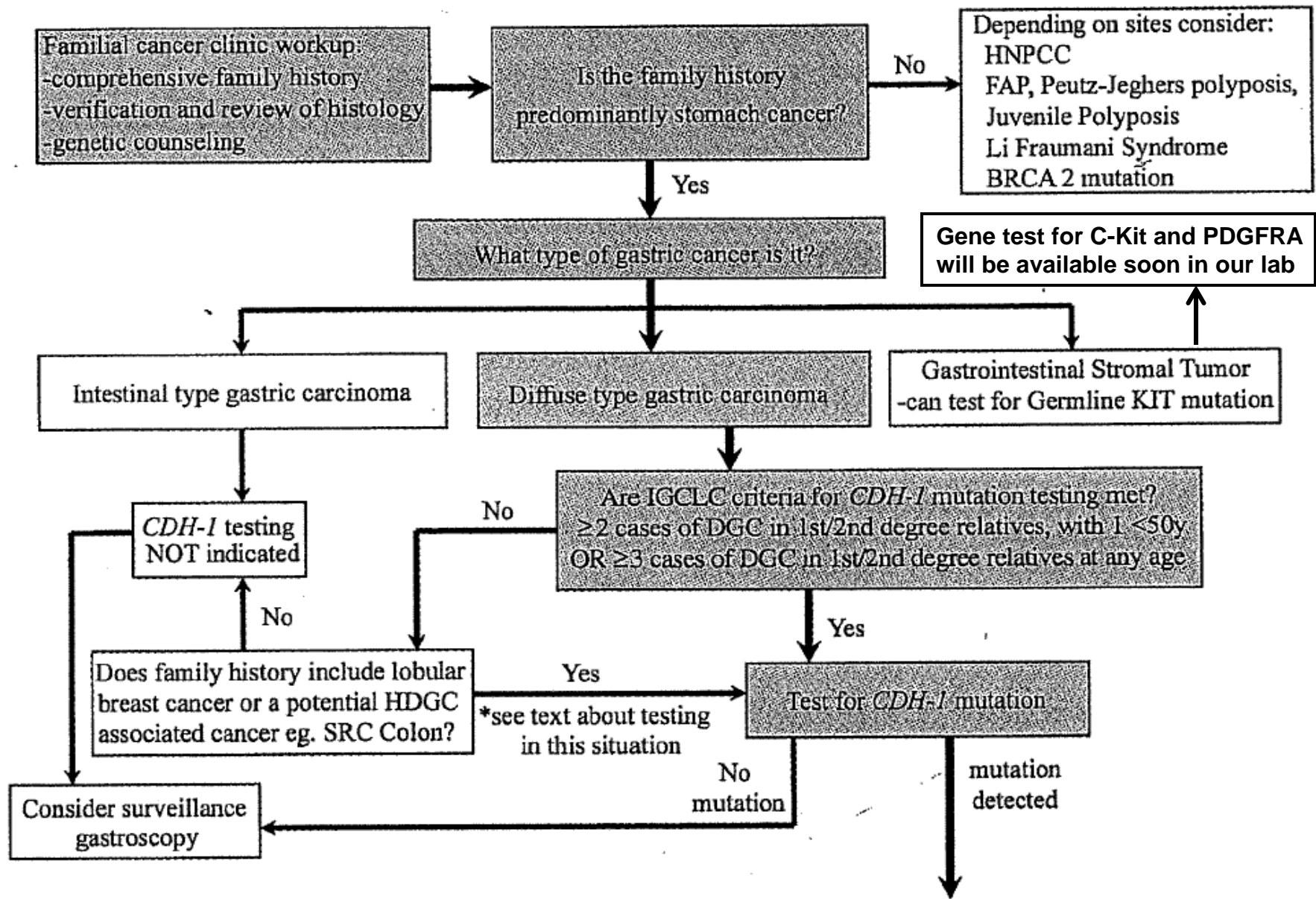
Breast Cancer Res 2001, **3**:289–293

CDH1 somatic mutation

- 472 human tumors and 15 different cancer cell lines derived from 10 different tissues have been screened for CDH1 mutation. So far, frequent somatic mutations (50%) have been identified only in sporadic DGC, LBC.
- For sporadic DGC, most somatic mutations are missense (ex 8, 9) or exon skipping
- For sporadic LBC, most somatic mutations are truncating.
- Hypermethylation of CDH1 Promoter is the common 2nd hit for DGC.

Signet ring cell cancer (SRCC) of the colon

- Signet ring carcinomas of the colon are rare, representing nine of 3000 (0.3%) of colon cancers in a series of colon cancers from Singapore, 27 of 2589 (1%) cases from Canada.
- Loss of E-cadherin expression
- Two missense mutation have been identified (W409R, 51yrs, no family history; Thr340Ala, 35 year old male)
- Given the loss of somatic E-cadherin expression in SRCCs, the SRCC phenotype and the rarity of this tumor type suggest that SRCC occasionally may be part of the HDGC tumor spectrum



Management of Hereditary Diffuse Gastric Cancer

Management

- **Gastric cancer.** Ideally, management of individuals who have a *CDH1* cancer-predisposing mutation is either intense surveillance for early detection and treatment of gastric cancer or prophylactic gastrectomy. **In most cases, the cancer is not detected until it reaches an incurable, advanced stage.**
 - 1) Endoscopy.** It is recommended that individuals at risk who do not wish to have prophylactic gastrectomy undergo a detailed 30-minute endoscopic examination of the gastric mucosa with multiple random biopsies and biopsies of subtle lesions at **6- to 12-month intervals** [Caldas et al 1999].
 - 2) Chromoendoscopy** , using indigo-carmin staining, has been shown to improve the detection rate of early gastric cancer [Stepp et al 1998 , Fennerty 1999].
- **Lobular breast cancer.** At-risk women should undergo regular breast screening as determined by their physicians, including a **clinical examination every six months and breast self-examinations**. Because lobular breast cancer is often **difficult to diagnose on clinical examination and mammography**, it may also be prudent to refer a woman who has a *CDH1* germline mutation to a **high-risk breast cancer screening program** and to **consider use of MRI**, which appears to be more sensitive than mammography in detecting tumors in such women
- **Colon cancer.** colonoscopy every **12-18 months beginning at age 5-10 years** prior to the youngest age of colon cancer onset in families in which both DGC and colon cancer have occurred.