

Update from the International Guideline meeting held in New Zealand plus an update on endoscopy screening

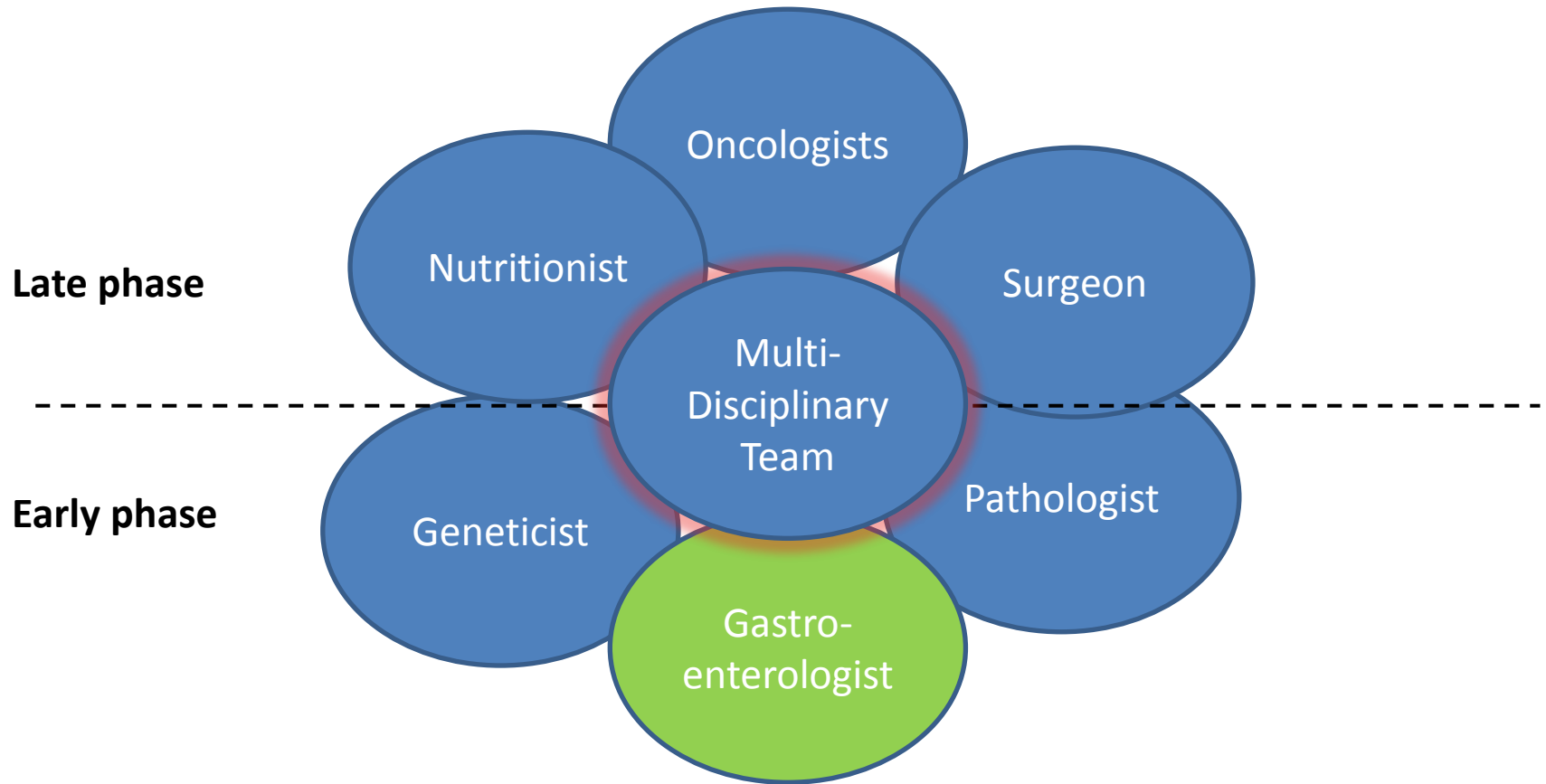
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HDGC workshop, Cambridge 6th June 2019

Multidisciplinary team for HDGC



The Cambridge HDGC endoscopy service

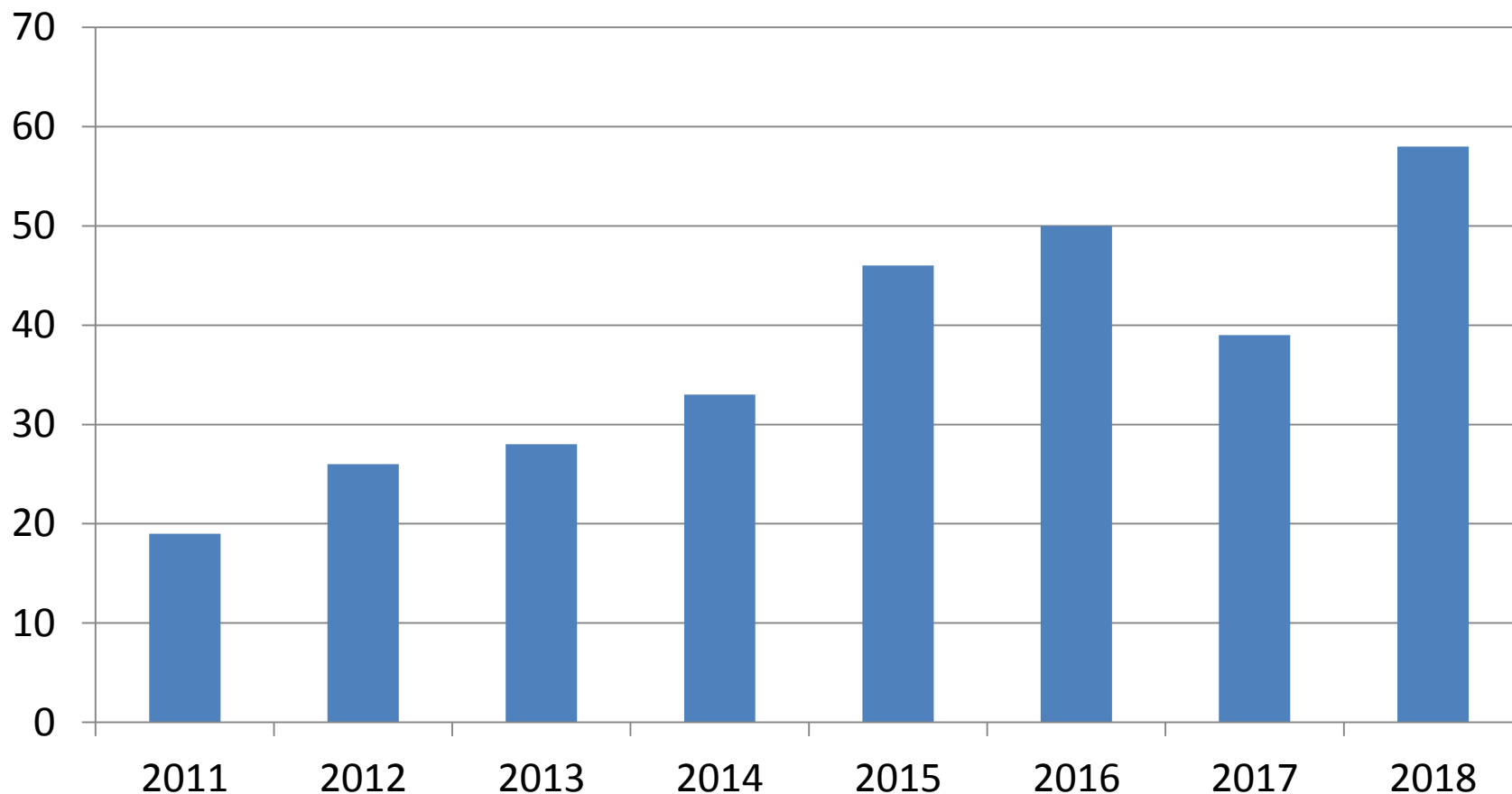
- 2 gastroenterologists, 4 pathologists, 1 full time research nurse, 3 UGI research nurses
- Dedicated research endoscopy unit (CCRC)
- State of the art endoscopy technology
- Direct access to clinic (face to face or telephone or telephone consultation) and to psychology service

Cambridge team



Endoscopy activity in the last 8 years

Number of HDGC surveillance endoscopies



Indications for endoscopy in HDGC

- Family history of diffuse gastric cancer prior to genetic testing
- Clinical diagnosis of HDGC but no CDH1 mutation found (>70%)
- CDH1 mutation carrier prior to surgery
- Individuals with CDH1 mutation who wish to delay surgery

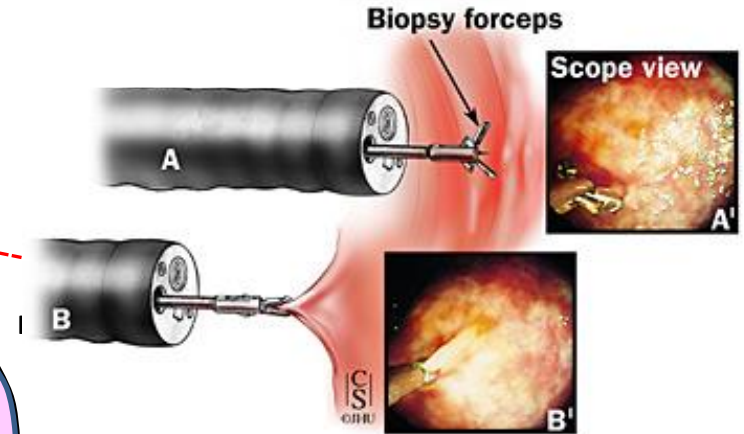
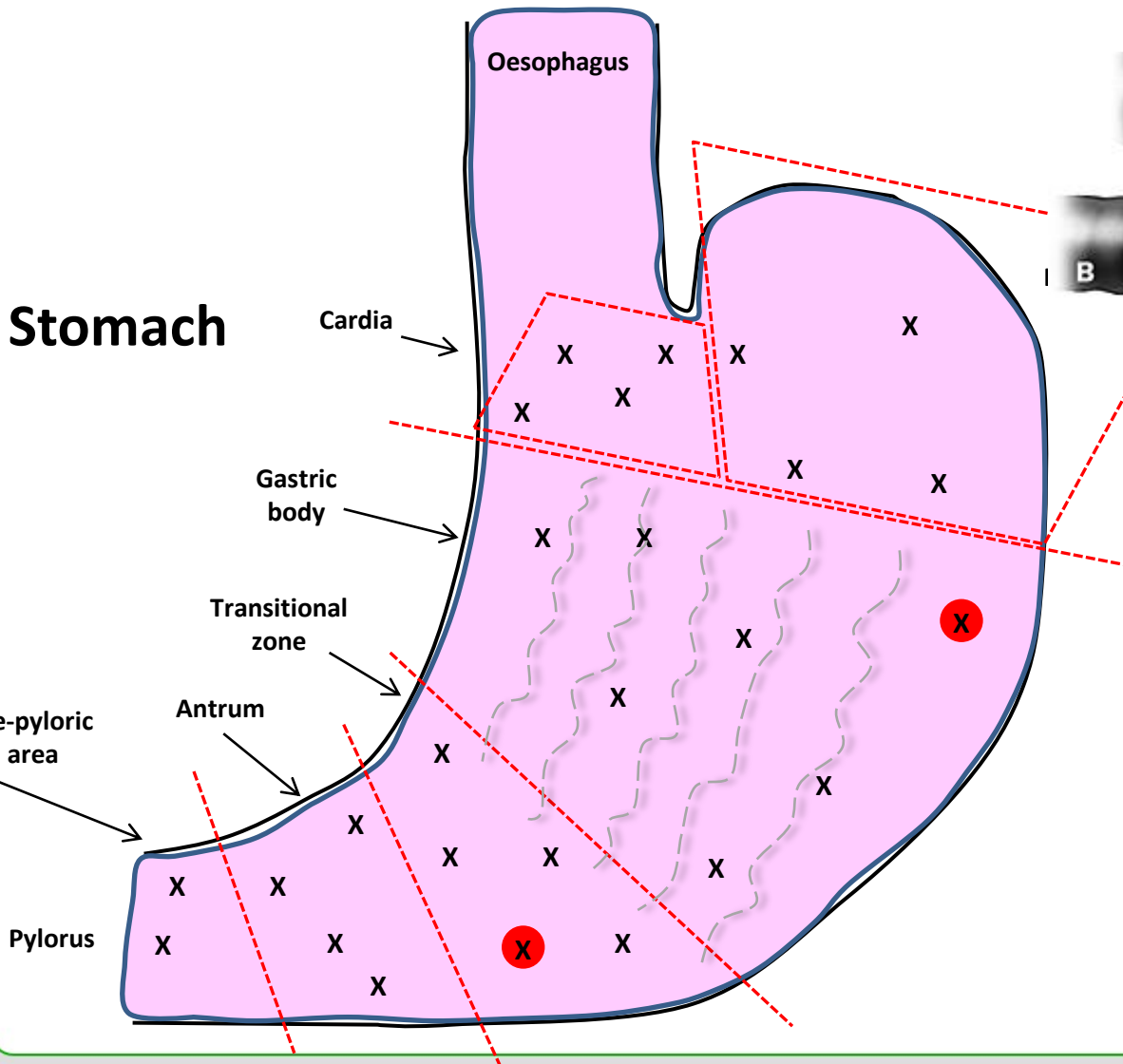
Advantages of endoscopy in CDH1 mutation carriers

- Stomach easily accessible with endoscopic cameras
- Endoscopy allows taking small tissue samples (biopsies) for pathological diagnosis
- In individuals with known genetic mutations endoscopy can inform about timing of surgery
- If genetic mutation is not known it can inform about whether surgery is needed
- Within research protocols, it helps understand the natural history of this hereditary condition and study molecular mechanisms

Disadvantages

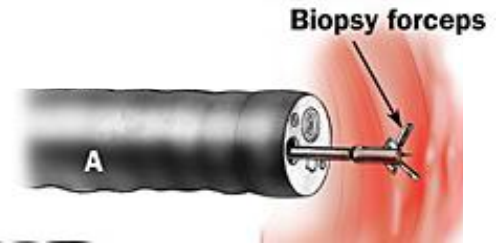
- False negative results cannot be excluded (small groups of cancerous cells can be missed by the random biopsies)
- Discomfort / mild pain
- Complications (bleeding, perforation – very rare)
- Psychological implications

Cambridge biopsy protocol



Number of samples:
At least 24 biopsies
(+ targeted biopsies)

Biopsies technique



	Single-Bite	Double-Bite	P-value
Comfort score	1[1-2]	1[1-3]	0.223
Fentanyl (mcg)	75[50-100]	100[75-100]	0.302
Midazolam (mg)	5[4-5]	5[5-7]	0.248
Specimen size	3[2-3.3]	2.5[2-3]	0.000
Detection of SRCC foci in random biopsies	3(13.6%)	4(18.2%)	0.500
Time spent to perform endoscopic biopsies (min.)	13±2.4	11±2.7	0.004

Results of our endoscopy research (I)

Patients with CDH1 mutation (30%)

Patients without CDH1 mutation (70%)

■ late stage cancer ■ early stage cancer ■ no cancer

■ early stage cancer ■ no cancer

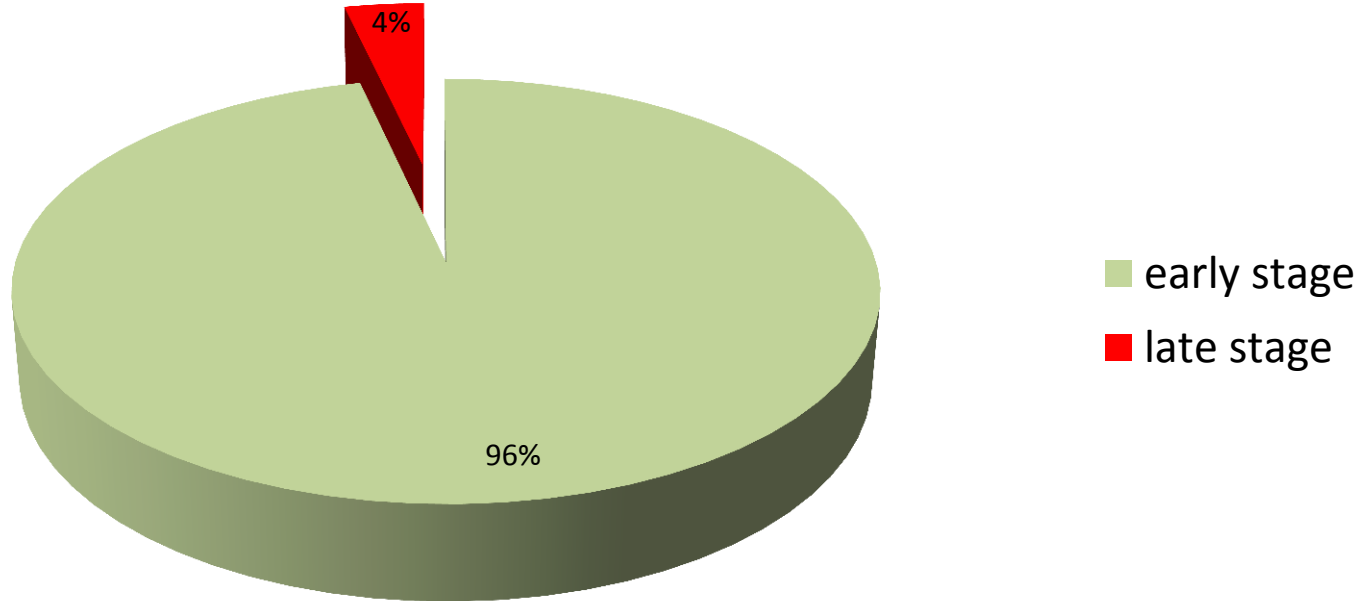
Recommended
frequency of
the endoscopy

6-12 months

3 years

Results of our endoscopy research (II)

Outcome of surgery informed by endoscopy



Conclusions

- The Cambridge HDGC MDT has an expert endoscopy team with 10 y experience in early diagnosis
- The number of endoscopies has more than doubled in the last 8 years
- High quality endoscopy is required with magnification
- In expert hands, endoscopic surveillance is safe and can inform the best timing for surgery
- None of our patients on endoscopic surveillance has died of this condition

Name of the condition

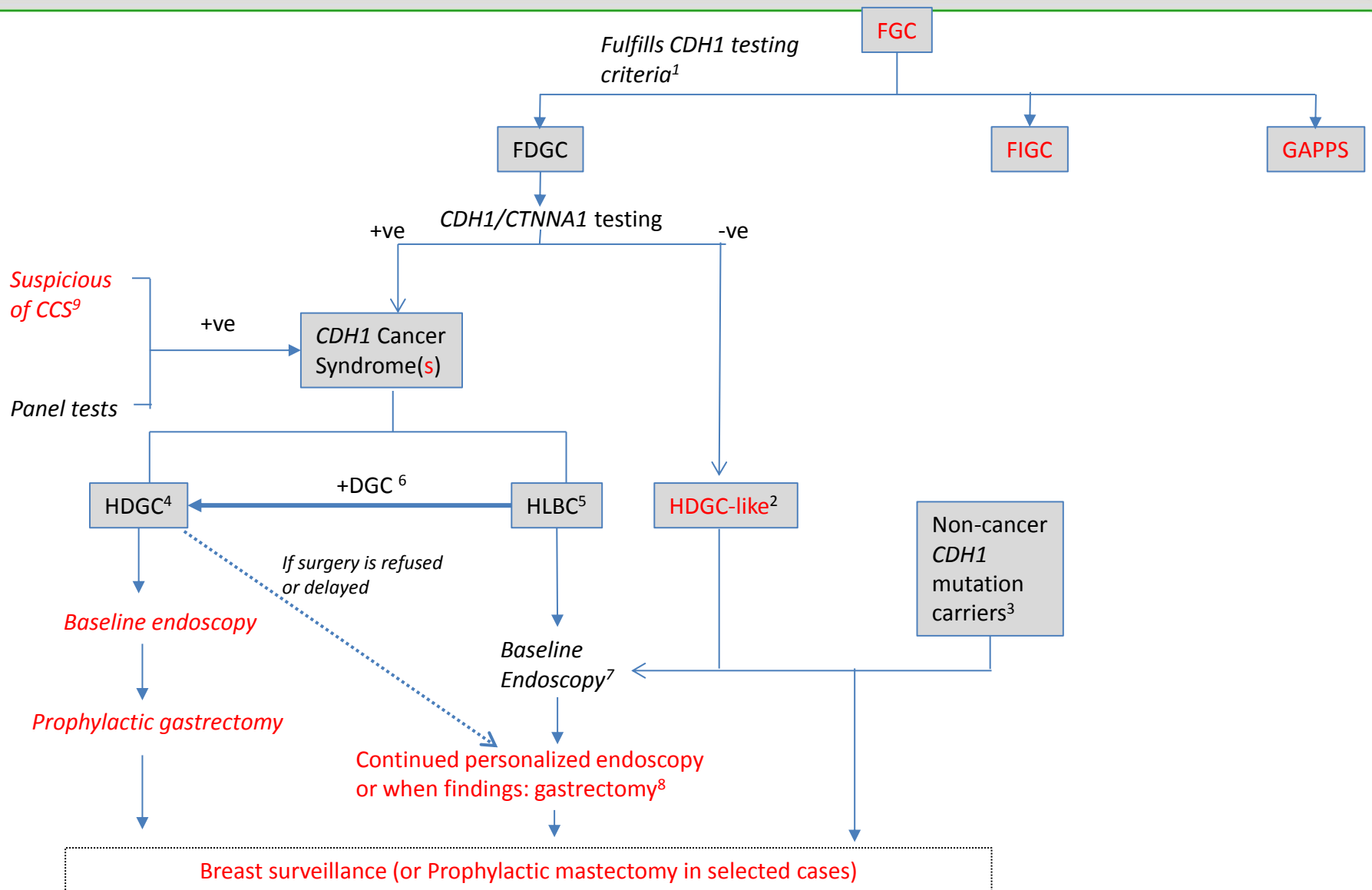
- HDGC does not reflect the involvement of breast in 40% of cases
- Many genetic cancer syndromes are named after the gene affected



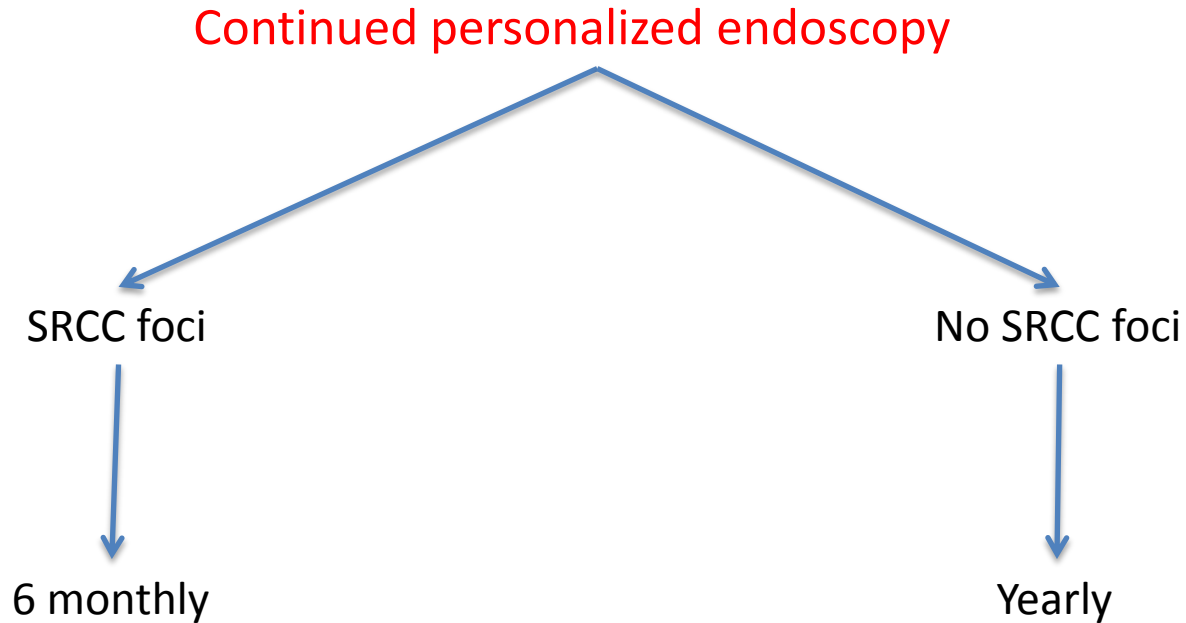
New proposed name:

CDH-1 (associated) cancer syndrome

Diagnostic/management Algorithm



Intervals for surveillance in CDH1 mutation carriers if gastrectomy not elected



Breast surveillance

Proposed recommendations

- Starts screening at 30y (with possible exception based on individual families) with MRI gadolinium, which needs to be timed with the menstrual cycle (10-14 day of the menstrual cycle)
- MRI from age 30 to 60 (except with women with dense breast)
- Mammography 35 or 40-75
- **Prophylactic mastectomy only in selected cases**

HDGC families without mutation

- Still 70% of all cases
- Variant of uncertain significance (VUS)
- Functional assays

- Importance of large multicentre database to identify different risk profiles and tailor surveillance intervals

New research studies

- Confocal endomicroscopy (Cambridge, NIH)
- DNA sequencing in gastric fluid (Paris)
- Markers of disease behavior on endoscopic biopsies (Porto)
- Drug screening Organoids with CDH1 mutation (Otago, NZ)
- New tests to assess CDH1 variants of uncertain significance (Porto)
- Booklet on drugs post-gastrectomy

QUESTIONS?