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# Fibrotic complications of inflammatory bowel disease

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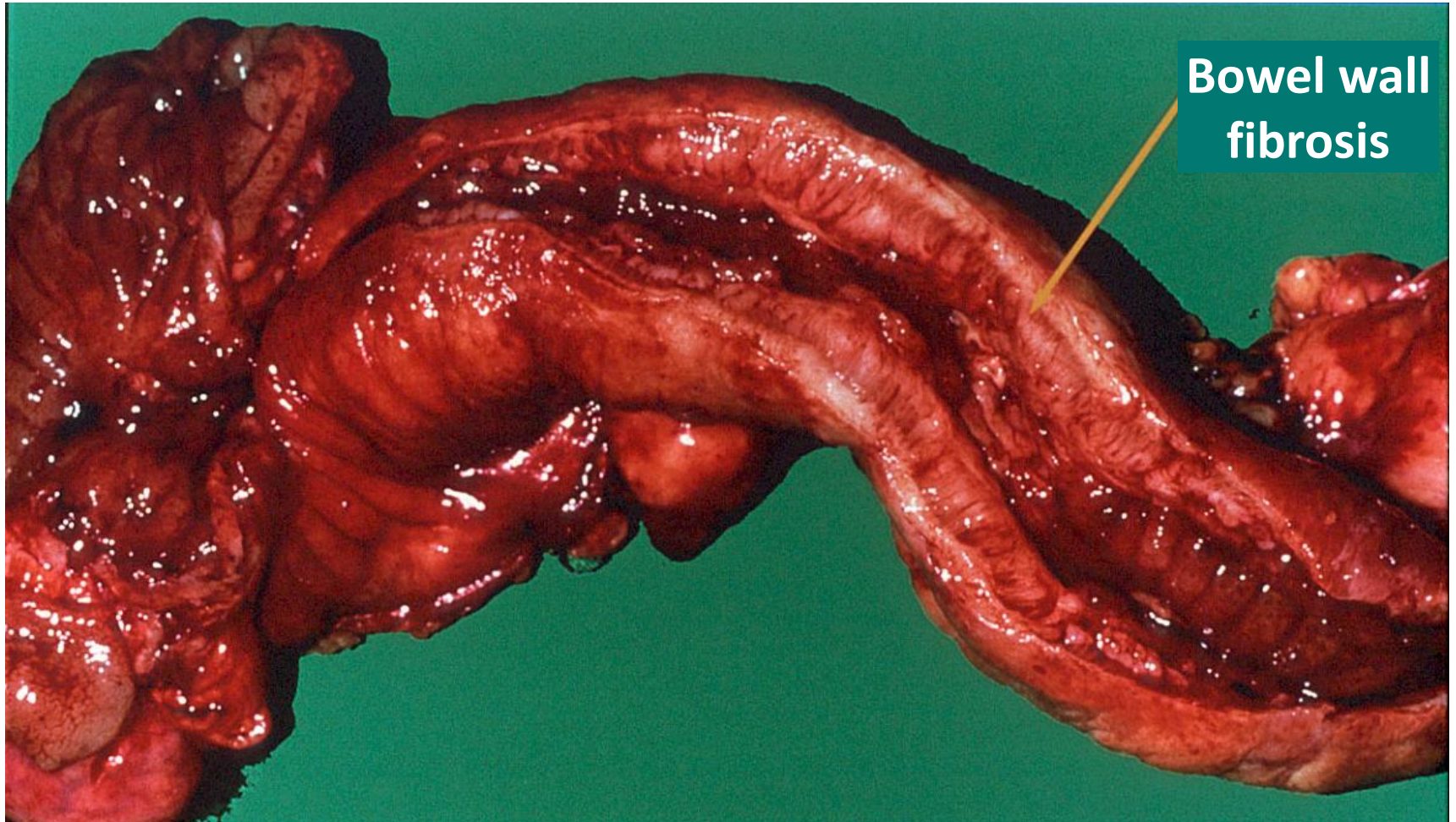


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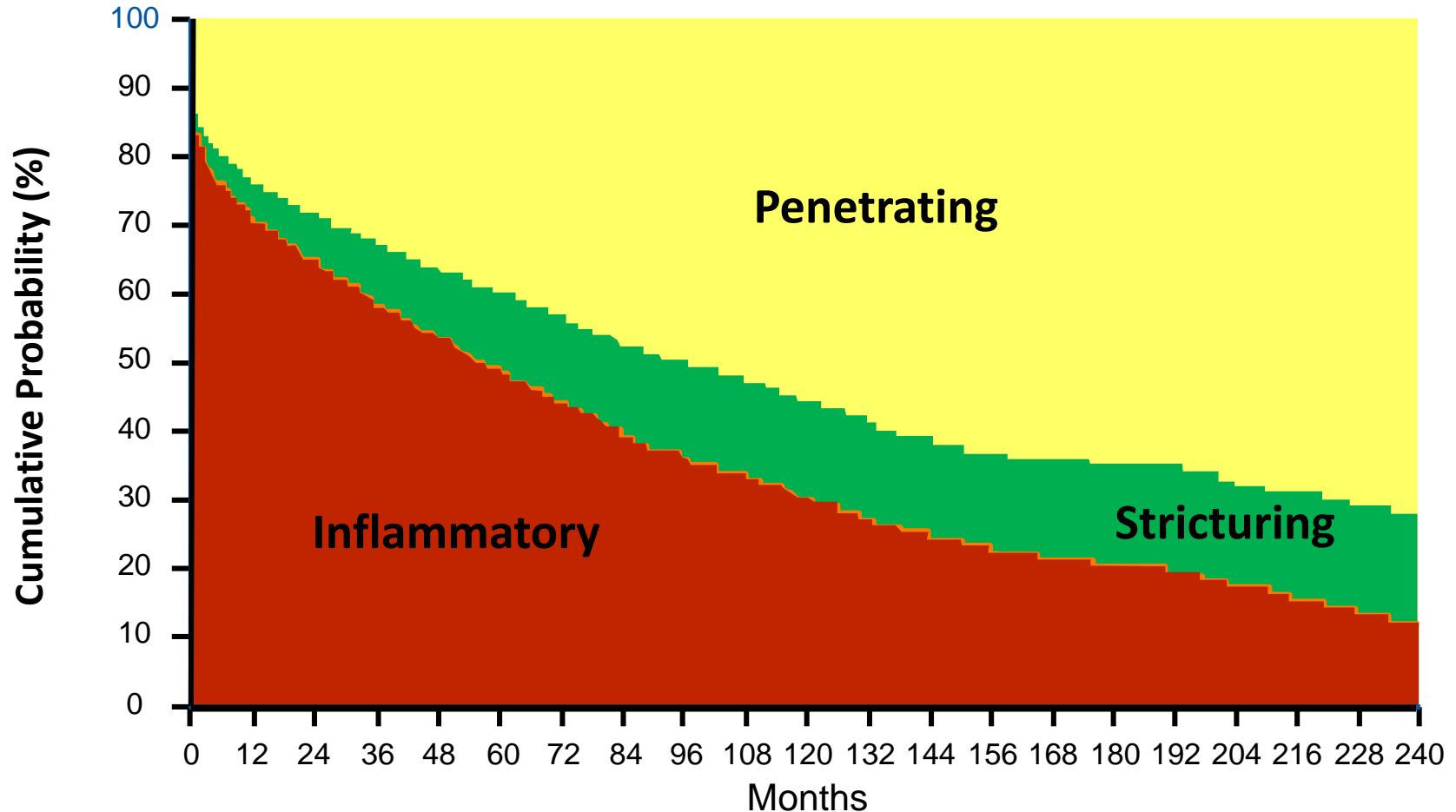


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# Fibrosis: Frequent cause of surgery



# Long-term evolution of disease behavior in CD – “true” situation?



Patients at risk:

N = 2002 552 229 95 37



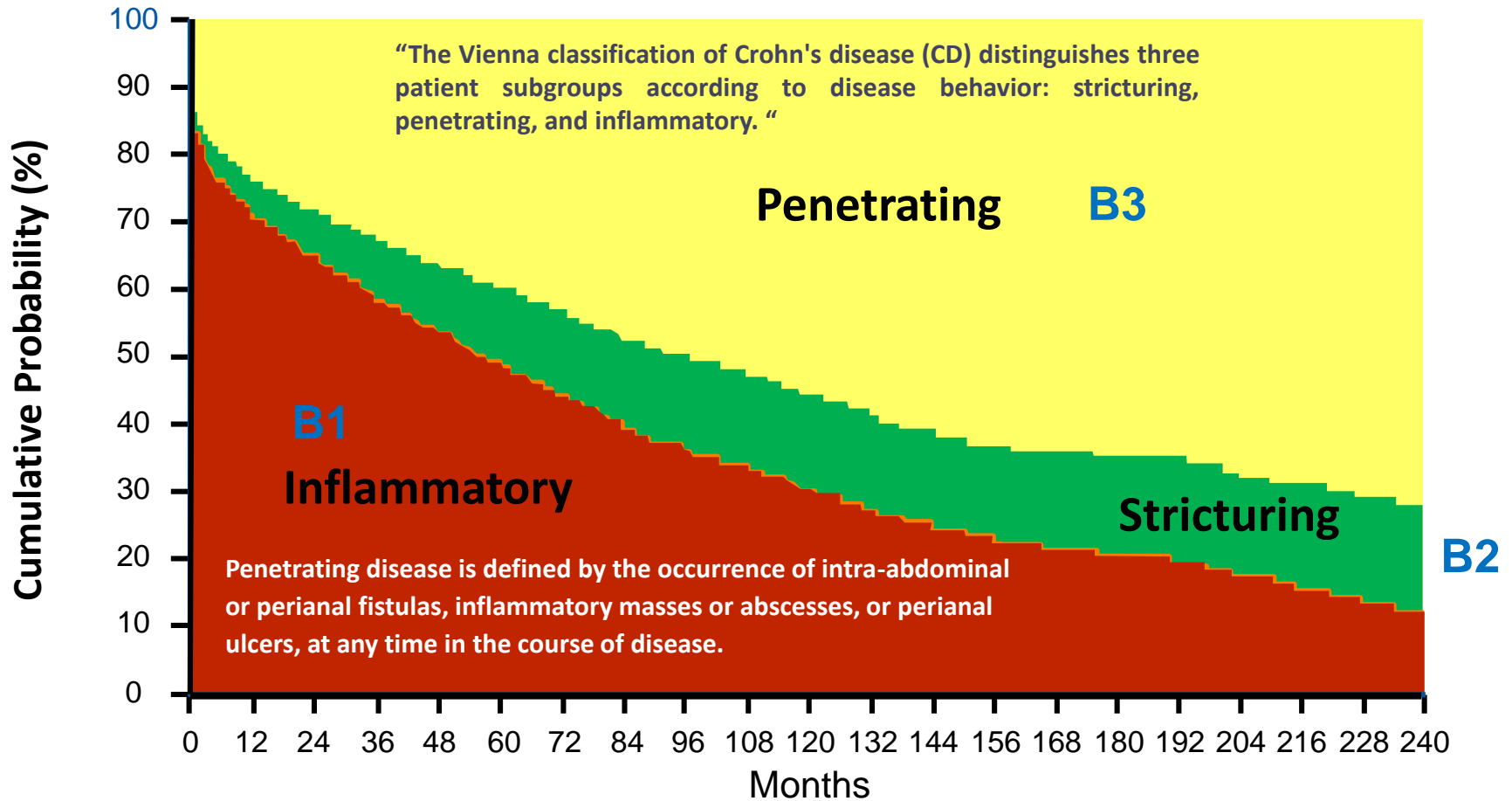
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Cosnes J et al. *Inflamm Bowel Dis.* 2002;8:244



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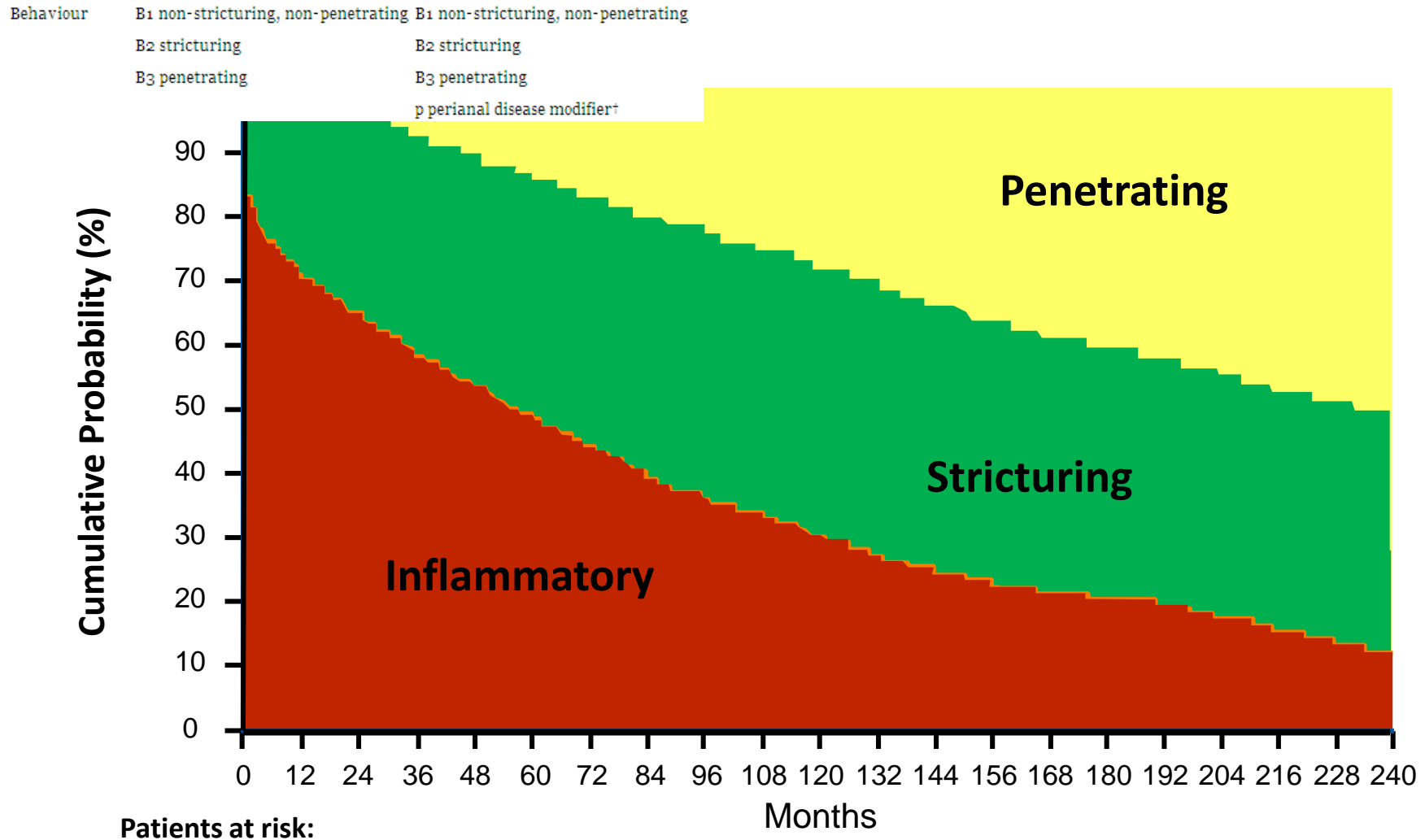
# Long-term evolution of disease behavior in CD – “true” situation?



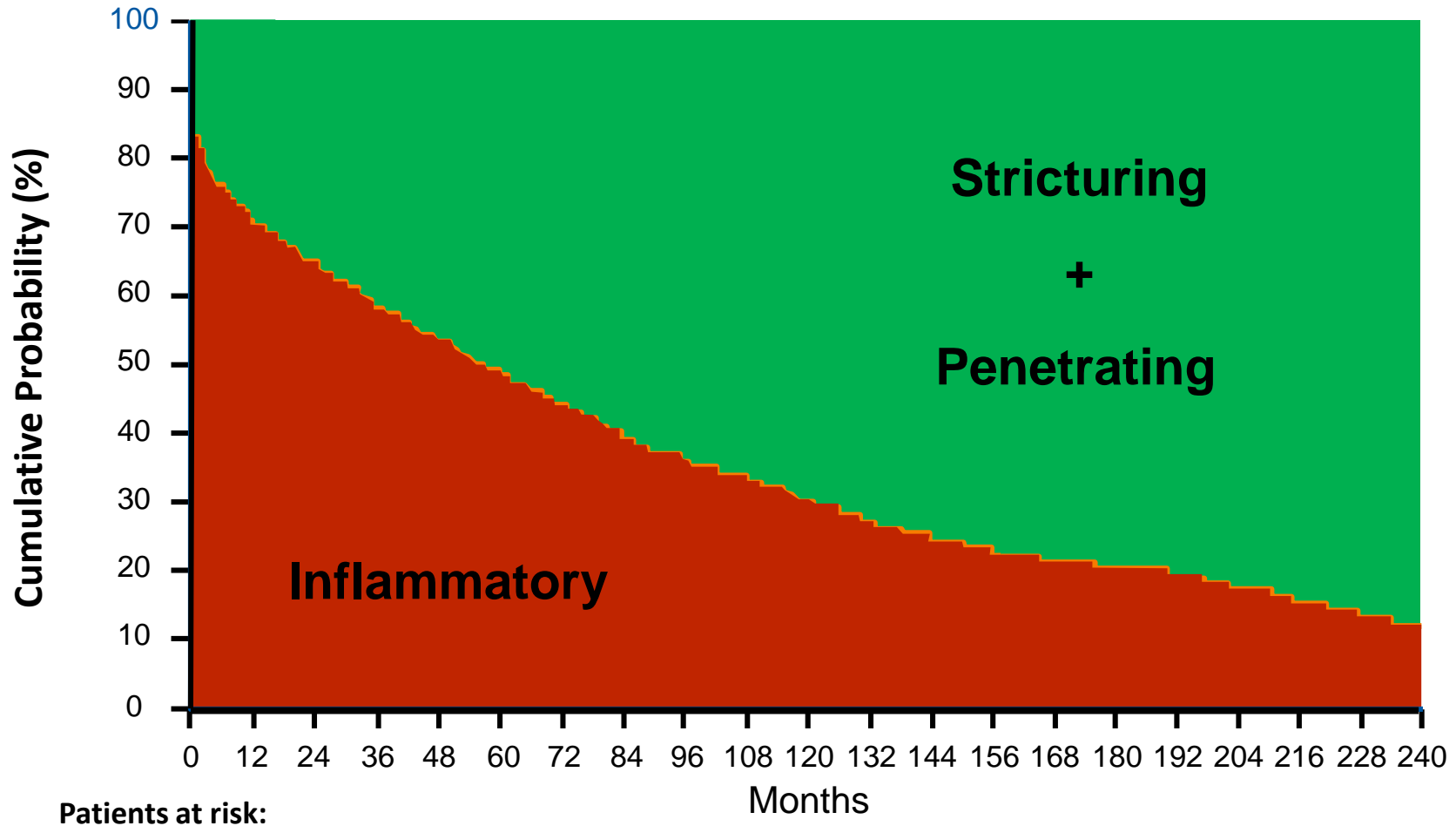
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# Long-term evolution of disease behavior in CD – “true” situation?



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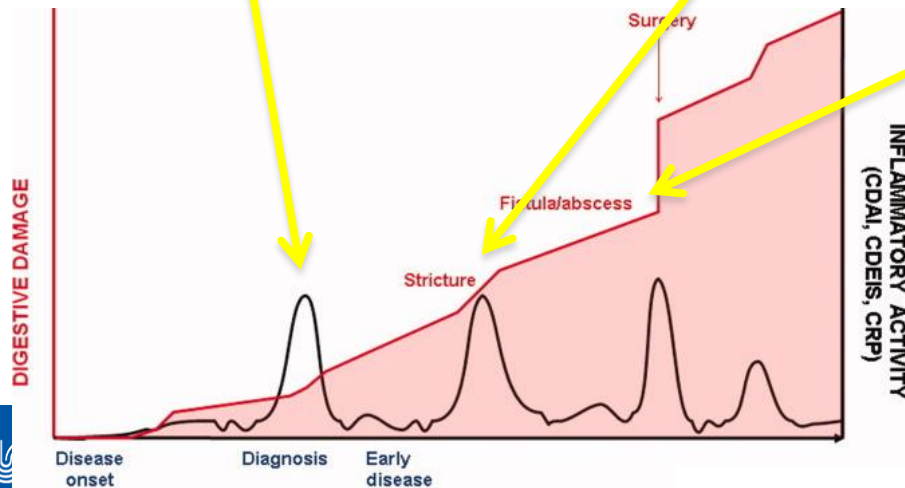
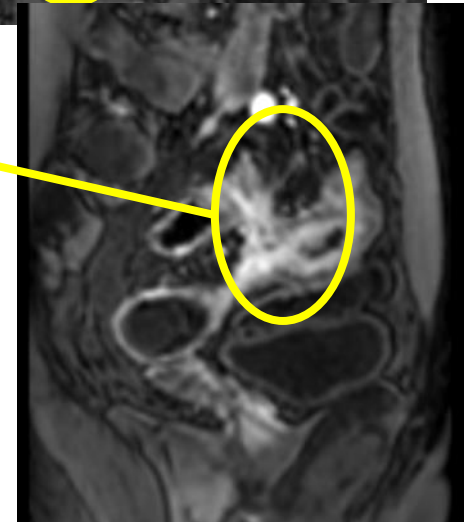
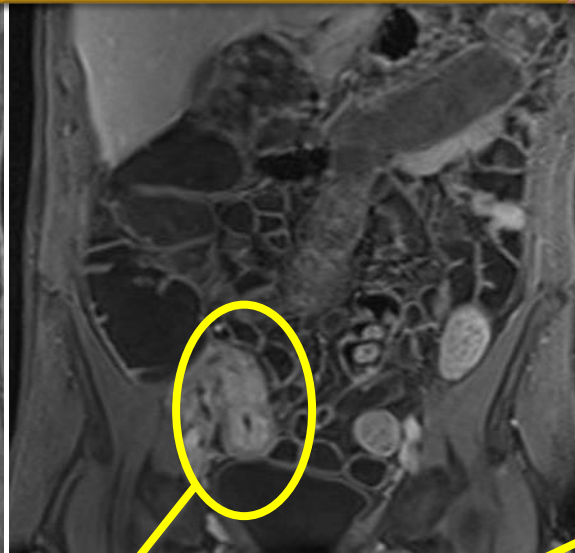
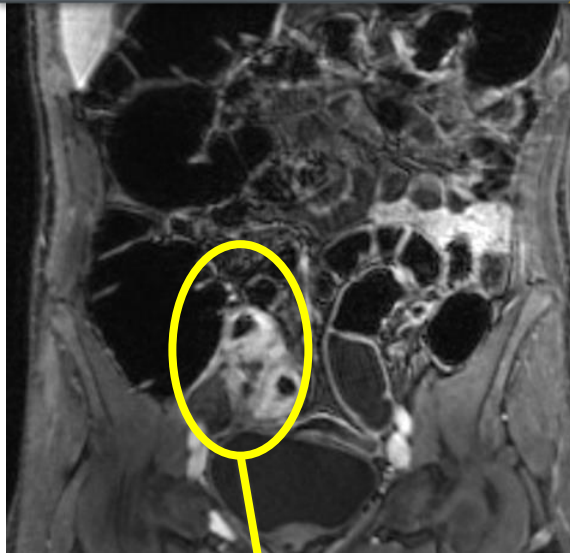




2008 inflammatory

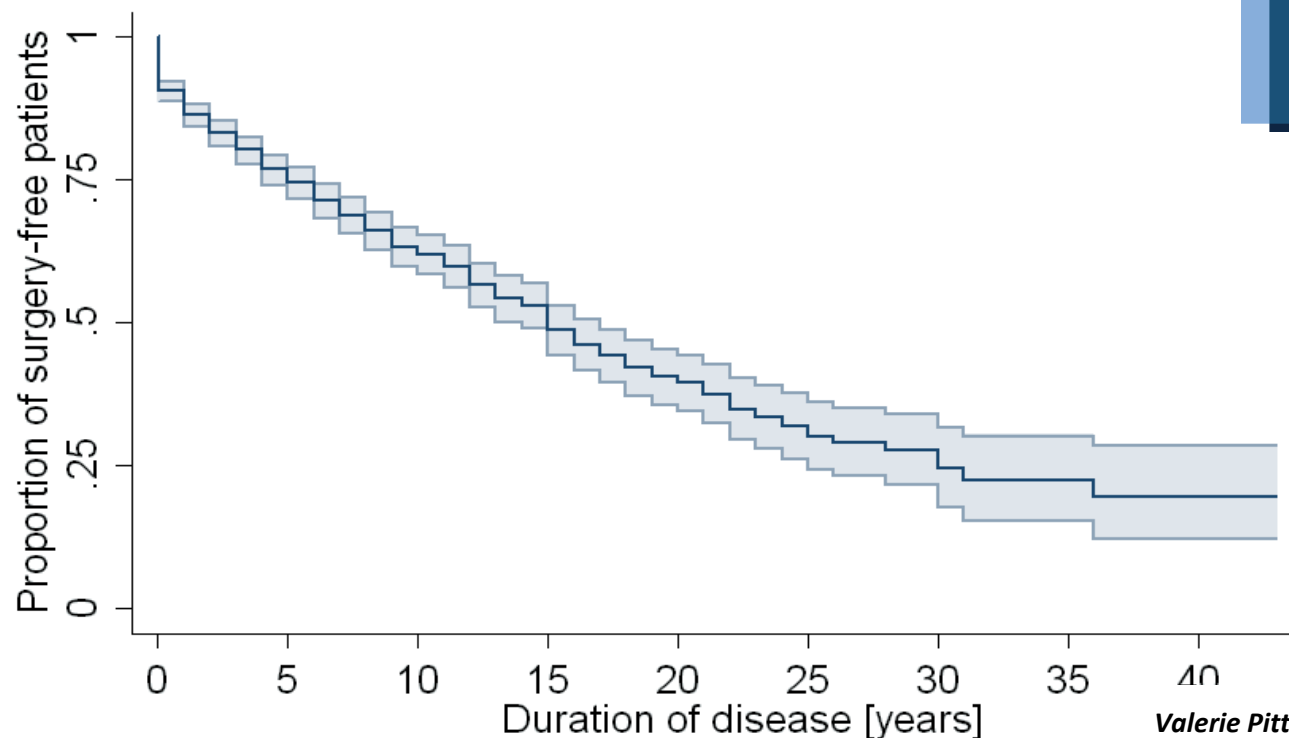
2011 fibrotic

2012 fibrosis and  
fistula



# Surgery is still frequent: Have we improved the medical therapy of IBD?

**SWISS IBD**  
cohort study



Number at risk

1138 562 312 169 72 37 17 9

*Valerie Pittet, Gerhard Rogler, Pierre Michetti, Nicolas Fournier, John-Paul Vader, Alain Schoepfer, Christian Mottet, Bernard Burnand, Florian Froehlich and the Swiss IBD Cohort Study Group*

Factors associated with time to first and repeat of resection surgery in Crohn's disease: results from the Swiss IBD Cohort, in press

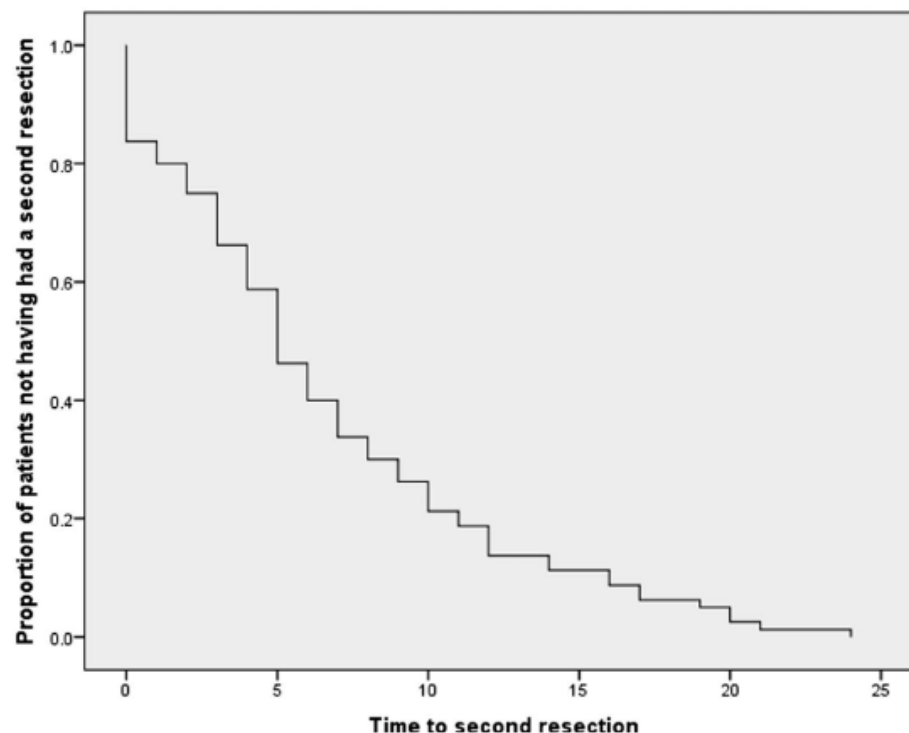


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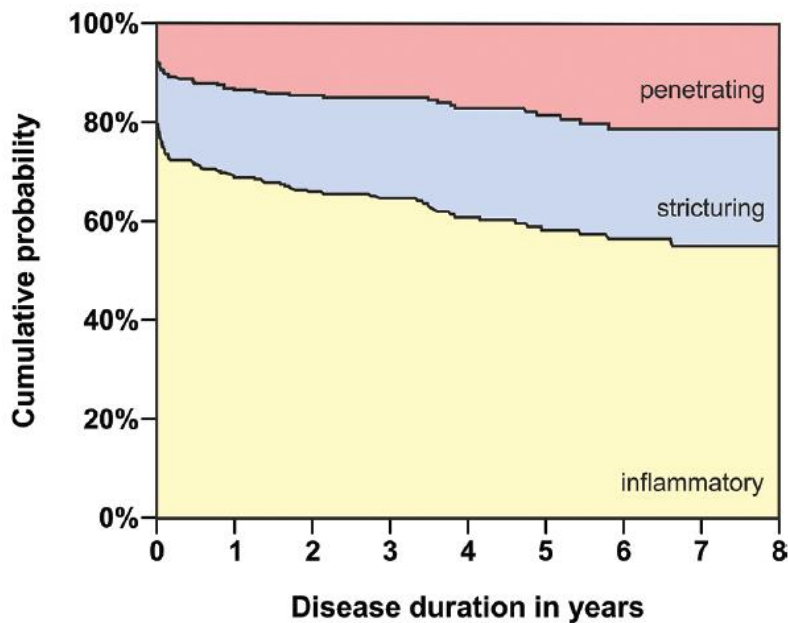
## Need for additional therapeutic options: Repetitive resective surgery in Swiss CD patients

- 305 patients with at least one surgery from the SIBDCS (median follow-up: 15 yrs).
- 1 surgery (n = 225) or more than 1 surgery (n = 80; 26%)
- Mean duration from diagnosis until first surgery not different between groups
- Mean time to second surgery: 6.7  $\pm$  5.74 years.
- Ileal disease location (odds ratio [OR], 2.42 significant risk factor

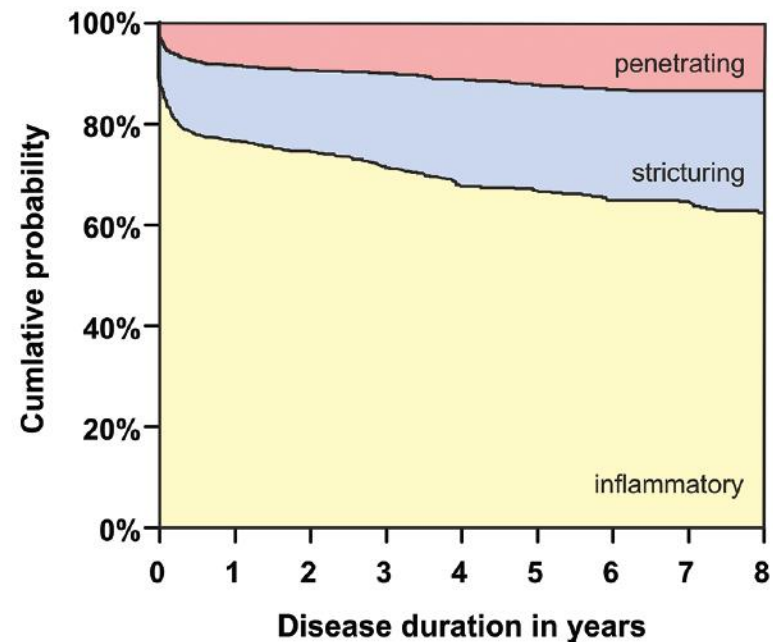


Incident IBD cases South-Limburg Area; Population-based IBD cohort with >93% coverage  
«Pre-biological cohort»: 1991-1998  
«Biologic cohort»: 1999 – 2011 (Follow up until 2014)

### Prebiological era

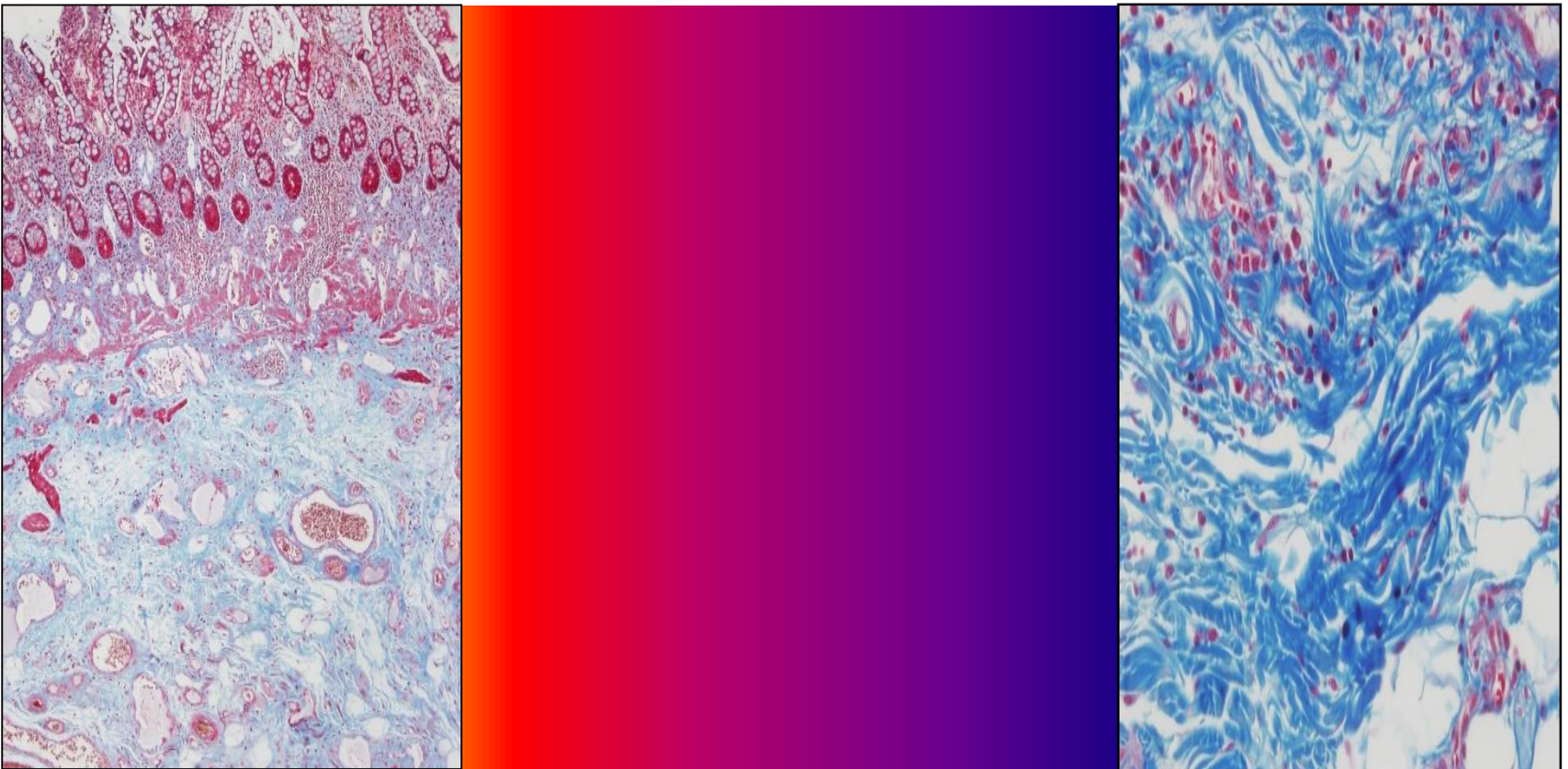


### Biological era

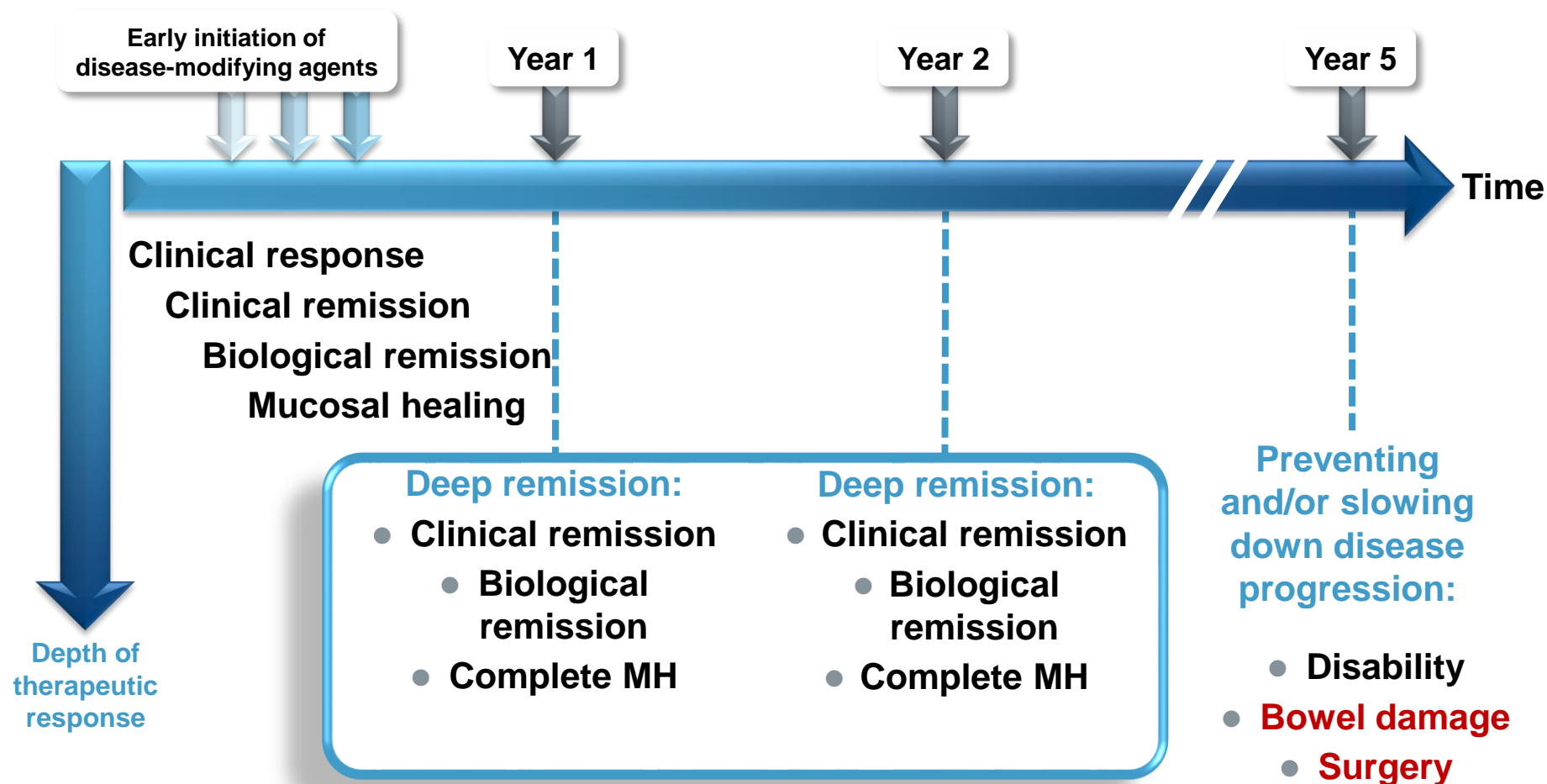


➔ Similar risk to develop fibrosis in the pre- and biological era

# Inflammation and fibrosis coexist in the majority of CD lesions



# The concept on a continuous digestive damage in CD ---- is most likely wrong!



# Problems associated with fibrosis in IBD I

- Fibrosis in CD is a significant unmet medical need
- It cannot be measured by endoscopy
- Current diagnostic tools do not allow for quantifying fibrosis
- Potential utilities:
  - determining disease progression
  - guiding treatment decisions
  - development of anti-fibrotic therapies

# Problems associated with fibrosis in IBD II

- Fibrosis cannot be treated by anti-inflammatory drugs
- Fibrosis can dissociate from the inflammatory condition
- New anti-fibrotic drugs are expected to enter the market soon

**Small bowel fibrosis currently cannot be assessed. There are new diagnostic needs:**

- Early diagnosis of fibrosis
- Quantification of fibrosis
- Morphological risk factors for progression



# Markers of Fibrosis in IBD – ready for clinical practice?

## Clinical markers

*Diagnosis < 40 years of age*

*Need for steroid therapy at diagnosis*

*Perianal fistulizing disease*

*Early use of azathioprine or anti-TNF*

*Weight loss > 5 kg*

*Smoking*

*Small bowel disease*

*Deep mucosal ulceration*

Beaugerie Gastro 2006

Beaugerie Gastro 2006

Beaugerie Gastro 2006

Lakatos World J Gastro 2009

Aldhous Am J Gastro 2007

Lakatos World J Gastro 2009

Allez World J Gastro 2010

## Genetic markers

*NOD2*

*ATG16L1*

*IL-23R*

*CX3CR1*

*MMP-3*

*IL12B*

*JAK2*

*MAGI1*

Adler Am J Gastro 2011

Fowler Am J Gastro 2008

Glas PlosOne 2007

Sabate Eur J Gastroenterol Hepatol 2008; Brand Am J Gastroenterol 2006

Meijer Dig Liver Dis 2007

Henckaerts Clin Gastroenterol Hepatol 2009

Cleynen Gut 2013

Alonso Gastroenterology 2015

# Markers of Fibrosis in IBD – ready for clinical practice?

## Epigenetic markers

miRNA-200a and 200b	Chen Int J Mol Med 2012
miRNA-29b	Nijhuis Clin Sci 2014
miRNA-19a/b	Lewis Inflamm Bowel Dis 2015

## Serology

ASCA	Rieder Inflamm Bowel Dis 2009; Amre Am J Gastro 2006
anti-OmpC	Dubinsky Am J Gastroenterol 2006, Mow Dig Dis Sci 2004; Xiong Eur J Gastro Hepatol 2014
anti-I2	Dubinsky Am J Gastroenterol 2006, Mow Dig Dis Sci 2004; Xiong Eur J Gastro Hepatol 2014
anti-CBir1	Dubinsky Am J Gastroenterol 2006, Mow Dig Dis Sci 2004; Xiong Eur J Gastro Hepatol 2014
anti-glycan antibodies	Rieder Inflamm Bowel Dis 2009; Seow Am J Gastro 2009
YKL40	Erzin J Gastroenterol Hepatol 2008

# A perspective: Molecular imaging in endoscopy?

- use of fluorescent monoclonal antibodies
- application of molecular beacons
- detection of cellular chromosomal changes/mutations with FISH
- Possibilities for molecular characterisation of tissue (bio-endoscopy)

# Endoscopic Therapy of Strictures

Study	Number of patients	Maximal caliber of dilation (mm)	% of patients with technical success	% of patients with clinical efficacy	% of major complications with regards to dilation	Symptomatic recurrence during follow-up (%)	Surgery during follow-up (%)
1	22	18	100	73	0	45	27
2	38	25	89	84	2	36	26
3	46	20	95	57	4	36	84
4	59	18	81	41	2	59	60
5	55	20	90	62	8	38	38
▪							
▪							
▪							
▪							
32	55	20	86	86	1	55	23
33	65	18	80	80	9	53	26
<b>Overall</b>	<b>1463</b>	<b>---</b>	<b>89.1</b>	<b>80.8</b>	<b>4.1</b>	<b>47.5</b>	<b>28.6</b>

# Endoscopic Therapy of Strictures

Number of patients	1463
Maximal caliber of dilation (mm)	25 mm
% of patients with technical success	89.1 %
% of patients with clinical efficacy	80.8 %
% of major complications with regards to dilation	4.1 %
Symptomatic recurrence during follow-up (%)	47.5 %
Surgery during follow-up (%)	28.6

# Summary

- Anti-fibrotic treatments are tested in clinical trials mainly in idiopathic pulmonary fibrosis and hepatic fibrosis
- Intestinal fibrosis is hard to assess
- Fibrosis is frequently treated with surgery and is the most important reason for surgery in CD patients these days
- Balloon dilatation is effective and safe and can reduce the number of surgeries



**Thank you for your attention**

