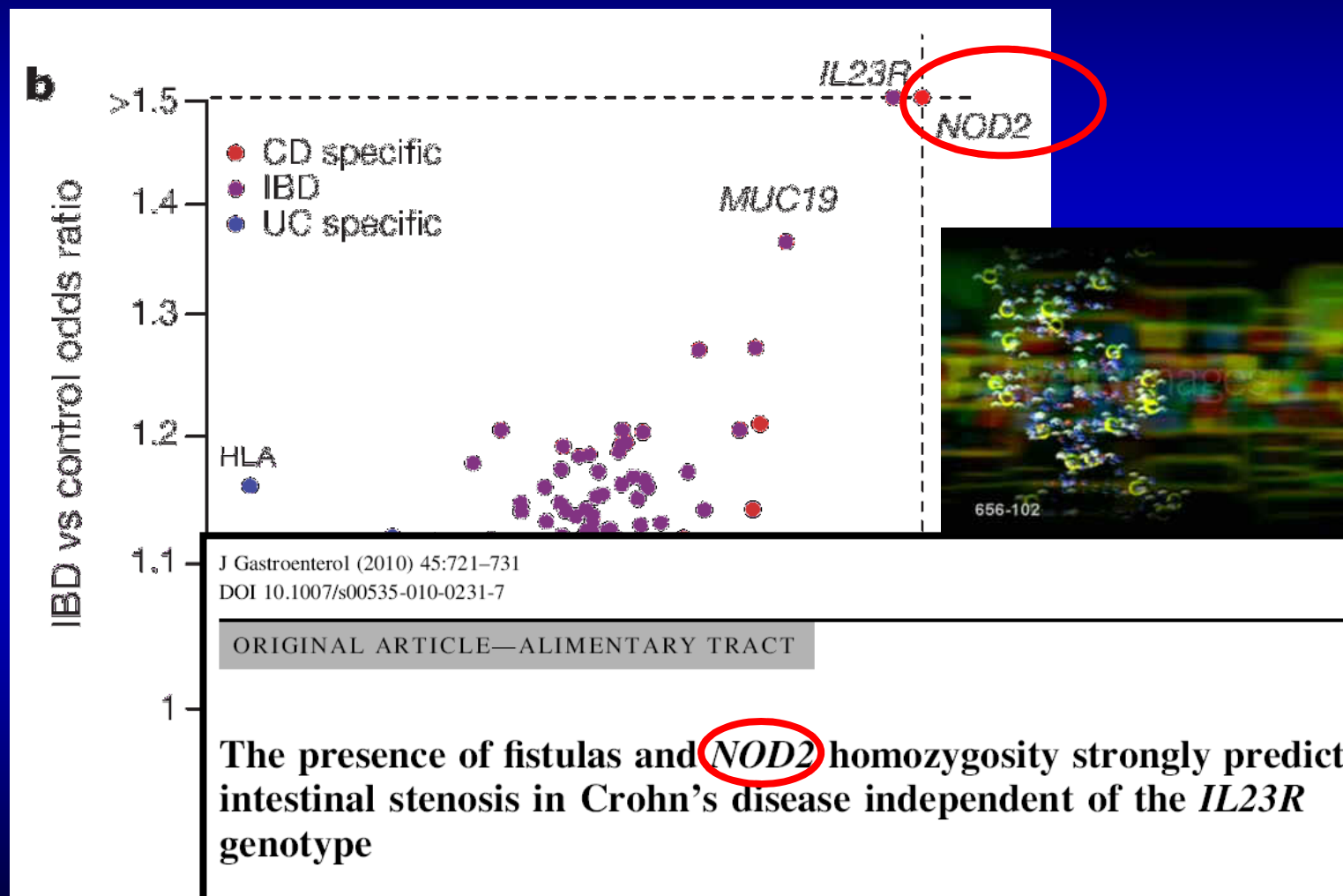


***NOD2* = major Crohn gene causing ileal stenosis**



Jostins L ... Brand S et al. *Nature* 2012;491:119-24.

Juergens M, Brand S et al. *J Gastroenterol* 2010;45:721-31.

Hypothesis: NOD2 mutations prevent infection with *Yersinia pestis*



Plague in Bern 1349:
2500 deaths
Death rate: 50%



Plague doctor



NOD2 1007fs (frame shift)-Mutation

Most important SNP in Crohn's disease

Insertion of C (3020insC) → frame shift (fs)
CCT-TGA → Stop Codon → truncated protein



Phenotype of 1007fs homozygous carriers

Ileal involvement	100%
Stenosis	100%
CD-related surgery	84,2%

Seiderer J, Schnitzler F, Brand S et al. *Scand J Gastroenterol* 2006; 41:1421-32.
Seiderer J, Brand S et al. *Inflamm Bowel Dis* 2006; 12:1114-21.

NOD2 1007fs Homozygosity = Burrill Crohn's Regional Ileitis

Landmark Article

Oct 15, 1932 (*JAMA* 1932; 99:1323-1329)

Regional Ileitis: A Pathologic and Clinical Entity

BURRILL B. CROHN, M.D., LEON GINZBURG, M.D., AND GORDON D. OPPENHEIMER, M.D.

WE PROPOSE TO DESCRIBE, in its pathologic and clinical details, a disease of the terminal ileum, affecting mainly young adults, characterized by a subacute or chronic necrotizing and cicatrizing inflammation. The ulceration of the mucosa is accompanied by a disproportionate connective tissue reaction of the remaining walls of the involved intestine, a process which frequently leads to stenosis of the lumen of the intestine, associated with the formation of multiple fistulas.

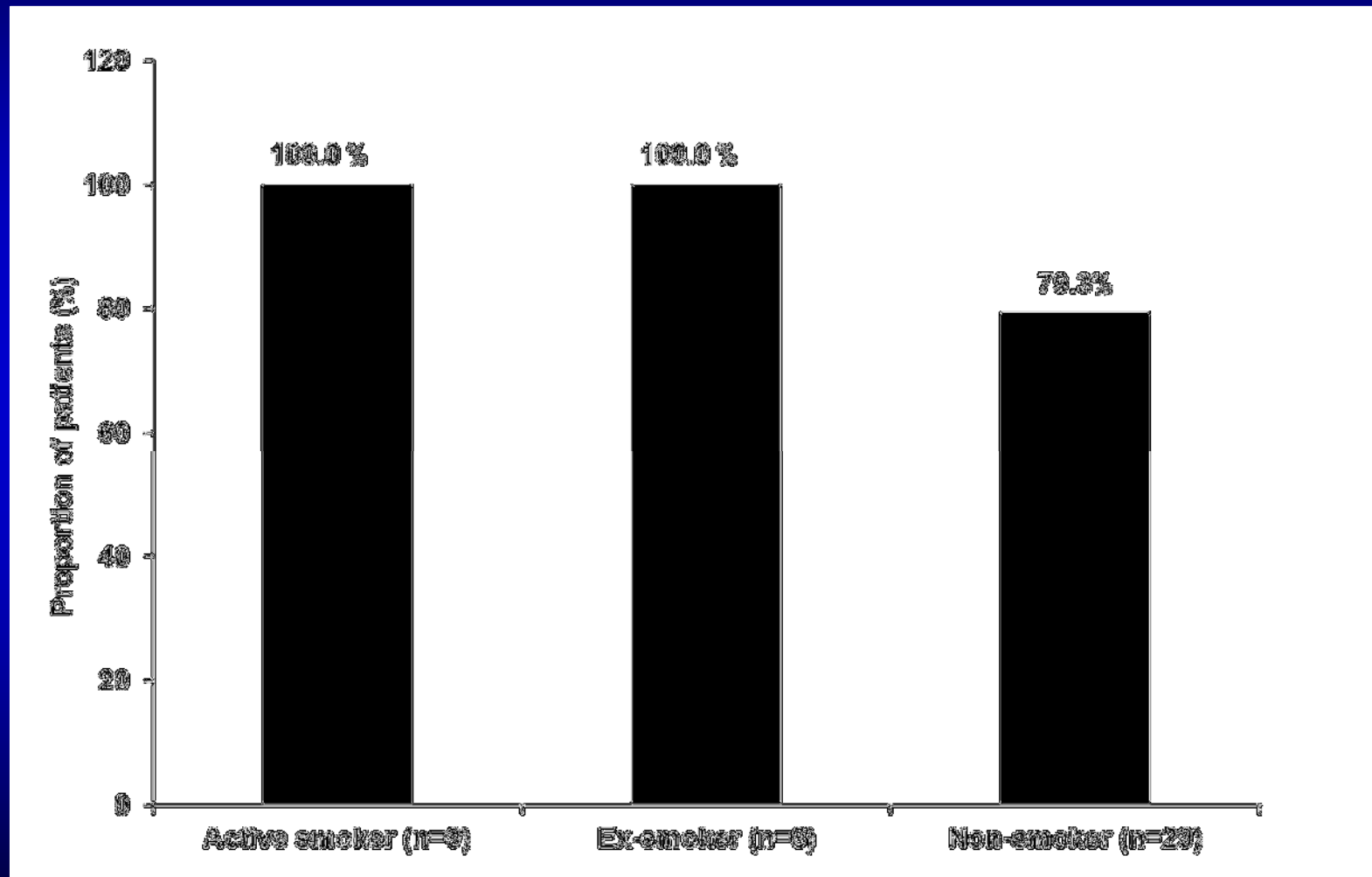
inflammatory lesions of the intestine whose etiology is either unknown or attributable to an unusual physical agent. It represents a hodge-podge or melting-pot in which are thrown all those benign inflammatory intestinal tumors which are neither neoplastic nor due to a specific bacterial agent. Within this group one finds descriptions of foreign body tumors, chronic perforating lesions with gross inflammatory reactions, traumas of the mesentery with intestinal reactions, Hodgkin's granuloma, a late pro-



**Burrill B. Crohn
(1884-1983)**

WE PROPOSE TO DESCRIBE, in its pathologic and clinical details, a disease of the terminal ileum, affecting mainly young adults, characterized by a subacute or chronic necrotizing and cicatrizing inflammation. The ulceration of the mucosa is accompanied by a disproportionate connective tissue reaction of the remaining walls of the involved intestine, a process which frequently leads to stenosis of the lumen of the intestine, associated with the formation of multiple fistulas.

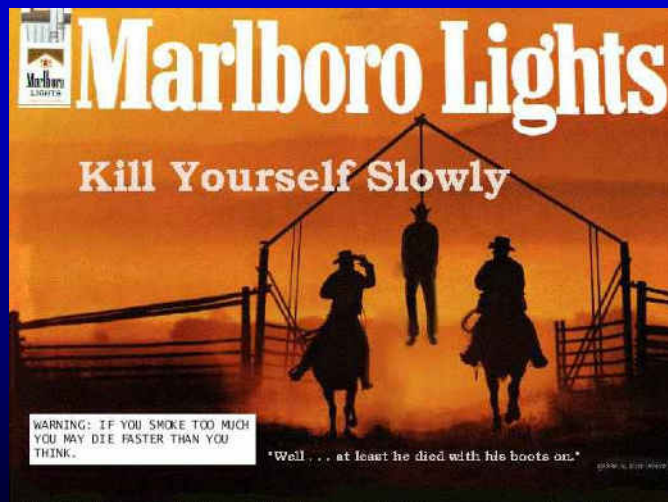
Smoking and *NOD2* 1007fs homozygosity lead to ileal stenosis requiring surgery



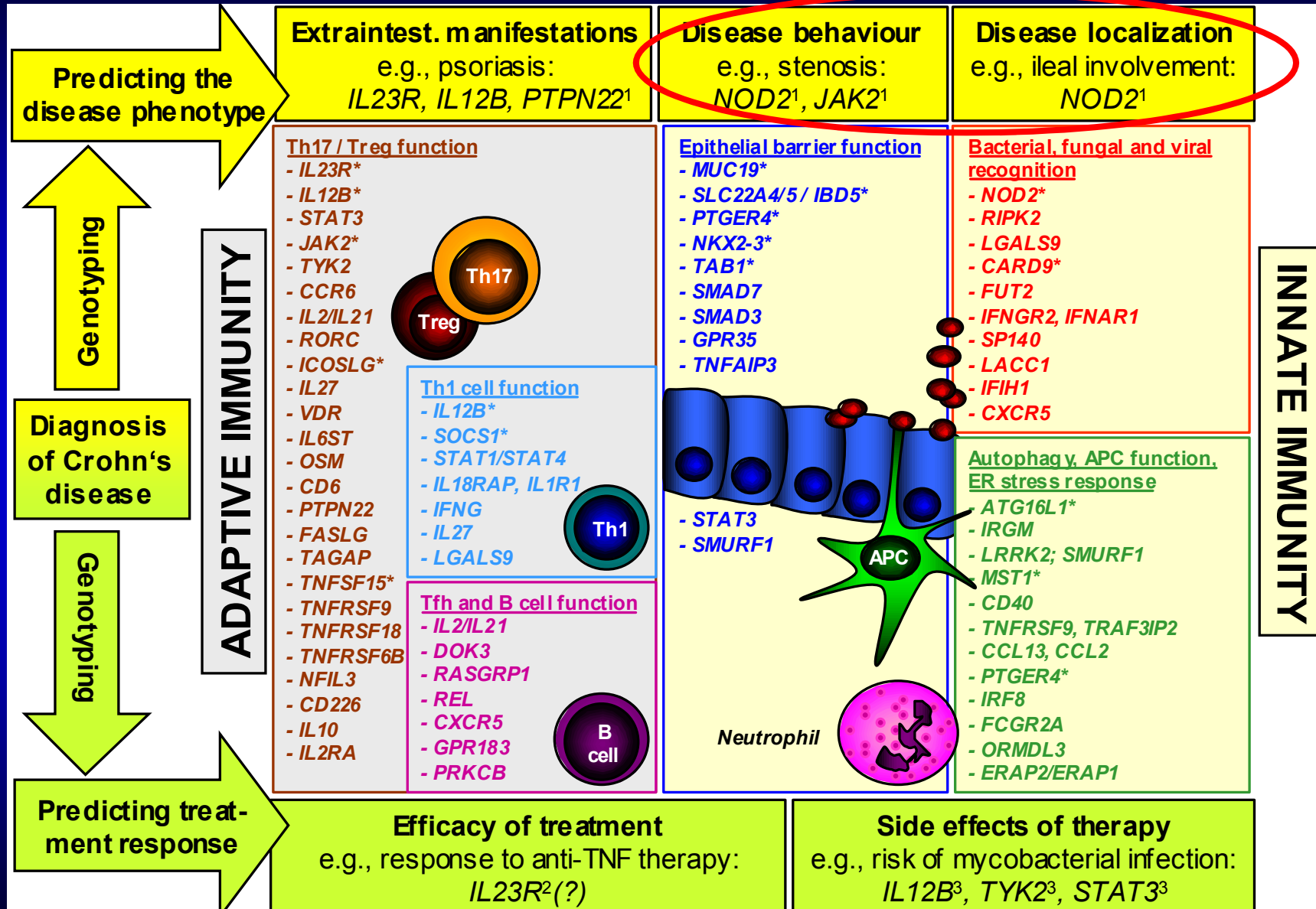
Schnitzler F ... Brand S et al. *submitted*

Crohn's disease and smoking

- **Smoking:** Crohn's risk: 2fold ↑, Ulcerative colitis risk ↓
- Smoking worsens course of CD and increases risk for fistulas, stenosis and post-operative re-stenosis
Lindberg E et al. *Gut* 1992;33:779-82.



The Future: Personalized Medicine



Not all CD patients will need a surgeon ...

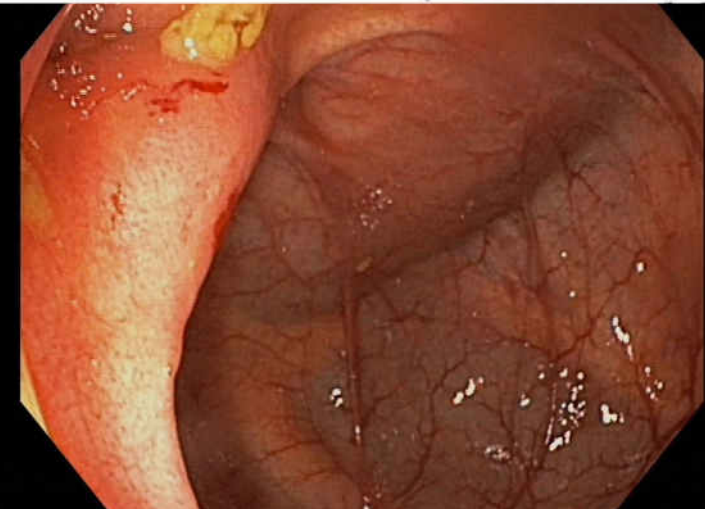
- Ileal Crohn's disease since 1965 (since 52 years!) - and still no surgery

Kantonsspital
St. Gallen
Chirurg. Klinik I

Ärztliche Zusammenfassung der Krankengeschichte von
[REDACTED] 1947 WaldAR

hospitalisiert vom 25. Februar bis 29. April 1965.

Notfallmässige Appendektomie am 25.2. wegen Verdacht auf Appendicitis acuta, die sowohl intraop., wie patho-histologisch bestätigt wurde. Intraop. Feststellung einer Ileitis terminalis. Die patho-histologische Diagnose ergab Sinuskatarrh der mesenterialen Lymphknoten, Ein Peritoneal-Exzusat ergab eine akute, chorn., histologisch unspez. Entzündung. Damit kann eine tuberkulöse Ursache für die Ileitis terminalis ausgeschlossen werden.

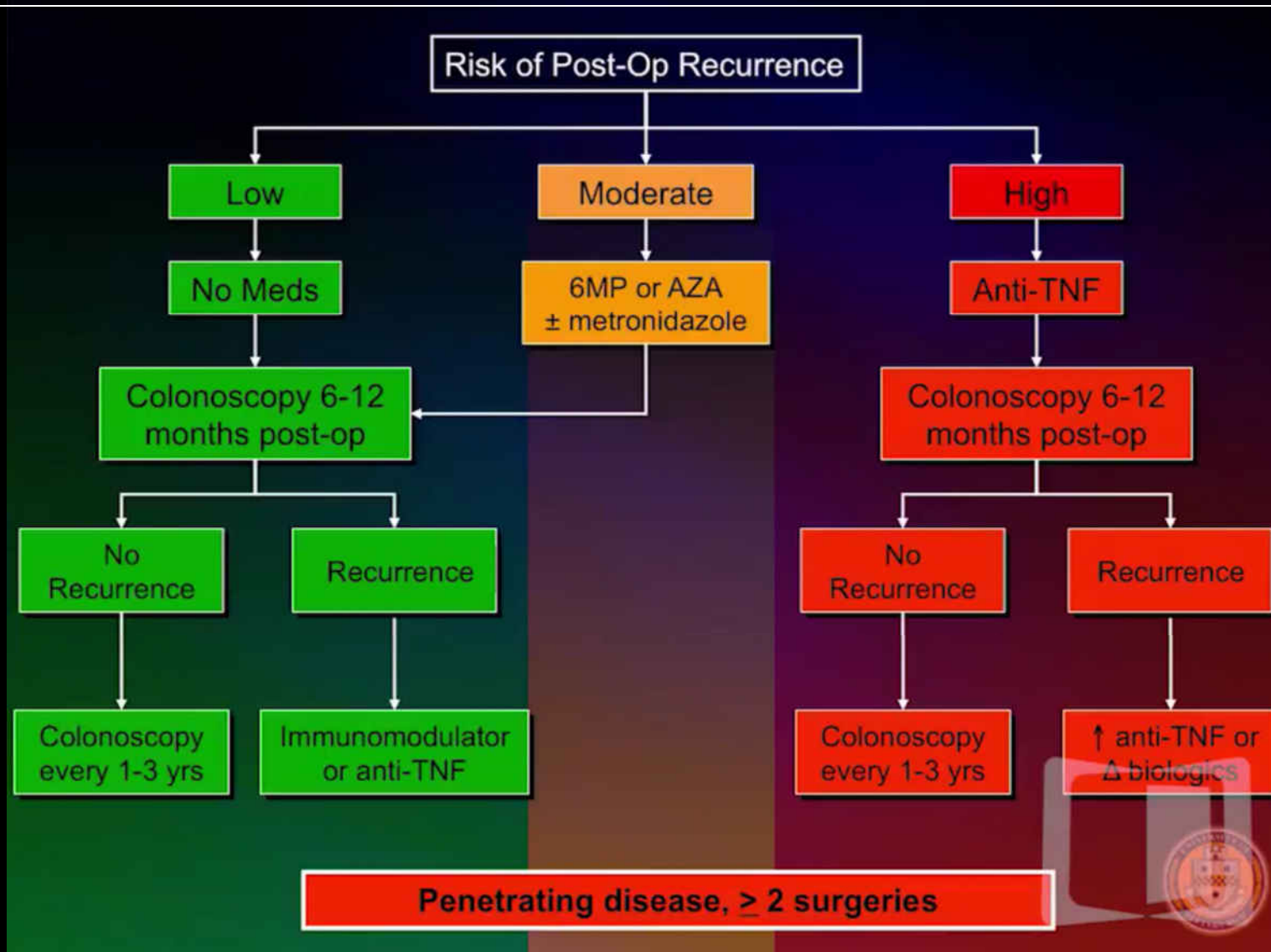


Risk factors for postoperative CD recurrence

- Early age of surgery
- Short time to first surgery
- Ileocolonic disease
- Active smoking
- Fistulizing disease
- History of prior resection
- Disease progress despite immunomodulators



How to treat Crohn's disease after surgery?

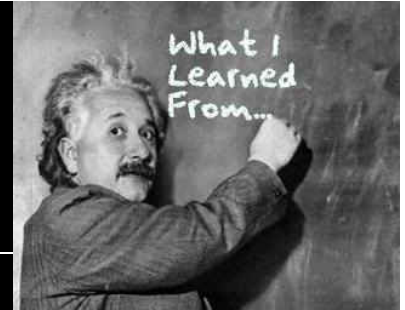


Regueiro M et al. *J Gastrointest Surg* 2016; 20: 1415-20.

Summary (4): Biomarkers in postoperative Crohn's disease

- **Calprotectin: good surveillance marker**
- **NOD2 1007fs homozygosity predicts ileal stenosis**
- **Stop smoking (before and) after surgery!**
- **Post-operative anti-TNF treatment of patients with high risk markers for CD recurrence recommended**

Take home message



- **Surgery is not curative of Crohn's disease, most patients will relapse after surgery and require immunosuppressives**
- **Anti-TNFs are more efficacious than thiopurines in preventing post-operative Crohn's disease**
- **Anti-TNF perioperatively likely safe, particularly when given several weeks before surgery and when drug levels are low (infliximab < 3 ug/ml)**
- **However, some studies showed an increased risk for postoperative complications for anti-TNFs likely due selection bias (more severe CD among the anti-TNF-treated patients)**











History of steroids

*Kendall, Pfiffner,
Reichenstein*

Adrenal gland extracts
successfully given to
patients with adrenal
insufficiency

1945

Hench, Kendall
Mayo-Klinik
Compound E
for rheumatoid
arthritis

1949

*Hench, Kendall,
Reichenstein*

Nobel Prize for steroids
in Medicine



1950

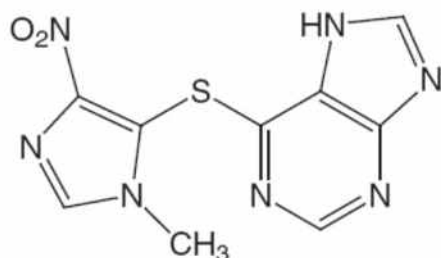
Schering Co.
Prednison
Prednisolon

1955

Azathioprine is a listed carcinogen

Azathioprine CAS No. 446-86-6

Known to be a human carcinogen
First Listed in the *Fourth Annual Report on Carcinogens* (1985)

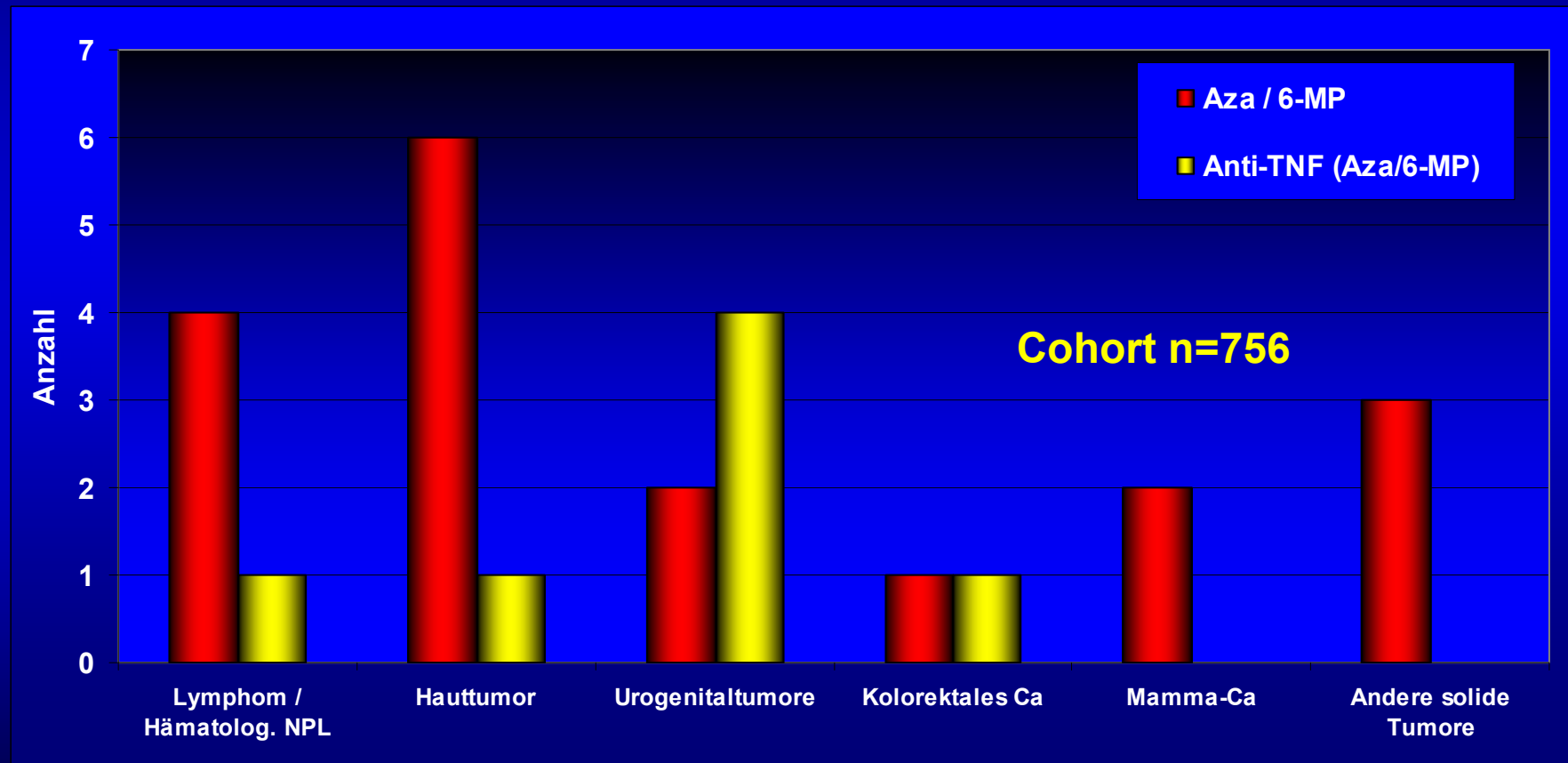


Carcinogenicity

Azathioprine is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans. Two large prospective epidemiological studies reported a high incidence of non-Hodgkin's lymphoma, squamous cell cancers of the skin, hepatobiliary carcinomas, and mesenchymal tumors in renal transplant patients, who are treated almost routinely with azathioprine and prednisone. Non-transplant patients (for example, patients with rheumatoid arthritis, systemic lupus and other collagen disorders, inflammatory bowel disease, and certain skin and renal diseases) treated with azathioprine also had an increased, although lower, risk of the same cancers as the transplant patients. Rheumatoid arthritis also is a risk factor for non-Hodgkin's lymphoma (IARC 1981, 1982, 1987).



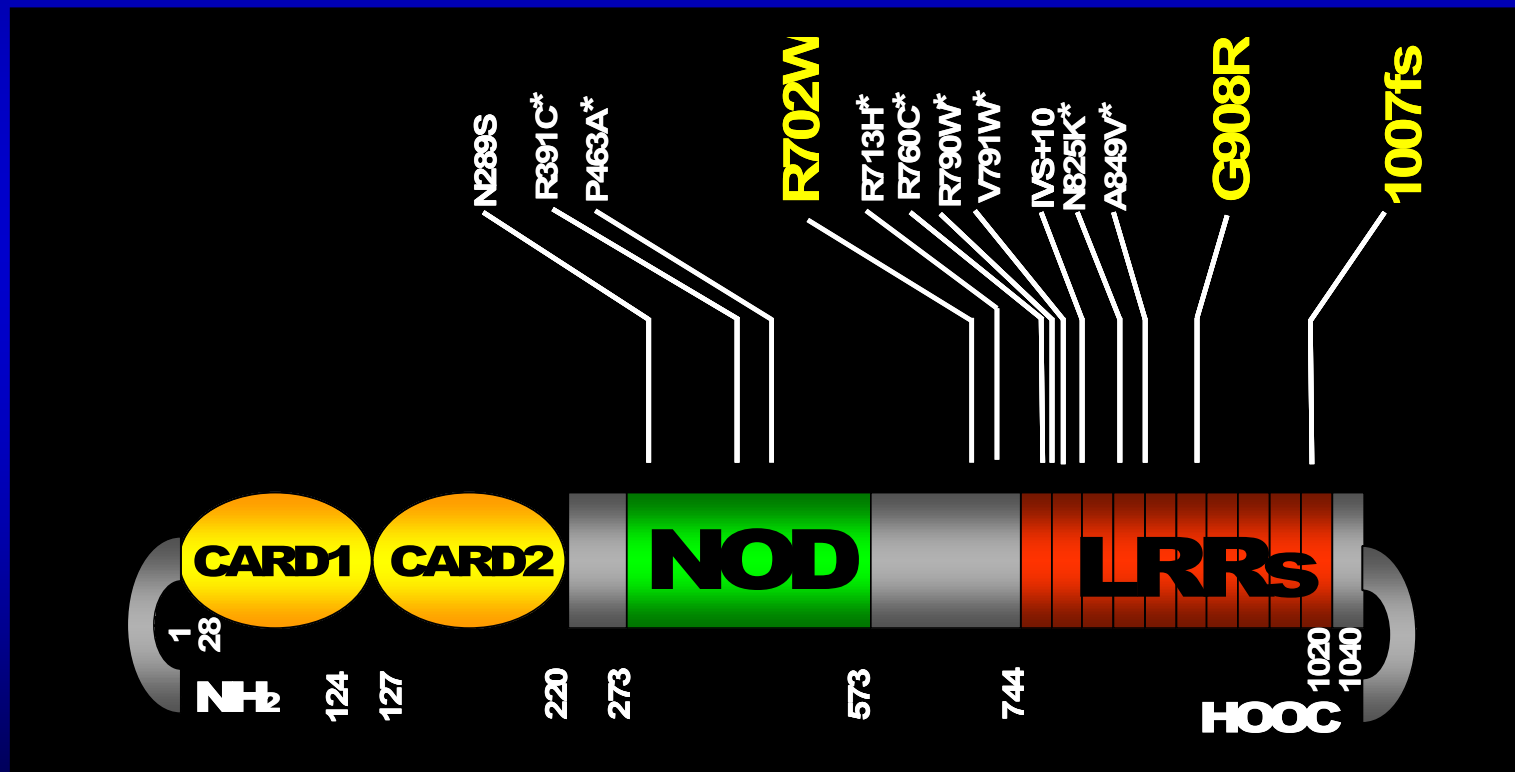
Malignancies during treatment with thiopurines or anti-TNF antibodies



Beigel F ... Brand S. *Pharmacoepidemiol Drug Saf* 2014;23:735-44.

NOD2

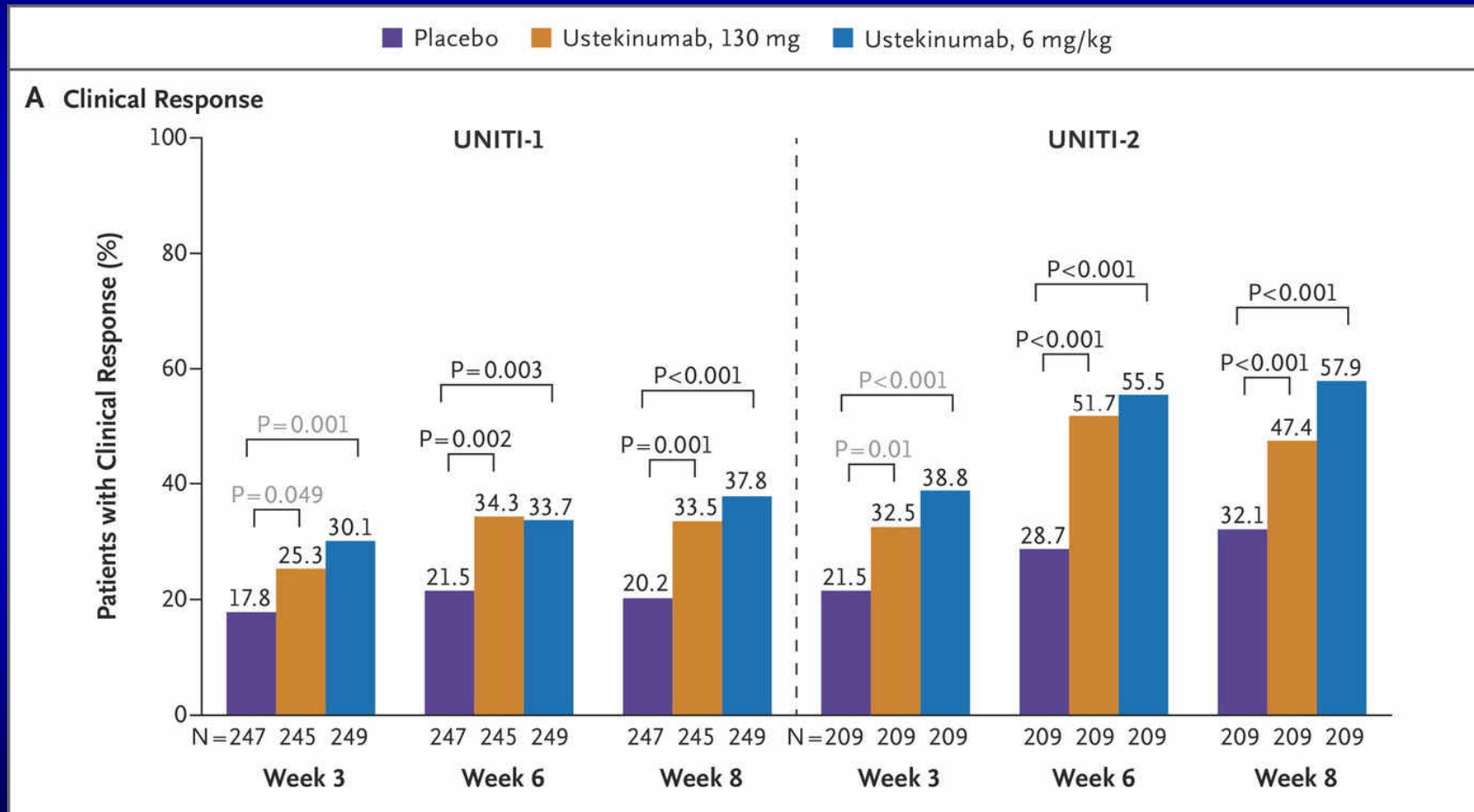
- Mutations increase CD risk but not UC risk
- Mutations in up to 40% of European CD patients



Schnitzler F, Brand S et al. Immunogenetics 2006; 58:99-106.

Seiderer J, Schnitzler F, Brand S et al. Scand J Gastroenterol 2006; 41:1421-32.

Ustekinumab is effective in Crohn's disease and has low rate of side effects



Feagan BG et al. *N Engl J Med* 2016;375:1946-1960.
November 17, 2016



The NEW ENGLAND
JOURNAL of MEDICINE

Meta-Analysis (2014): Preoperative infliximab use and postoperative complications

CURRENT STATUS

Impact of Preoperative Immunosuppressive Agents on Postoperative Outcomes in Crohn's Disease

Usama Ahmed Ali, M.Sc., M.D.¹ • Sean T. Martin, M.D.² • Abhishek D. Rao, B.A.³
Ravi P. Kiran, M.Sc., M.D.³

1 Department of Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

2 Department of Colorectal Surgery, St. Vincent's University Hospital, Dublin, Ireland

3 Division of Colorectal Surgery, Department of Surgery, Columbia University Medical Center, New York, New York

Ahmed Ali U et al.
Dis Colon Rectum 2014;57:663-74.



Preoperative infliximab use associated with slight increase in postoperative complications

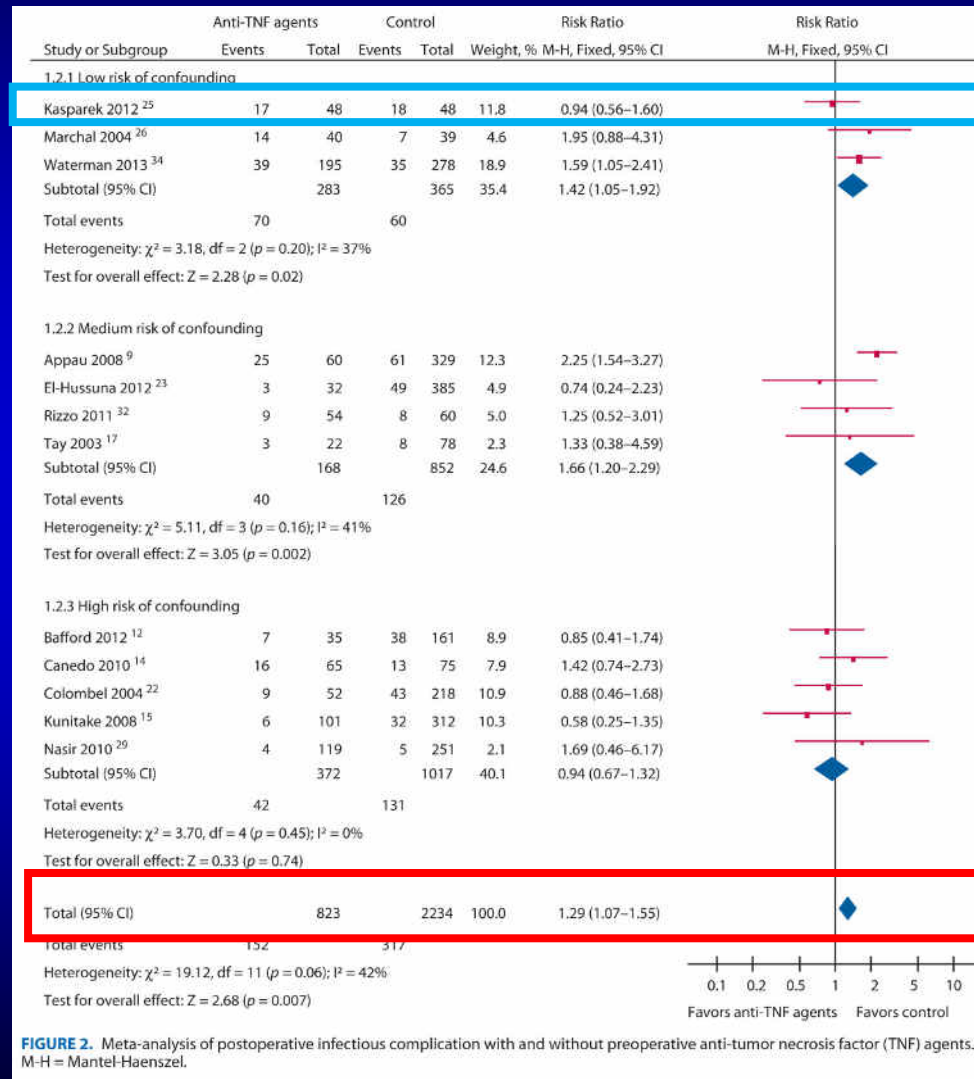


FIGURE 2. Meta-analysis of postoperative infectious complication with and without preoperative anti-tumor necrosis factor (TNF) agents. M-H = Mantel-Haenszel.

Meta-Analysis (2014): Preoperative infliximab use and postoperative complications

International Journal of Surgery 12 (2014) 224–230



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Contents lists available at [ScienceDirect](#)

International Journal of Surgery

journal homepage: www.journal-surgery.net



Original research

Preoperative infliximab use and postoperative complications in Crohn's disease: A systematic review and meta-analysis



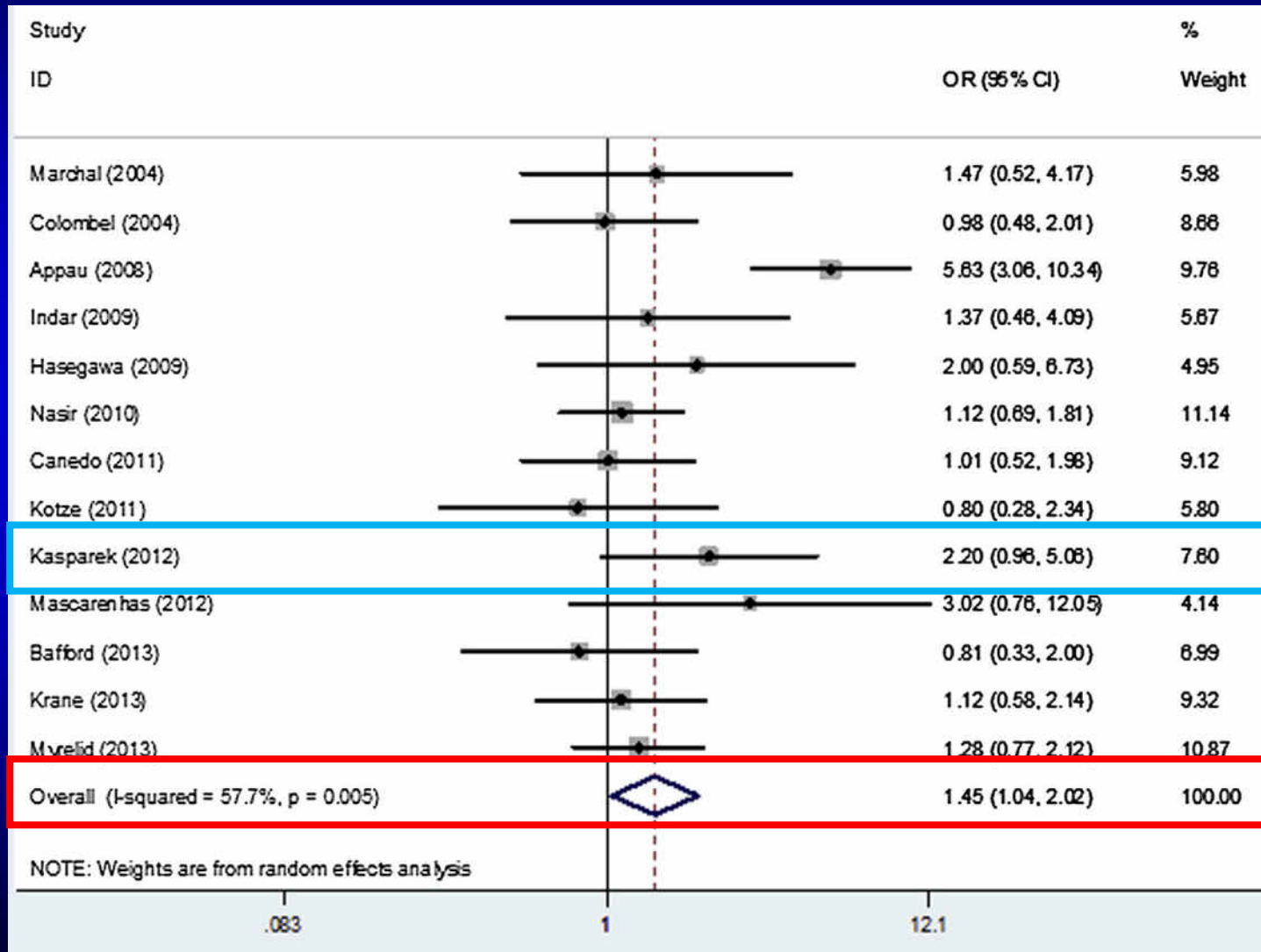
Zhi-Ping Yang^a, Liu Hong^a, Qiong Wu^a, Kai-Chun Wu, Dai-Ming Fan^{*}

Xijing Hospital of Digestive Diseases, Fourth Military Medical University, 127 West Changle Road, Xi'an 710032, China



Yang ZP et al. *Int J Surg* 2014;12:224-230.

Preoperative infliximab use associated with slight increase in postoperative complications



Yang ZP et al. *Int J Surg* 2014;12:224-230.

Anti-TNF therapy and postoperative complications



Available online at www.sciencedirect.com

ScienceDirect



REVIEW ARTICLE

The risks of post-operative complications following pre-operative infliximab therapy for Crohn's disease in patients undergoing abdominal surgery: A systematic review and meta-analysis☆



Greg Rosenfeld ^{a,*}, Hong Qian ^b, Brian Bressler ^a

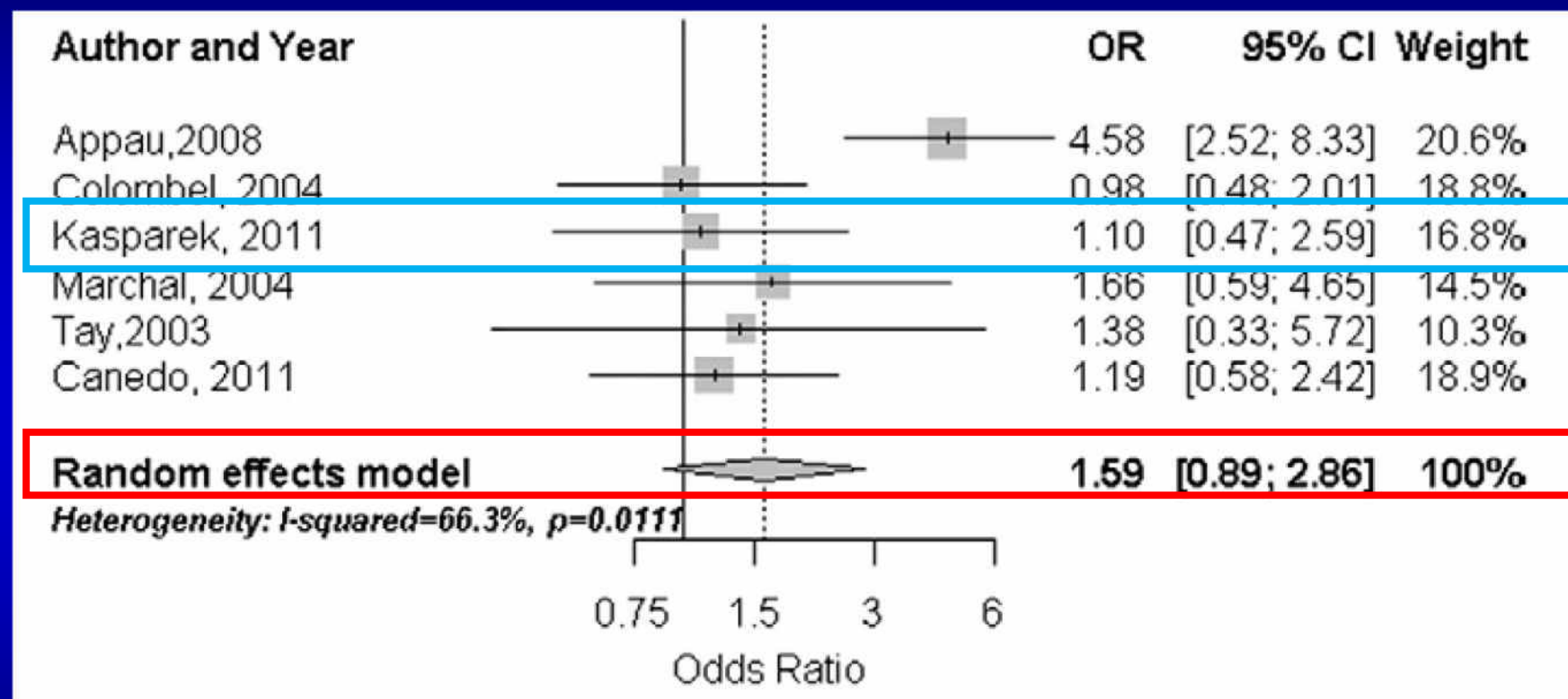
^a Division of Gastroenterology, Department of Medicine, University of British Columbia, Canada

^b St Paul's Hospital, Vancouver, British Columbia, Canada



Rosenfeld G et al. *J Crohns Colitis* 2013;7:868-77.

Anti-TNF therapy and postoperative complications



a: Forrest plot for major complications.

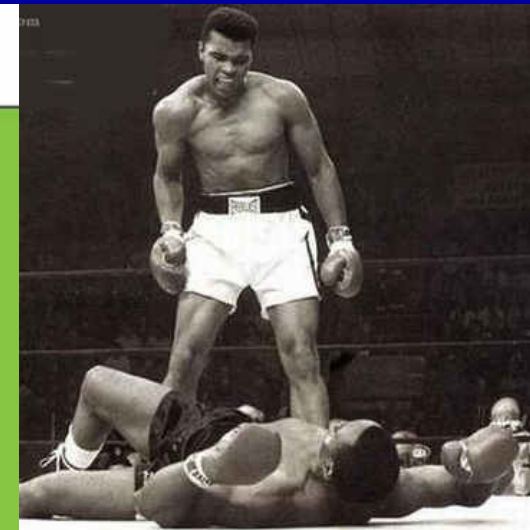
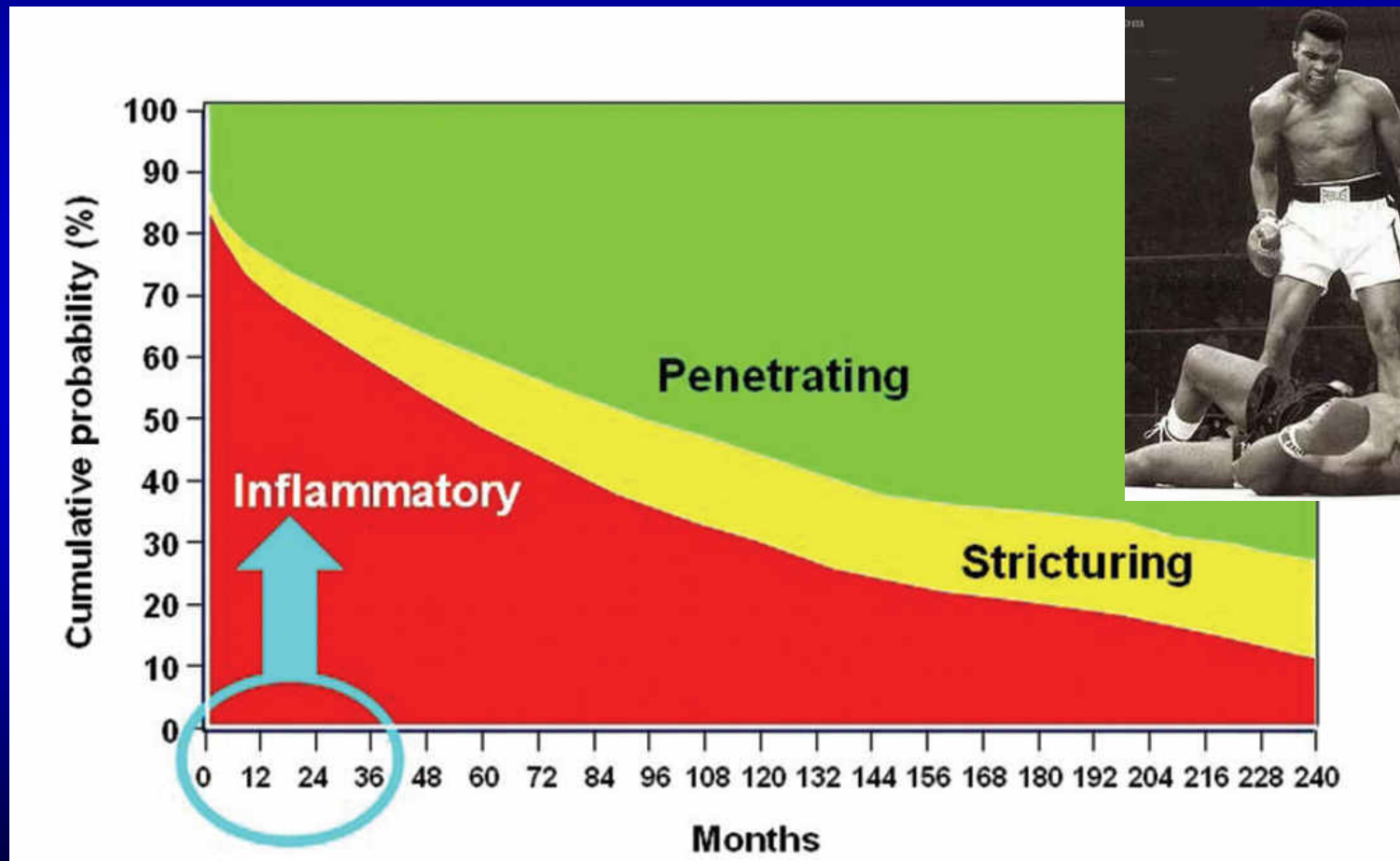
Rosenfeld G et al. *J Crohns Colitis* 2013;7:868-77.

No medical therapy possible in fibrostenotic Crohn's disease:

Crohn's disease:

Therefore, don't wait too long: Hit hard and hit early!

Entzündlicher Phänotyp > 80%



Cosnes J et al. *Inflamm Bowel Dis* 2002;8:244–50.

Role of Calprotectin in postoperative CD

Gastroenterology 2015;148:938–947

Measurement of Fecal Calprotectin Improves Monitoring and Detection of Recurrence of Crohn's Disease After Surgery



Emily K. Wright,^{1,2} Michael A. Kamm,^{1,2} Peter De Cruz,^{1,2} Amy L. Hamilton,^{1,2} Kathryn J. Ritchie,¹ Efrosinia O. Krejany,¹ Steven Leach,³ Alexandra Gorelik,⁴ Danny Liew,⁴ Lani Prideaux,^{1,2} Ian C. Lawrance,^{5,6} Jane M. Andrews,^{7,8} Peter A. Bampton,^{9,10} Simon L. Jakobovits,^{11,12} Timothy H. Florin,¹³ Peter R. Gibson,^{11,12} Henry Debinski,¹⁵ Finlay A. Macrae,^{2,16} Douglas Samuel,¹⁷ Ian Kronborg,¹⁸ Graeme Radford-Smith,^{14,19} Warwick Selby,²⁰ Michael J. Johnston,¹ Rodney Woods,¹ P. Ross Elliott,¹ Sally J. Bell,¹ Steven J. Brown,¹ William R. Connell,¹ Andrew S. Day,²¹ Paul V. Desmond,^{1,2} and Richard B. Geary²²

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Wright EK et al. *Gastroenterology* 2015;148:938-947.