PSC, IBD and Personalized Medicine

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CCFA

Personalized Medicine

- Exploration of how genetic or other personal biologic information and environmental exposure affect each person's risk to develop certain diseases or respond to medications

Genomic Medicine - A Primer

AE Guttmacher and FS Collins
New England Journal of Medicine
November 7, 2002

- **“The practice of medicine has now entered an era in which the individual patient's genome will help determine the optimal approach to care, whether it is preventive, diagnostic, or therapeutic.”**

Forces Driving Genomic Information into Your Clinical Practice

- **<u>The Food and Drug Administration (FDA)</u> –have added a recommendation to use genomic biomarkers for the optimal prescribing of certain medications.**
- **<u>Patients</u> - patients can now get genetic testing on their own, through Direct to Consumer (DTC) testing companies, and they may come to you for interpretation of results and follow-up.**
- **<u>Physicians</u>- physicians may order genetic testing**

The Big Uncertainties in PSC and IBD to Be Explored by Personalized Medicine

1. Causes of PSC and IBD
2. Responses to Medicines
3. Prognosis

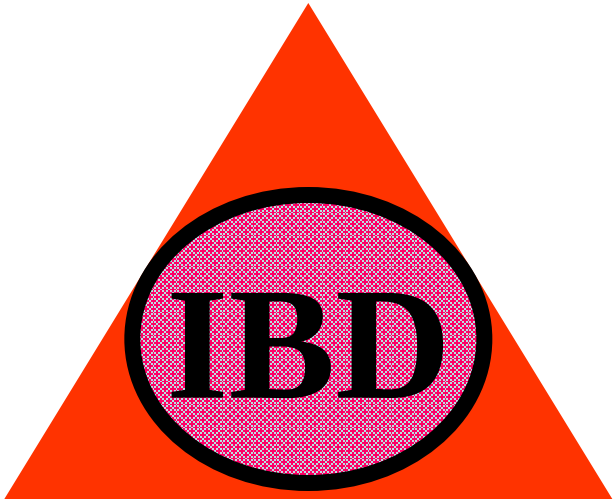
Principles of Mendelian Genetics

- **Single gene disorders (monogenic)**
- **Autosomal and X-linked inheritance**
- **Phenotypic gain or loss of function**
- **Dogma of “one gene, one phenotype”***
- **Relatively rare, however:**
  - Hereditary hemochromatosis (1:300)
  - Cystic fibrosis (1:3000)
  - More common as more children live into adulthood

*Beadle GW, Tatum EL. PNAS 1941;27:499-506

Cause of IBD

Immune



Genetic

Environment

CCFA Gut Microbiome Initiative

- Investigator: Dr. Jeffrey Gordon at Washington University, St Louis, MO
- Purpose: to identify and genetically profile the thousands of bacterial species that reside in the human intestinal tract in healthy individuals and to then determine how the bacterial environment is different in IBD patients.

CCFA microbiome project: Goals

1. Identify the bacterial species and genes present in the stool of normal individuals
2. Discover whether an individual's bacterial profile is determined by the person's genetic makeup or by environmental factors
3. Identify unique features of bacterial composition and function in IBD patients compared with normals

Other Pivotal CCFA-Sponsored Research

- OSCCAR registry
- DNA Bank

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CROHN'S & COLITIS FOUNDATION OF AMERICA

www.ccfa.org

OSCCAR

Ocean State
Crohn's & Colitis
Area Registry

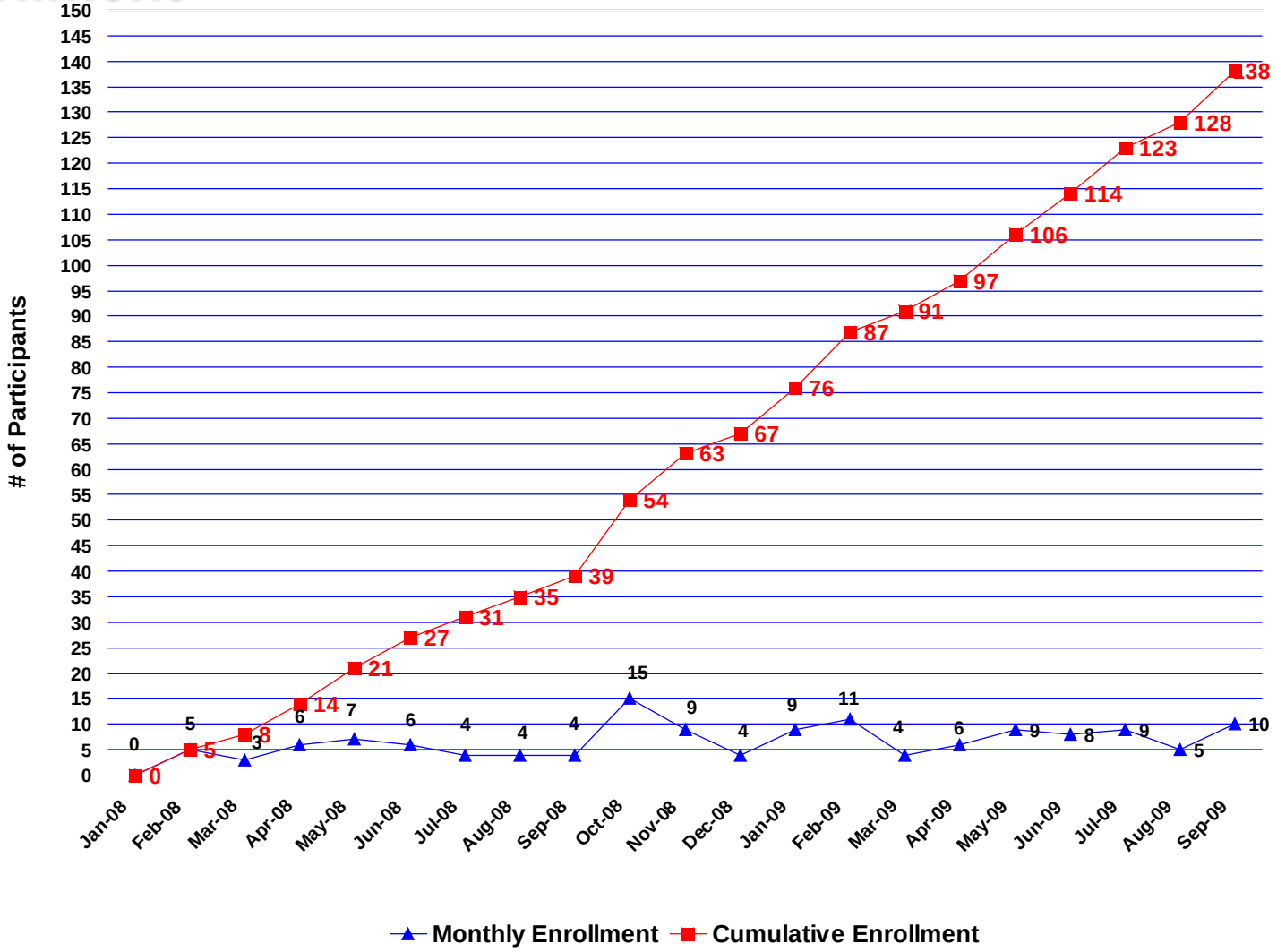
OSCCAR: Goals

- To create a prospective, population based inception cohort
  - → Large
  - → Diverse
  - → Representative of the full spectrum of disease
- To follow for outcomes over time
- To use clinical data and specimens collected close to diagnosis to develop ways to predict eventual outcome

OSCCAR: Early Findings

- Study roll-out began 1/1/2008
- Excellent acceptance by patients and referring doctors
- Incidence rate similar to what is seen in other population based cohorts
- Differences in symptoms at presentation between children and adults, men and women

Enrollment


# of Participants
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
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Jan-08
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11
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6
9
8
9
5
10
Monthly Enrollment
Cumulative Enrollment

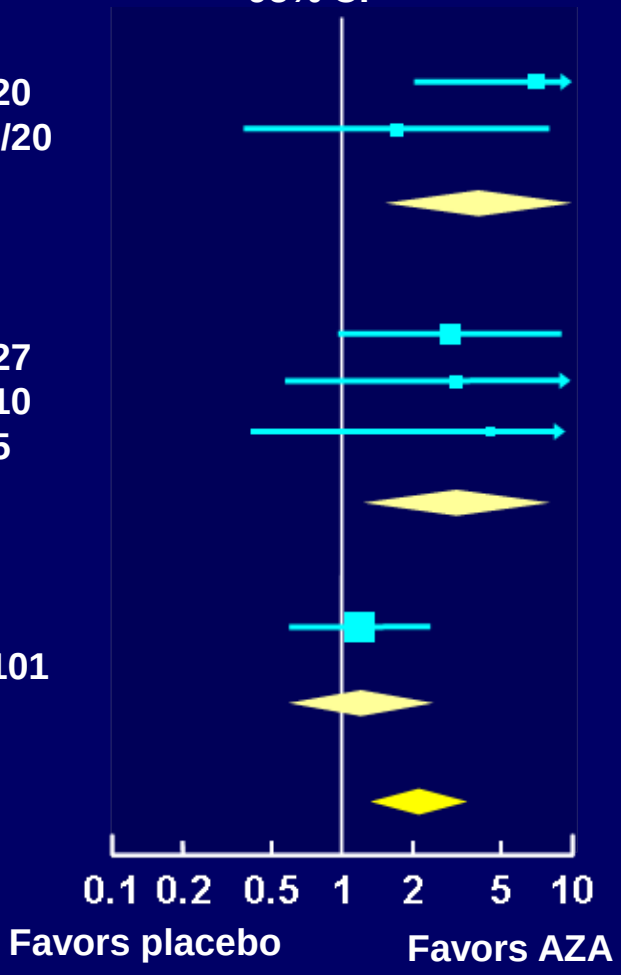
Predicting Response to Therapy

Wouldn’t It Be Nice to Know

- Who’s going to benefit?
- Who’s going to have an adverse reaction
- BEFORE we start treatment!

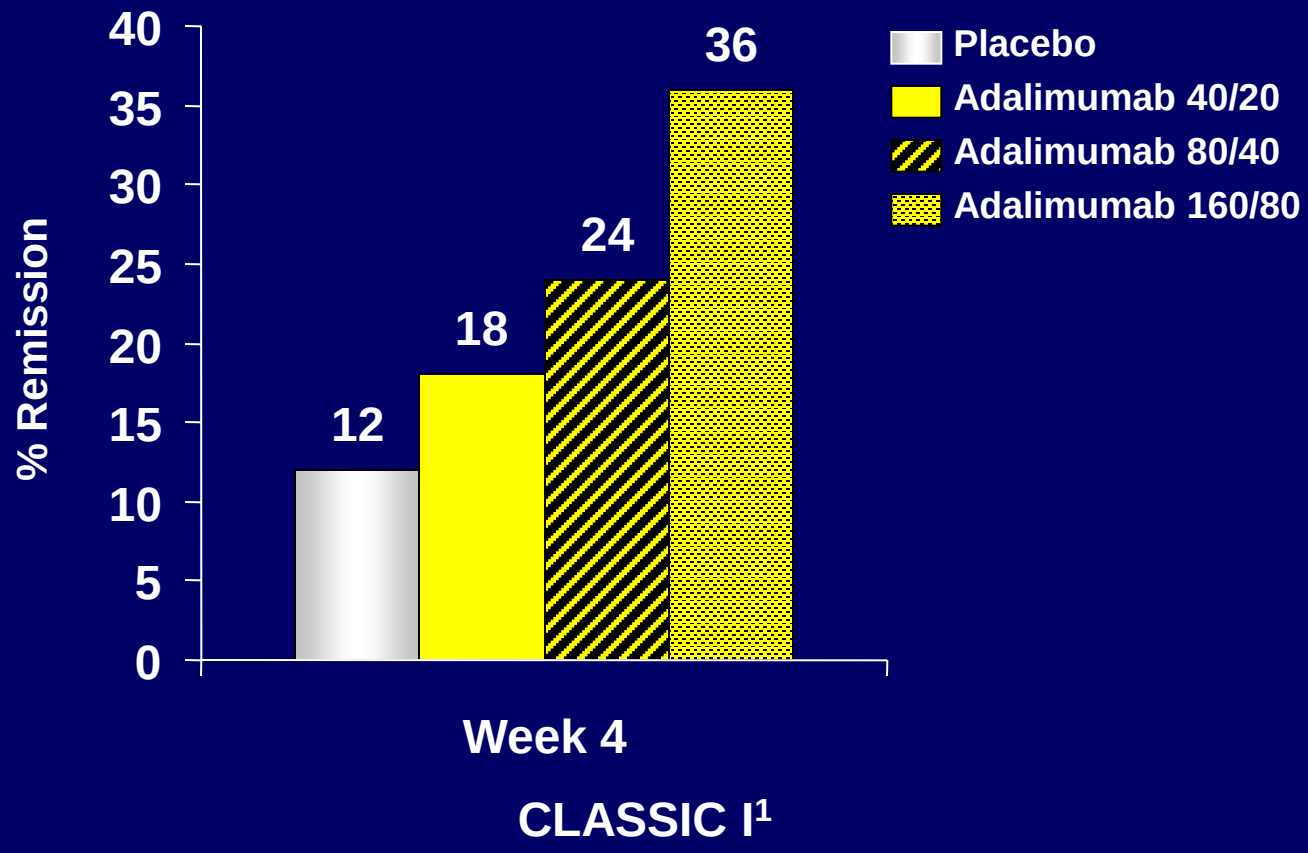
Maintenance of Remission with AZA

Study	Treatment n/N	Control n/N	Odds ratio 95% CI	Weight (%)	Odds ratio 95% CI
Azathioprine 2.5 mg/kg/day					
Candy 1995	14/25	2/20		15.1	7.12 (2.11–23.99)
Summers 1979	16/19	15/20		9.4	1.73 (0.37–8.05)
Subtotal (95% CI)	44	40		24.5	4.13 (1.59–10.71)
Azathioprine 2.0 mg/kg/day					
O'Donoghue 1978	13/23	8/27		17.9	2.95 (0.97–9.00)
Rosenberg1975	7/10	4/10		7.5	3.16 (0.57–17.62)
Willoughby 1971	4/5	2/5		3.9	4.48 (0.41–49.42)
Subtotal (95% CI)	38	42		29.3	3.17 (1.33–7.59)
Azathioprine 1.0 mg/kg/day					
Summers 1979	37/54	65/101		46.2	1.20 (0.60–2.41)
Subtotal (95% CI)	54	101		46.2	1.20 (0.60–2.41)
Total (95% CI)	**136**	**183**		**100.0**	**2.16 (1.35–3.47)**



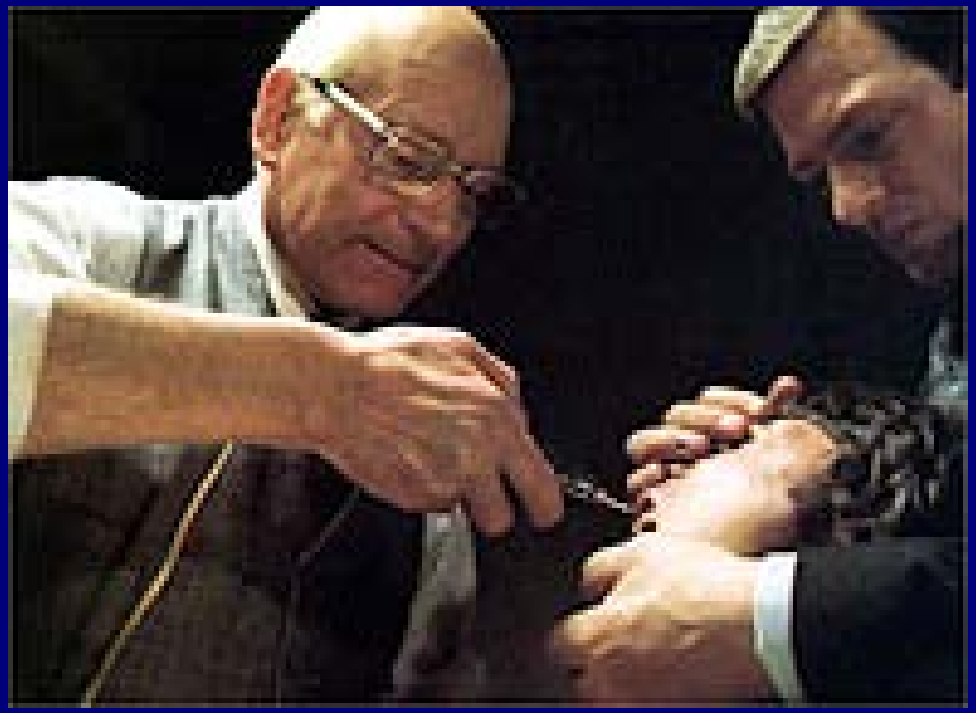
Pearson. Cochrane Database Syst Rev. 2007;1:CD000067.

Adalimumab: CLASSIC I



Hanauer, Gastroenterology, 2006

But is it safe?



General TNF Class-Effect Adverse Events

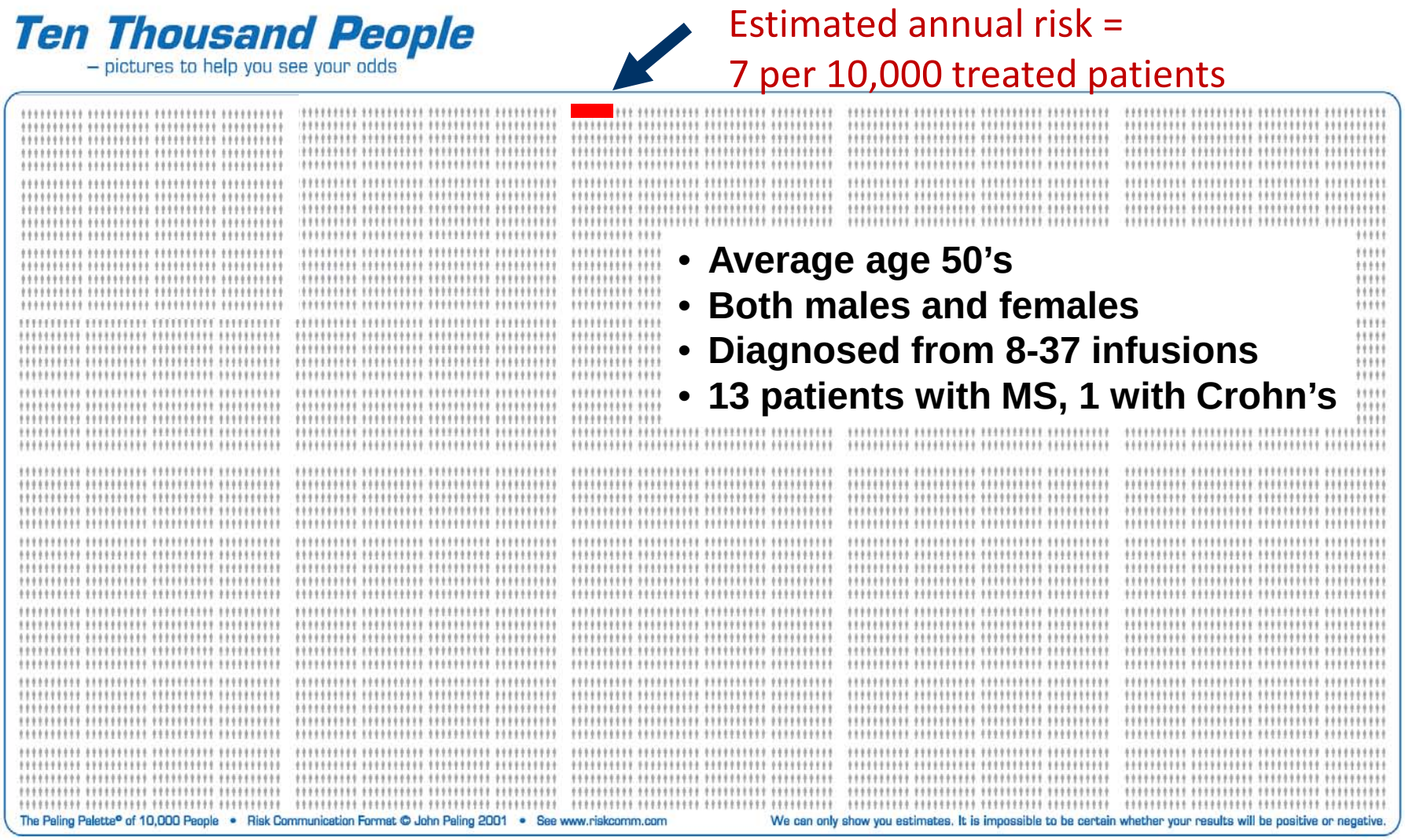
- Infection
  - Tuberculosis
  - Opportunistic infections
  - Serious infections
- Immunogenicity
  - Infusion reactions
  - Injection site reactions
  - Altered pharmacokinetics +/- loss of response
- Demyelinating Disease
- Congestive Heart Failure
- Malignancy
  - Lymphoma (esp. HSTC lymphoma)

Risk of Developing NH Lymphoma

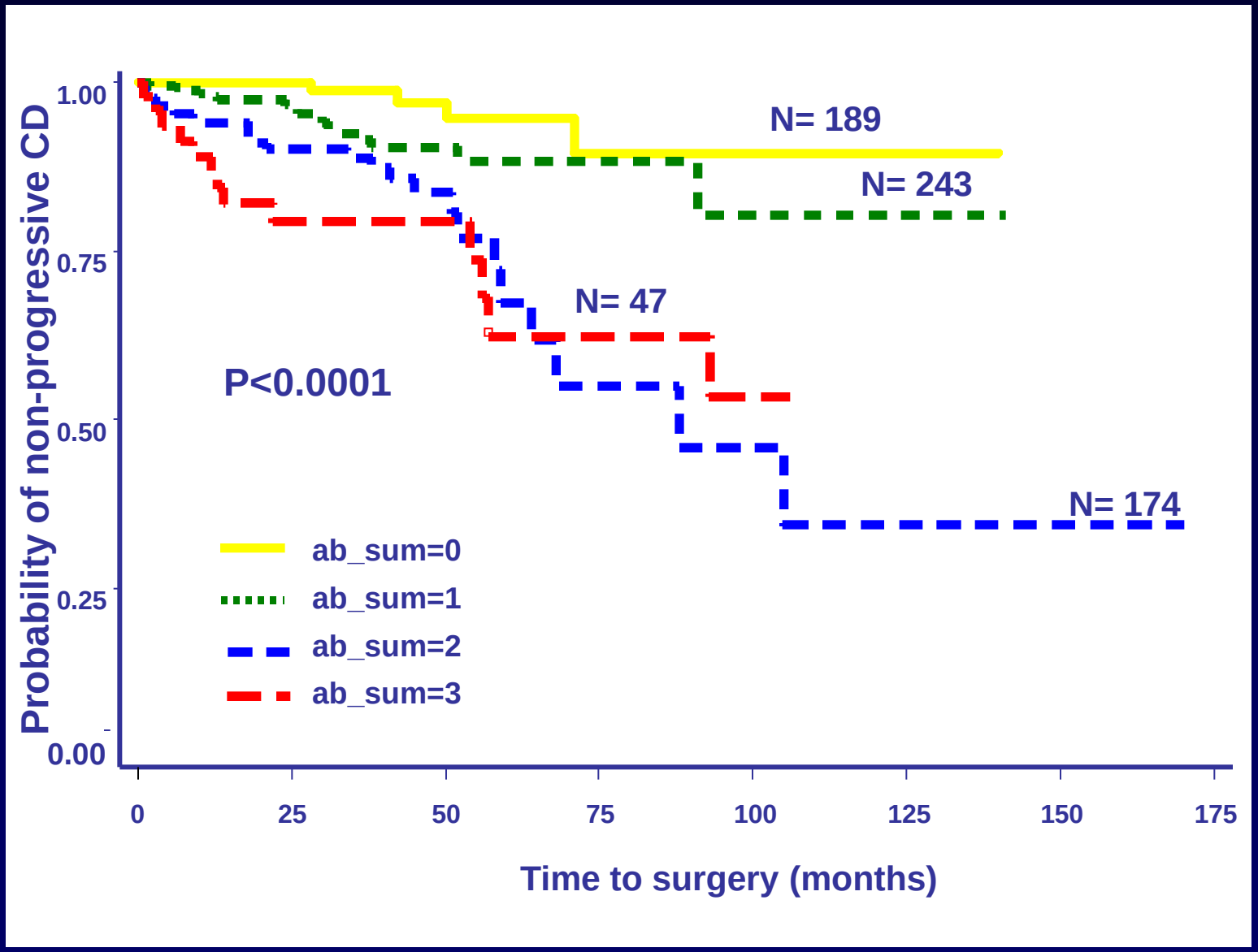
20 year old male receiving anti-TNF + Immunomodulator Therapy for 1 year

Estimated Risk of Developing PML

If 10,000 patients were treated with natalizumab for 1 year



Antibody Sum and Surgery

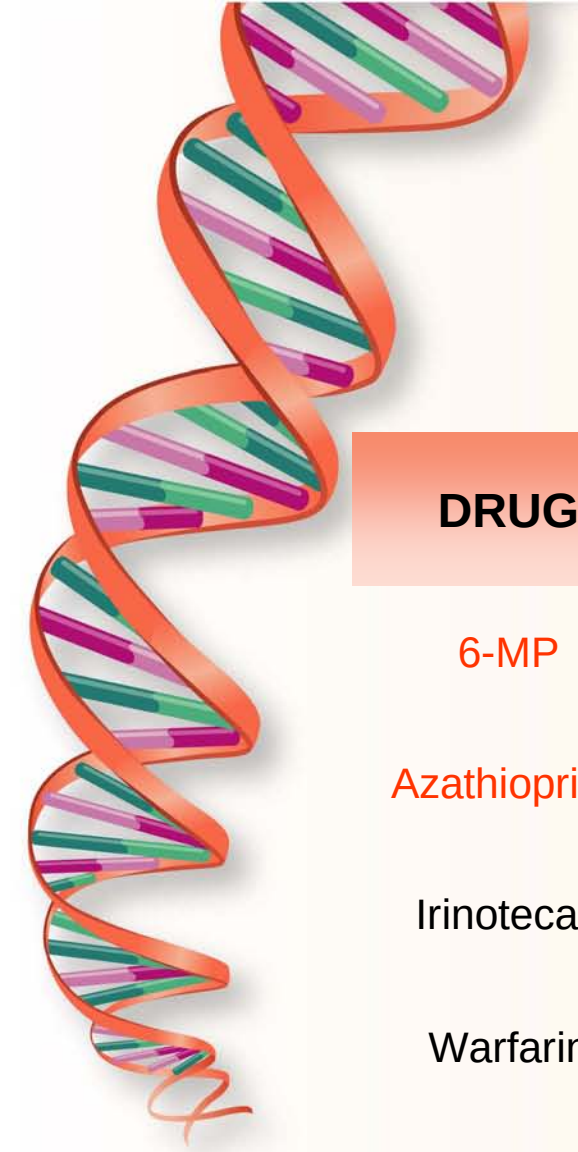


Dubinsky MC et al CGH 2008;6:1105

Pharmacogenomics (PG)

- **<u>Definition of PG</u> - the use of genetic or genomic information to guide the "selection of" or "dosing of" drugs.**

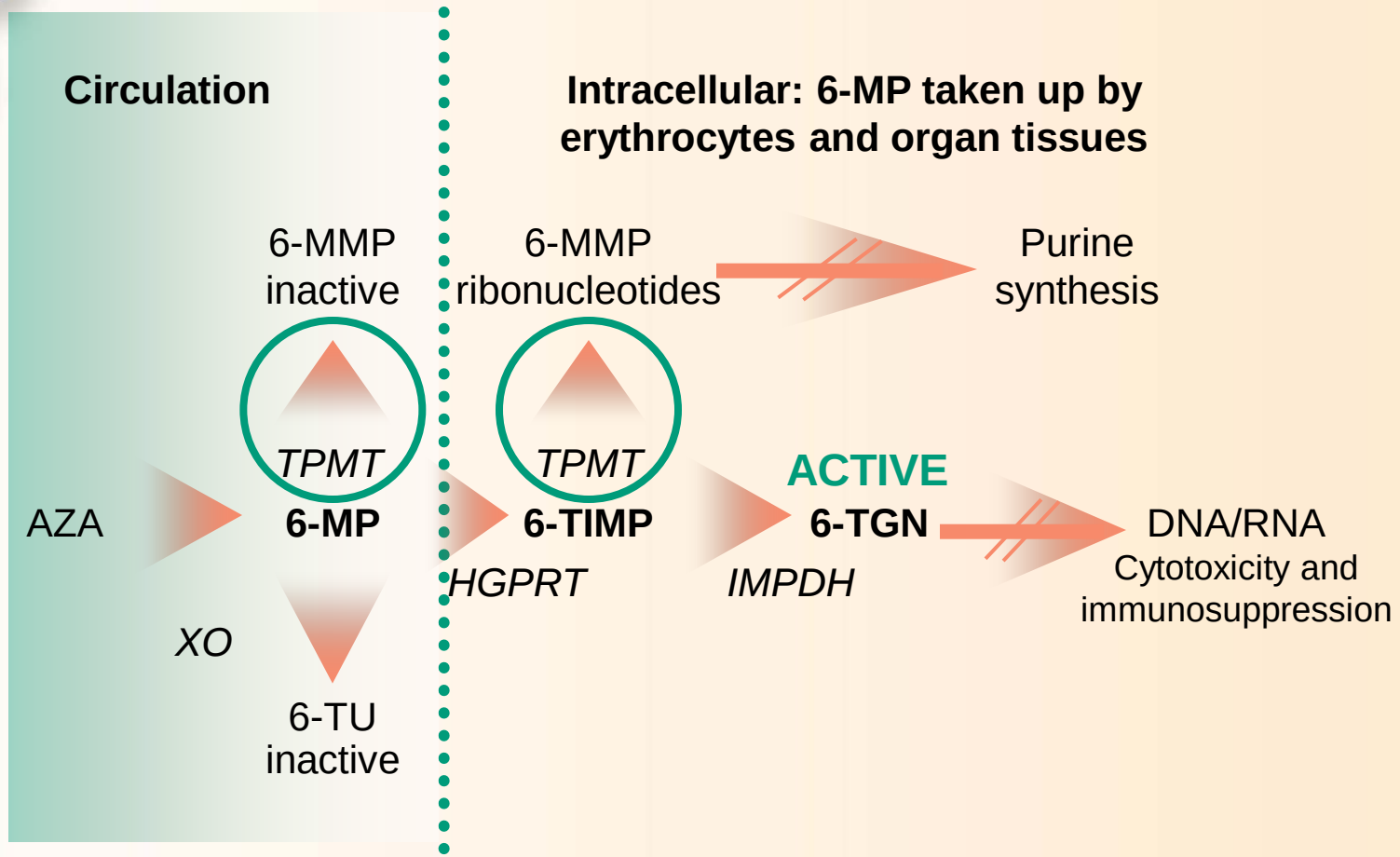
- **<u>Basic Principle Underlying PG</u> - genetic variation can effect the efficacy and the side effect profiles of medications by either altering the target or metabolism of the drug.**



Drugs for which "Relabeling" to Recommend PG Testing is Endorsed by FDA Advisory Committee

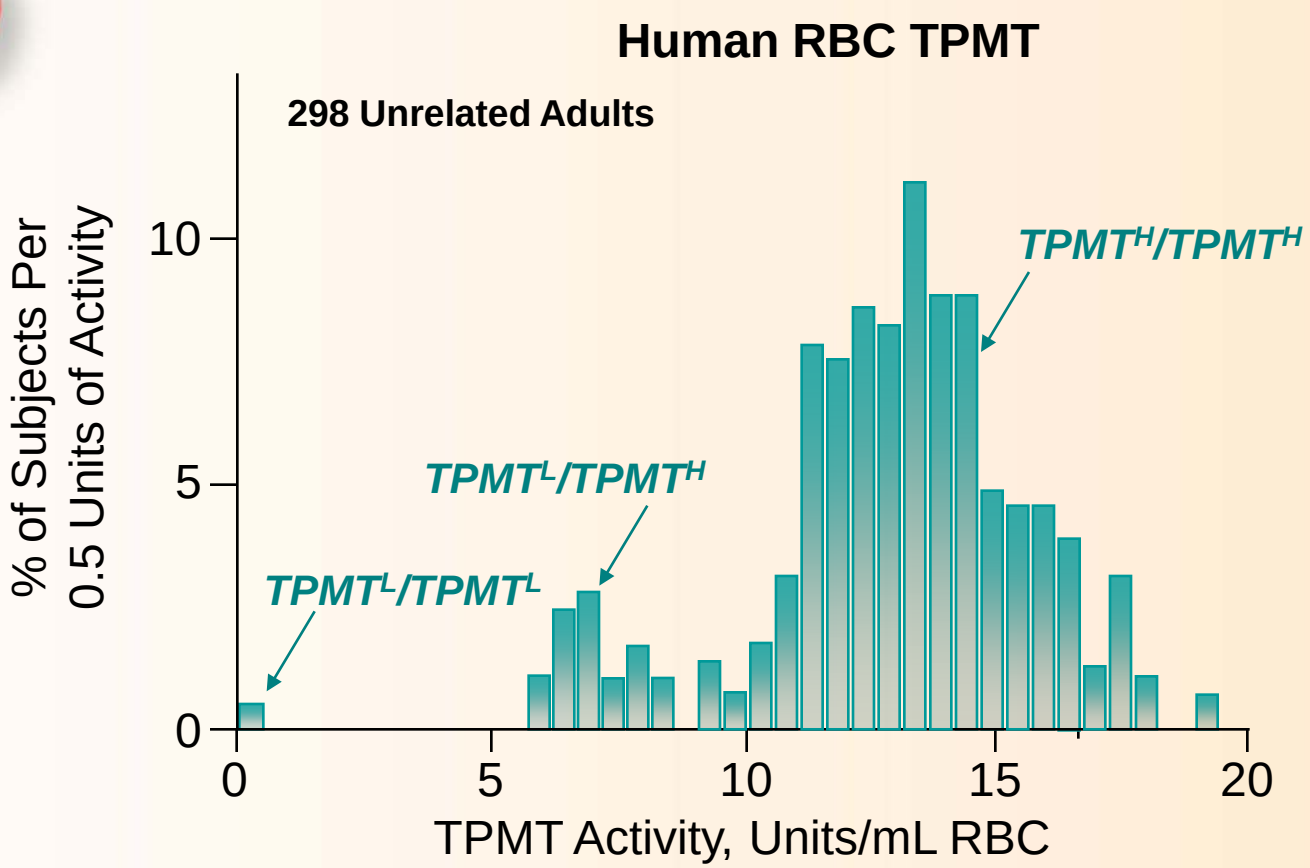
DRUG	ENZYME	GOAL	ENDORSED	RELABEL STATUS
6-MP	TPMT	Safety	2003	Complete
Azathioprine	TPMT	Safety	2003	Complete
Irinotecan	UGT	Safety	2004	Complete
Warfarin	2C9 and VKORC1	Safety	2005	Complete
Tamoxifen	2D6	Efficacy	2006	Pending

Thiopurine Methyltransferase (TPMT)



From: Provencale D, Onen JE, Inflamm Bowel Dis 2005;11:1119

TPMT RBC Enzyme Activity



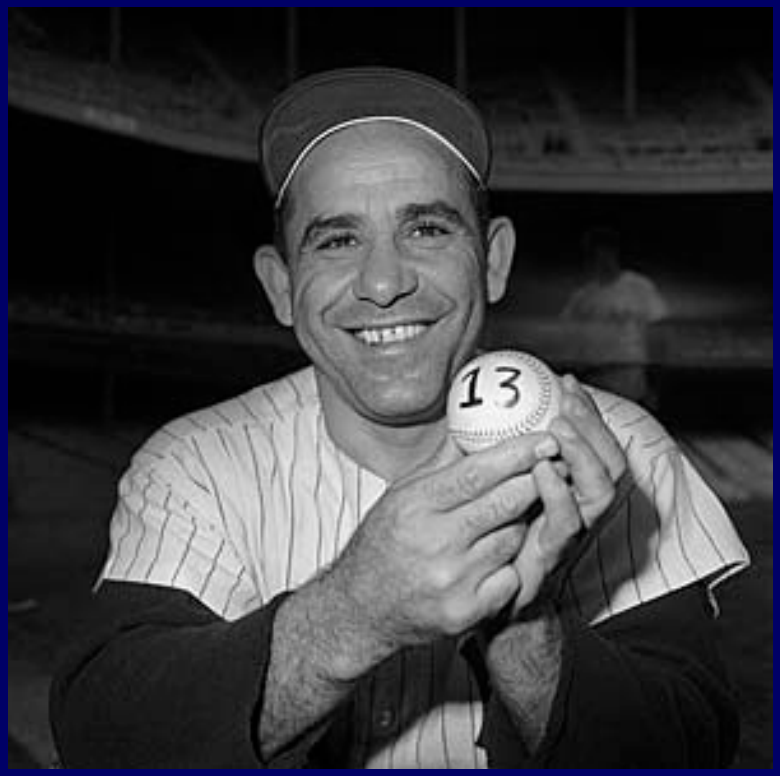
Weinshilboum R, Sladek SL. Am J Human Genet 1980;32:651-62

TPMT Genotypes: Efficacy/Toxicity

- **Efficacy: - improved early treatment response in $TPMT^{H}$ /$TPMT^{L}$ in ALL compared to $TPMT^{H}$ /$TPMT^{H}$**
  - Rationale for possible dose escalation in wt
  - Dose reduction in $TPMT^{H}$ /$TPMT^{L}$: efficacy?
- **Toxicity**
  - Severe, early leukopenia in 3% of patients
  - Known mutants responsible for 50% of leukopenia
    - Other mechanisms hypothesized

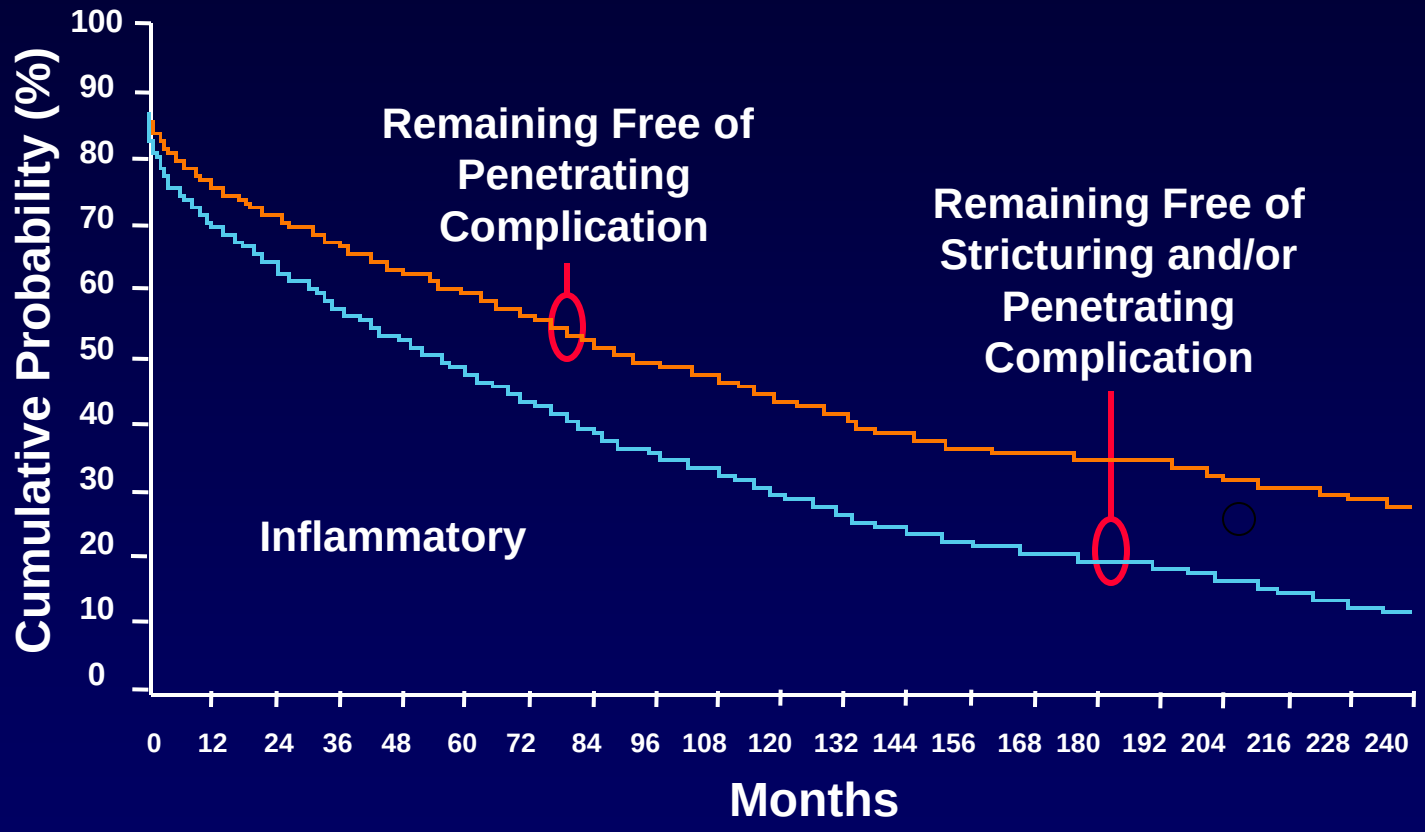
Stanulla M, Schaeffeler E, Flohr T, et al. JAMA 2005;293:1485-9
Campbell S, Kingstone K, Ghosh S. Aliment Pharmacol Ther 2002;16:389-98

Prognosis



- “It’s tough to make predictions . . .
- “especially about the future”

Crohn's Behavior: Survival Free of Intestinal Complications

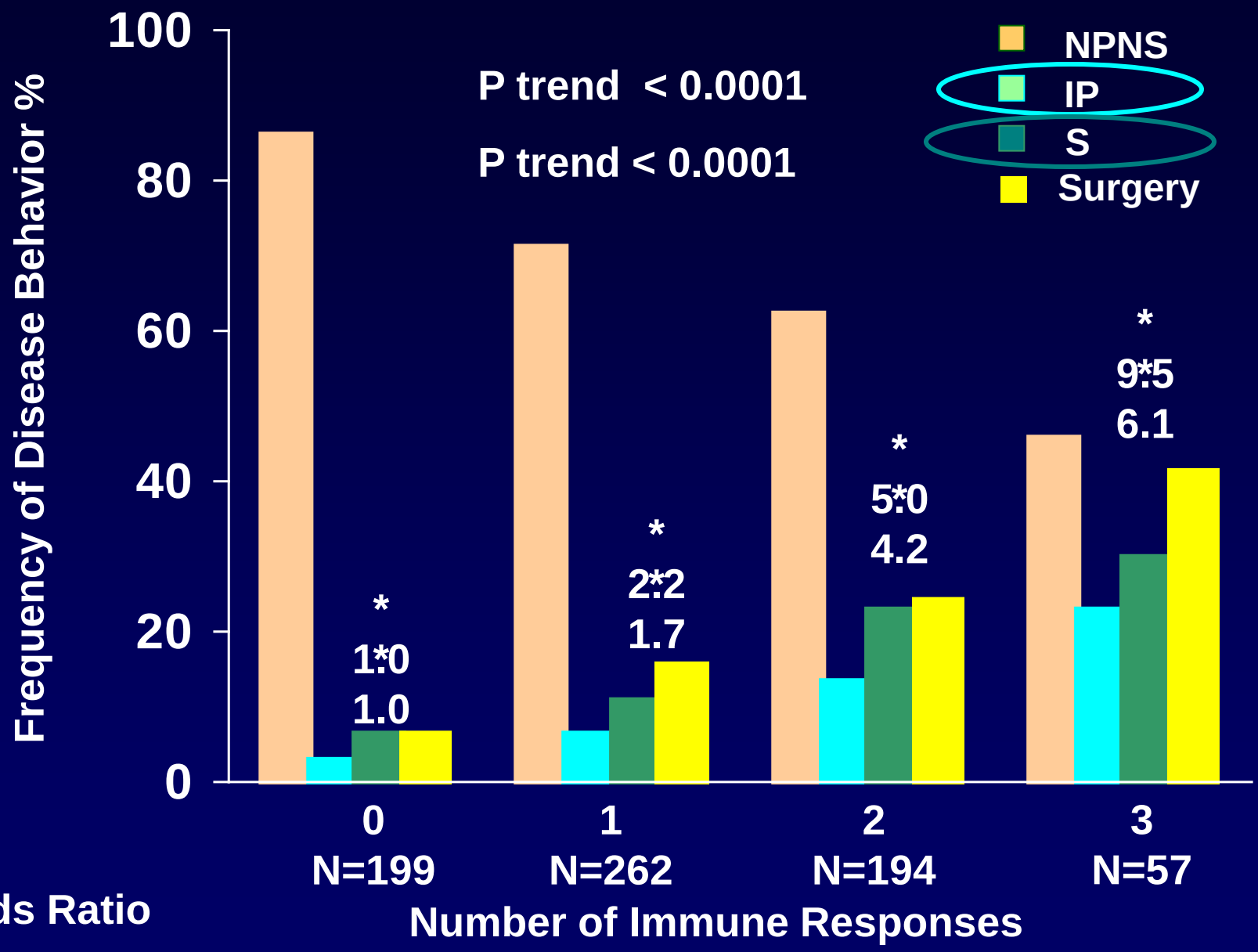


Patients at risk of any complication:

2002	552	229	95	37

Adapted from Cosnes J et al. Inflamm Bowel Dis 2002;8(4):244-250.

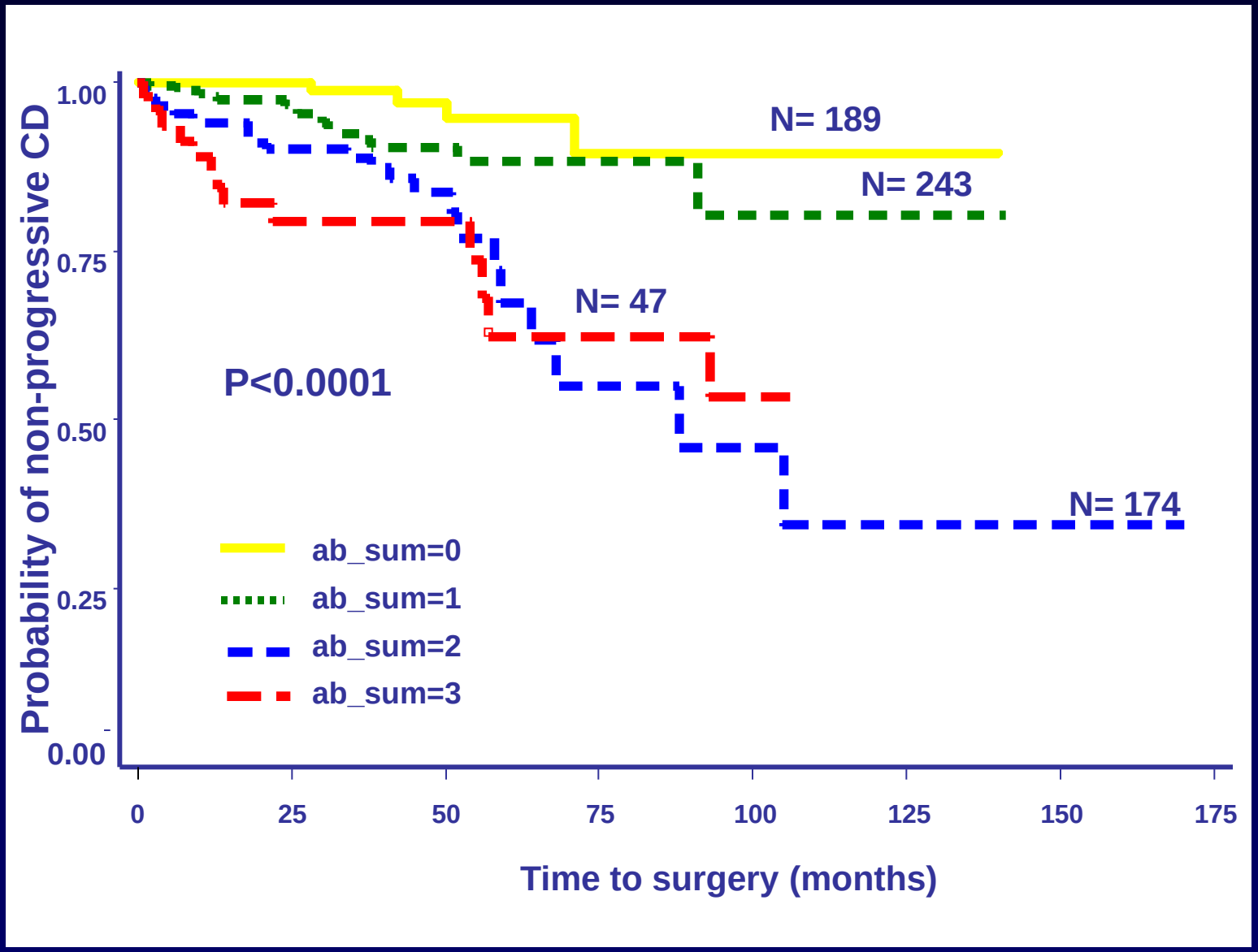
Antibody Sum and Disease Behavior



* Odds Ratio

Dubinsky MC et al CGH 2008;6:1105

Antibody Sum and Surgery



Dubinsky MC et al CGH 2008;6:1105