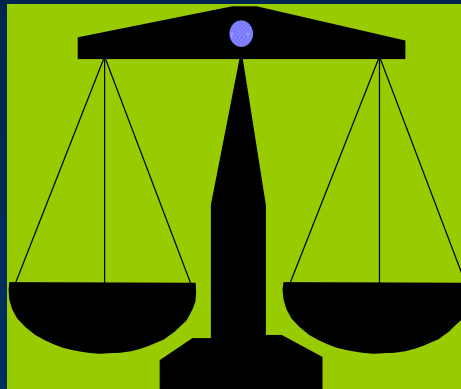


Addressing Risks and Benefits In IBD



Gil Y. Melmed, MD, MS
Assistant Professor of Medicine,
Cedars-Sinai Medical Center
David Geffen School of Medicine at UCLA

www.nomorecrohnsdisease.com

- "Jaw Dropping Discovery Leads To 4 Simple Steps That Are Guaranteed To Permanently Eliminate And Prevent Painful Crohn's Disease Once And For All With No Side Effects or Risk - Or Your Money Back"
- Without Expensive Procedures
- Without Extreme Dietary Changes
- Without Steroid Dependencies
- Without Risk!

www.nomorecrohnsdisease.com

The Risk is Commensurate
with the Reward

(Usually)

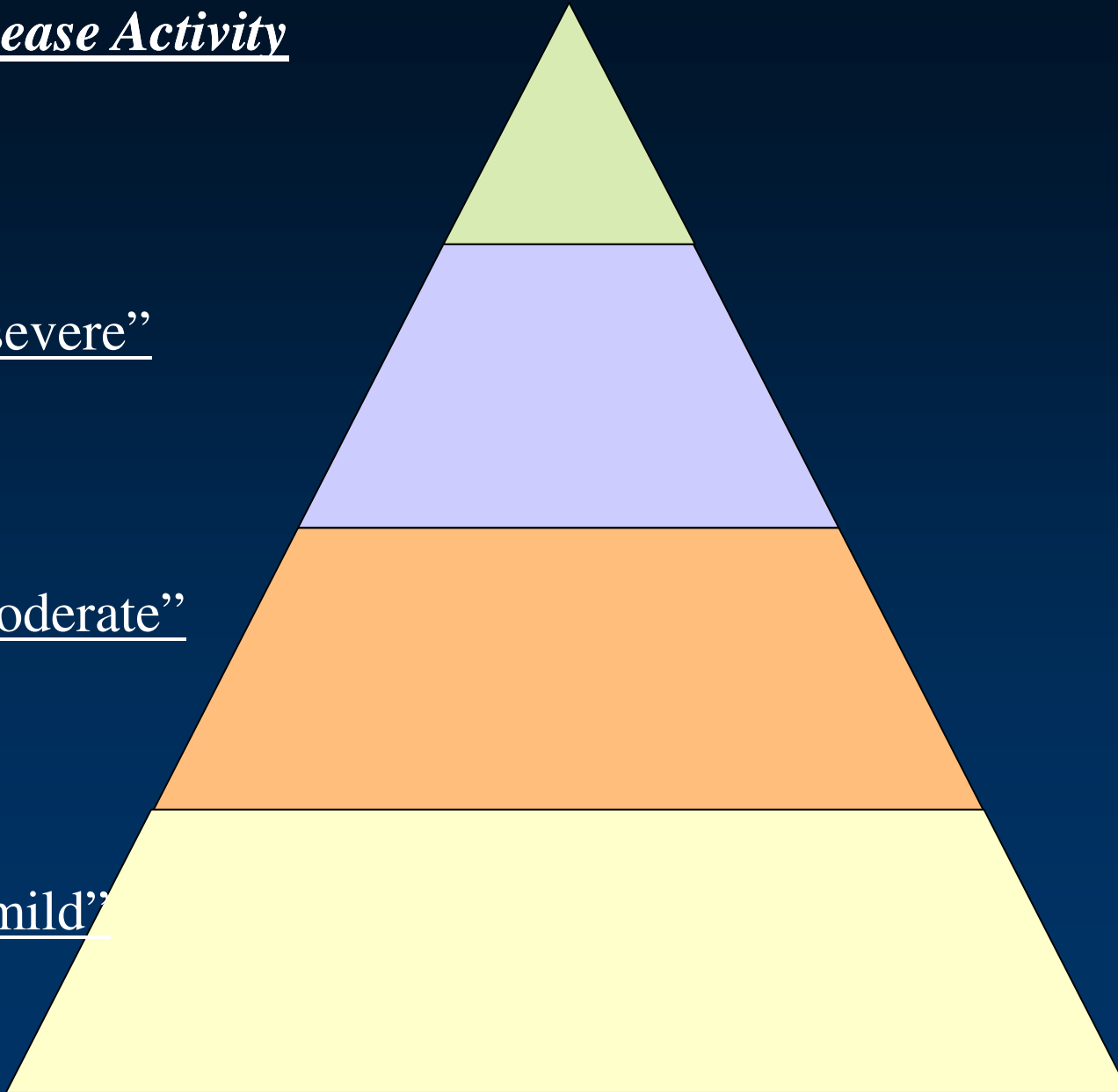
Disease Activity



“severe”

“moderate”

“mild”



Disease Activity

Degree of Risk

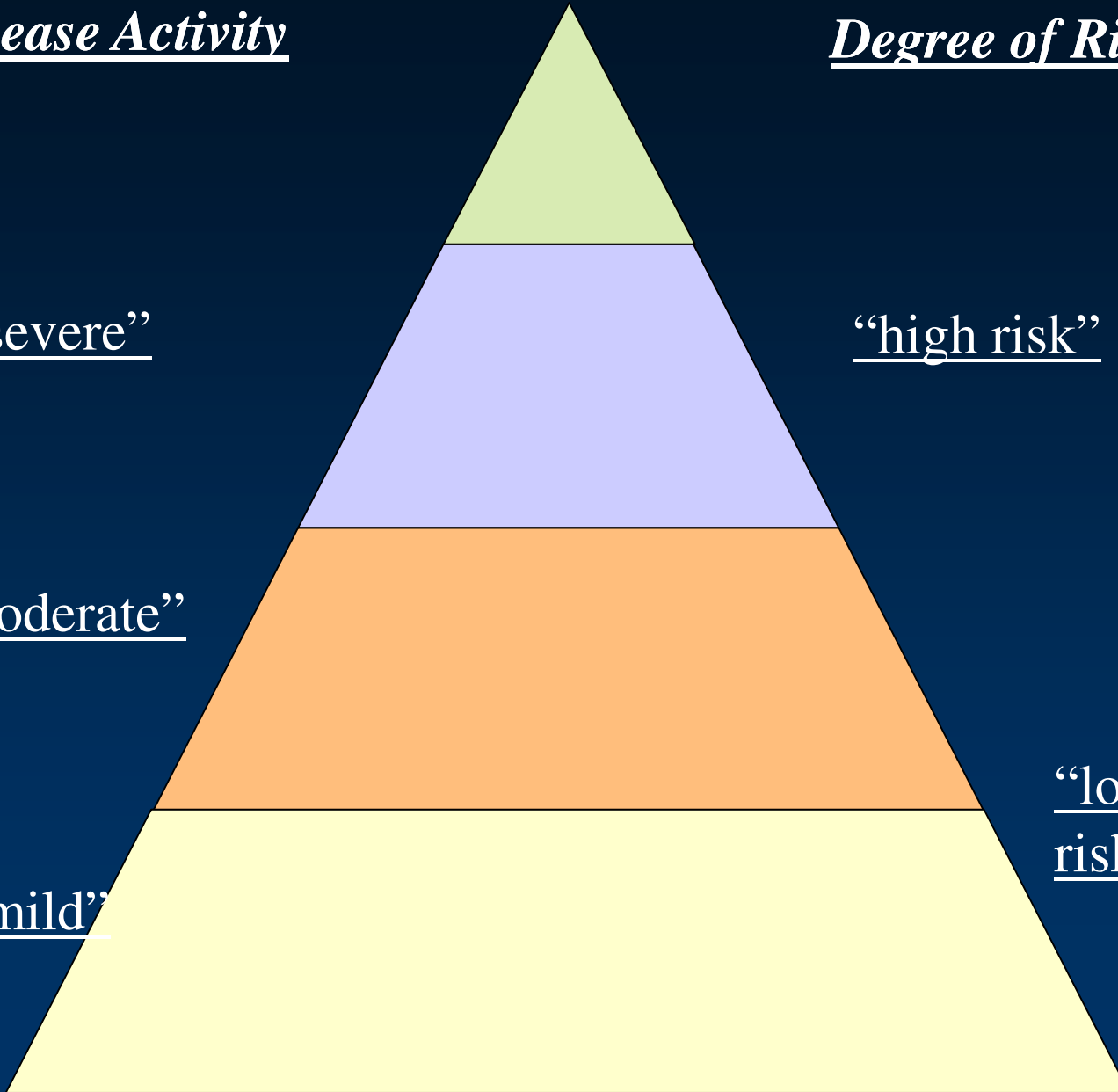
“severe”

“high risk”

“moderate”

“low
risk”

“mild”



Severity of Disease

Degree of Risk

Cyclosporin, Clinical Trials, Surgery

“high risk”

“severe”

Biologic Agents

(Remicade, Humira, Tysabri)

“moderate”

Oral steroids
(Prednisone,
Entocort)

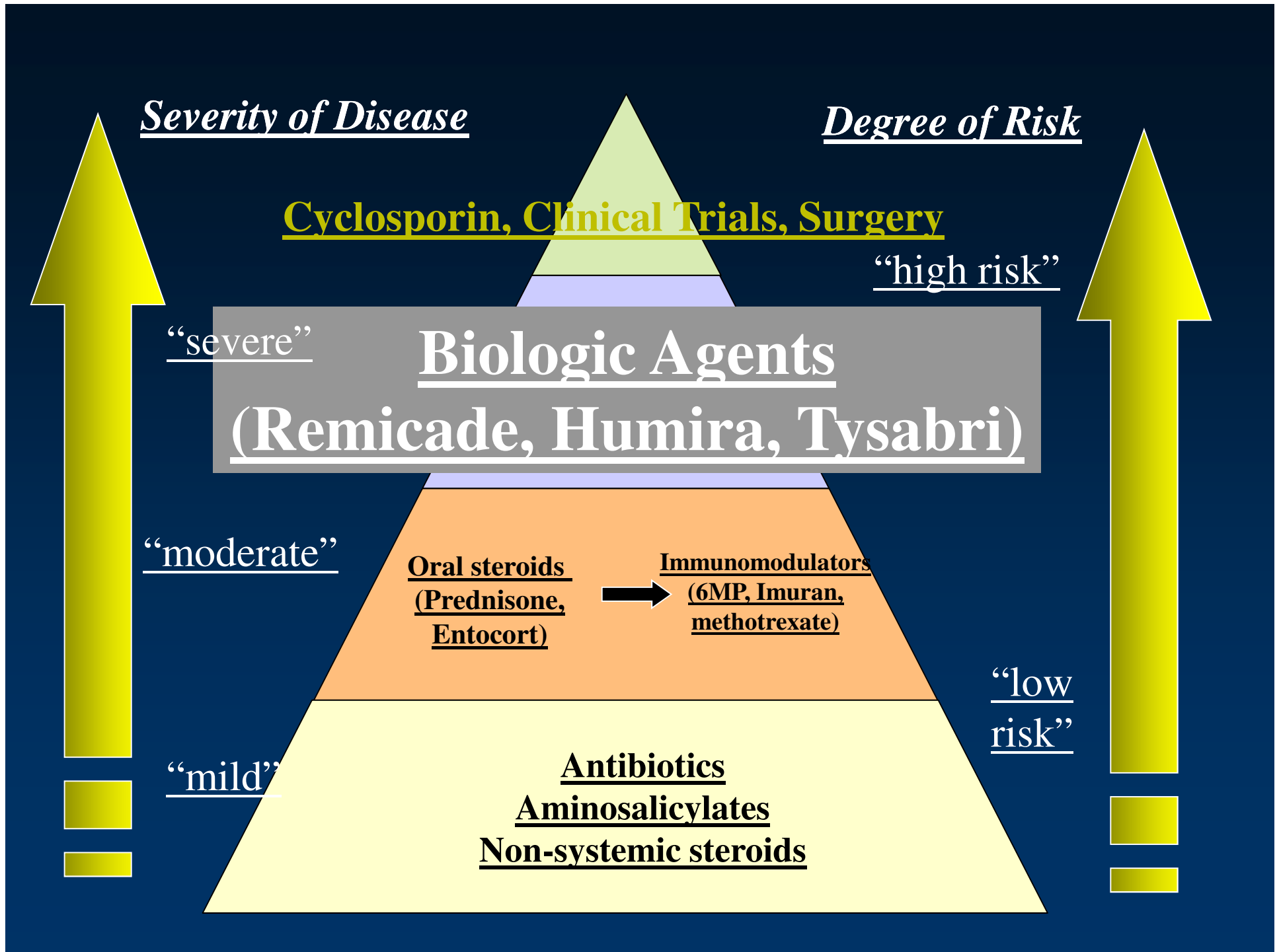


Immunomodulators
(6MP, Imuran,
methotrexate)

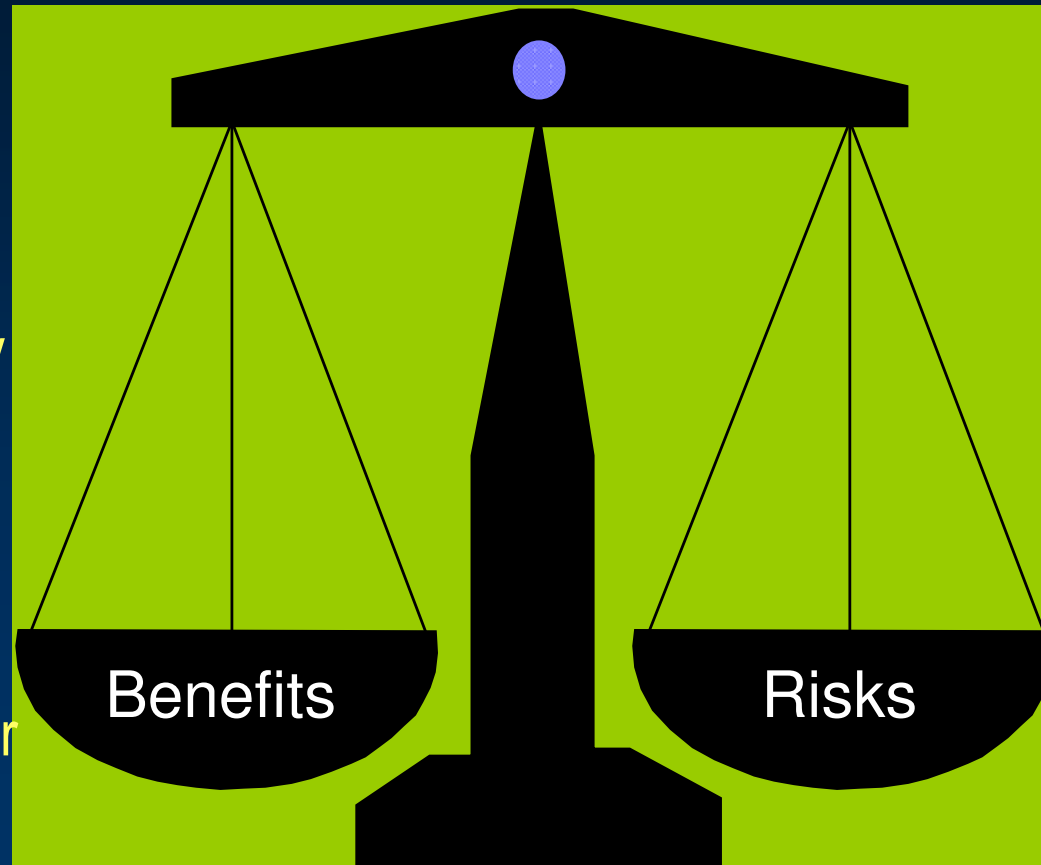
“low risk”

“mild”

Antibiotics
Aminosalicylates
Non-systemic steroids



Balancing Treatment Benefit and Risk



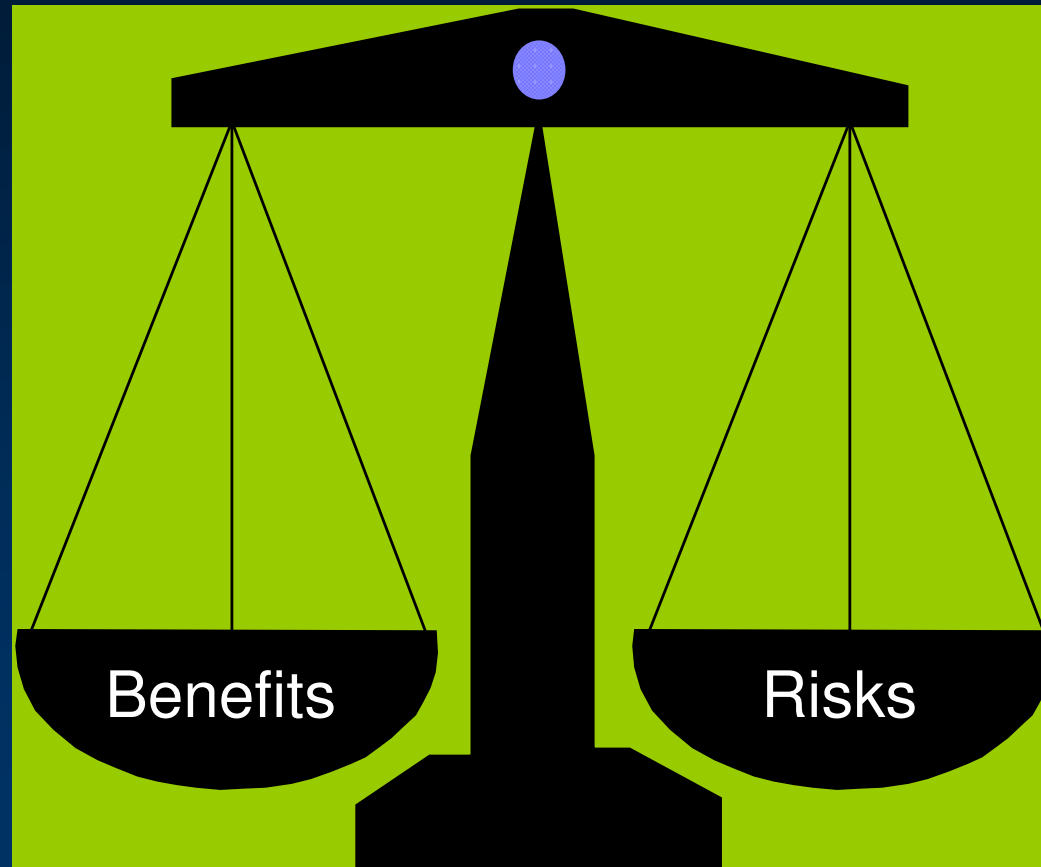
- Improved quality of life
- Avoid Surgery
- Growth and Development
- Reduce cancer risk?

- Known side effects
- Reactions
- Increased cancer risk?
- The Unknown

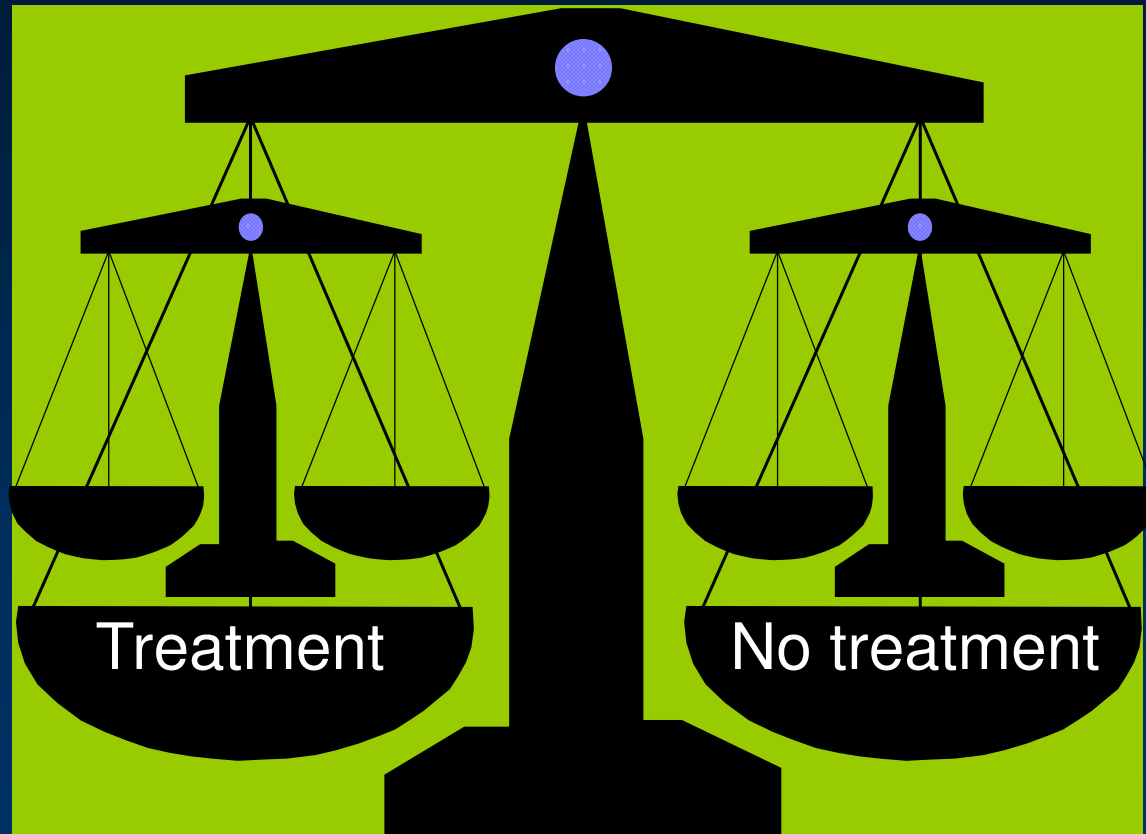
“There are **risks** and costs to a program of action. But they are far less than the **long-range risks** and costs of comfortable inaction.”

John F. Kennedy

Balancing Benefits and Risks of Treatment vs Benefits and Risks of No Treatment



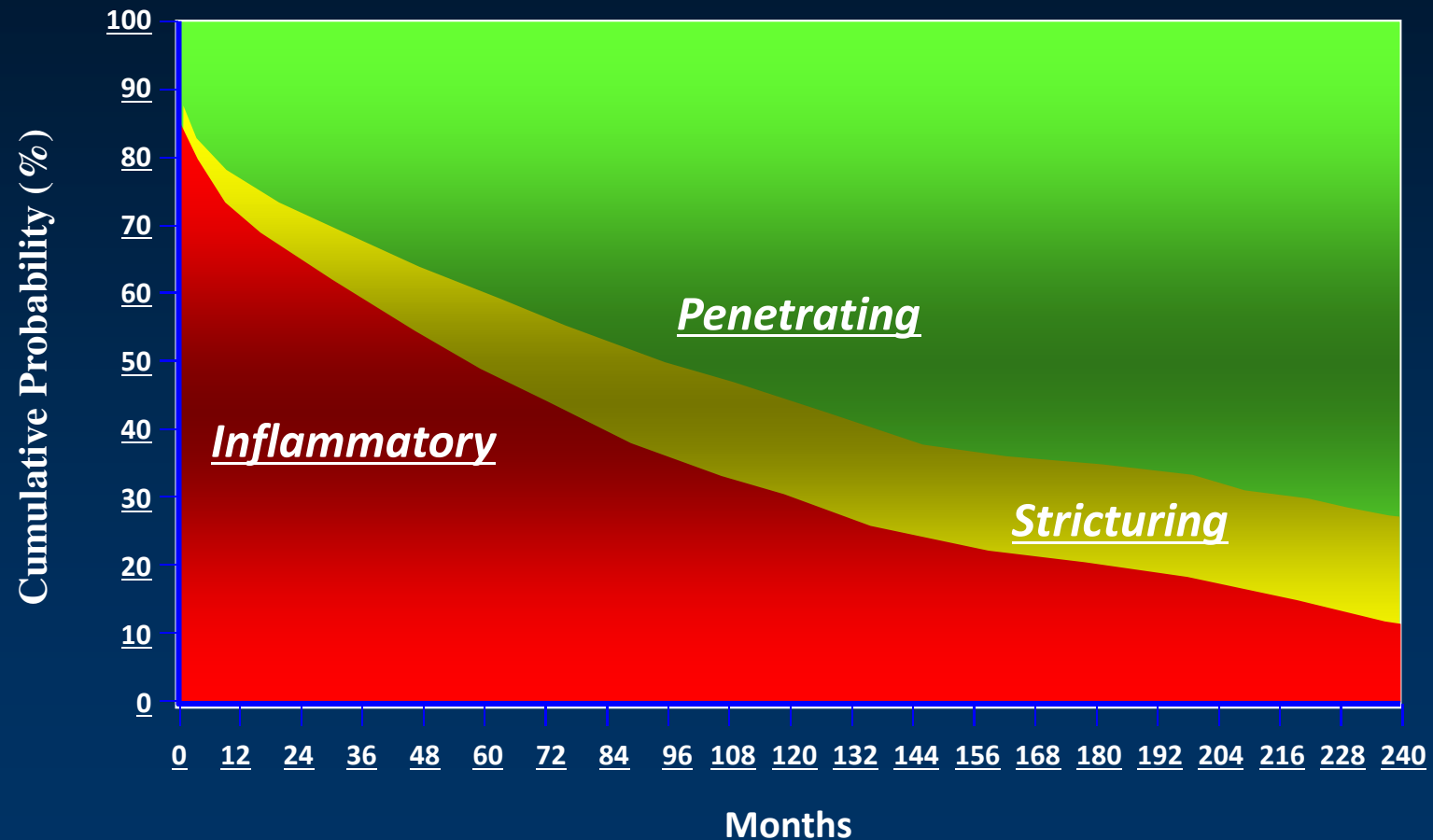
Balancing Benefits and Risks of Treatment vs Benefits and Risks of No Treatment



So... what ***are*** the risks of untreated disease?

i.e. what is
the ***natural history*** of IBD?

Long-term Evolution of Disease Behavior in CD



Patients at risk:

N= 2002

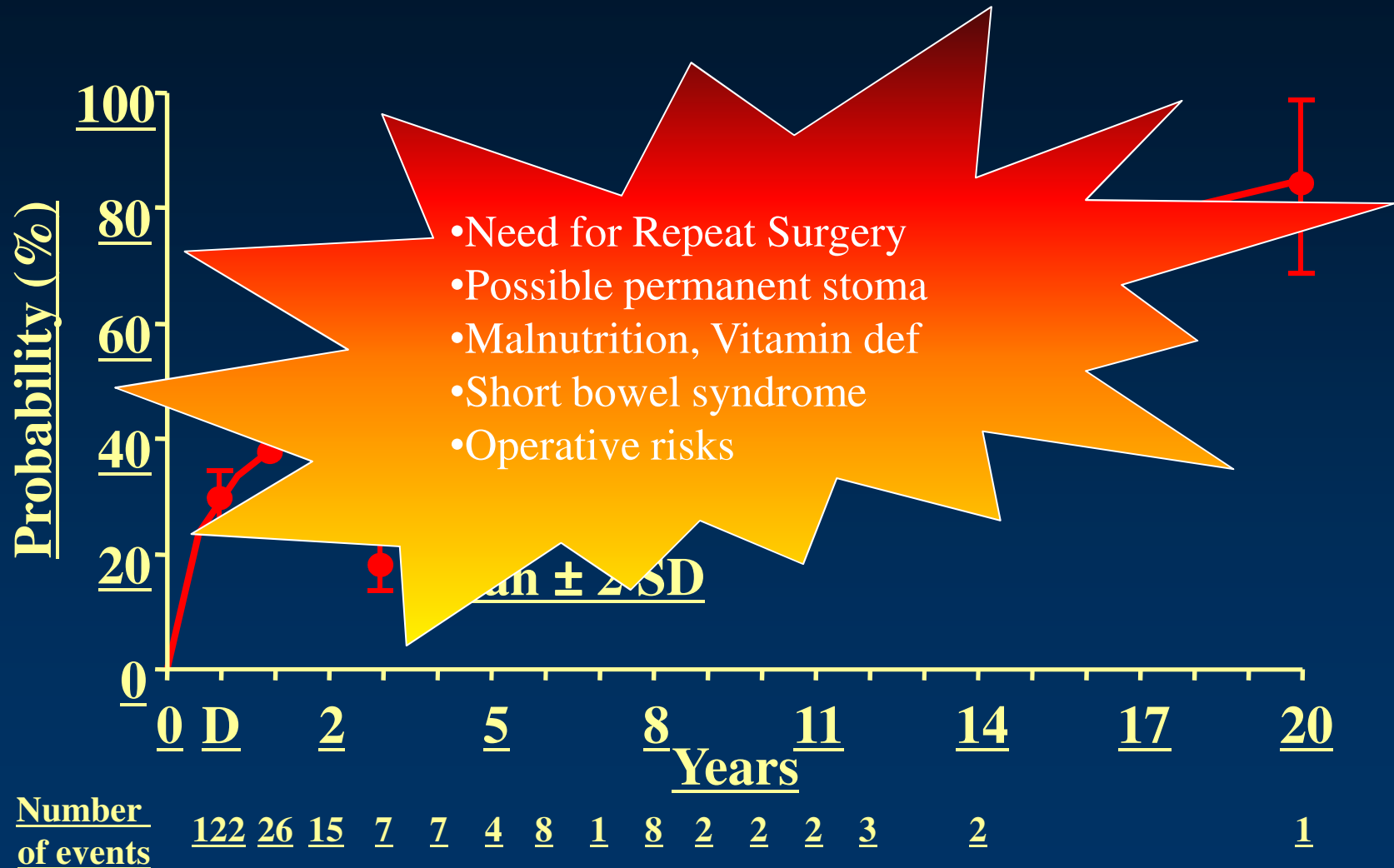
552

229

95

37

Cumulative Probability of Surgical Intervention in Crohn's Disease



Natural History of Ulcerative Colitis

- Acute severe colitis: untreated mortality 24%
- Up to 30% undergo colectomy at some point
- Increased risk of colon cancer (probably related to degree/duration of longstanding inflammation)

Lanholz et al. Gastroenterology 1992 103(5): 1444-51

Ekbom et al. NEJM 1990; 323 (18):1228-33

Rubin DT et al. Curr Treat Options Gastro 2006

What are the risks of
“Conventional Therapy?”

Steroids: Glass Half Empty or Half Full?

Event	Estimated Frequency
Any side-effect leading to stopping prednisone	55%
Ankle swelling	11%
Facial swelling	35%
Easy bruising	7%
Acne	50%
Memory problems	7%
Psychosis - confusion/agitation	1%
Infections	13%
Cataracts	9%
Increased intraocular pressure	22%
High blood pressure	13%
Osteoporosis	33%
Diabetes	Chance increases 10x

What are the main side-effects of 6MP/Azathioprine?

Event	Estimate Frequency (annual)
Stop therapy due to adverse event	11%
Allergic reactions	2%
Nausea	2%
Hepatitis/abnormal LFTs	2%
Pancreatitis	3%
Serious infections	5%
non-Hodgkin's lymphoma	0.04% (4/10,000)

Benefits of Biologics

- Decreased hospitalizations
- Decreased surgeries
- Improvement in HRQOL
- Improvement in work/productivity

So...

**What *are* the risks associated with
(biologic) therapy?**

Side-effects of anti-TNF agents

- **Hypersensitivity reactions**
 - infusion or injection site reactions
 - serum sickness/delayed hypersensitivity
- **Immunogenicity**
- **Headache**
- **Rash**
- **Infections**
 - *mild and serious*
- **Demyelinating disorders**
- **Psoriasis**
- **Autoantibodies**
- **Pancytopenia**
- **Heart failure**
- **Hepatotoxicity**
- **Malignancy**

Adverse Reactions Associated with anti-TNF Treatment

Event	Estimated Frequency (annual)
Stop therapy due to adverse event	10%
Infusion or injection site reactions	3%-20%
Drug related lupus-like reaction	1% (1/100)
Serious infections	3% (3/100)
Tuberculosis	0.05% (5/10,000)
Non-Hodgkin's lymphoma (combo)	0.06% (6/10,000)
Multiple sclerosis, heart failure, serious liver injury	Case reports only

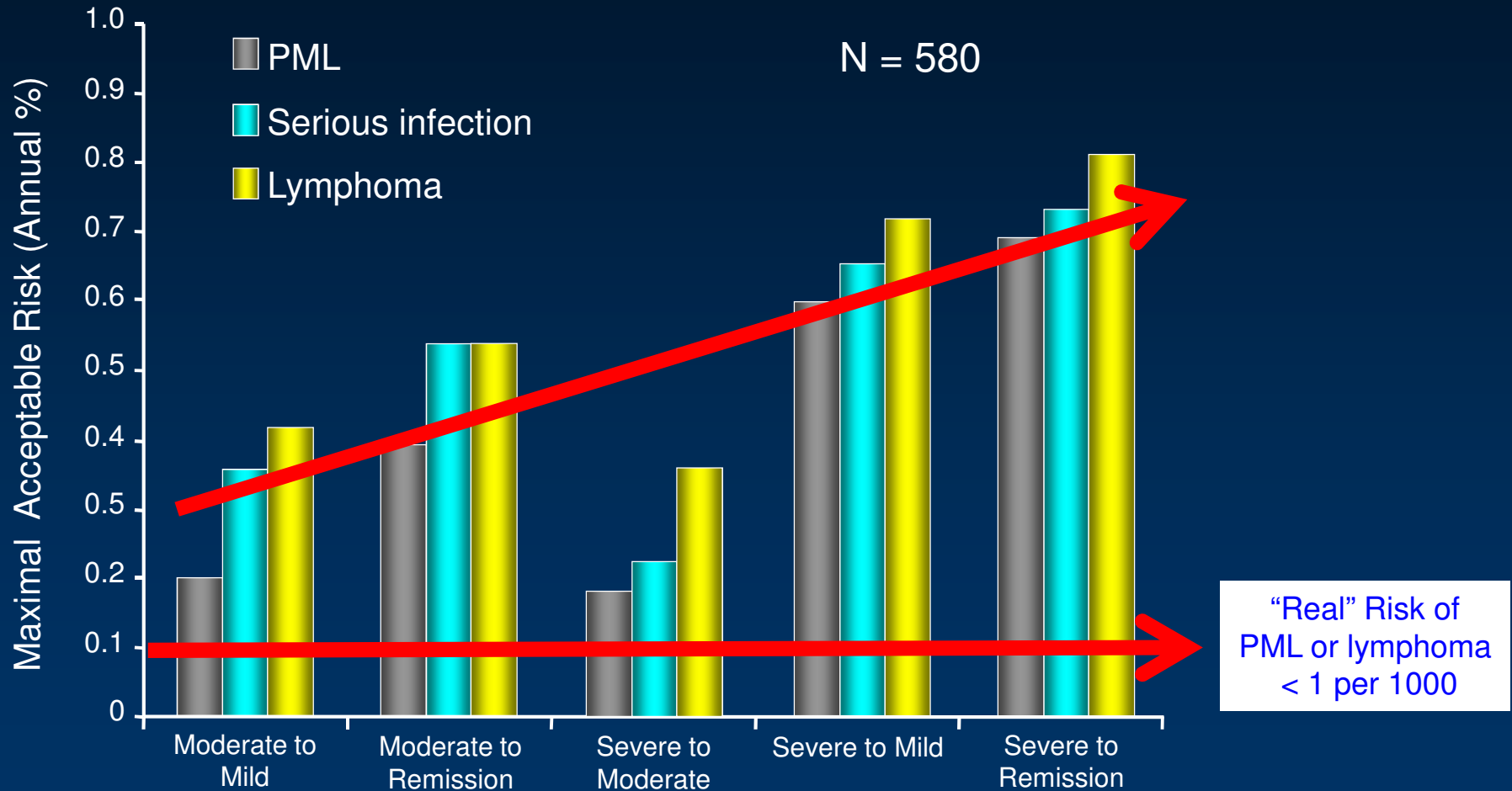
Hepatosplenic T-cell lymphoma

- 12 cases in IBD with **6MP/AZA** alone
- 19 cases in IBD patients taking **infliximab or adalimumab with 6MP/AZA**
 - Age range 12-58 years old
 - Average age = 26 years old
 - **Almost all are male (18/19)**
 - Infusions ranged from 1-24
 - 9 patients had ≤ 3 infusions
 - Four received adalimumab (after infliximab)
 - 1 received natalizumab (after 2 anti-TNFs)
 - Appears to be universally fatal

How Much Risk are Crohn's Patients Willing to Accept?

- Web-based survey of 580 patients with Crohn's disease
- Conjoint trade-off analysis
- Evaluated patients' willingness to accept the risk of treatment related side-effects in exchange for improvement in daily symptoms

Patients are Willing to Take High Risks



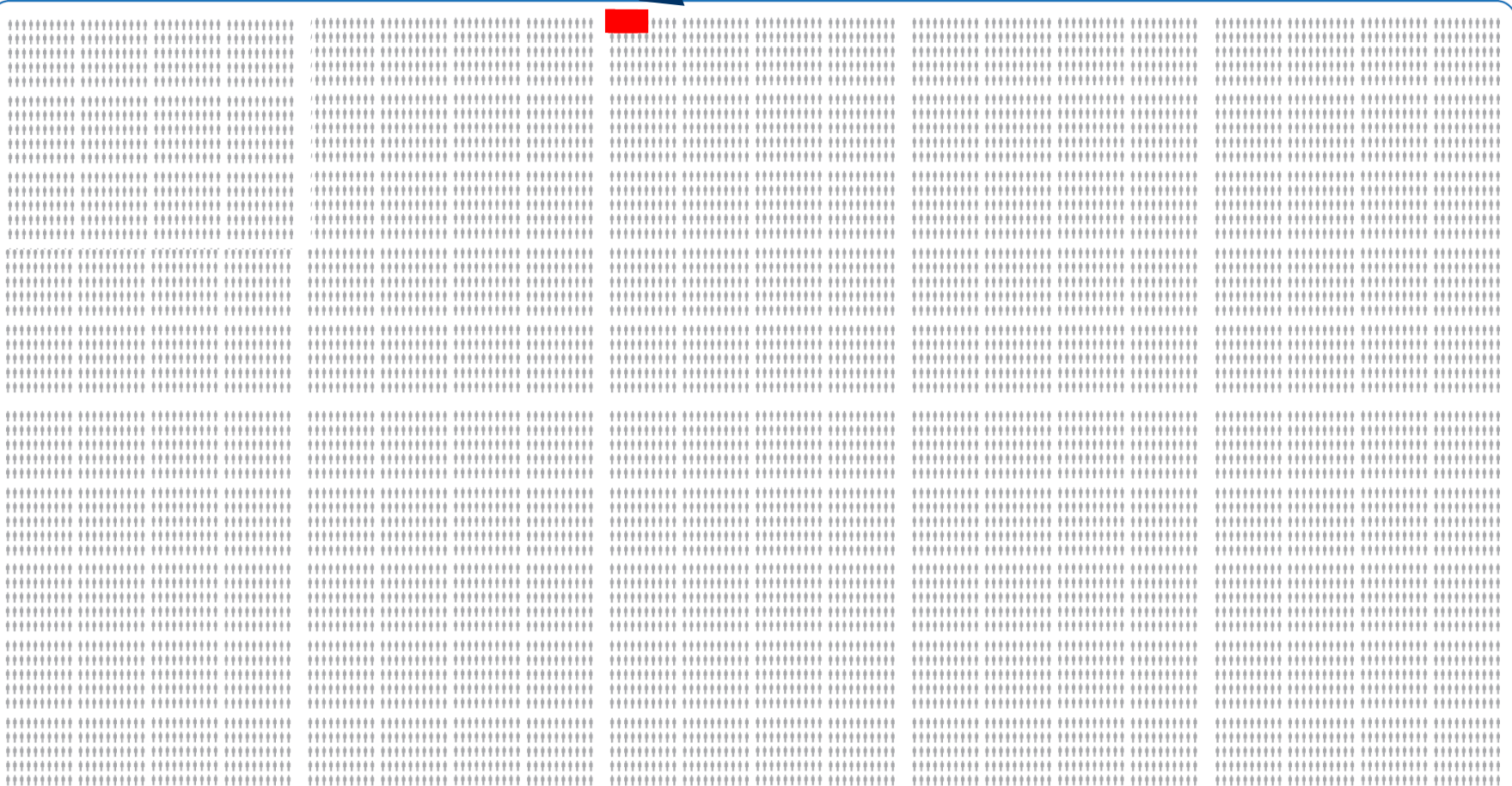
Risk of Developing NH Lymphoma

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

Ten Thousand People

– pictures to help you see your odds

Risk with combination therapy



The Paling Palette® of 10,000 People • Risk Communication Format © John Paling 2001 • See www.riskcomm.com

We can only show you estimates. It is impossible to be certain whether your results will be positive or negative.

Summary: Risks & Benefits

- IBD itself carries significant risks if untreated
- The risks of medical therapy are loosely correlated with respective benefits
- Biologics can reduce hospitalizations, surgeries, and improve health-related quality of life
- “Risks and Benefits” should to be communicated effectively
 - Relative to risk of untreated disease
 - Using understandable means



"We've considered every potential risk except
the risks of avoiding all risks."