Communicating Risks and Benefits to IBD Patients

2008 Advances in Inflammatory Bowel Diseases
Crohn's and Colitis Foundation's Clinical and Research Conference

Corey A. Siegel, MD
Assistant Professor of Medicine,
Dartmouth Medical School
Director, Dartmouth-Hitchcock IBD Center

How Can We Improve <u>Quality</u> of Care?

Institute of Medicine - *Crossing the Quality Chasm (2001)*

- **S**
- **T**
- **E**
- **E**
- **E**
- **P**

How Can We Improve Quality of Care?
Institute of Medicine - *Crossing the Quality Chasm (2001)*

- **S**afe → Avoiding injuries to patients from the care that is intended to help them
- **T**imely
- **E**ffective
- **E**fficient
- **E**quitable
- **P**atient Centered → Providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions

Understanding and Clearly
Communicating Risk & Benefit
Information Will Lead to

- **S**afe
- **T**imely
- **E**ffective &
- **E**fficient
- **E**quitable Care for IBD
- **P**atient Centered and Improve Quality

Safety Update
Numbers We Can Tell Our Patients

- Risks of the disease
- Risks of the "old" drugs
- Risks of the "new drugs"

Risk of Mortality in Crohn's with Steroids and Immunomodulators

- Retrospective cohort from UK (GPRD)
- 5,539 patients with Crohn's; 41,624 controls
- Evaluated mortality associated with Crohn's itself, prednisone, immunomodulators (most AZA & 6MP)
- Biologics not included in analysis

Exposure	Hazard Ratio	95% CI
Crohn's (mild)	1.27	1.07-1.51
Crohn's (severe)	2.44	1.84-3.25
Current prednisone	2.48	1.85-3.31
Current AZA/6MP	0.83	0.37-1.86

Lewis et al, AJG 2008;103:1428.

What is the risk of lymphoma associated with immunomodulators?

- Meta-analysis of 6 studies
- IBD patients treated with 6MP or Azathioprine have a 4-fold increased risk of developing lymphoma
- Subpopulation of Crohn's & NHL (on IM)

    4 cases NHL/11,012 patient-years

3.6 NHLs per 10,000 patient-years

Kandiel et al, Gut 2005; 54:1121.

Excess risk of lymphoproliferative disorders in IBD: CESAME results

- 20,802 patients with 50,225 pt-yrs of follow up
- 29.8% patients on AZA, 3.5% MTX, 4.6% biologics
- 18 patients with NHL, 1 patient with Hodgkin lymphoma

| 13 of 19 taking AZA (1-16 yrs exposure) | Of 13 tested 9/13 EBV positive | 9 patients younger than 60 years |

Interim Results...
More to learn from this study!

Beaugerie L, et al. DDW 2008: #818

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**
- **Autoantibodies**
- **Pancytopenia**
- **Heart failure**
- **Hepatotoxicity**
- **Malignancy**

Are serious infections more common if taking more than 1 medication?

- **TREAT registry**
  - Corticosteroids (HR 2.0, 95% CI 1.4-2.9)
  - Narcotics (HR 2.7, 95% CI 1.9-4.0)

- **Opportunistic infections**

Prednisone, 6MP/AZA, Infliximab	Odds Ratio (95% CI)
1 medication	2.9 (1.5–5.3)
2 or 3 medications	14.5 (4.9–43)

Lichtenstein CGH 2006; Toruner, Gastro 2008

Risks of Dying from Sepsis on Infliximab

Reference	Study Design	# Deaths from sepsis in patients taking infliximab	# of Patients
Ljung et al. Gut 2004	Population Based Cohort	1	191
Seiderer et al. Digestion 2004	Single-Center Cohort	0	92
Colombel et al. Gastroenterology 2004	Single-Center Cohort	5	500
Sands et al. NEJM 2004	Randomized Controlled Trial	2	282
Hanauer et al. Lancet 2002	Randomized Controlled Trial	1	573
Rutgeerts et al. Gastroenterology 1999	Randomized Controlled Trial	0	73

Risk of death from sepsis = 4/1000 pt-yrs

Siegel et al. *Clin Gastroenterol Hepatol*. 2006;4:1017-1024.

Who are the patients who are dying from sepsis related to anti-TNF?

- Older
  - Average age = 63 (systematic review); 67 (Mayo)
- Multiple co-morbidities
- Concomitant steroids and/or narcotics
- Long-standing disease

Young "healthy" patients are not in the clear, but probably less at risk

Siegel, CGH 2006; Colombel, Gastro 2004; Lichtenstein CGH 2006

Risk of NH Lymphoma with anti-TNF treatment for Crohn's Disease
Meta-analysis Results

- 8905 patients representing 20,602 pt-years of exposure
- 13 Non-Hodgkin lymphomas → **6.1 per 10,000 pt-years**
- Mean age 52, 62% male
- 10/13 exposed to IM* (so this is really a study of combo Rx)

	NHL rate per 10,000	SIR	95% CI
SEER all ages	1.9	-	-
IM alone	3.6	-	-
Anti-TNF vs SEER	6.1	3.23	1.5-6.9
Anti-TNF vs IM alone	6.1	1.7	0.5-7.1

*not reported in 2

Hepatosplenic T-cell lymphoma

- 9 cases in IBD with **6MP/AZA** alone
- 16 cases in IBD patients taking **infliximab or adalimumab** <u>with</u> **6MP/AZA**
  - Age range 12-58 years old
  - Average age = 23 years old
  - Almost all are male (15/16)
  - Infusions ranged from 1-24
  - 7 patients had ≤ 3 infusions
  - Three received adalimumab (after infliximab)
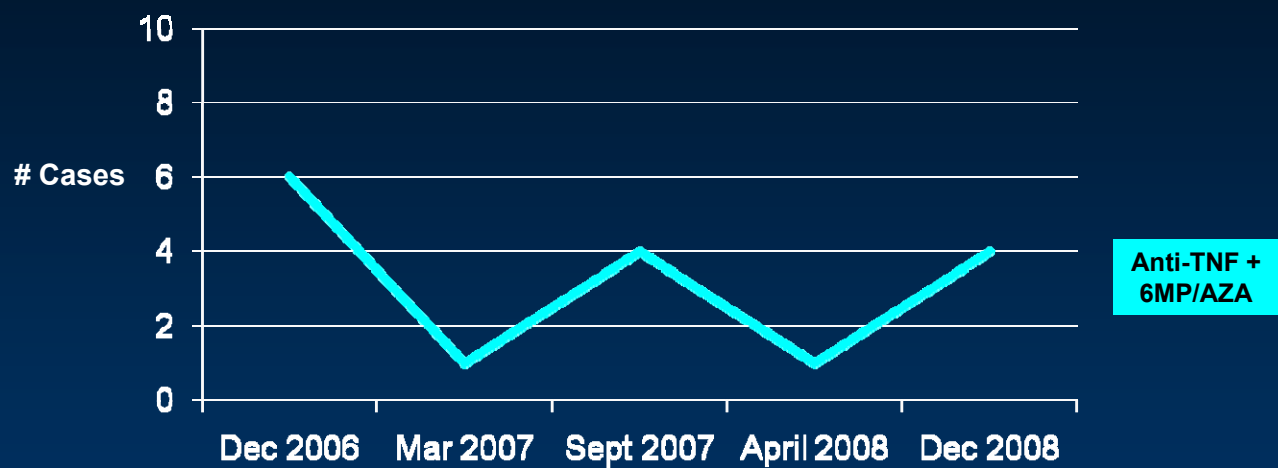 - Appears to be universally fatal

HSTCL – How big of a problem is this?

Cases

Anti-TNF + 6MP/AZA

6MP/AZA

Dec 2006   Mar 2007   Sept 2007   April 2008   Dec 2008
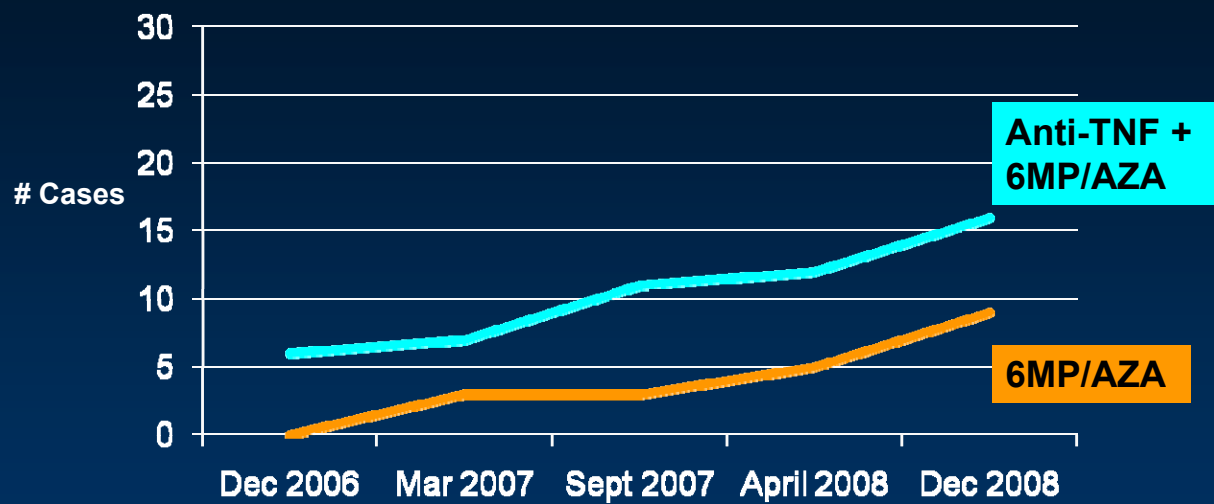
- Over 1 Million anti-TNF treated patients worldwide
- About 4.5 Million patient-years of exposure
- No anti-TNF monotherapy (but not many out there)

Centocor, data on file.

HSTCL – How big of a problem is this?

- In 2006 → 130,000 IBD patients treated with infliximab
- In 2008 → 170,000 IBD patients treated with infliximab

Natalizumab

- SIX cases of JC virus related progressive multifocal leukoencephalopathy
  - Five patients with multiple sclerosis
  - One patient with Crohn's disease
- As of late 2008
  - > 48,000 pts have received natalizumab
  - > 18,000 pts have been treated for longer than 1 year
- What is the tradeoff?
  - **Response at week 4 → NNT = 7**
    Maintenance of remission at week 36 → NNT = 6
  - **1 patient with PML over 1 year → NNH ≈ 3000**

Kleinschmidt-DeMasters BK, Tyler KL. *N Engl J Med.* 2005;353:369–374; Langer-Gould A et al. *N Engl J Med.* 2005;353:375–381. Van Assche G et al. *N Engl J Med.* 2005;353:362–368. Sands et al. Gastro 2008;134:A206. Sandborn et al. NEJM 2005. Targan et al. Gastro 2007;

Patient Centered
How should we tell patients?

If patients don't understand the treatment options, they cannot make informed medical decisions

Clear communication of risks and benefits
(by <u>us</u> – not by Google)

Numbers are Hard

- Numeracy (quantitative literacy)
  - ½ of patients were unable to convert:
    - 1% *to* 10 in 1000
  - 80% of patients were unable to convert:
    - 1 in 1000 *to* 0.1%
  - Patient have difficulty determining which is the higher risk:
    - 1 in 27 *versus* 1 in 37
  - Data interpretation test → 20%-87% correct

Schwartz LM et al. Ann Intern Med. 1997 Dec 1;127(11):966-72. Schwartz et al. Medi Decis Making 2005.

How well do our patients understand statistics?
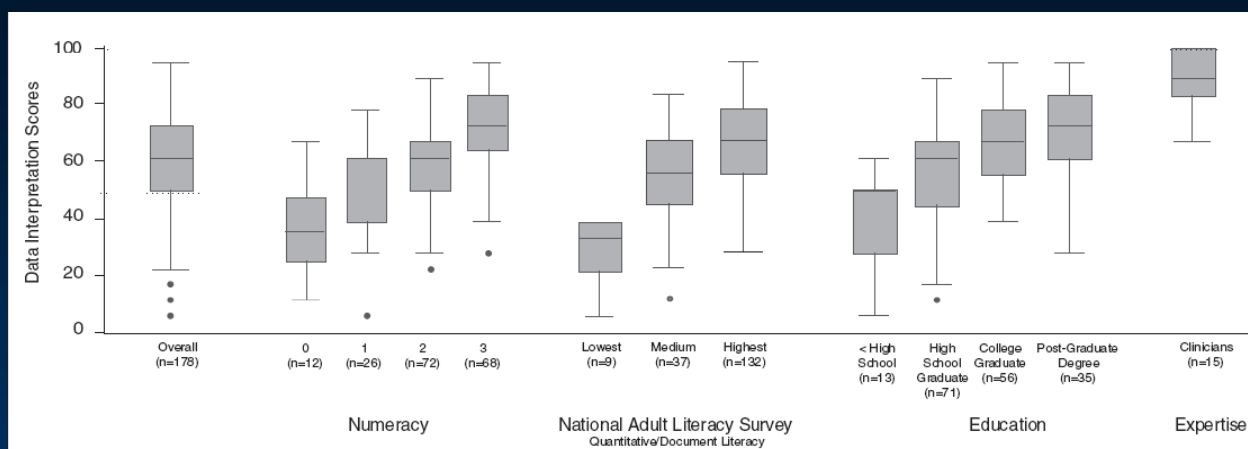
- 18 item test of medical data interpretation skills
- Wide-range of education level of the 178 participants
- Correct responses ranged from 20%-87%

Schwartz et al. Med Decis Making 2005

Tips for Clear Communication

- Less is more
- Absolute risks better than relative risk
- Avoid decimals (0.06%)
- Keep common denominators (x/1000)
- Visual aids help (turn numbers into pictures)
- Give perspective to other life risks
- Individualized estimates are best

Fagerlin et al. Am J Health Behav 2007. Peters et al. Health Affairs 2007.

Examples

-Numbers You Can Use -

Absolute Rates Are Best

Event	Estimated Frequency (annual, pt-years)
Non-Hodgkin Lymphoma (baseline)	2/10,000
Non-Hodgkin Lymphoma (on IM)	4/10,000
Non-Hodgkin Lymphoma (on anti-TNF)	6/10,000
Hepatosplenic T-cell Lymphoma	Unknown
Death from sepsis	4/1000
Tuberculosis	5/10,000

Adapted from Siegel CA. Comprehensive approach to patient risk. Risk versus benefit of biologics and immune suppressants. In: Targan S, Shanahan F, Karp L, eds . Inflammatory bowel disease: Translating basic science into clinical practice. In press, 2007.

SONIC Made Patient Friendly

508 patients were treated with either azathioprine, Remicade, or a combination of both medications. At the end of 6 months, this is what happened:

	Azathioprine	Remicade	Combination
How many people were free from symptoms and off of prednisone?	31% 32 in 100	44% 44 in 100	57% 57 in 100
How many had a completely normal colonoscopy after treatment?	17% 17 in 100	30% 30 in 100	44% 44 in 100
Serious Side Effects	**Equal across the groups**		

How often do the anti-TNF drugs improve symptoms of Crohn's disease? → NON-SMOKERS

75%
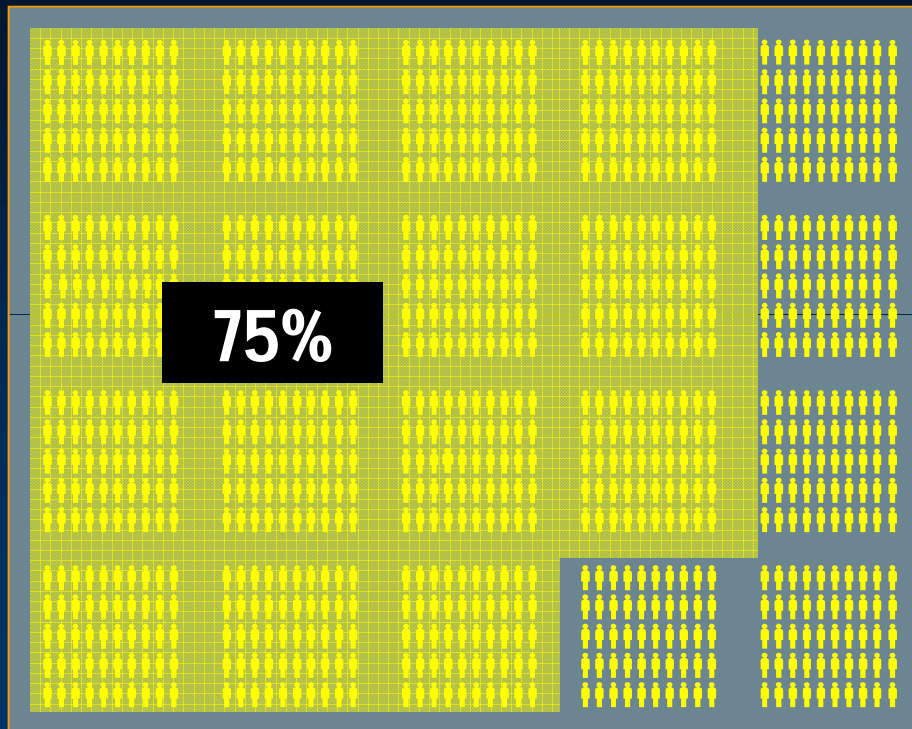
Parsi et al.
Gastro 2002

How often do the anti-TNF drugs improve symptoms of Crohn's disease? → SMOKERS

25%
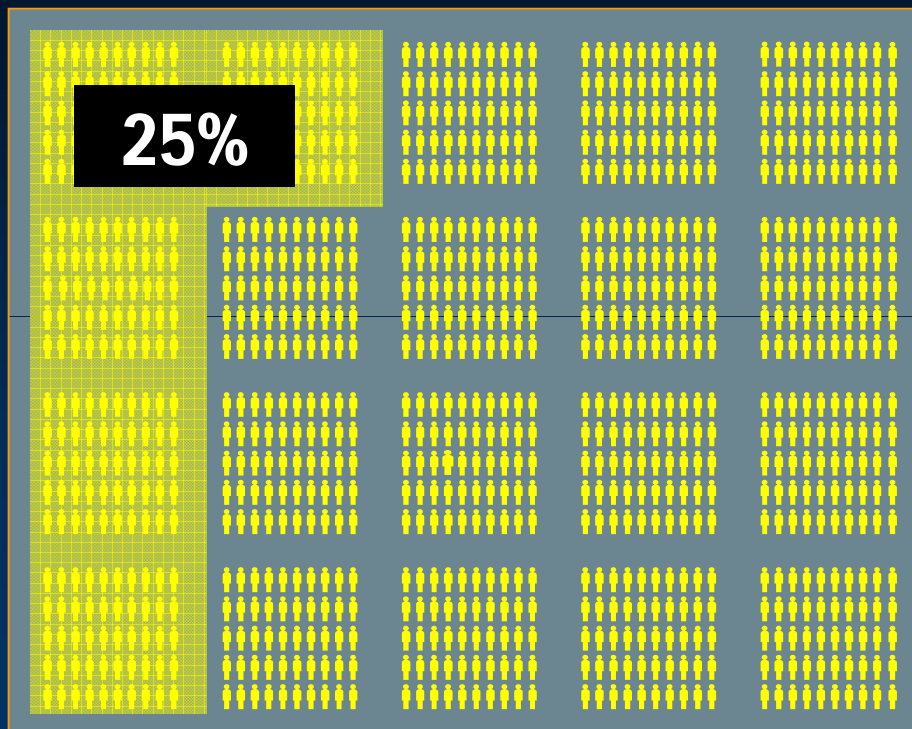
Parsi et al.
Gastro 2002

Risk of Developing NH Lymphoma

20 year old male receiving anti-TNF + Immunomodulator Therapy

Risk with combination therapy

Risk of Developing PML

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

Ten Thousand People
– pictures to help you see your odds

Estimated annual risk =
3 per 10,000 treated patients
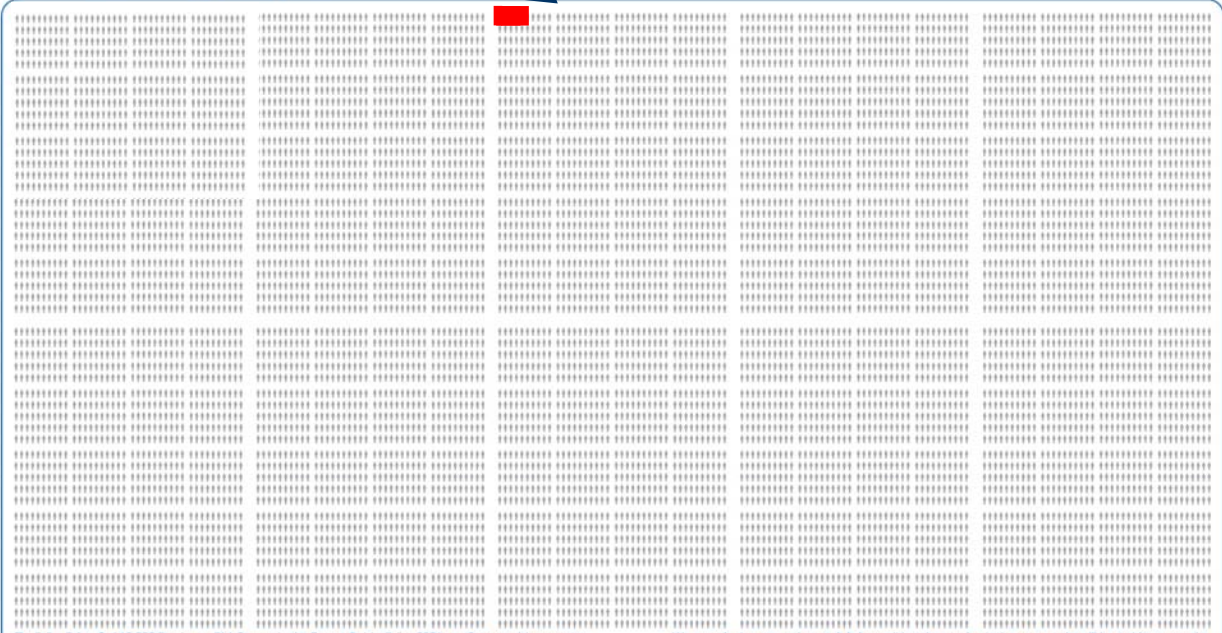
The Paling Palette® of 10,000 People • Risk Communication Format © John Paling 2001 • See www.riskcomm.com   We can only show you estimates. It is impossible to be certain whether your results will be positive or negative.
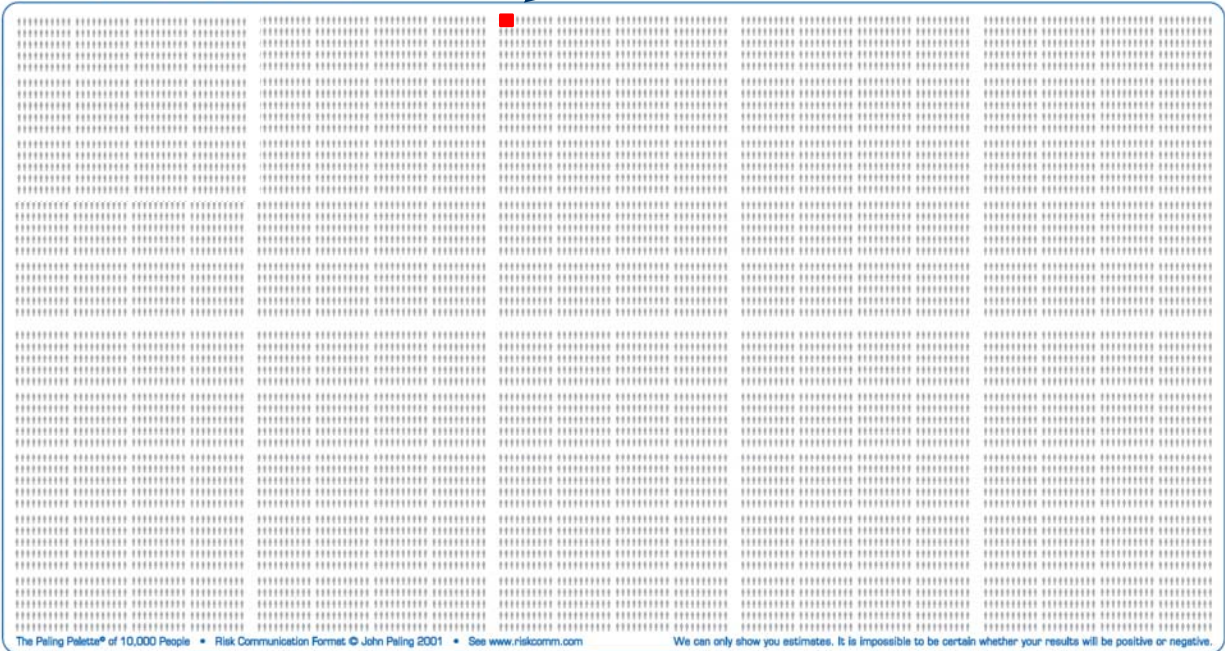
Life is Risky – Putting Risk in Perspective
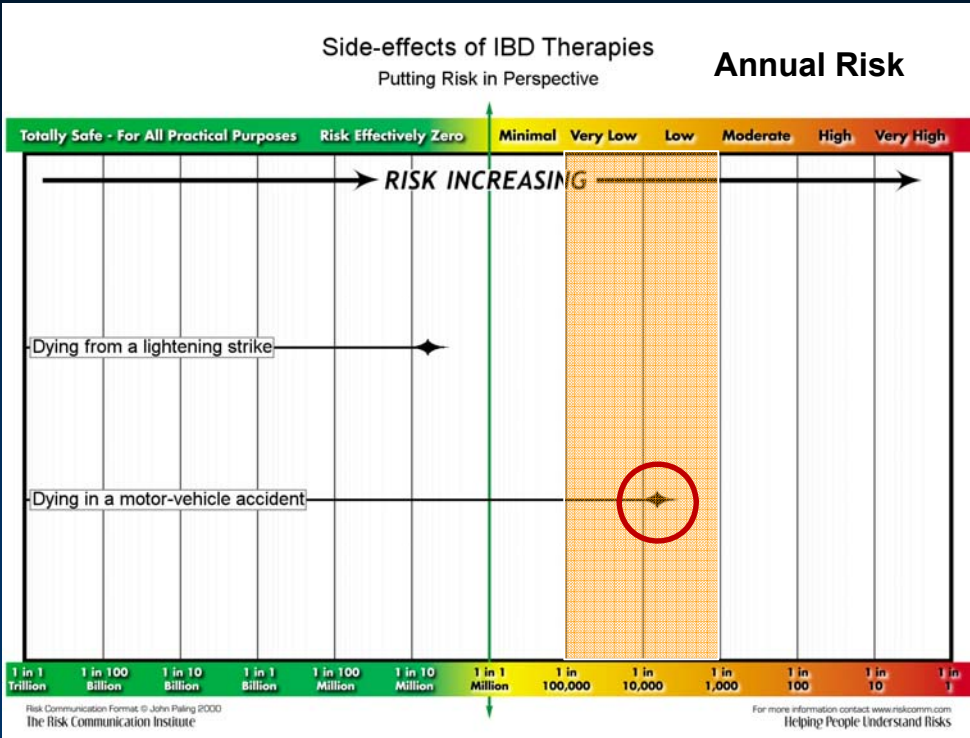
A Prediction Model to Communicate Individualized Risk and Benefit Information

- Start with a well defined data set
- Cox proportional analyses to develop best predictive model
- System Dynamics Analysis (SDA) to graphically display results
- Take individual patient characteristics to show patients the predicted risk of <u>their</u> disease and benefit of treatment
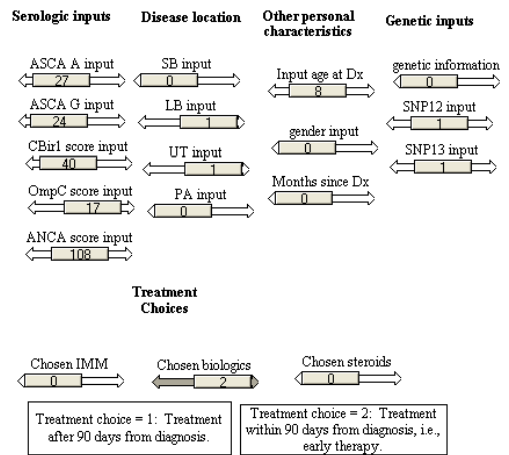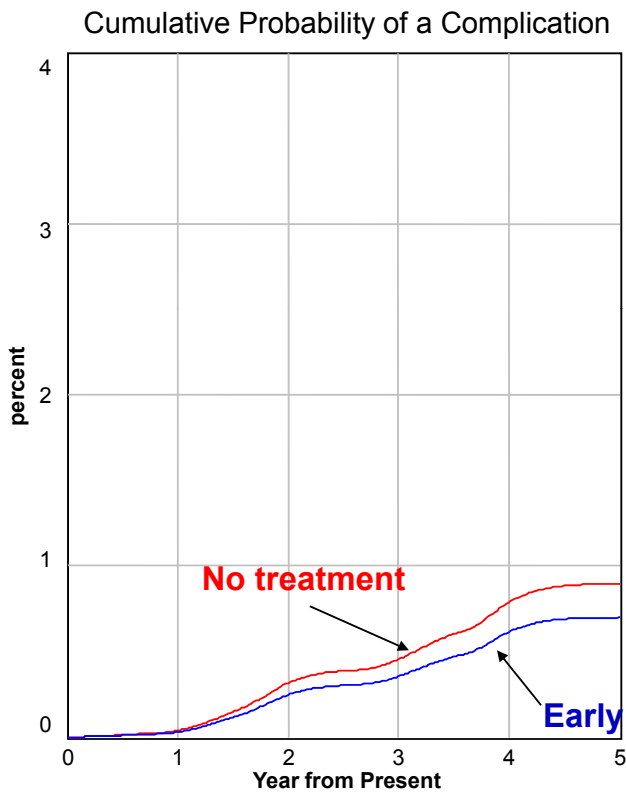
Siegel, Siegel, Dubinsky, Sands, Kugathasan, Hyams, Markowitz, et al.
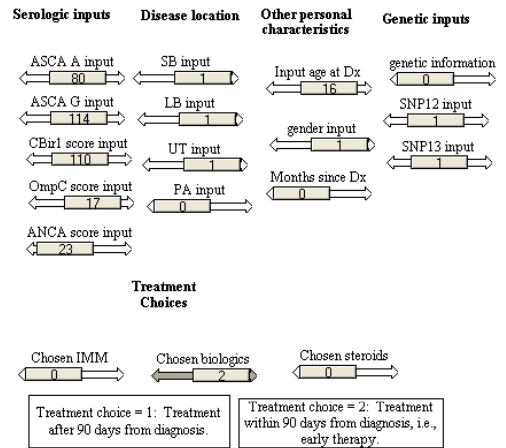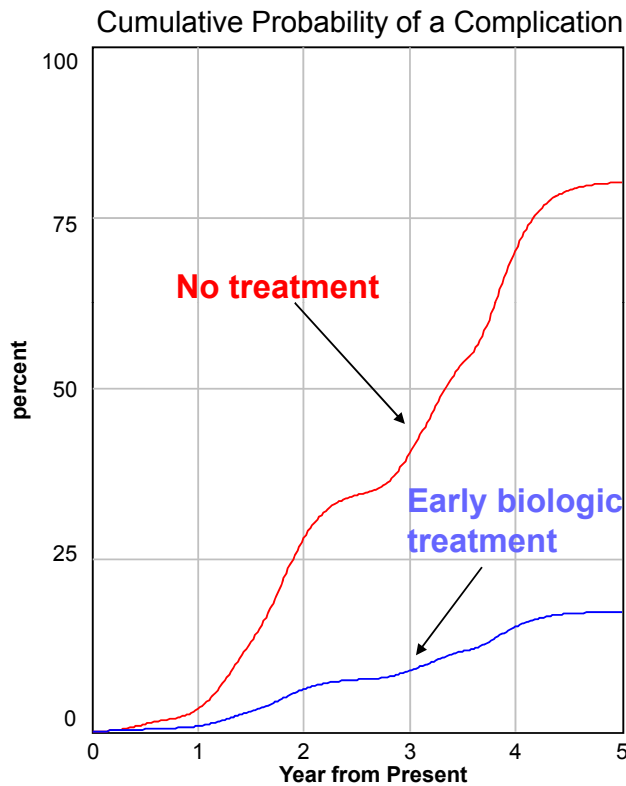
Conclusion

- The exact amount of risk of biologic therapy is uncertain, but in absolute terms, it is very small

- Don't let patients be scared by the wrong information (help them get it right – then they can decide)

- Tools are being developed to help us to better communicate with our patients

- By improving communication, we will be improving the quality of our care in IBD