



Inflammation: Was steht uns an prädiktiven Markern zur Verfügung?

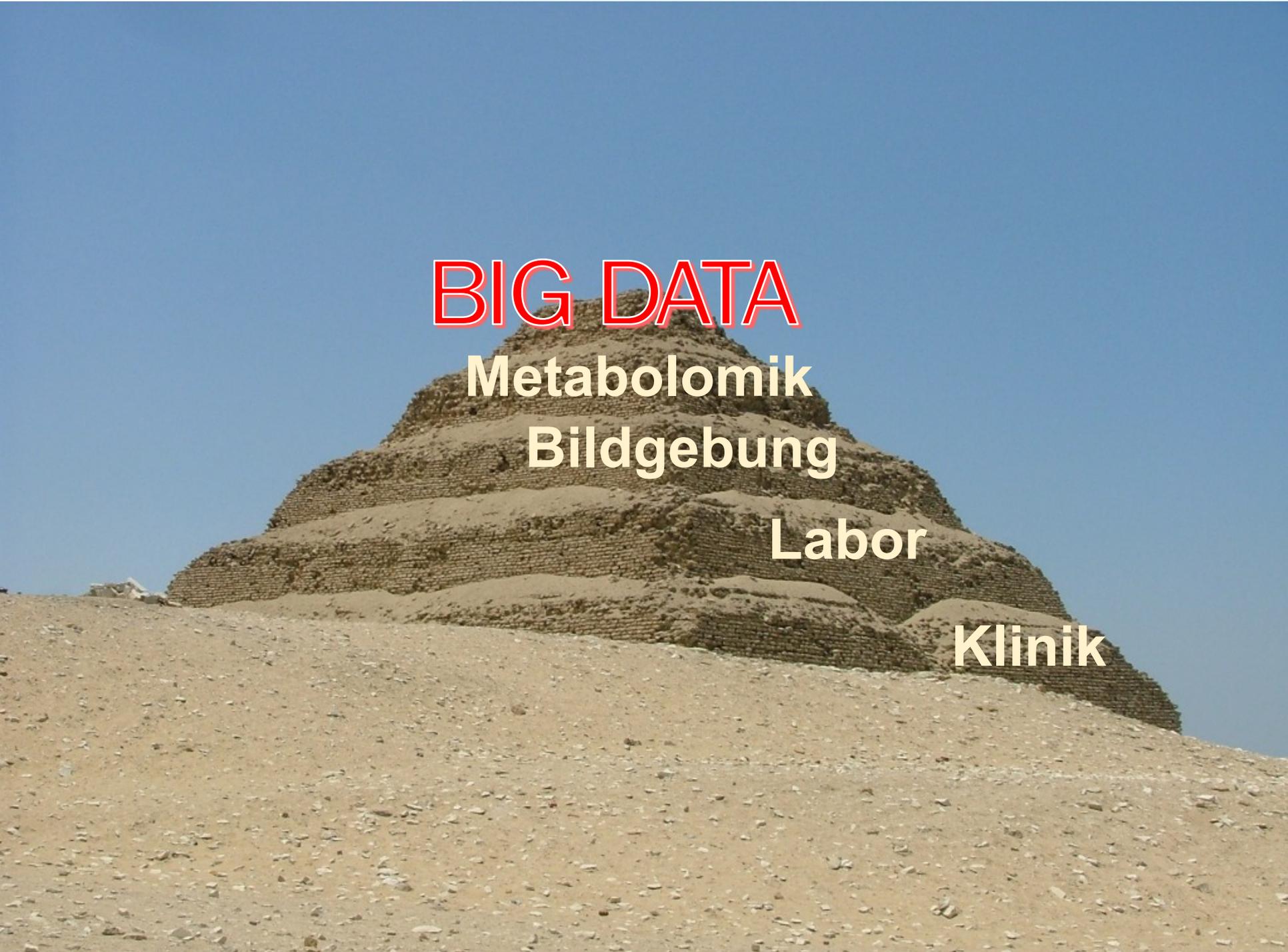
11. Jahrestagung der Gesellschaft für
Gastroenterologie und Hepatologie in
Berlin und Brandenburg

Gastroenterologie und Hepatologie 2017,
20.-21. Januar 2017



- **warum** sollten wir den Krankheitsverlauf abschätzen können ?
- **wie / womit** können wir den Krankheitsverlauf vorhersagen ?
- **welche Konsequenzen** ziehen wir hieraus ?

BIG DATA

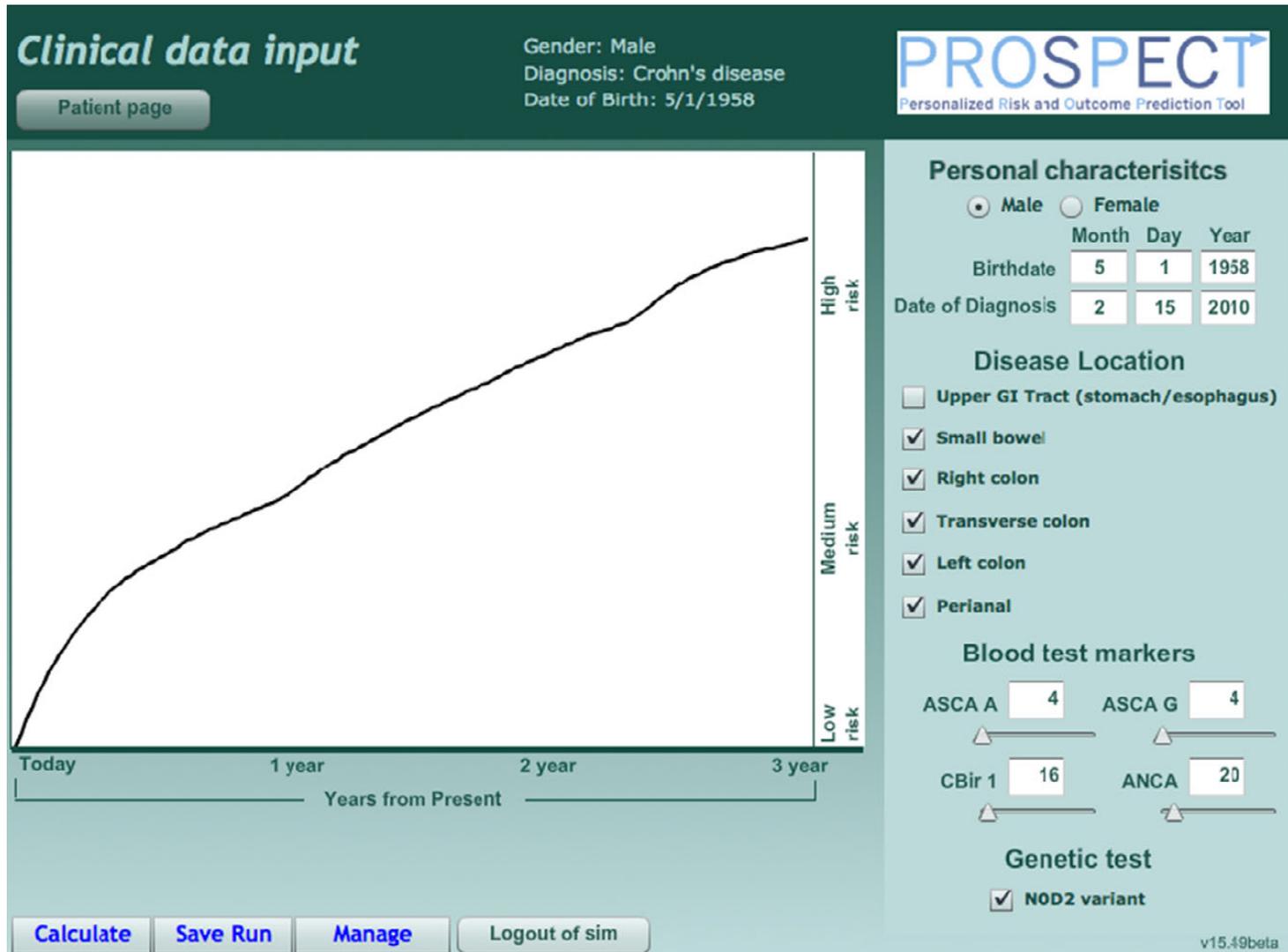
A photograph of a pyramid of bricks in a desert landscape. The pyramid is built from dark bricks and is partially covered in sand. The sky is clear and blue. The text is overlaid on the pyramid.

Metabolomik

Bildgebung

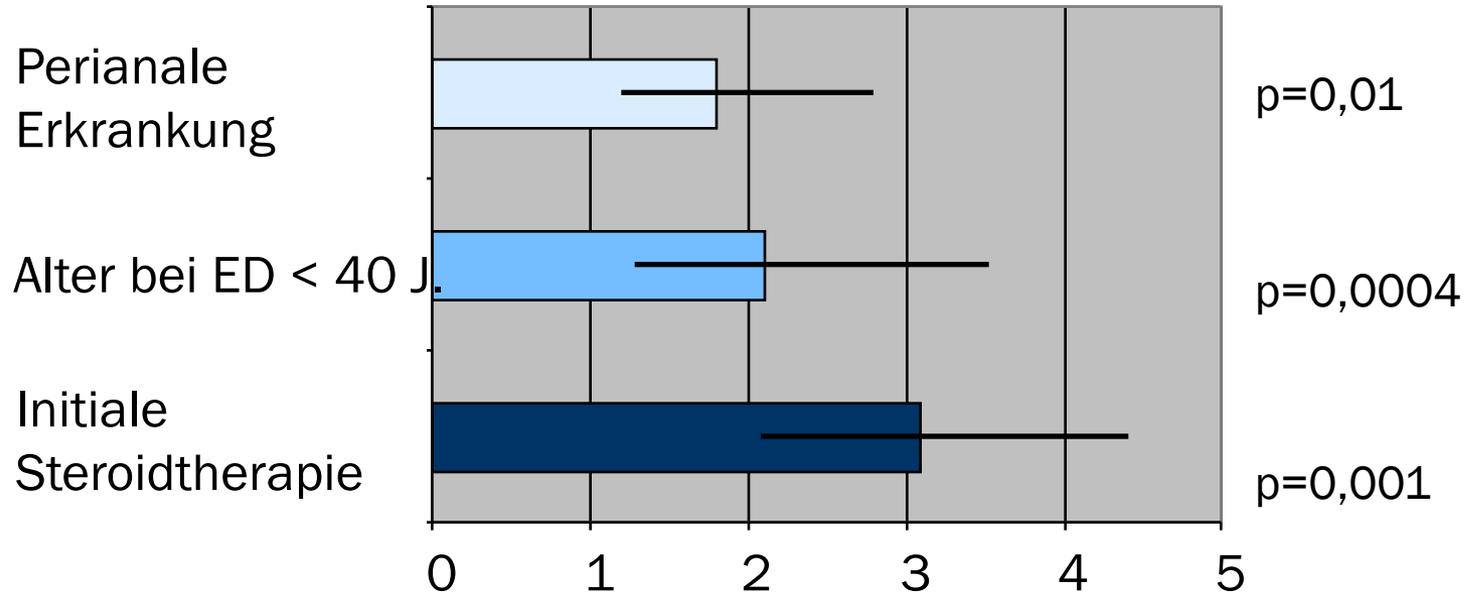
Labor

Klinik



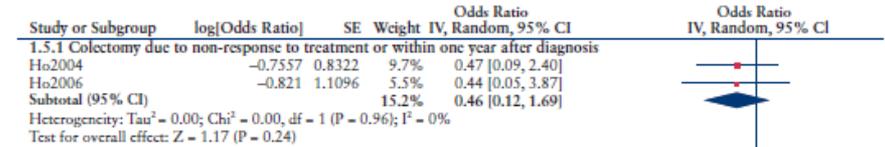
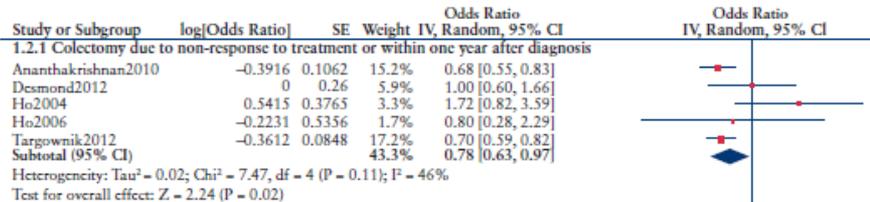
M. Crohn (n=1.188 Pat. in retrosp. Kohorte 1 und 302 Pat. in prospektiver Kohorte 2)

Schwerer M. Crohn	
> 2 Steroidtherapien	Steroidabhängigkeit
Hospitalisation	Symptome > 12 Monate
Immunsuppressiva	OP-Notwendigkeit



20 Publikationen

48.281 Patienten (Range 49-23.389)



1.2.2 Colectomy during disease course

Study or Subgroup	log(Odds Ratio)	SE	Weight	Odds Ratio	IV, Random, 95% CI
Aanathakrishnan2009	0.1043	0.4103	2.8%	1.11 [0.50, 2.48]	
Hoic2007	0.2156	0	0	0	
Kuryama2006	-0.77	0	0	0	
NGuyen2006	-0.1743	0	0	0	
Samuel2013	-0.741	0	0	0	
Shiga2010	-0.23	0	0	0	
Solberg2009	-0.186	0	0	0	
Triantafyllidis1998	-0.1108	0	0	0	
Subtotal (95%CI)					

Heterogeneity: Tau² = 0.04; Chi² = 13.68, df = 9 (P = 0.11); I² = 46%
 Test for overall effect: Z = 2.27 (P = 0.02)

Total (95%CI)
 Heterogeneity: Tau² = 0.02; Chi² = 23.74, df = 9 (P = 0.007); I² = 62%
 Test for overall effect: Z = 3.39 (P = 0.0007)
 Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%

Parameter	OR	CI
Weibliches Geschlecht	0,78	0,68-0,9
Rauchen	0,55	0,33-0,91
Hospitalisation	4,13	3,23-5,27
Ausgedehnte Erkrankung	3,68	2,39-5,69
Steroidtherapie (mind. einmalig)	2,1	1,05-4,22

1.4.1 Colectomy due to non-response to treatment

Study or Subgroup	log(Odds Ratio)	SE	Weight	Odds Ratio	IV, Random, 95% CI
Ananthakrishnan2010	1.03	0.37	15.2%	2.80 [1.30, 6.07]	
Desmond2012	0.8329	0.37	5.9%	2.30 [1.10, 4.84]	
Ho2004	2.1266	0.37	3.3%	8.36 [3.77, 18.11]	
Ho2006	2.3125	0.37	1.7%	10.0 [4.57, 22.27]	
Molnar2007	1.1569	0.37	17.2%	3.19 [1.59, 6.42]	
Subtotal (95% CI)			43.3%	3.68 [2.39, 5.69]	

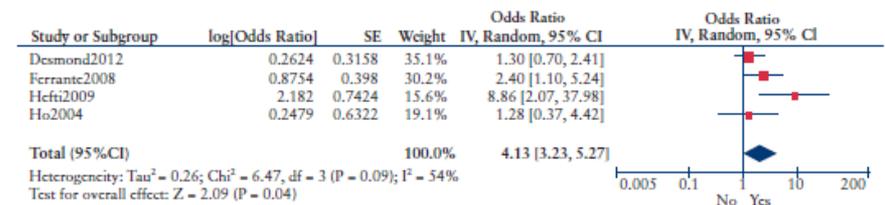
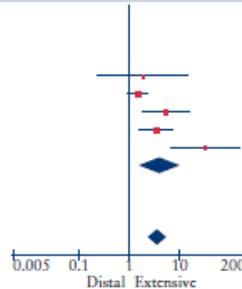
Heterogeneity: Tau² = 0.11; Chi² = 7.69, df = 4 (P = 0.10); I² = 47%
 Test for overall effect: Z = 5.53 (P < 0.00001)

1.4.2 Colectomy during disease course

Study or Subgroup	log(Odds Ratio)	SE	Weight	Odds Ratio	IV, Random, 95% CI
Aanathakrishnan2009	0.648	1.0536	3.5%	1.91 [0.24, 15.07]	
Kuryama2006	0.392	0.2316	15.0%	1.48 [0.94, 2.33]	
Shiga2010	1.6938	0.5421	8.6%	5.44 [1.88, 15.74]	
Solberg2009	1.2413	0.3872	11.6%	3.46 [1.62, 7.39]	
Triantafyllidis1998	3.4791	0.7817	5.5%	32.43 [7.01, 150.09]	
Subtotal (95%CI)			44.3%	4.06 [1.59, 10.38]	

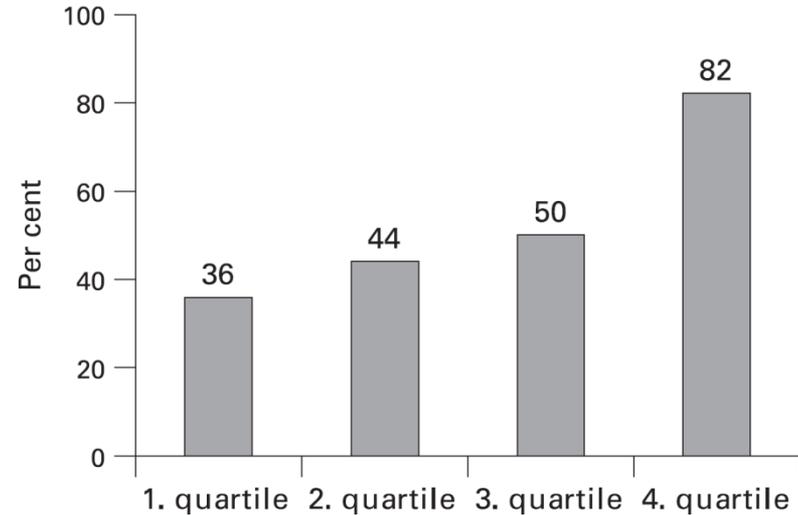
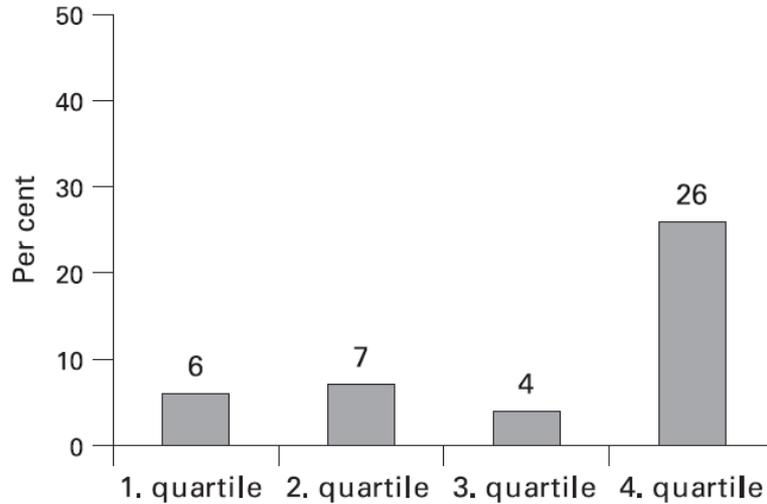
Heterogeneity: Tau² = 0.80; Chi² = 18.67, df = 4 (P = 0.0009); I² = 79%
 Test for overall effect: Z = 2.92 (P = 0.003)

Total (95%CI)
 Heterogeneity: Tau² = 0.27; Chi² = 27.43, df = 9 (P = 0.001); I² = 67%
 Test for overall effect: Z = 5.89 (P < 0.00001)
 Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.77); I² = 0%

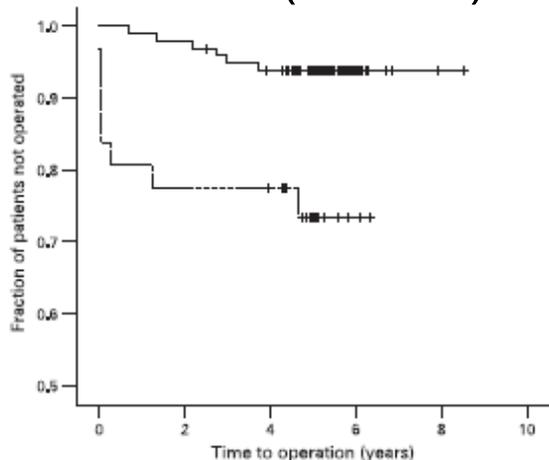


IBSEN-Kohorte

M. Crohn (n=454), C. ulcerosa (n=200)



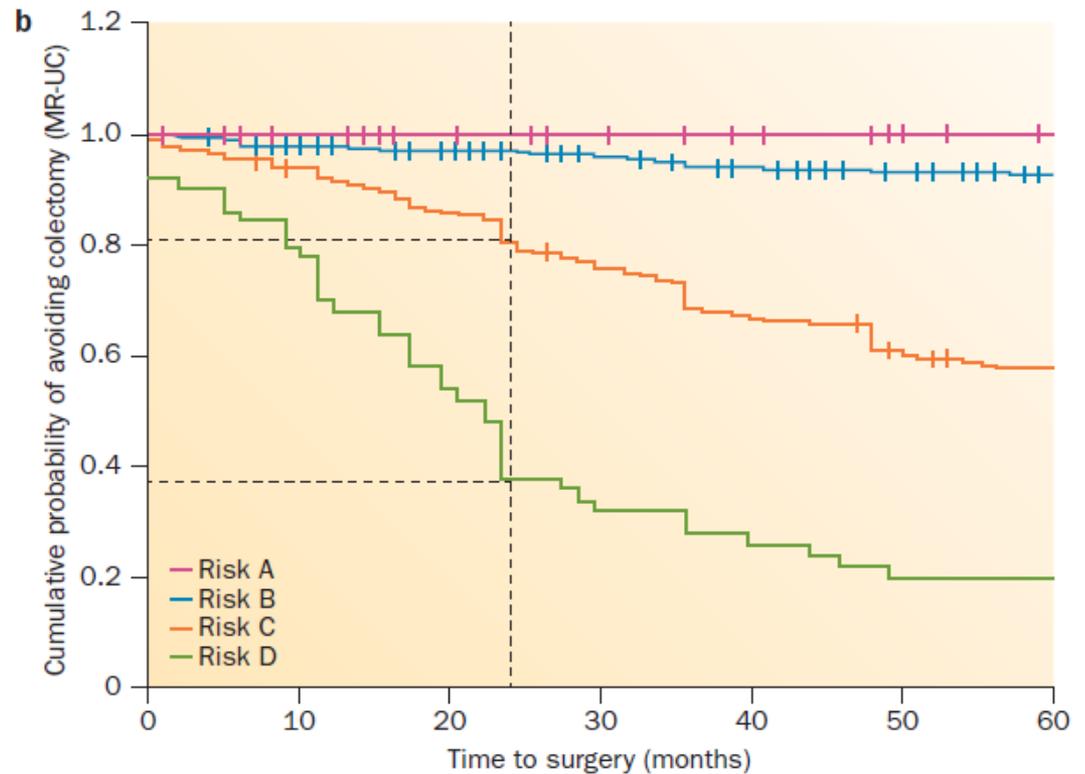
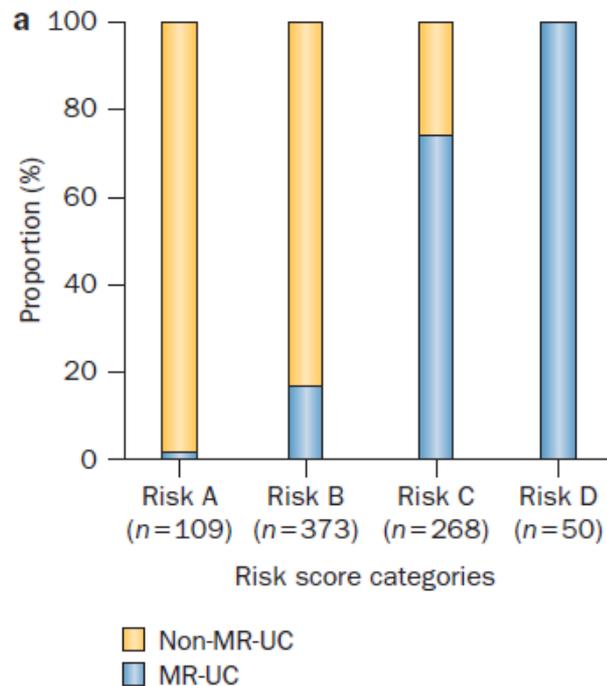
C. ulcerosa (Pancolitis)



M. Crohn (Ileitis terminalis)

CRP > 53 mg/l: OR 6.0
(CI 1.1 to 31.9, p=0.03)

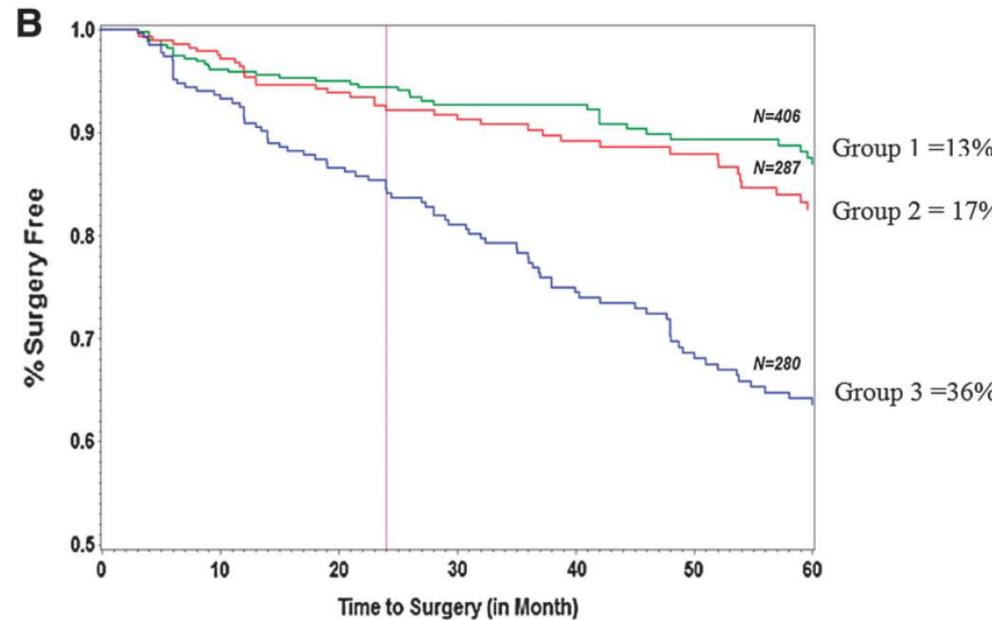
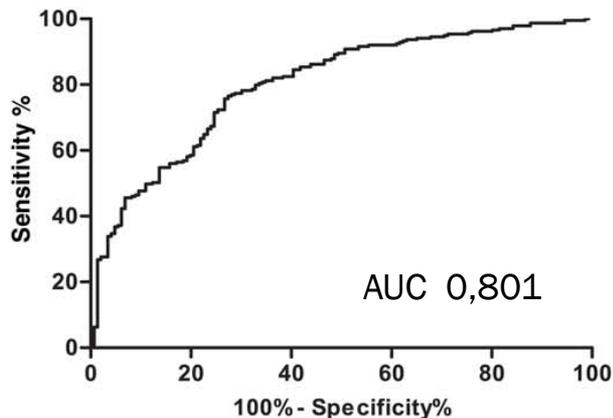
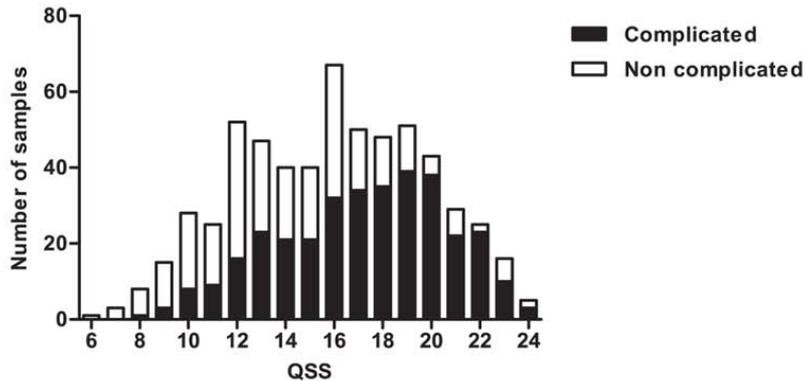
324 MR-CU-Patienten - 537 nicht MR-CU-Pat. - 2.601 Kontrollen
 Risk score basierend auf 46 SNPs

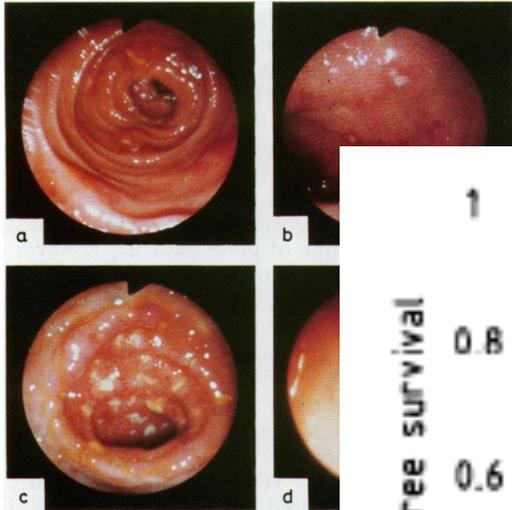


M. Crohn (n=593) – f/u 12 Jahre
 6 serologische Marker - NOD 2 (n=385)
 Komplikationen: stenosierender oder penetrierender Verlauf

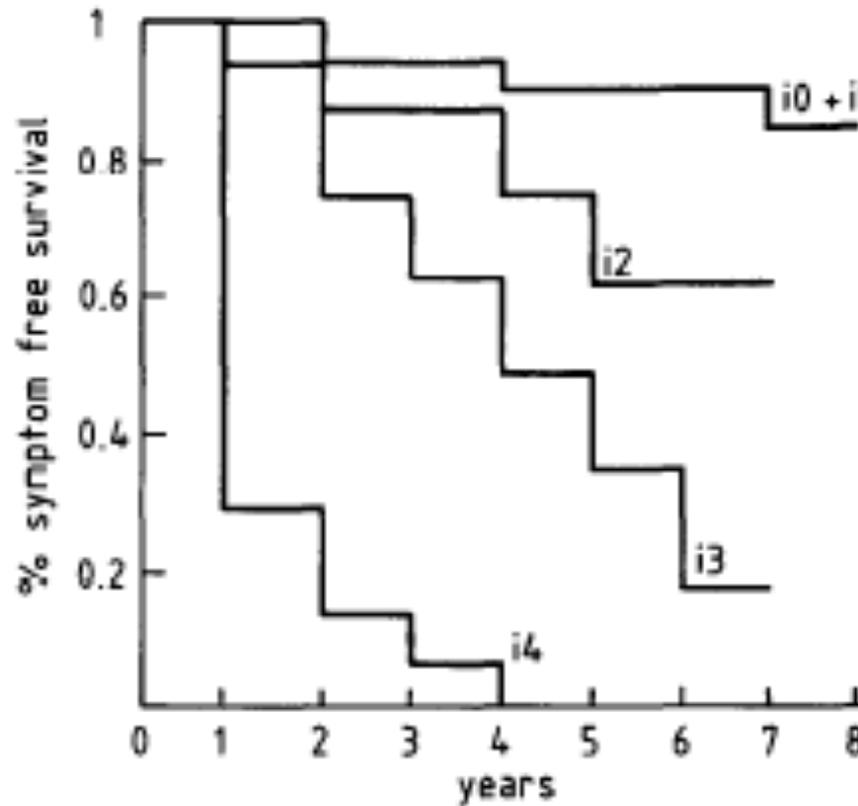
M. Crohn (n=1.115) – f/u 5 Jahre
 Resektion bei 239 Patienten (21,4%)
 5 Suszept.-Loci, klinische Parameter
 IL12B, IL23R, and C11orf30
 7q21 (CACNA2D1), 9q34 (RXRA, COL5A1).

A Non complicated and Complicated Disease QSS





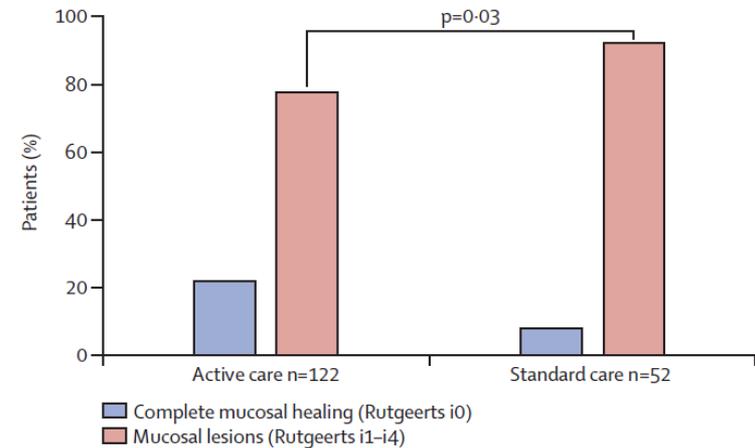
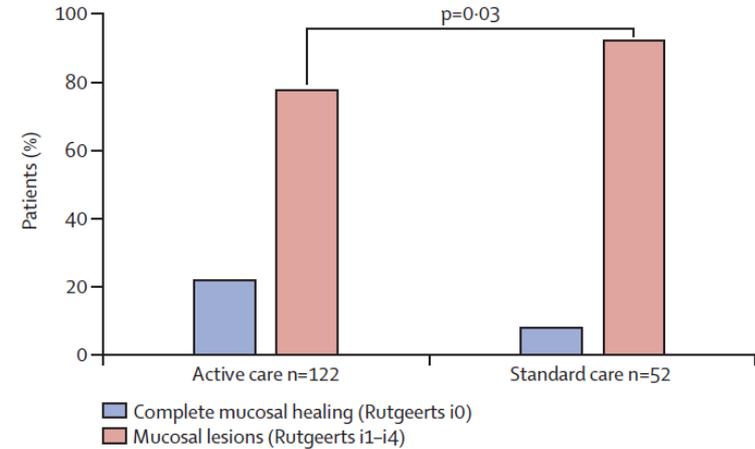
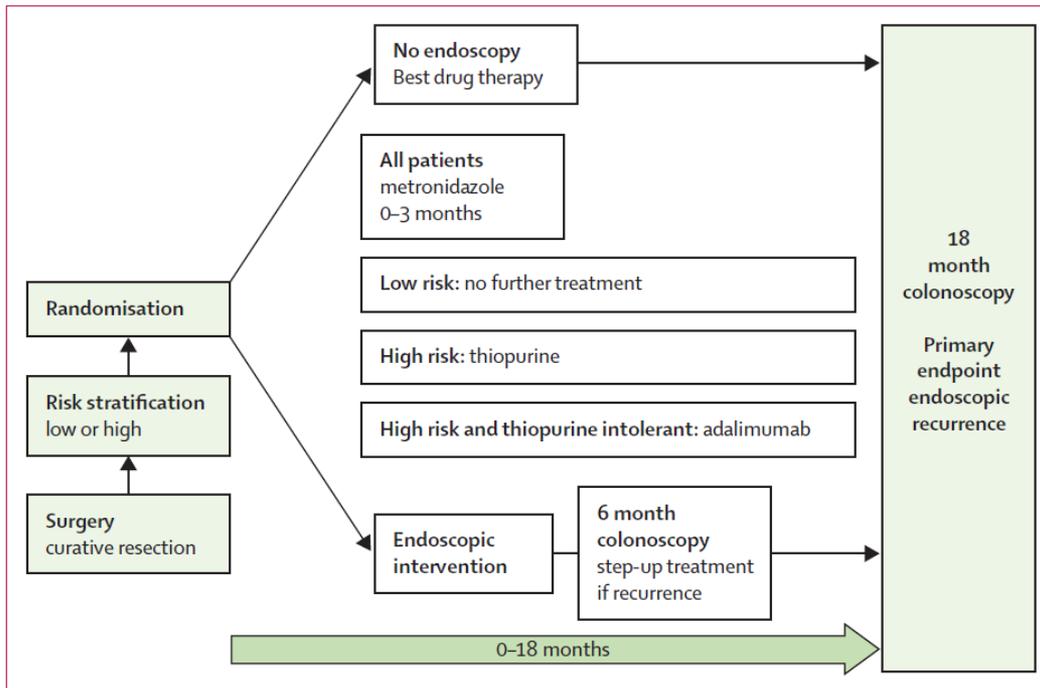
Score	Definition
i0	Keine Läsionen
i0 + i1	Keine Mukosa, skip lesions, (<1cm Länge)
i2	Polypoid, Dysplasie
i3	Polypoid, Dysplasie (≥10mm), Noduli, Stenose
i4	Polypoid, Dysplasie (≥10mm), Noduli, Stenose



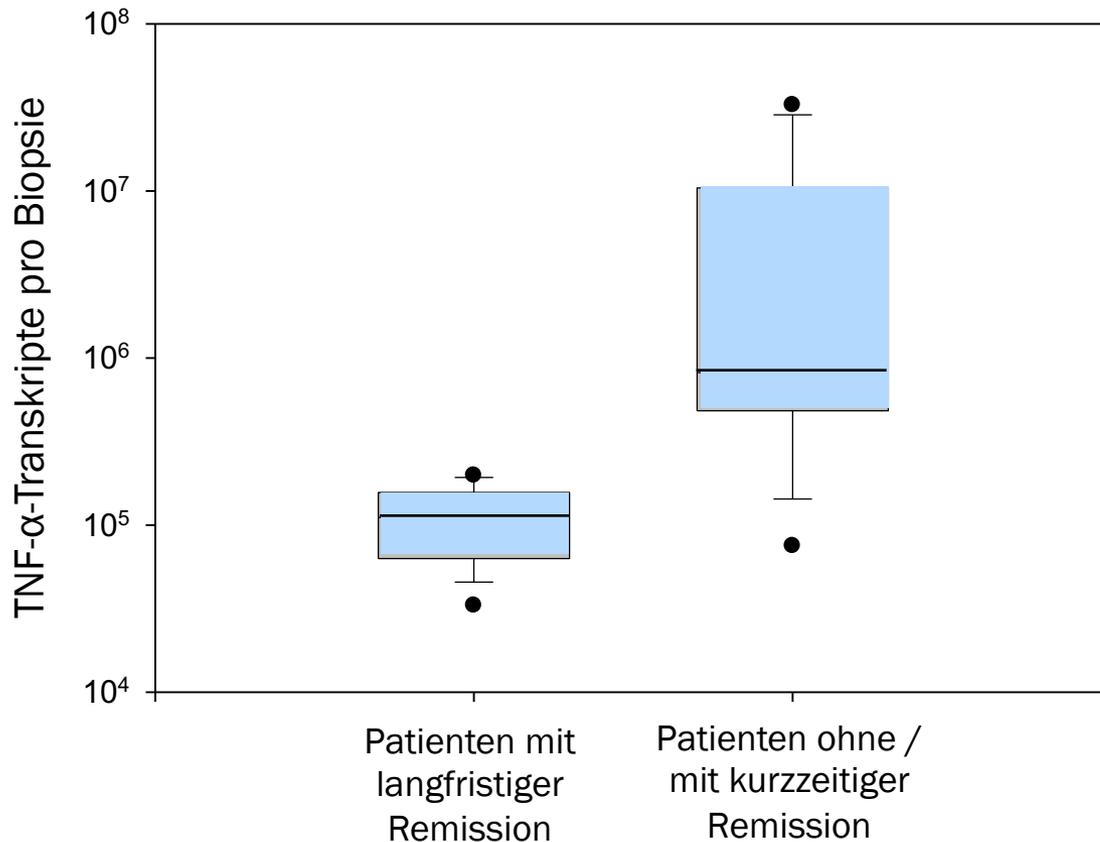
Rutgeerts et al., Gut 1984; 25: 665-72

Rutgeerts et al., Gastro 1990; 99: 956-63

174 Patienten mit ICR (active care: n=122; standard care: n=52)



M. Crohn, steroidrefraktär (n=19; 10x IFX, 9x Cyclophosphamid)
 Quantifizierung mukosaler TNF-Transkripte vor Therapiebeginn

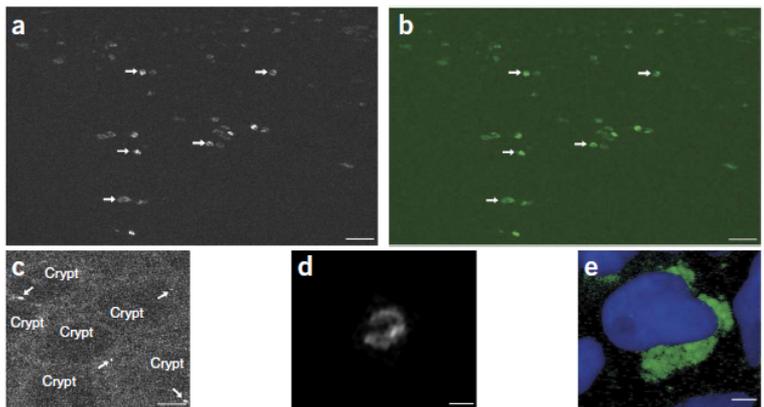
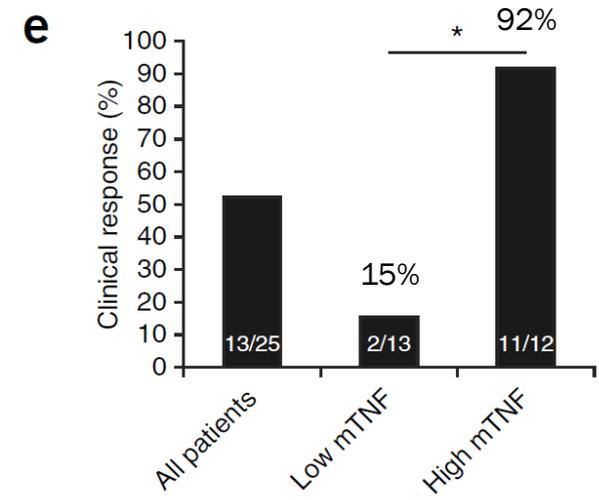
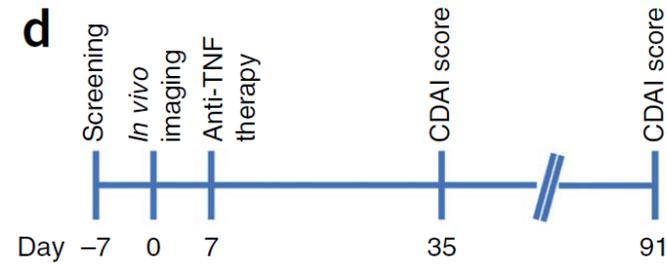
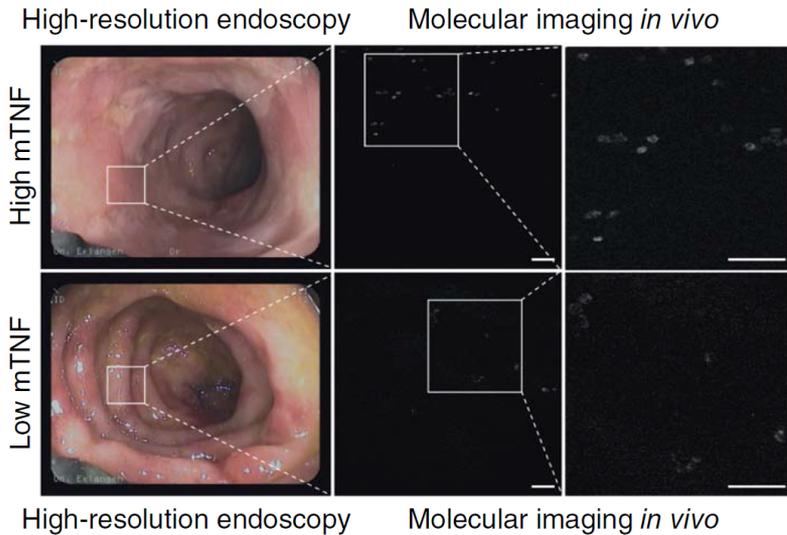


Grenzwert: 250 x 10³ tpb

Parameter	[%]
Sensitivität	100
Spezifität	87,5
PPV	91,7
NPV	87,5
Korrekt-klassifikationsrate	94,4

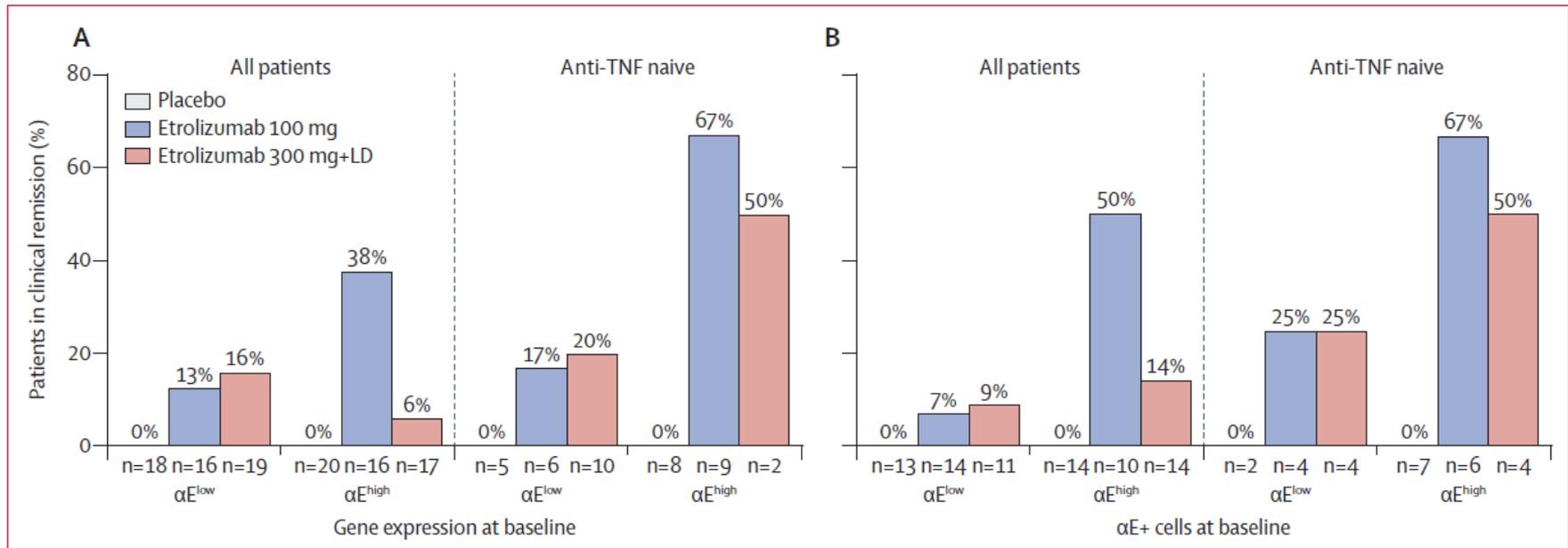
M. Crohn (n=25)

In vivo-mukosale Markierung mittels Fluoreszenz-markierter anti-mTNF-Ak, CLE

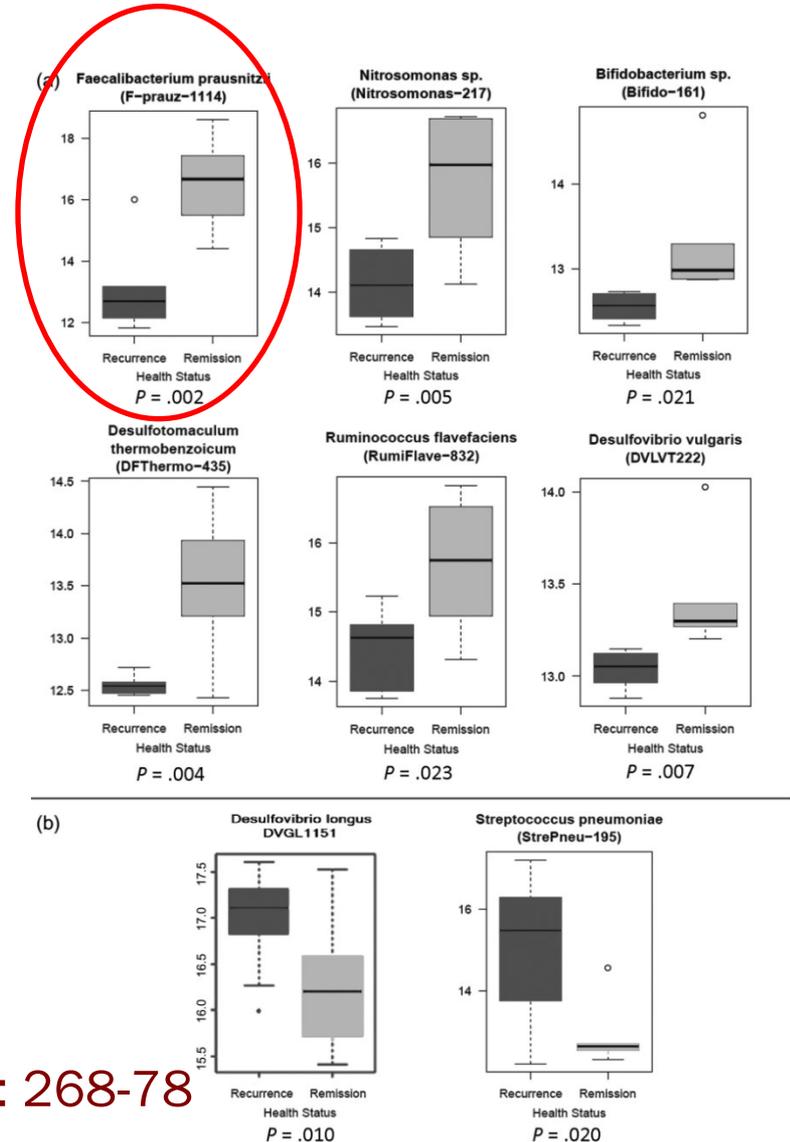
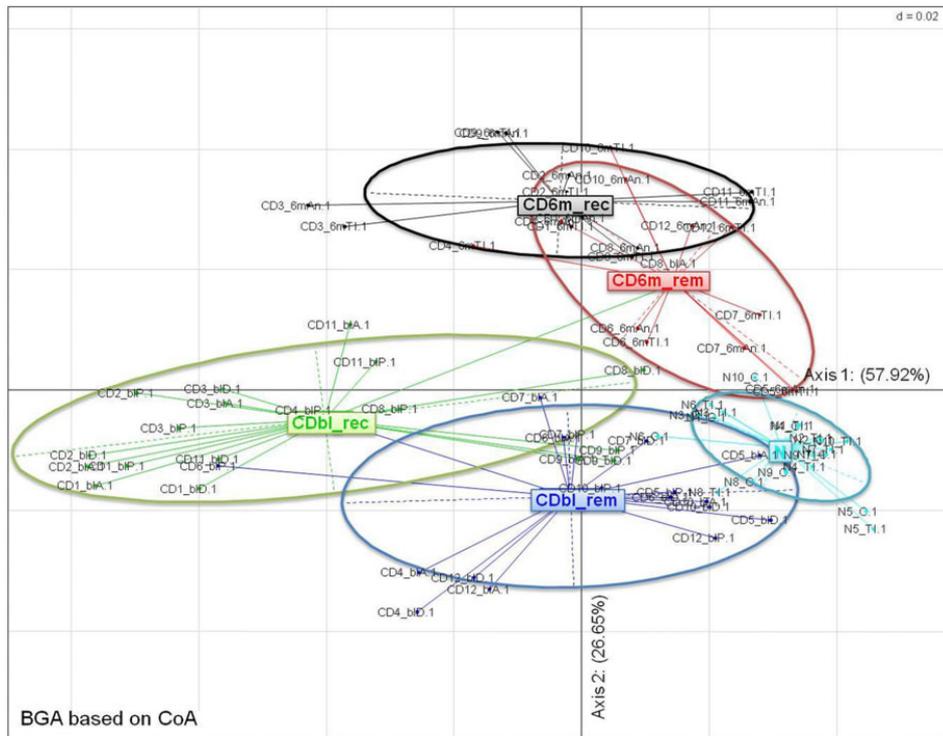


C. ulcerosa (n=124) – 40 Zentren, 11 Länder

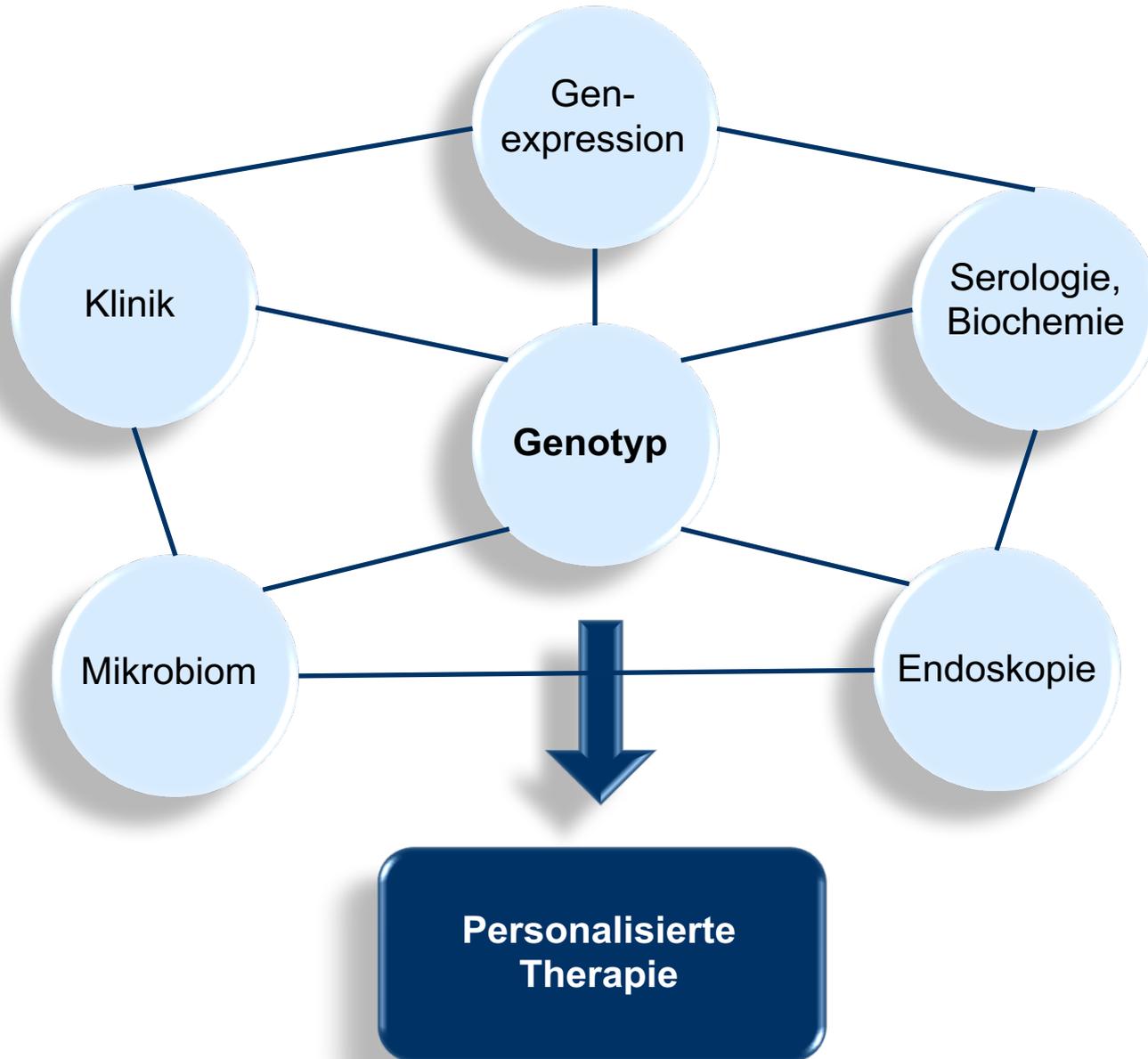
Randomisation 1:1:1, Placebo und 2 Dosierungsgruppen
 primärer Endpunkt: Remission zu Woche 10



12 Patienten - ICR - Koloskopie nach 6 Monaten - 6 Patienten mit Rezidiv

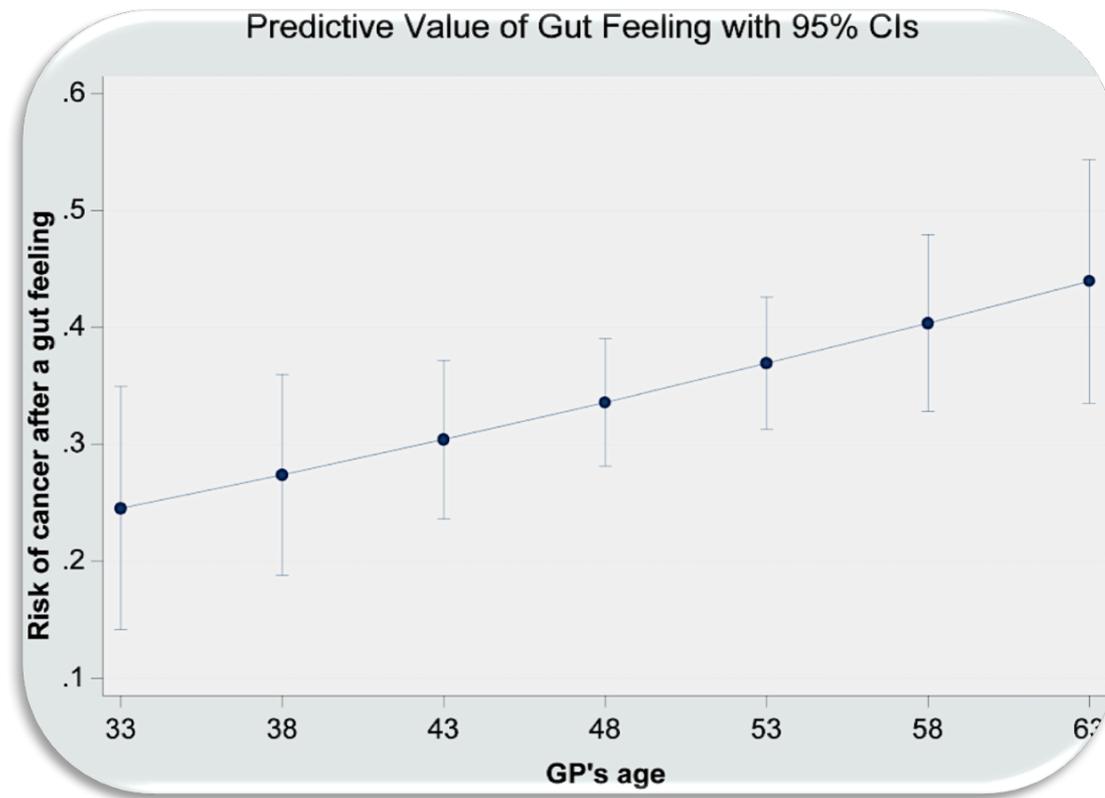


Parameter	Vorhergesagter Verlauf
Ausgedehnte Colitis	Kolektomie, Karzinome, Mortalittät
Progredientes Befallsmuster	Kolektomie
Primär-sklerosierende Cholangitis	Karzinome
Extra-intestinale Manifestationen	Kolektomie
Junges Alter bei Diagnosestellung	Kolektomie, Karzinome
Nicht-Rauchen	Rückfälle, Kolektomie
Hohe Inflammationslast	Kolektomie
Kein Ansprechen auf 1.-Linien-Therapie	Kolektomie
Kein «mucosal healing» nach 1 Jahr	Kolektomie
HLA Varianten	Kolektomie
ANCA-Antikörper	Kein Ansprechen auf anti-TNF-Antikörper





44 Praxen (59 niedergelassene Ärzte) – 120.000 Einwohner –
„mein Bauchgefühl sagt, dieser Patient hat ein Malignom“
 – Kontrolle nach 3 Monaten



- 341 Patienten - > neu diagnostizierter MC, prospektive Beobachtung
- Verlaufsbeobachtung über 24 Monate mit Visiten alle 3 Monate
- primärer Endpunkt: Hospitalisierung und/oder immunsuppressive / TNF-Antikörper-Therapie = kompl. Verlauf
- **Auswertung: 212 Patienten -> 115 mit kompl. Verlauf (54,2%)**

