Anhang

Recherche in PubMed: AG 1 – 1

	Patient	Intervention	Comparator	Outcome
AG 1 Diagnostik				
neutrophile Stuhlmarker	Patienten in Remission	alle 3 Monate fC	keine Diagnostik	Zeit bis zur Therapieintensivierung

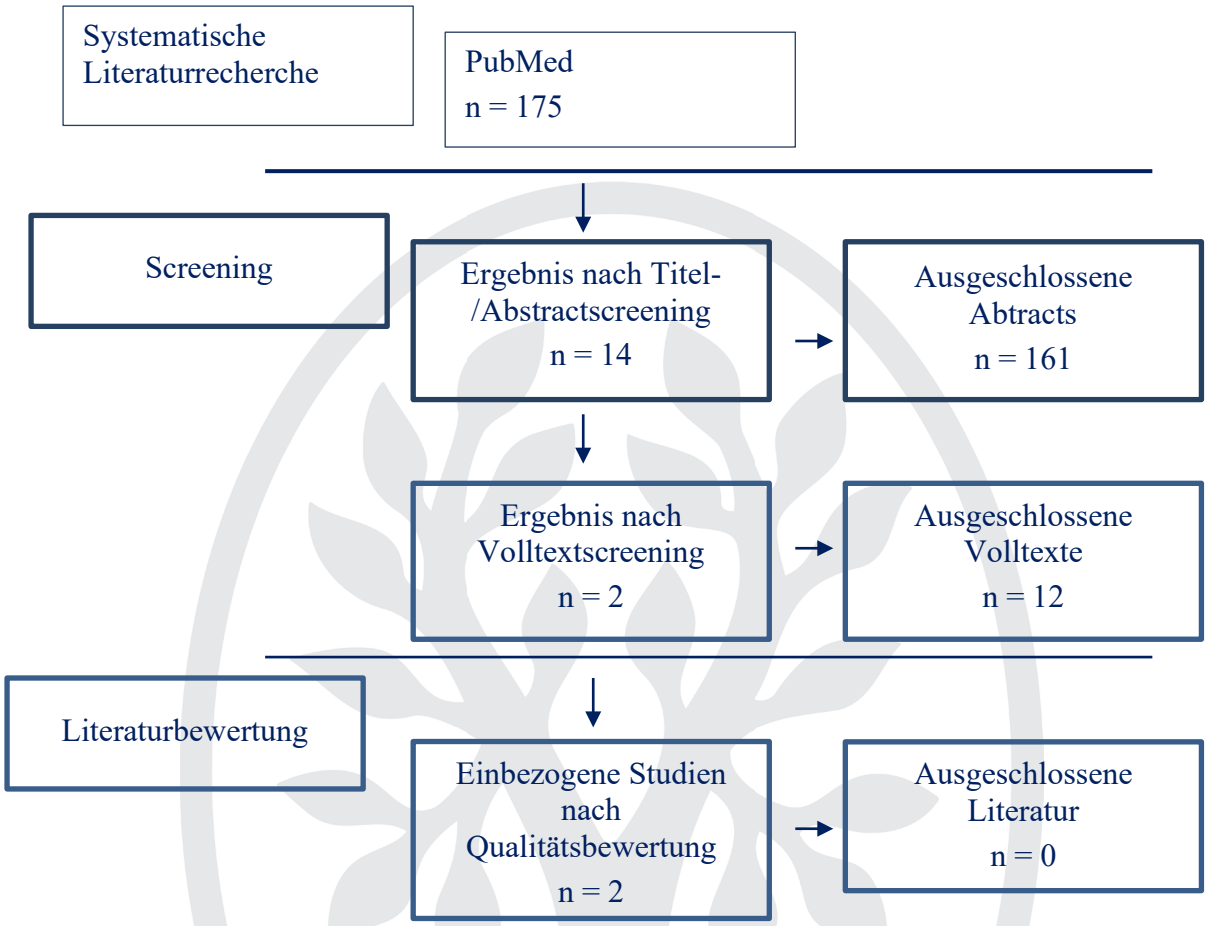
Date Run: 12.05.20

Population		
#1	**Crohn Disease[Mesh]** OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]	55.447
Intervention Comparator		
#2	**Leukocyte L1 Antigen Complex[Mesh]** OR Leukocyte L1 Antigen Complex[tiab] OR Calcium-Binding Myeloid Protein P8,14[tiab] OR Calcium Binding Myeloid Protein P8,14[tiab] OR Calgranulin[tiab] OR Calprotectin[tiab] OR Migratory Inhibitory Factor-Related Protein MRP[tiab] OR Migratory Inhibitory Factor Related Protein MRP[tiab] OR Myelomonocytic Antigen L1[tiab] OR Antigen L1, Myelomonocytic[tiab] OR L1 Antigen[tiab] OR Antigen, L1[tiab] OR 27E10 Antigen[tiab] OR Antigen, 27E10[tiab] OR Leukocyte L1 Protein[tiab] OR L1 Protein, Leukocyte[tiab] OR FCP[tiab]	5.921
Filter		
#3	#1 AND #2	899
#4	animals[mh] NOT humans[mh]	4.697.119
#5	#3 NOT #4	898
#6	(systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	574.647

#7	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])	1.452.556
#8	#6 OR #7	1.900.214
#9	#5 AND #8	190
#10	#9 Publication date 2012- Date of search, Articles in English, German	175
	Date of search 12.05.20	
	(("Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])) OR ((systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt]))) AND (((Crohn Disease[Mesh] OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR	

	Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]) AND (Leukocyte L1 Antigen Complex[Mesh] OR Leukocyte L1 Antigen Complex[tiab] OR Calcium-Binding Myeloid Protein P8,14[tiab] OR Calcium Binding Myeloid Protein P8,14[tiab] OR Calgranulin[tiab] OR Calprotectin[tiab] OR Migratory Inhibitory Factor-Related Protein MRP[tiab] OR Migratory Inhibitory Factor Related Protein MRP[tiab] OR Myelomonocytic Antigen L1[tiab] OR Antigen L1, Myelomonocytic[tiab] OR L1 Antigen[tiab] OR Antigen, L1[tiab] OR 27E10 Antigen[tiab] OR Antigen, 27E10[tiab] OR Leukocyte L1 Protein[tiab] OR L1 Protein, Leukocyte[tiab] OR FCP[tiab])) NOT (animals[mh] NOT humans[mh]))	

Ergebnis und PRISMA Flow Chart: AG 1 – 1



Recherche in PubMed: AG 1 – 2

	Patient	Intervention	Comparator	Outcome
AG 1 Diagnostik				
TDM	Patienten nach Biologikainduktion stherapie mit Ansprechen	TDM	kein TDM	Zeit bis zum Remissionsverlust

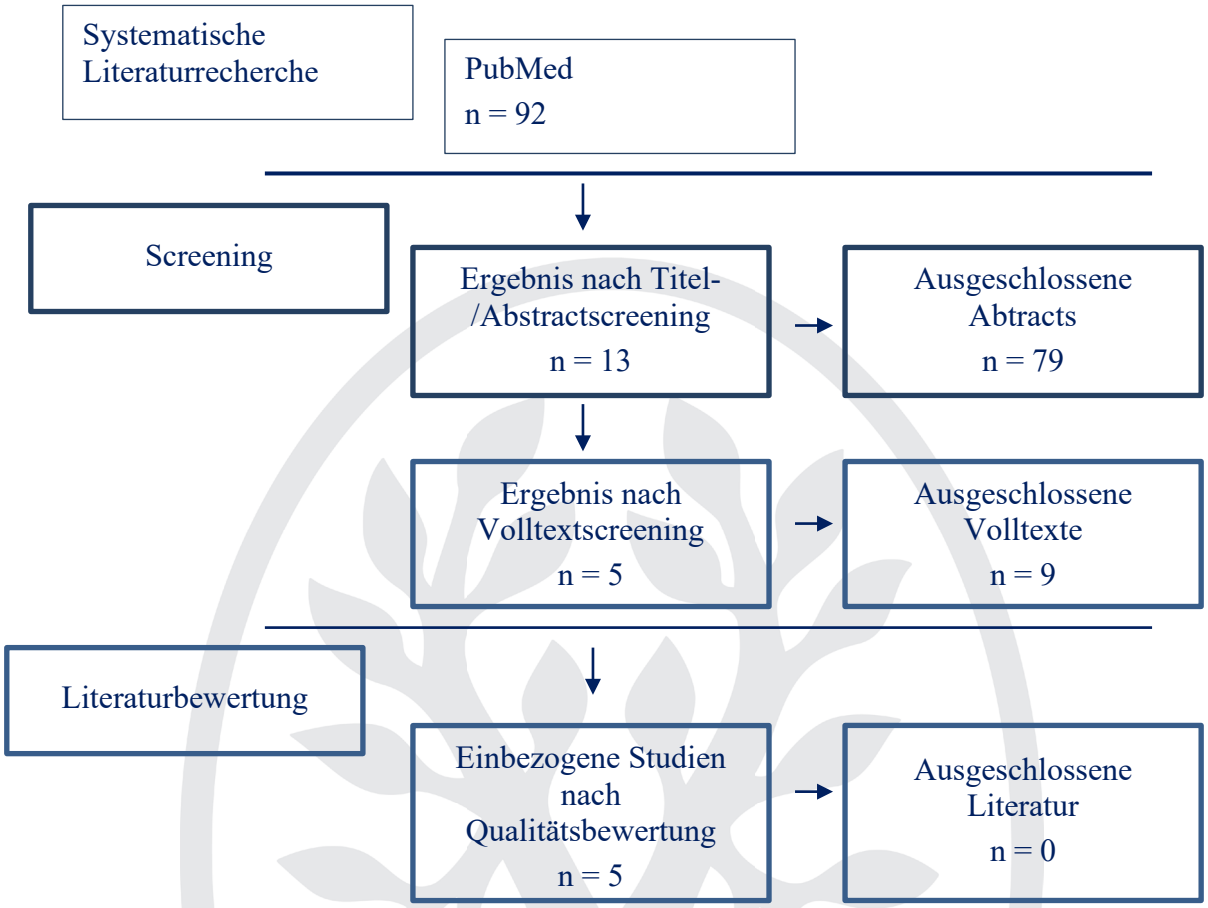
Date Run: 12.05.20

#1	**Crohn Disease[Mesh]** OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]	55.447
Intervention Comparator		
#2	**Drug Monitoring[Mesh]** OR drug monitoring[tiab] OR TDM[tiab] OR Monitoring, Drug[tiab] OR Therapeutic Drug Monitoring[tiab] OR Drug Monitoring, Therapeutic[tiab] OR Monitoring, Therapeutic Drug[tiab]	28.432
Filter		
#3	#1 AND #2	346
#4	animals[mh] NOT humans[mh]	4.697.119
#5	#3 NOT #4	344
#6	(systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	574.647
#7	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials,	1.452.556

	phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR "Double-Blind Method"[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])	
#8	#6 OR #7	1.900.214
#9	#5 AND #8	105
#10	#9 Publication date 2012- Date of search, Articles in English, German	92
	Date of search 12.05.20	
	(((Crohn Disease[Mesh] OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]) AND (Drug Monitoring[Mesh] OR drug monitoring[tiab] OR TDM[tiab] OR Monitoring, Drug[tiab] OR Therapeutic Drug Monitoring[tiab] OR Drug Monitoring, Therapeutic[tiab] OR Monitoring, Therapeutic Drug[tiab])) NOT (animals[mh] NOT humans[mh])) AND (((systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR "cochrane database syst rev"[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR "research synthesis"[tiab] OR "research integration"[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT "psycinfo database"[tiab]) OR pubmed[tiab] OR scopus[tiab] OR "web of science"[tiab] OR "data synthesis"[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR "meta-analysis as topic"[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])) OR ("Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR "Double-Blind Method"[Mesh] OR ((randomised[TIAB] OR randomized[TIAB])	

	AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab]))	

Ergebnis und PRISMA Flow Chart: AG 1 – 2



Recherche in PubMed: AG 2 – 1

	Patient	Intervention	Comparator	Outcome
Biomarker-geleitete Therapie	Patienten nach Biologika-induktionstherapie mit Ansprechen	CRP / fC	keine Intensivierung aufgrund von Biomarkern	Zeit bis zum klinischen Rezidiv

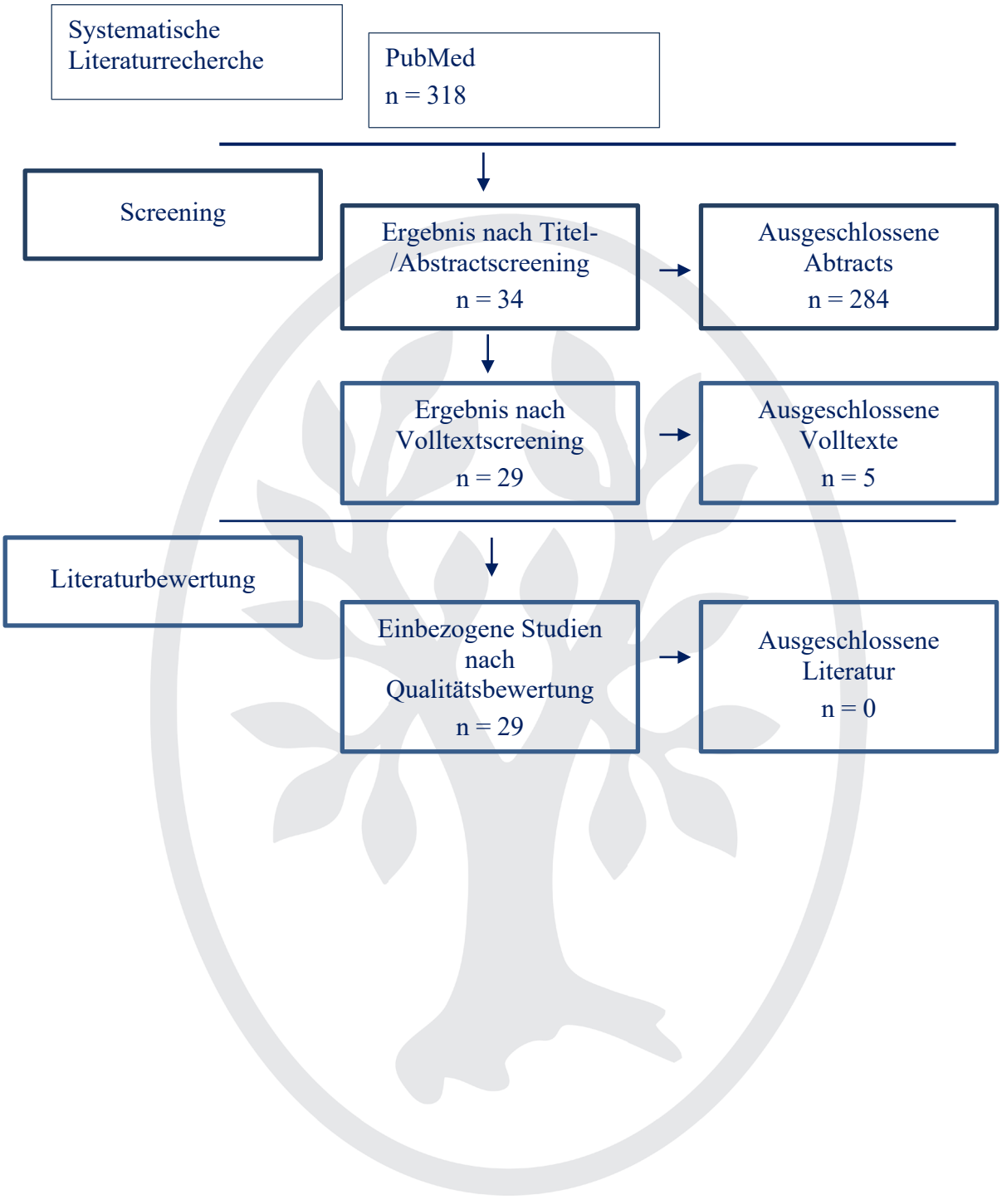
Date Run: 12.05.20

Population		
#1	**Crohn Disease[Mesh]** OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]	55.447
Intervention Comparator		
#2	**Leukocyte L1 Antigen Complex[Mesh]** OR Leukocyte L1 Antigen Complex[tiab] OR Calcium-Binding Myeloid Protein P8,14[tiab] OR Calcium Binding Myeloid Protein P8,14[tiab] OR Calgranulin[tiab] OR Calprotectin[tiab] OR Migratory Inhibitory Factor-Related Protein MRP[tiab] OR Migratory Inhibitory Factor Related Protein MRP[tiab] OR Myelomonocytic Antigen L1[tiab] OR Antigen L1, Myelomonocytic[tiab] OR L1 Antigen[tiab] OR Antigen, L1[tiab] OR 27E10 Antigen[tiab] OR Antigen, 27E10[tiab] OR Leukocyte L1 Protein[tiab] OR L1 Protein, Leukocyte[tiab] OR FCP[tiab]	5.921
#3	**C-Reactive Protein[Mesh]** OR C-Reactive Protein[tiab] OR C Reactive Protein[tiab] OR Protein, C-Reactive[tiab]	78.265
#4	#2 OR #3	83.468
Filter		
#5	#1 AND #4	2.184
#6	animals[mh] NOT humans[mh]	4.697.119
#7	#5 NOT #6	2.181
#8	(systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-	574.647

	analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	
#9	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])	1.452.556
#10	#8 OR #9	1.900.214
#11	#7 AND #10	466
#12	#11 Publication date 2012- Date of search, Articles in English, German	318
	Date of search 12.05.20	

	((((Leukocyte L1 Antigen Complex[Mesh] OR Leukocyte L1 Antigen Complex[tiab] OR Calcium-Binding Myeloid Protein P8,14[tiab] OR Calcium Binding Myeloid Protein P8,14[tiab] OR Calgranulin[tiab] OR Calprotectin[tiab] OR Migratory Inhibitory Factor-Related Protein MRP[tiab] OR Migratory Inhibitory Factor Related Protein MRP[tiab] OR Myelomonocytic Antigen L1[tiab] OR Antigen L1, Myelomonocytic[tiab] OR L1 Antigen[tiab] OR Antigen, L1[tiab] OR 27E10 Antigen[tiab] OR Antigen, 27E10[tiab] OR Leukocyte L1 Protein[tiab] OR L1 Protein, Leukocyte[tiab] OR FCP[tiab]) OR (C-Reactive Protein[Mesh] OR C-Reactive Protein[tiab] OR C Reactive Protein[tiab] OR Protein, C-Reactive[tiab])) AND (Crohn Disease[Mesh] OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab])) NOT (animals[mh] NOT humans[mh])) AND (("Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])) OR ((systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt]))))	

Ergebnis und PRISMA Flow Chart: AG 2 – 1



Recherche in PubMed: AG 2 – 2

	Patient	Intervention	Comparator	Outcome
Endoskopische und/oder histologische Mukosaheilung bei M. Crohn: Relevanz als Therapieziel bzw. als prognostischer Parameter				

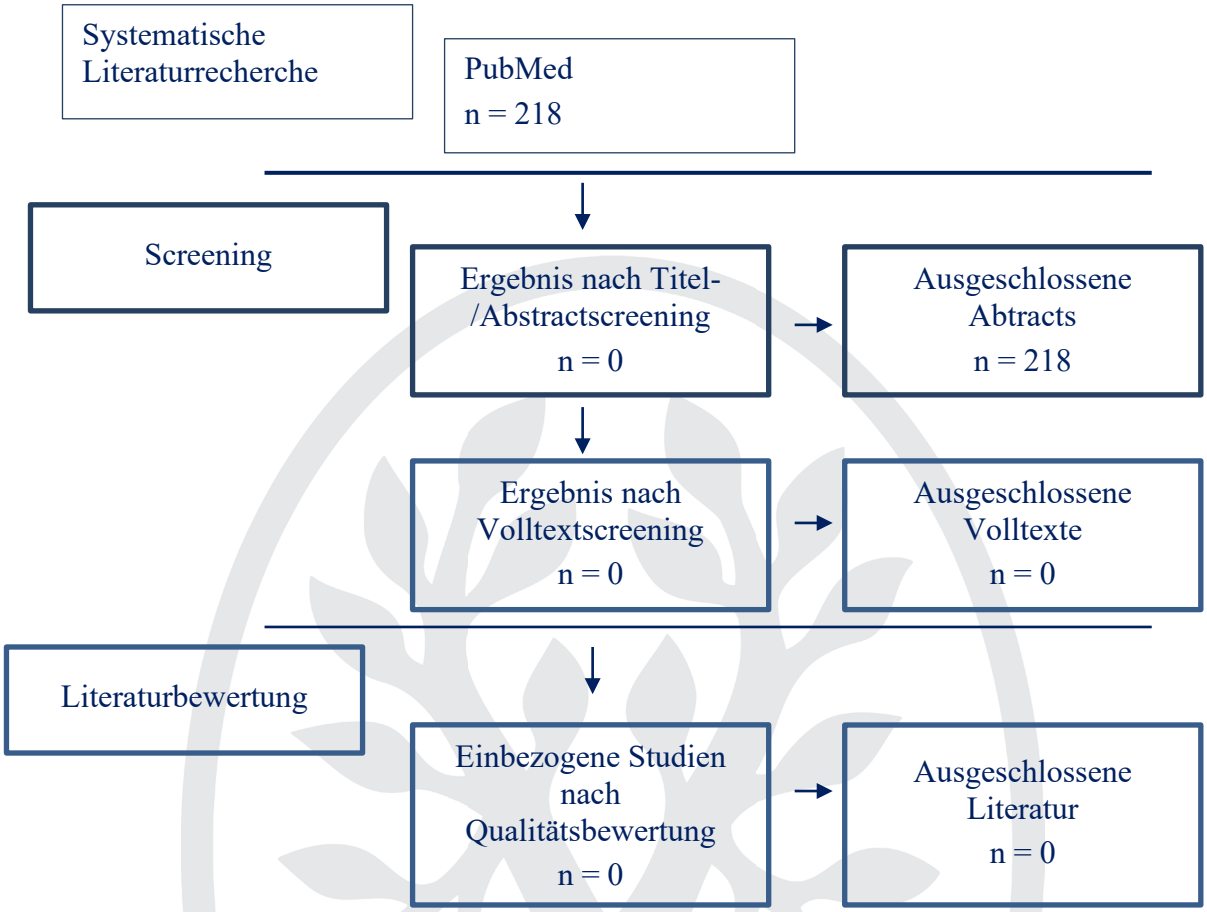
Date Run: 12.05.20

Population		
#1	**Crohn Disease[Mesh]** OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]	55.448
#2	**("Intestinal Mucosa"[Mesh] OR** Mucosa, Intestinal[tiab] OR Intestinal Glands[tiab] OR Gland, Intestinal[tiab] OR Glands, Intestinal[tiab] OR Intestinal Gland[tiab] OR Intestinal Epithelium OR **"Mucous Membrane"[Mesh]** OR Membrane, Mucous[tiab] OR Membranes, Mucous[tiab] OR Mucous Membranes[tiab] OR Mucosa[tiab] OR Mucosal Tissue[tiab] OR Mucosal Tissues[tiab] OR Tissue, Mucosal[tiab] OR Tissues, Mucosal[tiab] OR Lamina Propria[tiab] OR Propria, Lamina[tiab] OR Muscularis Mucosae[tiab] OR Mucosae, Muscularis[tiab] OR Epithelium, Intestinal[tiab]) AND (heal*[tiab]) OR "mucosal healing"[tiab]	30.082
Filter		
#3	#1 AND #2	1.857
#4	animals[mh] NOT humans[mh]	4.697.119
#5	#3 NOT #4	1.814
#6	(systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	574.647

#7	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])	1.452.556
#8	#6 OR #7	1.900.214
#9	#5 AND #8	315
#10	#9 Publication date 06/ 2012- Date of search, Articles in English, German	218
	Date of search 12.05.19	
	(((systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])) OR ("Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab]))) AND (((Crohn Disease[Mesh] OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis,	

	Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]) AND (("Intestinal Mucosa"[Mesh] OR Mucosa, Intestinal[tiab] OR Intestinal Glands[tiab] OR Gland, Intestinal[tiab] OR Glands, Intestinal[tiab] OR Intestinal Gland[tiab] OR Intestinal Epithelium OR "Mucous Membrane"[Mesh] OR Membrane, Mucous[tiab] OR Membranes, Mucous[tiab] OR Mucous Membranes[tiab] OR Mucosa[tiab] OR Mucosal Tissue[tiab] OR Mucosal Tissues[tiab] OR Tissue, Mucosal[tiab] OR Tissues, Mucosal[tiab] OR Lamina Propria[tiab] OR Propria, Lamina[tiab] OR Muscularis Mucosae[tiab] OR Mucosae, Muscularis[tiab] OR Epithelium, Intestinal[tiab]) AND (heal*[tiab]) OR "mucosal healing"[tiab])) NOT (animals[mh] NOT humans[mh]))	

Ergebnis und PRISMA Flow Chart: AG 2 – 2



Recherche in PubMed: AG 2 – 3

	Patient	Intervention	Comparator	Outcome
Biologika oder OP	akuter Schub ileozökaler Befall, kein Ansprechen auf Steroide, Biologika naiv	OP	Biologika	Zeit bis zum klinischen Rezidiv

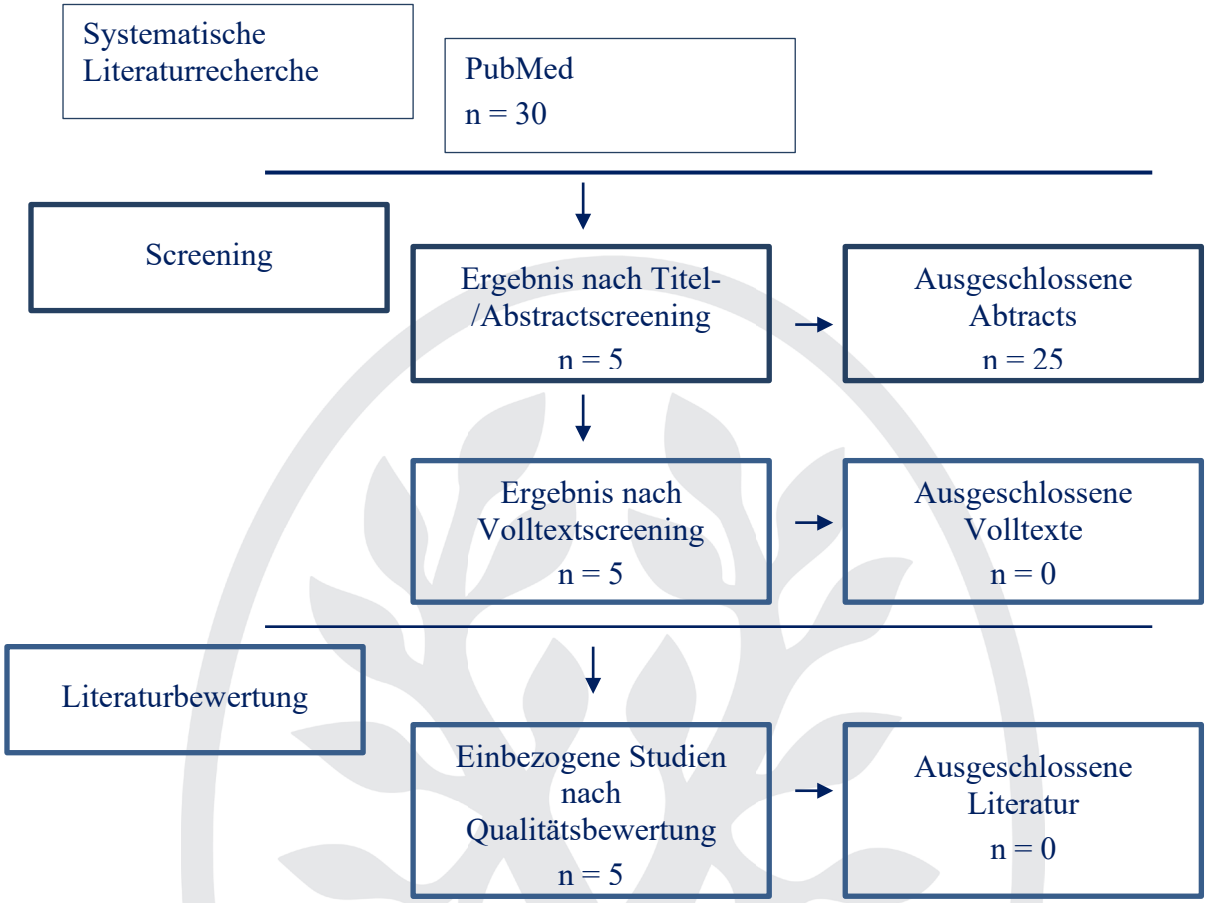
Date Run: 12.05.20

Population		
#1	**Crohn Disease[Mesh]** OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]	55.447
#2	**Ileocecal Valve[Mesh]** OR Ileocecal[tiab] OR ileo-cecal[tiab] OR ileal papilla, ileocaecal valve[tiab] OR Tulp's valve[tiab] OR Tulpius valve[tiab] OR Bauhin's valve[tiab] OR ileocecal eminence[tiab] OR valve of Varolius[tiab] OR colic valve[tiab] OR Valva ileocaecalis[tiab]	5.072
Filter		
#3	#1 AND #2	626
#4	animals[mh] NOT humans[mh]	4.697.119
#5	#3 NOT #4	615
#6	(systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	574.647
#7	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials,	1.452.556

	phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR "Double-Blind Method"[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])	
#8	#6 OR #7	1.900.214
#9	#5 AND #8	61
#10	#9 Publication date 2012- Date of search, Articles in English, German	30
	Date of search 12.05.19	
	(((Ileocecal Valve[Mesh] OR Ileocecal[tiab] OR ileo-cecal[tiab] OR ileal papilla, ileocaecal valve[tiab] OR Tulp's valve[tiab] OR Tulpius valve[tiab] OR Bauhin's valve[tiab] OR ileocecal eminence[tiab] OR valve of Varolius[tiab] OR colic valve[tiab] OR Valva ileocaecalis[tiab]) AND (Crohn Disease[Mesh] OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab])) NOT (animals[mh] NOT humans[mh])) AND (("Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR "Double-Blind Method"[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])) OR ((systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR "cochrane database syst rev"[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR "research synthesis"[tiab] OR "research integration"[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT "psycinfo database"[tiab]) OR pubmed[tiab] OR scopus[tiab] OR "web of science"[tiab] OR	

	“data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt]))	

Ergebnis und PRISMA Flow Chart: AG 2 – 3



Recherche in PubMed: AG 3 – 1

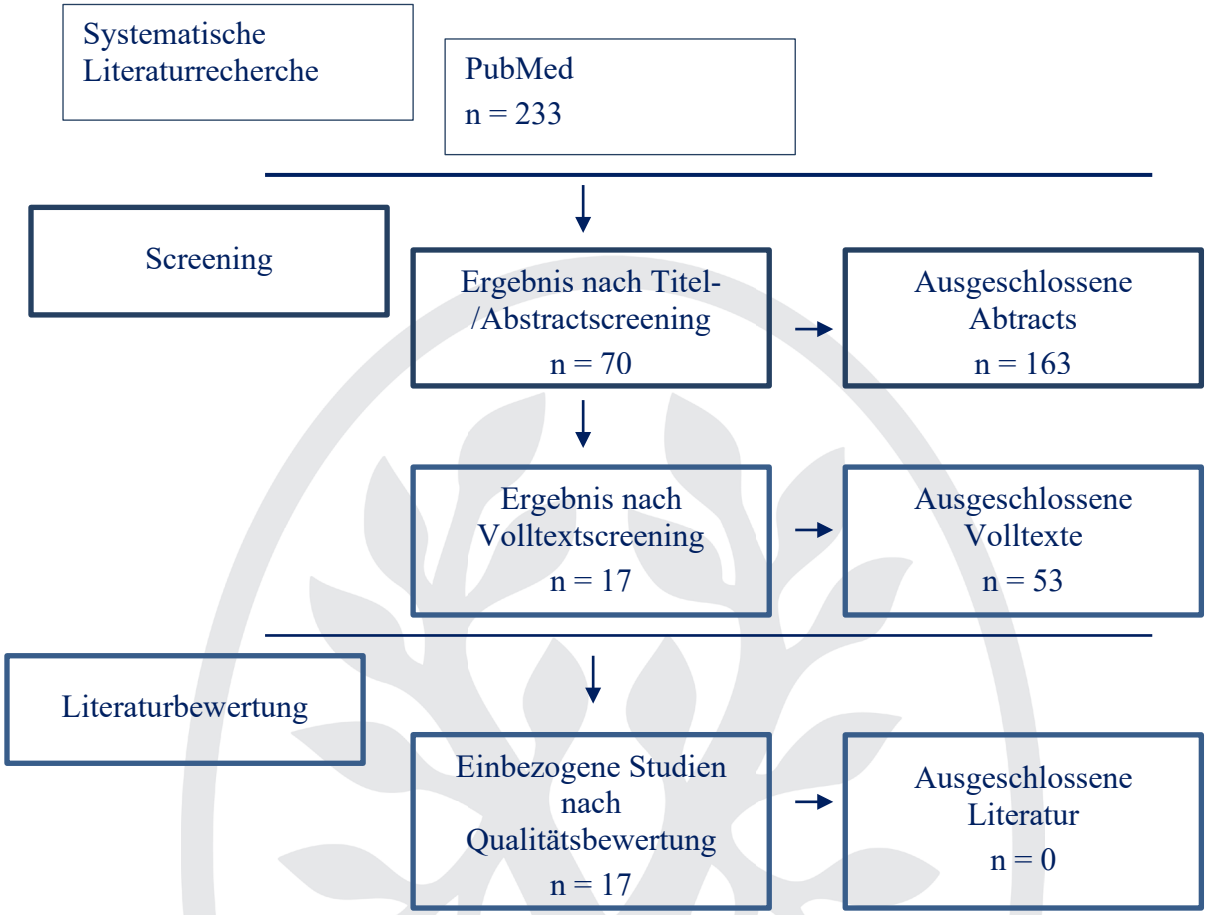
	Patient	Intervention	Comparator	Outcome
AG 3 Remissionserhaltung				
postoperative Therapie zum Remissionserhalt		Medikation	zuwarten	Zeit bis zum (klinischen) Rezidiv

Date Run: 12.05.20

Population		
#1	**Crohn Disease[Mesh]** OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]	55.448
Intervention Comparator		
#2	postoperative[tiab] OR post-operative[tiab]	518.011
Filter		
#3	#1 AND #2	2.264
#4	animals[mh] NOT humans[mh]	4.695.738
#5	#3 NOT #4	2.257
#6	(systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR "cochrane database syst rev"[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR "research synthesis"[tiab] OR "research integration"[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT "psycinfo database"[tiab]) OR pubmed[tiab] OR scopus[tiab] OR "web of science"[tiab] OR "data synthesis"[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR "meta-analysis as topic"[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	574.647
#7	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR	1.452.556

	"multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])	
#8	#6 OR #7	1.900.214
#9	#5 AND #8	405
#10	#9 Publication date 06/ 2012- Date of search, Articles in English, German	233
	Date of search 12.05.20	
	(("Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])) OR ((systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt]))) AND (((Crohn Disease[Mesh] OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]) AND (postoperative[tiab] OR post-operative[tiab])) NOT (animals[mh] NOT humans[mh]))	

Ergebnis und PRISMA Flow Chart: AG 3 – 1



Recherche in PubMed: AG 3 – 2

	Patient	Intervention	Comparator	Outcome
AG 3 Remissionserhaltung				
sekundärer Wirkungsverlust ohne Autoantikörper		Dosiserhöhung	Wechsel des Biologikums	Wiedereintreten der Remission

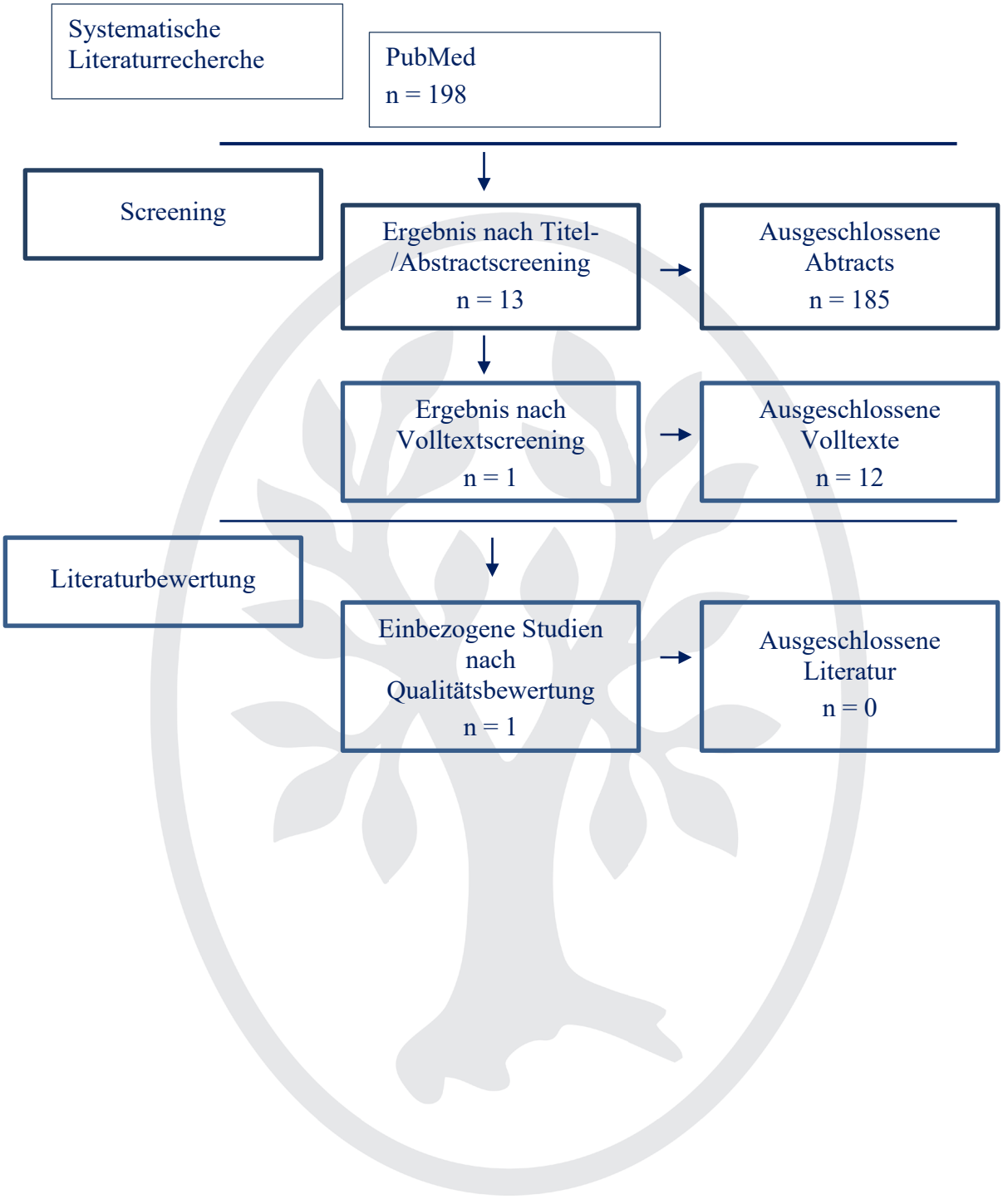
Date Run: 12.05.20

Population		
#1	**Crohn Disease[Mesh]** OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]	55.448
Intervention Comparator		
#2	**Biological Therapy[Mesh]** OR Biological Therapies[tiab] OR Therapies, Biological[tiab] OR Therapy, Biological[tiab] OR Biologic Therapy[tiab] OR Biologic Therapies[tiab] OR Therapies, Biologic[tiab] OR Therapy, Biologic[tiab] OR Biotherapy[tiab] OR Biotherapies[tiab] OR **"Biological Products"[Mesh]** OR biological[tiab] OR Anti TNF[tiab] OR Anti-tnf[tiab] OR **Adalimumab[Mesh]** OR Adalimumab[tiab] OR Humira[tiab] OR Adalimumab-adbm[tiab] OR Amjevita[tiab] OR Adalimumab-atto[tiab] OR Cyltezo[tiab] OR D2E7 Antibody[tiab] OR Antibody, D2E7[tiab] OR **golimumab [Supplementary Concept]** OR Simponi OR golimumab[tiab] OR **"vedolizumab" [Supplementary Concept]** OR vedolizumab[tiab] OR Entyvio[tiab] OR MLN0002[tiab] OR **Infliximab[Mesh]** OR Monoclonal Antibody cA2[tiab] OR cA2, Monoclonal Antibody[tiab] OR MAb cA2[tiab] OR Infliximab-abda[tiab] OR Renflexis[tiab] OR Infliximab-dyyb[tiab] OR Inflectra[tiab] OR Remicade[tiab] OR infliximab[tiab] OR **Certolizumab Pegol[Mesh]** OR Certolizumab[tiab] OR Cimzia[tiab] OR CDP870[tiab] OR CDP 870[tiab] OR **Ustekinumab[Mesh]** OR Ustekinumab[tiab] OR Stelara[tiab] OR CNTO 1275[tiab] OR CNTO-1275[tiab]	1.845.949
#3	(efficacy[tiab] AND (loss[tiab] OR lack[tiab])) OR **"Immunogenicity, Vaccine"[Mesh]** OR immunogenic*[tiab] OR switch[tiab] OR change[tiab]	1.233.902
#4	#2 AND #3	99.040
Filter		
#5	#1 AND #4	897
#6	animals[mh] NOT humans[mh]	4.695.738
#7	#5 NOT #6	883

#8	(systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	574.647
#9	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])	1.452.556
#10	#8 OR #9	1.900.214
#11	#7 AND #10	304
#12	#11 Publication date 2012- Date of search, Articles in English, German	198
	Date of search 12.05.20	
	(("Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])) OR ((systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab]	

	OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt]))) AND ((((Biological Therapy[Mesh] OR Biological Therapies[tiab] OR Therapies, Biological[tiab] OR Therapy, Biological[tiab] OR Biologic Therapy[tiab] OR Biologic Therapies[tiab] OR Therapies, Biologic[tiab] OR Therapy, Biologic[tiab] OR Biotherapy[tiab] OR Biotherapies[tiab] OR "Biological Products"[Mesh] OR biological[tiab] OR Anti TNF[tiab] OR Anti-tnf[tiab] OR Adalimumab[Mesh] OR Adalimumab[tiab] OR Humira[tiab] OR Adalimumab-adbm[tiab] OR Amjevita[tiab] OR Adalimumab-atto[tiab] OR Cyltezo[tiab] OR D2E7 Antibody[tiab] OR Antibody, D2E7[tiab] OR golimumab [Supplementary Concept] OR Simponi OR golimumab[tiab] OR "vedolizumab" [Supplementary Concept] OR vedolizumab[tiab] OR Entyvio[tiab] OR MLN0002[tiab] OR Infliximab[Mesh] OR Monoclonal Antibody cA2[tiab] OR cA2, Monoclonal Antibody[tiab] OR MAb cA2[tiab] OR Infliximab-abda[tiab] OR Renflexis[tiab] OR Infliximab-dyyb[tiab] OR Inflectra[tiab] OR Remicade[tiab] OR infliximab[tiab] OR Certolizumab Pegol[Mesh] OR Certolizumab[tiab] OR Cimzia[tiab] OR CDP870[tiab] OR CDP 870[tiab] OR Ustekinumab[Mesh] OR Ustekinumab[tiab] OR Stelara[tiab] OR CNTO 1275[tiab] OR CNTO-1275[tiab]) AND ((efficacy[tiab] AND (loss[tiab] OR lack[tiab])) OR "Immunogenicity, Vaccine"[Mesh] OR immunogenic*[tiab] OR switch[tiab] OR change[tiab])) AND (Crohn Disease[Mesh] OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab])) NOT (animals[mh] NOT humans[mh]))	

Ergebnis und PRISMA Flow Chart: AG 3 – 2



Recherche in PubMed: AG 4 – 1

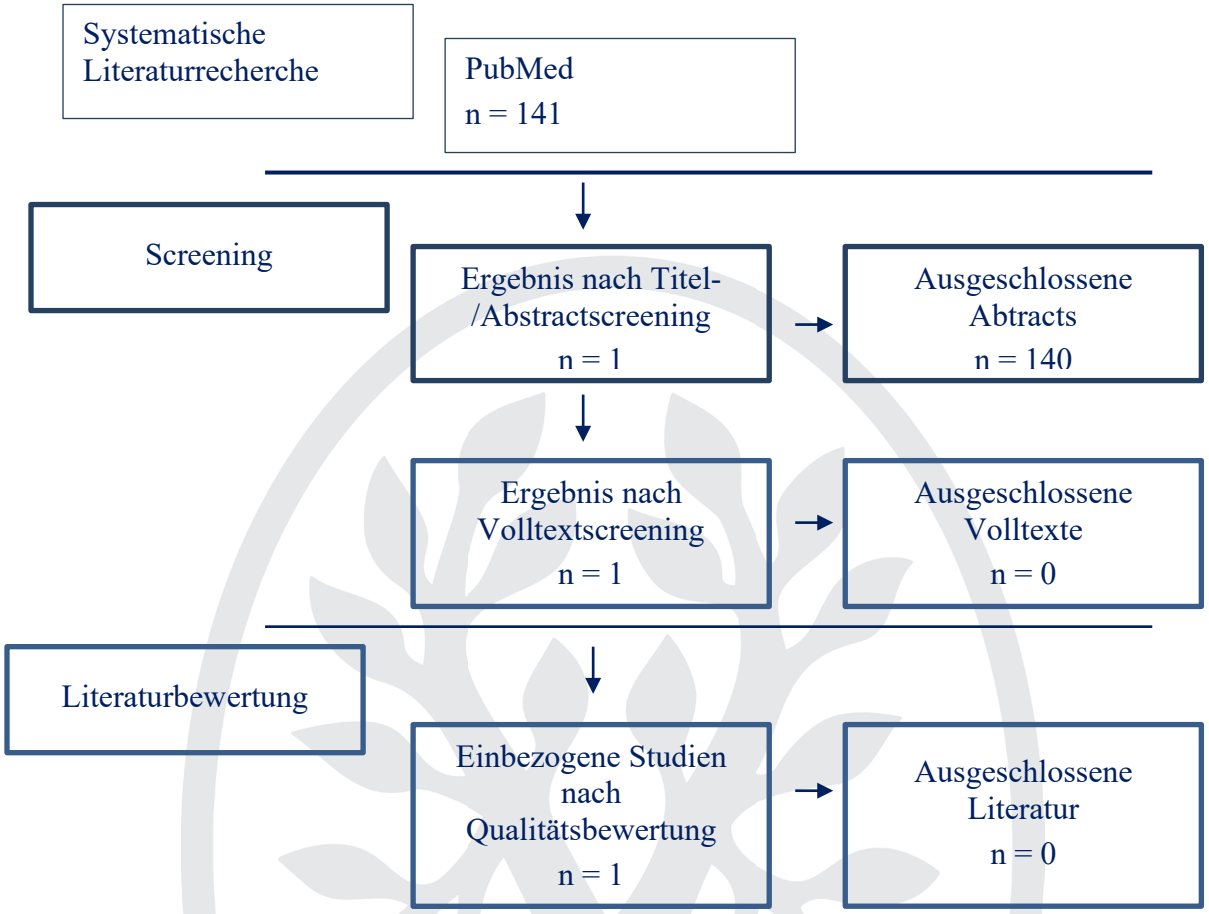
	Patient	Intervention	Comparator	Outcome
AG 4 Fisteln				
perianale Fisteln	Patient mit perianalen Fisteln	Antibiotikagabe	Biologica oder Placebo	Abheilen der Fisteln entsprechend MRT oder Scores

Date Run: 12.05.20

Population		
#1	**Crohn Disease[Mesh]** OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]	55.448
#2	**(Fistula[Mesh]** OR Fistul*[tiab]) AND (**"Anal Canal"[Mesh]** OR anal[tiab] OR perianal[tiab] OR peri-anal[tiab] OR Sphincter[tiab] OR Anus[tiab])	6.791
Filter		
#3	#1 AND #2	1.611
#4	animals[mh] NOT humans[mh]	4.695.738
#5	#3 NOT #4	1.606
#6	(systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	574.647
#7	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR	1.452.556

	((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])	
#8	#6 OR #7	1.900.214
#9	#5 AND #8	256
#10	#9 Publication date 2012- Date of search, Articles in English, German	141
	Date of search 12.05.20	
	(((Crohn Disease[Mesh] OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]) AND ((Fistula[Mesh] OR Fistul*[tiab]) AND ("Anal Canal"[Mesh] OR anal[tiab] OR perianal[tiab] OR peri-anal[tiab] OR Sphincter[tiab] OR Anus[tiab]))) NOT (animals[mh] NOT humans[mh])) AND (("Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])) OR ((systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])))	

Ergebnis und PRISMA Flow Chart: AG 4 – 1



Recherche in PubMed: AG 4 – 2

	Patient	Intervention	Comparator	Outcome
AG 4 Fisteln				
OP-Indikation	Patient mit abdominellen Fisteln	OP	Biologica	?

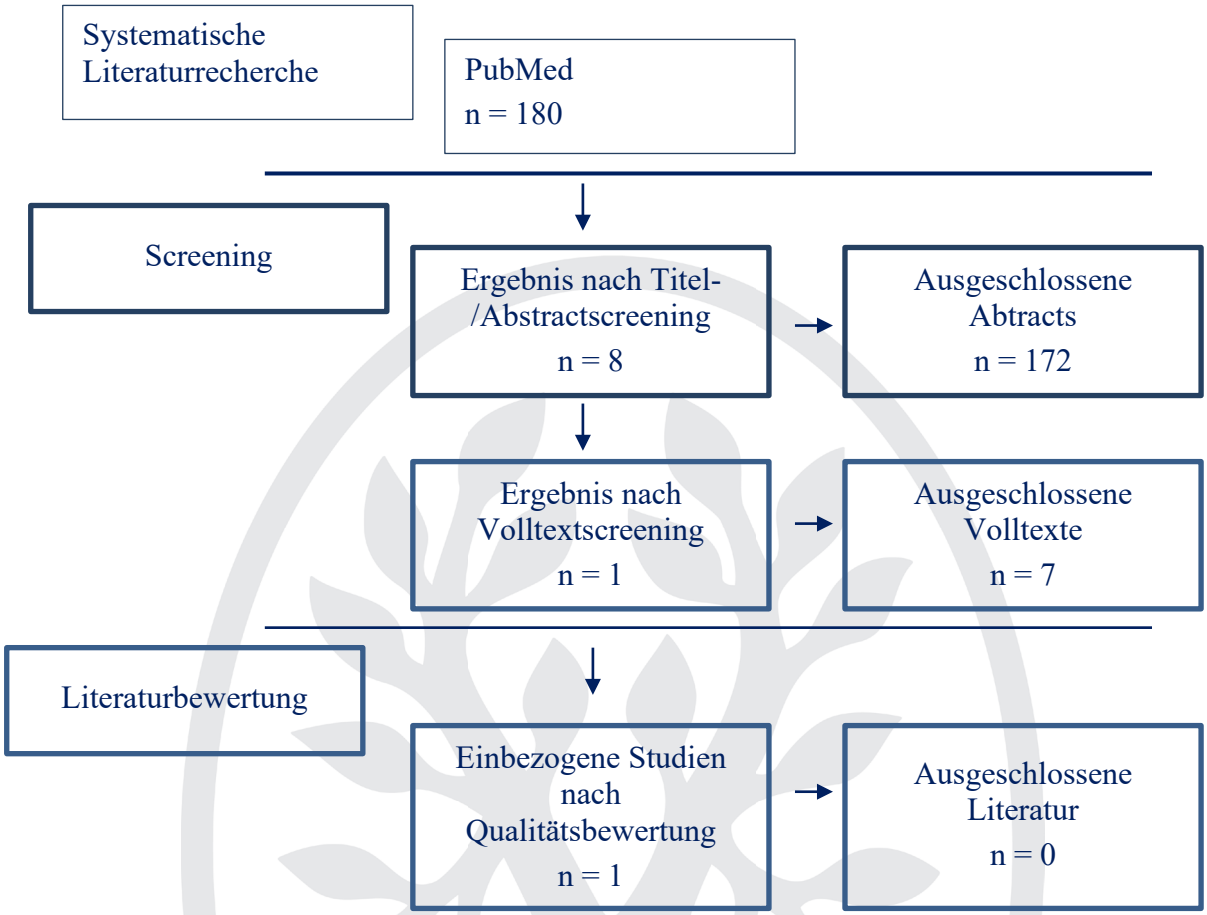
Date Run: 12.05.20

Population		
#1	**Crohn Disease[Mesh]** OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]	55.566
#2	**Fistula[Mesh]** OR Fistula*[tiab]	116.635
Intervention		
#3	**Biological Therapy[Mesh]** OR Biological Therapies[tiab] OR Therapies, Biological[tiab] OR Therapy, Biological[tiab] OR Biologic Therapy[tiab] OR Biologic Therapies[tiab] OR Therapies, Biologic[tiab] OR Therapy, Biologic[tiab] OR Biotherapy[tiab] OR Biotherapies[tiab] OR **"Biological Products"[Mesh]** OR biological[tiab] OR Anti TNF[tiab] OR Anti-tnf[tiab] OR **Adalimumab[Mesh]** OR Adalimumab[tiab] OR Humira[tiab] OR Adalimumab-adbm[tiab] OR Amjevita[tiab] OR Adalimumab-atto[tiab] OR Cyltezo[tiab] OR D2E7 Antibody[tiab] OR Antibody, D2E7[tiab] OR **golimumab [Supplementary Concept]** OR Simponi OR golimumab[tiab] OR **"vedolizumab" [Supplementary Concept]** OR vedolizumab[tiab] OR Entyvio[tiab] OR MLN0002[tiab] OR **Infliximab[Mesh]** OR Monoclonal Antibody cA2[tiab] OR cA2, Monoclonal Antibody[tiab] OR MAb cA2[tiab] OR Infliximab-abda[tiab] OR Renflexis[tiab] OR Infliximab-dyyb[tiab] OR Inflectra[tiab] OR Remicade[tiab] OR infliximab[tiab] OR **Certolizumab Pegol[Mesh]** OR Certolizumab[tiab] OR Cimzia[tiab] OR CDP870[tiab] OR CDP 870[tiab] OR **Ustekinumab[Mesh]** OR Ustekinumab[tiab] OR Stelara[tiab] OR CNTO 1275[tiab] OR CNTO-1275[tiab]	1.849.389
#4	**Surgical Procedures, Operative[Mesh]** OR Operative Surgical Procedure[tiab] OR Surgical Procedure, Operative[tiab] OR Procedure, Operative Surgical[tiab] OR Procedures, Operative Surgical[tiab] OR Operative Procedures[tiab] OR Operative Procedure[tiab] OR Procedure, Operative[tiab] OR Procedures, Operative[tiab] OR Operative Surgical Procedures[tiab] OR Surgery, Ghost[tiab] OR Ghost Surgery[tiab] OR surgical[tiab] OR surger*[tiab] OR operation[tiab]	4.139.020
Filter		
#4	#1 AND #2 AND (#3 OR #4)	2.839
#5	animals[mh] NOT humans[mh]	4.695.738

#6	#4 NOT #5	2.834
#7	(systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR "cochrane database syst rev"[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR "research synthesis"[tiab] OR "research integration"[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT "psycinfo database"[tiab]) OR pubmed[tiab] OR scopus[tiab] OR "web of science"[tiab] OR "data synthesis"[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR "meta-analysis as topic"[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	574.647
#8	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR "Double-Blind Method"[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])	1.452.556
#9	#7 OR #8	1.905.244
#10	#6 AND #9	400
#11	#10 Publication date 2012- Date of search, Articles in English, German	180
	Date of search 12.05.20	
	(((systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR "cochrane database syst rev"[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR "research synthesis"[tiab] OR "research integration"[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT "psycinfo database"[tiab]) OR pubmed[tiab] OR scopus[tiab] OR "web of science"[tiab] OR "data synthesis"[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR "meta-analysis as topic"[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])) OR ("Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR	

	"clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab]))) AND ((((Crohn Disease[Mesh] OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]) AND (Fistula[Mesh] OR Fistula*[tiab])) AND ((Biological Therapy[Mesh] OR Biological Therapies[tiab] OR Therapies, Biological[tiab] OR Therapy, Biological[tiab] OR Biologic Therapy[tiab] OR Biologic Therapies[tiab] OR Therapies, Biologic[tiab] OR Therapy, Biologic[tiab] OR Biotherapy[tiab] OR Biotherapies[tiab] OR "Biological Products"[Mesh] OR biological[tiab] OR Anti TNF[tiab] OR Anti-tnf[tiab] OR Adalimumab[Mesh] OR Adalimumab[tiab] OR Humira[tiab] OR Adalimumab-adbm[tiab] OR Amjevita[tiab] OR Adalimumab-atto[tiab] OR Cyltezo[tiab] OR D2E7 Antibody[tiab] OR Antibody, D2E7[tiab] OR golimumab [Supplementary Concept] OR Simponi OR golimumab[tiab] OR "vedolizumab" [Supplementary Concept] OR vedolizumab[tiab] OR Entyvio[tiab] OR MLN0002[tiab] OR Infliximab[Mesh] OR Monoclonal Antibody cA2[tiab] OR cA2, Monoclonal Antibody[tiab] OR MAb cA2[tiab] OR Infliximab-abda[tiab] OR Renflexis[tiab] OR Infliximab-dyyb[tiab] OR Inflectra[tiab] OR Remicade[tiab] OR infliximab[tiab] OR Certolizumab Pegol[Mesh] OR Certolizumab[tiab] OR Cimzia[tiab] OR CDP870[tiab] OR CDP 870[tiab] OR Ustekinumab[Mesh] OR Ustekinumab[tiab] OR Stelara[tiab] OR CNTO 1275[tiab] OR CNTO-1275[tiab]) OR (Surgical Procedures, Operative[Mesh] OR Operative Surgical Procedure[tiab] OR Surgical Procedure, Operative[tiab] OR Procedure, Operative Surgical[tiab] OR Procedures, Operative Surgical[tiab] OR Operative Procedures[tiab] OR Operative Procedure[tiab] OR Procedure, Operative[tiab] OR Procedures, Operative[tiab] OR Operative Surgical Procedures[tiab] OR Surgery, Ghost[tiab] OR Ghost Surgery[tiab] OR surgical[tiab] OR surger*[tiab] OR operation[tiab]))) NOT (animals[mh] NOT humans[mh]))	

Ergebnis und PRISMA Flow Chart: AG 4 – 2



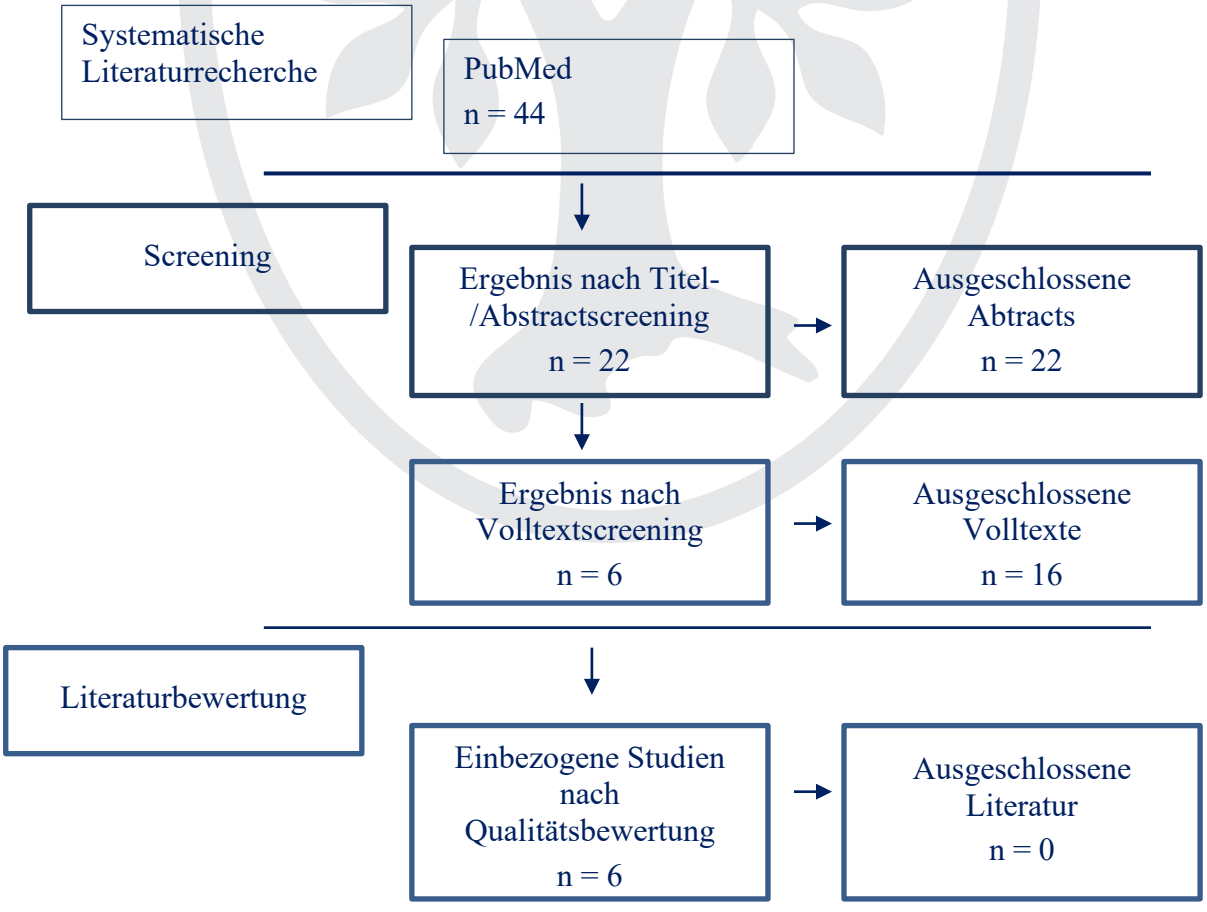
Recherche in PubMed: AG 5 – 1

	Patient	Intervention	Comparator	Outcome
Eisensubstitution	Patient mit Eisenmangel	i.v. Eisen	Eisen p.o.	Normalisierung des Hb, Anstieg der LQ

Date Run: 26.04.20

Search	Hits
((("crohn disease"[MeSH Terms]) OR ("inflammatory bowel diseases"[MeSH Terms])) AND (("iron-deficiency"[Title/Abstract]) OR ("iron deficiency"[title/abstract]))) Filters: Randomized Controlled Trial, Systematic Reviews, From 2012/06/02 to 2020/12/31, Humans	44

Ergebnis und PRISMA Flow Chart: AG 5 – 1



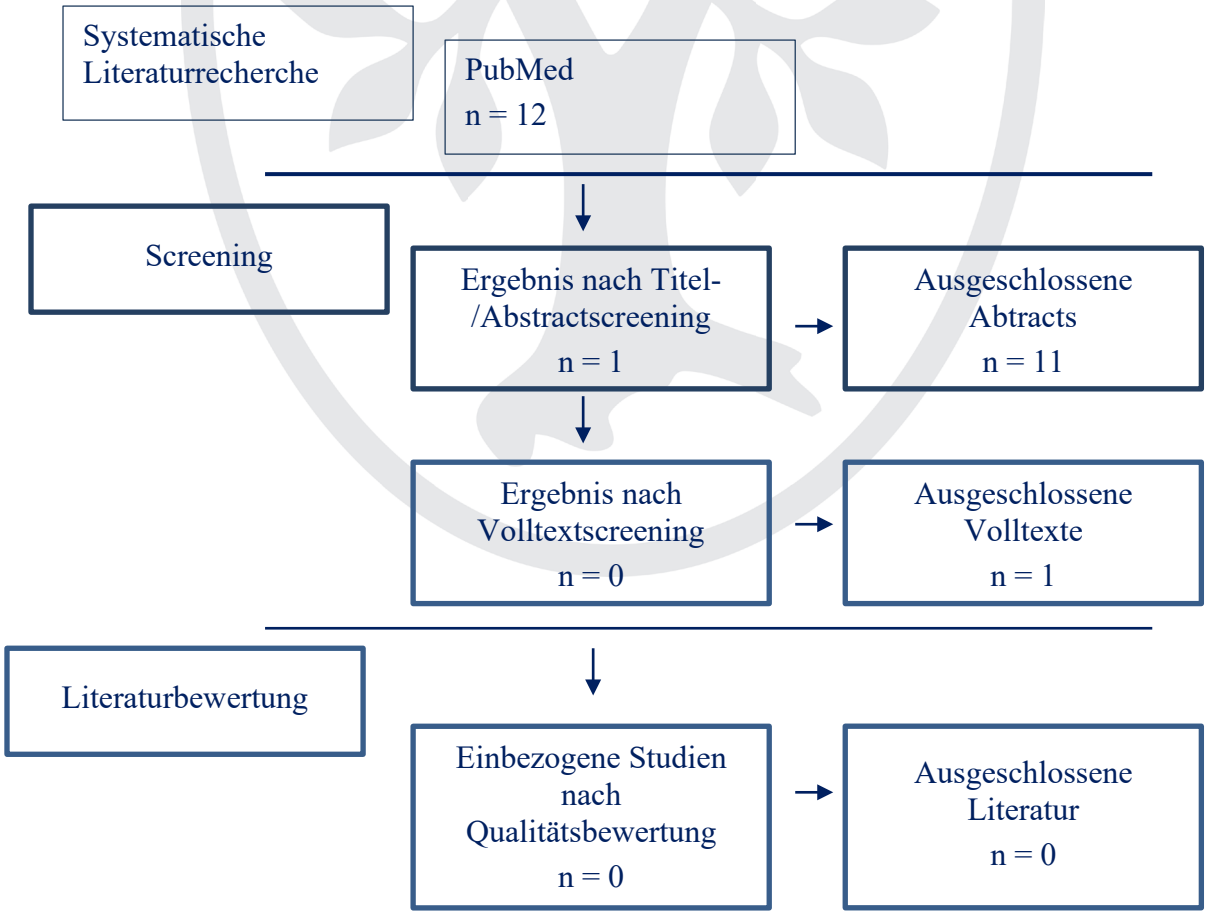
Recherche in PubMed: AG 5 – 2

	Patient	Intervention	Comparator	Outcome
Gelenkschmerzen	Patient mit Gelenkschmerzen	Biologicagabe	MTX	Regredienz der Gelenkschmerzen

Date Run: 26.04.20

Search	Hits
((("crohn disease"[MeSH Terms]) OR ("inflammatory bowel diseases"[MeSH Terms])) AND ((arthritis[Title/Abstract]) OR (arthropathy[Title/Abstract]) OR (spondylarthropathy[Title/Abstract]) or (spondylarthritis[Title/Abstract])) AND (methotrexate[Title/Abstract])) Filters: Randomized Controlled Trial, Systematic Reviews, From 2012/06/02 to 2020/12/31, Humans	12

Ergebnis und PRISMA Flow Chart: AG 5 – 2



Recherche in PubMed: AG 6 – 1

	Patient	Intervention	Comparator	Outcome
AG 6 besondere Situationen				
Diagnostik Kinder	Kind mit V.a. CED	Diagnostik	?	Sicherheit der Diagnosefindung

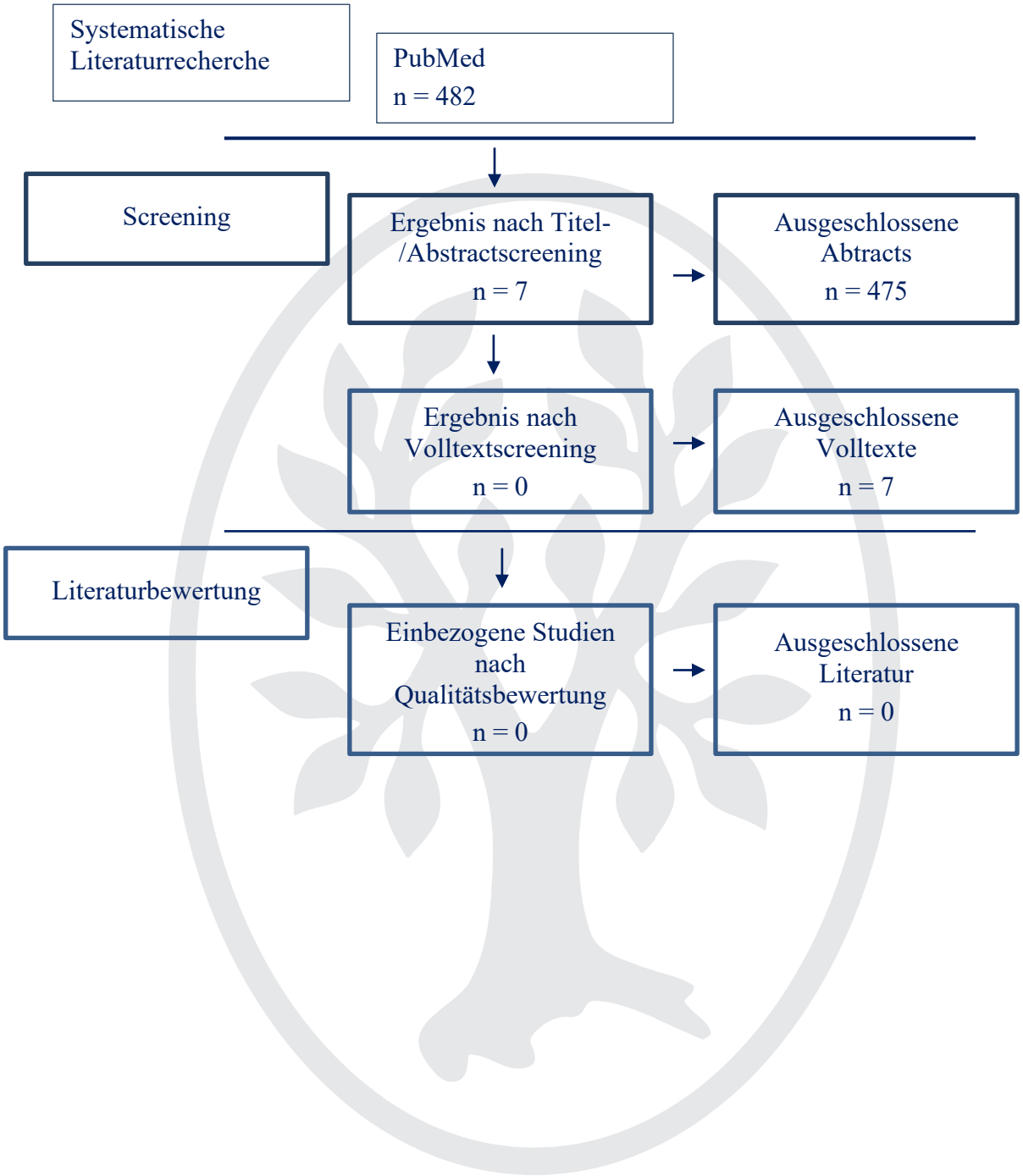
Date Run: 12.05.20

Population		
#1	**Crohn Disease[Mesh]** OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]	55.448
#2	**Colitis, Ulcerative[Mesh]** OR colitis, ulcerative[tiab] OR ulcerative colitis[tiab] OR colitis ulcerosa[tiab] OR Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab] OR Inflammatory Bowel Disease, Ulcerative Colitis Type[tiab] OR acute severe ulcerative colitis[tiab] OR ASUC[tiab]	48.193
#3	**Inflammatory Bowel Diseases[Mesh]** OR Inflammatory Bowel Disease[tiab] OR Bowel Diseases, Inflammatory[tiab] OR IBD[tiab]	99.417
#4	#1 OR #2 OR #3	111.406
#5	**Child[Mesh]** OR child*[tiab] OR **"Infant"[Mesh]** OR infant*[tiab]	2.914.126
#6	#4 AND #5	12.851
Intervention / Comparison		
#7	**Diagnosis[Mesh]** OR diagnos*[tiab] OR Diagnoses[tiab] OR Diagnoses and Examinations[tiab] OR Examinations and Diagnoses[tiab] OR Postmortem Diagnosis[tiab] OR Diagnoses, Postmortem[tiab] OR Diagnosis, Postmortem[tiab] OR Postmortem Diagnoses[tiab] OR Antemortem Diagnosis[tiab] OR Antemortem Diagnoses[tiab] OR Diagnoses, Antemortem[tiab] OR Diagnosis, Antemortem[tiab]	9.653.981
Filter		
#8	#6 AND #7	7.394
#9	animals[mh] NOT humans[mh]	4.695.738
#10	#8 NOT #9	7.378
#11	(systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature	574.647

	review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR "research synthesis"[tiab] OR "research integration"[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT "psycinfo database"[tiab]) OR pubmed[tiab] OR scopus[tiab] OR "web of science"[tiab] OR "data synthesis"[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR "meta-analysis as topic"[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	
#12	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR "Double-Blind Method"[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])	1.452.556
#13	#11 OR #12	1.900.214
#14	#10 AND #13	879
#15	#14 Publication date 2012- Date of search, Articles in English, German	482
	Date of search 12.05.20	
	(((Diagnosis[Mesh] OR diagnos*[tiab] OR Diagnoses[tiab] OR Diagnoses and Examinations[tiab] OR Examinations and Diagnoses[tiab] OR Postmortem Diagnosis[tiab] OR Diagnoses, Postmortem[tiab] OR Diagnosis, Postmortem[tiab] OR Postmortem Diagnoses[tiab] OR Antemortem Diagnosis[tiab] OR Antemortem Diagnoses[tiab] OR Diagnoses, Antemortem[tiab] OR Diagnosis, Antemortem[tiab]) AND ((((Crohn Disease[Mesh] OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]) OR (Colitis, Ulcerative[Mesh] OR colitis, ulcerative[tiab] OR ulcerative colitis[tiab] OR colitis ulcerosa[tiab] OR Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab] OR Inflammatory Bowel Disease, Ulcerative Colitis Type[tiab] OR acute severe ulcerative colitis[tiab] OR ASUC[tiab])) OR (Inflammatory Bowel Diseases[Mesh] OR Inflammatory Bowel Disease[tiab] OR Bowel Diseases,	

	Inflammatory[tiab] OR IBD[tiab])) AND (Child[Mesh] OR child*[tiab] OR "Infant"[Mesh] OR infant*[tiab]))) NOT (animals[mh] NOT humans[mh])) AND (("Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])) OR ((systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt]))))	

Ergebnis und PRISMA Flow Chart: AG 6 – 1



Recherche in PubMed: AG 6 – 2

	Patient	Intervention	Comparator	Outcome
AG 6 besondere Situationen				
ältere CED-Patienten	Patient mit CED >65 Jahre	Biologicather apie	Azathioprin	Remissionsinduktion, Therapiesicherheit

Date Run: 12.05.20

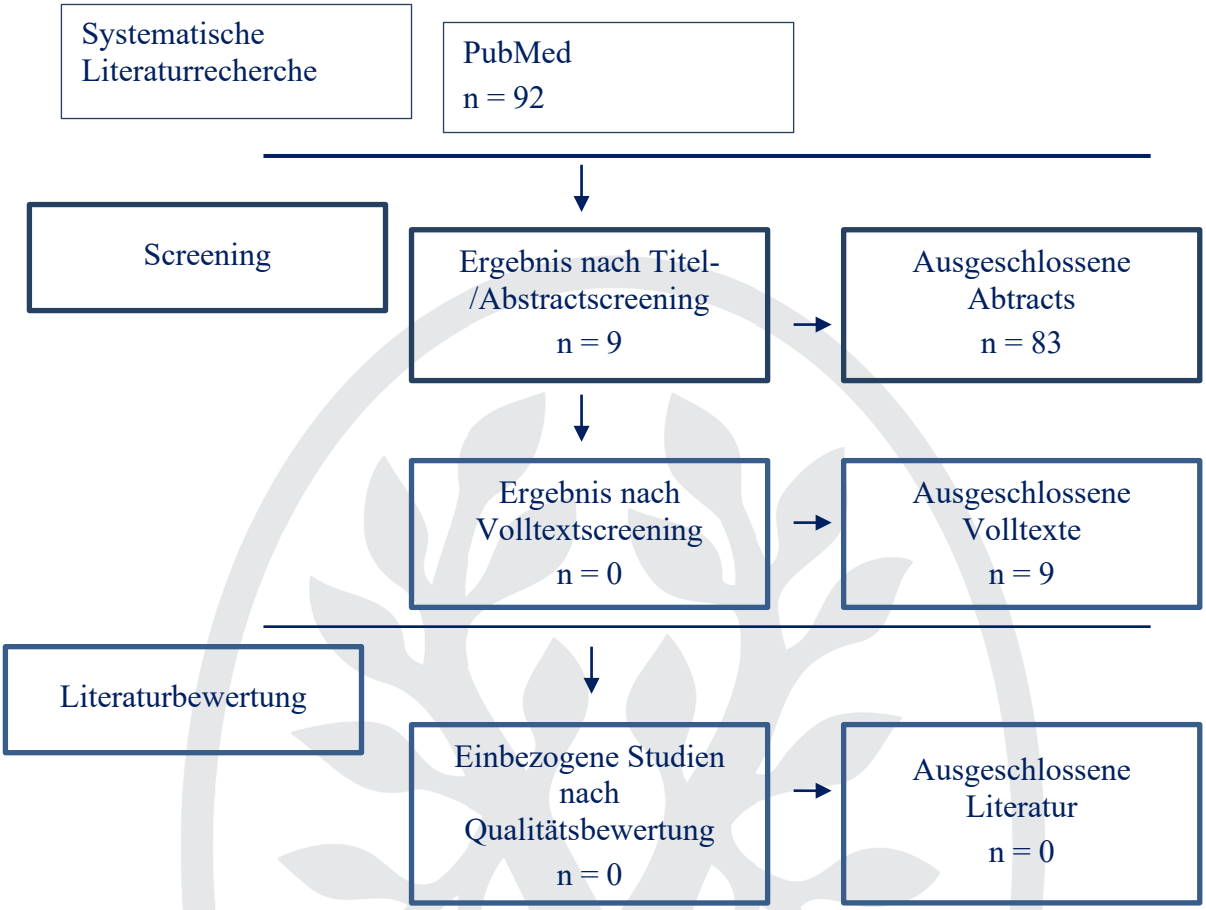
Population		
#1	**Crohn Disease[Mesh]** OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]	55.448
#2	**Colitis, Ulcerative[Mesh]** OR colitis, ulcerative[tiab] OR ulcerative colitis[tiab] OR colitis ulcerosa[tiab] OR Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab] OR Inflammatory Bowel Disease, Ulcerative Colitis Type[tiab] OR acute severe ulcerative colitis[tiab] OR ASUC[tiab]	48.193
#3	**Inflammatory Bowel Diseases[Mesh]** OR Inflammatory Bowel Disease[tiab] OR Bowel Diseases, Inflammatory[tiab] OR IBD[tiab]	99.417
#4	#1 OR #2 OR #3	111.406
Intervention / Comparison		
#5	**Biological Therapy[Mesh]** OR Biological Therapies[tiab] OR Therapies, Biological[tiab] OR Therapy, Biological[tiab] OR Biologic Therapy[tiab] OR Biologic Therapies[tiab] OR Therapies, Biologic[tiab] OR Therapy, Biologic[tiab] OR Biotherapy[tiab] OR Biotherapies[tiab] OR **"Biological Products"[Mesh]** OR biological[tiab] OR Anti TNF[tiab] OR Anti-tnf[tiab] OR **Adalimumab[Mesh]** OR Adalimumab[tiab] OR Humira[tiab] OR Adalimumab-adbm[tiab] OR Amjevita[tiab] OR Adalimumab-atto[tiab] OR Cyltezo[tiab] OR D2E7 Antibody[tiab] OR Antibody, D2E7[tiab] OR **golimumab [Supplementary Concept]** OR Simponi OR golimumab[tiab] OR **"vedolizumab" [Supplementary Concept]** OR vedolizumab[tiab] OR Entyvio[tiab] OR MLN0002[tiab] OR **Infliximab[Mesh]** OR Monoclonal Antibody cA2[tiab] OR cA2, Monoclonal Antibody[tiab] OR MAb cA2[tiab] OR Infliximab-abda[tiab] OR Renflexis[tiab] OR Infliximab-dyyb[tiab] OR Inflectra[tiab] OR Remicade[tiab] OR infliximab[tiab] OR **Certolizumab Pegol[Mesh]** OR Certolizumab[tiab] OR Cimzia[tiab] OR CDP870[tiab] OR CDP 870[tiab] OR **Ustekinumab[Mesh]** OR Ustekinumab[tiab] OR Stelara[tiab] OR CNTO 1275[tiab] OR CNTO-1275[tiab]	1.845.949

#6	**Azathioprine[Mesh]** OR Azothioprin*[tiab] OR Imurel[tiab] OR Imuran[tiab] OR Immuran[tiab]	14.726
#7	#5 AND #6	3.976
	Filter	
#8	#4 AND #7	622
#9	animals[mh] NOT humans[mh]	4.695.738
#10	#8 NOT #9	618
#11	(systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR "cochrane database syst rev"[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR "research synthesis"[tiab] OR "research integration"[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT "psycinfo database"[tiab]) OR pubmed[tiab] OR scopus[tiab] OR "web of science"[tiab] OR "data synthesis"[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR "meta-analysis as topic"[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	574.647
#12	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR "Double-Blind Method"[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])	1.452.556
#13	#11 OR #12	1.900.214
#14	#10 AND #13	171
#15	#14 Publication date 2012- Date of search, Articles in English, German	92
	Date of search 12.05.20	
	(("Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical	

	trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])) OR ((systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt]))) AND ((((Biological Therapy[Mesh] OR Biological Therapies[tiab] OR Therapies, Biological[tiab] OR Therapy, Biological[tiab] OR Biologic Therapy[tiab] OR Biologic Therapies[tiab] OR Therapies, Biologic[tiab] OR Therapy, Biologic[tiab] OR Biotherapy[tiab] OR Biotherapies[tiab] OR "Biological Products"[Mesh] OR biological[tiab] OR Anti TNF[tiab] OR Anti-tnf[tiab] OR Adalimumab[Mesh] OR Adalimumab[tiab] OR Humira[tiab] OR Adalimumab-adbm[tiab] OR Amjevita[tiab] OR Adalimumab-atto[tiab] OR Cyltezo[tiab] OR D2E7 Antibody[tiab] OR Antibody, D2E7[tiab] OR golimumab [Supplementary Concept] OR Simponi OR golimumab[tiab] OR "vedolizumab" [Supplementary Concept] OR vedolizumab[tiab] OR Entyvio[tiab] OR MLN0002[tiab] OR Infliximab[Mesh] OR Monoclonal Antibody cA2[tiab] OR cA2, Monoclonal Antibody[tiab] OR MAb cA2[tiab] OR Infliximab-abda[tiab] OR Renflexis[tiab] OR Infliximab-dyyb[tiab] OR Inflectra[tiab] OR Remicade[tiab] OR infliximab[tiab] OR Certolizumab Pegol[Mesh] OR Certolizumab[tiab] OR Cimzia[tiab] OR CDP870[tiab] OR CDP 870[tiab] OR Ustekinumab[Mesh] OR Ustekinumab[tiab] OR Stelara[tiab] OR CNTO 1275[tiab] OR CNTO-1275[tiab]) AND (Azathioprine[Mesh] OR Azothioprin*[tiab] OR Imurel[tiab] OR Imuran[tiab] OR Immuran[tiab])) AND (((Crohn Disease[Mesh] OR Crohn disease[tiab] OR Crohn's Enteritis[tiab] OR Regional Enteritis[tiab] OR Crohn's Disease[tiab] OR Crohns Disease[tiab] OR Inflammatory Bowel Disease 1[tiab] OR Enteritis, Granulomatous[tiab] OR Granulomatous Enteritis[tiab] OR Enteritis, Regional[tiab] OR Ileocolitis[tiab] OR Colitis, Granulomatous[tiab] OR Granulomatous Colitis[tiab] OR Ileitis, Terminal[tiab] OR Terminal Ileitis[tiab] OR Ileitis, Regional[tiab] OR Regional Ileitides[tiab] OR Regional Ileitis[tiab]) OR (Colitis, Ulcerative[Mesh] OR colitis, ulcerative[tiab] OR ulcerative colitis[tiab] OR colitis ulcerosa[tiab] OR Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab] OR	

	Inflammatory Bowel Disease, Ulcerative Colitis Type[tiab] OR acute severe ulcerative colitis[tiab] OR ASUC[tiab])) OR (Inflammatory Bowel Diseases[Mesh] OR Inflammatory Bowel Disease[tiab] OR Bowel Diseases, Inflammatory[tiab] OR IBD[tiab]))) NOT (animals[mh] NOT humans[mh]))	

Ergebnis und PRISMA Flow Chart: AG 6 – 2



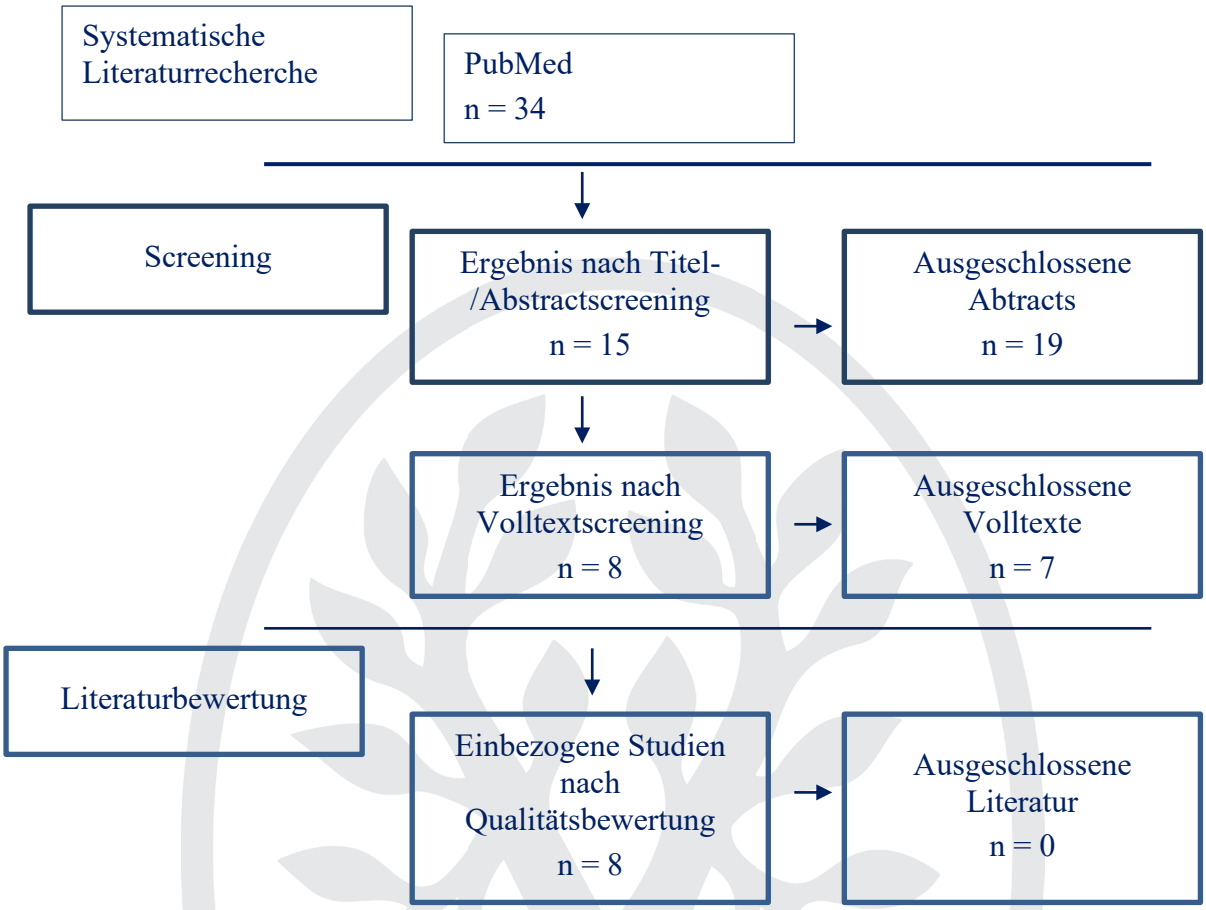
Recherche in PubMed: AG 7 – 1

	Patient	Intervention	Comparator	Outcome
Psychotherapie	Patient mit CED	Psychotherapie	keine Psychotherapie	QoL

Date Run: 27.04.20

Search	Hits
(((((((crohn disease[MeSH Terms]) OR crohn disease[Title/Abstract]) OR crohn's disease[Title/Abstract]) OR Inflammatory Bowel Disease 1[Title/Abstract]) OR Colitis, Granulomatous[Title/Abstract]) OR Ileitis, Terminal[Title/Abstract]) OR Terminal Ileitis[Title/Abstract] OR (inflammatory bowel disease[Title/Abstract]) OR inflammatory bowel diseases[Title/Abstract]) OR inflammatory bowel disease[mh:noexp]) AND ((Psychotherapy[MeSH Terms]) OR Psychotherapy[Title/Abstract] OR Logotherapy[Title/Abstract] OR Therapies, Schema[Title/Abstract] OR Schema Therapy[Title/Abstract] OR Psychotherapists, Clinical[Title/Abstract] OR Psychotherapist, Clinical[Title/Abstract] OR Psychotherapist[Title/Abstract] OR Psychotherapists[Title/Abstract] OR Psychotherapies[Title/Abstract]) Filters: Randomized Controlled Trial, Systematic Reviews, From 2012/06/02 to 2020/12/31, Humans	33

Ergebnis und PRISMA Flow Chart: AG 7 – 1



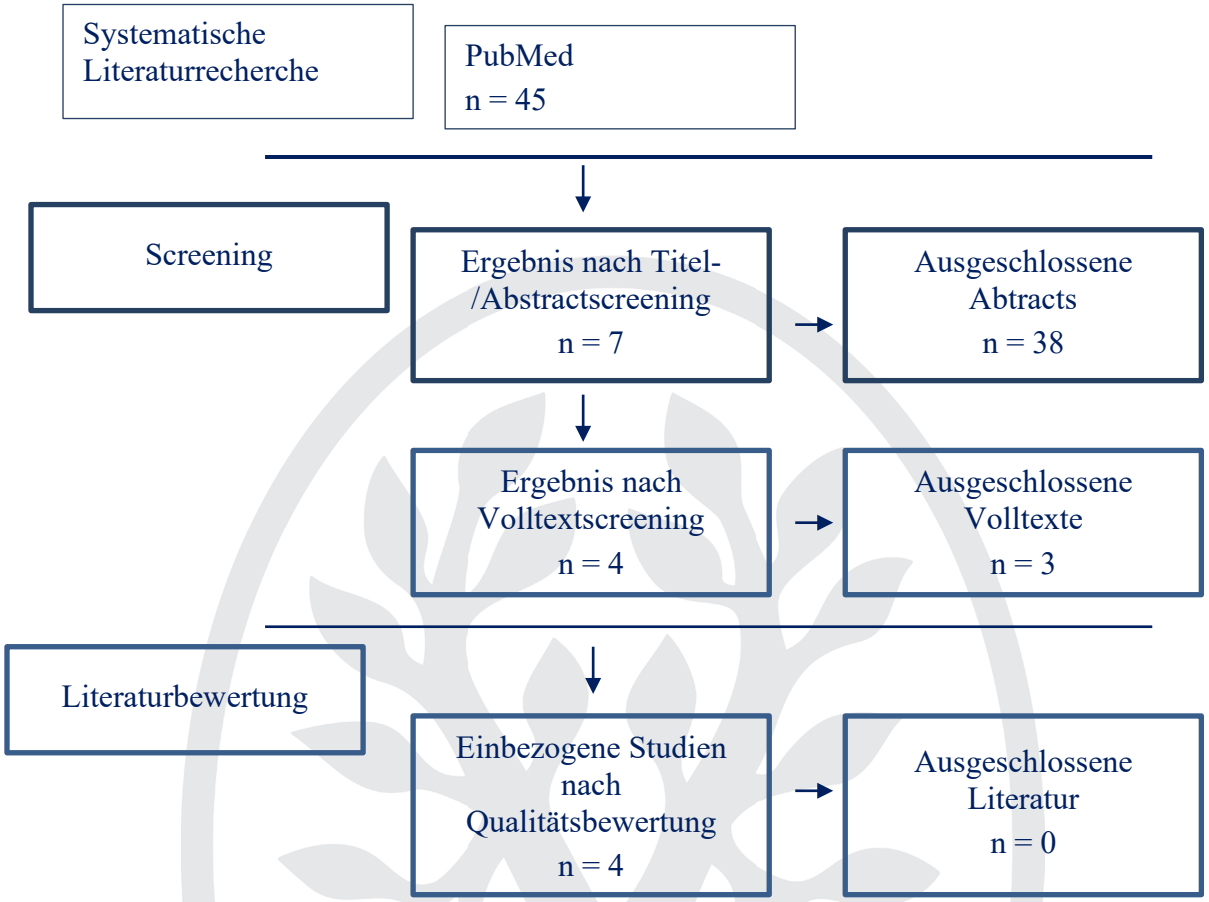
Recherche in PubMed: AG 7 – 2

	Patient	Intervention	Comparator	Outcome
Ernährung	Patient mit CED	Ernährungstherapie	keine Ernährungstherapie	Remissionsinduktion

Date Run: 27.04.20

Search	Hits
(Inflammatory Bowel Disease [mh:noexp] OR Inflammatory Bowel Disease[Title/Abstract] OR Inflammatory Bowel Diseases[Title/Abstract] OR Crohn Disease[MeSH Terms] OR Crohn Disease[Title/Abstract] OR Crohn's Disease[Title/Abstract] OR Crohns Disease[Title/Abstract] OR Inflammatory Bowel Disease 1[Title/Abstract] OR Colitis, Granulomatous[Title/Abstract] OR Ileitis, Terminal[Title/Abstract] OR Terminal Ileitis[Title/Abstract]) AND (((((((nutrition therapy[MeSH Terms]) OR nutrition therapy[Title/Abstract]) OR diet therapy[Title/Abstract]) OR nutritional support[Title/Abstract]) OR Medical Nutrition Therapy[Title/Abstract]) OR Nutrition Therapy, Medical[Title/Abstract])) Filters: Randomized Controlled Trial, Systematic Reviews, From 2012/06/02 to 2020/12/31, Humans	44

Ergebnis und PRISMA Flow Chart: AG 7 – 2



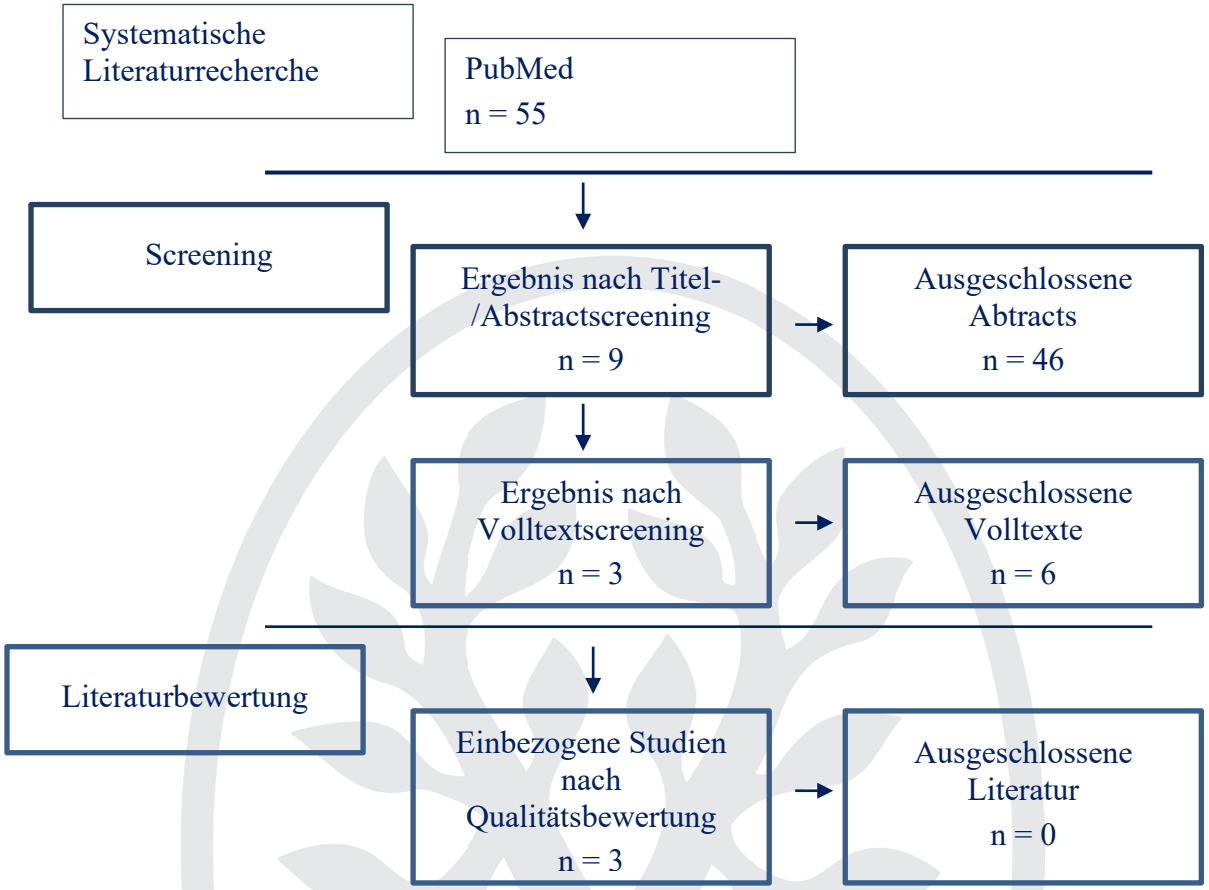
Recherche in PubMed: AG 7 – 3

	Patient	Intervention	Comparator	Outcome
Komplementär	Patient mit CED	Komplementärtherapie	keine Komplementärtherapie	Remissionsinduktion

Date Run: 27.04.20

Search	Hits
(((((((crohn disease[MeSH Terms]) OR crohn disease[Title/Abstract]) OR crohn's disease[Title/Abstract]) OR Inflammatory Bowel Disease 1[Title/Abstract]) OR Colitis, Granulomatous[Title/Abstract]) OR Ileitis, Terminal[Title/Abstract]) OR Terminal Ileitis[Title/Abstract] OR (inflammatory bowel disease[Title/Abstract]) OR inflammatory bowel diseases[Title/Abstract]) OR inflammatory bowel disease[mh:noexp]) AND ((Complementary Therapies[MeSH Terms]) OR Complementary Therapies[Title/Abstract] OR Alternative Medicine[Title/Abstract] OR Alternative Therapies[Title/Abstract] OR Therapies, Alternative[Title/Abstract] OR Complementary Medicine[Title/Abstract] OR Therapies, Complementary[Title/Abstract]) Filters: Randomized Controlled Trial, Systematic Reviews, From 2012/06/02 to 2020/12/31, Humans	55

Ergebnis und PRISMA Flow Chart: AG 7 – 3



Interessenkonflikt-Erklärungen – Tabellarische Zusammenfassung

1 Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z. B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung

2 Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)

3 Honorare für Vortrags- und Schulungstätigkeiten im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung

4 Bezahlte Autoren-/oder Coautorenschaft im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung

5 Forschungsvorhaben/Durchführung klinischer Studien: finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung vonseiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung

6 Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz): Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft

7 Indirekte Interessen: Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung

Stand November 2020

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
Aden, Konrad	-	Takeda, Jansen	Jannsen	-	Pfizer	-	Mitglied: Mitglied der DGVS sowie des Kompetenznetz Darmerkrankungen Schwerpunkt: Präzisionsmedizin bei chronisch entzündlichen Darmerkrankungen Federführung: keine Persönlich: keine	gering
Anlauf, Martin	Novartis Pharma	Ipsen Pharma	Novartis Pharma und Ipsen Pharma	-	-	-	Mitglied: Deutsche Gesellschaft Pathologie Berufsverband Pathologie Vorstand Patientengruppe NET Schwerpunkt: Neuroendokrine Neoplasien Federführung: Fortbildungen Neuroendokrine Neoplasien und Gastroupdates	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory Board) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16,

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							Persönlich: -	2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15
Atreya, Raja	Boehringer-Ingelheim InDex Pharmaceuticals	Abbvie Biogen Janssen-Cilag	Abbvie Biogen DrFalk Pharma Ferring Janssen-Cilag MSD Pfizer Roche Pharma Takeda Pharma	-	Biogen InDex Pharmaceuticals Takeda Pharma	-	Mitglied: Sprecher Beirat Grundlagenforschung, Deutsche Morbus Crohn/Colitis ulcerosa Vereinigung e.V. (DCCV) Mitglied: Vertreter für Deutschland (National Representative) in der European Crohn's and Colitis Organization Mitglied: Vorstandsmitglied Kompetenznetz Darmerkrankungen Mitglied: Mitglied Expertenbeirat Stiftung LebensBlicke Mitglied: Board GISG	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							Schwerpunkt: - Federführung: Arzt-Patienten-Seminar CED des Universitätsklinikums Erlangen Persönlich: Nein	
Baretton, Gustavo	Roche AG Merck Serono GmbH BMS Bristol Myers Squibb Hoffmann-La Roche AstraZeneca Roche Diagnostics BMS Roche Roche Merck Serono GmbH Astra Zeneca	- - - Roche Pharma AG Hoffmann La Roche BMS BMS Roche Roche BMS Amgen Novartis Roche BMS	- -	Roche Pharma AG	Roche	-	Mitglied: DGP, BV Deutscher Pathologien Schwerpunkt: Tumorpathologie Biomarker Federführung: - Persönlich: entfällt	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
	Pfizer Deutschland GmbH	MSD Sharp & Dohme GmbH						
Bettenworth, Dominik	Keine	Takeda AbbVie Amgen Janssen	Falk Foundation AbbVie MSD Pfizer Pharmacosmos Vifer Vifer Tillotts Janssen	-	-	Keine	Mitglied: Vorsitzender der Deutschen Arbeitsgemeinschaft für CED Mitglied: Mitglied und Vorsitzender des Nachwuchs-Komittees der Europäischen Crohn & Colitis Organisation Mitglied: Nationaler Repräsentant für Deutschland bei der Europäischen Crohn & Colitis Organisation Mitglied: Gutachter für Kongressabstracts und Forschungsanträge, Europäische Crohn & Colitis Organisation Mitglied: Gutachter für Kongressabstract der DGVS	Moderat (Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							Schwerpunkt: Diagnostik und Therapie von intestinaler Entzündung, intestinaler Fibrose sowie Patienten mit chronisch entzündlichen Darmerkrnankungen Federführung: Keine Persönlich: Keine	
Blödt, Susanne	Nein	Nein	CIEE-Non-profit organization	Keine	Keine	Keine	Mitglied: - Schwerpunkt: EBM, Leitlinien, Onkologie, Patientenperspektive- Federführung: - Persönlich: -	Keine
Blumenstein, Irina	AbbVie Deutschland GmbH Janssen-Cilag GmbH Pfizer GmbH	AbbVie Deutschland GmbH Amgen GmbH Celltrion GmbH	DGVS AbbVie Deutschland GmbH Biogen GmbH	Keine mit finanziellen Zuwendungen	Keine mit finanziellen Zuwendungen	Keine	Mitglied: Kongresssekretärin DGVS Jahrestagung Schwerpunkt: Verbesserung der Behandlungsrealität von CED Patient:innen	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory Boards)

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
	Takeda Pharma GmnbH	Janssen-Cilag GmbH Pharmacosmos GmbH Shire GmbH Takeda Pharma GmbH Tillots Pharma GmbH	Takeda Pharma GmbH CED Service GmbH Ferring GmbH Fraunhofer IME Fresenius GmbH Janssen-Cilag GmbH Pfizer Pharma GmbH Pharmacosmos GmbH RG GmbH Streamed up! Sonstige (Krankenhäuser, unabhängige				Chronisches Darmversagen Federführung: Zertifikatsseminar der DGVS Persönlich: keine	→Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
			Organisationen)					
Bläker, Michael	Abbvie Janssen MSD Takeda	Janssen MSD Takeda	Abbvie Falk Ferring Olympus	-	-	-	Mitglied: Hamburger AG Gastroenterologie Mitglied: AG Niedergelassener Gastroenterologen Hamburg Schwerpunkt: CED, Endoskopie Federführung: s.o. Persönlich: -	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15
Bokemeyer, Bernd	-	Abbvie MSD Shire	Abbvie Ferring MSD	-	Abbvie Ferring Given Imaging	-	Mitglied: - Schwerpunkt: - Federführung: -	Moderat (Zugehörigkeit zu Advisory

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
		Ferring Hospira Takeda Pfizer Janssen Boehringer Amgen	Merckle Falk Shield Therapeutics Pfizer Celltrion Takeda Janssen Amgen		Janssen Takeda Pfizer		Persönlich: -	Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15
Brechmann, Thorsten	Keine	Keine	AbbVie, Takeda, Kompetenznetz CED	Keine	Roche	Keine	Mitglied: DGVS, Kommission für Gesundheitsökonomie und medizinische Klassifikation, Ethikkommission der RUB, Kompetenznetz CED, DCCV. Schwerpunkt: Chronisch-entzündliche Darmerkrankungen,	Gering (Vortragstätigkeiten und Industriemittel)

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							Endoskopie, bildgebende Verfahren, Funktionsdiagnostik. Federführung: CED-Symposium Rhein-Ruhr. Gastroseminar. Persönlich: Keine.	
Bufler, Philip	DFG verschiedene wissenschaftliche Zeitschriften	Promethera GMP Orphan	AbbVie Nutricia Kompetenznetz CED	Verschiedene Autor/Coautorenschaften wissenschaftlicher Beiträge	Beteiligung an verschiedenen klinischen Studien PIBD-NET	Keine	Mitglied: keine Schwerpunkt: Immunologie Chronisch-entzündliche Darmerkrankungen Pädiatrische Gastroenterologie Experimentelle Hepatologie Federführung: Regelmäßige Fortbildungsveranstaltung für Berliner Kinderärzte und Kindergastroenterologen Persönlich: keine	Gering (Vortragstätigkeiten und Industriemittel, keine relevanten Beratertätigkeiten und Advisory Boards)

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
Böcker, Ulrich	Schlichtungs-Stelle für Arzthaftpflicht-fragen Hans-Böckler-Allee 3 30173 Hannover	Janssen-Cilag GmbH Johnson & Johnson Platz 1 41470 Neuss Takeda Pharma Vertrieb GmbH & Co. KG Jägerstraße 27 10117 Berlin	Takeda Pharma Vertrieb GmbH & Co. KG Jägerstraße 27 10117 Berlin Nutricia GmbH Allee am Röthelheimpark 11 91052 Erlangen Ärztekammer Berlin Shire Friedrichstrasse 149 10117 Berlin AbbVie Deutschland GmbH&CO KG Mainzer Straße 81 65189 Wiesbaden	-	-	-	Mitglied: Gastro Liga e.V. Friedrich-List-Str. 13, 35398 Gießen: Beiratsmitglied Mitglied: DCCV e.V., Reinhardtstr. 18, 10117 Berlin: Mitglied Mitglied: Verband der leitenden Krankenhausärzte Deutschlands, Haus der Ärzteschaft Tersteegenstr. 9, 40474 Düsseldorf: Stv. Vorsitzener Landesverband Berlin-Brandenburg Mitglied: Kompetenznetz Darmerkrankungen, Hopfenstr. 60 Â· 24103 Kiel: Mitglied Mitglied: Weitere Mitgliedschaften: Ärztekammer, AGA, Deutsche Gesellschaft für Innere Medizin (DGIM), Deutsche	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
			Falk Foundation Leinenweber-straße 5 79108 Freiburg				Gesellschaft f. Verdauungs- u. Stoffwechselkrankheiten und Berufsverband, Deutsche Krebsgesellschaft, Südwestdeutsche Gesellschaft für Innere Medizin, Deutsche Leberstiftung, Arbeitsgemeinschaft Leitender Gastroenterologischer Krankenhausärzte (ALGK) e.V., Verein gastroenterologisch tätiger Internisten Berlin Schwerpunkt: Chronisch entzündliche Darmerkrankungen Federführung: Interne und externe Fortbildungen in der Funktion des Chefarztes der Klinik	

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							für Gastroenterologie, Diabetologie und Hepatologie, Vivantes Klinikum Neukölln, u.a. Crohn-Colitis-Tag, Klinische Hepatologie in Neukölln Persönlich: -	
Dignaß, Axel	Janssen Tillotts Pfizer	MSD Abbvie Takeda Celgene/ BMS Pfizer Janssen Roche, Gilead, Pharmacosmos	Falk Pfizer Takeda Janssen Abbvie, MSD	-	Pfizer, Abbvie, Janssen, Gilead, Celgene/BMS, Falk	-	Mitglied: Vorstand DGVS, UEG Mitglied DGIM, ECCO, DKG, MDGG Schwerpunkt: - Federführung: - Persönlich: -	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8,

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
								6.15
Däbritz, Jan	Abbvie Sozialgericht Leipzig Sozialgericht Mecklenburg-Vorpommern	Shire Amgen	Abbvie Charité Universitäts-medizin Berlin Ferring Shire Klinikum Ernst von Bergmann Potsdam Kompetenz-netz Darmer-krankungen Gesellschaft für Pädiatrische Gastroenterologie und Ernährung e. V. Nestlé	Abbvie	Centogene	-	Mitglied: Gesellschaft für Pädiatrische Gastroenterologie und Ernährung (GPGE) Mitglied: Deutsche Gesellschaft für Kinder- und Jugendmedizin (DGKJ) Mitglied: Crohn-Colitis-Netz Mecklenburg-Vorpommern Mitglied: Kompetenznetz Darmerkrankungen Mitglied: Deutscher Hochschulverband (DHV) Schwerpunkt: Klinische Forschung: Chronisch entzündliche Darmerkrankungen	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							(insb. Morbus Crohn); Biomarker der intestinalen Entzündung; Ernährung; Arzneimittel für neuartige Therapien (ATMP); klinische Studien (IITs und Industrie-initiierte Studien); Versorgungsforschung (Transitionsmedizin) Schwerpunkt: Translationale Forschung: mukosale Immunität; angeborene Immunantwort; Epigenetik; Mikrobiom; Immunmodulation; experimentelle Modelle der intestinalen Entzündung Federführung: Heiner-Brunner-Seminar der Gesellschaft für	

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							Pädiatrische Gastroenterologie und Ernährung (GPGE) Federführung: Jahrestagung der Gesellschaft für Pädiatrische Gastroenterologie und Ernährung (GPGE) Federführung: Jahrestagung der Norddeutschen Gesellschaft für Kinder und Jugendmedizin (NDGKJ) Federführung: Internationales Symposiums & Workshop „Inborn Errors of Metabolism" Rostock Federführung: CED-Kurs der Gesellschaft für Pädiatrische Gastroenterologie und Ernährung (GPGE)	

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							Persönlich: Keine	
Ehehalt, Robert	Nur im Rahmen eines advisory boards (s.u.)	MSD, Sandoz, Janssen, Ferring, Takeda, Pfizer, Biogen, Amgen, Tillots,Celgene, Celltrion, Roche, Sandoz	Falk, Janssen, Abbvie, MSD, Ferring, Norgine, Takeda, Shield, Mundipharma, Pfizer, Vifor, Ardeypharm, Novartis, Microbiotika, Biogen, Ferring, Norgine, Celgene, Recordati, Fresenius, Tillotts, Diasorin, Ethicon, Innocur, Celltrion	Schattauer Elsevier Degruyter	IQVIA, Quintilles,FGK,Anfomed,Celgene,MedPharmTec,Falk,Janssen,Parexel,Biogen, Abbvie, Roche, Gilead, Celgene, InDexPharmaceutics, Theravance, Innocur	Boardmitglied bei Defensins therapeutics	Mitglied: DGVS, DCCV, SWDGG, DDG, BNG, Kompetenznetz Darmerkrankungen, ECCO, AGA Schwerpunkt: klinische Forschung (Medikamentenstudien Phase II-IV) Federführung: nicht federführend Persönlich: keine	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
Germer, Christoph-Thomas	Keine	PEG Einkaufsgenossenschaft	MED-UpDate GmbH	Keine	Keine	Keine	Mitglied: Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie Vorstandsmitglied/Präsident Mitglied: - Schwerpunkt: Leitlinienkoordinator Leitlinie Divertikulitis Federführung: Wissenschaftlicher Leiter DGAV-Chirugie UpDate Persönlich: keine Beziehungen	Gering (Vortragstätigkeiten, kein relevantes Advisory Board)
Gross, Cordula	Keine	Keine	Keine	Keine	Keine	Keine	Mitglied: DCCV e. V. Schwerpunkt: - Federführung: - Persönlich: -	Keine
Hartmann, Franz	Abbvie	Gastroliga	Recordati DGpharMed	Springer: Chronisch entzündl. Darmerkrank -	-	-	Mitglied: Gastroliga Vorstand Schwerpunkt: CED Federführung: -	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
				ungen 3. Auflage			Persönlich: -	Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15
Hartmann, Petra	Pfizer Janssen		Kompetenzn etz Darmerkrankungen AbbVie, Janssen, Takeda, Tillotts, Amgen	ECCO	Keine	Keine	Mitglied: keine Schwerpunkt: keine Federführung: Versorgungsassistenz CED Persönlich: keine	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12,

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
								2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15
Helwig, Ulf	-	MSD Amgen Biogen Takeda Janssen	Kompetenznetz MSD Abbvie Takeda Janssen Pfizer Gefis Norgine Shield Biogen - -	Abbvie Abbvie Abbvie Takeda Takeda Takeda	Robarts Shield KOmpetenznez Abbvie Janssen	-	Mitglied: DGVS Mitglied: DGIM Mitglied: BNG Mitglied: Kompetenznetz Darmerkankungen Mitglied: GISG Mitglied: IBUS Mitglied: BDI Mitglied: NDGG Mitglied: BNFI Schwerpunkt: Sonografie bei CED Schwerpunkt: Therapiemonitoring bei CED Schwerpunkt: Diagnostik bei CED	Moderat (Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							Schwerpunkt: Therapieadhärenz Federführung: Vorlesung Universität Kiel Federführung: Vorlesung Universität Oldenburg Federführung: Studentenkurs Universität Kiel Federführung: Fortbildungsveranstaltung CEDregional Federführung: - Persönlich: -	
Herrlinger, Klaus	Schlichtungsstelle für Arzthaftungsfragen	-	Falk Foundation	-	Asklepios ProResearch	-	Mitglied: DGVS DGIM DGI DDG NDDG Schwerpunkt: CED, Immunsuppression, Pharmakogenetik Federführung: CED kontrovers Heidberger Gastro Seminar Heidberger Hausärzteseminar	Gering (Vortragstätigkeiten und Industriemittel, keine relevanten Beratertätigkeiten)

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							Persönlich: -	
Hoffmann, Jörg C.	-	Amgen Astra Sandoz/Hexal Janssen Pfizer Steigerwald	Takeda Kompetenznetz CED Janssen Falk	Takeda	Abbvie Pfizer Takeda Janssen	-	Mitglied: DCCV Schwerpunkt: Äœbersetzung Harrison's Internal Medicine Schwerpunkt: Herausgeber CED Manual 3. Auflage, früher Thieme, jetzt Springer Federführung: - Persönlich: -	Moderat (Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15
Häuser, Winfried	IQWIG	Nein	Knappschaftskrankenhaus Püttlingen Bioevents (Kongressorganisation)	Institut de la Conference Hippocrate (Servier) Ecomed Verlag	Keine	Keine	Mitglied: Beirat der Deutschen Schmerzgesellschaft Mitglied: - Mitglied: Mitglied der Deutschen Gesellschaft für Psychosomatische	Gering (Vortragstätigkeiten und Autorenschaften, keine relevanten Beratertätigkeiten)

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
			Bioevents (Kongressorganisation)				Medizin und Psychotherapie Mitglied: Mitherausgeber der Pain Palliative and Supportive Care Group der Cochrane Collaboration Schwerpunkt: Versorgungsforschung; Systematische Übersichtsarbeiten; Patienten-Surveys Federführung: Nein Persönlich: Nein	
In der Smitten, Susanne	-	-	-	-	-	-	Mitglied: Mitgliedschaft in der Deutschen Morbus Crohn / Colitis ulcerosa Vereinigung (DCCV), Inselstraße 1, 10179 Berlin Schwerpunkt: - Federführung: - Persönlich: -	Keine

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
Juchems, Markus	-	-	-	Georg Thieme Verlag	Giotto Devicor Siemens Healthcare GmbH Bayer Vital GmbH Bracco Imaging Deutschland GmbH Terumo Deutschland GmbH Sirtex Medical Europe GmbH PharmaCept GmbH Canon Medical Systems GmbH i-SOLUTIONS Health GmbH Roche Pharma AG Portola Invoices c/o Clinverse Inc.	-	Mitglied: Vorstand AG Gastro-/Abdominaldiagnostik Schwerpunkt: - Federführung: - Persönlich: -	Keine
Kaltz, Birgit	-	-	DGVS	-	-	-	Mitglied: Kompetenznetz Darmerkrankungen Mitglied: DCCV e.V. Schwerpunkt: -	Keine

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							Federführung: - Persönlich: -	
Kienle, Peter	-	Takeda, Ethicon, Aesculap	Falk Foundation, Ethicon, Janssen, Takeda, Abbvie, Mundipharma, Stryker, Röchling	-	-	-	Mitglied: Mitglied DGVS, Mitglied DGAV, Mitglied Kompetenznetz Darmerkrankungen, Mitglied ECCO, Mitglied DCCV: Sprecher im Beirat für Chirurgie Schwerpunkt: Chirurgie bei CED Federführung: keine Persönlich: keine	Keine
Klaus, Jochen	Abbvie	Falk	Takeda	Janssen	Pfizer	Pharmacosmos	Mitglied: - Schwerpunkt: - Federführung: - Persönlich: -	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory Boards) →Enthaltung bei

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
								Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15
Kreis, Martin	Fa. Coloplast	Takeda	Coloplast Falk Foundation Johnson & Johnson Janssen Takeda	Keine	Takeda	Keine	Mitglied: Vorsitzender Deutsche Gesellschaft für Koloproktologie Mitglied: Vorsitzender Berliner Chirurgische Gesellschaft Mitglied: 2. Vorsitzender Berliner Krebsgesellschaft Schwerpunkt: postoperativer Ileus chronisch entzündliche Darmerkrankungen Chirurgische Onkologie	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6,

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							postoperative Funktionsstörungen Federführung: Nein Persönlich: Nein	5.7, 5.19, 6.8, 6.15
Kroesen, Anton-J.	-	-	Falk Abbvie	-	-	-	Mitglied: DGAV DGVS DGCH Schwerpunkt: Veranstaltung von Fortbildungen fachlicher Natur ohne Produktbezug Federführung: - Persönlich: -	Gering (Vortragstätigkeiten)
Kucharzik, Torsten	Janssen Gilead AbbVie - Takeda	Janssen - Takeda Pharma Amgen Biogen Hospira Mundipharma AbbVie	Dr. Falk Pharma AbbVie MSD	Zahlreiche Publikationen zum Thema CED in peer-reviewed Journalen, die in PubMed unter "Kucharzik" abrufbar sind.	Takeda	Keine	Mitglied: NDGG, Vorsitzender seit 2/2018 Mitglied: DGVS Beiratsmitglied Mitglied: DGIM Mitglied: BDI Mitglied: IBUS (finanziert u.a. durch AbbVie, Janssen, Takeda). Keine direkten	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
				Zahlreiche Buchprojekte zum Thema CED, z.B. eigenes Buchprojekt ("Therapie chronisch entzündlicher Darmerkrankungen" als Mitherausgeber im de Gruyter Verlag			Zuwendungen, diese gehen ausschließlich an den Verein. Mittel werden zur Ausbildung im Darmultraschall bei CED genutzt. Mitglied: Kompetenznetz Darmerkrankungen, Vorstandsmitglied Mitglied: AGA Mitglied: ECCO (Mitglied des GuiCom, ehemals Mitglieder des EduCom) Mitglied: DCCV Beiratsmitglied Schwerpunkt: CED, Bildgebende Diagnostik, Darmsonographie Federführung: DGVS Gastroenterologie Intensivkurs	2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							Federführung: Falk Gastroenterologie Symposium Lüneburg Federführung: CED kontrovers in Hamburg und Stuttgart (finanziert durch Dr. Falk GmbH) Persönlich: keine	
Kühbacher, Tanja	-	Takeda ABBVIE MSD Janssen Arena Mundipharma Tilliotts	Allmiral Takeda Ferring Falk Mundipharma Tilliots MSD ABBVIE Janssen	Arena Takeda Galapagos	-	-	Mitglied: DGVS Mitglied: DGIM Mitglied: AGA Mitglied: NDGG Mitglied: Stiftung Darmerkrankungen ehrenamtlicher Vorstand Mitglied: DCCV Mitglied: ALGK Mitglied: VLk Mitglied: ECCO Schwerpunkt: Mikrobiom Biologika Therapien,	Moderat (Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							Signaltransduktion, klinische Studien Federführung: - Persönlich: -	
Langhorst, Jost	Medizin Verlag Stuttgart Dr. Willmar Schwabe Repha GmbH Ferring Sanofi	-	Falk Foundation Arktibiotic Repha GmbH Celgene Dr. Wllmar Schwabe AbbVie Takeda	Nein	Dr. Willmar Schwabe Falk Foundation SteigerwaldArzneimittelwerke/Bayer Techlab	Nein	Mitglied: Leitlinienbeauftragter der Gesellschaft für Phytotherapie und der Deutschen Gesellschaft für Naturheilkunde, Sprecher der AG Psychosomatik in der Gastroenterologie der Deutschen Gesellschaft für Gastroenterologie, Deutsche Schmerzgesellschaft, Deutsches Kollegium für Psychosomatische Medizin Schwerpunkt: Mind/Body Medicine/Ordnungstherapie klassische Naturheilkunde und	Moderat (Beratertätigkeiten) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							traditionellen europäischen Heilverfahren ganzheitliche Prävention Phytotherapie chronisch entzündliche Darmerkrankungen (CED) Reizdarmsyndrom Fibromyalgiesyndrom non-invasive diagnostische Verfahren in der Gastroenterologie Federführung: Zusatzbezeichnung Naturheilkunde an den Kliniken Essen- Mitte EXPERTE IM FACHGEBIET im Bereich KOMPLEMENTÄRME DIZIN und Psychosomatik für die ZERTIFIZIERUNG CHRONISCH ENTZÜNDLICHE	

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							DARMERKRANKUNGEN der DEUTSCHEN GESELLSCHAFT FÜR VERDAUUNG UND STOFFWECHSELERKRANKUNGEN - DGVS Persönlich: nein	
Leifeld, Ludger	Keine	Keine	Bezahlte Vortragstätigkeit für Falk, Takeda, Abbvie, Fujinon, Janzen	Siehe pubmed	Prognos Studie	Keine	Mitglied: DGVS, NDGG, BVDG, DGI, DCCV, ALGK, DGIM, Kopetenznetz CED Schwerpunkt: Gastroenterologie Federführung: regelmäßig Persönlich: keine	Gering (Vortragstätigkeiten und Industriemittel)
Lynen Jansen, Petra	Nein	Nein	Lehrauftrag RWTH Aachen	Leitlinienpublikationen der DGVS	Nein	Keine	Mitglied: nein Schwerpunkt: Leitlinien Federführung: nein Persönlich: nein	Gering (Vortragstätigkeiten)

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
Lügering, Andreas	-	Abbvie Janssen Takeda MSD	Janssen Abbvie Falk MSD Takeda	Abbvie	-	-	Mitglied: DGVS, ECCO, DGIM, DGMIM, BNG, KN-CED Schwerpunkt: - Federführung: - Persönlich: -	Moderat (Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15
Maaser, Christian	-	Abbvie Takeda Biogen -	Abbvie Takeda -	Abbvie	Abbvie	Keine	Mitglied: DCCV/Beirat Mitglied: GISG/Sprechergremium Mitglied: IBUS/Vorsitzender Schwerpunkt: Darmsonografie bei CED Federführung: nein	Moderat (Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12,

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							Persönlich: -	2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15
Niess, Jan Hendrik	Nein	Abbvie Takeda Jannsen MSD Pfizer	Nein	Nein	Vifor	Nein	Mitglied: Schweizer Gesellschaft für Gastroenterologie Mitglied: Deutsche Gesellschaft für Gastroenterologie Mitglied: Kompetenznetz CED Mitglied: IBD Net Mitglied: European Crohn and Colitis Schwerpunkt: zahlreiche Publikationen zu translationalen Aspekten der chronisch entzündlichen Darmerkrankungen Federführung: nein	Moderat (Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							Persönlich: nein	
Ockenga, Johann	Sandoz Deutschland/ HEXAL AG Industriestr. 25 D-83607 Holzkirchen	Fresenius Kabi GmbH	Dr. Karl Schulze, Hannover ifi Institut für Infektiologie & Hepatologie Merz Aerztekammer Niedersachsen Falk Foundation e.v. GFO Kliniken Klinikum WHV Uniklinikum Essen Falk Foundation e.v.	-	Innovationsfond, GBA; Universität Köln	-	Mitglied: Präsident der Deutschen Gesellschaft für Ernährungsmedizin Mitglied: Task Force Quality of Care, UEG Mitglied: Education and clinical practice committee, European Society of Enteral and Parenteral Nutrition Schwerpunkt: - Federführung: Erstellung Leitlinie Ernährung bei Pankreaserkrankung der Deutschen Gesellschaft für Ernährungsmedizin Persönlich: -	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
Ott, Claudia	Takeda Janssen-Cilag	MSD Janssen-Cilag	Falk Foundation Falk Foundation AbbVie Abbvie Abbvie Abbvie Abbvie Abbvie Abbvie Abbvie Abbvie Abbvie MSD MSD MSD MSD MSD MSD Janssen-Cilag Janssen-Cilag	-	-	-	Mitglied: Gesellschaft für Gastroenterologie in Bayern, Beirätin Mitglied: DCCV, ärztliche Beirätin Schwerpunkt: Epidemiologie bei CED Federführung: - Persönlich: -	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
			Janssen-Cilag					
Posovszky, Carsten	Nestle Health Science Deutschland GmbH, Frankfurt Shire Deutschland GmbH	Takeda Deutschland Shire Deutschland Shire Deutschland GmbH	Firma Abbie Deutschland GmbH, Wiesbaden; Firma Nutricia GmbH, Erlangen; Technomatix - Medical Gmbh Pharmacosmos GmbH Wiesbaden Shire Austria GmbH part of Takeda Group Takeda Pharma AG, Schweiz Glattpark-Opfikon RG Gesellschaft	Dr.Falk Pharma GmbH Shire Deutschland GmbH Cogitando GmbH	Shire Deutschland GmbH	-	Mitglied: 2. Vorstand der Gesellschaft für pädiatrische Gastroenterologie (GPGE) e.V. Mitglied: Deutsche Morbus Crohn und Colitis Ulzerosa Vereinigung (DCCV) e.V. Mitglied: Deutsche Gesellschaft für Kinder- und Jugendmedizin (DGKJ) Mitglied: Deutsche Gesellschaft für Ultraschall in der Medizin (DEGUM) Mitglied: Deutsche Gesellschaft für Verdauung und Stoffwechsel (DGVS) Mitglied: Europäische Gesellschaft für	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
			für Information und Organisation mbH, Gräfelfing Di-Text Frank Digel Abbvie Deutschland GmbH DSAI e.v. Dr.Schär Deutschland GmbH DSAI e.V.				pädiatrische Gastroenterologie, Hepatologie und Ernährung (ESPGHAN) Schwerpunkt: entzündliche Darmerkrankungen, Immundefekte mit Darmbeteiligung, chronisches Darmversagen, seltene Darmerkrankungen, Lebendimpfung unter Immunsuppression, gastrointestinale Hormone, akute Gastroenteritis, chronische Bauchschmerzen, Endoskopie in der Pädiatrie Federführung: Leiter Qualitätszirkel pädiatrische Gastroenterologie Persönlich: keine	

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
Preiß, Jan	-	Takeda Biogen Amgen	DGVS DCCV bng CED Services	-	-	-	Mitglied: DGVS, DCCV, BNG, DGIM, ECCO Schwerpunkt: CED Federführung: - Persönlich: -	Moderat (Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15
Schmidt, Carsten	-	AbbVie Biogen Hospira Janssen-Cilag Takeda Janssen Takeda Abbvie	Berlin Chemie Falk Janssen Kompetenzn etz Darmerkrankungen MSD	AbbVie Takeda	Abbvie Abbvie	-	Mitglied: DGVS, Mitglied Mitglied: ECCO, Mitglied Mitglied: Kompetenznetz Darmerkrankungen, Mitglied Mitglied: GISG (German IBD Study	Moderat (Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12,

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
			Norgine Shield Therapeutics Takeda Abbvie Falk Takeda MSD Janssen Biogen Amgen Vifor Norgine				Group), Mitglied des Boards Mitglied: Mitteldeutsche Gesellschaft für Gastroenterologie, Mitglied des Wissenschaftlichen Beirates Mitglied: DGIM, Mitglied Schwerpunkt: Chronisch-entzündliche Darmerkrankungen, diagnostische und interventionelle Endoskopie Federführung: Arzt-Patienten-Seminare Federführung: Fortbildungsveranstaltungen für Ärzte Persönlich: -	2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15
Schnoy, Elisabeth	Janssen-Cilag Pharmacosmos	Takeda	Abbvie	Servier	-	Nein	Mitglied: DGVS, DGIM	Moderat (Beratertätigk

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							Schwerpunkt: Grundlagenforschung CED Federführung: Aufbau Universitätsklinikum Augsburg Persönlich: nein	eiten und Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15
Schreyer, Andreas	-	Takeda	Bayer	-	-	Aktienbesitz Siemens Healthineers	Mitglied: - Schwerpunkt: - Federführung: - Persönlich: -	Moderat (Zugehörigkeit zu Advisory Boards + Aktienbesitz) →Enthaltung bei Empfehlung

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
								2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15
Siegmund, Britta	-	Abbvie Abbvie Lilly Pfizer Celgene Janssen Prometheus Takeda webMD	Abbvie BerlinFlame Bocemtium CED Service GmbH FalkFoundation Ferring Forma Software Infektionsmedizin Janssen Klinikum Augsburg	Falk	Abbvie Abivax CED Service GmbH Celgene CromSource Falk Lilly Hoffmann - La Roche InDex Pharmaceuticals AB Janssen Medimmune Ltd Pfizer Receptos	Keine	Mitglied: DGVS Vorstand Mitglied: DCCV, Mitglied: UEG Mitglied: DGIM Mitglied: ECCO Schwerpunkt: mukosale Immunologie, CED Federführung: keine Persönlich: keine	Moderat (Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
			Uni Düsseldorf Novartis Pfizer Roche Takeda		Salix Takeda Vhsquared			
Stallmach, Andreas	-	MSD Takeda AMGEN	Falk Foundation AbbVie Janssen CLSCSL Behring GmbH MSD sharp Med update DGVS Takeda Pharma Vertrieb Pfizer Pharma GmbH streamupdate! GmbH	Elsevier Thieme Verlag Walter de Gruyter	-	-	Mitglied: IMPP und FKLM Mitglied: DGVS Mitglied: Deutsche Gesellschaft für Innere Medizin e. V. Mitglied: Mitteldeutsche Gesellschaft für Gastroenterologie e. V. Mitglied: Bundesverband Gastroenterologie Deutschland Mitglied: DCCV Mitglied: Verein Kompetenznetz chronische	Moderat (Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
							Darmerkrankungen e. V. Mitglied: Gastro-Liga Schwerpunkt: - Federführung: - Persönlich: -	
Sturm, Andreas	Abbvie, Janssen, BMS, Hospira, Pfizer, Mundipharm, Johnson&Johnson, Jansen, Samsung, MSD, Takeda	-	-	-	-	-	Mitglied: UEG, DGVS, ECCO Schwerpunkt: CED Federführung: - Persönlich: -	Moderat (Beratertätigkeiten) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
Teich, Niels	-	MSD, AbbVie, Takeda, Celgene, Janssen, Pfizer, Biogen, Amgen	CED Service GmbH, MSD, AbbVie, Takeda, Celgene, Janssen, Pfizer, Biogen, Amgen	Thieme, Springer	Pfizer, AbbVie, Gilead Celgene, Receptos	-	Mitglied: DGVS, DCCV, ALGK, ECCO, Bundesverband Gastroenterologie Deutschland, Verein Kompetenznetz chronische Darmerkrankungen e. V. Schwerpunkt: mukosale Immunologie, CED Federführung: keine Persönlich: keine	Moderat (Zugehörigkeit zu Advisory Boards) →Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15
Thomann, Anne	-	-	CED Service GmbH CED Service GmbH CED Service GmbH CED Service GmbH	-	Deutsche Forschungsgesellschaft	-	Mitglied: - Schwerpunkt: Schwerpunkt: Darm-Hirn-Achse bei chronisch-entzündlichen Darmerkrankungen. Publikationen (PMIDs):30983094,	Gering (Vortragstätigkeit, Industriemittel)

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
			Janssen Cilag GmbH				29734447, 28912568, 27655165 Federführung: - Persönlich: -	
Treese, Christoph	-	-	-	-	Astellars	-	Mitglied: DGVS / Gastroenterologie Mitglied: DGIM / Innere Medizin Schwerpunkt: Onkologie, Magenkarzinom Federführung: - Persönlich: -	Keine
Veltkamp, Claudia	-	Firma Janssen Firma Janssen	-	-	-	-	Mitglied: Mitglied DCCV Schwerpunkt: - Federführung: - Persönlich: -	Gering (kein relevanter Advisory Board)
Walldorf, Jens	-	Abbvie Takeda	Abbvie CED Service / Kompetenez natz CED	-	CED Service Millenium Pharmaceuticals MAPI Hoffmann-La Roche	-	Mitglied: DCCV Mitglied: DGVS Mitglied: DGIM Schwerpunkt: Familienplanung,	Moderat (Zugehörigkeit zu Advisory Boards)

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
			Falk MSD Pfizer Takeda Abbvie Janssen Takeda Vifor MSD Pfizer Amgen Norgine Shire Falk Shield DCCV		Celgene IQVIA Pfizer Essex Pharma Falk Pharma MSD AbbVie		Versorgungsqualität bei CED Federführung: - Persönlich: -	→Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15
Zeißig, Sebastian	Celltrion	Amgen, Biogen, Bristol-Myers Squibb, Ferring, Mylan, Janssen-	Abbvie, Amgen, Biogen, Falk, Ferring, Janssen-Cilag, MSD, Roche,	-	-	-	Mitglied: Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) Deutsche Gesellschaft für Innere Medizin	Moderat (Beratertätigkeiten und Zugehörigkeit zu Advisory Boards)

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
		Cilag, Pfizer, Takeda	Pfizer, Pharma Zentrale, Takeda				(DGIM) Kompetenznetz Darmerkrankungen Bundesverband Gastroenterologie Deutschland (BVGD) European Crohn´s and Colitis Organisation (ECCO) Deutsche Gesellschaft für Immunologie (DGfI) Schwerpunkt: Intestinale Immunologie Federführung: - Persönlich: -	→Enthaltung bei Empfehlung 2.11, 2.12, 2.13, 2.16, 2.17, 3.6, 3.8, 3.9, 3.10, 5.6, 5.7, 5.19, 6.8, 6.15
Zemke, Jennifer	-	-	MSD Kompetenznetz Darmerkrankung Mundipharma Pfizer Takeda	-	-	-	Mitglied: 2. Vorsitzende der FA-CED Schwerpunkt: - Federführung: - Persönlich: -	Gering (Vortragstätigkeiten)

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
			AbbVie Ärztekammer Westfalen Lippe					
Zopf, Yurdagül	- -	- -	Nutricia, MSD, Ferring, Schär	- -	Fresenius, Shire, Dr. Schär	- -	Mitglied: ... Schwerpunkt: Ernährung und Bewegung bei Krebserkrankung, Nahrungsmittelunverträglichkeiten, chronisch entzündliche Darmerkrankungen Federführung: Ernährung und Bewegung bei Krebserkrankung, Adipositas, Nahrungsmittelunverträglichkeiten, chronisch entzündliche Darmerkrankungen Persönlich: -	Gering (Vortragstätigkeiten, Industriemittel)

	Berater-/ Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Bewertung
de Laffolie, Jan	-	Abbvie pIBDahead Shire pharmacosmos	Shire	Keine	GPGE CEDATA GPGE GBA Innovationsfond	Keine	Mitglied: GPGE - AG Leiter CED GPGE - AG Mitgliedschaft chronisches Darmversagen GPGE - AG Mitgliedschaft Endoskopie ESPGHAN Mitglied Schwerpunkt: CED, Epidemiologie, Zöliakie, Kurzdarm Federführung: keine Persönlich: keine	Gering (keine relevanten Advisory Boards)
Lorenz, Pia	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: keine Schwerpunkt: nein Federführung: nein Persönlich: nein	Keine

Literatursammlung:

AG 1 Diagnostik-Frage 1

Inhalt: 21 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Ankersen, D. V. 2019		
Assa, A. 2019		
Brand, E. C. 2019		
Colombel, J. F. 2018	2	A multicentre, randomised, open-label, active-controlled, two-group, phase 3, efficacy and safety trial.
D'Haens, G. 2018	3	A proof-of-concept randomized double-blind controlled study.
Di Ruscio, M. 2017		
Gutiérrez, A. 2016		
Kopylov, U. 2016		
Lamb, C. A. 2019		
Lin, J. F. 2014		
Louis, E. 2012		
Mao, R. 2012		
Meuwis, M. A. 2013		
Molander, P. 2015		
Mosli, M. H. 2015		
Qiu, Y. 2015		
Reinisch, W. 2020		
Tham, Y. S. 2018		
Wright, E. K. 2016		
Wright, E. K. 2015		

Zhuge, Y. 2016		

OXFORD (2011) Appraisal Sheet: RCT: 2 Bewertung(en)

Colombel, J. F. et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet. 390. 2779-2789. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: A multicentre, randomised, open-label, active-controlled, two-group, phase 3, efficacy and safety trial. Number of Patient: 244 patients Recruitung Phase: Feb 11, 2011 until Nov 3, 2016 Inclusion Criteria: Adult patients were enrolled in the study, age 18–75 years, with Crohn's disease at baseline and a diagnosis of ileal, colonic (including rectal), or ileocolonic Crohn's disease (as confirmed by endoscopy not >6 years before baseline). Key inclusion criteria were: (1) moderate to severe Crohn's disease at baseline, defined as Crohn's Disease Activity Index (CDAI)9scores of 220–450 for patients not receiving prednisone at baseline, 200–450 for patients receiving 20 mg prednisone (or less) for 7 days or more before baseline, and >150–450 for patients receiving more than 20 mg prednisone for 7 days or more before baseline; (2) active endoscopic disease, defined as a total Crohn's Disease Endoscopic Index of Severity (CDEIS) of more than 6 and a sum of CDEIS subscores of more than 6 in one or more segments with ulcers; and (3) CRP of 5 mg/L or more, FC of 250 µg/g or more, or both. Exclusion Criteria: Exclusion criteria were previous or current use of biologics or immunomodulators, more than two previous courses of corticosteroids, or current use of corticosteroids for more than 3 months before screening. Patients with any fibrotic	Intervention: In both groups, treatment was escalated in a stepwise manner, from no treatment, to adalimumab induction followed by adalimumab every other week, adalimumab every week, and lastly to both weekly adalimumab and daily azathioprine. This escalation was based on meeting treatment failure criteria. Comparison: Two treatment algorithms: tight control and clinical management.	Primary: The primary endpoint of the study was the proportion of patients with mucosal healing, defined as a CDEIS of less than 4 and no deep ulcers 48 weeks after randomisation. Secondary: (1) deep remission (CDAI <150, CDEIS <4 and no deep ulcers, absence of draining fistula, discontinuation of corticosteroids for ≥8 weeks); (2) biological remission (FC <250 µg/g, CRP <5 mg/L, and CDEIS <4); (3) CDEIS of less than 4; (4) overall CDEIS of less than 4 plus CDEIS of less than 4 in every segment; (5) complete endoscopic remission (CDEIS=0); and(6) endoscopic response (CDEIS decrease of >5 points) Results: The study's primary endpoint of mucosal healing (CDEIS <4) and no deep ulcers at 48 weeks after randomisation was met in 56 (46%) patients in the tight control group compared with 37 (30%) patients in the clinical management group, with a CMH-adjusted risk difference of 16·1% (95% CI 3·9 to 28·3; p=0·010). A higher proportion of patients in the tight control group achieved the following key secondary endpoints 48 weeks after randomisation than in the clinical management group: deep remission, with a CMH-adjusted risk difference of 14·5% (2·9 to 26·0; p=0·014); biological remission, with a CMH-adjusted risk difference of 14·5% (4·1 to 25·0; p=0·006); and an overall CDEIS of less than 4, with a CMH-adjusted risk difference of 16·1% (3·9 to 28·3; p=0·010). No significant differences were observed between the groups regarding the proportion of patients with an overall CDEIS of less than 4 plus a CDEIS of less than 4 in every segment (CMH-adjusted risk difference of 5·9% [95% CI –5·2 to 17·0]; p=0·299), complete endoscopic remission (1·7% [–7·9 to 11·3]; p=0·728), or endoscopic response (11·5% [–0·8 to 23·9]; p=0·067;). A significantly higher proportion of patients achieved steroid-free remission in the tight control group than the clinical management group and clinical remission (CDAI <150) at 11, 23, 35, and 48 weeks after randomisation. A significantly greater mean change from baseline in CDAI was observed in the tight control group than in the clinical management group at 11, 35, and 48 weeks. The mean change from baseline in CRP concentration was not significantly different between tight control and clinical management. Author's Conclusion: CALM is the first study to show that timely escalation with an anti-tumour necrosis factor therapy on the basis of clinical symptoms combined with biomarkers in patients with early Crohn's disease results in better clinical and endoscopic outcomes than symptom-driven decisions alone.

stricture (passable or non-passable and regardless of symptoms), draining perianal fistulas, or non-perianal fistulas were excluded.		

Methodical Notes

Funding Sources: Funding AbbVie

COI: J-FC reports personal fees from AbbVie, Amgen, Boehringer Ingelheim, Celgene Corporation, Celltrion, Eli Lilly, Enterome, Ferring Pharmaceuticals, Genentech, Janssen, MedImmune, Merck & Co, Pfizer, Protagonist Therapeutics, PPM Services, Second Genome, Seres Therapeutics, Shire, Takeda, Theradiag, Intestinal Biotech Development, and Genfit outside the submitted work; and grants from AbbVie, Janssen, and Takeda outside the submitted work. RP reports grants and personal fees from AbbVie outside the submitted work. PB reports personal fees Articles2788www.thelancet.comVol 390 December 23/30, 2017from AbbVie, Takeda, Vifor Pharma, Hospira, Jannsen, Roche, Pfizer, Dr Falk Benelux, and Mundipharma; and reports grants from AbbVie, outside the submitted work. FB reports personal fees from Abbvie, MSD, Ferring Pharmaceuticals, Janssen, Takeda, Pfizer/Hospira, and Mundipharma outside the submitted work; and reports grants from AbbVie, Chiesi Farmaceutici, Ipsen, and Roche outside the submitted work. TV reports fees from advisory board membership of Hospira, Takeda, and Pfizer; and reports personal fees from Takeda outside the submitted work. GN reports personal fees from AbbVie, MSD, Takeda, Ferring Pharmaceuticals, Vifor Pharma, and Merck & Co outside the submitted work. AA reports personal fees from AbbVie, AstraZeneca, Biogen, Celltrion, Chiesi, Ferring Pharmaceuticals, Hospira, Janssen, Eli Lilly, MSD, Mitsubishi-Tanabe Pharma, Mundipharma, Nikkiso, Pfizer, Samsung, Sofar, Takeda, TiGenix, and Zambon outside the submitted work; and reports grants from MSD outside the submitted work. XH reports personal fees from AbbVie, Fresenius Kabi, Nutricia, MSD, Takeda, Vifor, Janssen, Arard, Laboratoires Mayoli-Spindler, Nestlé-Nutrition, and Ferring Pharmaceuticals outside the submitted work. ST reports personal fees from AbbVie, Centocor, Schering-Plough, Bristol-Myers Squibb, Chemocentryx, Cosmo Technologies, Elan Pharma International, Genentech, Giuliani Pharma, Merck & Co, Takeda, Otsuka Pharmaceutical, PDL Biopharma, Pfizer, Shire, Glenmark Pharmaceuticals, Warner Chilcott, Proximagen, VHsquared, TopiVert, Ferring Pharmaceuticals, Celgene, GlaxoSmithKline, Amgen, Biogen, Enterome, UCB Pharma, Boehringer Ingelheim, Grünenthal, Sigmoid Pharma, Oxford University Hospitals, University of Oxford, Santarus Inc, Tillotts Pharma, Procter & Gamble, Vifor, Given Imaging, Sanofi, Wiley Blackwell, Elsevier, Oxford University Press, Abbott Laboratories, and UEG outside the submitted work; reports grants from AbbVie, Schering-Plough, Takeda, Eli Lilly, Warner Chilcott, UCB Pharma, Ferring Pharmaceuticals, MSD, Procter & Gamble, IOIBD, Vifor, and Norman Collisson Foundation outside the submitted work; and institutional support for educationfrom IBD2020, Crohns Colitis Cure, Schering-Plough, Takeda, Synthon, Eli Lilly, Celgene, GlaxoSmithKline, Janssen, Grunenthal, Ferring Pharmaceuticals, MSD, Procter & Gamble, Vifor, ICHOM, and Warner Chilcott outside the submitted work. SD reports personal fees from AbbVie, Actelion Pharmaceuticals, Alfa Wasserman, AstraZeneca, Cellerix, Cosmo Pharmaceuticals, Ferring Pharmaceuticals, Genentech, Grunenthal, Johnson & Johnson, Millennium Pharmaceuticals, Merck & Co, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, Schering-Plough, Salix, Takeda, UCB Pharma, and Vifor outside the submitted work. WR reports personal fees from Abbott Laboratories, AbbVie, AESCA, Aptalis, Astellas Pharma, Janssen, Celltrion, Danone Austria, Elan, Falk Pharma GmbH, Ferring Pharmaceuticals, Immundiagnostik, Mitsubishi Tanabe Pharma, MSD, Otsuka Pharmaceutical, PDL, Pharmacosmos, PLS Educational, Schering-Plough, Shire, Takeda, Therakos, Vifor, Yakult, Amgen, AM-Pharma, AstraZeneca, Avaxia Biologics, Roland Berger GmBH, Bioclinica, Biogen IDEC, Boehringer Ingelheim, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Covance, Ernst & Young, Galapagos NV, Genentech, Gilead Sciences, Grünenthal, ICON, InDex Pharmaceuticals, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, LivaNova, Mallinckrodt Pharmaceuticals, MedImmune, Millennium Pharmaceuticals, Nestle, Novartis, Ocera Therapeutics, Parexel, Philip Morris Institute, Pfizer, Procter & Gamble, Prometheus, Provention Bio, Robarts Clinical Trials, Sandoz, Second Genome, SetPoint Medical, Sigmoid, TiGenix, UCB Pharma, Zealand Pharma, Zyngenia, and 4SC outside the submitted work; and grants from AbbVie, AESCA, Centocor, Falk Pharma GmbH, Immundiagnostik, and MSD outside the submitted work. WJS reports personal fees from AbbVie (during the conduct of the study and outside the submitted work), and from Prometheus Laboratories, Boehringer Ingelheim, Takeda, Atlantic Pharmaceuticals, Janssen, Bristol-Myers Squibb, Genentech, Nutrition Science Partners, Kyowa Hakko Kirin Pharma, Millennium Pharmaceuticals, Celgene Cellular Therapeutics, Santarus, Salix Pharmaceuticals, Catabasis Pharmaceuticals, Vertex Pharmaceuticals, Warner Chilcott, Gilead Sciences, Cosmo Pharmaceuticals, Ferring Pharmaceuticals, Sigmoid Biotechnologies, Tillotts Pharma, AM-Pharma BV, Dr August Wolff, Avaxia Biologics, Zyngenia, Ironwood Pharmaceuticals, InDex Pharmaceuticals, Nestlé, Lexicon Pharmaceuticals, UCB Pharma, Orexigen Therapeutics, Luitpold Pharmaceuticals, Baxter Healthcare, Ferring Research Institute, Amgen, Novo Nordisk, Mesoblast, Shire, Ardelyx, Actavis, Seattle Genetics, MedImmune (AstraZeneca), ActoGeniX NV, Lipid Therapeutics, Eisai, Qu Biologics, Toray Industries, Teva Pharmaceutical Industries, Eli Lilly, Chiasma, TiGenix, Adheron Therapeutics, Immune Pharmaceuticals, Celgene, Arena Pharmaceuticals,

Ambrx, Akros Pharma, Vascular Biogenics, Theradiag, Forward Pharma, Regeneron, Galapagos NV, Seres Therapeutics, Ritter Pharmaceuticals, Theravance Biopharma, Palatin Technologies, Biogen, and Western University (owner of Robarts Clinical Trials) outside the submitted work; reports grants from AbbVie (during the conduct of the study, and outside the submitted work), Prometheus Laboratories, Boehringer Ingelheim, Takeda, Atlantic Pharmaceuticals, Janssen, Bristol-Myers Squibb, Genentech, and Nutrition Science Partners; reports non-financial support from AbbVie; and reports patents for use of topical azathioprine to treat inflammatory bowel disorders (US 5691343), topical formulations of azathioprine to treat inflammatory bowel disorders (US 5905081), colonic delivery of nicotine to treat inflammatory bowel disease (South African patent 97/1020; US 5846983, 5889028, and 6166044; Mexico patent 209636; Europe patents 0954337 and 893998; Hong Kong patent HK1019043; China patent ZL97192177; Czech patent 293616; Canada patent 2246235), the use of azathioprine to treat Crohn's disease (US 5733915), azathioprine compositions for colonic administration (New Zealand patent 306062; Singapore patent 45647; Australia patent 707168; Czech patent 290428), intestinal absorption of nicotine to treat nicotine responsive conditions (Australia patent 718052; US 6238689), the use of topical azathioprine and thioguanine to treat colorectal adenomas (US 6166024), enema and enterically-coated oral dosage forms of azathioprine (US 6432967), a pharmaceutical composition for the treatment of inflammatory bowel disease (US 7341741), and intestinal absorption of nicotine to treat nicotine responsive conditions (Canada patent CA2260909), and for obesity treatment and device (US 7803195 B2) that is licensed to Enteromedics. PR reports personal fees from AbbVie, Bristol-Myers Squibb, Johnson & Johnson, Merck & Co, Takeda, UCB Pharma, Genentech, Tillotts Pharma, Pfizer, Celgene, Amgen, AstraZeneca, Robarts, outside the submitted work; and reports grants from AbbVie, Johnson & Johnson, UCB Pharma, and MSD outside the submitted work. DH reports grants and personal fees from AbbVie, AstraZeneca, Janssen, MSD, Bristol Myers Squibb, Cellerix, Centocor, Chemocentryx, ELAN, Falk Pharma GmbH, Ferring Pharmaceuticals, Genentech, Giuliani Pharma, IBM, Johnson & Johnson, Leo Pharma, Otsuka Pharmaceutical, Novimmune, PDL BioPharma, Philips, Procter & Gamble, Roche, Schering-Plough, Merck Serono, Tramedico, and UCB Pharma outside the submitted work; and reports grants from MSD, Centocor, Chemocentryx, Genentech, Novimmune, PDL BioPharma, Schering-Plough, Cytokine PharmaSciences, AM-Pharma, Vivify Health, Takeda, and Gilead outside the submitted work. SS reports personal fees AbbVie, Allergen, Biogen, Boehringer Ingelheim, Celltrion, Falk Pharma GmbH, Ferring Pharmaceuticals, Genentech, GlaxoSmithKline, MSD, Pfizer, Roche, Sandoz, Shire, and Takeda outside the submitted work. EN, BH, QZ, PM, JP, KW, AMR, and RBT report personal fees from AbbVie outside the submitted work; were AbbVie employees during writing of submitted work; and own AbbVie stock, options, or both. GD'H reports personal fees from AbbVie, Ablynx, Boehringer-Ingelheim, Celgene, Celltrion, and Galapagos NV outside the submitted work; and reports grants from AbbVie and Covidien outside the submitted work. ML and AD declare no competing interests.

Randomization: 1:1 ratio. The patient number and group of each stratum were assigned by a central randomisation schedule generated by AbbVie (Chicago, IL, USA) using WebRando software for randomisation and ClinPhone, an interactive voice and web response system for patient allocation. The subject randomisation schedule was generated by a designated person in the AbbVie statistics department, who was not involved in the rest of the study. The investigators and patients were masked to patient allocation and post-screening FC and CRP results, but treatments were open label.

Blinding: no

Dropout Rate/ITT-Analysis: 11 were enrolled but not randomly assigned, 61 patients did not complete the study.

Notes:
In Hinblick auf PICO Limitation: nicht alle Patienten bei Einschluss bzw. Randomisation in Remission.

D'Haens, G. et al. Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Concentrations Does Not Increase Clinical, Endoscopic, and Corticosteroid-Free Remission in Patients With Active Luminal Crohn's Disease. Gastroenterology. 154. 1343-1351.e1. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 Study type: A proof-of-concept randomized double-blind controlled study. Number of Patient: 122 biologic-naïve adult	Intervention: IFX was given intravenously at 5 mg/kg at weeks 0, 2, and 6 to all patients. Patients were randomized 1:1:1 at inclusion into 3 double-blind IFX maintenance regimens, administered every 8 weeks from week 14 to week 54 (end of the study period) as follows: IFX dose	Primary: The primary endpoint of the study was corticosteroid-free remission (CDAI <150) at all visits between week 22 and 54 associated with the absence of ulcers at week 54 and no surgery for bowel resection or abscess and no new fistula. Secondary: Prespecified secondary

patients with active CD. Recruitung Phase: July 2012 through September 2015 Inclusion Criteria: Patients recruited were adults with active luminal CD naive to biologics with an indication to start anti-TNF therapy in accordance with national guidelines and reimbursement criteria. Disease activity was confirmed by a Crohn's disease activity index (CDAI) >220 with objective signs of active inflammation (high-sensitivity CRP >5 mg/L and/or fecal calprotectin >250 µg/g) and visible ulcers at baseline ileocolonoscopy. Exclusion Criteria: Patients with an imminent need for surgery, critical gastrointestinal stricture and obstructive symptoms, using corticosteroid therapy at doses >40 mg/d prednisolone or equivalent, active systemic infection, evidence of tuberculosis, usual contraindications to anti-TNF or immunosuppressants, or other serious concomitant diseases were excluded.	increase by increments of 2.5 mg/kg, maximally 2 times to a maximum dose of 10 mg/kg (DIS1) according to a prespecified algorithm (outlined later in this article), IFX dose increase by increments of 5 mg/kg, maximally 1 time, to a maximum dose of 10 mg/kg (DIS2) according to the same prespecified algorithm Comparison: IFX dose increase by 5 to 10 mg/kg if patients had a CDAI >220 at the current visit or a CDAI between 150 and 220 in the 2 weeks before the current visit in line with the registered label of IFX	endpoints were the proportion of patients with no ulcers at weeks 12 and 54, clinical remission (CDAI <150) at each visit, sustained remission from week 14 onward, endoscopic remission (CDEIS <3) at weeks 12 and 54, endoscopic response (decrease of CDEIS score of atleast 50%) at weeks 12 and 54, IFX dose increase during the study period, IFX TL >3 µg/mL between weeks 14 and 54, adverse events, total use of infliximab, need for resection, and new fistula or abscesses. Results: The primary endpoint (CDAI <150) between week 22 and 54 off glucocorticosteroids, without new fistula and surgery and without ulcers at the week 54 ileocolonoscopywas reached in 15 (33%) of 45, 10 (27%) of 37, and 16 (40%) of 40 patients in the DIS1, DIS2, and the control group, respectively (P= .50). At week 12, 16 (36%), 6 (16%), and 16 (40%) patients had no ulcerations on endoscopy in the DIS1, DIS2, and control groups (P= .054); by week 54, these proportions increased to 19 (42%), 20 (54%), and 20 (50%) patients, respectively (P=.56). Endoscopic remission (CDEIS <3) was attained in 26 (58%), 13 (35%), and 15 (37.5%) patients in DIS1, DIS2, and the control group by week 12 (P = .070) and in 23 (51%), 19 (51%), and 21 (53%) patients by week 54 (P= 1.00) .Significant endoscopic improvement (CDEIS reduction >50%) was observed in 32 (71%), 24 (65%), and 26 (65%) patients by week 12 (P= .88), and in 28 (62%), 23 (62%), and 23 (57.5%) patients by week 54 (P= .89). A sustained IFX serum concentration >3 µg/mL between week 12 and 54 was observed in 21 (47%), 17 (46%), and 24 (60%) of the patients in DIS1, DIS2, and the control group, respectively (P= .38). The mean concentrations in patients continuously above the 3 µg/mL cutoff was 7.8 ± 2.9 µg/mL, 9.3 ± 5.2 µg/mL, and 9.7 ± 4.5 µg/mL in DIS1, DIS2, and the control group, respectively, vs3.6 ± 2.1 µg/mL, 4.3 ± 2.3 µg/mL, and 3.4 ± 2.3 µg/mL in patients not meeting that success criterion.Antibodies to IFX were measured at the end of the trial and were detected in 10 (22%), 6 (16%), and 5 (12.5%) patients in the DIS1, DIS2, and control groups. Author's Conclusion: In a prospective randomizedexploratory trial of patients with active CD, we found increasing dose of infliximab based on a combination of symptoms, biomarkers, andserum drug concentrations does not lead to corticosteroid-free clinical remission in a

		larger proportion of patients than increasing dose based on symptoms alone.

Methodical Notes

Funding Sources: This investigator-initiated trial was financially supported by Merck Sharp Dome and Janssen, which also provided the IFX study drug. Buhlmann Laboratories, Switzerland, kindly provided materials for Quantum Blue rapid measurements of fecal calprotectin. Prometheus Laboratories, San Diego, CA, performed the measurements of anti-infliximab antibodies at the end of the trial.

COI: Geert D'Haens declares grant support from Abbvie, Jansen, Merck Sharp Domem, and Pfizer; has served as advisor for Abbvie, Johnson andJohnson, Merck Sharp Dome, Mundipharma, Pfizer, Prometheus Laboratories/ Nestle, and Sandoz; and received speaker fees from Abbvie, Johnson and Johnson, Merck Sharp Dome, Mundipharma, and Pfizer. Severine Vermeire reports grant support from Abbvie, MSD, Takeda, and Pfizer; lecture fees from Abbie, MSD, Takeda, Ferring, Falk Pharma, Hospira, and Tillotts; and consultancy fees from Abbvie, MSD, Takeda, Ferring, Genentech/Roche, Shire, Pfizer, Galapagos, Mundipharma, Hospira, Celgene, Second Genome, and Janssen. Filip Baert reports research grants from Abbvie, Chiesi, Ipsen, MSD, and Roche;and speaker's and consultancy fees from Abbvie, Falk, Ferring, Janssen, Mundipharma, MSD, Pfizer, Takeda, and Vifor. Anthony Buisson declares consulting fees for Abbvie, Hospira, and Takeda; and lecture fees from Abbvie, Hospira, Takeda, MSD, Vifor Pharma, Sanofi-Aventis, and Ferring. Janneke vander Woude received grants from Abbvie, Jansen, Pfizer, Tramedico, and Falk; and speakers and consultancy fees from Abbvie, Falk, Ferring, Janssen, Mundipharma, MSD, Pfizer, Takeda, and Vifor. Edouard Louis has received fees from MSD, Abbvie, Takeda, Ferring, MSD, Chiesi, Mitsubishi Pharma, Hospira, Janssen, and Takeda; and is on the advisory board of Abbvie, Ferring, MSD, Takeda, Hospira, Mitsubishi Pharma, Celltrion, and Prometheus. Matthieu Allez received fees from Abbvie, MSD, Janssen, Takeda, Ferring, Mayoli, UCB, Novartis, Genentech,Pfizer, Novo Nordisk, and Falk. Alexandre Aubourg reports consultancy fees from MSD, Abbvie, and Takeda. Bas Oldenburg reports grants from MSD, Abbvie, Takeda, Cablon, Ferring, and Falk. Ann Gils has served as a speaker for MSD, Janssen Biologicals, Pfizer, Takeda, and Abbvie, and as a consultant for UCB; and has received Investigator-Initiated Research Grants from Pfizer. Guy Lambrecht, Peter Bossuyt, Benjamin Pariente, Yoram Bouhnik, Jerome Filippi, Philippe Van Hootegem, Jacques Moreau, Denis Franchimont, Martine De Vos, Fazia Mana, Laurent Peyrin-Biroulet, Hedia Brixi, Philip Caenepeel, MariekePierik, Sylvie Chevret, and David Laharie declare no competing interest in the presentstudy. KU Leuven licensed the infliximab, adalimumab, and vedolizumab ELISA to apDia and R-Biopharm and the use of monoclonal antibodies mAb-IFX6B7 and mAb-ADM6A10 in the lateral flow assay to R-Biopharm.

Randomization: Randomization at week 0 was centrally performed online (ClinInfo, Lyon, France), balanced by permutation blocks the size of which was not disclosed to investigators, and stratified by center, and previous use of azathioprine, 6-mercaptopurine, or methotrexate.

Blinding:

Dropout Rate/ITT-Analysis: Thirty-five (29%) of the patients dropped out of the trial before week 54: 13 (29%) of 45 in DIS1, 8 (22%) of 37 in DIS2, and 14 (35%) of 40 in the control group, after a median of 2.9, 4.6, and 5.8 months, respectively.

Notes:
In Hinblick auf PICO: Outcome nicht Zeit bis zur Therapieintensivierung, sondern steroid-freie Remission; Andere Faktoren (erhöhtes CRP, niedriger IFX-Spiegel) weitere mögliche Faktoren für Dosisanpassung. Patienten bei Studieneinschluss nicht in Remission. Insgesamt Studie zur Beantwortung der PICO-Frage nur sehr bedingt geeignet.

Literatursammlung:

AG 1 Diagnostik-Frage 2

Inhalt: 8 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Assa, A. 2019	2	Nonblinded, randomized controlled trial.
Colombel, J. F. 2018		
D'Haens, G. 2018	2	A proof-of-concept randomized double-blind controlled study.
Lamb, C. A. 2019		
Papamichael, K. 2017	3	multicenter, retrospective study
Papamichael, K. 2019	3	A multicentre retrospective cohort study.
Peyrin-Biroulet, L. 2014		
Vande Casteele, N. 2015	2	Randomized controlled trial

OXFORD (2011) Appraisal Sheet: RCT: 5 Bewertung(en)

Assa, A. et al. Proactive Monitoring of Adalimumab Trough Concentration Associated With Increased Clinical Remission in Children With Crohn's Disease Compared With Reactive Monitoring. Gastroenterology. 157. 985-996.e2. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: Nonblinded, randomized controlled trial. Number of Patient: 78 children with CD. Recruitung Phase: July 2015 through December 201 Inclusion Criteria: Patients recruited were biologic-naïve children (6–17years) with luminal CD who had responded to standard ADL induction at weeks 0 and 2, as indicated at week 4 by a reduction of Pediatric Crohn's Disease Activity Index (PCDAI) of at least 15 points from ADL initiation, or clinical remission(PCDAI<10 points). Exclusion Criteria: Patients were excluded in cases of prior exposure to anti-TNFa agents; current or previous bowel perforation; small bowel	Intervention: In group 1 (proactive group), patients were assessed during each visit for clinical and biologic disease activity, while treating physicians were also informed of ADL TC for all patients within 2 weeks of sampling. ADL treatment was intensified based on plasmatic TC only, meaning that patients with ADL TC<5mg/mL were intensified regardless of disease activity (PCDAI, CRP, and calprotectin). Comparison: In group 2 (reactive group), patients were also assessed during each visit for clinical and biologic disease activity, but physicians were informed of the TC only in cases of clinical or biologic LOR, with subsequent intensification of ADL treatment only in patients with LOR and TC<5mg/mL, meaning that patients with LOR (either	Primary: The primary endpoint of the study was sustained corticosteroid-free clinical remission (PCDAI<10 points) at all visits from weeks 8 to 72. Secondary: Secondary outcomes included corticosteroid-free clinical remission on ADL at weeks 48 and72; sustained biologic remission (defined by CRP <0.5 mg/dL and fecal calprotectin<150mg/g) from week 8 to 72, and at weeks 48 and 72; ADL discontinuation rate at 72 weeks; treatment modification rate during the study period; number of ADL TC measurements <5mg/mL between weeks 8 to 72; and cumulative dose of ADL and adverse events;

obstruction within the last 3 months; fixed non inflammatory stricture (thickened bowel wall with minimal or no enhancement oncross-sectional imaging); complicated or draining perianal fis-tula; previous malignancy; sepsis or active bacterial infection; previous surgical resection of the bowel, diagnosis of IBD-unclassified; or infection (actively tested in all patients) with hepatitis B, hepatitis C, tuberculosis or Clostridium difficile.	clinical and/or biologic) were intensified only if ADL TC was <5mg/mL. Patients in clinical and biologic remission were not intensified and their physicians were not informed of their TC	Results: The primary endpoint was reached in 31 (82%) of 38 and 19 (48%) of 40 in the proactive and reactive groups, respectively,P=.002. Author's Conclusion: Proactive monitoring of adalimumab trough concentrations and adjustment of doses and intervals resulted in significantly higher rates corticosteroid-free clinical remission than reactive monitoring (measuring trough concentration after loss of response.

Methodical Notes

Funding Sources: The study was supported by an unrestricted educational grant by AbbVie Pharmaceutical.

COI: Amit Assa: Consultation and lectures fees from AbbVie; and research grants from AbbVie and Janssen. Dan Turner: Consultation fees, research grants, royalties, or honorarium from Janssen, Pfizer, Ferring, AbbVie, Takeda, Biogen, Neopharm, Uniliver, Atlantic Health, Shire, Celgene, Lilly, and Roche. Batia Weiss: Consultationfees from Janssen, and lecture fees from AbbVie. Ron Shaoul: Consultation and lecture fees from AbbVie and Janssen, and research grant from Janssen. Raanan Shamir: Research grant from AbbVie. The remaining authors disclose no conflicts

Randomization: Randomization and coding were performed by a dedicated clinical trial assistant at the Schneider Children's Medical Center for all centers in blocks of 4 (1:1 ratiostratified by immunomodulators use and medical center).

Blinding: No blinding.

Dropout Rate/ITT-Analysis: Treatment termination in 5 (13%) in proactive group, 8 (20%) reactive group, respectively.

Notes:
In Hinblick auf PICO: Outcome nicht Zeit bis zum Remissionsverlust, sondern Steroid-freie Remission.

D'Haens, G. et al. Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Concentrations Does Not Increase Clinical, Endoscopic, and Corticosteroid-Free Remission in Patients With Active Luminal Crohn's Disease. Gastroenterology. 154. 1343-1351.e1. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: A proof-of-concept randomized double-blind controlled study. Number of Patient: 122 biologic-naïve adult patients with active CD. Recruitung Phase: July 2012 through September 2015	Intervention: IFX was given intravenously at 5 mg/kg at weeks 0, 2, and 6 to all patients. Patients were randomized 1:1:1 at inclusion into 3 double-blind IFX maintenance regimens, administered every 8 weeks from week 14 to week 54 (end of the study period) as follows: IFX dose increase by increments of 2.5 mg/kg, maximally 2 times to a maximum dose of 10 mg/kg (DIS1) according to a prespecified algorithm, IFX dose increase by increments of 5 mg/kg, maximally	Primary: The primary endpoint of the study was corticosteroid-free remission (CDAI <150) at all visits between week 22 and 54 associated with the absence of ulcers at week 54 and no surgery for bowel resection or abscess and no new fistula. Secondary: Prespecified secondary endpoints were the proportion of patients with no ulcers at weeks 12 and 54, clinical remission (CDAI <150) at each visit, sustained remission from week 14 onward, endoscopic remission (CDEIS <3) at weeks 12 and 54, endoscopic

Inclusion Criteria: Patients recruited were adults with active luminal CD naive to biologics with an indication to start anti-TNF therapy in accordance with national guidelines and reimbursement criteria. Disease activity was confirmed by a Crohn's disease activity index (CDAI) >220 with objective signs of active inflammation (high-sensitivity CRP >5 mg/L and/or fecal calprotectin >250 µg/g) and visible ulcers at baseline ileocolonoscopy. Exclusion Criteria: Patients with an imminent need for surgery, critical gastrointestinal stricture and obstructive symptoms, using corticosteroid therapy at doses >40 mg/d prednisolone or equivalent, active systemic infection, evidence of tuberculosis, usual contraindications to anti-TNF or immunosuppressants, or other serious concomitant diseases were excluded.	1 time, to a maximum dose of 10 mg/kg (DIS2) according to the same prespecified algorithm Comparison: IFX dose increase by 5 to 10 mg/kg if patients had a CDAI >220 at the current visit or a CDAI between 150 and 220 in the 2 weeks before the current visit in line with the registered label of IFX.	response (decrease of CDEIS score of atleast 50%) at weeks 12 and 54, IFX dose increase during the study period, IFX TL >3 µg/mL between weeks 14 and 54, adverse events, total use of infliximab, need for resection, and new fistula or abscesses. Results: The primary endpoint (CDAI <150) between week 22 and 54 off glucocorticosteroids, without new fistula and surgery and without ulcers at the week 54 ileocolonoscopy was reached in 15 (33%) of 45, 10 (27%) of 37, and 16 (40%) of 40 patients in the DIS1, DIS2, and the control group, respectively (P= .50). At week 12, 16 (36%), 6 (16%), and 16 (40%) patients had no ulcerations on endoscopy in the DIS1, DIS2, and control groups (P= .054); by week 54, these proportions increased to 19 (42%), 20 (54%), and 20 (50%) patients, respectively (P=.56). Endoscopic remission (CDEIS <3) was attained in 26 (58%), 13 (35%), and 15 (37.5%) patients in DIS1, DIS2, and the control group by week 12 (P = .070) and in 23 (51%), 19 (51%), and 21 (53%) patients by week 54 (P= 1.00) .Significant endoscopic improvement (CDEIS reduction >50%) was observed in 32 (71%), 24 (65%), and 26 (65%) patients by week 12 (P= .88), and in 28 (62%), 23 (62%), and 23 (57.5%) patients by week 54 (P= .89). A sustained IFX serum concentration >3 µg/mL between week 12 and 54 was observed in 21 (47%), 17 (46%), and 24 (60%) of the patients in DIS1, DIS2, and the control group, respectively (P= .38). The mean concentrations in patients continuously above the 3 µg/mL cutoff was 7.8 ± 2.9 µg/mL, 9.3 ± 5.2 µg/mL, and 9.7 ± 4.5 µg/mL in DIS1, DIS2, and the control group, respectively, vs3.6 ± 2.1 µg/mL, 4.3 ± 2.3 µg/mL, and 3.4 ± 2.3 µg/mL in patients not meeting that success criterion. Antibodies to IFX were measured at the end of the trial and were detected in 10 (22%), 6 (16%), and 5 (12.5%) patients in the DIS1, DIS2, and control groups. Author's Conclusion: Increasing dose of infliximab based on a combination of symptoms, biomarkers, and serum drug concentrations does not lead to corticosteroid-free clinical remission in a larger proportion of patients than increasing dose based on symptoms alone.

Methodical Notes

Funding Sources: This investigator-initiated trial was financially supported by Merck Sharp Dome and Janssen, which also provided the IFX study drug. Buhlmann Laboratories, Switzerland, kindly provided materials for Quantum Blue rapid. measurements of fecal calprotectin. Prometheus Laboratories, San Diego, CA, performed the measurements of anti-infliximab antibodies at the end of the trial.

COI: Geert D'Haens declares grant support from Abbvie, Jansen, Merck Sharp Domem, and Pfizer; has served as advisor for Abbvie, Johnson andJohnson, Merck Sharp Dome, Mundipharma, Pfizer, Prometheus Laboratories/ Nestle, and Sandoz; and received speaker fees from Abbvie, Johnson and Johnson, Merck Sharp Dome, Mundipharma, and Pfizer. Severine Vermeire reports grant support from Abbvie, MSD, Takeda, and Pfizer; lecture fees from Abbie, MSD, Takeda, Ferring, Falk Pharma, Hospira, and Tillotts; and consultancy fees from Abbvie, MSD, Takeda, Ferring, Genentech/Roche, Shire, Pfizer, Galapagos, Mundipharma, Hospira, Celgene, Second Genome, and Janssen. Filip Baert reports research grants from Abbvie, Chiesi, Ipsen, MSD, and Roche;and speaker's and consultancy fees from Abbvie, Falk, Ferring, Janssen, Mundipharma, MSD, Pfizer, Takeda, and Vifor. Anthony Buisson declares consulting fees for Abbvie, Hospira, and Takeda; and lecture fees from Abbvie, Hospira, Takeda, MSD, Vifor Pharma, Sanofi-Aventis, and Ferring. Janneke vander Woude received grants from Abbvie, Jansen, Pfizer, Tramedico, and Falk; and speakers and consultancy fees from Abbvie, Falk, Ferring, Janssen, Mundipharma, MSD, Pfizer, Takeda, and Vifor. Edouard Louis has received fees from MSD, Abbvie, Takeda, Ferring, MSD, Chiesi, Mitsubishi Pharma, Hospira, Janssen, and Takeda; and is on the advisory board of Abbvie, Ferring, MSD, Takeda, Hospira, Mitsubishi Pharma, Celltrion, and Prometheus. Matthieu Allez received fees from Abbvie, MSD, Janssen, Takeda, Ferring, Mayoli, UCB, Novartis, Genentech,Pfizer, Novo Nordisk, and Falk. Alexandre Aubourg reports consultancy fees from MSD, Abbvie, and Takeda. Bas Oldenburg reports grants from MSD, Abbvie, Takeda, Cablon, Ferring, and Falk. Ann Gils has served as a speaker for MSD, Janssen Biologicals, Pfizer, Takeda, and Abbvie, and as a consultant for UCB; and has received Investigator-Initiated Research Grants from Pfizer. Guy Lambrecht, Peter Bossuyt, Benjamin Pariente, Yoram Bouhnik, Jerome Filippi, Philippe Van Hootegem, Jacques Moreau, Denis Franchimont, Martine De Vos, Fazia Mana, Laurent Peyrin-Biroulet, Hedia Brixi, Philip Caenepeel, MariekePierik, Sylvie Chevret, and David Laharie declare no competing interest in the presentstudy. KU Leuven licensed the infliximab, adalimumab, and vedolizumab ELISA to apDia and R-Biopharm and the use of monoclonal antibodies mAb-IFX6B7 and mAb-ADM6A10 in the lateral flow assay to R-Biopharm.

Randomization: Randomization at week 0 was centrally performed online (ClinInfo, Lyon, France), balanced by permutation blocks the size of which was not disclosed to investigators, and stratified by center, and previous use of azathioprine, 6-mercaptopurine, or methotrexate.

Blinding: Serum samples for IFX concentrations were shipped to and measured at a single laboratory (KU Leuven, Leuven, Belgium) and the results were entered in the same CRF but remained invisible for the sites.

Dropout Rate/ITT-Analysis: Thirty-five (29%) of the patients dropped out of the trial before week 54: 13 (29%) of 45 in DIS1, 8 (22%) of 37 in DIS2, and 14 (35%) of 40 in the control group, after a median of 2.9, 4.6, and 5.8 months, respectively.

Notes:
In Hinblick auf PICO: Outcome nicht Zeit bis zum Remissionsverlust, sondern steroid-freie Remission. Andere Faktoren (erhöhtes CRP, niedriger IFX-Spiegel) weitere mögliche Faktoren für Dosisanpassung.

Papamichael, K. et al. Improved Long-term Outcomes of Patients With Inflammatory Bowel Disease Receiving Proactive Compared With Reactive Monitoring of Serum Concentrations of Infliximab. Clin Gastroenterol Hepatol. 15. 1580-1588.e3. 2017

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 Study type: multicenter, retrospective study Number of Patient: 264 patients Recruitung Phase: September 2006 to January 2015 Inclusion Criteria: Consecutive IBD patients who responded to infliximab induction therapy and subsequently received maintenance	Intervention: Proactive drug monitoring. Comparison: Reactive drug monitoring.	Primary: Time to treatment failure. Secondary: Time to first IBD-related surgery or hospitalization, serious infusion reaction, and detection of antibodies to infliximab. Results: In the entire cohort, 105 patients had a treatment failure during follow-up. Among patients who underwent proactive TDM, only 17 (13%) had a treatment failure, in contrast with 88 (66%) patients in the reactive TDM group. Multiple Cox regression analysis independently associated proactive drug monitoring, compared with reactive monitoring, with reduced risk for treatment failure (hazard ratio

therapy and underwent either proactive or reactive TDM, based on the first infliximab concentration or antibodies to infliximab (ATI) measurement. Exclusion Criteria: Patients were excluded if they underwent TDM only during the induction phase, subsequent proactive after first reactive TDM, total colectomy with an ileal pouch-anal anastomosis or a terminal ostomy prior to infliximab TDM initiation, had no follow-up visit after the initiation of infliximab TDM, or had a long drug holiday during infliximab maintenance therapy.		[HR],0.16; 95% confidence interval [CI], 0.09–0.27;P<.001 multiple cox regression analysis independently associated proactive drug monitoring with reactive reduced risk for ibd-related surgery ci hospitalization to infliximab and serious infusion reaction> Author's Conclusion: Proactive monitoring was associated with better clinical outcomes, including greater drug durability, less need for IBD-related surgery or hospitalization, and lower risk of antibodies to infliximab or serious infusion reactions

Methodical Notes

Funding Sources: Konstantinos Papamichael received a fellowship grant from the Hellenic Groupfor the Study of IBD.

COI: Byron P. Vaughn receives research support from Takeda and Genentech and has received compensation from Janssen and AbbVie for speaking and advisory boards. Mark T. Osterman received consultancy fees from Janssen, AbbVie, UCB, Takeda, Pfizer, and Lycera, and received research grant support from UCB. Adam S. Cheifetz received consultancy fees from AbbVie, Janssen, UCB, Takeda, Prometheus, and Pfizer. The remaining authors disclose no conflicts of interest.

Randomization: No randomization, retrospective study.

Blinding: No blinding, retrospective study.

Dropout Rate/ITT-Analysis: No dropouts.

Notes:

Papamichael, K. et al. Proactive Therapeutic Drug Monitoring of Adalimumab Is Associated With Better Long-term Outcomes Compared With Standard of Care in Patients With Inflammatory Bowel Disease. J Crohns Colitis. 13. 976-981. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 Study type: A multicentre retrospective cohort study. Number of Patient: 382 patients. Recruitung Phase: June 2006 to December 2015. Inclusion Criteria: Patients with IBD who received maintenance adalimumab therapy were eligible for the study and were followed until July 2016. Exclusion Criteria: Patients with early [≤8 weeks] failure, defined as drug discontinuation for either	Intervention: Proactive TDM. Comparison: Reactive TDM.	Primary: Time to treatment failure. Secondary: The need for an IBD-related surgery. Results: At the end of follow-up, nine [17%] patients with at least one proactive TDM had treatment failure [SLR, n = 8; SAE, n = 1] in contrast to 119 [36%] receiving standard of care [SLR, n = 91; SAE, n = 28], 31 with reactive TDM alone [SLR, n = 27; SAE, n = 4]. Multiple Cox regression analyses showed that at least one proactive TDM was independently associated with a reduced risk for treatment failure (hazard ratio [HR]: 0.4; 95% confidence interval [CI]: 0.2–0.9; p = 0.022). Author's Conclusion: At the end of follow-up, one patient [2%] with at least one proactive TDM had an IBD-related surgery in contrast to 28 [9%] with standard of care [nine patients with reactive TDM alone]. There was a trend towards a lower cumulative probability of IBD-

primary non-response or serious adverse event [SAE], and those with a previous total colectomy with an ileal pouch-anal anastomosis or ileostomy.		related surgery in patients with at least one proactive adalimumab testing compared with standard of care.

Methodical Notes

Funding Sources: KP is supported by Ruth L. Kirschstein NRSA Institutional Research Training Grant 5T32DK007760-18.

COI: ASC: received consultancy fees from AbbVie, Janssen, Takeda, Ferring, Miraca, AMAG, Arena, Samsung, and Pfizer, and research support from Miraca; BPV: receives research support from Takeda, Genentech, and Celgene and has received compensation from Janssen and AbbVie for speaking and advisory boards; the remaining authors disclose no conflict of interest.

Randomization: No Randomization.

Blinding: No Blinding.

Dropout Rate/ITT-Analysis: No Dropouts.

Notes:
Retrospective analysis.

Vande Casteele, N. et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology. 148. 1320-9.e3. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: Randomized controlled trial Number of Patient: 263 Patienten Recruitung Phase: August 2011 to April 2013. Inclusion Criteria: Eligibility criteria included age of at least 18 years and adiagnosis of moderate-to severe CD or UC confirmed by endoscopy and histology. Patients needed to be treated with maintenance infliximab therapy for at least 14 weeks and needed to be in stable clinical response. Exclusion Criteria: Patients who were on a nonstandard higher dosing regimen because of	Intervention: All patients were first dose optimized to have an infliximab TC within the in-terval of 3–7mg/mL (optimization phase) according to the TAXIT algorithm. Patients who successfully achieved an infliximab TC within the optimal interval were then assigned to infliximab dosing based on clinical symptoms and C-reactive protein (CRP), or to continue dosing based on infliximab TC (maintenance phase). In the concentration-based dosing group, individual infliximab TCs were evaluated at each infusion and the dosing regimen was changed for the next infusion according to the TAXIT algorithm to keep patients within the optimal infliximab TC interval. Comparison: In the clinically based dosing group, dosing of infliximab was guided based on symptoms and CRP (recorded at each infusion) according to standard clinical practice criteria.	Primary: Primary end point was defined as the proportion of patientsin each group in clinical and biological remission at year 1 after optimization. Secondary: Secondary end points were durable remission, relapse (defined as the need for infliximab dose escalation, ie, interval decrease and/or dose increase, the addition of steroids, or switch to another anti-inflammatory agent as decided by the treating physician), infliximab TC within the optimal interval, ATI positivity, total cost of infliximab treatment, and quality adjusted life years (QALY). Results: The randomized maintenance phase did not show an additional benefit to continue concentration-based dose adjustments over clinically based dose adjustments. Author's Conclusion: Targeting patients' infliximab TCs to 3–7mg/mL results in a

secondary loss of response to infliximab therapy at the time of screening were ineligible and patients with ATI>8mg/mL equivalents.		more efficient use of the drug. After dose optimization, continued concentration-based dosing was not superior to clinically based dosing for achieving remission after 1 year, but was associated with fewer flares during the course of treatment.

Methodical Notes

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COI: Niels Vande Casteele reports consultancy fees from MSD, Janssen Biologics, UCB, and speaker's fees from Abbvie, outside the submitted work. Marc Ferrante reports consultancy fees from Abbvie, Merck, Janssen Biologics, grants from Janssen Biologics, and speaker's fees from Merck, Tillots, Ferring, Abbvie, outside the submitted work. Gert Van Assche reports consultancy fees from Zealand Pharma, Shire, Abbott/Abbvie, Novartis, MSD, Janssen, BMS, Ferring, Chiesi, Takeda, grants from MSD, Abbott/Abbvie, Zealand Pharma, and speaker's fees from Janssen, Abbott/Abbvie, Ferring, Aptalis, Ferring, MSD, outside the submitted work; Vera Ballet has nothing to disclose; Griet Compernolle has nothing to disclose. Paul Rutgeerts reports consultancy fees from Amgen, Merck, UCB Pharma, Genentech, BMS, Abbvie, Janssen Biologics, Millennium, Neovacs, Actogenics, Prometheus Laboratories, Inc.,grants from UCB Pharma, Abbvie, Janssen Biologics, Merck, Prometheus Laboratories, Inc., and speaker's fees from Abbvie, Merck, outside the submitted work. Ann Gils reports grants from Pfizer, and speaker's fees from MSD, Janssen Biologicals, Pfizer, outside the submitted work. Séverine Vermeire reports consultancy fees from Takeda, Roche/Genentech, Merck, Centocor, Abbvie, UCB, Pfizer, Ferring, grants from Centocor, Abbvie,Merck, and speaker's fees from Merck, Abbvie, Takeda, Pfizer, Ferring, Falk, Centocor, outside the submitted work. The remaining authors disclose no conflicts.

Randomization: Randomization was performed by one person (VB) not in charge of the clinical care of patients using a computer-generated randomization schedule, with random block sizes.

Blinding: Both patients and treating physicians were blinded to individual infliximab trough and ATI concentrations.

Dropout Rate/ITT-Analysis: In total, 25 out of 251 randomized patients did not complete the study (10%).

Notes:
In Hinblick auf PICO: Endpunkt in dieser Studie nicht Zeit bis zum Remissionsverlust, sondern Anteil der Patienten in Remission.

Literatursammlung:

AG 2 akuter Schub-Frage 1

Inhalt: 32 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Abiko, Y. 2014	5	
Allegretti, J. R. 2017	3	retrospective observational
Ankersen, D. V. 2019	2	RCT
Assa, A. 2019	2	Nonblinded, randomized controlled trial.
Baert, F. 2016	4	prospektive obernational
Bek, S. 2016	1	sytematic review
Boube, M. 2020	2	RCT
Brand, E. C. 2019	1	systemaitc review
Colombel, J. F. 2018	2	A multicentre, randomised, open-label, active-controlled, two-group, phase 3, efficacy and safety trial.
Cornillie, F. 2014	3	post hoc analysis of RCT
D'Haens, G. 2018	2	A proof-of-concept randomized double-blind controlled study.
Di Ruscio, M. 2017	1	systematic review, meta analysis
Gutiérrez, A. 2016	3	prospektive observational
Kopylov, U. 2016	1	systematic review, metaanalysis
Lamb, C. A. 2019		
Levesque, B. G. 2014	3	yes
Lin, J. F. 2014	1	metaanalysis
Louis, E. 2012	3	prospective multicenter cohort study
Mao, R. 2012	1	systematic review, meta analysis
Meuwis, M. A. 2013	3	prospective cohort trial
Molander, P. 2015	3	Prospective multicenter study
Mosli, M. H. 2015	1	Systematic Review and Meta-Analysis
Peyrin-Biroulet, L. 2014	3	RCT, but not primary endpoint.

Qiu, Y. 2015	1	Meta-analysis of Prospective Studies
Reinisch, W. 2020	3	post-hoc analysis of RCT
Reinisch, W. 2012	1	post-hoc analysis of RCT
Tham, Y. S. 2018	2	systematic review, meta-analysis
Vande Casteele, N. 2015		
Waljee, A. K. 2019	1	cohort study
Wright, E. K. 2016	3	prospective, randomized controlled trial
Wright, E. K. 2015	3	Subgroup analysis (POCER)
Zhuge, Y. 2016	1	meta-analysis

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 10 Bewertung(en)

Bek, S. et al. Systematic review: genetic biomarkers associated with anti-TNF treatment response in inflammatory bowel diseases. Aliment Pharmacol Ther. 44. 554-67. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: sytematic review Databases: Pubmed Search period: October 2015 Inclusion Criteria: three individual searches were performed in PubMed using various alternative search terms for (i) “anti-TNF three individual searches were performed in PubMed using various alternative search terms for (i) “anti-TNF treatment”, (ii) “genetic variation”, and (iii) “autoimmune disease”, respectively. Subsequently, studies appearing in all of the three searches were identified resulting in 572 abstracts (latest search date: 27 October 2015). Figure 1 shows the search strategy and a full list of search terms is shown in Table S1. All studies suggesting that they pre- sented original data on polymorphisms and anti-TNF treatment response were retrieved (138 articles) and reviewed by three independent authors (SB, JVN, VA)	Population: A systematic review and meta-analysis were carried out according to the guidelines of ‘Preferred Reporting Items for Systematic Reviews and Meta-Analyses’ (PRISMA) statement.23 To identify the relevant primary literature three individual searches were performed in PubMed using various alternative search terms for (i) “anti-TNF treatment”, (ii) “genetic variation”, and (iii) “autoimmune	Primary: To identify polymorphisms and candidate genes from the literature that are associated with anti-tumour necrosis factor (TNF) treatment response in patients with inflammatory bowel diseases (IBD), Crohn’s disease (CD) and ulcerative colitis. Secondary: - Results: A functional polymorphism in FCGR3A was significantly associated with anti-TNF treatment response among CD patients using biological response criterion (decrease in C-reactive protein,	27 citations Systematic review: genetic biomarkers associated with anti-TNF treatment response in inflammatory bowel diseases. Bek S, Nielsen JV, Bojesen AB, Franke A, Bank S, Vogel U, Andersen V. Aliment Pharmacol Ther. 2016 Sep;44(6):554-67. doi: 10.1111/apt.13736. Epub 2016 Jul 15. PMID: 27417569 Free PMC article. Review. 2 Cite Share Treatments of inflammatory bowel disease toward personalized medicine. Kim KU, Kim J, Kim WH, Min H, Choi CH. Arch Pharm Res. 2021 Mar;44(3):293-309. doi: 10.1007/s12272-021-01318-6. Epub 2021 Mar 24. PMID: 33763844 Review. 3 Cite Share

Exclusion Criteria: Studies were excluded due to small numbers of study par- ticipants for treatment evaluation (less than 100 cases), missing data, not reporting original data and not report- ing data on anti-TNF response (78 studies).	disease", respectively. Subsequently, studies appearing in all of the three searches were identified resulting in 572 abstracts (latest search date: 27 October 2015). Figure 1 shows the search strategy and a full list of search terms is shown in Table S1. All studies suggesting that they presented original data on polymorphisms and anti-TNF treatment response were retrieved (138 articles) and reviewed by three independent authors (SB, JVN, VA). Studies were excluded due to small numbers of study participants for treatment evaluation (less than 100 cases), missing data, not reporting original data and not reporting data on anti-TNF response (78 studies). In total, 60 studies reported on genetic markers and anti-TNF response in autoimmune diseases whereof 15 reported on IBD (and the others on ankylosing	levels). Meta-analyses showed that polymorphisms in TLR2 (rs3804099, OR (95% CI) = 2.17 (1.35–3.47)], rs11938228 [OR = 0.64 (0.43–0.96)], TLR4 (rs5030728) [OR = 3.18 (1.63–6.21)], TLR9 (rs352139) [OR = 0.43 (0.21–0.88)], TNFRSF1A (rs4149570) [OR = 2.06 (1.02–4.17)], IFNG (rs2430561) [OR = 1.66 (1.05–2.63)], IL6 (rs10499563) [OR = 1.65 (1.04–2.63)] and IL1B (rs4848306) [OR = 1.88 (1.05–3.35)] were significantly associated with response among IBD patients using clinical response criteria. A positive predictive value of 0.96 was achieved by combining five genetic markers in an explorative analysis. Author's Conclusion: There are no genetic markers currently available which are adequately predictive of anti-TNF response for use in the clinic. Genetic markers bear the advantage that they do not change over time. Therefore, hypothesis-free approaches, testing a large number of polymorphisms in large, well-characterised cohorts, are required in order to identify	Prospective Validation of CD-62L (L-Selectin) as Marker of Durable Response to Infliximab Treatment in Patients With Inflammatory Bowel Disease: A 5-Year Clinical Follow-up. Bravo F, Macpherson JA, Slack E, Patuto N, Cahenzli J, McCoy KD, Macpherson AJ, Juillerat P; SATICC (Sensitivity to Anti-TNF Inhibition in Crohn's disease and ulcerative Colitis) study group. Clin Transl Gastroenterol. 2021 Feb 15;12(2):e00298. doi: 10.14309/ctg.0000000000000298. PMID: 33735154 Free PMC article. 4 Cite Share Predictors and Early Markers of Response to Biological Therapies in Inflammatory Bowel Diseases. Privitera G, Pugliese D, Rapaccini GL, Gasbarrini A, Armuzzi A, Guidi L. J Clin Med. 2021 Feb 19;10(4):853. doi: 10.3390/jcm10040853. PMID: 33669579 Free PMC article. Review. 5 Cite Share Personalized Medicine of Monoclonal Antibodies in Inflammatory Bowel Disease: Pharmacogenetics, Therapeutic Drug Monitoring, and Beyond. Di Paolo A, Luci G. Front Pharmacol. 2021 Feb 8;11:610806. doi: 10.3389/fphar.2020.610806. eCollection 2020. PMID: 33628180 Free PMC article. Review. 6 Cite Share IL6 genetic variants haplotype is associated with susceptibility and disease activity but not with therapy response in patients with inflammatory bowel disease. Gonçalves BP, Flauzino T, Inoue CJ, de Paula JCC, Galvão TC, de Alcantara CC, Miyazaki PK, Rosa L, Westmore S, Lozovoy MAB, Reiche EMV, Simão ANC. Int J Colorectal Dis. 2021

	arthritis, psoriasis and rheumatoid arthritis). No further studies were identified by searching the literature list of the retrieved articles. Intervention: none Comparison: Biomarkers	genetic profiles with larger effect sizes, which could be employed as biomarkers for treatment selection in clinical settings.	Feb;36(2):383-393. doi: 10.1007/s00384-020-03743-3. Epub 2020 Oct 12. PMID: 33047210 7 Cite Share Association of Tumor Necrosis Factor Receptor 1 Promoter Gene Polymorphisms (-580 A/G and -609 G/T) and TNFR1 Serum Levels with the Susceptibility to Gastric Precancerous Lesions and Gastric Cancer Related to H. pylori Infection in a Moroccan Population. Bounder G, Jouimyi MR, Boura H, Jouhadi H, Badre W, Benomar H, Kettani A, Lebrazi H, Maachi F. Biomed Res Int. 2020 Sep 24;2020:2451854. doi: 10.1155/2020/2451854. eCollection 2020. PMID: 33029495 Free PMC article. 8 Cite Share Personalizing Treatment in IBD: Hype or Reality in 2020? Can We Predict Response to Anti-TNF? Atreya R, Neurath MF, Siegmund B. Front Med (Lausanne). 2020 Sep 2;7:517. doi: 10.3389/fmed.2020.00517. eCollection 2020. PMID: 32984386 Free PMC article. Review. 9 Cite Share Is Polymorphism in the Apoptosis and Inflammatory Pathway Genes Associated With a Primary Response to Anti-TNF Therapy in Crohn's Disease Patients? Walczak M, Lykowska-Szuber L, Plucinska M, Stawczyk-Eder K, Zakerska-Banaszak O, Eder P, Krela-Kazmierczak I, Michalak M, Zywicki M, Karlowski WM, Szalata M, Dobrowolska A, Slomski R, Skrzypczak-Zielinska M. Front Pharmacol. 2020 Aug 14;11:1207. doi: 10.3389/fphar.2020.01207. eCollection 2020. PMID: 32922288 Free PMC article.

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Gene Signatures of Early Response to Anti-TNF Drugs in Pediatric Inflammatory Bowel Disease.
Salvador-Martín S, Raposo-Gutiérrez I, Navas-López VM, Gallego-Fernández C, Moreno-Álvarez A, Solar-Boga A, Muñoz-Codoceo R, Magallares L, Martínez-Ojinaga E, Fobelo MJ, Millán-Jiménez A, Rodriguez-Martinez A, Vayo CA, Sánchez C, Tolin M, Bossacoma F, Pujol-Muncunill G, González de Caldas R, Loverdos I, Blanca-García JA, Segarra O, Eizaguirre FJ, García-Romero R, Merino-Bohórquez V, Sanjurjo-Sáez M, López-Fernández LA.
Int J Mol Sci. 2020 May 9;21(9):3364. doi: 10.3390/ijms21093364.
PMID: 32397546 Free PMC article.
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Cite Share

The Interplay between Mucosal Microbiota Composition and Host Gene-Expression is Linked with Infliximab Response in Inflammatory Bowel Diseases.
Dovrolis N, Michalopoulos G, Theodoropoulos GE, Arvanitidis K, Kolios G, Sechi LA, Eliopoulos AG, Gazouli M.
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PMID: 32244928 Free PMC article.

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Cite Share

Predictors of response and disease course in patients with inflammatory bowel disease treated with biological therapy-the Danish IBD Biobank Project: protocol for a multicentre prospective cohort study.
Zhao M, Bendtsen F, Petersen AM, Larsen L, Dige A, Hvas C, Seidelin JB, Burisch J.
BMJ Open. 2020 Feb 25;10(2):e035756. doi: 10.1136/bmjopen-2019-035756.
PMID: 32102828 Free PMC article.

			13 **Cite Share** **Identification of Epigenetic Methylation Signatures With Clinical Value in Crohn's Disease.** **Moret-Tatay I, Cerrillo E, Sáez-González E, Hervás D, Iborra M, Sandoval J, Busó E, Tortosa L, Nos P, Beltrán B.** **Clin Transl Gastroenterol. 2019 Oct;10(10):e00083. doi: 10.14309/ctg.0000000000000083. PMID: 31663908 Free PMC article.** **14** **Cite Share** **Can molecular stratification improve the treatment of inflammatory bowel disease?** **Wang C, Baer HM, Gaya DR, Nibbs RJB, Milling S.** **Pharmacol Res. 2019 Oct;148:104442. doi: 10.1016/j.phrs.2019.104442. Epub 2019 Sep 3.** **PMID: 31491469 Free PMC article. Review.** **15** **Cite Share** **Predicting (side) effects for patients with inflammatory bowel disease: The promise of pharmacogenetics.** **Voskuil MD, Bangma A, Weersma RK, Festen EAM.** **World J Gastroenterol. 2019 Jun 7;25(21):2539-2548. doi: 10.3748/wjg.v25.i21.2539.** **PMID: 31210708 Free PMC article. Review.** **16** **Cite Share** **Molecular Profiling of Inflammatory Bowel Disease: Is It Ready for Use in Clinical Decision-Making?** **Lee HS, Cleynen I.** **Cells. 2019 Jun 4;8(6):535. doi: 10.3390/cells8060535.** **PMID: 31167397 Free PMC article. Review.** **17** **Cite Share** **Pre-Treatment Biomarkers of Anti-Tumour Necrosis Factor Therapy Response in Crohn's**

			Disease-A Systematic Review and Gene Ontology Analysis. Gole B, Potočnik U. Cells. 2019 May 28;8(6):515. doi: 10.3390/cells8060515. PMID: 31141991 Free PMC article. 18 Cite Share Impact of Genes and the Environment on the Pathogenesis and Disease Course of Inflammatory Bowel Disease. Zhao M, Burisch J. Dig Dis Sci. 2019 Jul;64(7):1759-1769. doi: 10.1007/s10620-019-05648-w. PMID: 31073736 Review. 19 Cite Share Genetic Studies of Inflammatory Bowel Disease-Focusing on Asian Patients. Park SC, Jeen YT. Cells. 2019 May 1;8(5):404. doi: 10.3390/cells8050404. PMID: 31052430 Free PMC article. Review. 20 Cite Share Ulcerative Colitis: Shifting Sands. D'Haens GRAM, Lindsay JO, Panaccione R, Schreiber S. Drugs R D. 2019 Jun;19(2):227-234. doi: 10.1007/s40268-019-0263-2. PMID: 30827006 Free PMC article. Review. Page 3 21 Cite Share Genetically determined high activities of the TNF-alpha, IL23/IL17, and NFkB pathways were associated with increased risk of ankylosing spondylitis. Sode J, Bank S, Vogel U, Andersen PS, Sørensen SB, Bojesen AB, Andersen MR, Brandslund I, Dessau RB, Hoffmann HJ, Glintborg B, Hetland ML, Locht H, Heegaard NH, Andersen V. BMC Med Genet. 2018 Sep 12;19(1):165. doi: 10.1186/s12881-018-0680-z.

				PMID: 30208882 Free PMC article. 22 Cite Share Olive oil polyphenols reduce oxysterols -induced redox imbalance and pro-inflammatory response in intestinal cells. Serra G, Incani A, Serreli G, Porru L, Melis MP, Tuberoso CIG, Rossin D, Biasi F, Deiana M. Redox Biol. 2018 Jul;17:348-354. doi: 10.1016/j.redox.2018.05.006. Epub 2018 May 16. PMID: 29793168 Free PMC article. 23 Cite Share Impact of red and processed meat and fibre intake on treatment outcomes among patients with chronic inflammatory diseases: protocol for a prospective cohort study of prognostic factors and personalised medicine. Christensen R, Heitmann BL, Andersen KW, Nielsen OH, Sørensen SB, Jawhara M, Bygum A, Hvid L, Grauslund J, Wied J, Glerup H, Fredberg U, Villadsen JA, Kjær SG, Fallingborg J, Moghadd SAGR, Knudsen T, Brodersen J, Frøjk J, Dahlerup JF, Bojesen AB, Sorensen GL, Thiel S, Færgeman NJ, Brandslund I, Bennike TB, Stensballe A, Schmidt EB, Franke A, Ellinghaus D, Rosenstiel P, Raes J, Boye M, Werner L, Nielsen CL, Munk HL, Nexøe AB, Ellingsen T, Holmskov U, Kjeldsen J, Andersen V. BMJ Open. 2018 Feb 8;8(2):e018166. doi: 10.1136/bmjopen-2017-018166. PMID: 29439003 Free PMC article. 24 Cite Share Systematic review and meta-analysis: pharmacogenetics of anti-TNF treatment response in rheumatoid arthritis. Bek S, Bojesen AB, Nielsen JV, Sode J, Bank S, Vogel U, Andersen V. Pharmacogenomics J. 2017 Oct;17(5):403-411. doi: 10.1038/tpj.2017.26. Epub 2017

				Jun 13. PMID: 28607508 Free PMC article. Review. 25 Cite Share A Proposal for a Study on Treatment Selection and Lifestyle Recommendations in Chronic Inflammatory Diseases: A Danish Multidisciplinary Collaboration on Prognostic Factors and Personalised Medicine. Andersen V, Holmskov U, Sørensen SB, Jawhara M, Andersen KW, Bygum A, Hvid L, Grauslund J, Wied J, Glerup H, Fredberg U, Villadsen JA, Kjær SG, Fallingborg J, Moghadd SAGR, Knudsen T, Brodersen J, Frøjk J, Dahlerup JF, Nielsen OH, Christensen R, Bojesen AB, Sorensen GL, Thiel S, Færgeman NJ, Brandslund I, Stensballe A, Schmidt EB, Franke A, Ellinghaus D, Rosenstiel P, Raes J, Heitmann B, Boye M, Nielsen CL, Werner L, Kjeldsen J, Ellingsen T. Nutrients. 2017 May 15;9(5):499. doi: 10.3390/nu9050499. PMID: 28505128 Free PMC article. 26 Cite Share Potential Impact of Diet on Treatment Effect from Anti-TNF Drugs in Inflammatory Bowel Disease. Andersen V, Hansen AK, Heitmann BL. Nutrients. 2017 Mar 15;9(3):286. doi: 10.3390/nu9030286. PMID: 28294972 Free PMC article. Review. 27 Cite Share Promise and peril in nanomedicine: the challenges and needs for integrated systems biology approaches to define health risk. Halappanavar S, Vogel U, Wallin H, Yauk CL. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2018 Jan;10(1):e1465. doi: 10.1002/wnan.1465. Epub 2017 Mar 15. PMID: 28294555 Free PMC

			article. Review. 28 Cite Share Genetically determined high activity of IL-12 and IL-18 in ulcerative colitis and TLR5 in Crohns disease were associated with non-response to anti-TNF therapy. Bank S, Andersen PS, Burisch J, Pedersen N, Roug S, Galsgaard J, Turino SY, Brodersen JB, Rashid S, Rasmussen BK, Avlund S, Olesen TB, Hoffmann HJ, Nexø BA, Sode J, Vogel U, Andersen V. Pharmacogenomics J. 2018 Jan;18(1):87-97. doi: 10.1038/tpj.2016.84. Epub 2017 Jan 31. PMID: 28139755

Methodical Notes

Funding Sources: none

COI: declared

Study Quality: drop-out indicated
study quality not addressed

Heterogeneity: Forest pmts of significant associations provided

Publication Bias: not addressed

Notes:

Brand, E. C. et al. Systematic Review and External Validation of Prediction Models Based on Symptoms and Biomarkers for Identifying Endoscopic Activity in Crohn's Disease. Clin Gastroenterol Hepatol. . . 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type: systemaitc review** **Databases: Pubmed Cochrane** **Search period: feb 14 2018** **Inclusion Criteria: explained** **We included articles based on the following eligibility criteria: (1) full-text articles published in peer-reviewed journals; (2) no language re-strictions; (3) a cross-sectional study design (ie, the developed model must predict the endoscopic outcome at the same moment**	**Population: defined** **Intervention: clear** **Comparison: clear**	**Primary: Biomarker for detection of CD activity** **Secondary: -** **Results: We screened 5303 articles and identified 27 models (from 21 studies) for our analysis. Seven models could be validated externally; in the T AILORIX data set, these models identified patients with endoscopic activity with AUROC values ranging from 0.61 (95% CI, 0.51-0.70) to 0.81 (95% CI, 0.76-0.86). In this data set, the AUROC value for FC concentration was 0.79 (95% CI, 0.74-0.85) and the AUROC**	**Serum 1,3-beta-D-glucan as a noninvasive test to predict histologic activity in patients with inflammatory bowel disease.** **Farias E Silva K, Nanini HF, Cascabulho CM, Rosas SLB, Santana PT, Carneiro AJV, Anaissie E, Nucci M, de Souza HSP.** **World J Gastroenterol. 2021 Mar 7;27(9):866-885. doi: 10.3748/wjg.v27.i9.866. PMID: 33727775 Free PMC article.** **Capsule Endoscopy Is Useful for Postoperative Tight Control Management in Patients with Crohn's**

in time); (4) studies exclusively aimed at adult Crohn's disease patients, or, if both ulcerative colitis and Crohn's disease patients were studied, enabling the extraction of data for Crohn's disease alone; (5) description of the prediction/diagnostic model, risk score, noninvasive index, clinical decision rule, or equivalent for the outcome ileocolonic We included articles based on the following eligibility criteria: (1) full-text articles published in peer-reviewed journals; (2) no language re-strictions; (3) a cross-sectional study design (ie, the developed model must predict the endoscopic outcome at the same moment in time); (4) studies exclusively aimed at adult Crohn's disease patients, or, if both ulcerative colitis and Crohn's disease patients were studied, enabling the extraction of data for Crohn's disease alone; (5) description of the prediction/diagnostic model, risk score, noninvasive index, clinical decision rule, or equivalent for the outcome ileocolonic Exclusion Criteria: explained		value for CRP level was 0.72 (95% CI, 0.66-0.77). The AUROC values for the validation in the UAI data set were similar. In the TAILORIX and/or UAI data set, 4 of the 7 models, as weil as the FC and CRP assays, were able to identify patients with endoscopic activity with positive predictive values of 90% or more. Two of the 7 models (but not the FC or CRP values) identified patients without endoscopic activity with a negative predictive value (NPV) of 90% or mure, leading to correct prediction of endoscopic healing in 3.2% to 11.3% of all patients. For example, applying the Herranz-Bachiller model (1 of 7 models) at a NPV of 92.1 % and a positive predictive value of 91.9% correctly identified 35.7% of all patients in whom ileocolonoscopy could be avoided for expected endoscopic activity or healing but incorrectly identified 3.2% of all patients. Most ileocolonoscopies (66.5% in TAILORIX and 72.6% in the UAI of all ileocolonoscopies) could be avoided correctly based on concentrations of FC of 100 µg/g or less and 250 µg/g or higher. However, using this range of FC concentrations to identify patients who do not require ileocolonoscopy caused 18.7% of all patients in the TAI-LORIX cohort and 19.8% of all patients in the UAI cohort to be predicted incorrectly to have endoscopic activity or healing. Author's Conclusion: endoscopy stays the gold standard	Disease. Shiga H, Abe I, Kusaka J, Shimoyama Y, Moroi R, Kuroha M, Kakuta Y, Kinouchi Y, Masamune A. Dig Dis Sci. 2021 Jan 25. doi: 10.1007/s10620-021-06841-6. Online ahead of print. PMID: 33495918 COVID-19 Pandemic: Which IBD Patients Need to Be Scoped-Who Gets Scoped Now, Who Can Wait, and how to Resume to Normal. Ng SC, Mak JWY, Hitz L, Chowers Y, Bernstein CN, Silverberg MS. J Crohns Colitis. 2020 Oct 21;14(Supplement_3):S791-S797. doi: 10.1093/ecco-jcc/jjaa128. PMID: 33085973 Free PMC article. Defining the Path Forward for Biomarkers to Address Unmet Needs in Inflammatory Bowel Diseases. Honig G, Heller C, Hurtado-Lorenzo A. Inflamm Bowel Dis. 2020 Sep 18;26(10):1451-1462. doi: 10.1093/ibd/izaa210. PMID: 32812036

Methodical Notes

Funding Sources: Medical university

COI: decalred

Study Quality: not addressed

Heterogeneity: low, not specifically addressed

Publication Bias:
Critical Appraisal. The risk of bias and applicability of the included studies was assessed independently by 2 authors (E.C.B. and J.J.v.d.V.) based on the Prediction model Risk Of Bias ASsessment Tool (PROBAST).1 7 Publications were assessed for risk of bias in 4 domains (participant selection, predictors, outcome, and

analyses) and for applicability in

Notes:

Di Ruscio, M. et al. Surrogate Fecal Biomarkers in Inflammatory Bowel Disease: Rivals or Complementary Tools of Fecal Calprotectin?. Inflamm Bowel Dis. 24. 78-92. 2017			
Evidence level/Study Types	**P - I - C**	**Outcomes/Results**	**Literature References**
Evidence level: 1 Study type: systematic review, meta analysis Databases: Medline and the Cochrane Library Search period: April 2017 Inclusion Criteria: A systematic electronic search of the English literature up to April 2017 was performed using Medline (EBSCO host) and the Cochrane Library. The search strategy used a combination of Medical Subject (MeSH) headings and key words as follows: “inflammatory bowel disease,” “Crohn’s disease,” “ulcerative colitis,” “fecal markers,” “fecal biomarkers,” “S100A12,” “high mobility group box 1,” “neopterin, polymorphonuclear neutrophil elastase,” “fecal hemoglobin,” “alpha1-antitrypsin,” “human neutrophil peptides,” “neutrophil gelatinase-associated lipocalin,” “chitinase 3-like-1,” “matrix metalloproteinase	Population: ok Intervention: none Comparison: ok	Primary: Fecal calprotectin, comparisons? Secondary: none Results: Out of 1023 citations, 125 eligible studies were identified. Data were grouped according to each fecal marker including S100A12, high-mobility group box 1, neopterin, polymorphonuclear neutrophil elastase, fecal hemoglobin, alpha1-antitrypsin, human neutrophil peptides, neutrophil gelatinase-associated lipocalin, chitinase 3-like-1, matrix metalloproteinase 9, lysozyme, M2-pyruvate kinase, myeloperoxidase, fecal eosinophil proteins, human beta-defensin-2, and beta-glucuronidase. Some of these markers showed a high sensitivity and specificity and correlated with disease activity, response to therapy, and mucosal healing. Furthermore, they showed a potential utility in the prediction of clinical relapse. Author's Conclusion: Several fecal biomarkers have the potential to become useful tools	Surrogate Fecal Biomarkers in Inflammatory Bowel Disease: Rivals or Complementary Tools of Fecal Calprotectin? Di Ruscio M, Vernia F, Ciccone A, Frieri G, Latella G. Inflamm Bowel Dis. 2017 Dec 19;24(1):78-92. doi: 10.1093/ibd/izx011. PMID: 29272479 Review. 2 Cite Share The Usefulness of Serum Vitamin D Levels in the Assessment of IBD Activity and Response to Biologics. Valvano M, Magistroni M, Mancusi A, D'Ascenzo D, Longo S, Stefanelli G, Vernia F, Viscido A, Necozione S, Latella G. Nutrients. 2021 Jan 22;13(2):323. doi: 10.3390/nu13020323. PMID: 33499406 Free PMC article. 3 Cite Share The Intestinal Barrier and Current Techniques for the Assessment of Gut Permeability. Schoultz I, Keita ÅV. Cells. 2020 Aug 17;9(8):1909. doi: 10.3390/cells9081909. PMID: 32824536 Free PMC article. Review. 4 Cite Share Paneth Cell-Derived Lysozyme Defines the Composition of Mucolytic Microbiota and the Inflammatory Tone of the Intestine. Yu S, Balasubramanian I, Laubitz D, Tong K, Bandyopadhyay S, Lin X, Flores J, Singh R, Liu Y, Macazana C, Zhao Y, Béguet-Crespel F, Patil K, Midura-Kiela MT, Wang D, Yap GS, Ferraris RP, Wei Z, Bonder EM, Häggblom MM, Zhang L, Douard V, Verzi MP, Cadwell K, Kiela PR, Gao N. Immunity. 2020 Aug 18;53(2):398-416.e8. doi: 10.1016/j.immuni.2020.07.010. PMID: 32814028 5 Cite Share S100A12 in Digestive Diseases and Health: A Scoping Review. Carvalho A, Lu J, Francis JD, Moore RE, Haley

9," "lysozyme,"" M2-pyruvate kinase," "myeloperoxidase," "fecal eosinophil proteins," "human beta-defensin-2," and "beta-glucuronidase." Four authors (M.D.R., F.V., A.C., and G.L.) screened the abstracts and identified relevant articles. Additional studies were identified via a manual review of the reference list of the identified studies and review articles. Any discrepancy was resolved by consensus, referring back to the original article. Out of 1023 citations, 125 eligible studies were identified. Data have been grouped according to each fecal marker. Exclusion Criteria: Only papers written in English that analyzed human stool samples were included. In vitro studies, animal studies, studies on blood/serum samples, and studies analyzing FC or FL alone were excluded.		complementing FC in IBD diagnosis and monitoring. However, wide variability in their accuracy in assessment of intestinal inflammation suggests the need for further studies.	KP, Doster RS, Townsend SD, Johnson JG, Damo SM, Gaddy JA. Gastroenterol Res Pract. 2020 Feb 26;2020:2868373. doi: 10.1155/2020/2868373. eCollection 2020. PMID: 32184815 Free PMC article. Review. 6 Cite Share Differential gene expression and gene-set enrichment analysis in Caco-2 monolayers during a 30-day timeline with Dexamethasone exposure. Robinson JM, Turkington S, Abey SA, Kenea N, Henderson WA. Tissue Barriers. 2019;7(3):e1651597. doi: 10.1080/21688370.2019.1651597. Epub 2019 Aug 22. PMID: 31438773 Free PMC article. 7 Cite Share Eosinophils in the gastrointestinal tract and their role in the pathogenesis of major colorectal disorders. Loktionov A. World J Gastroenterol. 2019 Jul 21;25(27):3503-3526. doi: 10.3748/wjg.v25.i27.3503. PMID: 31367153 Free PMC article. Review. 8 Cite Share Systematic review: outcomes and adverse events from randomised trials in Crohn's disease. Catt H, Hughes D, Kirkham JJ, Bodger K. Aliment Pharmacol Ther. 2019 Apr;49(8):978-996. doi: 10.1111/apt.15174. Epub 2019 Mar 3. PMID: 30828852 Free PMC article. 9 Cite Share Faecal Calprotectin. Pathirana WGW, Chubb SP, Gillett MJ, Vasikaran SD. Clin Biochem Rev. 2018 Aug;39(3):77-90. PMID: 30828114 Free PMC article. Review. 10 Cite Share Role of indoleamine 2,3-dioxygenase in pathology of the gastrointestinal tract. Acovic A, Gazdic M, Jovicic N, Harrell CR, Fellabaum C, Arsenijevic N, Volarevic V. Therap Adv Gastroenterol. 2018 Dec 6;11:1756284818815334. doi: 10.1177/1756284818815334. eCollection 2018. PMID: 30574192 Free PMC article. Review. Page 2	

			11 Cite Share Redefining the Practical Utility of Blood Transcriptome Biomarkers in Inflammatory Bowel Diseases. Ostrowski J, Dabrowska M, Lazowska I, Paziewska A, Balabas A, Kluska A, Kulecka M, Karczmarski J, Ambrozkiewicz F, Piatkowska M, Goryca K, Zeber-Lubecka N, Kierkus J, Socha P, Lodyga M, Klopocka M, Iwanczak B, Bak-Drabik K, Walkowiak J, Radwan P, Grzybowska-Chlebowczyk U, Korczowski B, Starzynska T, Mikula M. J Crohns Colitis. 2019 Apr 26;13(5):626-633. doi: 10.1093/ecco-jcc/jjy205. PMID: 30541017 Free PMC article. 12 Cite Share Indoleamine 2,3-dioxygenase-dependent expansion of T-regulatory cells maintains mucosal healing in ulcerative colitis. Acovic A, Simovic Markovic B, Gazdic M, Arsenijevic A, Jovicic N, Gajovic N, Jovanovic M, Zdravkovic N, Kanjevac T, Harrell CR, Fellabaum C, Dolicanin Z, Djonov V, Arsenijevic N, Lukic ML, Volarevic V. Therap Adv Gastroenterol. 2018 Aug 24;11:1756284818793558. doi: 10.1177/1756284818793558. eCollection 2018. PMID: 30159037 Free PMC article. 13 Cite Share Diagnostic Markers for Nonspecific Inflammatory Bowel Diseases. Derkacz A, Olczyk P, Komosinska-Vassev K. Dis Markers. 2018 Jun 11;2018:7451946. doi: 10.1155/2018/7451946. eCollection 2018. PMID: 29991970 Free PMC article. Review. 14 Cite Share Emerging concepts in non-invasive monitoring of Crohn's disease. Marlicz W, Skonieczna-Żydecka K, Dabos KJ, Łoniewski I, Koulaouzidis A. Therap Adv Gastroenterol. 2018 Apr 18;11:1756284818769076. doi: 10.1177/1756284818769076. eCollection 2018. PMID: 29707039 Free PMC article. Review.
Methodical Notes			
Funding Sources: none **COI: none** **Study Quality: OK, not specifically addressed** **Heterogeneity: low, not specifically addressed** **Publication Bias: not addressed**			

Notes:

Kopylov, U. et al. Fecal calprotectin for the prediction of small-bowel Crohn's disease by capsule endoscopy: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 28. 1137-44. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: systematic review, metaanalysis Databases: pub/Embase Search period: 1/200 to 11/2015 Inclusion Criteria: To capture as many articles and abstracts as possible, a broad search strategy was used by combining the terms 'capsule endoscopy' and 'calprotectin'. The search was performed with no limitations. The pool was supplemented with a hand search of relevant abstracts from major gastroenterological meetings. For a study to be included in this meta-analysis, the following predefined inclusion criteria had to be fulfilled: randomizedcontrolled trials, open-label prospective, observational studies, and case–control studies of FC and CE in patients undergoing evaluation for suspected CD or reassessment of CD activity. For studies with multiple indications for CE examination, only results pertaining to suspected CD or CD reassessment were considered for inclusion in our	Population: defined Intervention: The diagnostic accuracy [sensitivity, specificity, diagnostic odds ratio (DOR)] of FC for diagnosis of SBCD or evidence of active inflammation in the small-bowel in established CD was evaluated. The diagnosis of active SBCD was made in accordance to the criteria used in the original publications. We evaluated three FC level cut-offs as per availability of reports in the included studies: 50, 100, and 200 µg/g. Comparison: prediction	Primary: The aim of the current study was to assess the diagnostic accuracy of calprotectin for the prediction of active small-bowel disease on capsule endoscopy by performing a diagnostic test meta-analysis Secondary: - Results: Seven studies (463 patients) were entered into the final analysis. The DOR was significant for all the evaluated FC cutoffs (50 µg/g: sensitivity 0.83, specificity 0.53, DOR-5.64; 100 µg/g: sensitivity 0.68, specificity 0.71, DOR-5.01; 200 µg/g: sensitivity 0.42, specificity 0.94, DOR-13.64). On sensitivity analyses, when only studies addressing suspected Crohn's or retrospective studies were included, the results did not change significantly. For studies including patients with suspected CD only, the overall accuracy for FC cut-off 50 µg/g was further increased (sensitivity 0.89, specificity 0.55, DOR-10.3), with a negative predictive value of 91.8%. Author's Conclusion: Fecal calprotectin has a significant diagnostic accuracy for the detection of small-bowel CD. Our results suggest that in patients with suspected CD with calprotectin < 50 µg/g, the likelihood of positive diagnosis is very low.	Fecal calprotectin for the prediction of small-bowel Crohn's disease by capsule endoscopy: a systematic review and meta-analysis. Kopylov U, Yung DE, Engel T, Avni T, Battat R, Ben-Horin S, Plevris JN, Eliakim R, Koulaouzidis A. Eur J Gastroenterol Hepatol. 2016 Oct;28(10):1137-44. doi: 10.1097/MEG.0000000000000692. PMID: 27415156 Review. 2 Cite Share Capsule endoscopy in inflammatory bowel disease: when and how. Hilmi I, Kobayashi T. Intest Res. 2020 Jul;18(3):265-274. doi: 10.5217/ir.2019.09165. Epub 2020 Jul 7. PMID: 32623876 Free PMC article. Review. 3 Cite Share A Light-Weight Practical Framework for Feces Detection and Trait Recognition. Leng L, Yang Z, Kim C, Zhang Y. Sensors (Basel). 2020 May 6;20(9):2644. doi: 10.3390/s20092644. PMID: 32384651 Free PMC article. 4 Cite Share A novel PillCam Crohn's capsule score (Eliakim score) for quantification of mucosal inflammation in Crohn's disease. Eliakim R, Yablecovitch D, Lahat A, Ungar B, Shachar E, Carter D, Selinger L, Neuman S, Ben-Horin S, Kopylov U. United European Gastroenterol J. 2020 Jun;8(5):544-551. doi: 10.1177/2050640620913368. Epub 2020 Mar 12. PMID: 32213037 Free PMC article. 5 Cite Share Comparison of the use of wireless

study. Studies addressing patients undergoing evaluation for obscure GI bleeding or suspected small bowel malignancy were excluded. Only studies including more than 30 patients were eventually included. Exclusion Criteria: shown			capsule endoscopy with magnetic resonance enterography in children with inflammatory bowel disease. Hijaz NM, Attard TM, Colombo JM, Mardis NJ, Friesen CA. World J Gastroenterol. 2019 Jul 28;25(28):3808-3822. doi: 10.3748/wjg.v25.i28.3808. PMID: 31391775 Free PMC article. 6 Cite Share Should We Divide Crohn's Disease Into Ileum-Dominant and Isolated Colonic Diseases? Dulai PS, Singh S, Vande Casteele N, Boland BS, Rivera-Nieves J, Ernst PB, Eckmann L, Barrett KE, Chang JT, Sandborn WJ. Clin Gastroenterol Hepatol. 2019 Dec;17(13):2634-2643. doi: 10.1016/j.cgh.2019.04.040. Epub 2019 Apr 19. PMID: 31009791 Free PMC article. Review. 7 Cite Share Association Between Level of Fecal Calprotectin and Progression of Crohn's Disease. Kennedy NA, Jones GR, Plevris N, Patenden R, Arnott ID, Lees CW. Clin Gastroenterol Hepatol. 2019 Oct;17(11):2269-2276.e4. doi: 10.1016/j.cgh.2019.02.017. Epub 2019 Feb 14. PMID: 30772585 Free PMC article. 8 Cite Share Proteomic Evaluation of the Acute Radiation Syndrome of the Gastrointestinal Tract in a Murine Total-body Irradiation Model. Huang W, Yu J, Jones JW, Carter CL, Pierzchalski K, Tudor G, Booth C, MacVittie TJ, Kane MA. Health Phys. 2019 Apr;116(4):516-528. doi: 10.1097/HP.0000000000000951. PMID: 30624357 Free PMC article. 9 Cite Share Usefulness of fecal calprotectin by monoclonal antibody testing in adult Japanese with inflammatory bowel diseases: a prospective multicenter study. Nakamura S, Imaeda H, Nishikawa H, Iimuro M, Matsuura M, Oka H, Oku J,

Miyazaki T, Honda H, Watanabe K, Nakase H, Andoh A.
Intest Res. 2018 Oct;16(4):554-562. doi: 10.5217/ir.2018.00027. Epub 2018 Oct 10.
PMID: 30301337 Free PMC article.

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Cite Share

From bench to bedside: Fecal calprotectin in inflammatory bowel diseases clinical setting.
Mumolo MG, Bertani L, Ceccarelli L, Laino G, Di Fluri G, Albano E, Tapete G, Costa F.
World J Gastroenterol. 2018 Sep 7;24(33):3681-3694. doi: 10.3748/wjg.v24.i33.3681.
PMID: 30197475 Free PMC article. Review.
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Fecal calprotectin for detection of postoperative endoscopic recurrence in Crohn's disease: systematic review and meta-analysis.
Tham YS, Yung DE, Fay S, Yamamoto T, Ben-Horin S, Eliakim R, Koulaouzidis A, Kopylov U.
Therap Adv Gastroenterol. 2018 Jul 8;11:1756284818785571. doi: 10.1177/1756284818785571. eCollection 2018.
PMID: 30034529 Free PMC article.

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Small bowel imaging in Crohn's disease patients.
Gauci J, Sammut L, Sciberras M, Piscopo N, Micallef K, Cortis K, Ellul P.
Ann Gastroenterol. 2018 Jul-Aug;31(4):395-405. doi: 10.20524/aog.2018.0268. Epub 2018 May 4.
PMID: 29991884 Free PMC article. Review.

13
Cite Share

Emerging concepts in non-invasive monitoring of Crohn's disease.
Marlicz W, Skonieczna-Żydecka K, Dabos KJ, Łoniewski I, Koulaouzidis A.
Therap Adv Gastroenterol. 2018 Apr 18;11:1756284818769076. doi: 10.1177/1756284818769076.

				eCollection 2018. PMID: 29707039 Free PMC article. Review. 14 Cite Share A review of magnetic resonance enterography-based indices for quantification of Crohn's disease inflammation. Rozendorn N, Amitai MM, Eliakim RA, Kopylov U, Klang E. Therap Adv Gastroenterol. 2018 Apr 13;11:1756284818765956. doi: 10.1177/1756284818765956. eCollection 2018. PMID: 29686731 Free PMC article. Review. 15 Cite Share The role of inflammation in temporal shifts in the inflammatory bowel disease mucosal microbiome. Kiely CJ, Pavli P, O'Brien CL. Gut Microbes. 2018 Nov 2;9(6):477-485. doi: 10.1080/19490976.2018.1448742. Epub 2018 Sep 5. PMID: 29543557 Free PMC article. 16 Cite Share The Lewis score or the capsule endoscopy Crohn's disease activity index: which one is better for the assessment of small bowel inflammation in established Crohn's disease? Yablecovitch D, Lahat A, Neuman S, Levhar N, Avidan B, Ben-Horin S, Eliakim R, Kopylov U. Therap Adv Gastroenterol. 2018 Jan 14;11:1756283X17747780. doi: 10.1177/1756283X17747780. eCollection 2018. PMID: 29399042 Free PMC article. 17 Cite Share Validation of Neutrophil CD64 Blood Biomarkers to Detect Mucosal Inflammation in Pediatric Crohn's Disease. Minar P, Jackson K, Tsai YT, Sucharew H, Rosen MJ, Denson LA. Inflamm Bowel Dis. 2017 Dec 19;24(1):198-208. doi: 10.1093/ibd/izx022. PMID: 29272485 Free PMC article. 18

			Cite Share Balloon-Assisted Enteroscopy and Capsule Endoscopy in Suspected Small Bowel Crohn's Disease. Yen HH, Chang CW, Chou JW, Wei SC. Clin Endosc. 2017 Sep;50(5):417-423. doi: 10.5946/ce.2017.142. Epub 2017 Sep 29. PMID: 29017295 Free PMC article. Review. 19 Cite Share The impact of panenteric capsule endoscopy on the management of Crohn's disease. Eliakim R. Therap Adv Gastroenterol. 2017 Sep;10(9):737-744. doi: 10.1177/1756283X17720860. Epub 2017 Jul 24. PMID: 28932274 Free PMC article. Review. 20 Cite Share Fecal occult blood testing for the prediction of small-bowel pathology detected by capsule endoscopy: a systematic review and meta-analysis. Yung DE, Vijayan S, Avni T, Douglas S, Kopylov U, Koulaouzidis A. Ann Gastroenterol. 2017;30(2):186-191. doi: 10.20524/aog.2017.0122. Epub 2017 Jan 5. PMID: 28243039 Free PMC article. Page 3 21 Cite Share Capsule endoscopy for the diagnosis and follow up of Crohn's disease: a comprehensive review of current status. Jensen MD, Brodersen JB, Kjeldsen J. Ann Gastroenterol. 2017;30(2):168-178. doi: 10.20524/aog.2016.0119. Epub 2016 Dec 22. PMID: 28243037
Methodical Notes			
Funding Sources: none **COI: none** **Study Quality: The diagnostic accuracy [sensitivity, specificity, diagnostic odds ratio (DOR)] of FC for diagnosis of SBCD or evi- dence of active inflammation in the small-bowel in estab- lished CD was evaluated. The diagnosis of active SBCD was made in accordance to the criteria used in the original publications. We evaluated three FC level cut-offs as per availability of reports in the included studies: 50,**			

100, and 200 µg/g.
Quality assessment of diagnostic accuracy studies (QUADAS) 2 results for the studies included.

Heterogeneity: high
The I2 statistic was used and a value of more than 50% was used as a cut- off for significant heterogeneity. Because of the high het- erogeneity between the studies included, the DerSimoian–Laird random-effects model was applied. Sensitivity analysis using only the highest quality trials (defined as trials that were both blinded and published as full manuscripts) was carried out for comparisons with two or more high-quality trials. Methodological quality of the included studies was evaluated using the quality assessment of diagnostic accuracy studies (QUADAS) 2 scale [25]. Analyses were carried out using STATA 12 (StataCorp, College Station, Texas, USA) and RevMan 5.3 (Cochrane corporation, London, UK) software packages.

Publication Bias: not addressed

Notes:

Lin, J. F. et al. Meta-analysis: fecal calprotectin for assessment of inflammatory bowel disease activity. Inflamm Bowel Dis. 20. 1407-15. 2014

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: metaanalysis Databases: databases Medline, Web of Science, Cochrane Library, and EMBASE Search period: december 2013 Inclusion Criteria: if it met the inclusion criteria as follows: (1) the study evaluated FC for monitoring IBD activity; (2) an endoscopic scoring system was used as reference standard to assess inflammatory activity; (3) the study provided sufficient	Population: defined Intervention: measurement calproetctin Comparison: disease activity	Primary: The aim of our study was to evaluate the diagnostic accuracy of FC for differentiating between patients with active IBD and those in remission. Secondary: - Results: We included 13 studies (744 patients with UC and 727 with CD) in the final analysis. The area under the curve values were 0.89 (95% confidence interval, 0.86–0.92), 0.93 (0.89–0.97), and 0.88 (0.83–0.93) in the IBD, UC, and CD groups, respectively. For the IBD group at a cutoff value of 50 mg/g, the pooled sensitivity was 0.92 (0.90–0.94) and specificity 0.60 (0.52–0.67). For a cutoff value at 100 mg/g, the pooled sensitivity was 0.84 (0.80–0.88) and specificity was 0.66 (0.59–0.73). For a cutoff value at 250 mg/g, the pooled sensitivity was 0.80	Cite Share Meta-analysis: fecal calprotectin for assessment of inflammatory bowel disease activity. Lin JF, Chen JM, Zuo JH, Yu A, Xiao ZJ, Deng FH, Nie B, Jiang B. Inflamm Bowel Dis. 2014 Aug;20(8):1407-15. doi: 10.1097/MIB.0000000000000057. PMID: 24983982 2 Cite Share Factors Associated with Poor Quality of Life in a Canadian Cohort of Patients with Inflammatory Bowel Disease: A Cross-sectional Study. Nazarian A, Bishay K, Gholami R, Scaffidi MA, Khan R, Cohen-Lyons D, Griller N, Satchwell JB, Baker JP, Grover SC, Irvine EJ. J Can Assoc Gastroenterol. 2020 May 16;4(2):91-96. doi: 10.1093/jcag/gwaa014. eCollection 2021 Apr. PMID: 33855267 Free PMC article. 3 Cite Share Assessment of fecal calprotectin and fecal occult blood as point-of-care markers for soil-transmitted helminth attributable intestinal morbidity in a case-control substudy conducted in Côte d'Ivoire, Lao PDR and Pemba Island, Tanzania. Patel C, Keller L, Welsche S, Hattendorf J, Sayasone S, Ali SM, Ame SM, Coulibaly JT, Hürlimann E, Keiser J. EClinicalMedicine. 2021 Jan 30;32:100724. doi: 10.1016/j.eclinm.2021.100724. eCollection 2021 Feb. PMID: 33554091 Free PMC article. 4 Cite Share

details to construct a 2-by-2 table. Studies were excluded if conducted in pediatric patients with IBD. Exclusion Criteria: -		(0.76–0.84) and specificity was 0.82 (0.77–0.86). Author's Conclusion: The FC test is a reliable marker for assessing IBD disease activity and may have greater ability to evaluate disease activity in UC than CD	Increased Fecal Calprotectin Is Associated with Worse Gastrointestinal Symptoms and Quality of Life Scores in Children with Cystic Fibrosis. Beaufils F, Mas E, Mittaine M, Addra M, Fayon M, Delhaes L, Clouzeau H, Galode F, Lamireau T, Bui S, Enaud R. J Clin Med. 2020 Dec 17;9(12):4080. doi: 10.3390/jcm9124080. PMID: 33348735 Free PMC article. 5 Cite Share A Pilot Study Evaluating Novel Urinary Biomarkers for Crohn's Disease. Ho SS, Wall C, Gearry RB, Keenan J, Day AS. Inflamm Intest Dis. 2020 Nov;5(4):212-220. doi: 10.1159/000510682. Epub 2020 Oct 14. PMID: 33313074 Free PMC article. 6 Cite Share First United Arab Emirates consensus on diagnosis and management of inflammatory bowel diseases: A 2020 Delphi consensus. Alkhatry M, Al-Rifai A, Annese V, Georgopoulos F, Jazzar AN, Khassouan AM, Koutoubi Z, Nathwani R, Taha MS, Limdi JK. World J Gastroenterol. 2020 Nov 21;26(43):6710-6769. doi: 10.3748/wjg.v26.i43.6710. PMID: 33268959 Free PMC article. Review. 7 Cite Share COVID-19 Pandemic: Which IBD Patients Need to Be Scoped-Who Gets Scoped Now, Who Can Wait, and how to Resume to Normal. Ng SC, Mak JWY, Hitz L, Chowers Y, Bernstein CN, Silverberg MS. J Crohns Colitis. 2020 Oct 21;14(Supplement_3):S791-S797. doi: 10.1093/ecco-jcc/jjaa128. PMID: 33085973 Free PMC article. 8 Cite Share Biomarkers of Crohn's Disease to Support the Development of New Therapeutic Interventions. Porter AC, Aubrecht J, Birch C, Braun J, Cuff C, Dasgupta S, Gale JD, Hinton R, Hoffmann SC, Honig G, Linggi B, Schito M, Casteele NV, Sauer JM. Inflamm Bowel Dis. 2020 Sep 18;26(10):1498-1508. doi: 10.1093/ibd/izaa215. PMID: 32840322 9 Cite Share Normal fecal calprotectin levels in healthy children are higher than in adults and decrease with age. Velasco Rodríguez-Belvís M, Viada Bris JF, Plata

Fernández C, García-Salido A, Asensio Antón J, Domínguez Ortega G, Muñoz Codoceo RA.
Paediatr Child Health. 2020 Aug;25(5):286-292. doi: 10.1093/pch/pxz070. Epub 2019 Jun 17.
PMID: 32765164

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Analytical and clinical performance of the fully-automated LIAISONXL calprotectin immunoassay from DiaSorin in IBD patients.
Vicente-Steijn R, Jansen JM, Bisheshar R, Haagen IA.
Pract Lab Med. 2020 Jun 24;21:e00175. doi: 10.1016/j.plabm.2020.e00175. eCollection 2020 Aug.
PMID: 32637525 Free PMC article.
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Comparison of 18F-FDG PET-MR and fecal biomarkers in the assessment of disease activity in patients with ulcerative colitis.
Li Y, Khamou M, Schaarschmidt BM, Umutlu L, Forsting M, Demircioglu A, Haubold J, Koch AK, Bruckmann NM, Sawicki LM, Herrmann K, Boone JH, Langhorst J.
Br J Radiol. 2020 Aug;93(1112):20200167. doi: 10.1259/bjr.20200167. Epub 2020 Jun 24.
PMID: 32579403 Clinical Trial.

12
Cite Share

Ranking microbiome variance in inflammatory bowel disease: a large longitudinal intercontinental study.
Clooney AG, Eckenberger J, Laserna-Mendieta E, Sexton KA, Bernstein MT, Vagianos K, Sargent M, Ryan FJ, Moran C, Sheehan D, Sleator RD, Targownik LE, Bernstein CN, Shanahan F, Claesson MJ.
Gut. 2021 Mar;70(3):499-510. doi: 10.1136/gutjnl-2020-321106. Epub 2020 Jun 14.
PMID: 32536605 Free PMC article.

13
Cite Share

Microbiota changes induced by microencapsulated sodium butyrate in patients with inflammatory bowel disease.
Facchin S, Vitulo N, Calgaro M, Buda A, Romualdi C, Pohl D, Perini B, Lorenzon G, Marinelli C, D'Incà R, Sturniolo GC, Savarino EV.
Neurogastroenterol Motil. 2020 Oct;32(10):e13914. doi: 10.1111/nmo.13914. Epub 2020 May 31.
PMID: 32476236 Free PMC article.

14
Cite Share

MicroRNA-320a Monitors Intestinal Disease Activity in Patients With Inflammatory Bowel

Disease.
Cordes F, Demmig C, Bokemeyer A, Brückner M, Lenze F, Lenz P, Nowacki T, Tepasse P, Schmidt HH, Schmidt MA, Cichon C, Bettenworth D.
Clin Transl Gastroenterol. 2020 Mar;11(3):e00134. doi: 10.14309/ctg.0000000000000134.
PMID: 32352717 Free PMC article.

15
Cite Share

Endoscopy in inflammatory bowel diseases during the COVID-19 pandemic and post-pandemic period.
Iacucci M, Cannatelli R, Labarile N, Mao R, Panaccione R, Danese S, Kochhar GS, Ghosh S, Shen B.
Lancet Gastroenterol Hepatol. 2020 Jun;5(6):598-606. doi: 10.1016/S2468-1253(20)30119-9. Epub 2020 Apr 16.
PMID: 32305075 Free PMC article. Review.

16
Cite Share

Point-of-care gastrointestinal ultrasound in inflammatory bowel disease: An accurate alternative for disease monitoring.
Sathananthan D, Rajagopalan A, Van De Ven L, Martin S, Fon J, Costello S, Bryant RV.
JGH Open. 2019 Oct 9;4(2):273-279. doi: 10.1002/jgh3.12269. eCollection 2020 Apr.
PMID: 32280777 Free PMC article.

17
Cite Share

Measuring Vitamin D Status in Chronic Inflammatory Disorders: How does Chronic Inflammation Affect the Reliability of Vitamin D Metabolites in Patients with IBD?
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Methodical Notes

Funding Sources: none

COI: none

Study Quality: Study quality was assessed using the QUADAS (QUality Assessment of studies of Diagnostic Accuracy included in Systematic reviews) tool. Each item should be answered "yes," "no," or "unclear." We chose all of the 11 items and followed the guidelines for scoring each of them included in the tool recommended against using scales yielding a summary score because the interpretation of the summary score was problematic and potential misleading. Two reviewers evaluated the checklist ndependently. Disagreements were resolved by consensus.

During quality assessment, data extraction, and analysis process, we encountered many obstacles, highlighting the meth- odological flaws in the current studies. It is hoped that more widespread multicenter large samples and implementation of the Standards for the Reporting of Diagnostic Accuracy studies will enable readers to directly extract desired information. These can be emphasized as factors that should be considered and improved in future studies in the area.

Heterogeneity: high

The heterogeneity was detected by a chi-square test or Q-statistic and Higgins I-squared statistic (I2). A P value of less than 0.1 was considered statistically significant heterogeneity for the chi-square or Q-statistics. The percentage of I2 represented the degree of heterogeneity. I2 percentages of 25%, 50%, and 75% indicated a low, moderate, and high degree of heterogeneity,
The source of heterogeneity was explored using threshold analysis, meta-regression, and sensitivity analysis. Meta-regression covariate analysis included pretest probability, blinded design, and sample size. Sensitivity analysis was under- taken to assess the impact of a high pretest probability (pretest probability more than overall average pretest probability) and small sample studies (sample sizes ,100).

Publication Bias: Publication bias was assessed using Deeks' test. P , 0.05 was considered to indicate statistically significant publication bias
Although the funnel plot of publication bias showed some asymmetry due to the limited number of studies, the Deeks' test showed a statistically nonsignificant value (P ¼ 0.425), indicating no publication bias among the included studies.

Notes:

Mao, R. et al. Fecal calprotectin in predicting relapse of inflammatory bowel diseases: a meta-analysis of prospective studies. Inflamm Bowel Dis. 18. 1894-9. 2012

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: systematic review, meta analysis Databases: Medline, Web of Science, Cochrane Library, and EMBASE databases Search period: up to August 2011 Inclusion Criteria: A study was included when meeting the criteria as fol- lows: 1) prospective studies about using FC in predicting IBD relapse; 2) FC level for predicting IBD relapse was measured at remission; 3) estimates of diagnostic accuracy (such as sen- sitivity or specificity); 4) the identification of relapse is based on clinical activity indices or endoscopic findings; and 5) stud- ies were conducted in human, nonpediatric populations. Exclusion Criteria: -	Population: IBD Intervention: measurement fecal calprotectin Comparison: FC predictive capacity in IBD relapse	Primary: We aimed to perform a meta- analysis of the predictive capacity of FC in IBD relapse. Secondary: - Results: A total of 672 IBD patients (318 UC and 354 CD) from six different studies were analyzed. The pooled sensitivity and specificity of FC to predict relapse of quiescent IBD was 78% (95% confidence interval [CI]: 72–83) and 73% (95% CI: 68–77), respectively. The area under the summary receiver-operating characteristic (sROC) curve was 0.83 and the diagnostic odds ratio was 10.31 (95% CI: 5.05–21.06). The capacity of FC to predict relapse was comparable between UC and CD. In CD patients the predictive value of FC in isolated small bowel CD was not assessed due to insufficiency of available data. Compared with all enrolled CD patients, FC appeared to be more accurate in ileocolonic and colonic CD. Author's Conclusion: As a simple and noninvasive marker, FC is useful to predict relapse in quiescent IBD patients.	76 citations Fecal calprotectin in predicting relapse of inflammatory bowel diseases: a meta-analysis of prospective studies. Mao R, Xiao YL, Gao X, Chen BL, He Y, Yang L, Hu PJ, Chen MH. Inflamm Bowel Dis. 2012 Oct;18(10):1894-9. doi: 10.1002/ibd.22861. Epub 2012 Jan 11. PMID: 22238138 2 Cite Share Systematic Review: Patient Perceptions of Monitoring Tools in Inflammatory Bowel Disease. Goodsall TM, Noy R, Nguyen TM, Costello SP, Jairath V, Bryant RV. J Can Assoc Gastroenterol. 2020 Jan 24;4(2):e31-e41. doi: 10.1093/jcag/gwaa001. eCollection 2021 Apr. PMID: 33855269 Free PMC article. 3 Cite Share Serum biomarkers confirming stable remission in inflammatory bowel disease. Kessel C, Lavric M, Weinhage T, Brueckner M, de Roock S, Däbritz J, Weber J, Vastert SJ, Foell D. Sci Rep. 2021 Mar 23;11(1):6690. doi: 10.1038/s41598-021-86251-w. PMID: 33758351 Free PMC article. 4 Cite Share Fecal calprotectin is an early predictor of endoscopic response and histologic remission after the start of vedolizumab in inflammatory bowel disease. Pauwels RWM, van der Woude CJ, Erler NS, de Vries AC. Therap Adv Gastroenterol. 2020 Dec 24;13:1756284820979765. doi: 10.1177/1756284820979765. eCollection 2020. PMID: 33488771 Free PMC article. 5 Cite Share

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Management of Crohn's disease in poor responders to adalimumab.
de Boer NKh, Löwenberg M, Hoentjen F.
Clin Exp Gastroenterol. 2014 Apr 11;7:83-92. doi: 10.2147/CEG.S47627. eCollection 2014.
PMID: 24748811 Free PMC article. Review.

73
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Faecal levels of calprotectin in systemic sclerosis are stable over time and are higher compared to primary Sjögren's syndrome and rheumatoid arthritis.
Andréasson K, Saxne T, Scheja A, Bartosik I, Mandl T, Hesselstrand R.
Arthritis Res Ther. 2014 Feb 6;16(1):R46. doi: 10.1186/ar4475.
PMID: 24499541 Free PMC article.

74
Cite Share

Taking Crohn's disease personally.
Chowers Y.
Rambam Maimonides Med J. 2013 Apr 30;4(2):e0011. doi: 10.5041/RMMJ.10111. Print 2013 Apr.
PMID: 23908861 Free PMC article.

			75 Cite Share Utility of faecal calprotectin analysis in adult inflammatory bowel disease. Smith LA, Gaya DR. World J Gastroenterol. 2012 Dec 14;18(46):6782-9. doi: 10.3748/wjg.v18.i46.6782. PMID: 23239916 Free PMC article. 76 Cite Share Environmental enteropathy: critical implications of a poorly understood condition. Korpe PS, Petri WA Jr. Trends Mol Med. 2012 Jun;18(6):328-36. doi: 10.1016/j.molmed.2012.04.007. Epub 2012 May 25. PMID: 22633998 Free PMC article. Review. 77 Cite Share Cost utility of inflammation-targeted therapy for patients with ulcerative colitis. Saini SD, Waljee AK, Higgins PD. Clin Gastroenterol Hepatol. 2012 Oct;10(10):1143-51. doi: 10.1016/j.cgh.2012.05.003. Epub 2012 May 18. PMID: 22610010

Methodical Notes

Funding Sources: none declared

COI: not declared

Study Quality: Forest plots of the pooled sensitivity and specificity are shown in Figure 1. The sensitivity ranged from 0.68– 0.91 (pooled sensitivity 0.78, 95% CI: 0.72–0.83), while specificity ranged from 0.62–0.91 (pooled specificity 0.73, 95% CI: 0.68–0.77). The PLR was 2.81 (95% CI: 2.09– 3.78), NLR was 0.31 (95% CI: 0.2–0.47), and DOR was 10.31 (95% CI: 5.05–21.06). Chi-square values for sensitiv- ity, specificity, PLR, NLR, and DOR were 11.75 (P ¼ 0.038), 16.68, (P ¼ 0.005), 12.95 (P ¼ 0.024), 10.93, (P ¼ 0.0529), and 13.82 (P ¼ 0.016), respectively (Table 2). These indicated a significant heterogeneity across studies regarding sensitivity, PLR, NLR, and DOR, except for NLR.

Heterogeneity: As shown in Table 1, three publications had higher QUADAS scores (

Publication Bias: The Egger test showed that the potential publication bias was significant (P < 0.05).

Notes:

Mosli, M. H. et al. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. Am J Gastroenterol. 110. 802-19; quiz 820. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature

			References
Evidence level: 1 **Study type: Systematic Review and Meta-Analysis** **Databases: MEDLINE and EMBASE using Ovid SP, the Cochrane Library, and the ISI Web of Knowledge** **Search period: to 6 November 2014** **Inclusion Criteria: Cohort and case–control studies that evaluated the diagnostic accuracy of serum CRP, FC, and SL for assessment of endoscopic disease activity in patients with previously diagnosed UC or CD presenting with symptoms suggestive of endoscopically active disease were included. The search included all studies regardless of publication status or language. Study participants were pediatric or adult patients, of any age, previously diagnosed with UC or CD, with symptoms suggestive of endoscopic active disease, in which the presence or absence of active disease was confirmed by endoscopy. Studies that included healthy volunteers or patients with IBS as controls were also evaluated.** **Exclusion Criteria: see inclusion**	**Population: UC, CD and controls** **Intervention: measurement of fecal markers** **Comparison: time to flare**	**Primary: The objective was to evaluate the diagnostic accuracy of C-reactive protein (CRP), fecal calprotectin (FC), and stool lactoferrin (SL) for assessment of endoscopically defined disease activity in IBD.** **Secondary: -** **Results: Nineteen studies (n=2499 patients) were eligible. The pooled sensitivity and specificity estimates for CRP, FC, and SL were 0.49 (95% confidence interval (CI) 0.34–0.64) and 0.92 (95% CI 0.72–0.96), 0.88 (95% CI 0.84–0.90) and 0.73 (95% CI 0.66–0.79), and 0.82 (95% CI 0.73–0.88) and 0.79 (95% CI 0.62–0.89), respectively. FC was more sensitive than CRP in both diseases and was more sensitive in ulcerative colitis than Crohn's disease.** **Author's Conclusion: Although CRP, FC, and SL are useful biomarkers, their value in managing individual patients must be considered in specific clinical contexts.**	**96 citations**

Methodical Notes

Funding Sources: Funding for the IBD/FBD Review Group (1 September 2010—31 August 2015) has been provided by the Canadian Institutes of Health Research (CIHR) Knowledge Transla- tion Branch (CON—105529) and the CIHR Institutes of Nutrition, Metabolism and Diabetes (INMD), and Infection and Immunity (III) and the Ontario Ministry of Health and Long-Term Care (HLTC3968FL-2010-2235).

COI: declared

Study Quality: flow chart shown

Heterogeneity: sensitivity, specificity, PPV, NPV provided

Publication Bias: Publication bias. No statistically significant risk of publication bias was observed for all three biomarkers (CRP: coefficient=−19.34, P=0.117; 95% CI: −44.96 to 6.27, FC: coefficient=−9.712078, P=0.085; 95% CI: −20.86 to 1.43, and SL: coefficient=−20.84, P=0.277; 95% CI: −63.49 to 21.81)

Notes:

Qiu, Y. et al. Fecal calprotectin for evaluating postoperative recurrence of Crohn's disease: a meta-analysis of prospective studies. Inflamm Bowel Dis. 21. 315-22. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Meta-analysis of Prospective Studies Databases: PubMed, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials Search period: 1966 to March 2014 Inclusion Criteria: (1) studies in which FC was used to investigate suspected POR in CD, (2) raw data (for true-positive, false-positive, false-negative, and true-negative re- sults) that could be extracted or calculated from data in the original published study, and (3) studies that applied histopathological or ileocolonoscopic assessment as the reference standard. Exclusion Criteria: Studies were excluded if the crude rates of postoper-ative relapse or remission were not reported	Population: CD patients postoperative with endoscopy Intervention: surgery and endoscopy Comparison: postoperative recurrence dependent on calprotectin	Primary: Using meta-analysis, we aimed to evaluate the utility of FC as a noninvasive marker of recurrence in patients with CD who had undergone previous surgical resection Secondary: - Results: Ten articles met the inclusion criteria, and methodological quality was determined in detail for each study. The 10 studies presented FC levels in 613 postoperative CD patients. The pooled sensitivity and specificity values for assessing suspected endoscopic recurrence were 0.82 (95% confidence interval (CI), 0.73–0.89, 8 studies, n ¼ 391) and 0.61 (95% CI, 0.51–0.71), respectively. The overall positive and negative likelihood ratios were 2.11 (95% CI, 1.68–2.66) and 0.29 (95% CI, 0.197–0.44), respectively. The pooled sensitivity and specificity values for evaluating clinical relapse were 0.59 (95% CI, 0.47–0.71; 3 studies, n ¼ 183) and 0.88 (95% CI, 0.80–0.93), respectively. The overall positive and negative likelihood ratios were 5.10 and 0.47, respectively. Author's Conclusion: As a simple and noninvasive marker, FC is useful in evaluating recurrence of postoperative patients with CD	n=10 citations 1 Cite Share Fecal calprotectin for evaluating postoperative recurrence of Crohn's disease: a meta-analysis of prospective studies. Qiu Y, Mao R, Chen BL, He Y, Zeng ZR, Xue L, Song XM, Li ZP, Chen MH. Inflamm Bowel Dis. 2015 Feb;21(2):315-22. doi: 10.1097/MIB.0000000000000262. PMID: 25569739 2 Cite Share Medical therapies for postoperative Crohn's disease. Shah RS, Click BH. Therap Adv Gastroenterol. 2021 Feb 15;14:1756284821993581. doi: 10.1177/1756284821993581. eCollection 2021. PMID: 33643440 Free PMC article. Review. 3 Cite Share Assessment of disease activity in inflammatory bowel diseases: Non-invasive biomarkers and endoscopic scores. Rodrigues BL, Mazzaro MC, Nagasako CK, Ayrizono MLS, Fagundes JJ, Leal RF. World J Gastrointest Endosc. 2020 Dec 16;12(12):504-520. doi: 10.4253/wjge.v12.i12.504. PMID: 33362904 Free PMC article. Review. 4 Cite Share Follow-Up Ileocolonoscopy Is Underused in Crohn's Disease Patients after Ileocecal Resection despite Higher Total and Inpatient Health-Care Costs Compared to Controls. Vavricka SR, Greuter T, Brüngger B, Blozik E, Celeiro J,

				Schoepfer AM, Bähler C. Inflamm Intest Dis. 2020 Aug;5(3):100-108. doi: 10.1159/000507115. Epub 2020 May 26. PMID: 32999882 Free PMC article. 5 Cite Share Faecal calprotectin is the biomarker that best distinguishes remission from different degrees of endoscopic activity in Crohn's disease. E Penna FGC, Rosa RM, da Cunha PFS, de Souza SCS, de Abreu Ferrari ML. BMC Gastroenterol. 2020 Feb 13;20(1):35. doi: 10.1186/s12876-020-1183-x. PMID: 32054445 Free PMC article. 6 Cite Share Fecal calprotectin for detection of postoperative endoscopic recurrence in Crohn's disease: systematic review and meta-analysis. Tham YS, Yung DE, Fay S, Yamamoto T, Ben-Horin S, Eliakim R, Koulaouzidis A, Kopylov U. Therap Adv Gastroenterol. 2018 Jul 8;11:1756284818785571. doi: 10.1177/1756284818785571. eCollection 2018. PMID: 30034529 Free PMC article. 7 Cite Share Risk factors for postoperative recurrence of Crohn's disease with emphasis on surgical predictors. Gklavas A, Dellaportas D, Papaconstantinou I. Ann Gastroenterol. 2017;30(6):598-612. doi: 10.20524/aog.2017.0195. Epub 2017 Sep 26. PMID: 29118554 Free PMC article. Review. 8 Cite Share Fecal marker levels as predictors of need for endoscopic balloon dilation in

			Crohn's disease patients with anastomotic strictures. Lopes S, Andrade P, Rodrigues-Pinto E, Afonso J, Macedo G, Magro F. World J Gastroenterol. 2017 Sep 21;23(35):6482-6490. doi: 10.3748/wjg.v23.i35.6482. PMID: 29085198 Free PMC article. 9 Cite Share Inter- and intraobserver agreement in computed tomography enterography in inflammatory bowel disease. Horvat N, Tavares CC, Andrade AR, Cabral JC, Leao-Filho HM, Caiado AH, Ueda SK, Leite AZ, Sipahi AM, Rocha MS. World J Gastroenterol. 2016 Dec 7;22(45):10002-10008. doi: 10.3748/wjg.v22.i45.10002. PMID: 28018107 Free PMC article. 10 Cite Share Optimal delivery of follow-up care after surgery for Crohn's disease: current perspectives. Campbell JP, Vaughn BP. Clin Exp Gastroenterol. 2016 Aug 8;9:237-48. doi: 10.2147/CEG.S96078. eCollection 2016. PMID: 27540307

Methodical Notes

Funding Sources: not shown

COI: none declared

Study Quality: selection flow shown

Heterogeneity: sensitivity, specificity calculated

Publication Bias: QUADAS-2 Risk of Bias Assessment performed and low

Notes:

Tham, Y. S. et al. Fecal calprotectin for detection of postoperative endoscopic recurrence in Crohn's disease: systematic review and meta-analysis. Therap Adv Gastroenterol. 11. 1756284818785571. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level:	Population:	Primary: recurrence of	Global Studies of Using Fecal Biomarkers in

2 Study type: systematic review, meta-analysis Databases: A comprehensive literature search was conducted on 22 July 2017 using both PubMed and Embase databases. Search period: A comprehensive literature search was conducted on 22 July 2017 using both PubMed and Embase databases. Inclusion Criteria: (1) studies evaluating postoperative CD patients using both ileocolonoscopy and FC; (2) adult patients only; (3) studies that utilized RS for definition of endoscopic recurrence; (4) studies including at least 15 patients; (5) those published in full form in peer-reviewed literature. Exclusion Criteria: -	Crohns disease after ICR Intervention: calprotectin Comparison: calprotectin, endoscopy	disease Secondary: - Results: A total of 54 studies were retrieved; 9 studies were eligible for analysis. Diagnostic accuracy was calculated for FC values of 50, 100, 150 and 200 µg/g. A significant threshold effect was observed for all FC values. The optimal diagnostic accuracy was obtained for FC value of 150 µg/g, with a pooled sensitivity of 70% [95% confidence interval (CI) 59–81%], specificity 69% (95% CI 61–77%), and DOR 5.92 (95% CI 2.61–12.17). The area under the SROC curve was 0.73. Author's Conclusion: FC is an accurate surrogate marker of postoperative endoscopic recurrence in CD patients. The FC cut-off 150 µg/g appears to have the best overall accuracy. Serial FC evaluations may eliminate or defer the need for colonoscopic evaluation in up to 70% of postoperative CD patients.	Predicting Relapse in Inflammatory Bowel Disease. Liu F, Lee SA, Riordan SM, Zhang L, Zhu L. Front Med (Lausanne). 2020 Dec 17;7:580803. doi: 10.3389/fmed.2020.580803. eCollection 2020. PMID: 33392214 Free PMC article. Review. Ustekinumab Inhibits T Follicular Helper Cell Differentiation in Patients With Crohn's Disease. Globig AM, Sommer NP, Wild K, Schardey J, Zoldan K, Thomann AK, Schulte LA, Schreiner R, Reindl W, Klaus J, Schempp CM, Hofmann M, Thimme R, Boettler T, Hasselblatt P. Cell Mol Gastroenterol Hepatol. 2021;11(1):1-12. doi: 10.1016/j.jcmgh.2020.07.005. Epub 2020 Jul 15. PMID: 32679193
Methodical Notes			
Funding Sources: none COI: declared Study Quality: Data extraction and quality control were per- formed independently by two reviewers (YST, SF). Any disagreements were resolved by consen- sus and involvement of the senior authors. Where additional data were required, the corresponding author of the relevant article was contacted by email in an attempt to obtain the necessary data.			

Heterogeneity: The I2 statistic was used to quantify heterogeneity between the included studies.
low

Publication Bias: Risk of bias and overall quality of the included studies was assessed using the quality assessment of diagnostic accuracy studies (QUADAS)-2 scale.36 Statistical analyses in this study were carried out using the meta4diag,37 mada38 and INLA39 packages in R version 3.4.2.

Notes:

Zhuge, Y. et al. Fecal Calprotectin for predicting Relapse and Activity in Patients with Crohn's Disease: A Meta-analysis. Euroasian J Hepatogastroenterol. 6. 116-124. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: meta-analysis Databases: Medline (PubMed), the Cochrane central register of controlled trials, EMBASE, PubMed, EMBASE, the Cochrane Database of Systematic Reviews, and DARE Search period: from 1966 to August 2014: Inclusion Criteria: Clinical studies that described the predictive roles of FC in monitoring activity or relapse of CD were eligible for inclusion. Other criteria for inclusion included studies with adult populations, articles written in English, and evaluating relationship between FC and CD. Exclusion Criteria: Studies not written in English, animal studies, studies without proper control setting, absence of abstract, insufficient data, or those focusing on quality of life were excluded.	Population: CD Intervention: calprotectin measurement Comparison: prediction of flare	Primary: We aimed to perform a meta-analysis of the predictive capacity of fecal calprotectin (FC) in activity and relapse of Crohn's disease (CD). Secondary: - Results: A total of 1,252 CD patients from 18 different studies were analyzed. The pooled sensitivity and specificity of FC at a cutoff value of 50 µg/g to predict activity of CD were 0.91 [95% confidence interval (CI): 0.87–0.95] and 0.47 (95% CI: 0.35–0.59) respectively. The pooled sensitivity and specificity of FC at a cutoff value of larger than 150 µg/g to monitor relapse of CD was 0.75 (95% CI: 0.67–0.82) and 0.71 (95% CI: 0.66–0.76) respectively. The area under the summary receiver operating characteristic (SROC) curve of FC for detecting CD activity was 0.78 (50 µg/g), 0.88 (100 µg/g), 0.85 (>150 µg/g), and the diagnostic odds ratio (DOR) was 10.21 (50 µg/g), 10.20 (100 µg/g), 11.68 (>150 µg/g) respectively. Author's Conclusion: As a simple and noninvasive marker, FC is useful to predict the activity and relapse in CD patients, and the capacity of FC to predict CD activity was superior to its application in monitoring relapse of CD.	none

Methodical Notes

Funding Sources: none

COI: none

Study Quality: shown

Heterogeneity: Reference-positive patients/ total subjects were used to calculate the pretest probabil- ity of CD. The sensitivity and specificity of FC in a certain study were extracted or calculated using appropriate contingency tables. If there were potential problems in odds calculations for studies with sensitivities or speci- ficities of 100%, then a value of 0.5 was added to all cells of trials that contained zero.18 Positive likelihood and negative likelihood were determined as functions of these summary estimates; the derived estimates of sensitivity, specificity, and respective variances were also used to construct a summary receiver operating characteristic (SROC) curve.18 The area under the ROC curve was used as an alternative global measure of test performance.18 Diagnostic odds ratio (DOR) and the area under the SROC curve (AUC) were calculated to evaluate the diagnostic performance of FC in patients with CD.

Publication Bias: Though we tried to avoid any possible bias, there are still several limitations in our meta-analysis. First, the pooled results of the present study had relatively high heterogeneity and bias of publication. The sources of heterogeneity and publication bias include differences in populations, disease duration, treatment regimen, time of measuring FC, and cutoff value of FC. Second, the samples of included studies varied significantly. The pooled results were probably compromised due to the small number of eligible studies. Third, the refer- ence standard was similar in most included studies, but the application of various scoring systems to assess CD activity was a problem. Therefore, a standardized scoring method should be established to minimize variation and provide a better accuracy. Last, a few studies failed to provide sufficient data or information of interest.

Notes:

OXFORD (2011) Appraisal Sheet: RCT: 6 Bewertung(en)

Ankersen, D. V. et al. Individualized home-monitoring of disease activity in adult patients with inflammatory bowel disease can be recommended in clinical practice: A randomized-clinical trial. World J Gastroenterol. 25. 6158-6171. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: 102 Recruitung Phase: July 2015 to July 25 2016 Inclusion Criteria: yes Exclusion Criteria: yes	Intervention: different monitoring Comparison: monitoring	Primary: Adult IBD patients were consecutively randomized to 1-year open-label eHealth interventions (3M vs OD). Both intervention arms were screening for disease activity, quality of life and fatigue and were measuring medical compliance with the constant care web-application according to the screening interventions OD or 3M. Disease activity was assessed using home measured fecal calprotectin (FC) and a disease activity score. Secondary: - Results: In total, 102 patients were randomized (n = 52/50 3M/OD) at baseline, and 88 patients completed the 1-year study (n = 43 3M; n = 45 OD). No difference in the two screening procedures could be found regarding medical compliance (P = 0.58), fatigue (P = 0.86), quality of life (P = 0.17), mean time spent in remission (P > 0.32), overall FC relapse rates (P = 0.49), FC disease courses (P = 0.61), FC time to a severe relapse (P = 0.69) and remission (P = 0.88) during 1 year. Median (interquartile range) numbers of FC home-monitoring test-kits used per patient were significantly different, 3M: 6.0 (5.0-8.0) and OD: 4.0 (2.0-9.0), P = 0.04.

		Author's Conclusion: The two eHealth screening procedures are equally good in capturing a relapse and bringing about remission. However, the OD group used fewer FC home testkits per patient. Individualized screening procedures can be recommended for adult IBD patients in clinical web-practice.

Methodical Notes

Funding Sources: Calpro AS; Crohn Colitis patient society Denmark; and North Zealand University Hospital and Ferring Pharmaceuticals.

COI: decalred

Randomization: yes

Blinding: yes

Dropout Rate/ITT-Analysis: yes,

Notes:

Assa, A. et al. Proactive Monitoring of Adalimumab Trough Concentration Associated With Increased Clinical Remission in Children With Crohn's Disease Compared With Reactive Monitoring. Gastroenterology. 157. 985-996.e2. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: Nonblinded, randomized controlled trial.** **Number of Patient: 78 children with CD.** **Recruitung Phase: July 2015 through December 201** **Inclusion Criteria: Patients recruited were biologic-naïve children (6–17years) with luminal CD who had responded to standard ADL induction at weeks 0 and 2, as indicated at week 4 by a reduction of Pediatric Crohn's Disease Activity Index (PCDAI) of at least 15 points from ADL initiation, or clinical remission(PCDAI<10 points).** **Exclusion Criteria: Patients were excluded in cases of prior exposure to anti-TNFa agents; current or previous bowel perforation; small bowel obstruction within the last 3 months; fixed non inflammatory stricture (thickened bowel wall with minimal or no enhancement oncross-sectional imaging); complicated or draining perianal fis-tula; previous malignancy; sepsis or active bacterial infection;**	**Intervention: In group 1 (proactive group), patients were assessed during each visit for clinical and biologic disease activity, while treating physicians were also informed of ADL TC for all patients within 2 weeks of sampling. ADL treatment was intensified based on plasmatic TC only, meaning that patients with ADL TC<5mg/mL were intensified regardless of disease activity (PCDAI, CRP, and calprotectin).** **Comparison: In group 2 (reactive group), patients were also assessed during each visit for clinical and biologic disease activity, but physicians were informed of the TC only in cases of clinical or biologic LOR, with subsequent intensification of ADL treatment only in patients with LOR and TC<5mg/mL, meaning that patients with LOR (either clinical and/or biologic) were intensified only if ADL TC was <5mg/mL. Patients in clinical and biologic remission were not intensified and their physicians were not informed of their TC**	**Primary: The primary endpoint of the study was sustained corticosteroid-free clinical remission (PCDAI<10 points) at all visits from weeks 8 to 72.** **Secondary: Secondary outcomes included corticosteroid-free clinical remission on ADL at weeks 48 and72; sustained biologic remission (defined by CRP <0.5 mg/dL and fecal calprotectin<150mg/g) from week 8 to 72, and at weeks 48 and 72; ADL discontinuation rate at 72 weeks; treatment modification rate during the study period; number of ADL TC measurements <5mg/mL between weeks 8 to 72; and cumulative dose of ADL and adverse events;** **Results: The primary endpoint was reached in 31 (82%) of 38 and 19 (48%) of 40 in the proactive and reactive groups, respectively,P=.002.**

previous surgical resection of the bowel, diagnosis of IBD-unclassified; or infection (actively tested in all patients) with hepatitis B, hepatitis C, tuberculosis or Clostridium difficile.		Author's Conclusion: Proactive monitoring of adalimumab trough concentrations and adjustment of doses and intervals resulted in significantly higher rates corticosteroid-free clinical remission than reactive monitoring (measuring trough concentration after loss of response.

Methodical Notes

Funding Sources: The study was supported by an unrestricted educational grant by AbbVie Pharmaceutical.

COI: Amit Assa: Consultation and lectures fees from AbbVie; and research grants from AbbVie and Janssen. Dan Turner: Consultation fees, research grants, royalties, or honorarium from Janssen, Pfizer, Ferring, AbbVie, Takeda, Biogen, Neopharm, Uniliver, Atlantic Health, Shire, Celgene, Lilly, and Roche. Batia Weiss: Consultationfees from Janssen, and lecture fees from AbbVie. Ron Shaoul: Consultation and lecture fees from AbbVie and Janssen, and research grant from Janssen. Raanan Shamir: Research grant from AbbVie. The remaining authors disclose no conflicts

Randomization: Randomization and coding were performed by a dedicated clinical trial assistant at the Schneider Children's Medical Center for all centers in blocks of 4 (1:1 ratiostratified by immunomodulators use and medical center).

Blinding: No blinding.

Dropout Rate/ITT-Analysis: Treatment termination in 5 (13%) in proactive group, 8 (20%) reactive group, respectively.

Notes:
In Hinblick auf PICO: Outcome nicht Zeit bis zum Remissionsverlust, sondern Steroid-freie Remission.

Boube, M. et al. Variation of faecal calprotectin level within the first three months after bowel resection is predictive of endoscopic postoperative recurrence in Crohn's disease. Dig Liver Dis. . . 2020

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: 48 Recruitung Phase: November 2014 to September 2017 Inclusion Criteria: OK	Intervention: yes Comparison: yes	Primary: The primary endpoint was endoscopic POR at 6 months defined by an endoscopic Rutgeerts' score ≥i2b. Secondary: - Results: Among the 48 patients included, there was no significant difference of median Fcal levels at baseline (p = 0.15), M1 (p = 0.44) and M3 (p = 0.28) between patients with or without endoscopic POR at M6. Fcal kinetics during the first 3 months after surgery was significantly different between the patients with or without POR at M6 (p = 0.021). The median variation between Fcal level at baseline and M3 (Fcal M3–M0) was significantly higher in patients with endoscopic POR compared to those without POR (p = 0.01). Fcal M3–M0 > + 10% demonstrated the best performances to predict endo- scopic POR at M6 (AUC = 0.73, sensitivity = 64.7%[41.1–82.7], specificity = 87.5%[68.0–96.3], negative predic- tive value = 77.8%[57.5–91.4] and positive predictive value = 78.6%[49.2–95.3]). Author's Conclusion: Fcal variation within the first three months after ileocolonic resection is a promising predic- tor of early endoscopic POR in CD patients.

Exclusion Criteria: OK		

Methodical Notes

Funding Sources: PHRC inter-régional, Association François Aupetit, 3i Nature, CHU Clermont-Ferrand.

COI: None declared

Randomization: yes

Blinding: yes

Dropout Rate/ITT-Analysis: yes

Notes:

Colombel, J. F. et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet. 390. 2779-2789. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: A multicentre, randomised, open-label, active-controlled, two-group, phase 3, efficacy and safety trial. Number of Patient: 244 patients Recruitung Phase: Feb 11, 2011 until Nov 3, 2016 Inclusion Criteria: Adult patients were enrolled in the study, age 18–75 years, with Crohn's disease at baseline and a diagnosis of ileal, colonic (including rectal), or ileocolonic Crohn's disease (as confirmed by endoscopy not >6 years before baseline). Key inclusion criteria were: (1) moderate to severe Crohn's disease at baseline, defined as Crohn's Disease Activity Index (CDAI)9scores of 220–450 for patients not receiving prednisone at baseline, 200–450 for patients receiving 20 mg prednisone (or less) for 7 days or more before baseline, and >150–450 for patients receiving more than 20 mg prednisone for 7 days or more before baseline; (2) active endoscopic disease, defined as a total Crohn's Disease Endoscopic Index of Severity (CDEIS) of more than 6 and a sum of CDEIS subscores of more than 6 in one or more	Intervention: In both groups, treatment was escalated in a stepwise manner, from no treatment, to adalimumab induction followed by adalimumab every other week, adalimumab every week, and lastly to both weekly adalimumab and daily azathioprine. This escalation was based on meeting treatment failure criteria. Comparison: Two treatment algorithms: tight control and clinical management.	Primary: The primary endpoint of the study was the proportion of patients with mucosal healing, defined as a CDEIS of less than 4 and no deep ulcers 48 weeks after randomisation. Secondary: (1) deep remission (CDAI <150, CDEIS <4 and no deep ulcers, absence of draining fistula, discontinuation of corticosteroids for ≥8 weeks); (2) biological remission (FC <250 µg/g, CRP <5 mg/L, and CDEIS <4); (3) CDEIS of less than 4; (4) overall CDEIS of less than 4 plus CDEIS of less than 4 in every segment; (5) complete endoscopic remission (CDEIS=0); and(6) endoscopic response (CDEIS decrease of >5 points) Results: The study's primary endpoint of mucosal healing (CDEIS <4) and no deep ulcers at 48 weeks after randomisation was met in 56 (46%) patients in the tight control group compared with 37 (30%) patients in the clinical management group, with a CMH-adjusted risk difference of 16·1% (95% CI 3·9 to 28·3; p=0·010). A higher proportion of patients in the tight control group achieved the following key secondary endpoints 48 weeks after randomisation than in the clinical management group: deep remission, with a CMH-adjusted risk difference of 14·5% (2·9 to 26·0; p=0·014); biological remission, with a CMH-adjusted risk difference of 14·5% (4·1 to 25·0; p=0·006); and an overall CDEIS of less than 4, with a CMH-adjusted risk difference of 16·1% (3·9 to 28·3; p=0·010). No significant differences were observed between the groups regarding the proportion of patients with an overall CDEIS of less than 4 plus a CDEIS of less than 4 in every segment (CMH-adjusted risk difference of 5·9% [95% CI –5·2 to 17·0]; p=0·299), complete endoscopic remission (1·7% [–7·9 to 11·3]; p=0·728), or endoscopic response (11·5% [–0·8 to 23·9]; p=0·067;). A significantly higher proportion of patients achieved steroid-free remission in the tight control group than the clinical management group and clinical remission (CDAI <150) at 11, 23, 35, and 48 weeks after randomisation. A significantly greater mean change from

segments with ulcers; and (3) CRP of 5 mg/L or more, FC of 250 µg/g or more, or both. Exclusion Criteria: Exclusion criteria were previous or current use of biologics or immunomodulators, more than two previous courses of corticosteroids, or current use of corticosteroids for more than 3 months before screening. Patients with any fibrotic stricture (passable or non-passable and regardless of symptoms), draining perianal fistulas, or non-perianal fistulas were excluded.		baseline in CDAI was observed in the tight control group than in the clinical management group at 11, 35, and 48 weeks. The mean change from baseline in CRP concentration was not significantly different between tight control and clinical management. Author's Conclusion: CALM is the first study to show that timely escalation with an anti-tumour necrosis factor therapy on the basis of clinical symptoms combined with biomarkers in patients with early Crohn's disease results in better clinical and endoscopic outcomes than symptom-driven decisions alone.

Methodical Notes

Funding Sources: Funding AbbVie

COI: J-FC reports personal fees from AbbVie, Amgen, Boehringer Ingelheim, Celgene Corporation, Celltrion, Eli Lilly, Enterome, Ferring Pharmaceuticals, Genentech, Janssen, MedImmune, Merck & Co, Pfizer, Protagonist Therapeutics, PPM Services, Second Genome, Seres Therapeutics, Shire, Takeda, Theradiag, Intestinal Biotech Development, and Genfit outside the submitted work; and grants from AbbVie, Janssen, and Takeda outside the submitted work. RP reports grants and personal fees from AbbVie outside the submitted work. PB reports personal fees
Articles2788www.thelancet.comVol 390 December 23/30, 2017from AbbVie, Takeda, Vifor Pharma, Hospira, Jannsen, Roche, Pfizer, Dr Falk Benelux, and Mundipharma; and reports grants from AbbVie, outside the submitted work. FB reports personal fees from Abbvie, MSD, Ferring Pharmaceuticals, Janssen, Takeda, Pfizer/Hospira, and Mundipharma outside the submitted work; and reports grants from AbbVie, Chiesi Farmaceutici, Ipsen, and Roche outside the submitted work. TV reports fees from advisory board membership of Hospira, Takeda, and Pfizer; and reports personal fees from Takeda outside the submitted work. GN reports personal fees from AbbVie, MSD, Takeda, Ferring Pharmaceuticals, Vifor Pharma, and Merck & Co outside the submitted work. AA reports personal fees from AbbVie, AstraZeneca, Biogen, Celltrion, Chiesi, Ferring Pharmaceuticals, Hospira, Janssen, Eli Lilly, MSD, Mitsubishi-Tanabe Pharma, Mundipharma, Nikkiso, Pfizer, Samsung, Sofar, Takeda, TiGenix, and Zambon outside the submitted work; and reports grants from MSD outside the submitted work. XH reports personal fees from AbbVie, Fresenius Kabi, Nutricia, MSD, Takeda, Vifor, Janssen, Arard, Laboratoires Mayoli-Spindler, Nestlé-Nutrition, and Ferring Pharmaceuticals outside the submitted work. ST reports personal fees from AbbVie, Centocor, Schering-Plough, Bristol-Myers Squibb, Chemocentryx, Cosmo Technologies, Elan Pharma International, Genentech, Giuliani Pharma, Merck & Co, Takeda, Otsuka Pharmaceutical, PDL Biopharma, Pfizer, Shire, Glenmark Pharmaceuticals, Warner Chilcott, Proximagen, VHsquared, TopiVert, Ferring Pharmaceuticals, Celgene, GlaxoSmithKline, Amgen, Biogen, Enterome, UCB Pharma, Boehringer Ingelheim, Grünenthal, Sigmoid Pharma, Oxford University Hospitals, University of Oxford, Santarus Inc, Tillotts Pharma, Procter & Gamble, Vifor, Given Imaging, Sanofi, Wiley Blackwell, Elsevier, Oxford University Press, Abbott Laboratories, and UEG outside the submitted work; reports grants from AbbVie, Schering-Plough, Takeda, Eli Lilly, Warner Chilcott, UCB Pharma, Ferring Pharmaceuticals, MSD, Procter & Gamble, IOIBD, Vifor, and Norman Collisson Foundation outside the submitted work; and institutional support for educationfrom IBD2020, Crohns Colitis Cure, Schering-Plough, Takeda, Synthon, Eli Lilly, Celgene, GlaxoSmithKline, Janssen, Grunenthal, Ferring Pharmaceuticals, MSD, Procter & Gamble, Vifor, ICHOM, and Warner Chilcott outside the submitted work. SD reports personal fees from AbbVie, Actelion Pharmaceuticals, Alfa Wasserman, AstraZeneca, Cellerix, Cosmo Pharmaceuticals, Ferring Pharmaceuticals, Genentech, Grunenthal, Johnson & Johnson, Millennium Pharmaceuticals, Merck & Co, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, Schering-Plough, Salix, Takeda, UCB Pharma, and Vifor outside the submitted work. WR reports personal fees from Abbott Laboratories, AbbVie, AESCA, Aptalis, Astellas Pharma, Janssen, Celltrion, Danone Austria, Elan, Falk Pharma GmbH, Ferring Pharmaceuticals, Immundiagnostik, Mitsubishi Tanabe Pharma, MSD, Otsuka Pharmaceutical, PDL, Pharmacosmos, PLS Educational, Schering-Plough, Shire, Takeda, Therakos, Vifor, Yakult, Amgen, AM-Pharma, AstraZeneca, Avaxia Biologics, Roland Berger GmBH, Bioclinica, Biogen IDEC, Boehringer Ingelheim, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Covance, Ernst & Young, Galapagos NV, Genentech, Gilead Sciences, Grünenthal, ICON, InDex Pharmaceuticals, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, LivaNova, Mallinckrodt Pharmaceuticals, MedImmune, Millennium Pharmaceuticals, Nestle, Novartis, Ocera Therapeutics, Parexel, Philip Morris Institute, Pfizer, Procter & Gamble, Prometheus, Provention Bio, Robarts Clinical Trials, Sandoz, Second Genome, SetPoint Medical, Sigmoid, TiGenix, UCB Pharma, Zealand

Pharma, Zyngenia, and 4SC outside the submitted work; and grants from AbbVie, AESCA, Centocor, Falk Pharma GmbH, Immundiagnostik, and MSD outside the submitted work. WJS reports personal fees from AbbVie (during the conduct of the study and outside the submitted work), and from Prometheus Laboratories, Boehringer Ingelheim, Takeda, Atlantic Pharmaceuticals, Janssen, Bristol-Myers Squibb, Genentech, Nutrition Science Partners, Kyowa Hakko Kirin Pharma, Millennium Pharmaceuticals, Celgene Cellular Therapeutics, Santarus, Salix Pharmaceuticals, Catabasis Pharmaceuticals, Vertex Pharmaceuticals, Warner Chilcott, Gilead Sciences, Cosmo Pharmaceuticals, Ferring Pharmaceuticals, Sigmoid Biotechnologies, Tillotts Pharma, AM-Pharma BV, Dr August Wolff, Avaxia Biologics, Zyngenia, Ironwood Pharmaceuticals, InDex Pharmaceuticals, Nestlé, Lexicon Pharmaceuticals, UCB Pharma, Orexigen Therapeutics, Luitpold Pharmaceuticals, Baxter Healthcare, Ferring Research Institute, Amgen, Novo Nordisk, Mesoblast, Shire, Ardelyx, Actavis, Seattle Genetics, MedImmune (AstraZeneca), ActoGeniX NV, Lipid Therapeutics, Eisai, Qu Biologics, Toray Industries, Teva Pharmaceutical Industries, Eli Lilly, Chiasma, TiGenix, Adheron Therapeutics, Immune Pharmaceuticals, Celgene, Arena Pharmaceuticals, Ambrx, Akros Pharma, Vascular Biogenics, Theradiag, Forward Pharma, Regeneron, Galapagos NV, Seres Therapeutics, Ritter Pharmaceuticals, Theravance Biopharma, Palatin Technologies, Biogen, and Western University (owner of Robarts Clinical Trials) outside the submitted work; reports grants from AbbVie (during the conduct of the study, and outside the submitted work), Prometheus Laboratories, Boehringer Ingelheim, Takeda, Atlantic Pharmaceuticals, Janssen, Bristol-Myers Squibb, Genentech, and Nutrition Science Partners; reports non-financial support from AbbVie; and reports patents for use of topical azathioprine to treat inflammatory bowel disorders (US 5691343), topical formulations of azathioprine to treat inflammatory bowel disorders (US 5905081), colonic delivery of nicotine to treat inflammatory bowel disease (South African patent 97/1020; US 5846983, 5889028, and 6166044; Mexico patent 209636; Europe patents 0954337 and 893998; Hong Kong patent HK1019043; China patent ZL97192177; Czech patent 293616; Canada patent 2246235), the use of azathioprine to treat Crohn's disease (US 5733915), azathioprine compositions for colonic administration (New Zealand patent 306062; Singapore patent 45647; Australia patent 707168; Czech patent 290428), intestinal absorption of nicotine to treat nicotine responsive conditions (Australia patent 718052; US 6238689), the use of topical azathioprine and thioguanine to treat colorectal adenomas (US 6166024), enema and enterically-coated oral dosage forms of azathioprine (US 6432967), a pharmaceutical composition for the treatment of inflammatory bowel disease (US 7341741), and intestinal absorption of nicotine to treat nicotine responsive conditions (Canada patent CA2260909), and for obesity treatment and device (US 7803195 B2) that is licensed to Enteromedics. PR reports personal fees from AbbVie, Bristol-Myers Squibb, Johnson & Johnson, Merck & Co, Takeda, UCB Pharma, Genentech, Tillotts Pharma, Pfizer, Celgene, Amgen, AstraZeneca, Robarts, outside the submitted work; and reports grants from AbbVie, Johnson & Johnson, UCB Pharma, and MSD outside the submitted work. DH reports grants and personal fees from AbbVie, AstraZeneca, Janssen, MSD, Bristol Myers Squibb, Cellerix, Centocor, Chemocentryx, ELAN, Falk Pharma GmbH, Ferring Pharmaceuticals, Genentech, Giuliani Pharma, IBM, Johnson & Johnson, Leo Pharma, Otsuka Pharmaceutical, Novimmune, PDL BioPharma, Philips, Procter & Gamble, Roche, Schering-Plough, Merck Serono, Tramedico, and UCB Pharma outside the submitted work; and reports grants from MSD, Centocor, Chemocentryx, Genentech, Novimmune, PDL BioPharma, Schering-Plough, Cytokine PharmaSciences, AM-Pharma, Vivify Health, Takeda, and Gilead outside the submitted work. SS reports personal fees AbbVie, Allergen, Biogen, Boehringer Ingelheim, Celltrion, Falk Pharma GmbH, Ferring Pharmaceuticals, Genentech, GlaxoSmithKline, MSD, Pfizer, Roche, Sandoz, Shire, and Takeda outside the submitted work. EN, BH, QZ, PM, JP, KW, AMR, and RBT report personal fees from AbbVie outside the submitted work; were AbbVie employees during writing of submitted work; and own AbbVie stock, options, or both. GD'H reports personal fees from AbbVie, Ablynx, Boehringer-Ingelheim, Celgene, Celltrion, and Galapagos NV outside the submitted work; and reports grants from AbbVie and Covidien outside the submitted work. ML and AD declare no competing interests.

Randomization: 1:1 ratio. The patient number and group of each stratum were assigned by a central randomisation schedule generated by AbbVie (Chicago, IL, USA) using WebRando software for randomisation and ClinPhone, an interactive voice and web response system for patient allocation. The subject randomisation schedule was generated by a designated person in the AbbVie statistics department, who was not involved in the rest of the study. The investigators and patients were masked to patient allocation and post-screening FC and CRP results, but treatments were open label.

Blinding: no

Dropout Rate/ITT-Analysis: 11 were enrolled but not randomly assigned, 61 patients did not complete the study.

Notes:
In Hinblick auf PICO Limitation: nicht alle Patienten bei Einschluss bzw. Randomisation in Remission.

D'Haens, G. et al. Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Concentrations Does Not Increase Clinical, Endoscopic, and Corticosteroid-Free Remission in

Patients With Active Luminal Crohn's Disease. Gastroenterology. 154. 1343-1351.e1. 2018		
Population	**Intervention - Comparison**	**Outcomes/Results**
Evidence level: 2 **Study type: A proof-of-concept randomized double-blind controlled study.** **Number of Patient: 122 biologic-naïve adult patients with active CD.** **Recruitung Phase: July 2012 through September 2015** **Inclusion Criteria: Patients recruited were adults with active luminal CD naive to biologics with an indication to start anti-TNF therapy in accordance with national guidelines and reimbursement criteria. Disease activity was confirmed by a Crohn's disease activity index (CDAI) >220 with objective signs of active inflammation (high-sensitivity CRP >5 mg/L and/or fecal calprotectin >250 µg/g) and visible ulcers at baseline ileocolonoscopy.** **Exclusion Criteria: Patients with an imminent need for surgery, critical gastrointestinal stricture and obstructive symptoms, using corticosteroid therapy at doses >40 mg/d prednisolone or equivalent, active systemic infection, evidence of tuberculosis, usual contraindications to anti-TNF or immunosuppressants, or other serious concomitant diseases were excluded.**	**Intervention: IFX was given intravenously at 5 mg/kg at weeks 0, 2, and 6 to all patients. Patients were randomized 1:1:1 at inclusion into 3 double-blind IFX maintenance regimens, administered every 8 weeks from week 14 to week 54 (end of the study period) as follows: IFX dose increase by increments of 2.5 mg/kg, maximally 2 times to a maximum dose of 10 mg/kg (DIS1) according to a prespecified algorithm, IFX dose increase by increments of 5 mg/kg, maximally 1 time, to a maximum dose of 10 mg/kg (DIS2) according to the same prespecified algorithm** **Comparison: IFX dose increase by 5 to 10 mg/kg if patients had a CDAI >220 at the current visit or a CDAI between 150 and 220 in the 2 weeks before the current visit in line with the registered label of IFX.**	**Primary: The primary endpoint of the study was corticosteroid-free remission (CDAI <150) at all visits between week 22 and 54 associated with the absence of ulcers at week 54 and no surgery for bowel resection or abscess and no new fistula.** **Secondary: Prespecified secondary endpoints were the proportion of patients with no ulcers at weeks 12 and 54, clinical remission (CDAI <150) at each visit, sustained remission from week 14 onward, endoscopic remission (CDEIS <3) at weeks 12 and 54, endoscopic response (decrease of CDEIS score of atleast 50%) at weeks 12 and 54, IFX dose increase during the study period, IFX TL >3 µg/mL between weeks 14 and 54, adverse events, total use of infliximab, need for resection, and new fistula or abscesses.** **Results: The primary endpoint (CDAI <150) between week 22 and 54 off glucocorticosteroids, without new fistula and surgery and without ulcers at the week 54 ileocolonoscopy was reached in 15 (33%) of 45, 10 (27%) of 37, and 16 (40%) of 40 patients in the DIS1, DIS2, and the control group, respectively (P= .50).** **At week 12, 16 (36%), 6 (16%), and 16 (40%) patients had no ulcerations on endoscopy in the DIS1, DIS2, and control groups (P= .054); by week 54, these proportions increased to 19 (42%), 20 (54%), and 20 (50%) patients, respectively (P=.56). Endoscopic remission (CDEIS <3) was attained in 26 (58%), 13 (35%), and 15 (37.5%) patients in DIS1, DIS2, and the control group by week 12 (P = .070) and in 23 (51%), 19 (51%), and 21 (53%) patients by week 54 (P= 1.00) .Significant endoscopic improvement (CDEIS reduction >50%) was observed in 32 (71%), 24 (65%), and 26 (65%) patients by week 12 (P= .88), and in 28 (62%), 23 (62%), and 23 (57.5%) patients by week 54 (P= .89).** **A sustained IFX serum concentration >3 µg/mL between week 12 and 54 was observed in 21 (47%), 17 (46%), and 24 (60%) of the patients in DIS1, DIS2, and the control group, respectively (P= .38). The mean concentrations in patients continuously above the 3 µg/mL cutoff was 7.8 ± 2.9 µg/mL, 9.3 ± 5.2 µg/mL, and 9.7 ± 4.5 µg/mL in DIS1, DIS2, and the control group, respectively, vs3.6 ± 2.1 µg/mL, 4.3 ± 2.3 µg/mL, and 3.4 ± 2.3 µg/mL in patients not meeting that success criterion. Antibodies to IFX were**

		measured at the end of the trial and were detected in 10 (22%), 6 (16%), and 5 (12.5%) patients in the DIS1, DIS2, and control groups. Author's Conclusion: Increasing dose of infliximab based on a combination of symptoms, biomarkers, and serum drug concentrations does not lead to corticosteroid-free clinical remission in a larger proportion of patients than increasing dose based on symptoms alone.

Methodical Notes

Funding Sources: This investigator-initiated trial was financially supported by Merck Sharp Dome and Janssen, which also provided the IFX study drug. Buhlmann Laboratories, Switzerland, kindly provided materials for Quantum Blue rapid. measurements of fecal calprotectin. Prometheus Laboratories, San Diego, CA, performed the measurements of anti-infliximab antibodies at the end of the trial.

COI: Geert D'Haens declares grant support from Abbvie, Jansen, Merck Sharp Domem, and Pfizer; has served as advisor for Abbvie, Johnson andJohnson, Merck Sharp Dome, Mundipharma, Pfizer, Prometheus Laboratories/ Nestle, and Sandoz; and received speaker fees from Abbvie, Johnson and Johnson, Merck Sharp Dome, Mundipharma, and Pfizer. Severine Vermeire reports grant support from Abbvie, MSD, Takeda, and Pfizer; lecture fees from Abbie, MSD, Takeda, Ferring, Falk Pharma, Hospira, and Tillotts; and consultancy fees from Abbvie, MSD, Takeda, Ferring, Genentech/Roche, Shire, Pfizer, Galapagos, Mundipharma, Hospira, Celgene, Second Genome, and Janssen. Filip Baert reports research grants from Abbvie, Chiesi, Ipsen, MSD, and Roche;and speaker's and consultancy fees from Abbvie, Falk, Ferring, Janssen, Mundipharma, MSD, Pfizer, Takeda, and Vifor. Anthony Buisson declares consulting fees for Abbvie, Hospira, and Takeda; and lecture fees from Abbvie, Hospira, Takeda, MSD, Vifor Pharma, Sanofi-Aventis, and Ferring. Janneke vander Woude received grants from Abbvie, Jansen, Pfizer, Tramedico, and Falk; and speakers and consultancy fees from Abbvie, Falk, Ferring, Janssen, Mundipharma, MSD, Pfizer, Takeda, and Vifor. Edouard Louis has received fees from MSD, Abbvie, Takeda, Ferring, MSD, Chiesi, Mitsubishi Pharma, Hospira, Janssen, and Takeda; and is on the advisory board of Abbvie, Ferring, MSD, Takeda, Hospira, Mitsubishi Pharma, Celltrion, and Prometheus. Matthieu Allez received fees from Abbvie, MSD, Janssen, Takeda, Ferring, Mayoli, UCB, Novartis, Genentech,Pfizer, Novo Nordisk, and Falk. Alexandre Aubourg reports consultancy fees from MSD, Abbvie, and Takeda. Bas Oldenburg reports grants from MSD, Abbvie, Takeda, Cablon, Ferring, and Falk. Ann Gils has served as a speaker for MSD, Janssen Biologicals, Pfizer, Takeda, and Abbvie, and as a consultant for UCB; and has received Investigator-Initiated Research Grants from Pfizer. Guy Lambrecht, Peter Bossuyt, Benjamin Pariente, Yoram Bouhnik, Jerome Filippi, Philippe Van Hootegem, Jacques Moreau, Denis Franchimont, Martine De Vos, Fazia Mana, Laurent Peyrin-Biroulet, Hedia Brixi, Philip Caenepeel, MariekePierik, Sylvie Chevret, and David Laharie declare no competing interest in the presentstudy. KU Leuven licensed the infliximab, adalimumab, and vedolizumab ELISA to apDia and R-Biopharm and the use of monoclonal antibodies mAb-IFX6B7 and mAb-ADM6A10 in the lateral flow assay to R-Biopharm.

Randomization: Randomization at week 0 was centrally performed online (ClinInfo, Lyon, France), balanced by permutation blocks the size of which was not disclosed to investigators, and stratified by center, and previous use of azathioprine, 6-mercaptopurine, or methotrexate.

Blinding: Serum samples for IFX concentrations were shipped to and measured at a single laboratory (KU Leuven, Leuven, Belgium) and the results were entered in the same CRF but remained invisible for the sites.

Dropout Rate/ITT-Analysis: Thirty-five (29%) of the patients dropped out of the trial before week 54: 13 (29%) of 45 in DIS1, 8 (22%) of 37 in DIS2, and 14 (35%) of 40 in the control group, after a median of 2.9, 4.6, and 5.8 months, respectively.

Notes:
In Hinblick auf PICO: Outcome nicht Zeit bis zum Remissionsverlust, sondern steroid-freie Remission. Andere Faktoren (erhöhtes CRP, niedriger IFX-Spiegel) weitere mögliche Faktoren für Dosisanpassung.

Peyrin-Biroulet, L. et al. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. Gut. 63. 88?95. 2014

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 Study type: RCT, but not primary endpoint. Number of Patient: 188 Recruitung Phase: Inclusion Criteria: subjects eligible for inclusion in this trial were adult CD patients with moderate-to-severe disease (CDAI >220 and <450 who have had an inadequate response to one or more conventional therapies (sulfasalazine, mesalamine, antibio-tics, budesonide or oral corticosteroids). 9 Exclusion Criteria: only mentioned in the primary publication of the study	Intervention: endoscopy Comparison: relationships between clinical disease activity, CRP normalisation and mucosal healing in Crohn's disease (CD	Primary: We investigated the relationships between clinical disease activity, CRP normalisation and mucosal healing in Crohn's disease (CD). (primary of this study, but this one is analyzing data from the SONIC trial, which had a different primary aim) Secondary: - Results: 188 patients who had evaluable ileocolonoscopy with evidence of mucosal ulceration at baseline, CDAI scores and CRP values at baseline and week 26 were analysed. Seventy-two of 136 patients (53%) who had a CDAI<150 at week 26 achieved mucosal healing, and 38 of 90 patients (42%) achieved both CRP normalisation (CRP<0.8 mg/dL) and mucosal healing while in clinical remission. The positive predictive value (PPV) and negative predictive value (NPV) of CDAI to detect mucosal healing using 150 as a cut-off for CDAI were 65% and 53%, respectively. The PPV and NPV of CDAI to detect mucosal healing and CRP normalisation using 150 as a cut-off for CDAI were 79% and 42%, respectively. Author's Conclusion: Half the patients under azathioprine and/ or infliximab in clinical remission have endoscopic and/or CRP evidence of residual active CD, whereas other patients with endoscopic and CRP normalisation have persistent clinical symptoms. Clinical symptoms as scored by CDAI are not a reliable measure of the underlying inflammation.

Methodical Notes

Funding Sources: none declared

COI: declared

Randomization: in initial Sonic trial

Blinding: yes

Dropout Rate/ITT-Analysis: shown

Notes:

OXFORD (2011) Appraisal Sheet: Diagnostic Studies: 2 Bewertung(en)

Levesque, B. G. et al. A prospective cohort study to determine the relationship between serum infliximab concentration and efficacy in patients with luminal Crohn's disease. Aliment Pharmacol Ther. 39. 1126-35. 2014

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3	Number of patients / samples: 327	Results: The mean CDAI score, which decreased 1.05 points between infusions, did not correlate with the mean change in trough infliximab

Study type: yes	Reference standard: yes Validation: yes Blinding: not clear Inclusion of clinical information: yes Dealing with ambiguous clinical findings: no	concentration (+0.39 lg/mL; r = 0.099, P = 0.083), but was associated with the mean change in CRP concentration (r = 0.19, P < 0.001). Trough infliximab concentrations below 2.8–4.6 lg/mL best predicted a ≥ 70 point increase in the CDAI between infusions, and those below 2.7–2.8 lg/mL best predicted CRP >5 mg/mL at the second infusion. ATI at either visit decreased the proportion of patients with therapeutic infliximab trough levels compared with patients who were ATI negative (17.5% vs. 77.3% at visit 1 and 13.8% vs. 75.6% at visit 3; P < 0.001 for both comparisons). Author conclusions: This prospective study confirms the relationship between trough infliximab concentrations, inflammation and antibodies-to-infliximab. Infliximab trough concentrations below 3 lg/mL may increase the likelihood of symptoms and inflammation

Methodical Notes

Funding Sources: Industry

COI: declared

Notes:

Wright, E. K. et al. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. Gastroenterology. 148. 938-947.e1. 2015

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3 Study type: Subgroup analysis (POCER)	Number of patients / samples: 135 Reference standard: yes Validation: yes Blinding: no Inclusion of clinical information: Pocer Patients Dealing with ambiguous clinical findings: no	Results: Levels of FC were measured in 319 samples from 135 patients. The median FC level decreased from 1347 mg/g before surgery to 166 mg/g at 6 months after surgery, but was higher in patients with disease recurrence (based on endoscopic analysis; Rutgeerts score, i2) than in patients in remission (275 vs 72 mg/g, respectively; P < .001). Combined 6- and 18-month levels of FC correlated with the presence (r ¼ 0.42; P < .001) and severity (r ¼ 0.44; P < .001) of CD recurrence, but the CRP level and CDAI score did not. Levels of FC greater than 100 mg/g indicated endoscopic recurrence with 89% sensitivity and 58% specificity, and a negative predictive value (NPV) of 91%; this means that colonoscopy could have been avoided in 47% of patients. Six months after surgery, FC levels less than 51 mg/g in patients in endoscopic remission predicted maintenance of remission (NPV, 79%). In patients with endoscopic recurrence at 6 months who stepped-up treatment, FC levels decreased from 324 mg/g at 6 months to 180 mg/g at 12 months and 109 mg/g at 18 months. Author conclusions: In this analysis of data from

		a prospective clinical trial, FC measurement has sufficient sensitivity and NPV values to monitor for CD recurrence after intestinal resection. Its predictive value might be used to identify patients most likely to relapse. After treatment for recurrence, the FC level can be used to monitor response to treatment. It predicts which patients will have disease recurrence with greater accuracy than CRP level or CDAI score.

Methodical Notes

Funding Sources: Abbvie

COI:

Notes: prospektive Beobachtung bei POCER-STudie

OXFORD (2011) Appraisal Sheet: Prognostic Studies: 12 Bewertung(en)

Abiko, Y. et al. Serial changes of serum cytokines in Crohn's disease following treatment with adalimumab. Hepatogastroenterology. 61. 357-62. 2014

Population	Intervention	Outcomes/Results
Evidence level: 5 **Study type:** **Number of Patient:** **Recruitung Phase:** **Inclusion Criteria:** **Exclusion Criteria:**	**Intervention:** **Comparison:**	**Primary:** **Secondary:** **Results:** **Author's Conclusion:**

Methodical Notes

Funding Sources:

COI:

Randomization:

Blinding:

Dropout Rate/ITT-Analysis:

Notes:

Allegretti, J. R. et al. Predictors of Clinical Response and Remission at 1 Year Among a Multicenter Cohort of Patients with Inflammatory Bowel Disease Treated with Vedolizumab. Dig Dis Sci. 62. 1590-1596. 2017

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type: retrospective observational** **Number of Patient: 136**	**Intervention: clinical data,** **Comparison: none**	**Primary: Our aim was to evaluate the efficacy of VDZ at week 54 in inflammatory bowel disease (IBD) in a multicenter cohort of patients.**

Recruitung Phase: not indicated Inclusion Criteria: All patients C18 years of age who successfully completed induction therapy with VDZ and were receiving maintenance therapy for treatment of CD or UC were considered for inclusion in this study. Exclusion Criteria: Patients\18 years of age were excluded from this study. Any patient that experienced primary non-response to VDZ initiation was not eligible for this study. Primary non-response was defined as no clinical response to VDZ during the initial 14-week induction period. Patients with prior history of surgery resulting in an ileal pouch anal anastomosis or permanent stoma were also excluded. No other exclusion criteria were defined.		Secondary: none Results: Among 136 total patients (96 CD and 40 UC), 76 (56%) demonstrated clinical response or remission at week 54. In univariate analysis, for patients with CD concomitant initiation of immunomodulator therapy (2.71, 95% CI 1.11–6.57), the addition of an immunomodulator (OR 11.49, 3.16–41.75) and CRP\3 (4.92, 95% CI 1.99–12.15) was associated with increased odds of clinical response or remission at week 54. For UC patients, hospitalization after VDZ induction was associated with decreased odds of response or remission at week 54 (OR 0.22, 95% CI 0.05–0.88). On multivariate analysis in CD, addition of an immunomodulator (OR 8.33, 95% CI 2.15–32.26) remained significant predictors of clinical response or remission at week 54. Author's Conclusion: Among a multicenter cohort of patients with IBD demonstrating primary response to VDZ, the addition of combination therapy with an immunomodulator is a significant predictor of clinical response or remission at week 54 in patients with CD.

Methodical Notes

Funding Sources: none

COI: declared

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: not shown

Notes:

Baert, F. et al. Antibodies to adalimumab are associated with future inflammation in Crohn's patients receiving maintenance adalimumab therapy: a post hoc analysis of the Karmiris trial. Gut. 65. 1126-31. 2016

Population	Intervention	Outcomes/Results
Evidence level: 4 Study type: prospektive obernational Number of Patient:	Intervention: trough level Comparison: Clinical information on treatment modalities was collected from	Primary: Data on immunogenicity to adalimumab (ADL) therapy in patients with IBD is limited. We

Recruitung Phase: 536 Inclusion Criteria: All patients included in this study were Crohn's disease patients who were initially treated with IFX. Eight patients (6%) had no primary response. All other patients (94%) had an initial response and subsequently became intolerant to IFX (ie, having experienced an acute and/or delayed hypersensitivity reaction) or lost response (ie, worsening of clinical status as judged by the treating physician) despite dose adjustments. The present study included 148/168 (88%) patients of the Karmiris cohort, of whom serial serum samples were available for analysis of ADL concentration, ATA and different markers of inflammation (see below). Exclusion Criteria: -	the electronic charts of the patients. In addition to demographic data, the following were collected: disease duration, prior IFX use, concomitant use of immunomodulators (IMMs), induction scheme, need for dose escalation and reason for ADL discontinuation.	performed additional analyses on the Karmiris cohort using the homogeneous mobility shift assay (HMSA) focusing on the inter-relationship of serum ADL concentration, antibodies-to-adalimumab (ATA), inflammatory markers and sustained response. Secondary: - Results: ATA was detected in 20% of patients after a median of 34 (12.4–60.5) weeks. ATA-positive samples correlated with lower serum ADL concentration (p<0.001). Cox regression modelling showed that week 4 ADL concentration of <5 mg/mL significantly increased the future risk of ATA formation (HR=25.1; 95% CI 5.6 to 111.9; p=0.0002) and that IMM co-treatment prevented ATA formation (HR=0.23; 95% CI 0.06 to 0.86; p=0.0293). Regression modelling showed a negative correlation between CRP and ADL concentration (p=0.0001) and a positive one with ATA (p=0.0186). The model revealed that both lower serum ADL concentration and ATA were independently associated with future CRP (p=0.0213 and p=0.0013 respectively). ATA positivity was associated with discontinuation of ADL because of loss or response (OR=3.04; 95% CI 1.039 to 9.093; p=0.034). Author's Conclusion: ATA were detected in 20% of patients. Risk of ATA formation increased with lower early serum ADL concentration and in patients not on IMM. ATA and ADL were strongly associated with higher

		future CRP level and discontinuation of ADL.

Methodical Notes

Funding Sources: none

COI: declared

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: no

Notes:

Cornillie, F. et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. Gut. 63. 1721-7. 2014

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type: post hoc analysis of RCT** **Number of Patient: 573** **Recruitung Phase: 2/1999 to 3/2001** **Inclusion Criteria: Patients included in this analysis were responders at week 14; all received a full induction schedule of infliximab 5 mg/kg infusions given at weeks 0, 2 and 6.** **Exclusion Criteria: only those excluded in ACCENT I**	**Intervention: none** **Comparison: trough levels**	**Primary: To carry out a post hoc analysis of A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen I (ACCENT I) to evaluate the association between serum infliximab trough levels and C-reactive protein (CRP) after 14 weeks of induction treatment with durable sustained long-term response (Crohn's Disease Activity Index decrease ≥70 points and reduction ≥25% from baseline).** **Secondary: none** **Results: After induction with 5 mg/kg infliximab, 25% (37/147) and 33% (47/144) of patients sustained week 14 response to infliximab 5 or 10 mg/kg, respectively, administered every 8 weeks without dose escalation, through week 54. Median week 14 trough levels of patients with and without durable sustained response to infliximab 5 mg/kg were 4.0 and 1.9 µg/mL, respectively (p=0.0331). Optimal predictors of durable sustained response to maintenance infliximab 5 mg/kg were week 14 trough level ≥3.5 mg/mL and ≥60% CRP decrease (ORs (95% CI), 3.5 (1.1 to 11.4) and 7.3 (1.4**

		to 36.7)), respectively, in patients with raised baseline CRP (>8.0 mg/L); area under the ROC curve was 0.75 for both predictors. A ≥3.5 mg/mL week 14 infliximab serum level did not predict durable sustained response to 10 mg/kg maintenance infliximab. Author's Conclusion: Patients with durable sustained response to maintenance infliximab 5 mg/kg had higher postinduction trough levels than patients without durable sustained response. Serum infliximab trough levels ≥3.5 mg/mL and ≥60% CRP decrease were significantly associated with durable sustained response.

Methodical Notes

Funding Sources: industry

COI: declared

Randomization: yes

Blinding: yes

Dropout Rate/ITT-Analysis: yes (in initial study)

Notes:

Gutiérrez, A. et al. Gut Bacterial DNA Translocation is an Independent Risk Factor of Flare at Short Term in Patients With Crohn's Disease. Am J Gastroenterol. 111. 529-40. 2016

Population	Intervention	Outcomes/Results
Evidence level: 3 Study type: prospektive observational Number of Patient: 288 Recruitung Phase: unclear Inclusion Criteria: Consecutive patients diagnosed with Crohn's disease and controlled at	Intervention: Blood bactDNA Comparison: marker for flare	Primary: The primary endpoint was time--to--relapse as evaluated by CDAI>150 in the following 6 months. BactDNA in blood, the NOD2 genotype and serum

three hospitals in the area of Alicante, Spain, who were in remission, as determined by CDAI<150 were included in this prospective, observational multicenter study. The diagnosis of CD was established according to standard clinical, endoscopic, histological and radiographical criteria 30. Patients treated with antibiotics in the previous 4 weeks, patients with signs of active infection and those who refuse to sign informed consent to participate in		cytokine levels were determined at baseline. Secondary: - Results: A total of 288 patients were included. BactDNA was detected in 98 patients (34.0%). A variant-NOD2 genotype was identified in 114 patients (39.6%). Forty patients (14%) relapsed during follow-up. Multivariate survival analysis identified bactDNA as an independent risk factor of flare (hazard ratio (HR) 8.75 (4.02-19.06) 95% confidence interval (CI)). Hospitalization, surgery, switch of treatment, initiation and escalation of anti-tumor necrosis factor (TNF) therapy, steroids initiation, and increased fecal calprotectin levels at 6 months were associated with bactDNA at baseline. A logistic regression analysis showed bactDNA as an independent and significant predictive factor of hospitalization (odds ratio (OR) 11.9 (3.4-42.3); P<0.001), steroids startup (OR 8.5 (2.7-27.1); P<0.001), and switch of treatment (OR 3.5 (1.6-7.7); P=0.002) at 6 months. No relationship was observed between bactDNA and mucosal lesions in patients with colonoscopy at admission. Serum pro-inflammatory cytokines were significantly increased in patients with bactDNA or a variant-NOD2 genotype. The combination of both factors induced decreased anti-TNF- levels and a higher percentage of patients on intensified anti-TNF therapy. Author's Conclusion: BactDNA is an independent risk factor of relapse at 6 months in CD patients. BactDNA is also independently associated with an increased risk of hospitalization, switch of treatment, and steroids initiation.

the study were excluded. Twenty--five healthy controls were included in the study of NOD2 allelic variants distribution. Exclusion Criteria: not clear		

Methodical Notes

Funding Sources: Abbvie, Feder Program

COI: declared

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: no

Notes:

Louis, E. et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology. 142. 63-70 e5; quiz e31. 2012

Population	Intervention	Outcomes/Results
Evidence level: 3 Study type: prospective multicenter cohort study Number of Patient: 115 Recruitung Phase: March 2006 to December 2009 Inclusion Criteria: Eligible patients were at least 17 years of age and had received at least 1 year of therapy with scheduled infliximab and an antime- tabolite agent (azathioprine, 6-mercaptopurine, or methotrexate) for active luminal Crohn's disease. At least 2 infusions of infliximab had to have been administered during the past 6 months. The dose of the antimetabolite agent (azathioprine Exclusion Criteria: a history of severe acute or delayed infusion reaction to infliximab, initial indication for infliximab being predominantly fistulizing perianal disease without signif- icant luminal disease, persistence of active fistulizing disease, predominant jejunal or proximal ileal lesions, an ostomy, severe extraintestinal manifestations, and pregnancy or lactation	Intervention: termination of infliximab treatment Comparison: new flare of disease over time	Primary: We assessed the risk of relapse after infliximab therapy was discontinued in pa- tients on combined maintenance therapy with antime- tabolites and identified factors associated with relapse Secondary: - Results: After a median follow-up period of 28 months, 52 of the 115 patients experienced a relapse; the 1-year relapse rate was 43.9% Author's Conclusion: Ap- proximately 50% of patients with Crohn's disease who were treated for at least 1 year with infliximab and an antimetabolite agent experienced a relapse within 1 year after discontinuation of infliximab. However, pa- tients with a low risk of relapse can be identified using a combination of clinical and biologic markers.

Methodical Notes

Funding Sources: The GETAID received unrestricted study grants from the Association François Aupetit and the Société Nationale Française de Gastroentérologie.

COI: declared

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: yes shown

Notes:

Meuwis, M. A. et al. Serum calprotectin as a biomarker for Crohn's disease. J Crohns Colitis. 7. e678-83. 2013

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type:** prospective cohort trial **Number of Patient:** 115 **Recruitung Phase:** 2006 to 2009 **Inclusion Criteria:** Patients who were included in the study were in clinical remission with a CDAI b 150 under a combined treatment with infliximab (IFX) and anti-metabolites (azathi- oprine (N2 mg/kg), 6-mercaptopurine (N1.5 mg/kg) or meth- otrexate (N 15 mg weekly)) for at least one year and had been corticosteroid-free over the last 6 months. **Exclusion Criteria:** -	**Intervention:** stop of infliximab **Comparison:** time to relapse	**Primary:** The aim was to evaluate the value of serum calprotectin as a biomarker for Crohn's disease. **Secondary:** - **Results:** Medianserumcalprotectinwas8892ng/mL(range:410–125,000ng/mL)inCrohndisease patients as compared with 1318 ng/mL (range: 215.8–3770 ng/mL) in controls (P b 0.0001). Serum calprotectin was significantly higher for active disease (median = 19,584 ng/mL) than for inactive disease (median = 8353 ng/mL) (P b 0.0001). Serum calprotectin correlated with hsCRP (r = 0.4092, P b 0.0001) and CDAI (r = 0.4442, P b 0.0001), but not with CDEIS, on the contrary to fecal calprotectin (r = 0.6458, 0.5515, 0.2577 with P b 0.0001, P b 0.0001, P = 0.019 respectively). In multivariate analysis, serum calprotectin used as a discrete variable (threshold: 5675 ng/ml), appeared complementary to hsCRP (N 5 mg/l) and fecal calprotectin (N 250 µg/g) to predict relapse after infliximab withdrawal (P = 0.0173, 0.0024 and 0.0002; HR: 3.191, 3.561 and 4.120). **Author's Conclusion:** As a CD biomarker, serum calprotectin has a similar profile as hsCRP. It is also complementary to fecal calprotectin and hsCRP for prediction of relapse after infliximab withdrawal.

Methodical Notes

Funding Sources: Financial support for the STORI trial was provided by the SNFGE and the association François Aupetit.

COI: none

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: indicated

Notes:

Molander, P. et al. Does fecal calprotectin predict short-term relapse after stopping TNF?-blocking agents in inflammatory bowel disease patients in deep remission?. J Crohns Colitis. 9. 33-40. 2015

Population	Intervention	Outcomes/Results
Evidence level: 3 Study type: Prospective multicenter study Number of Patient: 52 Recruitung Phase: 02/2010 to 06/2012 Inclusion Criteria: Eligible patients were over 18 years of age, had established IBD diagnoses, had received TNFα-blocking maintenance therapy for at least 11 (median 16, range 11–78) months, and had been in corticosteroid-free remission over the previous 6 months before the inclusion. The maintenance therapy was unaltered during the prospective follow-up after discontinuation of TNFα-blocking therapy. Exclusion Criteria: The exclusion criteria included escalation of TNFα-blocking agents during the last six months, history of relapse after stopping TNFα-blocking agents, perianal disease with no other effective medication available, severe arthritis as a concomitant indication for TNFα-blocking therapy, and pregnancy	Intervention: Stop of infliximab treatment Comparison: one cohort, comparison flare or not	Primary: This prospective multicenter study examined whether elevated fecal calprotec tin (FC) concentrations after stoppingTNFαblocking therapy can predict clinical or endoscopic relapse. Secondary: we evaluated the impact of histological remission on the relapse risk Results: Of 52 enrolled patients, 49 (16 Crohn's disease, 33 ulcerative colitis/IBD unclassified) provided the stool samples requested and comprised the study group. During the followup, 15/49 (31%) relapsed, whereas 34 (69%) remained in remission. Patients relapsing showed constantly elevated FC levels for a median of 94 (13–317) days before the relapse. Significant increase in median FC levels was seen 2 (p = 0.0014), 4 (p = 0.0056), and 6 (p = 0.0029) months before endoscopic relapse. Constantly normal FC concentrations during the followup were highly predictive for clinical and endoscopic remission. Normal FC concentrations in patients with remission were associated with histological remission. Author's Conclusion: FC seems to increase and remain elevated before clinical or endoscopic relapse, suggesting that it can be used as a surrogate marker for predicting and identifying patients requiring close followup in clinical practice.

Methodical Notes

Funding Sources: his study was supported by grants from the Helsinki University Central Hospital Research Fund (EVO-grant), Finnish Cultural Foundation, Mary and George C. Ehrnrooth Foundation, Finnish Foundation for Gastroenterological Research, Sigrid Jusélius Foundation, and Foundation for Pediatric Research, and an unrestricted grant from Merck & Co., Inc. Finland.

COI: declared

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: shown

Notes:

Reinisch, W. et al. Association of Biomarker Cutoffs and Endoscopic Outcomes in Crohn's Disease: A Post Hoc Analysis From the CALM Study. Inflamm Bowel Dis. . . 2020

Population	Intervention	Outcomes/Results
Evidence level: 3 Study type: post-hoc	Intervention: tight versus conventional monitoring	Primary: Primary endpoint of CALM CDEIS <4 and no deep ulcers 48 weeks after randomization; endoscopic re- sponse was defined as CDEIS decrease >5 from baseline The purpose of this post hoc analysis of CALM was to identify drivers of

analysis of RCT Number of Patient: 244 Recruitung Phase: indicated in primary publication of CALM study Inclusion Criteria: in detail described in the original publication CALM Exclusion Criteria: in detail described in the original publication CALM	Comparison: he association between endoscopic end points and biomarker cutoffs was performed using χ2 test.	treatment escalation and evaluate the association between biomarker cutoff concentrations and endoscopic end points. Secondary: - Results: The proportion of patients who achieved the primary end point CDEIS <4 and no deep ulcers was significantly greater for those with FC <250 µg/g (74%; P < 0.001), with an additive effect for CRP <5 mg/L. The association of FC <250 µg/g with improved endoscopic outcomes was independent of disease location, although the greatest association was observed for ileocolonic disease. Fecal calprotectin <250 µg/g, CRP <5 mg/L, and CDAI <150 gave a sensitivity/specificity of 72%/63% and positive/negative predictive values of 86%/42% for CDEIS <4 and no deep ulcers 48 weeks after randomization. Author's Conclusion: This post hoc analys is of CALM demonstrated that a cutoff of FC<250µg/g is a useful surrogate marker for mucosal healing in CD

Methodical Notes

Funding Sources: Abbvie

COI: declared

Randomization: initial CALM study yes

Blinding: yes

Dropout Rate/ITT-Analysis: shown in flow chart

Notes: Posthof of RCT

Reinisch, W. et al. C-reactive protein, an indicator for maintained response or remission to infliximab in patients with Crohn's disease: a post-hoc analysis from ACCENT I. Aliment Pharmacol Ther. 35. 568-76. 2012

Population	Intervention	Outcomes/Results
Evidence level: 1 Study type: post-hoc analysis of RCT Number of Patient: 573	Intervention: Infliximab; CRP Comparison: Clinical outcome dependent on CRP	Primary: Serum C-reactive protein (CRP) levels at baseline and after infliximab induction therapy at week 14 were assessed as predictors for maintained response or remission through 54 weeks of treatment in patients with Crohn's disease who responded to induction therapy. Secondary: - Results: A significant association was observed between baseline CRP levels and main- tained remission. Forty-five percent of patients with baseline CRP ≥ 0.7 mg/dL vs. 22.0% with CRP < 0.7 mg/dL maintained remission (P = 0.012). CRP normalisa- tion during infliximab treatment (decrease from 0.5 mg/dL at baseline to < 0.5 mg/ dL at week 14) resulted in higher probability of

Recruitung Phase: 26.2.1999 to 15.3.2001 Inclusion Criteria: explained in original ACCENT I publication Exclusion Criteria: explained in original ACCENT I publication		maintained response (P < 0.001) or remission (P = 0.052). At week 14 low CRP levels were associated with main- tained response (56.6% of patients with CRP < 0.5 mg/dL vs. 37.2% with higher CRP, P = 0.005). No optimal predictive CRP cut-off point was observed. Author's Conclusion: High baseline CRP levels increased the likelihood of maintained remission. Normalised CRP levels at week 14 increased the likelihood of maintained response or remission during 1 year of infliximab maintenance therapy

Methodical Notes

Funding Sources: This study was funded in full by Schering-Plough, a subsidiary of Merck & Co. (Kenilworth, NJ, USA), and Janssen Research & Development, LLC (Spring House, PA, USA). Writing support was provided by Michaela Scheiner, a consultant medical writer, and James P Barrett, an employee of the Medical Affairs Publication
Group, Janssen Biotech, Inc. Critical statistical review was provided by Yinghua Lang, an employee of Jans- sen Research & Development, LLC and critical clinical review of the manuscript was provided by Freddy Cor- nillie, an employee of Medical Affairs Immunology Europe, Janssen Biologics Europe.

COI: declared

Randomization: yes

Blinding: yes

Dropout Rate/ITT-Analysis: shown

Notes:

Waljee, A. K. et al. Development and Validation of Machine Learning Models in Prediction of Remission in Patients With Moderate to Severe Crohn Disease. JAMA Netw Open. 2. e193721. 2019

Population	Intervention	Outcomes/Results
Evidence level: 1 Study type: cohort study Number of Patient: 401 Recruitung Phase: 2011 to 2015 Inclusion Criteria: The original clinical trial cohort had 1409 participants, 668 of whom were either randomized to placebo or lost to follow-up by week 8 of the trial and therefore excluded. The remaining 741 participants received ustekinumab at week 8. Of these, 462 participants had CRP measurements of 5 mg/L or higher at enrollment, suggesting active disease, and 61 participants were excluded for	Intervention: Random forest methods were used in building 2 models for predicting Crohn disease remission, with a CRP level lower than 5 mg/dL as a proxy for biological remission, beyond week 42 of ustekinumab treatment. The first model used only baseline data, and the second used data through week 8.	Primary: To identify patients with Crohn disease likely to be durable responders to ustekinumab before committing to long-term treatment. Random forest methods were used in building 2 models for predicting Crohn disease remission, with a CRP level lower than 5 mg/dL as a proxy for biological remission, beyond week 42 of ustekinumab treatment. The first model used only baseline data, and the second used data through week 8. Secondary: - Results: Intotal, 401 participants, withamean (SD) age of 36.3 (12.6) years and 170 male (42.4%), were included. The week-8 model had a mean area under the receiver operating characteristic curve (AUROC) of 0.78 (95% CI, 0.69-0.87). In the testing data set, 27 of 55 participants (49.1%) classified as likely to have treatment success achieved success with a CRP level lower than 5 mg/L after week 42, and 7 of 65

missing values. The final cohort comprised 401 participants, whose data were used for the week-8 model and sensitivity analyses (eTable in the Supplement). Exclusion Criteria: The baseline model excluded 30 additional patients for missing baseline laboratory tests and included 371 patients	Comparison: machine learning for prediction of response to ustekinumab	participants (10.8%) classified as likely to have treatment failure achieved this outcome. In the full cohort, 87 patients (21.7%) attained remission after week 42. A prediction model using the week-6 albumin to CRP ratio had an AUROC of 0.76 (95% CI, 0.71-0.82). Baseline ustekinumab serum levels did not improve the model's prediction performance. Author's Conclusion: InpatientswithactiveCrohndisease,demographicand laboratory data before week 8 of treatment appeared to allow the prompt identification of likely nonresponders to ustekinumab without the need for costly drug-level monitoring.

Methodical Notes

Funding Sources: This study was supported by career development grant CDA 11-217 and merit review award IIR 16-024 from the US Department of Veterans Affairs Health Services Research and Development Service (Dr Waljee), by grant R01 GM097117 from the National Institutes of Health (Drs Higgins and Waljee), and by grant T32AR007080-38 from the University of Michigan (Dr Wallace).
Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

COI: declared

Randomization: initial trials

Blinding: initial trials

Dropout Rate/ITT-Analysis: shown

Notes:

Wright, E. K. et al. Comparison of Fecal Inflammatory Markers in Crohn's Disease. Inflamm Bowel Dis. 22. 1086-94. 2016

Population	Intervention	Outcomes/Results
Evidence level: 3 Study type: prospective, randomized controlled trial Number of Patient: 135 Recruitung Phase: indicated in the primary publication of the POCER trial Inclusion Criteria: indicated in the primary publication of the POCER trialPatients may have had previous upper gut disease, but to be included in the study, no residual upper gut disease was present at the time of surgery. Patients were permitted to be on proton pump inhibitor therapy for symptomatic reflux disease. Patients were not permitted to be on aspirin or non steroidal anti-inflammatory drugs (NSAIDs) therapy and were instructed to avoid these during the study.	Intervention: sugery, endocopy, fecal markers Comparison: recurrence of disease	Primary: We evaluated fecal calprotectin (FC), lactoferrin (FL), and S100A12 (FS) using endoscopic validation in a prospective study of the progression of CD after intestinal resection. Secondary: - Results: FC, FL, and FS concentrations were elevated preoperatively (median: 1347, 40.9, and 8.4 mg/g, respectively). At 6 months postoperatively, marker concentrations decreased (166, 3.0, 0.9 mg/g) and were higher in recurrent disease than remission (275 versus 72 mg/g, P , 0.001; 5.7 versus 1.6 mg/g, P ¼ 0.007; 2.0 versus 0.8 mg/g, P ¼ 0.188). FC . 135 mg/g, FL . 3.4 mg/g, and FS . 10.5 mg/g indicated endoscopic recurrence (score $ i2) with a sensitivity, specificity, and negative predictive value (NPV) of 0.87, 0.66, and 91%; 0.70, 0.68, and 81%; 0.91, 0.12, and 71%, respectively. FC and FL correlated significantly with the presence and severity of endoscopic recurrence, whereas FS, CRP and CDAI did not.

Exclusion Criteria: indicated in the primary publication of the POCER trial		**Author's Conclusion: FC was the optimal fecal marker for monitoring disease activity in postoperative CD and was superior to CRP and CDAI. FL offered modest sensitivity for detecting recurrent disease, whereas S100A12 was sensitive but had low specificity and NPV.**

Methodical Notes

Funding Sources: AbbVie, Gutsy Group, Gandel Philanthropy, Angior Foun- dation, Crohn's Colitis Australia, and St Vincent's Research Endowment Fund provided research support. Bülhmann provided fCAL testing kits for Calprotectin. Techlab provided IBD EZ VUE Kits for Lactoferrin. The National Health and Medical Research Council (NHMRC) supported E. K. Wright, M. A. Kamm, and P. D. Cruz.

COI: declared

Randomization: POCER trial yes

Blinding: yes

Dropout Rate/ITT-Analysis: shown

Notes:

Literatursammlung:

AG 2 akuter Schub-Frage 3

Inhalt: 5 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
de Groof, E. J. 2019	1	randomized controlled trial
Fay, S. 2017	3	observational retrospective study
Tham, Y. S. 2018	1	systematic review, meta-analysis
Yung, D. E. 2017	1	Systematic Review and Meta-Analysis
Zarubova, K. 2017	3	prospective observational

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 2 Bewertung(en)

Tham, Y. S. et al. Fecal calprotectin for detection of postoperative endoscopic recurrence in Crohn's disease: systematic review and meta-analysis. Therap Adv Gastroenterol. 11. 1756284818785571. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: systematic review, meta-analysis Databases: A comprehensive literature search was conducted on 22 July 2017 using both PubMed and Embase databases. Search period: A comprehensive literature search was conducted on 22 July 2017 using both PubMed and Embase databases. Inclusion Criteria: (1) studies evaluating postoperative CD patients using both ileocolonoscopy and FC; (2) adult patients only;	Population: Crohns disease after ICR Intervention: calprotectin Comparison: calprotectin, endoscopy	Primary: recurrence of disease Secondary: - Results: A total of 54 studies were retrieved; 9 studies were eligible for analysis. Diagnostic accuracy was calculated for FC values of 50, 100, 150 and 200 µg/g. A significant threshold effect was observed for all FC values. The optimal diagnostic accuracy was obtained for FC value of 150 µg/g, with a pooled sensitivity of 70% [95% confidence interval (CI) 59–81%], specificity 69% (95% CI 61–77%), and DOR 5.92 (95% CI 2.61–12.17). The area under the SROC curve was 0.73. Author's Conclusion: FC is an accurate surrogate marker of postoperative endoscopic recurrence in CD patients. The FC cut-off 150 µg/g appears to have the best overall accuracy. Serial FC evaluations may eliminate or defer the need for colonoscopic evaluation	Liu F et al. Front Med (Lausanne). 2020 Dec 17;7:580803 Klobig AM et al. Cell Mol Gastroenterol Hepatol. 2021;11(1):1-12.

(3) studies that utilized RS for definition of endoscopic recurrence; (4) studies including at least 15 patients; (5) those published in full form in peer-reviewed literature. Exclusion Criteria: -		in up to 70% of postoperative CD patients.	

Methodical Notes

Funding Sources: none

COI: declared

Study Quality: OK

Heterogeneity: The I2 statistic was used to quantify heterogeneity between the included studies. Calculations provided

Publication Bias: Risk of bias and overall quality of the included studies was assessed using the quality assessment of diagnostic accuracy studies (QUADAS)-2 scale.36 Statistical analyses in this study were carried out using the meta4diag,37 mada38 and INLA39 packages in R version 3.4.2.

A summary of the QUADAS-2 assessment is given in Table 3. The included studies were gen- erally of good quality with mostly low risk of bias.

Notes:

Yung, D. E. et al. Capsule Endoscopy, Magnetic Resonance Enterography, and Small Bowel Ultrasound for Evaluation of Postoperative Recurrence in Crohn's Disease: Systematic Review and Meta-Analysis. Inflamm Bowel Dis. 24. 93-100. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic Review and Meta-Analysis Databases: PubMed and Embase databases Search period: on April 12, 2017 Inclusion Criteria: studies comparing CE, US, and MR enterography with ileocolonoscopy; • studies that included patients evaluated for postoperative endoscopic recurrence; • studies that utilized RS for definition of endoscopic recurrence; • published in full form in peer-reviewed literature. Exclusion Criteria: Data extraction and quality	Population: CD, postoperative Intervention: CE, MRE, and US with IC Comparison: CE, MRE, and US with IC for disease activity	Primary: The aim of our meta-analysis was to evaluate the accuracy of those modalities for detection of endoscopic recurrence in postoperative CD patients. Secondary: - Results: A total of 135 studies were retrieved; 14 studies were eligible for analysis. For CE, the pooled sensitivity was 100% (95% CI, 91%–100%), specificity was 69% (95% CI, 52%–83%), DOR was 30.8 (95% CI, 6.9–138), and AUC was 0.94. MRE had pooled sensitivity of 97% (95% CI, 89%–100%), specificity of 84% (95% CI, 62%–96%), DOR of 129.5 (95% CI, 16.4–1024.7), and AUC of 0.98. US had pooled sensitivity of 89% (95% CI, 85%–92%), specificity of 86% (95% CI, 78%–93%), DOR of 42.3 (95% CI, 18.6–96.0), and AUC 0.93. Author's Conclusion: CE, MRE, and	Sommer K, Wiendl M, Müller TM, Heidbreder K, Voskens C, Neurath MF, Zundler S. Front Med (Lausanne). 2021 Mar 23;8:643973. Quaresma AB, Baraúna FDSB, Teixeira FV, Saad-Hossne R, Kotze PG. J Clin Med. 2021 Feb 11;10(4):710. Hanzel J, Almradi A, Istl AC, Yang ML, Fleshner KA, Parker CE, Guizzetti L, Ma C, Singh S, Jairath V. Dig Dis Sci. 2021 Feb 26. Zanelli J, Chandrapalan S, Patel A, Arasaradnam RP. Therap Adv Gastroenterol. 2020 Aug 18;13:1756284820937089. Quaresma AB, Yamamoto T, Kotze PG. Therap Adv

control were performed in- dependently by 2 reviewers (OH, UK) using a predetermined spreadsheet form. Any disagreements were resolved by discus- sion. When 2 different techniques were evaluated for the same modality, the data were extracted separately per each modality.		US provide accurate assessment of postoperative endoscopic recurrence in CD. These modalities should gain wider use for detection of postoperative recurrence; the prognostic value of those diagnostic findings merits evaluation in further prospective studies.	Gastroenterol. 2020 Jul 16;13:1756284820931738.

Methodical Notes

Funding Sources: none

COI: none

Study Quality: The quality assessment of diagnostic accuracy studies (QUADAS)–2 scale was used to evaluate the quality of the included studies.13 Ileocolonoscopy was used as the "reference standard" for the "index tests" CE/MRE/US. Statistical analy- ses were conducted using Meta-DiSc 1.4 software14 (Ramon y, Cajal Hospital, Madrid, Spain).
--> general good quality

Heterogeneity: Study heterogeneity was estimated using the I2 statistic,

MRI: The included studies had low heterogeneity.
US: selection to achieve reduced heterogeneity

Publication Bias: ll but 1 study17 were of European origin. Included studies were gener- ally of good quality, with mostly a low risk of bias

Notes:

OXFORD (2011) Appraisal Sheet: RCT: 1 Bewertung(en)

de Groof, E. J. et al. Cost-effectiveness of laparoscopic ileocaecal resection versus infliximab treatment of terminal ileitis in Crohn's disease: the LIR!C Trial. Gut. 68. 1774-1780. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 1 Study type: randomized controlled trial Number of Patient: 143 randomized, Recruitung Phase: MAy 2008 to October 2015 Inclusion Criteria: adult patients with crohn's disease of the terminal ileum who failed >3 months of conventional immunomodulators or steroids without signs of	Intervention: a) ileocecal resection b) Infliximab Comparison: a) ileocecal resection b) Infliximab	Primary: quality of life and costs Secondary: costs Results: laparoscopic ileocaecal resection is a cost-effective treatment option compared with infliximab. No difference in Quality of life Author's Conclusion: In conclusion, this multicentre randomised trial showed that in patients with ileocaecal Crohn's disease in whom conventional therapy has failed, laparoscopic ileocaecal resection is associated with significantly more QALYs and higher IBDQ scores than infliximab at substantially lower costs. Therefore, laparoscopic ileocaecal resection is considered to be more cost-effective as compared with infliximab treatment in this group of patients.

critical strictures Exclusion Criteria: Patients with a prior ileocaecal resection, an affected segment >40cm, abdominal abscesses or fluid collections, or an American Society of Anes- thesiologists Score of III/IV were excluded		

Methodical Notes

Funding Sources: public

COI: declared

Randomization: yes

Blinding: no

Dropout Rate/ITT-Analysis: na

Notes:

OXFORD (2011) Appraisal Sheet: Prognostic Studies: 2 Bewertung(en)

Fay, S. et al. The Association Between Drug Levels and Endoscopic Recurrence in Postoperative Patients with Crohn's Disease Treated with Tumor Necrosis Factor Inhibitors. Inflamm Bowel Dis. 23. 1924-1929. 2017

Population	Intervention	Outcomes/Results
Evidence level: 3 Study type: observational retrospective study Number of Patient: 73 Recruitung Phase: 2009-2016 Inclusion Criteria: The study cohort included consecutive patients with CD who underwent bowel resection with ileocolonic anastomosis resection and were treated with anti-TNF agents postoperatively. Exclusion Criteria: na	Intervention: trough levels Endoscopy Comparison: Endoscopic outcome in relation to anti-TNF trough level	Primary: The primary outcome of the study was a correlation of SER with anti-TNF trough levels. Secondary: - Results: Seventy-three consecutive patients (32-infliximab, 41-adalimumab) were included in the study. The colonoscopies were performed after a median of 15 (7–43) months after surgery and 8 (6–15) months from treatment onset. SER was demonstrated in 26/73 (35.6%) of the patients. The need for dose optimization, as well as trough infliximab levels (2.4 mg/mL [0.45–4.1] versus 1.1 (0–0.6), P ¼ 0.008) and presence of antidrug antibodies (1/18 [5.6%] versus 10/14 [71.4%], P ¼ 0.0001) were significantly associated with a risk of SER. The optimal cutoff infliximab level for prediction of SER was 1.8 mg/mL. No association between adalimumab levels and antiadalimumab antibodies was demonstrated. Author's Conclusion: our study demonstrates that lower IFX levels and presence of anti-IFX antibodies are associated with the likelihood of significant anastomotic inflammation in postoperative CD. It is possible that relatively low IFX levels are sufficient to control anastomotic inflammation.

		No such association was demonstrated for ADA. Our results merit confirmation and validation in a large prospective setting

Methodical Notes

Funding Sources: not declared

COI: declared

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: no

Notes: consecutively recruited patients

Zarubova, K. et al. Endoscopic Recurrence 6 Months After Ileocecal Resection in Children With Crohn Disease Treated With Azathioprine. J Pediatr Gastroenterol Nutr. 65. 207-211. 2017

Population	Intervention	Outcomes/Results
Evidence level: 3 Study type: prospective observational Number of Patient: 21 Recruitung Phase: October 2011 until June 2015 Inclusion Criteria: an age of 0 to 19 years, a diagnosis of CD (according to Porto criteria and revised Porto criteria) (21), an indication of ICR (including combination with evacuation of abscess [n¼5], other ileal [n¼3] or partial (segmental) colonic resection [n¼3], strictureplasty [n¼1] or fistulectomy [n¼3]—none of the fistulas was in the perianal area), no residual disease, undergoing endoscopy/MRE before ICR, AZA monotherapy after ICR, patients and their legal representatives agreed to participate in the study, and signed informed consents. Exclusion Criteria: an active colonic inflammation not suitable for surgery (confirmed by endoscopy before	Intervention: postoperative treatment following center standards (defined) Comparison: Endoscopic recurrence 6 month after ICR between treatment groups	Primary: Endoscopic recurrence 6 month after ICR Secondary: - Results: Among 21 included patients, 13 achieved endoscopic remission (Rutgeerts score between patients who received prior anti-TNF-a therapy and those who did not. We did not find any clinically relevant factors associated with endoscopic recurrence rate at the sixth month. Author's Conclusion: Prior anti-TNF-a therapy does not seem to be a strong risk factor for endoscopic recurrence within 6 months after ICR. Further studies on large sample of patients are needed to identify potential predictors of disease recurrence.

ICR), an active or previous perianal disease, change of therapy (an interruption of AZA therapy or a newly started anti-TNF-a therapy) before the first endoscopy after ICR, and a follow-up in another hospital after surgery.		

Methodical Notes

Funding Sources: public (ministry of health Czech)

COI: none

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: n=26, shown

Notes: cohort

Literatursammlung:

AG 3 Remissionserhaltung-Frage 1

Inhalt: 22 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Auzolle, C. 2018	3	Porspektive, observational
Bakouny, Z. 2019	2	Metaanalysis
Buisson, A. 2012	2	Review of literature
Burr, N. E. 2019	1	Metaanalysis
De Cruz, P. 2015	2	RCT
De Cruz, P. 2015	2	Subgroup analysis of POCER study
Fay, S. 2017		
Gjuladin-Hellon, T. 2019	2	Metaanalysis
Huang, H. 2018	2	Metaanalysis
Lamb, C. A. 2019	1	Consensus paper
Lopez-Sanroman, A. 2017	3	RCT (Superiority)
Mowat, C. 2016	2	RCT
Qiu, Y. 2015		
Singh, S. 2015	1	Metaanalysis
Solon, J. G. 2013	2	Metaanalysis
Taxonera, C. 2019	3	RCT
Tham, Y. S. 2018		
Wright, E. K. 2015	3	Review
Wright, E. K. 2016		
Wright, E. K. 2015	2	Subgroup analysis (POCER)
Yang, Z. 2014	2	Metaanalysis
Yung, D. E. 2017		

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 10 Bewertung(en)

Bakouny, Z. et al. Comparative Efficacy of Anti-TNF Therapies For The Prevention of Postoperative Recurrence of Crohn's Disease: A Systematic Review and Network Meta-Analysis of Prospective Trials. J Clin Gastroenterol. 53. 409-417. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 Study type: Metaanalysis Databases: Pubmed, Cochrane, AGA Abstract (1x), EMBASE Search period: until August 4, 2017 Inclusion Criteria: (a) patients: adults aged 18 years or above diagnosed with CD who have had surgical resection of small bowel and/or colon with complete removal of macroscopically visible disease (either as a first-time resection or repeat resection). (b) Intervention: biological anti-TNF agents including infliximab, adalimumab, certolizumab pegol, golimumab, and etanercept which had been started a maximum of 3 months after surgery. (c) Comparator: any anti-TNF or non–anti-TNF active agent, absence of intervention, or placebo. (d) Outcome: endoscopic and/or clinical recurrence of CD following surgery (with a minimum of 6 mo of follow-up), as well the rate of medication discontinuation due to adverse events. (e) Study design: prospective interventional comparative randomized/nonrandomized trials. Exclusion Criteria: Reviews, retrospective, noncomparative, or observational studies and studies investigating the treatment of CD postoperative recurrence with anti-TNF agents.	Population: CD patients Intervention: non Comparison: anti-TNF vs placebo or other therapies	Primary: The primary outcome was the comparison of the rates of endoscopic recurrence following surgical resection between different anti-TNF treatments Secondary: 1. Comparison of clinical recurrence rates between anti-TNF treatments. 2. Comparison of endoscopic and clinical recurrence rates between the different anti-TNF treatments and nonbiological treatments Results: We identified 9 studies, including 571 patients and 5 treatment agents, among which 2 anti-TNF drugs (adalimumab and infliximab). Compared with infliximab, our NMA yielded the following results for endoscopic recurrence: adalimumab [odds ratio (OR), 0.92; 95% confidence interval (CI), 0.18-4.75], thiopurines (OR, 4.11; 95% CI, 0.68-24.78), placebo (OR, 4.39; 95% CI, 0.70-27.68), and Mesalamine (OR, 37.84; 95% CI, 3.77-379.42). For clinical recurrence: adalimumab (OR, 1.03; 95% CI, 0.17-6.03), thiopurines (OR, 1.40; 95% CI, 0.20-10.02), placebo (OR, 1.77; 95% CI, 1.01-3.10), and mesalamine (OR, 16.54; 95% CI, 1.55-176.24). Author's Conclusion: On the basis of a NMA combining direct and indirect evidence either adalimumab or infliximab may be used in the postoperative prophylaxis of CD recurrence. There is currently a lack of evidence on the use of other anti-TNF agents in this setting.	Aliment Pharmacol Ther. 2018;48:924–932
Methodical Notes			
Funding Sources: non COI: Study Quality: Heterogeneity: Publication Bias: Notes: RCTs und nicht RCTs eingeschlossen			

Buisson, A. et al. Review article: the natural history of postoperative Crohn's disease recurrence. Aliment Pharmacol Ther. 35. 625-33. 2012

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 Study type: Review of literature Databases: Medline Search period: 1966 to September, 2011 Inclusion Criteria: placebo arms of RCTs Exclusion Criteria: non RCTs	Population: CD patients Intervention: none Comparison: none	Primary: RATES OF CLINICAL AND ENDOSCOPIC RECURRENCE Secondary: Identificaton of risk factors Results: In randomised controlled trials, clinical recurrence in the first year after surgery occurred in 10–38% of patients, whereas endoscopic recurrence in the first year was reported in 35–85% of patients. In population-based studies, approximately half of patients experienced clinical recurrence at 10 years. In referral centres, 48–93% of the patients had endoscopic lesions (Rutgeerts' score 1) in the neoterminal ileum within 1 year after surgery, whereas 20–37% had symptoms suggestive of clinical recurrence. Three years after surgery, the endoscopic postoperative recurrence rate increased to 85–100%, and symptomatic recurrence occurred in 34–86% of patients. Smoking is the strongest risk factor for postoperative recurrence, increasing by twofold, the risk of clinical recurrence. Prior intestinal resection, penetrating behaviour, perianal disease and extensive bowel disease (>50 cm) are established risk factors for postoperative recurrence. Risk factors for postoperative recurrence remain poorly defined in population-based cohorts. Author's Conclusion: Endoscopic and clinical postoperative recurrence remains common in patients with Crohn's disease, and the identification of risk factors may allow targeted strategies to reduce this recurrence rate.	Aliment Pharmacol Ther 2012; 35: 625–633

Methodical Notes

Funding Sources: none

COI:

Study Quality: review by authors

Heterogeneity:

Publication Bias:

Notes:
epidemiologic study, risk factors, natural course of disease

Burr, N. E. et al. Systematic Review and Network Meta-Analysis of Medical Therapies to Prevent Recurrence of Post-Operative Crohn's Disease. J Crohns Colitis. 13. 693-701. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References

Evidence level: 1 Study type: Metaanalysis Databases: Cochrane, Embase, Medline Search period: until July 2018 Inclusion Criteria: RCTs recruiting adults [age ≥ 16 years] with established CD, and with a history of intestinal resection. The intervention had to be an established drug, or a combination of established drugs, for the management of post-operative prophylaxis of CD, including 5-ASAs, antibiotics, immunomodulators, anti-TNF-α therapies, or any combination thereof, started within 3 months of surgery. The comparator could be another established drug, or placebo. Exclusion Criteria: We excluded RCTs in which prophylactic medication was commenced after endoscopic recurrence of CD had already been established, or beyond 12 months post-surgery; trials comparing different doses of the same medication, without an alternative intervention or comparator arm; and trials in which subclinical relapse was defined based only on radiological evidence.	Population: CD Patients Intervention: none Comparison:	Primary: Endoscopic recurrence of CD at 12 months after the initial resection. Secondary: Clinical recurrence of CD at 12 months after the initial resection. Results: included 10 RCTs, containing 751 patients, in our primary analysis of endoscopic recurrence of CD at 12 months. Anti-tumour necrosis factor [TNF]-α therapies were significantly better than placebo, either alone [P-score 0.98, RR 0.13; 95% CI 0.04–0.39] or in combination with 5-aminosalicylates [5-ASAs] [P-score 0.81, RR 0.30; 95% CI 0.12–0.75], or 5-nitroimidazoles [P-score 0.75, RR 0.40; 95% CI 0.23–0.69]. Combination therapy with a thiopurine and 5-nitroimidazole was also more effective than placebo [P-score 0.59, RR 0.56; 95% CI 0.40–0.80], as was thiopurine monotherapy [P-score 0.31, RR 0.84; 95% CI 0.74–0.94]. However, neither 5-nitroimidazoles nor 5-ASAs alone were superior to placebo. Author's Conclusion: In network meta-analysis, anti-TNF-α therapies alone, or in combination, appear to be the best medications for preventing endoscopic post-operative recurrence of CD.	Journal of Crohn's and Colitis, 2019, 693–701
Methodical Notes			

Funding Sources: none

COI:

Study Quality: 14 RCTs

Heterogeneity: low

Publication Bias: none

Notes:
Metaanalysis of RCTs

Gjuladin-Hellon, T. et al. Azathioprine and 6-mercaptopurine for maintenance of surgically-induced remission in Crohn's disease. Cochrane Database Syst Rev. 8. Cd010233. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Metaanalysis **Databases:** MEDLINE;Embase;PubMed; Cochrane; IBD Group Specialized Register **Search period:** until 26 July 2018 **Inclusion Criteria:** Randomised controlled trials which compared AZA or 6-MP agents to either a no treatment control, placebo or any other active intervention, with treatment durations of at least three months **Exclusion Criteria:** not fit inclusion	**Population:** CD patients **Intervention:** no **Comparison:** AZA vs placebo or other therapies	**Primary:** Clinical relapse **Secondary:** Endoscopic relapse; Radiologic relapse; Surgical relapse; Histologic relapse; Adverse event; Serieous adverse events, Life quality **Results:** At 12 to 36 months, 51% (109/215) of AZA/6-MP participants relapsed compared to 64% (124/193) of placebo participants (RR 0.79; 95% CI 0.67 to 0.92; 408 participants; 3 studies; I2 = 0%; moderate certainty evidence). The certainty of the evidence regarding the eNicacy of AZA or 6-MP for maintaining postoperative clinical remission compared to 5-ASA compounds was low. **Author's Conclusion:** Moderate certainty evidence suggests that AZA and 6-MP may be superior to placebo for maintenance of surgically-induced remission in participants with CD.	Gjuladin-Hellon T, Iheozor-Ejiofor Z, Gordon M, Akobeng AK. Azathioprine and 6-mercaptopurine for maintenance of surgically-induced remission in Crohn's disease. Cochrane Database of Systematic Reviews 2019, Issue 8

Methodical Notes

Funding Sources: Cochrane

COI:

Study Quality: Metaanalysis

Heterogeneity:

Publication Bias:

Notes:

Huang, H. et al. A Meta-Analysis of Efficacy and Safety of Infliximab for Prevention of Postoperative Recurrence in Patients with Crohn's Disease. Biomed Res Int. 2018. 2615978. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 Study type: Metaanalysis Databases: PubMed, Medline, Embase, and Web of Science Search period: 2000 until 6/2018 Inclusion Criteria: RCTs mit (1) patients diagnosed with CD based on tissue biopsy and treated with Infiximab; (2) double-blind, randomized, placebo-controlled or prospective studies; and (3) the outcome measures regarding the rates of CD recurrence Exclusion Criteria:	Population: CD patients Intervention: none Comparison: IFX vs placebo or other therapies	Primary: efficacy and safety of Infiximab for the prevention of recurrence in patients with CD across studies. The outcomes included in the metaanalysis were the rates of endoscopic recurrence and clinical recurrence. Secondary: Results: A total of 7 prospective trials were included in our meta-analysis (N=455). Infiximab decreased the rates of endoscopic recurrence (RR =0.421; 95% CI 0.328 to 0.539; p<0.001), and there was a signifcant reduction in rates of clinical recurrence in the Infiximab-treated group (RR =0.519; 95% CI 0.349 to 0.774; p=0.001). Furthermore, Infiximab treatment did not show adverse efects as other systematic therapeutic drugs, indicating that Infiximab treatment is effective and well tolerated. Author's Conclusion: Compared with the controls, Infiximab is a promising therapeutic agent for the management of CD patients.	BioMed Research International Volume 2018, Article ID 2615978, 10 pages

Methodical Notes

Funding Sources: National Natural Science Foundation of China (No. 81603622) and Natural Science Foundation of Jiangsu Province of China (No. BK20161319).

COI: none

Study Quality:

Heterogeneity:

Publication Bias:

Notes:
RCTs and cohort studies

Lamb, C. A. et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 68. s1-s106. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Consensus	Population: CD patients Intervention: A systematic review of	Primary: Secondary: Results:	Lamb CA, et al. Gut 2019;68:s1–s106. doi:10.1136/gutjnl-2019-318484

paper Databases: Medline, Embase Search period: until 3/2017 Inclusion Criteria: Exclusion Criteria:	88247 publications and a Delphi consensus process involving 81 multidisciplinary clinicians and patients Comparison:	Author's Conclusion: Statement 71. We suggest that Crohn's disease patients with significant risk factors for disease recurrence following ileocolonic resection (particularly smoking) or with recurrent disease at 6months post-surgery colonoscopy may be started on thiopurines (GRADE: weak recommendation, low-quality evidence) or anti-TNF therapy (GRADE: weak recommendation, low-quality evidence. Agreement: 94.4%). Statement 72. We recommend that mesalazine should not be given to prevent recurrence after ileocolonic Crohn's disease resection (GRADE: strong recommendation, moderate-quality evidence. Agreement: 97.2%). Statement 70. We suggest that, following ileocolonic resection for Crohn's disease, ileocolonoscopy may be performed at 6months to assess the neoterminal ileum in order to consider treatment escalation if mucosal inflammation (Rutgeerts i2 or above) (GRADE: weak recommendation, low-quality evidence). If the anastomosis is not within reach of endoscopic examination, then cross-sectional imaging with MR enterogram may be performed (Agreement: 89.2%). Statement 69. We recommend that all patients smoking after intestinal resection for Crohn's disease should be actively encouraged to stop (GRADE: strong recommendation, moderatequality evidence. Agreement: 100%).	

Methodical Notes

Funding Sources:

COI:

Study Quality:

Heterogeneity:

Publication Bias:

Notes:
Guideline keine Literatur

Singh, S. et al. Comparative efficacy of pharmacologic interventions in preventing relapse of Crohn's disease after surgery: a systematic review and network meta-analysis. Gastroenterology. 148. 64-76.e2; quiz e14. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Metaanalysis Databases: Embase, Medline, Cochrane, Web of Science Search period: until 2015 Inclusion Criteria: RCTs that metthe following inclusion criteria: (1) patients: adults (age,>18 y)with established CD, with a history of small-bowel and/orcolonic resection surgery, with removal of macroscopicallyvisible disease; (2) intervention: established therapies for themanagement of postoperative prophylaxis for CD includingmesalamine, antibiotics, budesonide, immunomodulators, andanti-TNF agents, started within 3 months of surgery; (3)comparator: another active agent, placebo, or no intervention;and (4) outcome: clinical and/or endoscopic relapse with atleast 6 months of follow-up evaluation after surgery. Exclusion Criteria: (1) observational studies, (2) trials in which prophylactic medication was started after established endoscopic recurrence of CD or more than 3 months after surgery (or when timing of initiation was not reported), (3) trials comparing different doses of the same medication without an alternative intervention/comparator arm, (4) trials of medications not approved for CD therapy (eg, probiotics), and (5) studies in which subclinical relapse was defined based on imaging only, without any endoscopic documentation.	Population: CD patients Intervention: Prophylactic Medication after surgery Comparison: Comparison of AZA, placebo, mesalamine and anti-TNF	Primary: Preventing clinical relapse and endoscopic relapse. Secondary: Results: We identified 21trials comprising 2006 participants comparing 7 treatmentstrategies. In a network meta-analysis, compared with placebo, mesalamine (relative risk [RR], 0.60; 95% credibleinterval [CrI], 0.37–0.88), antibiotics (RR, 0.26; 95% CrI,0.08–0.61), immunomodulator monotherapy (RR, 0.36;95% CrI, 0.17–0.63), immunomodulator with antibiotics(RR, 0.11; 95% CrI, 0.02–0.51), and anti-TNF monotherapy(RR, 0.04; 95% CrI, 0.00–0.14), but not budesonide (RR,0.93; 95% CrI, 0.40–1.84), reduced the risk of clinicalrelapse. Likewise, compared with placebo, antibiotics (RR,0.41; 95% CrI, 0.15–0.92), immunomodulator monotherapy(RR, 0.33; 95% CrI, 0.13–0.68), immunomodulator withantibiotics (RR, 0.16; 95% CrI, 0.04–0.48), and anti-TNFmonotherapy (RR, 0.01; 95% CrI, 0.00–0.05), but neithermesalamine (RR, 0.67; 95% CrI, 0.39–1.08) nor budesonide(RR, 0.86; 95% CrI, 0.61–1.22), reduced the risk of endo-scopic relapse. Anti-TNF monotherapy was the most effective pharmacologic intervention for postoperativeprophylaxis, with large effect sizes relative to all otherstrategies (clinical relapse: RR, 0.02–0.20; endoscopicrelapse: RR, 0.005–0.04). Author's Conclusion: Anti-TNF monotherapy appears to be the most effective strategy for postoperative prophylaxis for CD.	Gastroenterology 2015;148:64–76

Methodical Notes
Funding Sources: Supported by the Center for the Science of Healthcare Delivery, Mayo Clinic,and Center for Clinical and Translational Science grant UL1 TR000135 fromthe National Center for Advancing Translational Sciences, a component ofthe National Institutes of Health, as well as National Institutes of Health grantEB001981 **COI:** **Study Quality:** **Heterogeneity:** **Publication Bias:** no **Notes:** older review

Solon, J. G. et al. The effect of NOD2 polymorphism on postsurgical recurrence in Crohn's disease: a systematic review and meta-analysis of available literature. Inflamm Bowel Dis. 19. 1099-105. 2013

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type:** Metaanalysis **Databases:** Medline, Embase, and Ovid and Cochrane **Search period:** until 5/12 **Inclusion Criteria:** Studies published comparing expression of NOD2 polymorphisms with recurrence of CD after surgery **Exclusion Criteria:**	**Population:** CD patients **Intervention:** **Comparison:** NOD2 polymorphism expression and recurrance	**Primary:** **Secondary:** **Results:** : Six cohort studies comprising 1003 patients with CD were included. A total of 340 patients (33.9%) expressed at least 1 of the 3 common NOD2 polymorphisms. The 1003 patients underwent surgical resection with 335 (33%) developing surgical recurrence. Of 340 NOD2-expressing patients, 130 (39%) required further resection, whereas 202 of 663 patients (30.5%) without the variant underwent repeat resection. NOD2 was not significantly associated with surgical recurrence (odds ratio: 1.58, 95% confidence interval: 0.97–2.57, P ¼ 0.064), most likely because of study heterogeneity (Cochran Q: 12.36, P ¼ 0.030, I2: 59.6%). The sensitivity of any mutation in predicting disease recurrence was 39.7% and specificity was 69%, with the area under the receiver operating characteristic curve being 0.64. **Author's Conclusion:** Patients with CD with a NOD2 polymorphism do not have an increased risk of surgical recurrence compared with patients without the variant. These data provide insufficient evidence to support postoperative medical prophylaxis based solely on the presence of NOD2 polymorphism.	**Inflamm Bowel Dis Volume 19, Number 5, April 2013**

Methodical Notes
Funding Sources: none **COI:** none

Study Quality:

Heterogeneity:

Publication Bias:

Notes:

Wright, E. K. et al. Impact of drug therapy and surgery on quality of life in Crohn's disease: a systematic review. Inflamm Bowel Dis. 21. 1187-94. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type: Review** **Databases: Medline(EBSCOhost) and Cochrane databases** **Search period: January 1970 to August 2013** **Inclusion Criteria: Articles on QoLand Crohn's disease** **Exclusion Criteria:**	**Population: CD patients** **Intervention: non** **Comparison: non**	**Primary: QoL after surgery** **Secondary:** **Results: Remission seems to improve QoL, irrespective of whether it is achieved with drug therapy or surgery** **Author's Conclusion: Remission seems to improve QoL, irrespectiveof whether it is achieved with drug therapy or surgery.The effect of routine and targeted postoperative prophylaxis to prevent recurrenceof Crohn's disease in facilitating significant and durable improve-ments in health-related QoL is not known.**	**Inflamm Bowel Dis 2015;21:1187–1194**

Methodical Notes

Funding Sources: no funding

COI:

Study Quality: only review

Heterogeneity:

Publication Bias:

Notes:
review by one author
do not answer key question!

Yang, Z. et al. A network meta-analysis on the efficacy of 5-aminosalicylates, immunomodulators and biologics for the prevention of postoperative recurrence in Crohn's disease. Int J Surg. 12. 516-22. 2014

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type: Metaanalysis** **Databases: PubMed**	**Intervention:** **Comparison:**	**Primary:** **Secondary:** **Results: Fifteen trials involving 1507 patients were included in this analysis. Biological agents wereassociated with a large and significant reduction of both endoscopic and**	**International Journal of Surgery Volume 12, Issue 5, May 2014, Pages 516-522**

Search period: until 5 November, 2013 Inclusion Criteria: Exclusion Criteria:		clinical recurrence comparedwith placebo, 5-aminosalicylates, or immunomodulators. Immunomodulators showed greater efficacy interms of endoscopic and clinical recurrence prophylaxis compared with 5-aminosalicylates or placebo,but with higher incidence of adverse events. 5-aminosalicylates were superior to placebo for prevention of clinical recurrence, without increasing the rate of side effect. Author's Conclusion: 5-aminosalicylates, immunomodulators, and biologics are more efficacious than placebo forpostoperative CD prevention. Biologics are found to be the most effective medications to prevent CD recurrence.	

Methodical Notes

Funding Sources: none

COI: none

Study Quality:

Heterogeneity:

Publication Bias: Evaluation of publications by 2 reviewers

Notes:
old metaanalysis

Studie sollte ggf. rausgenommen werden!!!!!!!!!!!!!!!

Evaluation of studies by 2 reviewer

OXFORD (2011) Appraisal Sheet: RCT: 5 Bewertung(en)

De Cruz, P. et al. Crohn's disease management after intestinal resection: a randomised trial. Lancet. 385. 1406-17. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: 174 Recruitung Phase: 2009-2011 Inclusion Criteria: Patients with Crohn's disease undergoing intestinal resection of all macroscopic disease, with an endoscopically accessible anastomosis Exclusion Criteria: Patients were excluded if they had	Intervention: Drug therapy based on risk of recurrence Escalation of therapy dependend on clinic endoscopic outcome after 6 months Comparison: Colonscopy after 6 months vs no colonoscopy	Primary: Presence and severity of endoscopic recurrence 18 months aftersurgery Secondary: Clinical recurrence (CDAI>150 or 200), need for further surgery, C-reactive protein (normal ≤5 mg/L), and drug efficacy in prevention of mucosal recurrence. Results: At 18 months, endoscopic recurrence occurred in 60 (49%) patients in the active care group and 35 (67%) patients in the standard care group (p=0·03). Complete mucosal normality was maintained in 27 (22%) of 122 patients in the active care group versus four (8%) in the standard care group (p=0·03) Author's Conclusion: Treatment according to clinical risk of recurrence, with early colonoscopy and treatment step-up for recurrence, is better than conventional drug therapy alone for prevention of postoperative

an anastomosis that was endoscopically inaccessible by standard colonoscopy; if there was persisting macroscopic abnormality after surgical resection; if they had an end stoma (ileostomy or colostomy); if they were not suitable to undergo endoscopy because of comorbidities or an unwell clinical state; if they were unable to give informed consent; if there was any suspicion of perforation of the gastrointestinal tract; or if they were pregnant.		Crohn's disease recurrence. Selective immunesuppression, adjusted for early recurrence, rather than routine use, leads to disease control in most patients. Clinical risk factors predict recurrence, but patients at low risk also need monitoring. Early remission does not preclude the need for ongoing monitoring.

Methodical Notes

Funding Sources: AbbVie, Gutsy Group, Gandel Philanthropy, Angior Foundation, Crohn's Colitis Australia, and the National Health and Medical Research Council.

COI:

Randomization: 2:1

Blinding: no

Dropout Rate/ITT-Analysis: 37 von 182 Pt, low dropout rate, ITT

Notes:
many aspects, study for best strategy

all patients recieved metronidazole after surger for 3 months

De Cruz, P. et al. Efficacy of thiopurines and adalimumab in preventing Crohn's disease recurrence in high-risk patients - a POCER study analysis. Aliment Pharmacol Ther. 42. 867-79. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: Subgroup analysis of POCER study Number of Patient: 101 Recruitung Phase: 2009-2011 Inclusion Criteria: High risk Pt for	Intervention: Therapy with AZA or ADA Comparison: AZA vs ADA in patients with AZA-intolerance	Primary: Presence and severity of endoscopic recurrence 6 months after surgery. Secondary: Secondary outcome measures included clinical recurrence of Crohn's disease, defined as a Crohn's Disease Activity Index (CDAI) ≥200.21 Clinical remission was assessed for both scores of less than 150 or 200. Symptom recurrence was defined as any Crohn's related symptoms (irrespective of the calculated CDAI score) that either led to withdrawal, unscheduled colonoscopy or change in treatment. Other measures included need for further surgery for Crohn's disease, and C-reactive protein (CRP, normal ≤5 mg/L). An increase or decrease from baseline CDAI was not calculated as symptoms

recurrence after surgery, > 18y Exclusion Criteria: low risk pt		related to recent surgery could skew the baseline CDAI. Results: Endoscopic recurrence (Rutgeerts score i2–i4) occurred in 33 of 73 (45%) thiopurine vs. 6 of 28 (21%) adalimumab-treated patients [intentionto-treat (ITT); P = 0.028] or 24 of 62 (39%) vs. 3 of 24 (13%) respectively [per-protocol analysis (PPA); P = 0.020]. Complete mucosal endoscopic normality (Rutgeerts i0) occurred in 17/73 (23%) vs. 15/28 (54%) (ITT; P = 0.003) and in 27% vs. 63% (PPA; P = 0.002). The most advanced disease (Rutgeerts i3 and i4) occurred in 8% vs. 4% (thiopurine vs. adalimumab). Author's Conclusion: In Crohn's disease patients at high risk of post-operative recurrence adalimumab is superior to thiopurines in preventing early disease recurrence.

Methodical Notes

Funding Sources: Abbvie

COI:

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: low dropout, ITT

Notes:
comparision of AZA vs ADA (if intolerant to AZA)

all patients received metronidazole for 3 months

Lopez-Sanroman, A. et al. Adalimumab vs Azathioprine in the Prevention of Postoperative Crohn's Disease Recurrence. A GETECCU Randomised Trial. J Crohns Colitis. 11. 1293-1301. 2017

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 Study type: RCT (Superiority) Number of Patient: 91 Recruitung Phase: 2012-2015 Inclusion Criteria: >18y, recetion of all inflamed sections Exclusion Criteria: Postsurgical stoma, resection for short indolent stenosis [< 10 cm], anastomosis that was inaccessible to standard endoscopy, local macroscopic disease after resection, and the usual contraindications to anti-TNFα therapy	Intervention: AZA or ADA Comparison: ADA vs AZA	Primary: Endoscopic recurrence at 1 year Secondary: Clinical remission at 1y Results: We recruited 91 patients [median age 35.0 years, disease duration 6.0 years, 23.8% smokers, 7.1% previous resections]. The study drugs were administered to 84 patients. Treatment was discontinued owing to adverse events in 11 patients [13.1%]. Discontinuation was significantly less frequent in the ADA [4.4%] than in the AZA group [23.2%] (dif.: 18.6% [95% CI 4.1–33.2], p = 0.011). According to the intention-to-treat analysis, therapy failed in 23/39 patients in the AZA

		group [59%] and 19/45 patients in the ADA group [42.2%] [p = 0.12]. In the per-protocol analysis [61 patients with centrally evaluable images], recurrence was recorded in 8/24 [33.3%] patients in the AZA and 11/37 [29.7%] in the ADA group [p = 0.76]. No statistically significant differences between the groups were found for recurrence in magnetic resonance images, biological markers of activity, surgical procedures, or hospital admissions. Author's Conclusion: ADA has not demonstrated a better efficacy than AZA [both associated with metronidazole] for prophylaxis of POR-CD in an unselected population, although tolerance to ADA is significantly better.

Methodical Notes

Funding Sources: AbbVie

COI:

Randomization: yes

Blinding: yes

Dropout Rate/ITT-Analysis: low dropout , ITT

Notes:
no risk stratification, all patients were treated
all patients got metronidazole

Mowat, C. et al. Mercaptopurine versus placebo to prevent recurrence of Crohn's disease after surgical resection (TOPPIC): a multicentre, double-blind, randomised controlled trial. Lancet Gastroenterol Hepatol. 1. 273-282. 2016

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: 240 Recruitung Phase: 2008-2012 Inclusion Criteria: Patients aged at least 16 years (Scotland) or 18 years (England and	Intervention: 6-MP Comparison: Placebo vs 6-MP	Primary: CInical recurrence and need of rescue therapy Secondary: Endoscopic recurrence, life quality Results: 16 (13%) of patients in the mercaptopurine group versus 26 (23%) patients in the placebo group had a clinical recurrence of Crohn's disease and needed anti-inflammatory rescue treatment or primary surgical intervention (adjusted hazard ratio [HR] 0·54, 95% CI 0·27–1·06; p=0·07; unadjusted HR 0·53, 95% CI 0·28–0·99; p=0·046). In a subgroup analysis, three (10%) of 29 smokers in the mercaptopurine group and 12 (46%) of 26 in the placebo group had a clinical recurrence that needed treatment (HR 0·13, 95% CI 0·04–0·46), compared with 13 (13%) of 99 non-smokers in the mercaptopurine group and 14 (16%) of 86 in the placebo group (0·90, 0·42–1·94; pinteraction=0·018). The eff ect of mercaptopurine did not signifi cantly diff er from placebo for any of the other planned subgroup analyses (previous thiopurines, previous infl iximab or methotrexate, previous

Wales) who had a diagnosis of Crohn's disease12 and an ileocolic or small bowel resection within the preceding 3 months were eligible for inclusion. Exclusion Criteria: Key exclusion criteria were residual active Crohn's disease present after surgery, known intolerance or hypersensitivity to thiopurines, known need for further surgery, strictureplasty alone, formation of a stoma, active or untreated malignancy, absent thiopurine methyltransferase activity, substantial abnormalities of liver function tests or full blood count, and pregnancy.		surgery, duration of disease, or age at diagnosis) Author's Conclusion: Mercaptopurine is eff ective in preventing postoperative clinical recurrence of Crohn's disease, but only in patients who are smokers.

Methodical Notes

Funding Sources: Medical Research Council and National Institute of Health Research's Effi cacy and Mechanism Evaluation Programme, Scottish Government Chief Scientist Offi ce, and the National Institute of Health Research National Portfolio.

COI:

Randomization: yes

Blinding: yes

Dropout Rate/ITT-Analysis: low dropout, ITT

Notes:
no risk stratification, just in subgroups

Taxonera, C. et al. Quality of life during one year of postoperative prophylactic drug therapy after intestinal resection in Crohn's patients: Results of the APPRECIA trial. Dig Liver Dis. 51. 529-535. 2019

Population	Intervention	Outcomes/Results

	- Comparison	
Evidence level: 3 Study type: RCT Number of Patient: 61 Recruitung Phase: 2012 to January 2015 Inclusion Criteria: Patients included in APPRECIA who received at least one dose of the study drug were eligible. The study population for HRQoL assessment were patients who completed the questionnaires and had evaluable data. Exclusion Criteria:	Intervention: ADA or AZA Comparison: ADA vs AZA	Primary: Quality of life during one year of postoperative prophylactic drug therapy after intestinal resection in Crohn's patients Secondary: Results: Six cohort studies comprising 1003 patients with CD were included. A total of 340 patients (33.9%) expressed at least 1 of the 3 common NOD2 polymorphisms. The 1003 patients underwent surgical resection with 335 (33%) developing surgical recurrence. Of 340 NOD2-expressing patients, 130 (39%) required further resection, whereas 202 of 663 patients (30.5%) without the variant underwent repeat resection. NOD2 was not significantly associated with surgical recurrence (odds ratio: 1.58, 95% confidence interval: 0.97–2.57, P ¼ 0.064), most likely because of study heterogeneity (Cochran Q: 12.36, P ¼ 0.030, I2: 59.6%). The sensitivity of any mutation in predicting disease recurrence was 39.7% and specificity was 69%, with the area under the receiver operating characteristic curve being 0.64. Author's Conclusion: HRQoL improved after intestinal resection in CD, irrespective of the postoperative therapy used(ADAorAZA). Outcomes in HRQoL were associated with prevention of endoscopic recurrence, since improvements in HRQoL were only significant in patients with endoscopic remission at 1 year.
Methodical Notes		
Funding Sources: Abbvie COI: Randomization: yes Blinding: no Dropout Rate/ITT-Analysis: high dropout Notes: no risk straification, only small patient group, high dopout		

OXFORD (2011) Appraisal Sheet: Diagnostic Studies: 1 Bewertung(en)

Wright, E. K. et al. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. Gastroenterology. 148. 938-947.e1. 2015		
Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 2 Study type: Subgroup analysis (POCER)	Number of patients / samples: 135 Reference standard: yes	Results: Levels of FC were measured in 319 samples from 135 patients. The median FC level decreased from 1347 mg/g before surgery to 166 mg/g at 6 months after surgery, but was higher in patients with

	Validation: yes Blinding: no Inclusion of clinical information: Pocer Patients Dealing with ambiguous clinical findings: no	disease recurrence (based on endoscopic analysis; Rutgeerts score, i2) than in patients in remission (275 vs 72 mg/g, respectively; P < .001). Combined 6- and 18-month levels of FC correlated with the presence (r ¼ 0.42; P < .001) and severity (r ¼ 0.44; P < .001) of CD recurrence, but the CRP level and CDAI score did not. Levels of FC greater than 100 mg/g indicated endoscopic recurrence with 89% sensitivity and 58% specificity, and a negative predictive value (NPV) of 91%; this means that colonoscopy could have been avoided in 47% of patients. Six months after surgery, FC levels less than 51 mg/g in patients in endoscopic remission predicted maintenance of remission (NPV, 79%). In patients with endoscopic recurrence at 6 months who stepped-up treatment, FC levels decreased from 324 mg/g at 6 months to 180 mg/g at 12 months and 109 mg/g at 18 months. Author conclusions: In this analysis of data from a prospective clinical trial, FC measurement has sufficient sensitivity and NPV values to monitor for CD recurrence after intestinal resection. Its predictive value might be used to identify patients most likely to relapse. After treatment for recurrence, the FC level can be used to monitor response to treatment. It predicts which patients will have disease recurrence with greater accuracy than CRP level or CDAI score.

Methodical Notes

Funding Sources: Abbvie

COI:

Notes: prospektive Beobachtung bei POCER-STudie

OXFORD (2011) Appraisal Sheet: Prognostic Studies: 1 Bewertung(en)

Auzolle, C. et al. Male gender, active smoking and previous intestinal resection are risk factors for post-operative endoscopic recurrence in Crohn's disease: results from a prospective cohort study. Aliment Pharmacol Ther. 48. 924-932. 2018

Population	Intervention	Outcomes/Results
Evidence level: 3 Study type: Porspektive, observational Number of Patient: 289 Recruitung Phase: 2010-2017 Inclusion Criteria: Age >18 years, ileal or ileocolonic CD and indication of CD-	Intervention: non Comparison: non	Primary: Endoscopic recurrence Rutgeerts score ≥i2. Baseline factors associated with endoscopic recurrence were searched by univariate and multivariate regression analysis. Secondary: Results: MTwo hundred and eighty-nine CD patients were included. Endoscopy within 1 year following surgery was performed in 225 (78%) patients (104M/121F). Mean age and disease duration were 35 (12.2) and 8.8 (8.9) years respectively. Seventy (32%) patients were active smokers at surgery. One hundred and forty-two (63%)

related intestinal surgery (ileocolonic resection) Exclusion Criteria: other operations		patients received at least one anti-TNF therapy before surgery. After surgery, 40 (18%) patients received thiopurines and 66 (29%) received an anti-TNF agent. Endoscopic recurrence occurred in 107 (47%) patients. In multivariate analysis, male gender (OR = 2.48 [IC 95% 1.40-4.46]), active smoking at surgery (OR = 2.65 [IC 95% 1.44-4.97]) and previous resection (OR = 3.03 [IC 95% 1.36-7.12]) were associated with a higher risk of endoscopic recurrence. Inversely, post-operative anti-TNF treatment decreased the risk of endoscopic recurrence (OR = 0.50 [IC 95% 0.25-0.96]). Author's Conclusion: Male gender, active smoking at surgery and previous intestinal resection are associated with a higher risk of endoscopic post-operative recurrence, while post-operative anti-TNF treatment is associated with a lower risk.

Methodical Notes

Funding Sources: Association Francois Aupetit, Helmsley Charitable Trust, and MSD France laboratories

COI:

Randomization: none

Blinding: none

Dropout Rate/ITT-Analysis: 64 dropouts, no ITT

Notes:

Literatursammlung:

AG 3 Remissionserhaltung-Frage 2

Inhalt: 11 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Assa, A. 2019		
Baert, F. 2016		
Bakouny, Z. 2019		
Bek, S. 2016		
Da, W. 2013	1	Systemic Review
De Cruz, P. 2015		
Gutiérrez, A. 2016		
Levesque, B. G. 2014		
Papamichael, K. 2017		
Papamichael, K. 2019		
Taxonera, C. 2019		

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 1 Bewertung(en)

Da, W. et al. Adalimumab for Crohn's disease after infliximab treatment failure: a systematic review. Eur J Gastroenterol Hepatol. 25. 885-91. 2013

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systemic Review Databases: The search included PubMed, Google Scholar, and the Cochrane Library using a combination of search terms 'adalimumab AND inflix- imab AND Crohn's'. A total of 498 related studies were identified in the search, 10 of which were found by hand searching of reference lists (Fig. 1). Of these studies, 19 fulfilled the inclusion criteria and were reviewed in full. Seven of these studies reported only subjective measures of treatment response and were excluded. Two studies	Population: Crohn´s Disease patients Intervention: RCTs or cohort studies of adalimumab treatment in patients with CD who had received previous infliximab treatment and experienced treatment failure (unresponsiveness, loss of response, or intolerance/hypersensitivity) Comparison:	Primary: The major outcome measures of interest were the response and remission rates as indicated by the Crohn's Disease Activity Index (CDAI), the Harvey–Bradshaw Index (HBI), and fistula closure. Secondary: Secondary outcomes of interest were the rate of AEs and the rate of discontinuation because of AEs. Results: Luminal disease	

did not specify the reason(s) for discontinuation of infliximab and were also excluded. Hence, 10 studies were included in the review. Search period: Inception until September 2012 Inclusion Criteria: Studies were eligible for inclusion in the review if they fulfilled the following criteria: RCTs or cohort studies of adalimumab treatment in patients with CD who had received previous infliximab treatment and experienced treatment failure (unresponsiveness, loss of response, or intolerance/hypersensitivity); reported efficacy results; and reported in English. Exclusion Criteria: Studies were excluded from the review if they included only subjective measures of efficacy or did not specify the reason for discontinuation of infliximab.		remission rates ranged from 12 to 67% during induction and 29 to 72% during maintenance therapy. Fistulizing disease remission rates ranged from 5 to 50% during induction and 27 to 68% during maintenance therapy. Luminal disease response rates ranged from 29 to 83% during induction and 31 to 59% during maintenance therapy. Fistulizing disease response rates ranged from 15 to 44% during induction and 41 to 56% during maintenance therapy. The overall AE rate ranged from 13 to 69%. Most AEs were mild to moderate in severity. The rate of discontinuation because of AEs ranged from 0 to 14%. The findings reported in the current literature support adalimumab as an efficacious and safe treatment for CD in patients who have failed infliximab treatment. Author's Conclusion: In summary, the findings highlighted in this systematic review suggest that adalimumab can be efficacious and has favorable safety and tolerability for the treatment of CD in patients who have failed infliximab treatment. Patients who have failed infliximab treatment may therefore benefit from subsequent treatment with adalimumab. Further study is required to identify factors that may help identify patients who are most likely to respond to adalimumab treatment after failing infliximab treatment.	

Methodical Notes
Funding Sources: Acknowledgements **No funding sources have been described.** **COI: Acknowledgements** **Conflicts of interest** **There are no conflicts of interest.** **Study Quality:** **Heterogeneity:** **Publication Bias:** **Notes:**

Literatursammlung:

AG 5 EIM, Komplikationen-Frage 1

Inhalt: 6 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Abhyankar, Anita 2015	1	Systematischer Review und Metaanalyse
Aksan, A 2017	1	Systematischer Review und Metaanalyse von RCTs.
Avni, T. 2013	1	Systematischer Review und Meta-Analyse von RCTs
Bonovas, Stefanos 2016	1	Systematic Review und Metaanalyse von RCTs
Nielsen, Ole Haagen 2015	2	Systematischer Review
Reinisch, Walter 2013	2	Individueller RCT

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 5 Bewertung(en)

Abhyankar, Anita et al. Iron Replacement in Patients with Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. Inflamm. Bowel Dis. 21. 1976-81. 2015			
Evidence level/Study Types	**P - I - C**	**Outcomes/Results**	**Literature References**
Evidence level: 1 Study type: Systematischer Review und Metaanalyse Databases: MEDLINE, CINAHL, EMBASE Search period: 1966-2014 Inclusion Criteria: RCTs mit Vgl. i.v. zu p.o.-Eisen. Primäroutcome Hb-Anstieg > 2g/dl Exclusion Criteria: Review Artikel oder keine	Population: CED-Patienten mit Eisenmangelanämie Intervention: Eisenpräparat Comparison: i.v. oder p.o. Eisenpräparat	Primary: Hb-Anstieg > 2g/dl Secondary: Mittlere Hb-Veränderungen, mittlere Veränderung Serum-Ferritin, Therapiebeendigung wegen Nebenwirkungen. Results: Primäroutcome Hb-Anstieg >2g/dl identisch (RR 1,1) zwischen i.v. und p.o.-Eisen Hb-Anstieg um 0.6g/dl höher in iv im Vgl zu po-Gruppe (statistisch nicht signifikant) Bei Einschluss von Studien mit Behandlungsdauer >12	1. Kulnigg S, Stoinov S, Simanenkov V, et al. A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. Am J Gastroenterol. 2008;103:1182–92. [PubMed] [Google Scholar] 2. Gisbert JP, Gomollón F. Common misconceptions in the diagnosis and management of anemia in inflammatory bowel disease. Am J Gastroenterol. 2008;103:1299–307. [PubMed] [Google Scholar] 3. Wells CW, Lewis S, Barton JR, et al. Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease

Information zu Primäroutcome oder keine CED-Patienten		Wochen Vorteil iv gegenüber po Mittlererer Ferritin-Anstieg größer bei iv Therapiebeendigung wg. NW geringer bei iv im Vgl. zu po Author's Conclusion: We found no significant difference between IV and PO iron in correcting iron-deficiency anemia in patients with IBD in this metaanalysis. Patients who received IV iron had a greater rise in serum ferritin and were less likely to stop treatment due to adverse events, when compared with those who received PO iron.	patients. Inflamm Bowel Dis. 2006;12:123–30. [PubMed] [Google Scholar] 4. Weinstock LB, Bosworth BP, Scherl EJ, et al. Crohn's disease is associated with restless legs syndrome. Inflamm Bowel Dis. 2010;16:275–9. [PMC free article] [PubMed] [Google Scholar] 5. Nissenson AR, Wade S, Goodnough T, et al. Economic burden of anemia in an insured population. J Manag Care Pharm. 2005;11:565–74. [PubMed] [Google Scholar] 6. Stein J, Hartmann F, Dignass AU. Diagnosis and management of iron deficiency anemia in patients with IBD. Nat Rev Gastroenterol Hepatol. 2010;7:599–610. [PubMed] [Google Scholar] 7. Kulnigg S, Gasche C. Systematic review: managing anaemia in Crohn's disease. Aliment Pharmacol Ther. 2006;24:1507–23. [PubMed] [Google Scholar] 8. Gasche C, Berstad A, Befrits R, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. Inflamm Bowel Dis. 2007;13:1545–53. [PubMed] [Google Scholar] 9. Lee TW, Kolber MR, Fedorak RN, et al. Iron replacement therapy in inflammatory bowel disease patients with iron deficiency anemia: a systematic review and meta-analysis. J Crohns Colitis. 2012;6:267–75. [PubMed] [Google Scholar] 10. Reinisch W, Staun M, Tandon RK, et al. A randomized, open-label, non-inferiority study of intravenous iron isomaltoside 1,000 (Monofer) compared with oral iron for treatment of anemia in IBD (PROCEED) Am J Gastroenterol. 2013;108:1877–88. [PMC free article] [PubMed] [Google Scholar] 11. Lindgren S, Wikman O, Befrits R, et al. Intravenous iron sucrose is superior to oral iron sulphate for correcting anaemia and restoring iron stores in IBD patients: A randomized,

			controlled, evaluator-blind, multicentre study. Scand J Gastroenterol. 2009;44:838–45. [PubMed] [Google Scholar] 12. Assche G, Van Dignass A, Reinisch W, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. J Crohns Colitis. 2010;4:63–101. [PubMed] [Google Scholar] 13. Lichtenstein GR, Hanauer SB, Sandborn WJ. Management of Crohn's disease in adults. Am J Gastroenterol. 2009;104:465–83. quiz 464, 484. [PubMed] [Google Scholar] 14. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010;105:501–23. quiz 524. [PubMed] [Google Scholar] 15. Avni T, Bieber A, Steinmetz T, et al. Treatment of anemia in inflammatory bowel disease–systematic review and meta-analysis. PLoS One. 2013;8:e75540. [PMC free article] [PubMed] [Google Scholar] 16. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64:401–6. [PubMed] [Google Scholar] 17. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence–study limitations (risk of bias) J Clin Epidemiol. 2011;64:407–15. [PubMed] [Google Scholar] 18. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283:2008–12. [PubMed] [Google Scholar] 19. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88. [PubMed] [Google Scholar] 20. Higgins JPT, Thompson SG. Quantifying heterogeneity in a

			meta-analysis. Stat Med. 2002;21:1539–58. [PubMed] [Google Scholar] 21. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34. [PMC free article] [PubMed] [Google Scholar] 22. Erichsen K, Ulvik RJ, Nysaeter G, et al. Oral ferrous fumarate or intravenous iron sucrose for patients with inflammatory bowel disease. Scand J Gastroenterol. 2005;40:1058–65. [PubMed] [Google Scholar] 23. Schröder O, Mickisch O, Seidler U, et al. Intravenous iron sucrose versus oral iron supplementation for the treatment of iron deficiency anemia in patients with inflammatory bowel disease–a randomized, controlled, open-label, multicenter study. Am J Gastroenterol. 2005;100:2503–9. [PubMed] [Google Scholar] 24. Gisbert JP, Bermejo F, Pajares R, et al. Oral and intravenous iron treatment in inflammatory bowel disease: hematological response and quality of life improvement. Inflamm Bowel Dis. 2009;15:1485–91. [PubMed] [Google Scholar] 25. Avni T, Leibovici L, Gafter-Gvili A. Iron supplementation for the treatment of chronic heart failure and iron deficiency: systematic review and meta-analysis. Eur J Heart Fail. 2012;14:423–9. [PubMed] [Google Scholar] 26. Evstatiev R, Marteau P, Iqbal T, et al. FERGIcor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. Gastroenterology. 2011;141:846–853.e1–2. [PubMed] [Google Scholar]
Methodical Notes			
Funding Sources: Keine Angabe **COI: Keine** **Study Quality: Quality: Moderate** **Heterogeneity: Wenig Heterogenität im Primäroutcome. Sekundäroutcomes mittlerer Hb-Anstieg, Ferritin-Anstieg und Nebenwirkungen mit relevanter Heterogenenität.**			

Publication Bias: Kein Publication bias

Notes:
Limitationen: Vergleich verschiedener Eisenformulierungen und unterschiedlicher Therapiedauern. Allerdings unterschiedliche Sensitivitätsanalysen um dem Rechnung zu tragen.

Aksan, A et al. Systematic review with network meta-analysis: comparative efficacy and tolerability of different intravenous iron formulations for the treatment of iron deficiency anaemia in patients with inflammatory bowel disease. Aliment. Pharmacol. Ther. 45. 1303-1318. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematischer Review und Metaanalyse von RCTs. Databases: PUBMED, SCOPUS, Web of Science and the Cochrane Library (Cochrane Database of Sys- tematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Methodology Register) Search period: Bis Juni 2016 (kein Startdatum). Inclusion Criteria: original studies analysing the efficacy and safety of intravenous iron as monotherapy for iron deficiency anaemia in patients with IBD Exclusion Criteria: Studien in Kindern und Schwangeren.	Population: CED-Patienten mit Eisenmangelanämie Intervention: i.v. vs. po Eisen. Verschiedenen Eisenpräparate. Comparison: i.v. vs. po Eisen. Verschiedenen Eisenpräparate.	Primary: Hb-Normalisierung oder Hb-Anstieg ≥ 2g/dl Secondary: Nebenwirkungen Results: Eisen iv. gg.über po überlegen bzgl Primäroutcome Eisencarboxymaltose gg.über Eisensucrose überlegen In Netzwerk-Metaanalyse nur Eisencarboxymaltose oralem Eisen überlegen. Eisensucrose, Eisenisomaltose gegenüber p.o. Eisen mit nicht-signifikantem Vorteil. Bessere Verträglichkeit von i.v.-Eisen gegenüber oralem Eisen. Author's Conclusion: Ferric carboxymaltose was the most effective intravenous iron formulation, followed by iron sucrose. In addition, ferric carboxymaltose tended to be better tolerated.	1Portela F, Lago P, Cotter J, et al. Anaemia in patients with inflammatory bowel disease - a nationwide cross-sectional study. Digestion 2016; 93: 214–20. Crossref CAS PubMed Web of Science®Google Scholar 2Goodhand JR, Kamperidis N, Rao A, et al. Prevalence and management of anemia in children, adolescents, and adults with inflammatory bowel disease. Inflamm Bowel Dis 2012; 18: 513– 9. Wiley Online Library PubMed Web of Science®Google Scholar 3Dignass AU, Gasche C, Bettenworth D, et al. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. J Crohn's Colitis 2015; 9: 211– 22. Crossref PubMed Web of Science®Google Scholar 4Ebinger M, Leidl R, Thomas S, et al. Cost of outpatient care in patients with inflammatory bowel disease in a German University Hospital. J Gastroenterol Hepatol 2004; 19: 192– 9. Wiley Online Library CAS PubMed Web of Science®Google Scholar 5Werlin SL, Grand RJ. Severe colitis in children and adolescents: diagnosis course, and treatment. Gastroenterology 1977; 1: 828– 32. Google Scholar 6Wells CW, Lewis S, Barton JR, Corbett S. Effects of changes in hemoglobin level on quality of life and cognitive function in

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Methodical Notes

Funding Sources: Nicht dargestellt.

COI: Declaration of personal interests: Axel U. Dignass has received consultancy fees from Abbott, MSD, Ferring, UCB, Otsuka, Roche/ Genentech, Takeda, Pharmacosmos, Holystone Biotech and Falk Foundation. Dr. Dignass has also received grants from Institut f€ur Gemeinwohl and Stiftung Leben mit Krebs as well as payment for lectures including service on speakers' bureaus from Falk Foundation, Ferring, MSD, Abbott, Otsuka, Vifor, Stiftung Leben mit Krebs, Kompetenznetz CED, Takeda and Pharmacosmos. Additionally, Dr. Dignass has received payment for manuscript preparation from Falk

Foundation and payment for development of education presentations from Abbott, Pharmacosmos, Falk Foundation and Ferring. J€urgen Stein has received consultancy fees from AbbVie, Fresenius-Kabi, Immundiagnostik, MSD, Pharmacosmos, Takeda and Vifor. Dr. Stein has also received payment for lectures from Abbvie, Falk Foundation, Ferring, Immundiagnostik, MSD, Pharmacosmos, Takeda, Thermofischer and Vifor. Additionally, Dr. Stein has received payment for manuscript preparation from Abbvie, Falk Foundation and MSD. Ayseg€ul Aksan, Hatice Isık and Heinfried H. Radeke have no conflicts of interest.

Study Quality: Limitationen durch unterschiedliche Behandlungsdauer, Behandlungsintensität und unterschiedliche Hb-Werte bei Studieneinschluss.

Heterogeneity: Wenig Heterogenität.

Publication Bias: Entspricht den eingeschlossenen Primärstudien

Notes:
Systematischer Review und Metaanalyse von RCTs.

Avni, T. et al. Treatment of anemia in inflammatory bowel disease--systematic review and meta-analysis. PLoS One. 8. e75540. 2013

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematischer Review und Meta-Analyse von RCTs Databases: MEDLINE (1/1966 to 1/2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 3 of March, 2013 and NLM gateway. Conference proceedings of the American Society of Gastroenterology, from 2007 onwards. We also searched clinical trials databases for ongoing and unpublished trials: http://www.controlled-trials.com, http://www.clinicaltrials.gov/ct and http://clinicaltrials.nci.nih.gov. Search period: Bis 1/2013. Inclusion Criteria: RCTs mit Vergleich einer Eisenmangelanämie-Behandlung bei CED Exclusion Criteria: Nicht klar	Population: CED-Patienten mit Eisenmangelanämie Intervention: Vgl. Eisensubstitution iv vs. oral sowie Vergleiche verschiedener Eisenpräparate oral sowie unterschiedlicher i.v. Eisenpräparate gegeneinander und gegenüber Placebo. Comparison: Vgl. Eisensubstitution iv vs. oral sowie Vergleiche verschiedener Eisenpräparate oral sowie unterschiedlicher i.v. Eisenpräparate gegeneinander und gegenüber Placebo.	Primary: Hb-Anstieg um ≥2g/dl Secondary: Secondary outcomes included disease severity scores (Inflammatory Bowel Disease Questionnaire (IBDQ) scores [20], The Harvey-Bradshaw Simple Index scores (HBSI) [21], Crohn's Disease Activity Index (CDAI) diary card [22] and UC [23]); iron indices (ferritin concentration and transferrin saturation (TSAT), Hb levels or absolute change in Hb level at the end of follow-up; red blood cell transfusion requirements, inflammatory markers	1. Gasche C (2000) Complications of inflammatory bowel disease. Hepatogastroenterology 47: 49–56. [PubMed] [Google Scholar] 2. Gasche C, Lomer MC, Cavill I, Weiss G (2004) Iron, anaemia, and inflammatory bowel diseases. Gut 53: 1190–1197. [PMC free article] [PubMed] [Google Scholar] 3. Ohira Y, Edgerton VR, Gardner GW, Senewiratne B, Barnard RJ, et al. (1979) Work capacity, heart rate and blood lactate responses to iron treatment. Br J Haematol 41: 365–372. [PubMed] [Google Scholar] 4. Wells CW, Lewis S, Barton JR, Corbett S (2006) Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. Inflamm Bowel Dis 12: 123–130. [PubMed] [Google

definiert		(CRP levels); number of patients with treatment failure; adverse effects (AEs) (severe AEs, AEs leading to discontinuation and by involved organ), QOL scores, and mortality. Results: Überlegenheit von iv-Eisen gegenüber po Eisen (RR 1.25) bezüglich Primäroutcome Ferritin-Level ebenfalls höher bei iv. vs. po Eisen Author's Conclusion: iv iron vs. po iron with improved Hb response, no added toxicity and no negative effect on disease activity	Scholar] 5. Cucino C, Sonnenberg A (2001) Cause of death in patients with inflammatory bowel disease. Inflamm Bowel Dis 7: 250–255. [PubMed] [Google Scholar] 6. Ebinger M, Leidl R, Thomas S, Von Tirpitz C, Reinshagen M, et al. (2004) Cost of outpatient care in patients with inflammatory bowel disease in a German University Hospital. J Gastroenterol Hepatol 19: 192–199. [PubMed] [Google Scholar] 7. Werlin SL, Grand RJ (1977) Severe colitis in children and adolescents: diagnosis. Course, and treatment. Gastroenterology 73: 828–832. [PubMed] [Google Scholar] 8. Gasche C, Reinisch W, Lochs H, Parsaei B, Bakos S, et al. (1994) Anemia in Crohn's disease. Importance of inadequate erythropoietin production and iron deficiency. Dig Dis Sci 39: 1930–1934. [PubMed] [Google Scholar] 9. Horina JH, Petritsch W, Schmid CR, Reicht G, Wenzl H, et al. (1993) Treatment of anemia in inflammatory bowel disease with recombinant human erythropoietin: results in three patients. Gastroenterology 104: 1828–1831. [PubMed] [Google Scholar] 10. Hoffbrand AV, Stewart JS, Booth CC, Mollin DL (1968) Folate deficiency in Crohn's disease: incidence, pathogenesis, and treatment. Br Med J 2: 71–75. [PMC free article] [PubMed] [Google Scholar] 11. Taffet SL, Das KM (1983) Sulfasalazine. Adverse effects and desensitization. Dig Dis Sci 28: 833–842. [PubMed] [Google Scholar] 12. Lamers CB, Griffioen G, van Hogezand RA,

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Methodical Notes

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COI: The authors have declared that no competing interests exist

Study Quality: Unterschiedliche Beobachtungsdauer, Hb-Einschlusskriterien, und Erkrankungsaktivität in den Primärstudien

Heterogeneity: Limitierte Heterogenität bzgl Primärendpunkt. Signifikante Heterogenität bzgl. Sekundärendpunkten.

Publication Bias: Not reported.

Notes:
Systematischer Review und Meta-Analyse von RCTs

Bonovas, Stefanos et al. Intravenous Versus Oral Iron for the Treatment of Anemia in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Medicine (Baltimore). 95. e2308. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic Review und Metaanalyse von RCTs Databases: Medline, Embase, Scopus, and the Web of Science database. We also searched the Cochrane Central Register of Controlled Trials, the Cochrane Inflammatory Bowel Disease Group Specialized Trials Register, the WHO International Clinical Trials Registry Platform, and the ClinicalTrials.gov website for completed but unpublished studies; and recent international conference proceedings (European Crohn's and Colitis Organisation,2011–2015; Digestive Disease Week, 2010–2015; and the United European Gastroenterology Week, 2010–2014). Search period: Start der jeweiligen Datenbank bis	Population: Patienten mit Eisenmangelanämie bei CED Intervention: i.v. vs. po Eisen mit unterschiedlichen Präparaten Comparison: i.v. vs. po Eisen mit unterschiedlichen Präparaten	Primary: Hb-Anstieg um ≥ 2g/dl zum Ende des Beobachtungszeitraumes Secondary: Nebenwirkungen Results: Überlegenheit im Primäroutcome von i.v. im Vgl. zu po-Eisen (66 vs. 52%) Geringere Rate von Therapiebeendigung bei iv-Eisen vs. po Eisen Author's Conclusion: IV iron appears to be more effective and better tolerated than oral iron for the treatment of IBD-associated anemia	1. Fiorino G, Allocca M, Danese S. Commentary: anaemia in inflammatory bowel disease—the most common and ignored extra intestinal manifestation. Aliment Pharmacol Ther 2014; 39:227–228. Cited Here | View Full Text | PubMed | CrossRef 2. Fiorino G, Allocca M, Danese S. Anemia in inflammatory bowel disease: the opening of Pandora's box? Clin Gastroenterol Hepatol 2015; 13:1767–1769. Cited Here | View Full Text | PubMed | CrossRef 3. Bager P, Befrits R, Wikman O, et al High burden of iron deficiency and different types of anemia in inflammatory bowel disease outpatients in Scandinavia: a longitudinal 2-year follow-up study. Scand J Gastroenterol 2013; 48:1286–1293. Cited Here | PubMed 4. Abitbol V, Borderie D, Polin V, et al Diagnosis of

Juli 2015 Inclusion Criteria: RCTs mit iv vs. po Eisensubstitution bei Eisenmangelanämie bei CED Exclusion Criteria: Beobachtungsstudien, Patienten ohne CED, pädiatrische Populationen.			iron deficiency in inflammatory bowel disease by transferrin receptor-ferritin index. Medicine (Baltimore) 2015; 94:e1011. Cited Here | View Full Text | PubMed | CrossRef 5. Gisbert JP, Gomollón F. Common misconceptions in the diagnosis and management of anemia in inflammatory bowel disease. Am J Gastroenterol 2008; 103:1299–1307. Cited Here | View Full Text | PubMed | CrossRef 6. Stein J, Hartmann F, Dignass AU. Diagnosis and management of iron deficiency anemia in patients with IBD. Nat Rev Gastroenterol Hepatol 2010; 7:599–610. Cited Here | View Full Text | PubMed | CrossRef 7. Gasche C, Lomer MC, Cavill I, et al Iron, anaemia, and inflammatory bowel diseases. Gut 2004; 53:1190–1197. Cited Here | View Full Text | PubMed | CrossRef 8. Dignass AU, Gasche C, Bettenworth D, et al European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. J Crohns Colitis 2015; 9:211–222. Cited Here | PubMed 9. Gomollón F, Gisbert JP. Anemia and inflammatory bowel diseases. World J Gastroenterol 2009; 15:4659–4665. Cited Here | PubMed | CrossRef 10. Wells CW, Lewis S, Barton JR, et al Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. Inflamm Bowel Dis 2006; 12:123–130.

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Methodical Notes

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COI: GF has served as a consultant and advisory board member for MSD, Takeda, AbbVie, and Janssen. LP-B has received consulting fees from Merck, Abbott, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Shire, Therakos, Pharmacosmos, Pile`ge, BMS, UCB-pharma, Hospira, Celltrion, Takeda, Biogaran, Boehringer-Ingelheim, Lilly, Pfizer, and HAC-pharma, and lecture fees from Merck, Abbott, Takeda, Janssen, Ferring, Norgine, Tillots, Vifor, Therakos, and HAC-pharma. SD has served as a speaker, consultant, and advisory board member for Schering-Plough, Abbott Laboratories, Merck, UCB-pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Danone, Alpha Wasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor, and Johnson & Johnson. All other authors have no conflicts of interest to disclose.

Study Quality: Alle inkludierten Primärstudien mit high risk of bias, weil nicht verblindet. Keine Unterscheidung der verschiedenen iv-Eisenpräparate. Unterschiedliche Behandlungszeiträume

Heterogeneity: Wenig Heterogenität.

Publication Bias: Keine Evidenz für Publication Bias.

Notes:

Systematic Review und Metaanalyse von RCTs

Nielsen, Ole Haagen et al. Management of Iron-Deficiency Anemia in Inflammatory Bowel Disease: A Systematic Review. Medicine (Baltimore). 94. e963. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 Study type: Systematischer Review Databases: PubMed, EMBASE, the Cochrane Library, and the websites of WHO, FDA, and EMA covered prospective trials investigating the management of iron-deficiency anemia in IBD published since 2004. Search period: Januar 2004-März 2015 Inclusion Criteria: original prospective studies evaluating the treatment of iron-deficiency anemia (ie, normalization of Hb concentration) in IBD patients with a minimum observation time of 4 weeks were included Exclusion Criteria: reviews and nonhuman investigations	Population: CED-Patienten mit Eisenmangelanämie Intervention: Eisensubstitionen, oral und/oder iv. Comparison: Eisensubstitionen, oral und/oder iv.	Primary: Nicht formal definiert. Secondary: Hb-Anstieg, Nebenwirkungen Results: - bei milder Anämie (Hb≥10g/dl) und kurzem Follow-up (4 Wochen), Überlegenheit von iv-Eisen gegenüber po-Eisen bzgl. Anstieg des Ferritins, aber nicht des Hb - bei stärkerer Eisenmangelanämie iv-Eisen bzgl. po-Eisen in Hinblick auf Hb-Anstieg überlegen Author's Conclusion: Based on the data presented, oral iron therapy should be preferred for patients with quiescent disease stages and trivial iron deficiency anemia unless such patients are intolerant or have an inadequate response, whereas intravenous iron supplementation may be of advantage in patients with aggravated anemia or flares of IBD because inflammation hampers intestinal absorption of iron.	1. Filmann N, Rey J, Schneeweiss S, et al. Prevalence of anemia in inflammatory bowel diseases in european countries: a systematic review and individual patient data meta-analysis. Inflamm Bowel Dis 2014; 20:936–945. Cited Here | View Full Text | PubMed | CrossRef 2. Fiorino G, Allocca M, Danese S. Commentary: anaemia in inflammatory bowel disease: the most common and ignored extra intestinal manifestation. Aliment Pharmacol Ther 2014; 39:227–228. Cited Here | View Full Text | PubMed | CrossRef 3. Kulnigg S, Gasche C. Systematic review: managing anaemia in Crohn's disease. Aliment Pharmacol Ther 2006; 24:1507–1523. Cited Here | View Full Text | PubMed | CrossRef 4. Wilson A, Reyes E, Ofman J. Prevalence and outcomes of anemia in inflammatory bowel disease: a systematic review of the literature. Am J Med 2004; 116:44S–49S. Cited Here | PubMed 5. Larsen S, Bendtzen K, Nielsen OH. Extraintestinal manifestations of inflammatory bowel disease: epidemiology, diagnosis, and management. Ann Med 2010; 42:97–114. Cited Here | PubMed | CrossRef 6. Goodhand JR, Kamperidis N, Rao A, et al. Prevalence and management of anemia in children, adolescents, and adults with inflammatory bowel disease. Inflamm Bowel Dis 2012; 18:513–519. Cited Here | View Full Text | PubMed | CrossRef 7. Bager P, Befrits R, Wikman O, et al. High burden of iron deficiency and different types of anemia in inflammatory bowel disease outpatients in Scandinavia: a longitudinal 2-year follow-up study.

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Methodical Notes

Funding Sources: The National Danish Health Care System and Austrian Research Funds (FWF-TRP188) funded the research but had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

COI: OHN, MA, andMChave no conflicts of interest to disclose.GWhas received lecture honoraria from Vifor Pharma and Pharmacosmos.

Study Quality: Studies were heterogeneous in design (ie, inclusion criteria and iron compositions administered, such as oral and low- or high-dose intravenous drugs), different enrollment populations as well as different lengths of therapy, and outcomes. Further, in some of the studies, a minimum 4-week treatment period was employed, although it is questionable whether such a short interval is always effective for the correction of iron deficiency in IBD, and thus the efficacy of the oral supplementation may be underestimated compared with a full treatment period of, for example, 3 months.

Heterogeneity: Heterogenes Studiendesign

Publication Bias: Keine Angaben.

Notes:
Systematischer Review von RCTs und prospektiven Studien

OXFORD (2011) Appraisal Sheet: RCT: 1 Bewertung(en)

Reinisch, Walter et al. A randomized, open-label, non-inferiority study of intravenous iron isomaltoside 1,000 (Monofer) compared with oral iron for treatment of anemia in IBD (PROCEED). Am. J. Gastroenterol. 108. 1877-88. 2013

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: Individueller RCT Number of Patient: 225 Eisenisomaltosid, 113 Eisensulfat Recruitung Phase: December 2009 to July 2012. Inclusion Criteria: Patients ≥ 18 years of age with a diagnosis of IBD and a score of ≤ 5 on the Harvey –	Intervention: Eisenbedarf nach Ganzoni-Formel berechnet. Dann: - Gruppe A1: 1000mg Eisenisomaltosid i.v. pro Woche bis zum errechneten Bedarf - Gruppe A2: 500mg Eisenisomaltosid i.v. pro Woche bis zum errechneten Bedarf Comparison: 200mg Eisensulfat täglich für 8 Wochen	Primary: Hb-Veränderung im Vgl. Woche 8 zu baseline Secondary: Th e secondary end points included change in Hb concentration from baseline to weeks 2 and 4, change in concentrations of s- ferritin and TSAT from baseline to week 8, number of patients who discontinued study because of lack of response or intolerance of investigational drugs, change in total QoL score from baseline to weeks 4 and 8 as measured by the Infl ammatory Bowel Disease Questionnaire (29), and safety (adverse events (AEs), vital signs,

Bradshaw index for Crohn ' s disease (25) or a partial Mayo score of ≤ 6 for ulcerative colitis (26), a Hb < 12 g / dl (7.45 mmol / l), and a transferrin saturation (TSAT) < 20 % Exclusion Criteria: intolerance to oral iron treatment, other primary causes of anemia, hemochromatosis, hemosiderosis, hypersensitivity to IV iron complexes or iron sulfate, a history of multiple allergies, active intestinal tuberculosis / amoebic infections, liver cirrhosis, active hepatitis, acute infections, rheumatoid arthritis along with symptoms or signs of active joint infl ammation, untreated vitamin B 12 / folate defi ciency, pregnant or nursing women, and patients with extensive active bleeding necessitating blood transfusion or with planned elective surgery during the study		electrocardiogram, s -phosphate, and other safety hematology and biochemistry parameters). Results: Überlegenheit von Eisensulfat gegenüber Eisenisomaltoside in Bezug auf den primären Endpunkt, mit Signifikanz in der per protocol-Analyse, aber nicht im full analysis set (p=0.04) Eisenisomaltosid überlegen bezüglich Ferritin-Anstieg, aber paradoxerweise Transferrinsättigungsanstieg höher in der Eisensulfat-Gruppe Keine Gruppenunterschiede in der Lebensqualität Keine Gruppenunterschiede bzgl. Sicherheit Prädiktoren besserer Wirksamkeit von Eisenisomaltosid waren CRP, baseline HB und höherer Eisenbedarf Author's Conclusion: We could not demonstrate non-inferiority of IV iron isomaltoside 1,000 compared with oral iron in this study. Based on the dose – response relationship observed with the IV iron compound, we suggest that the true iron demand of IV iron was underestimated by the Ganzoni formula in our study. Alternative calculations including Hb and CRP should be explored to gauge iron stores in patients with IBD.

Methodical Notes

Funding Sources: Th e study was funded by Pharmacosmos A / S. Pharmacosmos A / S was responsible for setup of the study, collection, analyses, and interpretation of the data, and in the writing of the report.

COI: Lars L. Th omsen is employed by Pharmacosmos A / S, and the investigators / institutions received a fee per patients.

Randomization: Permuted block randomization was used to assign patients in a 1:1:1 ratio to receive either treatment A1 (weekly infusion of up to 1,000 mg iron isomaltoside 1,000 until reaching cumulative dosage), A2 (weekly 500 mg bolus injections of iron isomaltoside 1,000 until reaching cumulative dosage), or B (200 mg oral iron sulfate daily for 8 weeks). Th e block size was 6. Th e randomization list was prepared centrally by a Contract Research Organization, Max Neeman International Data Management Centre, using a validated computer program (Statistical Analysis Soft ware (SAS) 9.1.3, SAS Institute Inc, Cary, NC) PROC PLAN procedure). Th e randomization was stratifi ed by whether the patient had received IV iron treatment in the past or not.

Blinding: Kein Blinding

Dropout Rate/ITT-Analysis: Dropout-Rate 9-16% pro Gruppe. ITT und PP-Analyse durchgeführt

Notes:
Individueller RCT

Literatursammlung:

AG 7 Ernährung, Psycho, Komplementär-Frage 1

Inhalt: 10 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Bennebroek Evertsz', Floor 2017	2	RCT
Berrill, James W 2014	2	RCT
Keerthy, Divya 2016	3	RCT
Levy, Rona L 2016	2	RCT
Mikocka-Walus, Antonina 2017	2	RCT
Mikocka-Walus, Antonina 2015	2	RCT
Stapersma, Luuk 2018	2	RCT
Szigethy, Eva 2015	3	Randomised controled ? trial
Vogelaar, Lauran 2014	2	RCT
Wynne, Brona 2019	2	RCT

OXFORD (2011) Appraisal Sheet: RCT: 10 Bewertung(en)

Bennebroek Evertsz', Floor et al. Effectiveness of cognitive-behavioral therapy on quality of life, anxiety, and depressive symptoms among patients with inflammatory bowel disease: A multicenter randomized controlled trial. J Consult Clin Psychol. 85. 918-925. 2017

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: 118 Recruitung Phase: Inclusion Criteria: (a) Diagnose von Morbus Crohn (CD) oder Colitis ulcerosa (UC) (b) Alter über 18 Jahre (c) Punktzahl von 23 auf der Subskala für psychische Gesundheit der Medical Outcomes Study Short Form 36 Health Survey (d) körperliche und geistige Fähigkeit, an	Intervention: 8 wöchige kognitiv-verhaltenstherapeutische Therapie Comparison: Wartekontrollgruppe	Primary: Inflammatory Bowel Disease Questionnaire [IBDQ] Secondary: Hospital Anxiety and Depression Scale–Depression Subscale [HADS-D] Center for Epidemiologic Studies Depression Scale [CES-D]) anxiety (HADS–Anxiety Subscale [HADS-A]) generic QoL (SF-36) Results: Die CBT hatte eine positive Wirkung auf die krankheitsspezifische Lebensqualität, Depression, Angstzustände und die allgemeine Lebensqualität. Author's Conclusion: IBD-spezifische CBT ist wirksam bei der Verbesserung der Lebensqualität und bei der Verringerung von Angst und Depression bei IBD-Patienten mit schlechter Lebensqualität. Kliniker sollten ein Screening auf schlechte geistige

acht wöchentlichen Sitzungen teilzunehmen (e) Beherrschung der niederländischen Sprache Exclusion Criteria: (a) aktuelle Psychotherapie (b) schwere andere psychiatrische Störungen (z.B. Drogenmissbrauch, bipolare Störungen oder Psychosen)		Lebensqualität einbeziehen und erwägen, CBT anzubieten.

Methodical Notes

Funding Sources: keine Angabe

COI: keine Angabe

Randomization: TENALEA Clinical Trial Data Management System software (http:// www.formsvision.com)

Blinding: keine Angabe (Wartekontrollgruppe?)

Dropout Rate/ITT-Analysis: 10 Patienten in der Interventions-, 12 in der Wartekontrollgruppe

Notes:

Berrill, James W et al. Mindfulness-based therapy for inflammatory bowel disease patients with functional abdominal symptoms or high perceived stress levels. J Crohns Colitis. 8. 945-55. 2014

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: 66 Recruitung Phase: gastroenterology clinics at the University Hospital Llandough and the University Hospital of Wales, Cardiff, United Kingdom between February 2011 and May 2012 Inclusion Criteria: 1. age 18–65 years 2. diagnosis of UC or CD that was in remission based on a clinical index score and a C-reactive protein level b 10 mg/l 3. presence of IBS-	Intervention: Multi-convergent therapy (MCT) for 16 weeks Comparison: waiting list control group	Primary: Inflammatory Bowel Disease Questionnaire (IBDQ) Secondary: - descriptive analysis of the acceptability and feasibility of administering MCT to an IBD population - the effect of MCT on disease activity - levels of perceived stress and coping mechanisms Separate exploratory sub-group analyses were performed on those patients with FC b 150 µg/g at baseline, those recruited with IBS-type symptoms at baseline, and those recruited with a high perceived stress level at baseline. Results: A higher mean IBDQ score was observed in the active group compared to controls at the 4-month assessment, but this was not statistically significant nor did it reached the predefined clinically significant difference of 20. In patients with IBS-type symptoms at baseline there was a significantly higher mean IBDQ score in the active group compared to controls. Author's Conclusion: IBS-type symptoms in patients with IBD represent a potential therapeutic target to improve quality of life. This study suggests that MCT may be useful in the management of these symptoms but larger studies are required to confirm this.

type symptoms or a high perceived stress level Exclusion Criteria: 1. pregnancy 2. presence of ileostomy or colostomy 3. previous colectomy 4. change in IBD medication (including use of steroids) within 3 months of study entry 5. change in psychotropic medication within 3 months of study entry 6. diagnosis of cognitive impairment 7. previous psychological therapy		

Methodical Notes

Funding Sources: The South East Wales Trials Unit is funded by the National Institute for Social Care and Health Research (NISCHR)

COI: No

Randomization: YES

Blinding: NO

Dropout Rate/ITT-Analysis: 7 by 4 months-follow-up

Notes:

Keerthy, Divya et al. Effect of Psychotherapy on Health Care Utilization in Children With Inflammatory Bowel Disease and Depression. J. Pediatr. Gastroenterol. Nutr. 63. 658-664. 2016

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 Study type: RCT Number of Patient: 70 Recruitung Phase: Pediatric GI clinics and inpatient units at Children's Hospital of Pittsburgh of UPMC and Boston Children's Hospital Inclusion Criteria: - major or minor	Intervention: One year of psychotherapy Comparison: healthcare utilization 12-months prior to psychotherapy compared to the 12 month following the conclusion of psychotherapy	Primary: - frequency of hospitalization Secondary: - inpatient hospital days - outpatient gastrointestinal visits - number of emergency room visits - radiological exams - endoscopies Results: All study measures of healthcare utilization were significantly reduced after psychotherapy (p <0.01) – including gastrointestinal-related hospitalization frequency, inpatient days, outpatient visit, emergency room visits, radiological exams, and endoscopies.

depression by DSM-IV-TR criteria Exclusion Criteria: - current or past history of eating disorder requiring hospitalization - bipolar disorder or psychotic disorder according to DSM-IV TR criteria - antidepressant medications within one month of study entry - major depressive episode requiring psychiatric hospitalization within three months of study entry - suicide attempt within one month of study entry - history of substance abuse or dependence within one month of study entry and/or current psychotherapy		Author's Conclusion: Psychotherapy for comorbid depression in pediatric patients with IBD is associated with decreased GI-related healthcare utilization.

Methodical Notes

Funding Sources: This research was funded by the National Institute of Mental Health (R01 MH07777), the NIH Director's Innovator Award (1DP2OD001210), NIMH training grant (R25MH054318), and the Crohn's & Colitis Foundation of America Research Fellowship Award #3590.

COI: A.B. has received consulting fees from Millenium, Dyax, Cubist, and Nutricia, lecture fees from Merck, and royalties from UpToDate. D.R.D. has received royalties from American Psychiatric Publishing Inc. E.M.S. is a paid advisor for Merck, Abbvie, and iHope Networks Inc has received payment for expert testimony in a malpractice case, has received payment from Imedex for speaking at a CCFA meeting, and receives royalties as book editor from American Psychiatric Publishing Inc.

Randomization: yes

Blinding: no

Dropout Rate/ITT-Analysis: 147 were not included in this analysis because 86 were diagnosed less than 1 year before enrollment and 61 were followed less than 1 year after enrollment.

Notes:

Levy, Rona L et al. Effects of a Cognitive Behavioral Therapy Intervention Trial to Improve Disease Outcomes in Children with Inflammatory Bowel Disease. Inflamm. Bowel Dis. 22. 2134-48. 2016

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: 185 Recruitung Phase:	Intervention: (1) cognitive behavioral therapy condition Comparison:	Primary: - quality of life - number of missed school days due to CD or UC Secondary: - Parent report only - Child report only - Parent and Child Report - Physician Report - anxiety or depression

Pediatric GI clinics at Seattle Children's Hospital and Mary Bridge Children's Hospital in Tacoma, WA. Inclusion Criteria: (1) child aged 8 to 17 years (2) child received a diagnosis of Crohn's or UC and was at least 3 months after diagnosis (3) child lived with the participat- ing parent or caregiver for at least the last 3 months (4) child and parent were willing and able to complete the questionnaires and agreed to participate in the intervention and follow-up evalua- tions (5) child was medically approved to engage in normal activities (e.g., attend school, extracurricular activities). Exclusion Criteria: (1) a chronic disease other than IBD (e.g., pancreatitis, diabetes, epilepsy) (2) major surgery within the past year unrelated to IBD (3) developmental disabilities requiring full-time special education or impairing ability to communicate (4) non-English speaking	(2) an education support condition designed to control for time and attention.	Results: There was a significant overall treatment effect for school absences due to Crohn's disease or ulcerative colitis (P , 0.05) at 6 months after treatment. There was also a significant overall effect after treatment for child-reported quality of life (P , 0.05), parent-reported increases in adaptive child coping (P , 0.001), and reductions in parents' maladaptive responses to children's symptoms (P , 0.05). Author's Conclusion: This trial suggests that a brief cognitive behavioral intervention for children with inflammatory bowel disease and their parents can result in improved child functioning and quality of life, and for some children may decrease disease activity.

Methodical Notes

Funding Sources: Supported by a grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (award number R01HD050345 to R. L. Levy).

COI: NO

Randomization: Yes

Blinding: Yes

Dropout Rate/ITT-Analysis: 16

Notes:

Mikocka-Walus, Antonina et al. Cognitive-Behavioural Therapy for Inflammatory Bowel Disease: 24-Month Data from a Randomised Controlled Trial. Int J Behav Med. 24. 127-135. 2017

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: 176 Recruitung Phase: Two gastroenterology clinics in Australia Inclusion Criteria: - established diagnosis of IBD - in clinical remission or had mild symptoms only for at least 3 months - aged 18 years or over - competence to consent Exclusion Criteria: - mental illness (e.g. psychosis, schizophrenia or any other serious mental disorder requiring one-to-one therapy which could not be offered as part of the trial) - receiving psychotherapy	Intervention: cognitive-behavioural therapy (CBT) over 10 weeks face to face or online AND standard care for IBD Comparison: standard care for IBD	Primary: remission at 24 months (established using the CDAI) Secondary: - subjective view of IBD activity measured by a question How well con- trolled is your IBD - disease activity measured on the blood parameters: C-reactive protein (CRP), haemoglobin (Hb), platelet, white cell count (WCC) - quality of life as measured on the Short Form 36 Health Status Questionnaire (SF-36) - mental health status (anxiety and depression as measured on the HADS and the State-Trait Anxiety Inventory (STAI) - stress measured on the Revised Social Readjustment Rating Scale (RSRRS)and coping as measured on the Brief COPE and the IBD Stages of Change Coping Questionnaire (IBDSCCQ) at 24 months Results: CBT did not significantly influence disease activity as measured by disease activity indices at 24 months Author's Conclusion: We conclude that CBT does not influ- ence the course of IBD over 24 months. Given the high rate of attrition, particularly in the CBT group, future trials should consider a personalised approach to psychotherapy, perhaps combining online and one-to-one therapist time.

Methodical Notes

Funding Sources: The study received additionally unsolicited funding from Abbott Australia, MSD Australia and Janssen. Support was also provided by untied research funding held in the Department of Gastroenterology and Hepatology at the RAH and from JMA's personal research fund earned from consulting work for pharma and educational lectures. Study sponsors had no involvement in the study design, in the collection, analysis and interpretation of data, in the writing of the man- uscript or in the decision to submit the manuscript for publication.

COI: NO

Randomization: Yes

Blinding: No

Dropout Rate/ITT-Analysis: 101

Notes:

Mikocka-Walus, Antonina et al. Cognitive-behavioural therapy has no effect on disease activity but improves quality of life in subgroups of patients with inflammatory bowel disease: a pilot randomised controlled trial. BMC Gastroenterol. 15. 54. 2015

Population	Intervention - Comparison	Outcomes/Results

Evidence level: 2 Study type: RCT Number of Patient: 174 Recruitung Phase: Participants were recruited from two Gastroenterology Clinics in Australia, together serving approximately 2,000 IBD patients. Inclusion Criteria: Patients had to meet ALL of the following criteria: 1). a clinically established diagnosis of IBD (according to usual clinical practice by combination of clinical, radiologic, endoscopic and histologic grounds in a tertiary care IBD centre); 2). current clinical remission or mild symptoms only for at least 3 months as evidenced by disease activity index, notes review, blood results and report from their treating gastroenterologist, if necessary (complete loss of GI symptoms in IBD is uncommon even during endoscopic remission); 3). sufficient English to understand, answer questionnaires and participate in therapy; 4). 18 years old or older; 5). competence to consent; 6). willingness to complete CBT sessions. Exclusion Criteria: Patients were excluded if they met ANY of the following: 1). serious mental illness (e.g. psychosis, schizophrenia) or alcohol/substance dependence as diagnosed by the Clinical Psychologist; 2). currently undergoing psychotherapy; 3). significant cognitive impairment. Antidepressants were not an exclusion as antidepressants are commonly used in IBD not necessarily to treat anxiety or depression but rather, in a similar fashion they are used in functional gut disorders, to manage pain and abdominal discomfort and thus may be considered usual care.	Intervention: CBT was a 10-week group program designed specifically for this patient population by senior clinical psychologists working at the hospital Clinical Psychology Unit (not study investigators). The CBT program (2 hours each week) consisted of: 1) Education about IBD and CBT; 2) Stress and relaxation; 3) Automatic thoughts and cognitive distortions; 4) Cognitive restructuring; 5) Exposure and overcoming avoidance; 6) Coping strategies; 7) Assertiveness training; 8) Relationships and communication; 9) Attention and distraction; and 10) Relapse prevention for mental health problems. Attendance at each weekly session was noted by the psychologist and registered by the CBT website in the case of online groups.Compliance with the program was monitored by the psychologist on a regular basis and strategies to minimise attrition included regular reminders (telephone, email). Non-compliant patients were contacted by the psychologist individually and inquired about their views on how this may be improved. Withdrawing patients were asked for permission to retain data to date. Treatment fidelity was maintained by using the same	Primary: IBD remission at 12 months since baseline Secondary: mental health status and quality of life (QoL) Results: Participants were 174 patients with IBD (90 +CBT, 84 SC). There was no difference in remission rates between groups, with similar numbers flaring at 12 months. Groups did not differ in anxiety, depression or coping at 6 or 12 months (p >0.05). When only participants classified as ‘in need’ (young, high baseline IBD activity, recently diagnosed; poor mental health) were examined in the post-hoc analysis (n = 74, 34 CBT and 40 controls), CBT significantly improved mental QoL (p = .034, d = .56) at 6 months. Online CBT group had a higher score on Precontemplation than the F2F group, which is consistent with less developed coping with IBD in the cCBT group (p = .045). Author's Conclusion: uture studies should direct psychological interventions to patients ‘in need’and attempt to recruit larger samples to compensate for significant attrition when using online CBT.

	protocol for both groups within the CBT arm. Online CBT was provided using the university IT infrastructure support. Comparison: standard care	

Methodical Notes

Funding Sources: the study received additionally unsolicited funding from Abbott Australia, MSD Australia and Janssen. Support was also provided by untied research funding held in the Department of Gastroenterology and Hepatology at the RAH and from JMA's personal research fund earned from consulting work for pharma and educational lectures. No editorial support was received in the preparation of this paper. Study sponsors had no involvement in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

COI:

Randomization: A simple randomisation method was used using a table of computer generated random numbers (in blocks of four) in the proportion of 2:1 (experimental vs. control). This proportion was used as we predicted problems in recruiting to the experimental arm (due to a larger participant burden) and assumed that we needed to approach twice as many experimental participants to eventually obtain the same number of participants in both groups. A randomisation schedule was created by the researcher with no direct patient contact using computer software (AE). Participants were enrolled by Research Nurses (not this study 's investigators) who also assigned participants to interventions.

Blinding: iven impossibility of blinding the intervention, we decided to withdraw the information regarding the intervention from the controls.

Dropout Rate/ITT-Analysis: High number in losses to follow-up: Intervention group: n=92, follow up 6 month: n=51, follow up 12 month: n=42. Control group: n=84, follow up 6 month: n=65, follow up 12 month: n=64.

Notes:
groups do not seem similar at the start of the trial. No p-values mentioned. High numbers in losses to follow-up.

Stapersma, Luuk et al. Effectiveness of Disease-Specific Cognitive Behavioral Therapy on Anxiety, Depression, and Quality of Life in Youth With Inflammatory Bowel Disease: A Randomized Controlled Trial. J Pediatr Psychol. 43. 967-980. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: Number of patients: 70. CAU group: 33; CAU + CBT group: 37. Recruitung Phase: Initially, only	Intervention: The PASCET-PI is a disease-specific CBT protocol, developed for adolescents with IBD and depression. The PASCET-PI contained 10 weekly individual sessions, delivered in 3 months. Conform the protocol, six of these	Primary: Primary analysis concerned the reliable change in anxiety and depressive symptoms after 3 months (immediate posttreatment assessment). Fisher's exact test: In the primary analysis, RCI

patients 10–20 years old were included. A few months after the start of the recruitment,patients of age 21–25 years were also included, to include more patients in young adulthood as well, to cover the transition phase.

Included for baseline screening for symptoms of anxiety
and depression were adolescents and young adults
of age 10–25 years with a confirmed diagnosis of IBD
(CD, UC, or inflammatory bowel disease-unclassified
[IBD-U]; Figure 1). Between October 2014 and
October 2016, patients were consecutively recruited
from the pediatric or (pediatric) gastroenterology
departments of two academic hospitals and four community hospitals.

Inclusion Criteria: Inclusion baseline screening:
Included for baseline screening for symptoms of anxiety and depression were adolescents and young adults of age 10–25 years with a confirmed diagnosis of IBD (CD, UC, or inflammatory bowel disease-unclassified [IBD-U].

Inclusion RCT:
Only youth with subclinical anxiety and/or depressive symptoms were included in the RCT.

Exclusion Criteria: Exclusion baseline screening:
Exclusion criteria were (1) intellectual disability; (2) current treatment for mental health problems (pharmacological and/or psychological); (3) insufficient mastery of the Dutch language; (4) a diagnosis of selective mutism, bipolar disorder, schizophrenia/psychotic disorder, autism spectrum disorders, obsessive-compulsive disorder, posttraumatic or acute stress-disorder, substance use disorder (parent- or self-reported or from medical file); (5) CBT in the past year (at least eight sessions); and (6) participation in another interventional study, all assessed by the treating physician using medical files (unless otherwise specified).

sessions were face-to-face, the remaining four sessions were by phone at a prearranged moment (to advance adherence and lower the treatment burden). In addition, three family sessions (for patients and their parents) were held (only for patients equal or younger than 20 years), and following the weekly sessions, three monthly individual booster sessions were held by telephone (this was after the immediate post[-treatment] assessment).

The original PASCET-PI was developed for depression, therapists were instructed how to make the exercises more anxiety-tailored, an anxiety hierarchy and step-bystep exercise was added, and an extra anxiety handout was provided to the patients. For patients of age 21–25 years, the practice book was made more ageappropriate.

Comparison: The control group received standard medical care (care-asusual, CAU) only, as this resembles the current care best.

CAU consisted of regular medical appointments with the (pediatric) gastroenterologist every 3months, consisting of a 15-min consultation discussing overall well-being, disease activity, results of diagnostics tests, medication use, and future diagnostic/treatment plans.

values did not differ between the two groups for both anxiety and depression. Overall, patients in both groups either remained stable or improved in their symptoms of anxiety and depression.

Exploratory analyses:
The same pattern was seen. No significant time–group interaction effect was found for anxiety and IBDQ the effect of time was significant, whereas for the CDI, this was not the case. These findings show that, after 3 months, all patients improved in their symptoms of anxiety and depression, as well as in their HRQOL. Even when these analyses were carried out only in patients who showed relatively “high” subclinical problems (“high” n=40 vs. “low” n=30), no group differences were found on the anxiety and depression outcomes (data not shown).

Over all: No group differences were found on the anxiety and depression outcomes.

Secondary: Additional research questions were as follows: (1) What is the course of anxiety and depressive symptoms and HRQOL in subgroups based on age, regarding the effect of CBT? (2) What is the influence of age, gender, and disease type on the course of anxiety and depressive symptoms and HRQOL, regarding the effect of CBT? By these questions, we aim to examine which patients may benefit most from the diseasespecific CBT.

(1)
In exploratory analyses for the four separate agegroups (classified by the four age-attuned questionnaires:
SCARED [10–20 years], HADS [21–25 years], CDI [10–17 years], BDI-II [18–25 years]), no differences were found between the groups as to the change in anxiety, depression, or HRQOL.

Over all: No age effect.

(2)

Exclusion RCT: **Patients with clinical anxiety and/or depression were excluded, as we deemed it unethical to randomize them.**		**We explored the possible influence of gender and disease type on the effect of the PASCETPI by conducting linear mixed model analyses separately in subgroups (male vs. female and CD vs. UC and IBD-U). Overall, none of the subgroup analyses showed a difference between two groups on anxiety, depression, or HRQOL, except for a significant lower score on the BDI-II in the CAU group (n=6) than in the CBT group (n=3) for the subgroup analysis in men (data not shown).** **Over all: Gender and disease type do not seem to influence the effect of CBT.** **Results: Overall, all participants improved significantly in their anxiety and depressive symptoms and HRQOL, regardless of group, age, gender, and disease type. Primary chi-square tests and exploratory linear mixed models showed no difference in outcomes between the PASCET-PI and the CAU group.** **Author's Conclusion: In youth with IBD and subclinical anxiety and/or depressive symptoms, preliminary results of immediate post-treatment assessment indicated that a diseasespecific CBT added to standard medical care did not perform better than standard medical care in improving psychological symptoms or HRQOL.**

Methodical Notes

Funding Sources: This work was supported by Stichting Vrienden van het Sophia (grant number 985 to J.C.E.), Stichting Crohn en Colitis Ulcerosa Fonds Nederland/Maag Lever Darm Stichting (grant number 14.307.04 to E.M.W.J.U.), Fonds NutsOhra (grant number 1303-012 to E.M.W.J.U.), and Stichting Theia (grant number 2013201 to E.M.W.J.U.). J.C.E. received financial support from MSD (research support), Janssen (advisory board), and AbbVie (advisory board). E.M.S. received financial support from NIH (grant), Crohn and Colitis Fund America (grant), AbbVie (consultancy), Merck (consultancy), and IHOPE Network (consultancy) and royalties for book editing from APPI. For the remaining authors, none was declared.

COI: None declared.

Randomization: Patients with subclinical anxiety and/or depressive symptoms were randomized to PASCET-PI and CAU versus CAU alone, with a ratio of 1: 1.
An independent biostatistician provided a computer-generated blocked randomization
list with randomly chosen block sizes and stratification by center using the blockrand package in the R software package, thereby providing numbered envelopes per center. Patients were enrolled by one of the investigators (GB).

Blinding: The interviewer (LS) and treating physicians were blinded for the result of randomization (they were not informed and had no access to files containing this information). Patients could not be blinded.

Dropout Rate/ITT-Analysis: 2 patients in the CAU + CBT group were lost for follow up.

Notes:

Szigethy, Eva et al. Effect of 2 psychotherapies on depression and disease activity in pediatric Crohn's disease. Inflamm. Bowel Dis. 21. 1321-8. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 Study type: Randomised controled ? trial Number of Patient: From the 161 with CD, 82 were randomized to CBT and 79 to SNDT. At 3 months, 69 youth completed CBT, and 66 completed SNDT treatments. Recruitung Phase: Youth ages 9 to 17 years with either CD or UC and their parents were recruited from Children's Hospital of Pittsburgh and Boston Children's Hospital between 2008 and 2012 using a protocol approved by the Institutional Review Boards at both sites. Inclusion	Intervention: Randomized subjects underwent up to 12 weekly sessions of either CBT 22,23 or SNDT. Therapists (n = 10) experienced in treating physically ill youth were trained in both manual-based interventions and received weekly supervision. All sessions were audiotaped to allow for quality assurance and to assure treatment fidelity. Each treatment was tailored to the developmental level of each youth. Up to 75% of sessions could be completed by telephone. More detailed descriptions of each intervention have been described previously.33 Comparison: supportive nondirective therapy (supportive listening). Randomized subjects underwent up to 12 weekly sessions of either CBT 22,23 or SNDT.	Primary: Secondary: Results: Total CDRS-R scores in the overall sample significantly decreased over time after both treatments (P , 0.0001). Treatment with CBT was associated with a significantly greater improvement in the Pediatric Crohn's disease Activity Index (P = 0.05) and somatic depressive subtype (P = 0.03) in those with active inflammatory bowel disease (n = 95) compared with supportive nondirective therapy. After excluding those on steroids (n = 34), there was a significant improvement in total CDRS-R (P = 0.03) and in Pediatric Crohn's disease Activity Index (P = 0.03) after CBT. Author's Conclusion: Psychotherapy may be a useful adjunct to treat depression in the context of CD-related inflammation in youth who are not concurrently on higher dose steroids.

Criteria: inclusion criteria see literatur #20 **Exclusion Criteria:**		

Methodical Notes

Funding Sources: E. Szigethy currently has a senior investigator research grant from the Crohn's and Colitis Foundation of America (CCFA) and has received funding from NIH Directors Innovator Award (DP2 OD001210), has served as a consultant for Merck and AbbVie Advisor Boards, has received honoraria from Imedex, the CME organizers for the CCFA for educational presentations and is co-editor of the book, Cognitive Behavioral Therapy for Children and Adolescents for which she receives royalties from APPI Press. She is also a consultant for iHOPE Network. J. Weisz is a co-editor for the book, Cognitive Behavioral Therapy for Children and Adolescents. J. Gonzalez-Heydrich has received grant support from the Tommy Fuss Fund, the Al Rashed Family, GlaxoSimthKline, Johnson & Johnson, Abbott Laboratories, Pfizer Inc., AkzoNobel/Organon, and the NIMH. He has been a consultant for Abbott Laboratories, Pfizer, Johnson & Johnson (Janssen, McNeil Consumer Health), Novartis, Parke-Davis, GlaxoSmithKline, AstraZeneca, and Seaside Therapeutics. D. Kupfer holds joint ownership of copyright for the Pittsburgh Sleep Quality Index (PSQI); he and his spouse, Dr. Ellen Frank are stockholders in Psychiatric Assessments, Inc. and Health Rhythms, Inc. He is stockholder in AliphCom. Dr. Frank also received royalties from the American Psychological Association and Guilford Press; is a member of the Advisory Board of Servier International, and Editorial Consultant for American Psychiatric Press.

COI: The remaining authors have no conflicts of interest to disclose.

Randomization:

Blinding: The Pediatric Crohn's Disease Activity Index Score was rated by a blinded gastroenterologist.

Dropout Rate/ITT-Analysis: In the parent study, a total of 765 unique subjects with IBD were screened (550 with CD) with a total of 217 meeting criteria for randomization. From the 161 with CD, 82 were randomized to CBT and 79 to SNDT. At 3 months, 69 youth completed CBT, and 66 completed SNDT treatments.

Notes:
Primary and Secondary measures were not defined.

An possible limitation is the lack of adjustment for the overall level of statistical significance of the study for multiple comparisons as the study was hypothesis-generating in nature.

Vogelaar, Lauran et al. Fatigue management in patients with IBD: a randomised controlled trial. Gut. 63. 911-8. 2014

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: RCT** **Number of Patient: Overall, 98 patients were enrolled in the study, 49 in the SFT group and 49 in the CAU group. One patient declined further participation after randomisation.** **Recruitung Phase:**	**Intervention: Solution-focused therapy (SFT): 7-session solution-focused course, focussing on coping styles for fatigue. The course consisted of six group sessions during 3 months,and was completed by a booster session at month 6. Duration**	**Primary: The primary objective of the study was to assess the effect of SFT on fatigue and QoL at month 6. This was measured with the CIS,28 Fatigue Severity Scale-9 (FSS-9),29–31 Inflammatory Bowel Disease Questionnaire (IBDQ),32 33 Short Form-36 (SF-36)34 35 and EuroQol (EQ-5D)36 at baseline, month 3, month 6 and month 9.** **Secondary: The secondary objective was to investigate the effect of SFT on anxiety and depression, sleep quality, disease activity, medication use, side effects to medication and laboratory parameters (CRP, leucocytes and**

Inclusion Criteria: Men and women aged ≥18 years and diagnosed with IBD with a CIS-fatigue score of ≥35 were eligible for inclusion. Patients had to be in remission defined as a Crohn's Disease Index (CDAI) <150 or Clinical Activity Index (CAI) (ulcerative colitis index) <10 and a C-reactive protein (CRP) <10. The diagnosis of IBD (at least 6 months in duration) was radiologically or endoscopically/histologically confirmed. Exclusion Criteria: Pregnant or breastfeeding women were not included. Patients were also excluded if they had a history of lymphoproliferative disease or cancer, other than skin basocellular carcinoma; other gastrointestinal disease than IBD; listeriosis; HIV infection; immunodeficiency syndrome; central nervous system (CNS) demyelinating disease; chronic hepatitis B or C virus infection or untreated tuberculosis. Patients were excluded if they had poorly controlled medical conditions, including anaemia, low iron levels, diabetes mellitus, kidney disease, liver disease and unstable ischaemic heart disease; a known pre-existing condition that could interfere with the patient's participation such as psychiatric conditions or CNS trauma or active seizure disorders. Additionally, patients were excluded if they had undergone surgery in the past 12 weeks prior to the screening visit. Patients with a history of clinically significant drug or alcohol abuse in the last 2 years were not allowed to participate in this study.	of each session was 1.5 h. Each group consisted of seven patients. In the fifth session, a partner, family member, or close relative participated. The course consisted of psychoeducation about IBD and fatigue and SFT. SFT is a brief form of psychotherapy. The focus is on the existing adequate coping abilities of patients, rather than on their problems. For the purpose of this study, the SFTwas modified to focus on fatigue management. Comparison: Care as usual (CAU). Not further defined.	haemoglobin). Measurements of these items were performed at baseline, month 3, month 6 and month 9 with the Hospital Anxiety and Depression Scale (HADS),37 Pittsburgh Sleep Quality Index (PSQI),38 CDAI39 40 or CAI,41 a questionnaire focusing on current medication use and side effects, and laboratory parameters on full blood. Results: Ninety-eight patients were included, of whom 63% were women, mean age was 40.1 years. After the SFT course, 17 (39%) patients in the SFT group had a CIS-fatigue score below 35 compared with eight (18%) of patients in the CAU group (p=0.03). The SFT group also showed a greater reduction in fatigue across the first 6 months compared with the CAU group (CISfatigue: p=<0.001 and CIS-total: p=0.001). SFT was associated with a significant higher mean IBD questionnaire change at 3 months (p=0.020). At 9 months, no significant differences between the two groups were observed. Author's Conclusion: SFT has a significant beneficial effect on the severity of fatigue and QoL in patients with quiescent IBD. However, this effect diminished during follow-up.

Methodical Notes

Funding Sources:

COI: All authors state that there are no potential conflicts of interest during the work under consideration for publication. CW has participated in the advisory board of Centocor, MSD, FALK Benelux, Abbott laboratories and Ferring during the last 3 years and received financial compensation for these activities.

Randomization: Patients were randomised to the treatment or control arm in blocks of 14 subjects using randomisation lists drawn from a computer-generated series of random numbers. Randomisation was conducted by the second author. The randomisation lists were anonymised for the randomisation process.

Blinding: Due to study design, blinding was not possible.

Dropout Rate/ITT-Analysis: One patient in the intervention group declined further participation and did not receive allocated intervention.

Notes:
Methological quality seems good. Care as usual was not further defined.

Wynne, Brona et al. Acceptance and Commitment Therapy Reduces Psychological Stress in Patients With Inflammatory Bowel Diseases. Gastroenterology. 156. 935-945.e1. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: 122 Recruitung Phase: between March 2015 and October 2016 Inclusion Criteria: IBD patients with psychosocial dysfunction at screening, based on a perceived stress score of 5 or more on a scale ranging from 1 to 1024 or a quality-of-life score of greater than 80 on a scale ranging from 0 to 400 (with higher scores indicating a poorer quality of life),25 were eligible for the study. Patients with radiologic and histologic diagnosis of Crohn's disease or ulcerative colitis. Participants aged between 18 and 65 years with inactive or stable mildly active disease, as defined by a physician based on symptoms, physical examination, and laboratory blood tests and by incorporating the short Crohn's Disease Activity Index (CDAI) or short Mayo score during the	Intervention: The ACT (Acceptance and commitment therapy) program consisted of 8 90-minute weekly sessions in groups of 14–16 participants. The course manual was based on contemporary ACT models and tailored toward IBD patients with an emphasis on reducing stress, and all program materials are available in the supplementary materials. A single experienced psychologist who was a peer-reviewed ACT trainer provided all interventions. Each treatment session was observed and rated by an independent psychologist to assess the therapists' adherence to the treatment protocol. Comparison: treatment as usual, standard IBD medical care	Primary: The primary endpoint was change in stress symptoms, assessed with the Depression Anxiety Stress Scale. Secondary: Secondary endpoints included changes in perceived stress, anxiety, depression, quality-of-life domains, disease activity, and cortisol concentration in hair. Results: Overall, 79 participants were included in the complete case intention-to-treat analysis. There were 39% and 45% reductions in stress in the treatment group from baseline to 8 and 20 weeks, respectively, compared with 8% and 11% in the control group (group time interaction, P ¼ .001). ACT was associated with reduced perceived stress (P ¼ .036) and depression (P ¼ .010), but not anxiety (P ¼ .388), compared with control individuals. In the intentionto-treat analysis, changes in all 4 quality-of-life domains over time were similar in the ACT and control groups. In the per-protocol analysis, the overall well-being quality-of-life domain improved in the ACT group compared with the control group (P ¼ .009). Subjective and objective disease activity measurements were similar between groups over the study period (all P values >.05). Hair cortisol concentrations correlated with stress (rs ¼ 0.205, P ¼ .050) and anxiety (rs ¼ 0.208,

assessment as appropriate,26,27 were eligible. Exclusion Criteria: Pregnant women, participants previously exposed to a stress management program, those attending psychiatric or psychological services, and those receiving antidepressant medication were excluded from the study. Steroids were not permitted in the 3 months before screening because of their potential psychological and endocrinologic effects, and participants were required to have been taking stable doses of all IBD medications at screening for a minimum of 3 months.		P ¼ .046) at baseline but did not change significantly in the ACT group over the study period compared with the control group (P ¼ .831). Author's Conclusion: In a randomized controlled trial of patients with IBD, an 8-week ACT therapy course improved stress and other indices of psychological health.ClinicalTrials

Methodical Notes

Funding Sources: This work was partly supported by an educational grant from Tillotts Pharma AG, which had no role in study design, data acquisition, data analysis, or manuscript writing. KH is a University College Dublin Newman Fellow sponsored by Boston Scientific.

COI: CR has served as a speaker for Janssen, MSD, and AbbVie. GD has served as a speaker, a consultant, and an advisory board member for AbbVie, Merck, Sharp & Dohm, Pfizer, Amgen, Janssen, Shire, Takeda, and Tillotts and has received research funding from AbbVie, MSD, and Pfizer. HM has served as a speaker for Dr Falk Pharma and MSD, serves as a consultant for Boston Scientific, and has received funding from Pfizer. The remaining authors disclose no conflicts.

Randomization: Eligible participants were randomly assigned 1:1 to a group. A stratified randomization procedure was used with participants allocated to treatment and control groups according to sex and disease type with a Web-based randomization protocol by a researcher not involved in recruitment.

Blinding: Blinding not possible. Randomization with a Web-based randomization protocol by a researcher not involved in recruitment.

Dropout Rate/ITT-Analysis: 122 patients
21 withdrew
22 failed to attend 1 of their follow-up visits
--> 79 included in the itt-analysis, drop-out 35%

Notes:

Literatursammlung:

AG 7 Ernährung, Psycho, Komplementär-Frage 2

Inhalt: 5 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Keerthy, Divya 2016		
Levine, Arie 2019	2	nvestigator-initiated prospective randomizedcontrolled trial with 2 interventional arms comparing CDEDwith 50% PEN (group 1) with EEN (group 2) administeredorally over 12 weeks in a pediatric population with mild tomoderate active luminal disease
Limketkai, Berkeley N 2019	1	Cochrane Review
Narula, Neeraj 2018	1	Cochrane Review
Pigneur, Bénédicte 2019	2	prospective randomised induction trial

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 2 Bewertung(en)

Limketkai, Berkeley N et al. Dietary interventions for induction and maintenance of remission in inflammatory bowel disease. Cochrane Database Syst Rev. 2. CD012839. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Cochrane Review Databases: The Cochrane IBD Group Specialized Register, CENTRAL, MEDLINE, Embase, Web of Science, Clinicaltrials.gov and the WHOICTRP from inception to 31 January 2019 were scanned. Also scanned	Population: Patients with active crohn's disease Intervention: The intervention is a controlled manipulation of the subject's oraldiet by a deliberate change in the consumption of food (i.e.	Primary: Induction of remission Secondary: 1. Clinical improvement as defined by the included studies;2. Corticosteroid-free remission;3. Surrogate biomarkers of inflammation (i.e., erythrocytesedimentation rate [ESR] and C-reactive protein [CRP]), fecalbiomarkers (i.e., calprotectin);4. Endoscopic endpoints of improvement and remission;5. Histologic endpoints of improvement and remission;6. Health-related quality of life as measured by the InflammatoryBowel Disease Questionnaire (IBDQ), Short Inflammatory BowelDisease Questionnaire (SIBDQ), or related surveys;7. Hospitalizations;8. Need for surgery;9. Progression of disease from a state of inflammation-only diseaseto stricturing/obstructing to penetrating/fistulizing disease;10.Escalation of therapy including the need to add or modifypharmacologic therapy due to lack of efficacy at inducing ormaintaining remission aRer enrollment in the trial;11.Adverse events;12.Withdrawal due to adverse events;	see pdf

reference lists of included studies, relevant reviews and guidelines. Search period: to 31 January 2019 Inclusion Criteria: randomized controlled trials (RCTs) that compared the effects of dietary manipulations to other diets in participants with IBD were included Exclusion Criteria: Studies that exclusively focused on enteral nutrition, oral nutrient supplementation, medical foods, probiotics, and parenteral nutritionwere excluded.	noformulas or supplements used) for a specified period of time. Comparison: normal diet	and13.Serious adverse events Results: The effect of high fiber, low refined carbohydrates, low microparticle, low calcium, symptoms-guided diet and highly restricted organic dieton clinical remission in active CD is uncertain. In one study, remission was achieved at 4 weeks in 100% (4/4) of low refined carbohydratesparticipants compared to 0% (0/3) of usual diet participants. In a pooled analysis of two studies, 44% (23/52) of low microparticleparticipants achieved remission at 16 weeks compared to 25% (13/51) of usual diet participants. One study found that 50% (16/32) ofsymptoms-guided participants achieved remission compared to 0% (0/19) of usual diet participants. One study found that 50% (4/8) ofhighly-restricted organic diet participants achieved remission at 24 weeks compared to 50% (5/10) of usual diet participants. One studyfound that 37% (16/43) of low-calcium participants achieved remission at 16 weeks compared to 30% (12/40) of usual diet participants. Author's Conclusion: The effects of dietary interventions on CD are uncertain.	

Methodical Notes

Funding Sources: Funding for the Cochrane IBD Group (May 1, 2017 - April 30, 2022)has been provided by Crohn's and Colitis Canada (CCC).Funding for ZIE, TH, and partial funding for MG was providedthrough a larger NIHR Cochrane Programme Grant in the UK.

COI: Berkeley N Limketkai: None knownZipporah Iheozor-Ejiofor: None knownTeuta Gjuladin-Hellon: None knownAlyssa Parian: None knownLaura E Matarese: None knownKelly Bracewell: None knownJohn K MacDonald: None knownMorris Gordon has received travel fees to attend international scientific and training meeting such as DDW, Advances in IBD, ESPGHAN,BSPGHAN and Cochrane focused international events from companies including: Abbott, Nutricia, Biogaia, Ferring, Allergan, and Tillots.Gerard E Mullin has received grants or grants pending (paid to institution) from Abbott Laboratories; and royalties from Rodale Press,Oxford University Press, and CRC Press for books written and or edited on nutrition, generically, and only a few chapters as an expert onthe role of diet in IBD

Study Quality: The majority of studies have small numbers.

Heterogeneity: Due to different interventions and small study population there is a relevant heterogeneity

Publication Bias:

Notes:

Narula, Neeraj et al. Enteral nutritional therapy for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 4. CD000542. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1	Population: Patients	Primary: The primary outcome was clinical remission.	see reference

Study type: Cochrane Review Databases: MEDLINE, Embase and CENTRAL Search period: from inception to 5 July 2017. Inclusion Criteria: Randomized controlled trials involving patients with activeCD were considered for inclusion. Studies comparing one type ofEN toanother type of EN or conventional corticosteroids were selected for review. Exclusion Criteria:	with active crohn's disease Intervention: exclusive EN as primary therapy to induce remission Comparison: steroid therapy	Secondary: Secondary outcomes includedadverse events, serious adverse events and withdrawal due to adverse events Results: Meta-analysis of eight trials (223 participants) demonstrated no difference in remission ratesbetween EN and steroids. Fifty per cent (111/223) of patients in the EN group achieved remission compared to 72% (133/186) ofpatients in the steroid group (RR 0.77, 95% CI 0.58 to 1.03; GRADE very low quality). Subgroup analysis by age showed a differencein remission rates for adults but not for children. In adults 45% (87/194) of EN patients achieved remission compared to 73% (116/158) of steroid patients (RR 0.65, 95% CI 0.52 to 0.82; GRADE very low quality).In children, 83% (24/29) of EN patients achievedremission compared to 61% (17/28) of steroid patients (RR 1.35,95% CI 0.92 to 1.97; GRADE very low quality). A per-protocolanalysis produced similar results (RR 0.93, 95% CI 0.75 to 1.14). The per-protocol subgroup analysis showed a difference in remissionrates for both adults (RR 0.82, 95% CI 0.70 to 0.95) and children(RR 1.43, 95% CI 1.03 to 1.97). There was no difference inadverse event rates (RR 1.39, 95% CI 0.62 to 3.11; GRADE very low quality). However, patients on EN were more likely to withdrawdue to adverse events than those on steroid therapy (RR 2.95, 95% CI 1.02 to 8.48; GRADE very low quality). Author's Conclusion: Very low quality evidence suggests that corticosteroid therapy may be more effective than EN for induction of clinical remission inadults with active CD. Very low quality evidence also suggeststhat EN may be more effective than steroids for induction of remissionin children with active CD.	list

Methodical Notes

Funding Sources: no information

COI: Neeraj Narula has no known declarations of interest to declare.Amit Dhillon has no known declarations of interest to declare.Dongni Zhang has no known declarations of interest to declare.Mary Sherlock has served as an advisory board member for Abbvie and Jannsen and received travel expenses from Abbvie to attend anIBD meeting in 2015.Melody Tondeur has no known declarations of interest to declare.Walter Reinisch has served as a speaker, a consultant or an advisory board member for Abbott Laboratories, Abbvie, Aesca, Amgen, AMPharma, Aptalis, Astellas, Astra Zeneca, Avaxia, Bioclinica,Biogen IDEC, Bristol-Myers Squibb, Cellerix, Chemocentryx,Celgene,Centocor, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Grünenthal, Janssen, Johnson & Johnson,Kyowa Hakko Kirin Pharma, Lipid Therapeutics, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Novartis, Ocera, Otsuka,PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Robarts Clinical Trial, Schering-Plough, Setpointmedical, Shire,Takeda,Therakos, Tigenix, UCB, Vifor, Yakult, Zyngenia, and 4SC.Mary Zachos has served as an advisory board member for Abbvie,Janssen and Ferrin

Study Quality:

Heterogeneity: adult and pediatric population: statistically signifi-cant heterogeneity was identified (I2= 67%).
adult population alone: o significant heterogeneity was demonstrated for
this analysis (i2= 36%)

Publication Bias:

Notes:
The review was done as a Cochrane Review

OXFORD (2011) Appraisal Sheet: RCT: 2 Bewertung(en)

Levine, Arie et al. Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial. Gastroenterology. 157. 440-450.e8. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: nvestigator-initiated prospective randomizedcontrolled trial with 2 interventional arms comparing CDEDwith 50% PEN (group 1) with EEN (group 2) administeredorally over 12 weeks in a pediatric population with mild tomoderate active luminal disease Number of Patient: Seventy-eight patients were randomized (40 toCDEDþPEN and 38 to EEN) and included in the analysisfrom 10 pediatric IBD clinics in Israel (from September2013) and 2 in Canada (from December 2016) until May2018, Recruitung Phase: from September 2013 until May 2018 Inclusion Criteria: Children (aged 4–18 years) with mild to moderate luminalCD, defined by a pediatric CD activity index (PCDAI)10 and40 and evidence for active inflammation at enrollment, suchas elevated C-reactive protein (CRP)>5 g/L, erythrocytesedimentation rate>20 mm/h, or calprotectin>200mg/g,within 36 months from diagnosis, were eligible for enrollment. Exclusion Criteria: Exclusion criteria consisted of recent use of steroids or recent initiation or dose adjustmentfor immunomodulators, past or current biologics use, primarycolonic disease with significant rectal involvement, or activeperianal disease.	Intervention: Group 1 received the CDED stage 1 with 50% PEN forcalculated energy requirement (Modulen; Nestlé Health Science, Vevey, Switzerland) for thefirst 6 weeks, and then thestage 2 diet with 25% PEN for the next 6 weeks. Group 2received standard of care EEN (Modulen) for 6 weeks followedby 25% PEN during weeks 6 to 12, with gradual reintroductionof table foods between week 6 and 9 as per local preference,such that all patients were exposed to PENþfree diet by week12. All formulas could be given only orally Comparison:	Primary: The primary endpoint of this studywas the patient's tolerance to the diet by week 6 defined bywithdrawal from the study because of patient's refusal tocontinue the diet. Secondary: response, defined as a drop in PCDAI of 12.5 points or remission, on an ITT analysis at week 6; remission at week 6 (definedas PCDAI<10 as well as by the more stringent<10, or lessthan 7.5 without height component). Other secondary endpoints included decrease or normalization of inflammatory markers at week 6 (CRP, ESR, calprotectin), remission and normalization of CRP at week 12, and poor adherence. Results: our patients withdrewfrom the study because of intolerance by 48 hours, 74 patients(mean age 14.2±2.7 years) were included for remissionanalysis. The combination of CDED and PEN was tolerated in 39children (97.5%), whereas EEN was tolerated by 28 children(73.6%) (P=0.002; odds ratio for tolerance of CDED and PEN,13.92; 95% confidence interval [CI] 1.68–115.14). At week 6,30 (75%) of 40 children given CDED plus PEN were incorticosteroid-free remission vs 20 (59%) of 34 children givenEEN (P¼.38). At week 12, 28 (75.6%) of 37 children givenCDED plus PEN were in corticosteroid-free remission comparedwith 14 (45.1%) of 31 children given EEN and then PEN (P=0.01; odds ratio for remission in children given CDED and PEN,3.77; CI 1.34–10.59) Author's Conclusion: CDED plus PEN was better tolerated than EEN in children with mild to moderate CD. Both diets were effective ininducing remission by week 6. The combination CDED plus PENinduced sustained remission in a significantly higher proportion of patients than EEN,

Methodical Notes

Funding Sources: nitial funding for the study in Israel was provided by unrestricted grants fromthe Azrieli Foundation and Nestlé Health Science to AL. Nestlé HealthScience also kindly provided Modulen to all participating sites to ensureuniformity of the formula used among participants and provide the formulato enrolled patients for the duration of the study. The conduct of the studyin Canada (Halifax, Edmonton) was supported by local divisional funds, aWomen and Children's Health Research Institute (WCHRI) ResearchCapacity Building Award (EW) and a Canadian Institutes of Health Research(CIHR) New Investigator award (JVL)

COI: AL reports grants, from Nestlé HealthScience, and grants from Janssen unrelated to thisfield; advisory boards,travel, speaker fees or DSMBs from Celgene, Takeda and AbbVie, and alicensing and consulting agreement with IP with Nestlé health to developnew products based on diet. EW reports personal fees from Janssen,personal fees from AbbVie, outside the submitted work. RSB reportspersonal fees from Consulting to Nestlé Health Science, during the conductof the study; personal fees from Invited speaker by Nestlé Health Science,personal fees from Invited speaker by Takeda, outside the submitted work.RS reports personal fees from Janssen, AbbVie, Mead Johnson, Lapidot andAbbott, outside the submitted work. JVL reports consulting, travel and/orspeaker fees and research support from AbbVie, Janssen, Nestlé HealthScience, Merck, P&G, GSK, Illumina, Otsuka.

Randomization: Patients were randomized 1:1 in previously generatedrandom blocks of 6.

Blinding: Blinding was not possible

Dropout Rate/ITT-Analysis: 4 patients, an ITT analysis was performed

Notes:

Pigneur, Bénédicte et al. Mucosal Healing and Bacterial Composition in Response to Enteral Nutrition Vs Steroid-based Induction Therapy-A Randomised Prospective Clinical Trial in Children With Crohn's Disease. J Crohns Colitis. 13. 846-855. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type:** prospective randomised induction trial **Number of Patient:** Nineteen patients with new-onset active CD (Harvey-Bradshaw index [HBI] >5), aged from 6 to 17 years, were included in this prospective randomised induction trial with CS [n = 6] or EEN [n = 13] **Recruitung Phase:** A total of 19 patients [13 EEN/6 steroids] were included over 36 months, with an overall acceptance rate of participation in this trial of 23%. **Inclusion Criteria:** Children/adolescents with newly diagnosed CD [age range: 6–17 years] with active disease (Harvey-Bradshaw Index [HBI] >5) **Exclusion Criteria:** treatment by antibiotics during the 4 weeks preceding inclusion, cor-ticosteroids, biologic therapies, immunosuppressive treatment, iso-lated oral or perianal disease location, risk of non-adherence to study protocol, and potential need for surgical therapy	**Intervention:** Exclusive enteral nutrition [EEN] (Modulen IBD) over 8 weeks **Comparison:** Corticosteroids initially 1 mg/Kg per day [up to a maximum of 60 mg] during the induction period [4 weeks] and then tapered over 3 months.	**Primary:** achievement of mucosal healing with a Crohn's Disease Endoscopic Index of Severity [CDEIS] less than 3 points or a drop of >70% at follow-up endoscopy [8 weeks] compared with initial diagnostic endoscopy. **Secondary:** clinical remission defined as a Harvey-Bradshaw Index [HBI] less than 5 and biological remission [mucosal and systemic inflamma-tory parameters]. **Results:** At 8 weeks, clinical remission [HBI <5] was achieved in 13/13 patients on EEN and 5/6 patients on steroids; the mucosal healing rate was significantly higher in the EEN [89%] compared with steroid group [17%]. **Author's Conclusion:** Both steroid and EEN induced clinical remission. However, patients with EEN-induced remission showed a higher rate of mucosal healing

Methodical Notes

Funding Sources: The present work was supported by a non-restricted grant of Nestle France (producer of the enteral nutrition product)

COI: OG received financial support for research from Danone, Fresenius Kabi, Biocodex, Shire. JD received financial support for research from Danone, fees for lecture and editorial work from Janssen and Biocodex, consultancy and shares as co-founder from Enterome and MaaT Pharma. FR has received research supports from Nestlé Nutrition Institute, AbbVie, MSD, Jansen and Jansen, and lecture fees from AbbVie, Danone, Nutricia, Nestlé, and served as member of advisory board: DEVELOP [Centocor], CAPE [AbbVie], LEA [AbbVie], SAC for MSD France, Nestlé Nutrition Institute, Nestlé Health Science, Danone, MeadJohnson; Nutricia, Takeda, Celgene, Biogen, Shire, Pfizer, Therakos.

Randomization: randomisation was amended to a 1 to 2 ratio [one in the CS group for 2 patients in the EEN group

Blinding: not possible

Dropout Rate/ITT-Analysis: overall acceptance rate of participation in this trial of 23%.

Notes:

Literatursammlung:

AG 7 Ernährung, Psycho, Komplementär-Frage 3

Inhalt: 4 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Bao, Chun-Hui 2014	2	RCT
Reinisch, Walter 2013		
Sun, Jing 2015	2	RCT
Zhu, Weiming 2015	2	RCT

OXFORD (2011) Appraisal Sheet: RCT: 3 Bewertung(en)

Bao, Chun-Hui et al. Randomized controlled trial: moxibustion and acupuncture for the treatment of Crohn's disease. World J. Gastroenterol. 20. 11000-11. 2014

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: Baseline 92 (n=46 treatment and control group) 85 patients completed the trial (treatment n=43, control n=42) follow up: 77 patients (treatment n=40, control n=37) Recruitung Phase: From January 2010 to April 2013, CD patients treated at the acupuncture outpatient center for inflammatory bowel disease of the Shanghai Institute of Acupuncture and Meridian, the Endoscopy Center of Zhongshan Hospital at Fudan University, the Department of AcupunctureMoxibustion of Shuguang Hospital affiliated with the	Intervention: The treatment group received herb-partitioned moxibustion combined with acupuncture. The acupoints are listed in Table 1 and Figure 1; these acupoints were selected based on TCM principles according to the clinical manifestations of the patients. All of these acupoints were shown to be effective for the treatment of CD. 3 times a week for 12 weeks. Comparison: The control group received wheat ban-partitioned moxibustion and superficial acupuncture 1-2 cm beside the	Primary: CDAI (CD activity index) Secondary: laboratory indicators such as hemoglobin (HGB), C-reactive protein (CRP), erythrocyte sedimentation rate, quality-of-life, endoscopic ratings, and intestinal histology scores. Results: The CDAI scores of both the treatment and control groups were significantly reduced after treatment compared with those measured before treatment. However, the degree of improvement in the treatment group was significantly greater than that of the control group. The improvement in symptoms in patients of the treatment group was sustained at follow-up, whereas that of the control group was not. The overall efficacy of the treatment was significantly greater than that of the control. Both groups demonstrated significant improvements in quality-of-life ratings after treatment, but the improvement was significantly greater in the treatment group than in the control group. In addition, the patients in the treatment group showed significantly increased HGB and significantly decreasedCRP levels and histopathological scores at the end of treatment, whereas the control group did not exhibit significant changes. Author's Conclusion: Moxibustion with acupuncture provided significant therapeutic benefits in patients with active CD beyond the placebo effect and is therefore an effective and safe treatment for active CD.

Shanghai University of Traditional Chinese Medicine, and the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with the Shanghai University of Traditional Chinese Medicine were recruited as subjects for this study Inclusion Criteria: Patients who - had a confirmed diagnosis of mild or moderate CD (CD Activity Index (CDAI) values ranging from 151 to 350) - had not taken medications such as salicylic acid drugs and/or prednisone (at a dose ≤ 15 mg) for at least 1 month - had not taken immunosuppressants or used anti-TNF-α biological agents for 3 month prior to enrollment in the study Exclusion Criteria: - Pregnant or lactating patients - patients with serious diseases of the heart, brain, liver, kidney, or hematopoietic system - patients with mental illness - patients with other severe diseases	acupoint. 3 times a week for 12 weeks.	

Methodical Notes

Funding Sources: Supported by Shanghai Municipal Health Bureau, No. 20124028; The Ministry of Education Program for New Century Excellent Talents, No. NCET-13-0907; Shanghai Municipal Science and Technology Commission, No. 13ZR1439400; and Shanghai Top Clinical Medical Center of Acupuncture, Moxibustion and Tuina

COI: nothing mentioned

Randomization: Yes.
Simple random sampling method by generating a random number table using the SPSS 16.0 software.

Blinding: Yes.
All patients were blinded during the trial and were therefore unaware of the specific treatment they received. All subjects in each treatment session were treated in a private room to avoid potential communication and comparison among subjects. In addition, a blinded evaluation was conducted in which a third researcher who was unaware of the group assignments assessed the treatment outcomes. Blinded statistical data analysis was also conducted in which the researchers, operators, and

statisticians were separated from one another.

Dropout Rate/ITT-Analysis: The effective rate of acupuncture and moxibustion in the treatment of CD is 56%.
In this study they previously used a non-randomized concurrent
control method to conduct a pilot study that demonstrated an effective rate of herb-partitioned moxibustion and acupuncture in the treatment of CD of 86.67%.
Therefore, the current study established an expected effective rate value of 85%.
The required sample size for each group was equal to 42 (n = 42 patients). With the addition of a 10% dropout rate (four patients), the two
groups needed to include no less than 92 patients. The PP analysis indicated that the total treatment efficacies of the treatment and control groups were 83.72% and 40.48%, respectively, with a statistically significant difference (P = 0.000). The ITT analysis indicated that
the total treatment efficacies of the treatment and control
groups were 78.26% and 36.96%, respectively, with a statistically significant difference (P = 0.000) (Table 4).

Notes:
After enrollment, the patients who were using CD medications maintained their drug dosage unchanged. If their conditions deteriorated during the treatment period
or if the patients needed to increase their dose or take other medications, these subjects were withdrawn from the study. During the follow-up period, patients were allowed to adjust their dose of Western medicine after recording each adjustment. If patients increased their dose, became sicker, or took other drugs, these subjects were also withdrawn.

Sun, Jing et al. Tripterygium wilfordii Hook F as Maintenance Treatment for Crohn's Disease. Am. J. Med. Sci. 350. 345-51. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: 198 (mesalazine n=59, high-dose n=71, low-dose n=68) Recruitung Phase: e Inflammatory Bowel Disease Center of Jinling Hospital during the period of December 2010 to January 2014. The protocol of the study was approved by Ethics Committee of Jinling Hospital, Medical School of Nanjing University (date: June 20, 2010; Project number 175).	Intervention: highdose-group 2.0 mg/kg daily (maximum, 120 mg/d) lowdose-group 1.5 mg/kg daily The high-dosage regimen was determined referring to previous clinical trial testing the effects of similar Tripterygium wilfordii Hook F extracts for the CD and nephritis. All recruited patients were evaluated at baseline, every 2 weeks for 8 weeks and every 4 weeks since then. Vital signs and laboratory values (blood cell count, liver enzymes, serum bilirubin, creatinine, blood urea nitrogen and C-reactive protein) were measured at each study visit. Patients received ileocolonoscopy in a 26-week interval or when patients have clinical symptom indicating recurrence. An endoscopist who was blind to the treatment assignment performed the ileocolonoscopy. Comparison: mesalazine 3 g daily	Primary: The primary endpoint was clinical recurrence, defined as CD Activity Index score (CDAI) > 150 points together with an increase of 60 points.25 In addition, a recurrence also included any patient who required medical or surgical treatment with or without a measurement of the CDAI score. Secondary: The secondary endpoint was drug adverse events at 26 and 52 weeks since drug adverse events at 26 and 52 weeks since initiation. The following were also analyzed: the changes in scores of CDAI, Inflammatory Bowel Disease Questionnaire (IBDQ) and Simple Endoscopic Score for Crohn's Disease (SESCD) throughout the study. Drug adherence was assessed using a daily diary and by pill counts. Results: A total of 137 patients completed the study. At week 52, a significant lower proportion of patients in the high-dose TwHF group (7/71) had clinical recurrence compared with patients in the low-dose TwHF (15/68, P 5 0.047) or mesalazine group (17/59, P 5 0.006), whereas the difference between the lowdose TwHF group and the mesalazine group was not significant (P 5 0.503). Patients receiving mesalazine experienced less adverse events than those receiving high-dose TwHF (P 5 0.029) and those receiving low-dose TwHF (P 5 0.048), but no significant difference was found about drug adverse events resulted

Inclusion Criteria: Inclusion criteria were as follows: Patients were 16 to 75 years old with a confirmed diagnosis of CD. The diagnosis of CD was based on radiologic, endoscopic or histologic evidence at least 6 months before receipt of study treatment.21 The activity of CD was mild to moderate (a CD Activity Index score from 150 to 450) before induced remission with medications and was remission (a CD Activity Index score bellow 150) when patients were enrolled. **Exclusion Criteria: The exclusion criteria were as follows: Patients who had active infection, short bowel syndrome, leucopenia (white blood cell count, 4 3 109/L), cancer, or clinically important renal or hepatic disease, and any condition associated with poor compliance with medical treatment. For women, pregnancy tests were performed during the study,**		**withdrawal in the 3 groups (P . 0.05). In addition, compared with low-dose TwHF and mesalazine, the authors also detected significant superiority of highdose TwHF arm in the decrease of CDAI and SESCD (P , 0.05).** **Author's Conclusion: 2.0 mg/kg daily TwHF was well tolerated and prolonged remission in patients with CD.**	

and they were required to have negative results. Patients who were pregnant, breastfeeding or had pregnancy plan were not eligible. Patients were also not eligible if they had a history of TwHF and/or mesalazine intolerance or had received treatment with anti-TNF-a agents, corticosteroids, oral antibiotics or nonsteroidal antiinflammatory drugs (NSAIDs) within the preceding 4 weeks.		

Methodical Notes

Funding Sources: ? not known

COI: The authors have no financial or other conflicts of interest to disclose.

Randomization: Yes.
The patients were randomized according to a computer-generated randomization schedule.

Blinding: ? not known

Dropout Rate/ITT-Analysis: 137/198 patients reached week 56 --> total dropout 61 (=30,8%)
mesalazine: 36/59 finished, dropout: 39%
high-dose 55/71 finished, dropout: 22,5%
low-dose 46/68 finished, dropout: 32%
dropuout till week 26:
mesalazine n=11
high-dose n=8
low-dose n=12
dropout from week 26 till week 52:
mesalazine n=12
high-dose n=8
low-dose n=10

Notes:
The authors estimated that 177 patients would have to be studied to detect a 20% absolute difference in the proportion of patients maintaining remission while taking the most effective dose of TwHF, assuming a recurrence at
week 52 of 30% in the mesalazine group (a 5 0.05; b 5
0.20), according to a predetermined proportion of 1:1:1. Clinical recurrence was evaluated in the intention-to-treat population. The analyses used last observation carried forward in our assessments. To analyze cumulative remission maintain rates, the authors used the Kaplan-Meier method, and differences in clinical recurrence were assessed with the log-rank test. Fisher's exact test and chi-square test were also used. Quantitative variables were described using the mean 6 standard deviation (M 6 SD) and were compared using a 2-sided Mann-Whitney
U-test. P , 0.05 was considered to be statistically significant.

Each statistical analysis was performed using the Dr. SPSS II program, version 19.0 for Windows (SPSS, Inc, Chicago, IL)

Zhu, Weiming et al. Tripterygium wilfordii Hook. f. versus azathioprine for prevention of postoperative recurrence in patients with Crohn's disease: a randomized clinical trial. Dig Liver Dis. 47. 14-9. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: 90 Recruitung Phase: Between November 2009 and October 2012, eligible patients with ileal or ileocolic CD undergoing macroscopic disease resection with anastomoses, which were side-to-side and stapled, were recruited for this study. Inclusion Criteria: eligible patients with ileal or ileocolic CD undergoing macroscopic disease resection with anastomoses, which were side-to-side and stapled, Exclusion Criteria: Women of childbearing age were required to have a negative pregnancy test and to use adequate birth control measures during the entire study. Patients who received proximal intestinal resections or had an ileocolonic stoma or strictureplasty at the time of ileocolic anastomosis were excluded. Patients with short bowel syndrome, who wished to become pregnant during the study, who had a low white blood cell(WBC) count atinclusion (<4000), or who had malignancies and/or ongoing infectious disease (such as active hepatitis) were also excluded. Patients were not eligible if they had a history of TwHF and/orAZAintolerance or had received treatment with anti-tumour necrosis factor (TNF-) agents, corticosteroids, oral antibiotics, or non-steroidal	Intervention: TwHF 1.5 mg/kg/day The patients assigned to the TwHF group received oral administration of TwHF (Taizhou Pharmaceutical Co., Jiangsu Province, China) 3 times per day. The following medications were prohibited during the study: other immunosuppressants, corticosteroids, thiopurinol, allopurinol or oxipurinol, 5-ASA, antiTNF therapy, oral antibiotics for more than 2 weeks, NSAIDs for more than 1 week, and AZA-containing or TwHF-containing drugs other than the study drug. Comparison: azathioprine 2.0 mg/kg/day The following medications were prohibited during the study: other immunosuppressants, corticosteroids, thiopurinol, allopurinol or oxipurinol, 5-ASA, antiTNF therapy, oral antibiotics for more than 2 weeks, NSAIDs for more than 1 week, and AZA-containing or TwHF-containing drugs other than the study drug.	Primary: presenting symptoms of CD having to undergo another medical or surgical treatment, with the recurrence being confirmed by endoscopic evidence Secondary: The secondary end point of this study was the proportion of patients with significant endoscopic recurrence in the neoterminal ileum at 26 and 52 weeks after surgery, defined as an endoscopic index ≥2 according to Rutgeerts' endoscopic score. Results: 47 patients completed the trial. Clinical recurrence was observed in 6/45 patients in the TwHF group and 4/45 patients in the azathioprine group at week 26 (P = 0.74). At week 52, 8/45 azathioprine patients and 12/45 TwHF patients had clinical recurrence (P = 0.45). During the first 26 weeks, 56.8% ofthe patients in the TwHF group versus 47.7% in the azathioprine group experienced endoscopic recurrence (P = 0.52). However, at week 52, 74.4% of patients in the TwHF group and 50% in the azathioprine group had endoscopic recurrence (P = 0.03). Author's Conclusion: TwHF was less effective in maintaining endoscopic remission at week 52, even though TwHF was comparable to azathioprine for preventing postoperative clinical recurrence

anti-inflammatory drugs (NSAIDs) within the preceding 4 weeks.		

Methodical Notes

Funding Sources: This work was partly supported by National Ministry of Health for the Digestive Disease (Grant 201002020) and National Natural Science Foundation of China (Grants 81200263 and 81170365).

COI: non declared

Randomization: Yes.
The patients were randomized in a 1:1 ratio of AZA 2.0 mg/kg/day or TwHF 1.5 mg/kg/day using a randomization programme.

Blinding: Not mentioned.
At weeks 26 and 52, an ileocolonoscopy was performed by an endoscopist who was blind to the treatment assignment

Dropout Rate/ITT-Analysis: Dropout till week 26/52:
TwHF n=8/6, azathioprin n=7/12
ITT:
Clinical recurrence was evaluated in the intention-to-treat (ITT) population. Endoscopic examinations were analyzed in all ITT patients in whom endoscopy was performed at week 26 and at week 52 or at the time of study withdrawal. The analyses employed non-responder imputation (NRI) and last-observationcarried-forward (LOCF)in many assessments. To evaluate the effect of drug therapy on endoscopic recurrence and clinical recurrence between the treatment groups at 26 and 52 weeks, Fisher's exact test or the chi-square test was used. Quantitative variables were described using the mean ± standard deviation (SD) and were compared using a two sided Mann–Whitney U-test. $P < 0.05$ was considered to be statistically significant.

Notes:

Versionsnummer: 5.0

Erstveröffentlichung: 11/1996

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