Supplementary material for Butzke B et al., The cost-effectiveness of UGT1A1 genotyping before colorectal cancer treatment with irinotecan from the perspective of the German statutory health insurance, Acta Oncol, 2015; doi:10.3109/0284186X.2015.1053983

Supplementary Online Appendix 1: Main assumptions

The main assumptions made in the model are as follows:

Irinotecan treatment:

- Colorectal cancer treatment with irinotecan can result in sever neutropenia and diarrhea
- The UGT1A1 genotype can predict individuals risks to develop sever neutropenia and diarrhea
- Patients with neutropenia/diarrhea can either be treated on an outpatient basis or an inpatient basis which both causes costs
- Patients with severe neutropenia/diarrhea have an reduction in quality of life which lasts for one week
- Dose-reduction and the administration of growth factors can both decrease the risk for neutropenia
- In addition, dose-reduction can decrease the risk for diarrhea
- Dose-reduction and the administration of growth factors are not assumed to affect the effectiveness of the irinotecan treatment
- Irinotecan treatment is limited to a maximum of 26 weeks (13 Markov cycles)

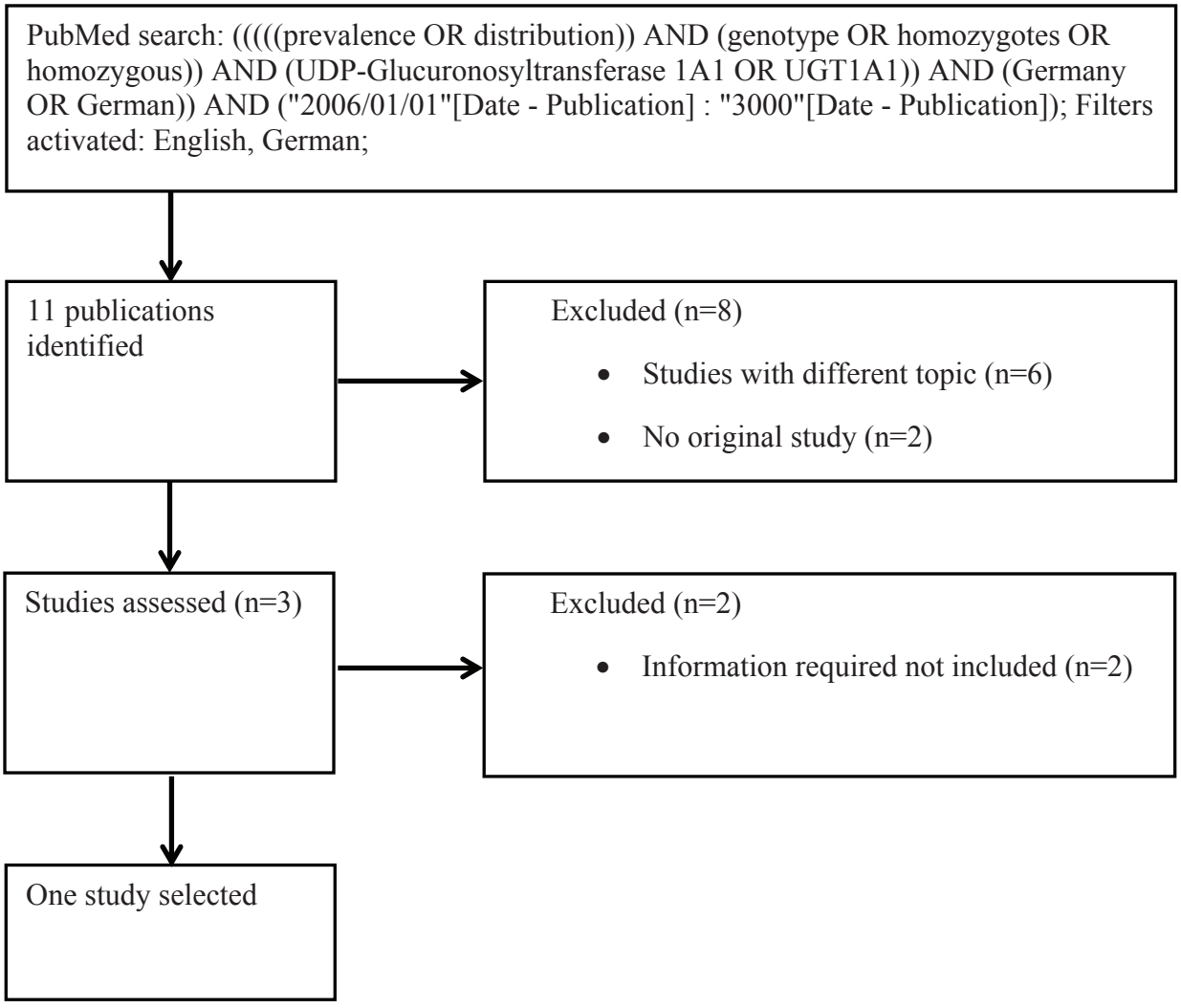
Subsequent Therapy:

- After the occurrence of severe side-effects an alternative chemotherapy regime is administered
- The duration of the subsequent therapy line was limited to a maximum of 24 weeks
- The subsequent line of therapy is only assumed to influence costs but it does not affect overall survival and quality of life

Online Appendix 2: Literature reviews

1.1 Distribution of UGT1A1 genotypes in Germany

1.1.1 Flowchart of the structured literature search



Schulz et al. UGT1A1 gene polymorphism: impact on toxicity and efficacy of irinotecan-based regimens in metastatic colorectal cancer. World J Gastroenterol. 2009 Oct 28;15(40):5058-66.

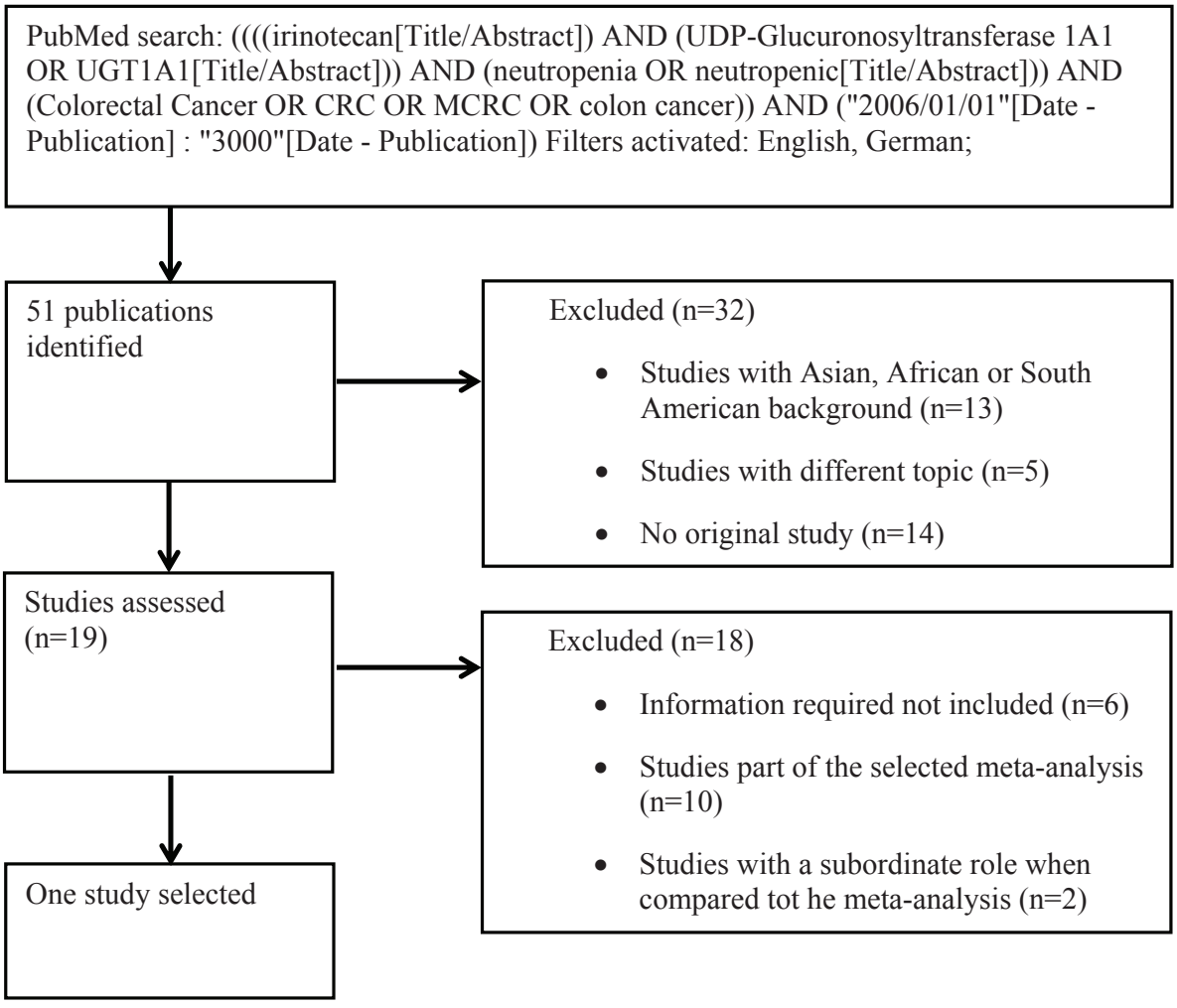
1.1.2 List of identified studies.

(((((prevalence OR distribution)) AND (genotype OR homozygotes OR homozygous)) AND (UDP-Glucuronosyltransferase 1A1 OR UGT1A1)) AND (Germany OR German)) AND ("2006/01/01"[Date - Publication] : "3000"[Date - Publication]); Filters activated: English, German; 02.06.2013; 11 studies;				
	Title	Author	Journal	Ex- or Included
1	Gilbert's syndrome--a frequent cause of unconjugated hyperbilirubinemia in children after orthotopic liver transplantation.	Kathemann S, Lainka E, Baba HA, Hoyer PF, Gerner P.	Pediatr Transplant. 2012 Mar;16(2):201-4.	**Excluded** due to different study topic;
2	Loci from a genome-wide analysis of bilirubin levels are associated with gallstone risk and composition.	Buch S, Schafmayer C, Völzke H, Seeger M, Miquel JF, Sookoian SC, Egberts JH, Arlt A, Pirola CJ, Lerch MM, John U, Franke A, von Kampen O, Brosch M, Nothnagel M, Kratzer W, Boehm BO, Bröring DC, Schreiber S, Krawczak M, Hampe J.	Gastroenterology. 2010 Dec;139(6):1942-1951.e2.	**Excluded** due to different study topic;
3	Gilbert-Meulengracht's syndrome and pharmacogenetics: is jaundice just the tip of the iceberg?	Strassburg CP.	Drug Metab Rev. 2010 Feb;42(1):168-81.	**Excluded,** no original study;
4	UGT1A1 gene polymorphism: impact on toxicity and efficacy of irinotecan-based regimens in metastatic colorectal cancer.	Schulz C, Heinemann V, Schalhorn A, Moosmann N, Zwingers T, Boeck S, Giessen C, Stemmler HJ.	World J Gastroenterol. 2009 Oct 28;15(40):5058-66.	**Included;** "Genotypes were retrospectively evaluated by gene scan analysis on the ABI 310 sequencer of the TATAA box in the promoter region of the UGT1A1 gene in blood samples from 105 patients who had received 1st line irinotecan-based chemotherapy for mCRC."
5	UGT1A1 genotyping: a predictor of irinotecan-associated side effects and drug efficacy?	Schulz C, Boeck S, Heinemann V, Stemmler HJ.	Anticancer Drugs. 2009 Nov;20(10):867-79.	**Excluded,** no original study;

6	Genetic polymorphisms in phase I and phase II enzymes and breast cancer risk associated with menopausal hormone therapy in postmenopausal women.	MARIE-GENICA Consortium on Genetic Susceptibility for Menopausal Hormone Therapy Related Breast Cancer Risk.	Breast Cancer Res Treat. 2010 Jan;119(2):463-74.	**Excluded** due to different study topic;
7	Gilbert's syndrome and hyperbilirubinemia in protease inhibitor therapy--an extended haplotype of genetic variants increases risk in indinavir treatment.	Lankisch TO, Behrens G, Ehmer U, Möbius U, Rockstroh J, Wehmeier M, Kalthoff S, Freiberg N, Manns MP, Schmidt RE, Strassburg CP.	J Hepatol. 2009 May;50(5):1010-8.	**Excluded** due to different study topic;
8	The inverse starving test is not a suitable provocation test for Gilbert's syndrome.	Teich N, Lehmann I, Rosendahl J, Tröltzsch M, Mössner J, Schiefke I	BMC Res Notes. 2008 Jun 24;1:35.	**Excluded** due to different study topic;
9	Pharmacogenetics in colorectal cancer: a systematic review.	Funke S, Brenner H, Chang-Claude J.	Pharmacogenomics. 2008 Aug;9(8):1079-99.	**Excluded,** information required (distribution of genotype in the German population) not included;
10	Gilbert's Syndrome and irinotecan toxicity: combination with UDP-glucuronosyltransferase 1A7 variants increases risk.	Lankisch TO, Schulz C, Zwingers T, Erichsen TJ, Manns MP, Heinemann V, Strassburg CP.	Cancer Epidemiol Biomarkers Prev. 2008 Mar;17(3):695-701.	**Excluded,** information required not (distribution of genotype in the German population) included;
11	Coinheritance of Gilbert syndrome-associated UGT1A1 mutation increases gallstone risk in cystic fibrosis.	Wasmuth HE, Keppeler H, Herrmann U, Schirin-Sokhan R, Barker M, Lammert F.	Hepatology. 2006 Apr;43(4):738-41.	**Excluded** due to different study topic;

1.2 Probability of severe neutropenia

1.2.1 Flowchart of the structured literature search



Liu et al. Association of UGT1A1*28 polymorphisms with irinotecan-induced toxicities in colorectal cancer: a meta-analysis in Caucasians. Pharmacogenomics J. 2013 Mar 26. [Epub ahead of print]

→ Evaluation of all the single studies which were included in the meta-analysis; Most suitable study in terms of study population and availability of required information was selected together with Fuat Oduncu and Björn Stollenwerk;

1.2.2 List of identified studies.

((((irinotecan[Title/Abstract]) AND (UDP-Glucuronosyltransferase 1A1 OR UGT1A1[Title/Abstract])) AND (neutropenia OR neutropenic[Title/Abstract])) AND (Colorectal Cancer OR CRC OR MCRC OR colon cancer)) AND ("2006/01/01"[Date - Publication] : "3000"[Date - Publication]) Filters activated: English, German; 20.05.2013; 51 studies;				
	Title	Author	Journal	Ex- or included
1	Usefulness of one-point plasma SN-38G/SN-38 concentration ratios as a substitute for UGT1A1 genetic information after irinotecan administration.	Hirose K, Yamashita K, Takada H, Kaneda N, Fukami K, Maruo E, Kitamura M, Hasegawa J, Maeda Y.	Int J Clin Oncol. 2013 Apr 19. [Epub ahead of print]	**Excluded,** Japanese study;
2	Therapeutic Targeting of CPT-11 Induced Diarrhea: A Case For Prophylaxis.	Swami U, Goel S, Mani S.	Curr Drug Targets. 2013 Apr 15. [Epub ahead of print]	**Excluded** due to different study topic;
3	Differential toxicity biomarkers for irinotecan- and oxaliplatin-containing chemotherapy in colorectal cancer.	Cortejoso L, García MI, García-Alfonso P, González-Haba E, Escolar F, Sanjurjo M, López-Fernández LA.	Cancer Chemother Pharmacol. 2013 Mar 31. [Epub ahead of print]	**Excluded,** subordinate role when compared with meta-analysis;
4	Association of UGT1A1*28 polymorphisms with irinotecan-induced toxicities in colorectal cancer: a meta-analysis in Caucasians.	Liu X, Cheng D, Kuang Q, Liu G, Xu W.	Pharmacogenomics J. 2013 Mar 26. [Epub ahead of print]	**Included:** meta-analysis;
5	Refining the UGT1A Haplotype Associated with Irinotecan-Induced Hematological Toxicity in Metastatic Colorectal Cancer Patients Treated with 5-Fluorouracil/Irinotecan-Based Regimens.	Lévesque E, Bélanger AS, Harvey M, Couture F, Jonker D, Innocenti F, Cecchin E, Toffoli G, Guillemette C.	J Pharmacol Exp Ther. 2013 Apr;345(1):95-101.	**Excluded,** subordinate role when compared with meta-analysis;
6	Polymorphisms of the UDP-glucuronosyl transferase 1A genes are associated with adverse events in cancer patients receiving irinotecan-based chemotherapy.	Inoue K, Sonobe M, Kawamura Y, Etoh T, Takagi M, Matsumura T, Kikuyama M, Kimura M, Minami S, Utsuki H, Yamazaki T, Suzuki T, Tsuji D, Hayashi H, Itoh K.	Tohoku J Exp Med. 2013;229(2):107-14.	**Excluded,** Japanese study;

7	UGT1A1 predicts outcome in colorectal cancer treated with irinotecan and fluorouracil.	Wang Y, Shen L, Xu N, Wang JW, Jiao SC, Liu ZY, Xu JM.	World J Gastroenterol. 2012 Dec 7;18(45):6635-44.	**Excluded,** Chinese study;
8	UGT1A1 gene polymorphisms and the toxicities of FOLFIRI in Chinese han patients with gastrointestinal cancer.	Zhou CF, Ma T, Su Y, Ye ZB, Ji J, Yu YY, Zhang J, Liu BY, Zhu ZG.	Anticancer Agents Med Chem. 2013 Feb;13(2):235-41.	**Excluded,** Chinese study;
9	Correlation between plasma concentration ratios of SN-38 glucuronide and SN-38 and neutropenia induction in patients with colorectal cancer and wild-type UGT1A1 gene.	Hirose K, Kozu C, Yamashita K, Maruo E, Kitamura M, Hasegawa J, Omoda K, Murakami T, Maeda Y.	Oncol Lett. 2012 Mar;3(3):694-698. Epub 2011 Dec 22.	**Excluded,** Japanese study;
10	Safety, pharmacokinetics, and activity of EZN-2208, a novel conjugate of polyethylene glycol and SN38, in patients with advanced malignancies.	Kurzrock R, Goel S, Wheler J, Hong D, Fu S, Rezai K, Morgan-Linnell SK, Urien S, Mani S, Chaudhary I, Ghalib MH, Buchbinder A, Lokiec F, Mulcahy M.	Cancer. 2012 Dec 15;118(24):6144-51.	**Excluded** due to different study topic;
11	Phase II and gene expression analysis trial of neoadjuvant capecitabine plus irinotecan followed by capecitabine-based chemoradiotherapy for locally advanced rectal cancer: Hoosier Oncology Group GI03-53.	Chiorean EG, Sanghani S, Schiel MA, Yu M, Burns M, Tong Y, Hinkle DT, Coleman N, Robb B, LeBlanc J, Clark R, Bufill J, Curie C, Loehrer PJ, Cardenes H.	Cancer Chemother Pharmacol. 2012 Jul;70(1):25-32.	**Excluded,** information required not included;
12	A Phase II study of clinical outcomes of 3-week cycles of irinotecan and S-1 in patients with previously untreated metastatic colorectal cancer: influence of the UGT1A1 and CYP2A6 polymorphisms on clinical activity.	Choi YH, Kim TW, Kim KP, Lee SS, Hong YS, Ryu MH, Lee JL, Chang HM, Ryoo BY, Kim HS, Shin JG, Kang YK.	Oncology. 2012;82(5):290-7.	**Excluded,** Korean study;
13	The value of genetic polymorphisms to predict toxicity in metastatic colorectal patients with irinotecan-based regimens.	Lamas MJ, Duran G, Balboa E, Bernardez B, Candamio S, Vidal Y, Mosquera A, Giraldez JM, Lopez R, Carracedo A, Barros F.	Cancer Chemother Pharmacol. 2012 Jun;69(6):1591-9.	**Excluded,** covered by the meta-analysis by Lui et al. (study #4).

14	A phase I study of infusional 5-fluorouracil, leucovorin, oxaliplatin and irinotecan in Japanese patients with advanced colorectal cancer who harbor UGT1A1*1/*1,*1/*6 or *1/*28.	Sunakawa Y, Fujita K, Ichikawa W, Ishida H, Yamashita K, Araki K, Miwa K, Kawara K, Akiyama Y, Yamamoto W, Nagashima F, Saji S, Sasaki Y.	Oncology. 2012;82(4):242-8.	**Excluded,** Japanese study;
15	Feasibility of biweekly combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in patients with metastatic solid tumors: results of a two-step phase I trial: XELIRI and XELIRINOX.	Mazard T, Ychou M, Thezenas S, Poujol S, Pinguet F, Thirion A, Bleuse JP, Portales F, Samalin E, Assenat E.	Cancer Chemother Pharmacol. 2012 Mar;69(3):807-14.	**Excluded,** information required not included;
16	Pharmacokinetic and pharmacogenetic predictive markers of irinotecan activity and toxicity	Di Paolo A, Bocci G, Polillo M, Del Re M, Di Desidero T, Lastella M, Danesi R.	Curr Drug Metab. 2011 Dec;12(10):932-43.	**Excluded,** no original study
17	A genotype-directed phase I-IV dose-finding study of irinotecan in combination with fluorouracil/leucovorin as first-line treatment in advanced colorectal cancer.	Marcuello E, Páez D, Paré L, Salazar J, Sebio A, del Rio E, Baiget M.	Br J Cancer. 2011 Jun 28;105(1):53-7.	**Excluded,** information required not included;
18	Concurrence of UGT1A polymorphism and end-stage renal disease leads to severe toxicities of irinotecan in a patient with metastatic colon cancer.	Huang SH, Chao Y, Wu YY, Luo JC, Kao CH, Yen SH, Li CP.	Tumori. 2011 Mar-Apr;97(2):243-7.	**Excluded,** Taiwanese study;
19	Regimen selection for first-line FOLFIRI and FOLFOX based on UGT1A1 genotype and physical background is feasible in Japanese patients with advanced colorectal cancer.	Ishida H, Fujita K, Akiyama Y, Sunakawa Y, Yamashita K, Mizuno K, Miwa K, Kawara K, Ichikawa W, Ando Y, Saji S, Sasaki Y.	Jpn J Clin Oncol. 2011 May;41(5):617-23.	**Excluded,** Japanese study;
20	Prospective phase II study of FOLFIRI for mCRC in Japan, including the analysis of UGT1A1 28/6 polymorphisms.	Okuyama Y, Hazama S, Nozawa H, Kobayashi M, Takahashi K, Fujikawa K, Kato T, Nagata N, Kimura H, Oba K, Sakamoto J, Mishima H.	Jpn J Clin Oncol. 2011 Apr;41(4):477-82.	**Excluded,** Japanese study;
21	Clinical implications of UGT1A1*28 genotype testing in colorectal cancer patients.	Shulman K, Cohen I, Barnett-Griness O, Kuten A, Gruber SB, Lejbkowicz F, Rennert G.	Cancer. 2011 Jul 15;117(14):3156-62.	**Excluded,** covered by the meta-analysis by Lui et al. (study #4).

22	Phase I/II study of FOLFIRI in Japanese patients with advanced colorectal cancer.	Yamashita K, Nagashima F, Fujita K, Yamamoto W, Endo H, Miya T, Narabayashi M, Kawara K, Akiyama Y, Ando Y, Ando M, Sasaki Y.	Jpn J Clin Oncol. 2011 Feb;41(2):204-9.	**Excluded,** Japanese study;
23	Understanding chemotherapy treatment pathways of advanced colorectal cancer patients to inform an economic evaluation in the United Kingdom.	Shabaruddin FH, Elliott RA, Valle JW, Newman WG, Payne K.	Br J Cancer. 2010 Jul 27;103(3):315-23.	**Excluded,** no original study
24	UGT1A and TYMS genetic variants predict toxicity and response of colorectal cancer patients treated with first-line irinotecan and fluorouracil combination therapy.	Martinez-Balibrea E, Abad A, Martínez-Cardús A, Ginés A, Valladares M, Navarro M, Aranda E, Marcuello E, Benavides M, Massutí B, Carrato A, Layos L, Manzano JL, Moreno V.	Br J Cancer. 2010 Aug 10;103(4):581-9.	**Excluded,** covered by the meta-analysis by Lui et al. (study #4).
25	Pharmacogenetic predictors of adverse events and response to chemotherapy in metastatic colorectal cancer: results from North American Gastrointestinal Intergroup Trial N9741	McLeod HL, Sargent DJ, Marsh S, Green EM, King CR, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Thibodeau SN, Grothey A, Morton RF, Goldberg RM.	J Clin Oncol. 2010 Jul 10;28(20):3227-33.	**Excluded,** covered by the meta-analysis by Lui et al. (study #4).
26	Pharmacogenetics of irinotecan disposition and toxicity: a review.	Fujita K, Sparreboom A. Curr Clin Pharmacol. 2010 Aug;5(3):209-17. Review.	Curr Clin Pharmacol. 2010 Aug;5(3):209-17.	**Excluded,** no original study
27	Prediction of irinotecan and 5-fluorouracil toxicity and response in patients with advanced colorectal cancer.	Glimelius B, Garmo H, Berglund A, Fredriksson LA, Berglund M, Kohnke H, Byström P, Sørbye H, Wadelius M.	Pharmacogenomics J. 2011 Feb;11(1):61-71.	**Excluded,** covered by the meta-analysis by Lui et al. (study #4).
28	A CYP3A4 phenotype-based dosing algorithm for individualized treatment of irinotecan.	van der Bol JM, Mathijssen RH, Creemers GJ, Planting AS, Loos WJ, Wiemer EA, Friberg LE, Verweij J, Sparreboom A, de Jong FA.	Clin Cancer Res. 2010 Jan 15;16(2):736-42.	**Excluded,** information required not included;

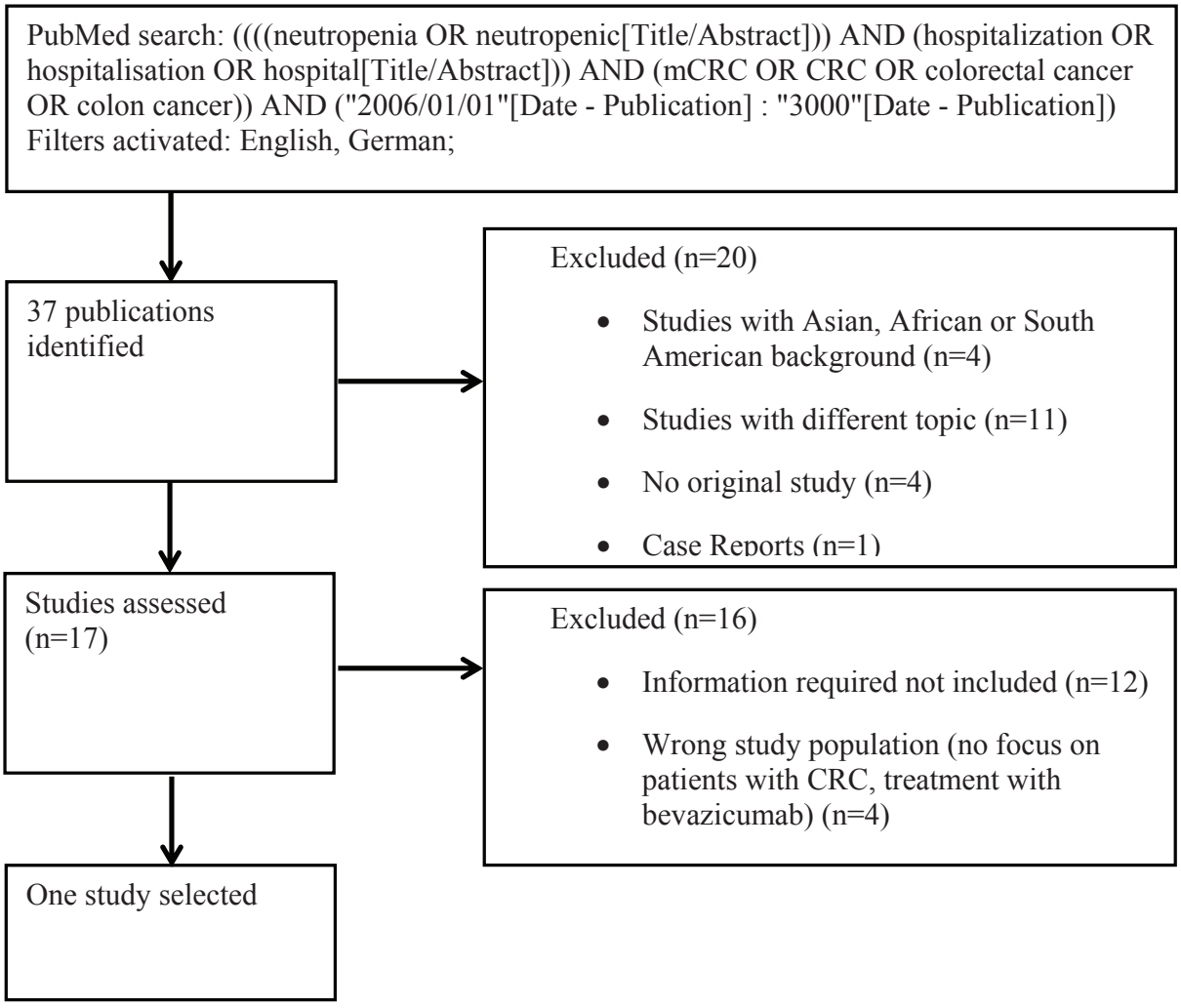
29	Cost-effectiveness of UGT1A1*28 genotyping in preventing severe neutropenia following FOLFIRI therapy in colorectal cancer.	Pichereau S, Le Louarn A, Lecomte T, Blasco H, Le Guellec C, Bourgoin H.	J Pharm Pharm Sci. 2010;13(4):615-25.	**Excluded,** no original study
30	Genotype-driven phase I study of irinotecan administered in combination with fluorouracil/leucovorin in patients with metastatic colorectal cancer.	Toffoli G, Cecchin E, Gasparini G, D'Andrea M, Azzarello G, Basso U, Mini E, Pessa S, De Mattia E, Lo Re G, Buonadonna A, Nobili S, De Paoli P, Innocenti F.	J Clin Oncol. 2010 Feb 10;28(5):866-71.	**Excluded,** information required not included;
31	Chemotherapy: Optimizing irinotecan regimens for colorectal cancer.	Yim KL, Cunningham D.	Nat Rev Clin Oncol. 2009 Oct;6(10):560-1.	**Excluded,** no original study;
32	Utility of Pretreatment Bilirubin Level and UGT1A1 Polymorphisms in Multivariate Predictive Models of Neutropenia Associated with Irinotecan Treatment in Previously Untreated Patients with Colorectal Cancer.	Parodi L, Pickering E, Cisar LA, Lee D, Soufi-Mahjoubi R.	Arch Drug Inf. 2008 Dec;1(3):97-106.	**Excluded,** covered by the meta-analysis by Lui et al. (study #4).
33	Cost effectiveness of pharmacogenetic testing for uridine diphosphate glucuronosyltransferase 1A1 before irinotecan administration for metastatic colorectal cancer.	Gold HT, Hall MJ, Blinder V, Schackman BR.	Cancer. 2009 Sep 1;115(17):3858-67.	**Excluded,** no original study;
34	UGT1A1*28 genotype predicts gastrointestinal toxicity in patients treated with intermediate-dose irinotecan.	Ferraldeschi R, Minchell LJ, Roberts SA, Tobi S, Hadfield KD, Blackhall FH, Mullamitha S, Wilson G, Valle J, Saunders M, Newman WG.	Pharmacogenomics. 2009 May;10(5):733-9.	**Excluded,** covered by the meta-analysis by Lui et al. (study #4).
35	Pharmacogenetics in chemotherapy of colorectal cancer.	Henriette Tanja L, Guchelaar HJ, Gelderblom H.	Best Pract Res Clin Gastroenterol. 2009;23(2):257-73.	**Excluded,** no original study;
36	Comprehensive pharmacogenetic analysis of irinotecan neutropenia and pharmacokinetics.	Innocenti F, Kroetz DL, Schuetz E, Dolan ME, Ramírez J, Relling M, Chen P, Das S, Rosner GL, Ratain MJ.	J Clin Oncol. 2009 Jun 1;27(16):2604-14.	**Excluded** due to different study topic;

37	Can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? An evidence-based review.	Palomaki GE, Bradley LA, Douglas MP, Kolor K, Dotson WD.	Genet Med. 2009 Jan;11(1):21-34.	**Excluded,** no original study;
38	Recommendations from the EGAPP Working Group: can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group.		Genet Med. 2009 Jan;11(1):15-20.	**Excluded,** no original study;
39	Irinotecan and uridine diphosphate glucuronosyltransferase 1A1 pharmacogenetics: to test or not to test, that is the question.	Deeken JF, Slack R, Marshall JL.	Cancer. 2008 Oct 1;113(7):1502-10.	**Excluded,** no original study;
40	UGT1A1*28 genotype and irinotecan dosage in patients with metastatic colorectal cancer: a Dutch Colorectal Cancer Group study.	Kweekel DM, Gelderblom H, Van der Straaten T, Antonini NF, Punt CJ, Guchelaar HJ; Dutch Colorectal Cancer Group study.	Br J Cancer. 2008 Jul 22;99(2):275-82.	**Excluded,** covered by the meta-analysis by Lui et al. (study #4).
41	Cost-effectiveness of UGT1A1 genotyping in second-line, high-dose, once every 3 weeks irinotecan monotherapy treatment of colorectal cancer.	Obradovic M, Mrhar A, Kos M.	Pharmacogenomics. 2008 May;9(5):539-49.	**Excluded,** no original study;
42	Irinotecan pharmacogenetics: influence of pharmacodynamic genes.	Hoskins JM, Marcuello E, Altes A, Marsh S, Maxwell T, Van Booven DJ, Paré L, Culverhouse R, McLeod HL, Baiget M.	Clin Cancer Res. 2008 Mar 15;14(6):1788-96.	**Excluded** due to different study topic;
43	UGT1A1*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma.	Liu CY, Chen PM, Chiou TJ, Liu JH, Lin JK, Lin TC, Chen WS, Jiang JK, Wang HS, Wang WS.	Cancer. 2008 May 1;112(9):1932-40.	**Excluded,** Chinese study;

44	Increased frequency of uridine diphosphate glucuronosyltransferase 1A1 7/7 in patients experiencing severe irinotecan-induced toxicities.	Fakih MG, Ross ME, Starostik P.	Clin Colorectal Cancer. 2007 Jul;6(8):583-7.	**Excluded,** information required not included;
45	Role of UGT1A1*6, UGT1A1*28 and ABCG2 c.421C>A polymorphisms in irinotecan-induced neutropenia in Asian cancer patients.	Jada SR, Lim R, Wong CI, Shu X, Lee SC, Zhou Q, Goh BC, Chowbay B.	Cancer Sci. 2007 Sep;98(9):1461-7.	**Excluded,** Chinese study;
46	Pharmacogenetic profiling in patients with advanced colorectal cancer treated with first-line FOLFIRI chemotherapy.	Ruzzo A, Graziano F, Loupakis F, Santini D, Catalano V, Bisonni R, Ficarelli R, Fontana A, Andreoni F, Falcone A, Canestrari E, Tonini G, Mari D, Lippe P, Pizzagalli F, Schiavon G, Alessandroni P, Giustini L, Maltese P, Testa E, Menichetti ET, Magnani M.	Pharmacogenomics J. 2008 Aug;8(4):278-88.	**Excluded,** covered by the meta-analysis by Lui et al. (study #4).
47	Insights, challenges, and future directions in irinogenetics.	Kim TW, Innocenti F.	Ther Drug Monit. 2007 Jun;29(3):265-70.	**Excluded,** no original study;
48	Pharmacogenetics of irinotecan: clinical perspectives on the utility of genotyping.	Innocenti F, Ratain MJ.	Pharmacogenomics. 2006 Dec;7(8):1211-21.	**Excluded,** no original study;
49	Pharmacogenetics and irinotecan therapy.	Hahn KK, Wolff JJ, Kolesar JM.	Am J Health Syst Pharm. 2006 Nov 15;63(22):2211-7.	**Excluded,** no original study;
50	Uridine diphosphate glucuronosyl transferase 1A1 promoter polymorphism predicts the risk of gastrointestinal toxicity and fatigue induced by irinotecan-based chemotherapy.	Massacesi C, Terrazzino S, Marcucci F, Rocchi MB, Lippe P, Bisonni R, Lombardo M, Pilone A, Mattioli R, Leon A.	Cancer. 2006 Mar 1;106(5):1007-16.	**Excluded,** covered by the meta-analysis by Lui et al. (study #4).
51	A pilot study on the safety of combining chrysin, a non-absorbable inducer of UGT1A1, and irinotecan (CPT-11) to treat metastatic colorectal cancer.	Tobin PJ, Beale P, Noney L, Liddell S, Rivory LP, Clarke S.	Cancer Chemother Pharmacol. 2006 Feb;57(3):309-16.	**Excluded** due to different study topic;

1.3 Hospitalisation due to severe neutropenia

1.3.1 Flowchart of the structured literature search



Shulman et al. Clinical implications of UGT1A1*28 genotype testing in colorectal cancer patients. Cancer. 2011 Jul 15;117(14):3156-62.

1.3.2 List of identified studies.

((((neutropenia OR neutropenic[Title/Abstract])) AND (hospitalization OR hospitalisation OR hospital[Title/Abstract])) AND (mCRC OR CRC OR colorectal cancer OR colon cancer)) AND ("2006/01/01"[Date - Publication] : "3000"[Date - Publication]) Filters activated: English, German; 16.05.2013; 37 studies				
	Title	Author	Journal	Ex- or included
1	A retrospective study of the clinical and economic burden during hospitalizations among cancer patients with febrile neutropenia.	Dulisse B, Li X, Gayle JA, Barron RL, Ernst FR, Rothman KJ, Legg JC, Kaye JA.	J Med Econ. 2013 Apr 12. [Epub ahead of print]	**Excluded** due to different study topic;
2	Retrospective study as first-line chemotherapy combined anti-VEGF antibody with fluoropyrimidine for frail patients with unresectable or metastatic colorectal cancer.	Yoshida M, Goto M, Kii T, Nishitani H, Kawabe S, Kuwakado S, Asaishi K, Miyamoto T, Higuchi K.	Digestion. 2013;87(1):59-64.	**Excluded,** Japanese study;
3	Pegfilgrastim prophylaxis is associated with a lower risk of hospitalization of cancer patients than filgrastim prophylaxis: a retrospective United States claims analysis of granulocyte colony-stimulating factors (G-CSF).	Naeim A, Henk HJ, Becker L, Chia V, Badre S, Li X, Deeter R.	BMC Cancer. 2013 Jan 8;13:11.	**Excluded** due to different study topic;
4	UGT1A1 gene polymorphisms and the toxicities of FOLFIRI in Chinese han patients with gastrointestinal cancer.	Zhou CF, Ma T, Su Y, Ye ZB, Ji J, Yu YY, Zhang J, Liu BY, Zhu ZG.	Anticancer Agents Med Chem. 2013 Feb;13(2):235-41.	**Excluded,** Chinese study;
5	Costs associated with febrile neutropenia in the US.	Michels SL, Barron RL, Reynolds MW, Smoyer Tomic K, Yu J, Lyman GH.	Pharmacoeconomics. 2012 Sep 1;30(9):809-23.	**Excluded,** no original study;
6	Chemotherapy patients with C. difficile colitis have outcomes similar to immunocompetent C. difficile patients.	Stewart DB, Yacoub E, Zhu J.	J Gastrointest Surg. 2012 Aug;16(8):1566-72.	**Excluded** due to different study topic;

7	Elevated serum cytokine levels using cytometric bead arrays predict culture-positive infections in childhood oncology patients with febrile neutropenia.	Badurdeen S, Hodge G, Osborn M, Scott J, St John-Green C, Tapp H, Zola H, Revesz T.	J Pediatr Hematol Oncol. 2012 Jan;34(1):e36-8.	**Excluded** due to different study topic;
8	Absolute neutrophil values in malignant patients on cytotoxic chemotherapy.	Madu AJ, Ibegbulam OG, Ocheni S, Madu KA, Aguwa EN.	Niger J Med. 2011 Jan-Mar;20(1):120-3.	**Excluded,** African study;
9	Costs of hospital events in patients with metastatic colorectal cancer.	Overbeek JA, Zhao Z, van Herk-Sukel MP, Barber BL, Gao S, Herings RM.	J Med Econ. 2011;14(5):656-61.	**Excluded,** information required not included;
10	Molecular epidemiology and risk factors for colonization by vancomycin-resistant Enterococcus in patients with hematologic malignancies.	Almyroudis NG, Lesse AJ, Hahn T, Samonis G, Hazamy PA, Wongkittiroch K, Wang ES, McCarthy PL Jr, Wetzler M, Segal BH.	Infect Control Hosp Epidemiol. 2011 May;32(5):490-6.	**Excluded** due to different study topic;
11	Successful closure of anal cancer-related fistulas with upfront intra-arterial chemotherapy: a report of 8 cases.	Kridel R, Cochet S, Roche B, Bressoud A, Gervaz P, Betz M, Roth AD.	Dis Colon Rectum. 2011 May;54(5):566-9.	**Excluded** due to different study topic;
12	Clinical implications of UGT1A1*28 genotype testing in colorectal cancer patients.	Shulman K, Cohen I, Barnett-Griness O, Kuten A, Gruber SB, Lejbkowicz F, Rennert G.	Cancer. 2011 Jul 15;117(14):3156-62.	**Included;**
13	Toxicity associated with capecitabine plus oxaliplatin in colorectal cancer before and after an institutional policy of capecitabine dose reduction.	Baird R, Biondo A, Chhaya V, McLachlan J, Karpathakis A, Rahman S, Barbachano Y, Cunningham D, Chau I.	Br J Cancer. 2011 Jan 4;104(1):43-50.	**Excluded,** information required not included;
14	Bevacizumab in combination with FOLFIRI chemotherapy in patients with metastatic colorectal cancer: an assessment of safety and efficacy in the province of Newfoundland and Labrador.	Dranitsaris G, Edwards S, Edwards J, Leblanc M, Abbott R.	Curr Oncol. 2010 Oct;17(5):12-6.	**Excluded,** wrong study population (treatment with Bevacizumab);

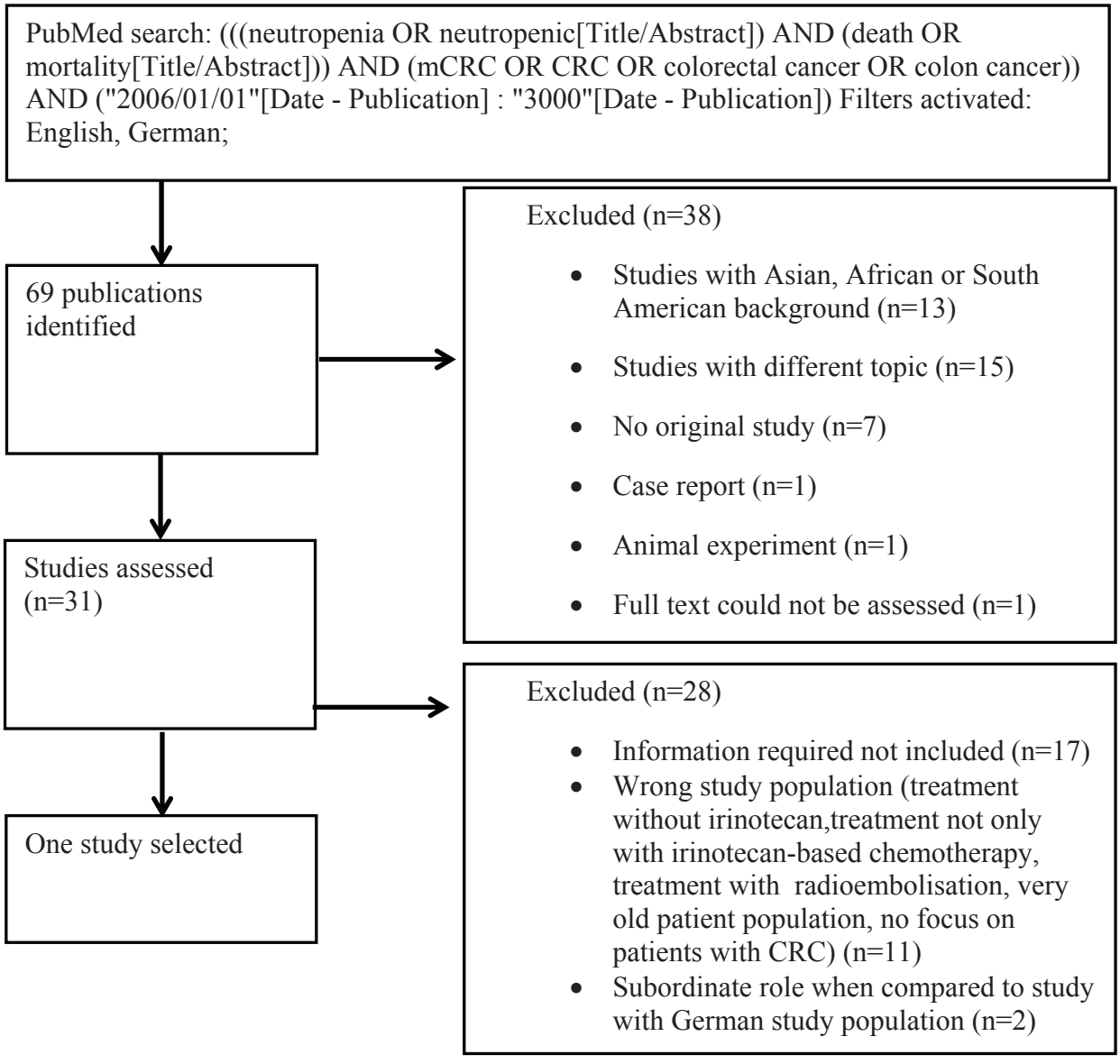
15	A multicenter phase-II study of 5-FU, leucovorin and oxaliplatin (FOLFOX6) in patients with pretreated metastatic colorectal cancer.	Kato K, Inaba Y, Tsuji Y, Esaki T, Yoshioka A, Mizunuma N, Mizuno T, Kusaba H, Fujii H, Muro K, Shimada Y, Shirao K.	Jpn J Clin Oncol. 2011 Jan;41(1):63-8.	**Excluded,** Japanese study;
16	Trends in G-CSF use in 990 patients after EORTC and ASCO guidelines.	Falandry C, Campone M, Cartron G, Guerin D, Freyer G.	Eur J Cancer. 2010 Sep;46(13):2389-98.	**Excluded** due to different study topic;
17	Risk of mortality in patients with cancer who experience febrile neutropenia.	Lyman GH, Michels SL, Reynolds MW, Barron R, Tomic KS, Yu J.	Cancer. 2010 Dec 1;116(23):5555-63.	**Excluded,** wrong study population (no focus on patients with CRC);
18	Understanding chemotherapy treatment pathways of advanced colorectal cancer patients to inform an economic evaluation in the United Kingdom.	Shabaruddin FH, Elliott RA, Valle JW, Newman WG, Payne K.	Br J Cancer. 2010 Jul 27;103(3):315-23.	**Excluded** due to different study topic;
19	Development and validation of a prediction model for the risk of developing febrile neutropenia in the first cycle of chemotherapy among elderly patients with breast, lung, colorectal, and prostate cancer.	Hosmer W, Malin J, Wong M.	Support Care Cancer. 2011 Mar;19(3):333-41.	**Excluded,** information required not included;
20	Cost-effectiveness of UGT1A1*28 genotyping in preventing severe neutropenia following FOLFIRI therapy in colorectal cancer.	Pichereau S, Le Louarn A, Lecomte T, Blasco H, Le Guellec C, Bourgoin H.	J Pharm Pharm Sci. 2010;13(4):615-25.	**Excluded,** no original study;
21	Incidence, risk factors, and impact of severe neutropenia after hyperthermic intraperitoneal mitomycin C.	Lambert LA, Armstrong TS, Lee JJ, Liu S, Katz MH, Eng C, Wolff RA, Tortorice ML, Tansey P, Gonzalez-Moreno S, Lambert DH, Mansfield PF.	Ann Surg Oncol. 2009 Aug;16(8):2181-7.	**Excluded** due to different study topic;
22	Hematologic complications of critical illness: anemia, neutropenia, thrombocytopenia, and more.	Munro N.	AACN Adv Crit Care. 2009 Apr-Jun;20(2):145-54.	**Excluded** due to different study topic;

23	Diagnosis, incidence, and outcomes of suspected typhlitis in oncology patients--experience in a tertiary pediatric surgical center in the United Kingdom.	Mullassery D, Bader A, Battersby AJ, Mohammad Z, Jones EL, Parmar C, Scott R, Pizer BL, Baillie CT.	J Pediatr Surg. 2009 Feb;44(2):381-5.	**Excluded** due to different study topic;
24	A Markov model assessing the effectiveness and cost-effectiveness of FOLFOX compared with FOLFIRI for the initial treatment of metastatic colorectal cancer.	Tumeh JW, Shenoy PJ, Moore SG, Kauh J, Flowers C.	Am J Clin Oncol. 2009 Feb;32(1):49-55.	**Excluded,** no original study;
25	Redefining adjuvant chemotherapy in patients with stage III colon cancer: X-ACT trial.	Glen H, Cassidy J.	Expert Rev Anticancer Ther. 2008 Apr;8(4):547-51.	**Excluded,** information required not included;
26	Impact of neutropenia on delivering planned chemotherapy for solid tumours.	Khan S, Dhadda A, Fyfe D, Sundar S.	Eur J Cancer Care (Engl). 2008 Jan;17(1):19-25.	**Excluded,** information required not included;
27	The oncology acute toxicity unit (OATU): an outpatient facility for improving the management of chemotherapy toxicity.	Majem M, Galán M, Pérez FJ, Muñoz M, Chicote S, Soler G, Navarro M, Martínez-Villacampa M, García del Muro X, Dotor E, Laquente B, Germà JR.	Clin Transl Oncol. 2007 Dec;9(12):784-8.	**Excluded,** information required not included;
28	Severe enteropathy among patients with stage II/III colon cancer treated on a randomized trial of bolus 5-fluorouracil/leucovorin plus or minus oxaliplatin: a prospective analysis.	Kuebler JP, Colangelo L, O'Connell MJ, Smith RE, Yothers G, Begovic M, Robinson B, Seay TE, Wolmark N.	Cancer. 2007 Nov 1;110(9):1945-50.	**Excluded,** information required not included;
29	Increased frequency of uridine diphosphate glucuronosyltransferase 1A1 7/7 in patients experiencing severe irinotecan-induced toxicities.	Fakih MG, Ross ME, Starostik P.	Clin Colorectal Cancer. 2007 Jul;6(8):583-7.	**Excluded,** information required not included;
30	Oxaliplatin, 5-fluorouracil/leucovorin and epirubicin as first-line treatment in advanced gastric carcinoma: a phase II study.	Neri B, Pantaleo P, Giommoni E, Grifoni R, Paoletti C, Rotella V, Pantalone D, Taddei A, Mercatelli A, Tonelli P.	Br J Cancer. 2007 Apr 10;96(7):1043-6.	**Excluded,** information required not included;

31	Conformal radiotherapy of the dominant liver metastasis: a viable strategy for treatment of unresectable chemotherapy refractory colorectal cancer liver metastases.	Krishnan S, Lin EH, Gunn GB, Chandra A, Beddar AS, Briere TM, Das P, Delclos ME, Janjan NA, Crane CH.	Am J Clin Oncol. 2006 Dec;29(6):562-7.	**Excluded,** information required not included;
32	Pharmacogenetics and irinotecan therapy.	Hahn KK, Wolff JJ, Kolesar JM.	Am J Health Syst Pharm. 2006 Nov 15;63(22):2211-7.	**Excluded,** no original study;
33	Severe enteropathy associated with raltitrexed and oxaliplatin chemotherapy: report of two patients experiencing this rare, potentially lethal gastrointestinal adverse event.	Wenzel C, Urbauer E, Schwarz C, Funk G, Oehler L, Kornek GV, Scheithauer W.	Anticancer Drugs. 2006 Aug;17(7):865-8.	**Excluded,** case study with two patients;
34	A phase I clinical and pharmacokinetic study of CS-682 administered orally in advanced malignant solid tumors.	Delaunoit T, Burch PA, Reid JM, Camoriano JK, Kobayash T, Braich TA, Kaur JS, Rubin J, Erlichman C.	Invest New Drugs. 2006 Jul;24(4):327-33.	**Excluded,** wrong study population (no focus on patients with CRC);
35	The bottom line: outcomes after conservation treatment in anal cancer.	Dwyer MK, Gebski VJ, Jayamohan J.	Australas Radiol. 2006 Feb;50(1):46-51.	**Excluded,** information required not included;
36	A phase I and pharmacokinetic study of a powder-filled capsule formulation of oral irinotecan (CPT-11) given daily for 5 days every 3 weeks in patients with advanced solid tumors.	Pitot HC, Adjei AA, Reid JM, Sloan JA, Atherton PJ, Rubin J, Alberts SR, Duncan BA, Denis L, Schaaf LJ, Yin D, Sharma A, McGovren P, Miller LL, Erlichman C.	Cancer Chemother Pharmacol. 2006 Aug;58(2):165-72.	**Excluded,** information required not included;
37	Phase I trial of UCN-01 in combination with topotecan in patients with advanced solid cancers: a Princess Margaret Hospital Phase II Consortium study.	Hotte SJ, Oza A, Winquist EW, Moore M, Chen EX, Brown S, Pond GR, Dancey JE, Hirte HW.	Ann Oncol. 2006 Feb;17(2):334-40. Epub 2005 Nov 10.	**Excluded,** wrong study population (no focus on patients with CRC);

1.4 Risk of death due to hospitalisation with severe neutropenia

1.4.1 Flowchart of the structured literature search



Schultheis et al. Regorafenib in combination with FOLFOX or FOLFIRI as first- or second-line treatment of colorectal cancer: results of a multicenter, phase Ib study. Ann Oncol. 2013 Mar 13. [Epub ahead of print]

1.4.2 List of identified studies.

(((neutropenia OR neutropenic[Title/Abstract]) AND (death OR mortality[Title/Abstract])) AND (mCRC OR CRC OR colorectal cancer OR colon cancer)) AND ("2006/01/01"[Date - Publication] : "3000"[Date - Publication]) Filters activated: English, German; 20.05.2013; 69 studies;				
	Title	Author	Journal	Ex- or included
1	FOLFOXIRI in combination with panitumumab as first-line treatment in quadruple wild-type (KRAS, NRAS, HRAS, BRAF) metastatic colorectal cancer patients: a phase II trial by the Gruppo Oncologico Nord Ovest (GONO).	Fornaro L, Lonardi S, Masi G, Loupakis F, Bergamo F, Salvatore L, Cremolini C, Schirripa M, Vivaldi C, Aprile G, Zaniboni A, Bracarda S, Fontanini G, Sensi E, Lupi C, Morvillo M, Zagonel V, Falcone A.	Ann Oncol. 2013 May 10. [Epub ahead of print]	**Excluded** due to different study topic;
2	The impact of chemotherapy-associated neutrophil/ lymphocyte counts on prognosis of adjuvant chemotherapy in colorectal cancer.	Chu-Yuan H, Jing P, Yi-Sheng W, He-Ping P, Hui Y, Chu-Xiong Z, Guo-Jian L, Guo-Qiang W.	BMC Cancer. 2013 Apr 3;13:177.	**Excluded,** Chinese study;
3	A randomized, placebo-controlled phase 2 study of ganitumab or conatumumab in combination with FOLFIRI for second-line treatment of mutant KRAS metastatic colorectal cancer.	Cohn AL, Tabernero J, Maurel J, Nowara E, Sastre J, Chuah BY, Kopp MV, Sakaeva DD, Mitchell EP, Dubey S, Suzuki S, Hei YJ, Galimi F, McCaffery I, Pan Y, Loberg R, Cottrell S, Choo SP.	Ann Oncol. 2013 Mar 19. [Epub ahead of print]	**Excluded,** information required not included;
4	Regorafenib in combination with FOLFOX or FOLFIRI as first- or second-line treatment of colorectal cancer: results of a multicenter, phase Ib study.	Schultheis B, Folprecht G, Kuhlmann J, Ehrenberg R, Hacker UT, Köhne CH, Kornacker M, Boix O, Lettieri J, Krauss J, Fischer R, Hamann S, Strumberg D, Mross KB.	Ann Oncol. 2013 Mar 13. [Epub ahead of print]	**Included:** Germany, 20 patients (FOLFIRI), one case of febrile neutropenia, no death due to febrile neutropenia
5	A retrospective study of the clinical and economic burden during hospitalizations among cancer patients with febrile neutropenia.	Dulisse B, Li X, Gayle JA, Barron RL, Ernst FR, Rothman KJ, Legg JC, Kaye JA.	J Med Econ. 2013 Apr 12. [Epub ahead of print]	**Excluded,** full text could not be assessed;

6	Is Intensive Chemotherapy Safe for Rural Cancer Patients?	Pathmanathan S, Burgher B, Sabesan S.	Intern Med J. 2013 Jan 24. [Epub ahead of print]	**Excluded**, wrong study population: (treatment without Irinotecan);
7	Is there still a role for mitomycin-based combination chemotherapy in treating patients with nonsmall cell lung cancer? A single institution experience.	Vitale FV, Malaponte E, Calì S, Antonelli G, Panebianco V, Blandino R, Ferraù F.	J Oncol Pharm Pract. 2012 Oct 3. [Epub ahead of print]	**Excluded** due to different study topic;
8	TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial.	Yoshino T, Mizunuma N, Yamazaki K, Nishina T, Komatsu Y, Baba H, Tsuji A, Yamaguchi K, Muro K, Sugimoto N, Tsuji Y, Moriwaki T, Esaki T, Hamada C, Tanase T, Ohtsu A.	Lancet Oncol. 2012 Oct;13(10):993-1001.	**Excluded,** Japanese study;
9	Costs associated with febrile neutropenia in the US.	Michels SL, Barron RL, Reynolds MW, Smoyer Tomic K, Yu J, Lyman GH.	Pharmacoeconomics. 2012 Sep 1;30(9):809-23.	**Excluded,** no original study;
10	Chemotherapy patients with C. difficile colitis have outcomes similar to immunocompetent C. difficile patients.	Stewart DB, Yacoub E, Zhu J.	J Gastrointest Surg. 2012 Aug;16(8):1566-72.	**Excluded** due to different study topic;
11	Predictors of irinotecan toxicity and efficacy in treatment of metastatic colorectal cancer.	Paulík A, Grim J, Filip S.	Acta Medica (Hradec Kralove). 2012;55(4):153-9.	**Excluded,** no original study;
12	Feasibility of biweekly combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in patients with metastatic solid tumors: results of a two-step phase I trial: XELIRI and XELIRINOX.	Mazard T, Ychou M, Thezenas S, Poujol S, Pinguet F, Thirion A, Bleuse JP, Portales F, Samalin E, Assenat E.	Cancer Chemother Pharmacol. 2012 Mar;69(3):807-14.	**Excluded** due to different study topic;

13	Oxaliplatin-based chemotherapy in the treatment of elderly patients with metastatic colorectal cancer (CRC).	Berretta M, Zanet E, Nasti G, Lleshi A, Frustaci S, Fiorica F, Bearz A, Talamini R, Lestuzzi C, Lazzarini R, Fisichella R, Cannizzaro R, Iaffaioli RV, Berretta S, Tirelli U.	Arch Gerontol Geriatr. 2012 Sep-Oct;55(2):271-5.	**Excluded**, wrong study population: very old patients (65-75 years, median age 71 years)
14	Costs of hospital events in patients with metastatic colorectal cancer.	Overbeek JA, Zhao Z, van Herk-Sukel MP, Barber BL, Gao S, Herings RM.	J Med Econ. 2011;14(5):656-61.	**Excluded,** information required not included;
15	Phase II study of bevacizumab and chemoradiation in the preoperative or adjuvant treatment of patients with stage II/III rectal cancer.	Spigel DR, Bendell JC, McCleod M, Shipley DL, Arrowsmith E, Barnes EK, Infante JR, Burris HA 3rd, Greco FA, Hainsworth JD.	Clin Colorectal Cancer. 2012 Mar;11(1):45-52.	**Excluded**, wrong study population: treatment without Irinotecan;
16	Bevacizumab combined with chemotherapy in the second-line treatment of metastatic colorectal cancer: results from the phase II BEVACOLOR study.	Bennouna J, Borg C, Delord JP, Husseini F, Trillet-Lenoir V, Faroux R, François E, Ychou M, Goldwasser F, Bouché O, Senellart H, Kraemer S, Douillard JY.	Clin Colorectal Cancer. 2012 Mar;11(1):38-44.	**Excluded**, wrong study population: treatment not only with Irinotecan-based chemotherapy;
17	Concurrence of UGT1A polymorphism and end-stage renal disease leads to severe toxicities of irinotecan in a patient with metastatic colon cancer.	Huang SH, Chao Y, Wu YY, Luo JC, Kao CH, Yen SH, Li CP.	Tumori. 2011 Mar-Apr;97(2):243-7.	**Excluded,** Taiwanese study;
18	Radioembolization in combination with systemic chemotherapy as first-line therapy for liver metastases from colorectal cancer.	Kosmider S, Tan TH, Yip D, Dowling R, Lichtenstein M, Gibbs P.	J Vasc Interv Radiol. 2011 Jun;22(6):780-6.	**Excluded**, wrong study population: treatment with radioambolisation;

19	Phase II study of panitumumab, oxaliplatin, 5-fluorouracil, and concurrent radiotherapy as preoperative treatment in high-risk locally advanced rectal cancer patients (StarPan/STAR-02 Study).	Pinto C, Di Fabio F, Maiello E, Pini S, Latiano T, Aschele C, Garufi C, Bochicchio A, Rosati G, Aprile G, Giaquinta S, Torri V, Bardelli A, Gion M, Martoni A.	Ann Oncol. 2011 Nov;22(11):2424-30.	**Excluded,** information required not included;
20	HAX-1: a family of apoptotic regulators in health and disease.	Yap SV, Koontz JM, Kontrogianni-Konstantopoulos A.	J Cell Physiol. 2011 Nov;226(11):2752-61.	**Excluded** due to different study topic;
21	Clinical implications of UGT1A1*28 genotype testing in colorectal cancer patients.	Shulman K, Cohen I, Barnett-Griness O, Kuten A, Gruber SB, Lejbkowicz F, Rennert G.	Cancer. 2011 Jul 15;117(14):3156-62.	**Excluded,** information required not included;
22	Bevacizumab plus FOLFIRI-3 in chemotherapy-refractory patients with metastatic colorectal cancer in the era of biotherapies.	Ghiringhelli F, Vincent J, Guiu B, Chauffert B, Ladoire S.	Invest New Drugs. 2012 Apr;30(2):758-64. .	**Excluded:** Subordinate role when compared to study with German study population (also no death from toxicity)
23	Differences in efficacy and safety between capecitabine and infusional 5-fluorouracil when combined with irinotecan for the treatment of metastatic colorectal cancer.	Montagnani F, Chiriatti A, Licitra S, Aliberti C, Fiorentini G.	Clin Colorectal Cancer. 2010 Oct;9(4):243-7.	**Excluded**, no original study;
24	Feasibility of oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX-4) in cirrhotic or liver transplant patients: experience in a cohort of advanced hepatocellular carcinoma patients.	Coriat R, Mir O, Cessot A, Brezault C, Ropert S, Durand JP, Cacheux W, Chaussade S, Goldwasser F.	Invest New Drugs. 2012 Feb;30(1):376-81.	**Excluded** due to different study topic;
25	Risk of mortality in patients with cancer who experience febrile neutropenia.	Lyman GH, Michels SL, Reynolds MW, Barron R, Tomic KS, Yu J.	Cancer. 2010 Dec 1;116(23):5555-63.	**Excluded**, wrong study population: treatment not only with Irinotecan-based chemotherapy;

26	Irinotecan plus S-1 (IRIS) versus fluorouracil and folinic acid plus irinotecan (FOLFIRI) as second-line chemotherapy for metastatic colorectal cancer: a randomised phase 2/3 non-inferiority study (FIRIS study).	Muro K, Boku N, Shimada Y, Tsuji A, Sameshima S, Baba H, Satoh T, Denda T, Ina K, Nishina T, Yamaguchi K, Takiuchi H, Esaki T, Tokunaga S, Kuwano H, Komatsu Y, Watanabe M, Hyodo I, Morita S, Sugihara K.	Lancet Oncol. 2010 Sep;11(9):853-60.	**Excluded,** Japanese study;
27	Preoperative chemoradiation with irinotecan and capecitabine in patients with locally advanced resectable rectal cancer: long-term results of a Phase II study.	Hong YS, Kim DY, Lim SB, Choi HS, Jeong SY, Jeong JY, Sohn DK, Kim DH, Chang HJ, Park JG, Jung KH.	Int J Radiat Oncol Biol Phys. 2011 Mar 15;79(4):1171-8.	**Excluded,** Korean study;
28	Comorbidity, age and overall survival in cetuximab-treated patients with advanced colorectal cancer (ACRC)--results from NCIC CTG CO.17: a phase III trial of cetuximab versus best supportive care.	Asmis TR, Powell E, Karapetis CS, Jonker DJ, Tu D, Jeffery M, Pavlakis N, Gibbs P, Zhu L, Dueck DA, Whittom R, Langer C, O'Callaghan CJ.	Ann Oncol. 2011 Jan;22(1):118-26.	**Excluded,** information required not included;
29	Emergency department management of hematologic and oncologic complications in the patient infected with HIV.	Scott SB.	Emerg Med Clin North Am. 2010 May;28(2):325-33.	**Excluded** due to different study topic;
30	A phase II trial of FOLFOX6 and cetuximab in the first-line treatment of patients with metastatic colorectal cancer.	Boccia RV, Cosgriff TM, Headley DL, Badarinath S, Dakhil SR.	Clin Colorectal Cancer. 2010 Apr;9(2):102-7.	**Excluded**, wrong study population: treatment without Irinotecan;
31	FOLFOX4 in the treatment of metastatic colorectal cancer in elderly patients: a prospective study.	Berretta M, Cappellani A, Fiorica F, Nasti G, Frustaci S, Fisichella R, Bearz A, Talamini R, Lleshi A, Tambaro R, Cocciolo A, Ristagno M, Bolognese A, Basile F, Meneguzzo N, Berretta S, Tirelli U.	Arch Gerontol Geriatr. 2011 Jan-Feb;52(1):89-93.	**Excluded**, wrong study population: very old patients (67-82 years, median age 72 years);

32	The duration of functioning of a subcutaneous implantable port for the treatment of hematological tumors: a single institution-based study.	Ohno H, Mizumoto C, Otsuki Y, Oguma S, Yoshida Y	Int J Clin Oncol. 2010 Apr;15(2):172-8.	**Excluded,** Japanese study;
33	A systematic review of FOLFOXIRI chemotherapy for the first-line treatment of metastatic colorectal cancer: improved efficacy at the cost of increased toxicity.	Montagnani F, Chiriatti A, Turrisi G, Francini G, Fiorentini G.	Colorectal Dis. 2011 Aug;13(8):846-52.	**Excluded** due to different study topic;
34	Phase II study of S-1 plus leucovorin in patients with metastatic colorectal cancer.	Koizumi W, Boku N, Yamaguchi K, Miyata Y, Sawaki A, Kato T, Toh Y, Hyodo I, Nishina T, Furuhata T, Miyashita K, Okada Y.	Ann Oncol. 2010 Apr;21(4):766-71.	**Excluded,** Japanese study;
35	Gemcitabine plus irinotecan as first-line weekly therapy in locally advanced and/or metastatic pancreatic cancer.	Neri B, Cipriani G, Grifoni R, Molinara E, Pantaleo P, Rangan S, Vannini A, Tonelli P, Valeri A, Pantalone D, Taddei A, Bechi P.	Oncol Res. 2009;17(11-12):559-64.	**Excluded** due to different study topic;
36	Treatment of fluorouracil-refractory patients with liver metastases from colorectal cancer by using yttrium-90 resin microspheres plus concomitant systemic irinotecan chemotherapy.	van Hazel GA, Pavlakis N, Goldstein D, Olver IN, Tapner MJ, Price D, Bower GD, Briggs GM, Rossleigh MA, Taylor DJ, George J.	J Clin Oncol. 2009 Sep 1;27(25):4089-95.	**Excluded** due to different study topic;
37	FOLFOX-4 Regimen as a First-line Therapy for Cuban Patients with Metastatic Colorectal Cancer.	Lami L, Areces F, Lence JJ, Arbesú MA.	MEDICC Rev. 2009 Jul;11(3):34-8.	**Excluded,** study from Cuba;
38	A feasibility study of UFT/LV and irinotecan (TEGAFIRI) in advanced or metastatic colorectal cancer: Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) PROG 0304.	Ishida H, Miyake Y, Fukunaga M, Watanabe Y, Kato T, Takemoto H, Furukawa H.	Jpn J Clin Oncol. 2009 Sep;39(9):601-5.	**Excluded,** Japanese study;

39	Incidence, risk factors, and impact of severe neutropenia after hyperthermic intraperitoneal mitomycin C.	Lambert LA, Armstrong TS, Lee JJ, Liu S, Katz MH, Eng C, Wolff RA, Tortorice ML, Tansey P, Gonzalez-Moreno S, Lambert DH, Mansfield PF.	Ann Surg Oncol. 2009 Aug;16(8):2181-7.	**Excluded** due to different study topic;
40	Initial safety report of NSABP C-08: A randomized phase III study of modified FOLFOX6 with or without bevacizumab for the adjuvant treatment of patients with stage II or III colon cancer.	Allegra CJ, Yothers G, O'Connell MJ, Sharif S, Colangelo LH, Lopa SH, Petrelli NJ, Goldberg RM, Atkins JN, Seay TE, Fehrenbacher L, O'Reilly S, Chu L, Azar CA, Wolmark N.	J Clin Oncol. 2009 Jul 10;27(20):3385-90.	**Excluded,** information required not included;
41	Neutropaenia as a prognostic factor in metastatic colorectal cancer patients undergoing chemotherapy with first-line FOLFOX.	Shitara K, Matsuo K, Takahari D, Yokota T, Inaba Y, Yamaura H, Sato Y, Najima M, Ura T, Muro K.	Eur J Cancer. 2009 Jul;45(10):1757-63.	**Excluded,** Japanese study;
42	Can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? An evidence-based review.	Palomaki GE, Bradley LA, Douglas MP, Kolor K, Dotson WD.	Genet Med. 2009 Jan;11(1):21-34.	**Excluded**, no original study;
43	Recommendations from the EGAPP Working Group: can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan?	Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group.	Genet Med. 2009 Jan;11(1):15-20.	**Excluded**, no original study;
44	Results of a phase II trial of cetuximab plus capecitabine/irinotecan as first-line therapy for patients with advanced and/or metastatic colorectal cancer.	Cartwright T, Kuefler P, Cohn A, Hyman W, Berger M, Richards D, Vukelja S, Nugent JE, Ruxer RL Jr, Boehm KA, Asmar L.	Clin Colorectal Cancer. 2008 Nov;7(6):390-7.	**Excluded,** information required not included;
45	Use of the folinic acid/5-fluorouracil/irinotecan (FOLFIRI 1) regimen in elderly patients as a first-line treatment for metastatic colorectal cancer: a Phase II study.	François E, Berdah JF, Chamorey E, Lesbats G, Teissier E, Codoul JF, Badetti JL, Hébert C, Mari V.	Cancer Chemother Pharmacol. 2008 Nov;62(6):931-6.	**Excluded,** information required not included;

46	Palliative chemotherapy in elderly patients with common metastatic malignancies: A Hellenic Cooperative Oncology Group registry analysis of management, outcome and clinical benefit predictors.	Pentheroudakis G, Fountzilas G, Kalofonos HP, Golfinopoulos V, Aravantinos G, Bafaloukos D, Papakostas P, Pectasides D, Christodoulou C, Syrigos K, Economopoulos T, Pavlidis N; Hellenic Cooperative Oncology Group.	Crit Rev Oncol Hematol. 2008 Jun;66(3):237-47.	**Excluded**, wrong study population: very old patients (65–91 years, median age 71 years);
47	A randomized phase III multicenter trial comparing irinotecan in combination with the Nordic bolus 5-FU and folinic acid schedule or the bolus/infused de Gramont schedule (Lv5FU2) in patients with metastatic colorectal cancer.	Glimelius B, Sørbye H, Balteskard L, Byström P, Pfeiffer P, Tveit K, Heikkilä R, Keldsen N, Albertsson M, Starkhammar H, Garmo H, Berglund A.	Ann Oncol. 2008 May;19(5):909-14.	**Excluded,** information required not included;
48	FOLFOX in patients aged between 76 and 80 years with metastatic colorectal cancer: an exploratory cohort of the OPTIMOX1 study.	Figer A, Perez-Staub N, Carola E, Tournigand C, Lledo G, Flesch M, Barcelo R, Cervantes A, André T, Colin P, Louvet C, de Gramont A.	Cancer. 2007 Dec 15;110(12):2666-71.	**Excluded**, wrong study population: very old patients (76-80 years);
49	Tritherapy with fluorouracil/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX): a phase II study in colorectal cancer patients with non-resectable liver metastases.	Ychou M, Viret F, Kramar A, Desseigne F, Mitry E, Guimbaud R, Delpero JR, Rivoire M, Quénet F, Portier G, Nordlinger B.	Cancer Chemother Pharmacol. 2008 Jul;62(2):195-201.	**Excluded**, Subordinate role when compared to study with German study population (also no death from toxicity)
50	Recombinant human keratinocyte growth factor palifermin reduces oral mucositis and improves patient outcomes after stem cell transplant.	Beaven AW, Shea TC.	Drugs Today (Barc). 2007 Jul;43(7):461-73. Review.	**Excluded** due to different study topic;
51	Efficacy and safety of an irinotecan plus bolus 5-fluorouracil and L-leucovorin regimen for metastatic colorectal cancer in Japanese patients: experience in a single institution in Japan.	Yoshino T, Boku N, Onozawa Y, Hironaka S, Fukutomi A, Yamaguchi Y, Hasuike N, Yamazaki K, Machida N, Ono H.	Jpn J Clin Oncol. 2007 Sep;37(9):686-91.	**Excluded,** Japanese study;

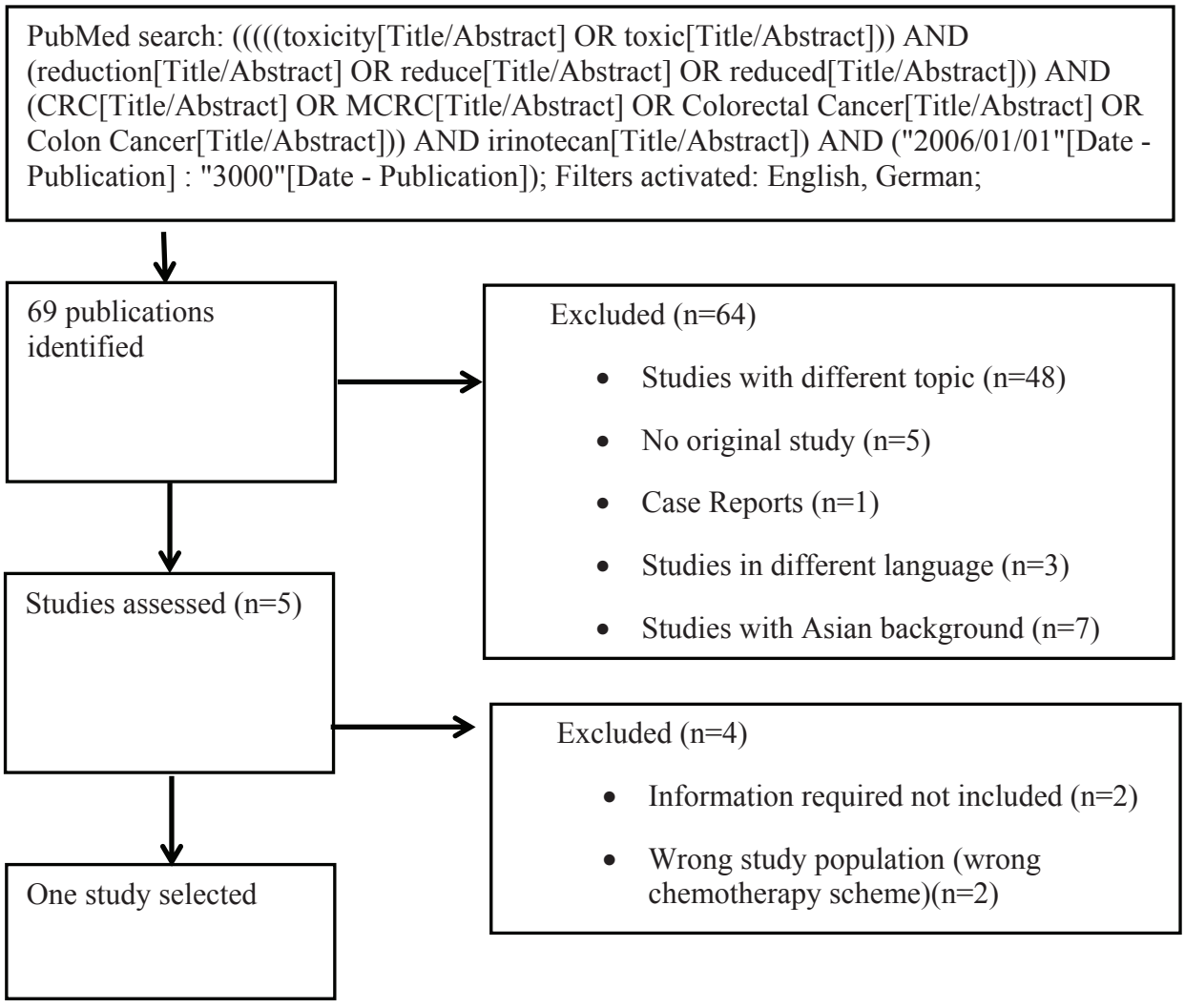
52	Irinotecan-based chemotherapy in a metastatic colorectal cancer patient under haemodialysis for chronic renal dysfunction: two cases considered.	Vénat-Bouvet L, Saint-Marcoux F, Lagarde C, Peyronnet P, Lebrun-Ly V, Tubiana-Mathieu N.	Fukuoka Igaku Zasshi. 2007 Jun;98(6):253-9.	**Excluded** due to different study topic;
53	Clinical outcomes of FOLFOX/FOLFIRI for the Japanese patients with far-advanced or recurrent colorectal cancer.	Saeki H, Higashi H, Maehara S, Tanaka J, Makino I, Imamura S, Aso M, Katoh H, Kakeji Y, Maehara Y.	Fukuoka Igaku Zasshi. 2007 Jun;98(6):253-9.	**Excluded,** Japanese study;
54	Front-line bevacizumab in combination with oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) in patients with metastatic colorectal cancer: a multicenter phase II study.	Emmanouilides C, Sfakiotaki G, Androulakis N, Kalbakis K, Christophylakis C, Kalykaki A, Vamvakas L, Kotsakis A, Agelaki S, Diamandidou E, Touroutoglou N, Chatzidakis A, Georgoulias V, Mavroudis D, Souglakos J.	BMC Cancer. 2007 May 30;7:91.	**Excluded,** information required not included;
55	Radioembolization of liver metastases from colorectal cancer using yttrium-90 microspheres with concomitant systemic oxaliplatin, fluorouracil, and leucovorin chemotherapy.	Sharma RA, Van Hazel GA, Morgan B, Berry DP, Blanshard K, Price D, Bower G, Shannon JA, Gibbs P, Steward WP.	J Clin Oncol. 2007 Mar 20;25(9):1099-106.	**Excluded** due to different study topic;
56	Phase I study of bryostatin 1 and gemcitabine.	El-Rayes BF, Gadgeel S, Shields AF, Manza S, Lorusso P, Philip PA.	Clin Cancer Res. 2006 Dec 1;12(23):7059-62.	**Excluded**, wrong study population: only four patients with CRC;
57	Pharmacogenetics and irinotecan therapy.	Hahn KK, Wolff JJ, Kolesar JM.	Am J Health Syst Pharm. 2006 Nov 15;63(22):2211-7.	**Excluded,** no original study;
58	Effect of neutropenia and treatment delay on the response to antifungal agents in experimental disseminated candidiasis.	Hope WW, Drusano GL, Moore CB, Sharp A, Louie A, Walsh TJ, Denning DW, Warn PA.	Antimicrob Agents Chemother. 2007 Jan;51(1):285-95.	**Excluded,** animal experiment;

59	Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer.	Goldberg RM, Tabah-Fisch I, Bleiberg H, de Gramont A, Tournigand C, Andre T, Rothenberg ML, Green E, Sargent DJ.	J Clin Oncol. 2006 Sep 1;24(25):4085-91. Erratum in: J Clin Oncol. 2008 Jun 10;26(17):2925-6.	**Excluded,** information required not included;
60	Capecitabine: a new adjuvant option for colorectal cancer.	Berg DT.	Clin J Oncol Nurs. 2006 Aug;10(4):479-86.	**Excluded** due to different study topic;
61	Severe enteropathy associated with raltitrexed and oxaliplatin chemotherapy: report of two patients experiencing this rare, potentially lethal gastrointestinal adverse event.	Wenzel C, Urbauer E, Schwarz C, Funk G, Oehler L, Kornek GV, Scheithauer W.	Anticancer Drugs. 2006 Aug;17(7):865-8.	**Excluded,** case report with two patients;
62	Decreasing dosage of irinotecan, 5-flurouracil (5-FU) and leucovorin (LV) in the treatment of advanced and/or metastatic colorectal cancer: a phase II study.	Huang JS, Yen CL, You YT, Wang CH, Lan YJ, Lai CH, Chueh TC, Liaw CC	Chang Gung Med J. 2006 May-Jun;29(3):297-305.	**Excluded,** Taiwanese study;
63	Trends in recommendations for myelosuppressive chemotherapy for the treatment of solid tumors.	Smith RE.	J Natl Compr Canc Netw. 2006 Aug;4(7):649-58.	**Excluded,** no original study;
64	Phase III trial comparing 4-day chronomodulated therapy versus 2-day conventional delivery of fluorouracil, leucovorin, and oxaliplatin as first-line chemotherapy of metastatic colorectal cancer: the European Organisation for Research and Treatment of Cancer Chronotherapy Group.	Giacchetti S, Bjarnason G, Garufi C, Genet D, Iacobelli S, Tampellini M, Smaaland R, Focan C, Coudert B, Humblet Y, Canon JL, Adenis A, Lo Re G, Carvalho C, Schueller J, Anciaux N, Lentz MA, Baron B, Gorlia T, Lévi F; European Organisation for Research and Treatment of Cancer Chronotherapy Group.	J Clin Oncol. 2006 Aug 1;24(22):3562-9.	**Excluded,** information required not included;

65	Randomised study of sequential versus combination chemotherapy with capecitabine, irinotecan and oxaliplatin in advanced colorectal cancer, an interim safety analysis. A Dutch Colorectal Cancer Group (DCCG) phase III study.	Koopman M, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FL, de Jong RS, Rodenburg CJ, Vreugdenhil G, Akkermans-Vogelaar JM, Punt CJ.	Ann Oncol. 2006 Oct;17(10):1523-8.	**Excluded,** information required not included;
66	Randomized controlled trial of reduced-dose bolus fluorouracil plus leucovorin and irinotecan or infused fluorouracil plus leucovorin and oxaliplatin in patients with previously untreated metastatic colorectal cancer: a North American Intergroup Trial.	Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts S.	J Clin Oncol. 2006 Jul 20;24(21):3347-53.	**Excluded,** information required not included;
67	XELOX (capecitabine plus oxaliplatin) as first-line treatment for elderly patients over 70 years of age with advanced colorectal cancer.	Feliu J, Salud A, Escudero P, Lopez-Gómez L, Bolaños M, Galán A, Vicent JM, Yubero A, Losa F, De Castro J, de Mon MA, Casado E, González-Barón M.	Br J Cancer. 2006 Apr 10;94(7):969-75.	**Excluded,** information required not included;
68	The bottom line: outcomes after conservation treatment in anal cancer.	Dwyer MK, Gebski VJ, Jayamohan J.	Australas Radiol. 2006 Feb;50(1):46-51.	**Excluded,** information required not included;
69	Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer.	Chau I, Brown G, Cunningham D, Tait D, Wotherspoon A, Norman AR, Tebbutt N, Hill M, Ross PJ, Massey A, Oates J.	J Clin Oncol. 2006 Feb 1;24(4):668-74.	**Excluded,** information required not included;

1.5 Impact on side effects by dose reduction

1.5.1 Flowchart of the structured literature search



Toffoli et al. The role of UGT1A1*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. J Clin Oncol. 2006 Jul 1;24(19):3061-8.

List of identified studies.

(((((toxicity[Title/Abstract] OR toxic[Title/Abstract])) AND (reduction[Title/Abstract] OR reduce[Title/Abstract] OR reduced[Title/Abstract])) AND (CRC[Title/Abstract] OR MCRC[Title/Abstract] OR Colorectal Cancer[Title/Abstract] OR Colon Cancer[Title/Abstract])) AND irinotecan[Title/Abstract]) AND ("2006/01/01"[Date - Publication] : "3000"[Date - Publication]); Filters activated: English, German; 28.05.2013; 69 studies;				
	Title	Author	Journal	Ex- or included
1	FOLFOXIRI in combination with panitumumab as first-line treatment in quadruple wild-type (KRAS, NRAS, HRAS, BRAF) metastatic colorectal cancer patients: a phase II trial by the Gruppo Oncologico Nord Ovest (GONO).	Fornaro L, Lonardi S, Masi G, Loupakis F, Bergamo F, Salvatore L, Cremolini C, Schirripa M, Vivaldi C, Aprile G, Zaniboni A, Bracarda S, Fontanini G, Sensi E, Lupi C, Morvillo M, Zagonel V, Falcone A.	Ann Oncol. 2013 Aug;24(8):2062-7. doi: 10.1093/annonc/mdt165. Epub 2013 May 10.	**Excluded** due to different study topic;
2	Therapeutic targeting of CPT-11 induced diarrhea: a case for prophylaxis.	Swami U, Goel S, Mani S.	Curr Drug Targets. 2013 Jun;14(7):777-97. Review.	**Excluded** due to different study topic;
3	Association of UGT1A1*28 polymorphisms with irinotecan-induced toxicities in colorectal cancer: a meta-analysis in Caucasians.	Liu X, Cheng D, Kuang Q, Liu G, Xu W.	Pharmacogenomics J. 2014 Apr;14(2):120-9. doi: 10.1038/tpj.2013.10. Epub 2013 Mar 26.	**Excluded** due to different study topic;
4	Geriatric factors predict chemotherapy feasibility: ancillary results of FFCD 2001-02 phase III study in first-line chemotherapy for metastatic colorectal cancer in elderly patients.	Aparicio T, Jouve JL, Teillet L, Gargot D, Subtil F, Le Brun-Ly V, Cretin J, Locher C, Bouché O, Breysacher G, Charneau J, Seitz JF, Gasmi M, Stefani L, Ramdani M, Lecomte T, Mitry E.	J Clin Oncol. 2013 Apr 10;31(11):1464-70. doi: 10.1200/JCO.2012.42.9894. Epub 2013 Mar 4.	**Excluded** due to different study topic;
5	UGT1A1 predicts outcome in colorectal cancer treated with irinotecan and fluorouracil.	Wang Y, Shen L, Xu N, Wang JW, Jiao SC, Liu ZY, Xu JM.	World J Gastroenterol. 2012 Dec 7;18(45):6635-44. doi: 10.3748/wjg.v18.i45.6635.	**Excluded,** Chinese study.

6	Feasibility, safety and pharmacokinetic study of hepatic administration of drug-eluting beads loaded with irinotecan (DEBIRI) followed by intravenous administration of irinotecan in a porcine model.	Lewis AL, Holden RR, Chung ST, Czuczman P, Kuchel T, Finnie J, Porter S, Foster D.	J Mater Sci Mater Med. 2013 Jan;24(1):115-27. doi: 10.1007/s10856-012-4768-2. Epub 2012 Sep 27.	**Excluded** due to different study topic;
7	Aspirin as adjuvant therapy for colorectal cancer--reinterpreting paradigms.	Chia WK, Ali R, Toh HC.	Nat Rev Clin Oncol. 2012 Oct;9(10):561-70. doi: 10.1038/nrclinonc.2012.137. Epub 2012 Aug 21. Review.	**Excluded** due to different study topic;
8	Irinotecan (CPT-11) chemotherapy alters intestinal microbiota in tumour bearing rats.	Lin XB, Dieleman LA, Ketabi A, Bibova I, Sawyer MB, Xue H, Field CJ, Baracos VE, Gänzle MG.	PLoS One. 2012;7(7):e39764. doi: 10.1371/journal.pone.0039764. Epub 2012 Jul 26.	**Excluded** due to different study topic;
9	Outcome of first line systemic treatment in elderly compared to younger patients with metastatic colorectal cancer: a retrospective analysis of the CAIRO and CAIRO2 studies of the Dutch Colorectal Cancer Group (DCCG).	Venderbosch S, Doornebal J, Teerenstra S, Lemmens W, Punt CJ, Koopman M.	Acta Oncol. 2012 Sep;51(7):831-9. doi: 10.3109/0284186X.2012.699193. Epub 2012 Jul 16.	**Excluded** due to different study topic;
10	Theranostic nanoparticles based on PEGylated hyaluronic acid for the diagnosis, therapy and monitoring of colon cancer.	Choi KY, Jeon EJ, Yoon HY, Lee BS, Na JH, Min KH, Kim SY, Myung SJ, Lee S, Chen X, Kwon IC, Choi K, Jeong SY, Kim K, Park JH.	Biomaterials. 2012 Sep;33(26):6186-93. doi: 10.1016/j.biomaterials.2012.05.029. Epub 2012 Jun 9.	**Excluded** due to different study topic;

11	The value of genetic polymorphisms to predict toxicity in metastatic colorectal patients with irinotecan-based regimens.	Lamas MJ, Duran G, Balboa E, Bernardez B, Candamio S, Vidal Y, Mosquera A, Giraldez JM, Lopez R, Carracedo A, Barros F.	Cancer Chemother Pharmacol. 2012 Jun;69(6):1591-9. doi: 10.1007/s00280-012-1866-2. Epub 2012 Apr 26.	**Excluded,** required information not included;
12	A phase II study of capecitabine, irinotecan, and bevacizumab in patients with previously untreated metastatic colorectal cancer.	Renouf DJ, Welch S, Moore MJ, Krzyzanowska MK, Knox J, Feld R, Liu G, MacKay H, Petronis J, Wang L, Chen E.	Cancer Chemother Pharmacol. 2012 May;69(5):1339-44. doi: 10.1007/s00280-012-1843-9. Epub 2012 Feb 15.	**Excluded d**ue to different study topic;
13	Randomised phase-II trial of CAPIRI (capecitabine, irinotecan) plus bevacizumab vs FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) plus bevacizumab as first-line treatment of patients with unresectable/metastatic colorectal cancer (mCRC).	Souglakos J, Ziras N, Kakolyris S, Boukovinas I, Kentepozidis N, Makrantonakis P, Xynogalos S, Christophyllakis Ch, Kouroussis Ch, Vamvakas L, Georgoulias V, Polyzos A.	Br J Cancer. 2012 Jan 31;106(3):453-9. doi: 10.1038/bjc.2011.594. Epub 2012 Jan 12.	**Excluded**, wrong study population (wrong chemotherapy regimen – patients were treated with 250mgm-2 Irinotecan ("reduced" dose FOLFIRI-scheme 180mgm-2). A reduced dose compared to FOLFIRI is missing);
14	Use of bevacizumab in metastatic colorectal cancer: report from the Mexican opinion and analysis forum on colorectal cancer treatment with bevacizumab (September 2009).	Zinser-Sierra JW, Rodríguez-Ramírez S, Villalobos-Valencia R, Ramírez-Márquez M.	Drugs R D. 2011;11(2):101-11. doi: 10.2165/11590440-000000000-00000. Review.	**Excluded** due to different study topic;
15	[Effective cetuximab monotherapy for a case of recurrence rectal cancer after multiple previous chemotherapy treatment (FOLFOX, FOLFIRI)].	Tomita M, Kuboi K, Kameyama N, Mitsuhashi H, Matsumoto N, Hasegawa Y, Sekimoto Y.	Gan To Kagaku Ryoho. 2011 Jan;38(1):121-4. Japanese.	**Excluded,** in different language.

16	Regimen selection for first-line FOLFIRI and FOLFOX based on UGT1A1 genotype and physical background is feasible in Japanese patients with advanced colorectal cancer.	Ishida H, Fujita K, Akiyama Y, Sunakawa Y, Yamashita K, Mizuno K, Miwa K, Kawara K, Ichikawa W, Ando Y, Saji S, Sasaki Y.	Jpn J Clin Oncol. 2011 May;41(5):617-23. doi: 10.1093/jjco/hyr010. Epub 2011 Feb 9.	**Excluded,** Japanese study;
17	Prospective phase II study of FOLFIRI for mCRC in Japan, including the analysis of UGT1A1 28/6 polymorphisms.	Okuyama Y, Hazama S, Nozawa H, Kobayashi M, Takahashi K, Fujikawa K, Kato T, Nagata N, Kimura H, Oba K, Sakamoto J, Mishima H.	Jpn J Clin Oncol. 2011 Apr;41(4):477-82. doi: 10.1093/jjco/hyr001. Epub 2011 Feb 7.	**Excluded,** Japanese study;
18	Chemotherapy of metastatic colorectal cancer.	[No authors listed]	Prescrire Int. 2010 Oct;19(109):219-24. Review.	**Excluded** due to different study topic;
19	Phase I/II study of FOLFIRI in Japanese patients with advanced colorectal cancer.	Yamashita K, Nagashima F, Fujita K, Yamamoto W, Endo H, Miya T, Narabayashi M, Kawara K, Akiyama Y, Ando Y, Ando M, Sasaki Y.	Jpn J Clin Oncol. 2011 Feb;41(2):204-9. doi: 10.1093/jjco/hyq197. Epub 2010 Oct 21.	**Excluded,** Japanese study;
20	Efficacy of the monoclonal antibody EGFR inhibitors for the treatment of metastatic colorectal cancer.	Fakih M, Wong R.	Curr Oncol. 2010 Jul;17 Suppl 1:S3-17.	**Excluded** due to different study topic;
21	Dosing considerations for capecitabine-irinotecan regimens in the treatment of metastatic and/or locally advanced colorectal cancer.	Cartwright T, McCollum D, Boehm KA.	Am J Clin Oncol. 2010 Jun;33(3):307-13. doi: 10.1097/COC.0b013e3181d27361. Review.	**Excluded** due to different study topic;
22	Hyaluronan-Irinotecan improves progression-free survival in 5-fluorouracil refractory patients with metastatic colorectal cancer: a randomized phase II trial.	Gibbs P, Clingan PR, Ganju V, Strickland AH, Wong SS, Tebbutt NC, Underhill CR, Fox RM, Clavant SP, Leung J, Pho M, Brown TJ.	Cancer Chemother Pharmacol. 2011 Jan;67(1):153-63. doi: 10.1007/s00280-010-1303-3. Epub 2010 Mar 24.	**Excluded** due to different study topic;

23	Treatment-related toxicity and supportive care in metastatic colorectal cancer.	Zafar SY, Marcello JE, Wheeler JL, Rowe KL, Morse MA, Herndon JE 2nd, Abernethy AP.	J Support Oncol. 2010 Jan-Feb;8(1):15-20.	**Excluded,** no original study
24	Successful long-term management of a patient with late-stage metastatic colorectal cancer treated with panitumumab.	Seront E, Marot L, Coche E, Gala JL, Sempoux C, Humblet Y.	Cancer Treat Rev. 2010 Feb;36 Suppl 1:S11-4. doi: 10.1016/S0305-7372(10)70002-5.	**Excluded,** case report
25	Association of molecular markers with toxicity outcomes in a randomized trial of chemotherapy for advanced colorectal cancer: the FOCUS trial.	Braun MS, Richman SD, Thompson L, Daly CL, Meade AM, Adlard JW, Allan JM, Parmar MK, Quirke P, Seymour MT.	J Clin Oncol. 2009 Nov 20;27(33):5519-28. doi: 10.1200/JCO.2008.21.6283. Epub 2009 Oct 26.	**Excluded** due to different study topic;
26	Capecitabine in combination with irinotecan (XELIRI), administered as a 2-weekly schedule, as first-line chemotherapy for patients with metastatic colorectal cancer: a phase II study of the Spanish GOTI group.	Garcia-Alfonso P, Muñoz-Martin A, Mendez-Ureña M, Quiben-Pereira R, Gonzalez-Flores E, Perez-Manga G.	Br J Cancer. 2009 Oct 6;101(7):1039-43. doi: 10.1038/sj.bjc.6605261. Epub 2009 Sep 8.	**Excluded,** required information not included;
27	Metronomic 5-fluorouracil, oxaliplatin and irinotecan in colorectal cancer.	Fioravanti A, Canu B, Alì G, Orlandi P, Allegrini G, Di Desidero T, Emmenegger U, Fontanini G, Danesi R, Del Tacca M, Falcone A, Bocci G.	Eur J Pharmacol. 2009 Oct 1;619(1-3):8-14. doi: 10.1016/j.ejphar.2009.08.020. Epub 2009 Aug 18.	**Excluded** due to different study topic;
28	Pharmacogenetics of solid tumors: directed therapy in breast, lung, and colorectal cancer: a paper from the 2008 william beaumont hospital symposium on molecular pathology.	Snozek CL, O'Kane DJ, Algeciras-Schimnich A.	J Mol Diagn. 2009 Sep;11(5):381-9. doi: 10.2353/jmoldx.2009.090003. Epub 2009 Jul 30. Review.	**Excluded** due to different study topic;

29	Cost effectiveness of pharmacogenetic testing for uridine diphosphate glucuronosyltransferase 1A1 before irinotecan administration for metastatic colorectal cancer.	Gold HT, Hall MJ, Blinder V, Schackman BR.	Cancer. 2009 Sep 1;115(17):3858-67. doi: 10.1002/cncr.24428.	**Excluded,** no original study
30	Pharmacogenetics in chemotherapy of colorectal cancer.	Henriette Tanja L, Guchelaar HJ, Gelderblom H.	Best Pract Res Clin Gastroenterol. 2009;23(2):257-73. doi: 10.1016/j.bpg.2009.02.011. Review.	**Excluded,** no original study
31	TACE of liver metastases from colorectal cancer adopting irinotecan-eluting beads: beneficial effect of palliative intra-arterial lidocaine and post-procedure supportive therapy on the control of side effects.	Fiorentini G, Aliberti C, Benea G, Montagnani F, Mambrini A, Ballardini PL, Cantore M.	Hepatogastroenterology. 2008 Nov-Dec;55(88):2077-82.	**Excluded** due to different study topic;
32	Single and combined supplementation of glutamine and n-3 polyunsaturated fatty acids on host tolerance and tumour response to 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin (CPT-11)/5-fluorouracil chemotherapy in rats bearing Ward colon tumour.	Xue H, Le Roy S, Sawyer MB, Field CJ, Dieleman LA, Baracos VE.	Br J Nutr. 2009 Aug;102(3):434-42. doi: 10.1017/S0007114508199482. Epub 2009 Mar 2.	**Excluded** due to different study topic;
33	Can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? An evidence-based review.	Palomaki GE, Bradley LA, Douglas MP, Kolor K, Dotson WD.	Genet Med. 2009 Jan;11(1):21-34. doi: 10.1097/GIM.0b013e31818efd77. Review.	**Excluded,** no original study
34	A pilot human evaluation of a formulation of irinotecan and hyaluronic acid in 5-fluorouracil-refractory metastatic colorectal cancer patients.	Gibbs P, Brown TJ, Ng R, Jennens R, Cinc E, Pho M, Michael M, Fox RM.	Chemotherapy. 2009;55(1):49-59. doi: 10.1159/000180339. Epub 2008 Dec 8.	**Excluded** due to different study topic;

35	Pharmacogenomics of tamoxifen and irinotecan therapies.	Algeciras-Schimnich A, O'Kane DJ, Snozek CL.	Clin Lab Med. 2008 Dec;28(4):553-67. doi: 10.1016/j.cll.2008.05.004. Review.	**Excluded** due to different study topic;
36	Clinical pharmacokinetics of irinotecan-based chemotherapy in colorectal cancer patients.	Di Paolo A, Bocci G, Danesi R, Del Tacca M.	Curr Clin Pharmacol. 2006 Sep;1(3):311-23. Review.	**Excluded** due to different study topic;
37	Metastatic rectal cancer responding to third-line therapy employing bevacizumab after failure of oxaliplatin and irinotecan: case report.	Shitara K, Munakata M, Muto O, Sakata Y.	Jpn J Clin Oncol. 2008 Jul;38(7):493-6. doi: 10.1093/jjco/hyn046. Epub 2008 Jun 20.	**Excluded** due to different study topic;
38	Targeted therapy of cancer: new roles for pathologists in colorectal cancer.	Hamilton SR.	Mod Pathol. 2008 May;21 Suppl 2:S23-30. doi: 10.1038/modpathol.2008.14. Review.	**Excluded** due to different study topic;
39	[Polymorphisms of UGT1A gene and irinotecan toxicity in Chinese colorectal cancer patients].	Wang Y, Xu JM, Shen L, Xu N, Wang JW, Jiao SC, Zhang JS, Song ST, Li J, Bao HY, Yang L, Li F.	Zhonghua Zhong Liu Za Zhi. 2007 Dec;29(12):913-6. Chinese.	**Excluded,** different language;
40	Safety of irinotecan and infusional fluorouracil/leucovorin (FOLFIRI) in Japan: a retrospective review of 48 patients with metastatic colorectal cancer.	Fuse N, Doi T, Ohtsu A, Yano T, Hamamoto Y, Minashi K, Tahara M, Muto M, Asaka M, Yoshida S.	Int J Clin Oncol. 2008 Apr;13(2):144-9. doi: 10.1007/s10147-007-0737-z. Epub 2008 May 8.	**Excluded,** Japanese study;
41	The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation.	Hind D, Tappenden P, Tumur I, Eggington S, Sutcliffe P, Ryan A.	Health Technol Assess. 2008 May;12(15):iii-ix, xi-162. Review.	**Excluded** due to different study topic;

42	Changes of immunological parameters reflect quality of life-related toxicity during chemotherapy in patients with advanced colorectal cancer.	Yoshimatsu K, Kuhara K, Itagaki H, Aizawa M, Yokomizo H, Fujimoto T, Otani T, Osawa G, Kobayashi R, Ogawa K.	Anticancer Res. 2008 Jan-Feb;28(1B):373-8.	**Excluded** due to different study topic;
43	Gilbert's Syndrome and irinotecan toxicity: combination with UDP-glucuronosyltransferase 1A7 variants increases risk.	Lankisch TO, Schulz C, Zwingers T, Erichsen TJ, Manns MP, Heinemann V, Strassburg CP.	Cancer Epidemiol Biomarkers Prev. 2008 Mar;17(3):695-701. doi: 10.1158/1055-9965.EPI-07-2517.	**Excluded** due to different study topic;
44	Panitumumab: human monoclonal antibody against epidermal growth factor receptors for the treatment of metastatic colorectal cancer.	Wu M, Rivkin A, Pham T.	Clin Ther. 2008 Jan;30(1):14-30. doi: 10.1016/j.clinthera.2008.01.014. Review.	**Excluded** due to different study topic;
45	UGT1A1*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma.	Liu CY, Chen PM, Chiou TJ, Liu JH, Lin JK, Lin TC, Chen WS, Jiang JK, Wang HS, Wang WS.	Cancer. 2008 May 1;112(9):1932-40. doi: 10.1002/cncr.23370.	**Excluded,** Chinese study;
46	Chronomodulated capecitabine in combination with short-time oxaliplatin: a Nordic phase II study of second-line therapy in patients with metastatic colorectal cancer after failure to irinotecan and 5-flourouracil.	Qvortrup C, Yilmaz M, Ogreid D, Berglund A, Balteskard L, Ploen J, Fokstuen T, Starkhammar H, Sørbye H, Tveit K, Pfeiffer P.	Ann Oncol. 2008 Jun;19(6):1154-9. doi: 10.1093/annonc/mdn002. Epub 2008 Feb 14.	**Excluded** due to different study topic;
47	Vaccination of colorectal cancer patients with TroVax given alongside chemotherapy (5-fluorouracil, leukovorin and irinotecan) is safe and induces potent immune responses.	Harrop R, Drury N, Shingler W, Chikoti P, Redchenko I, Carroll MW, Kingsman SM, Naylor S, Griffiths R, Steven N, Hawkins RE.	Cancer Immunol Immunother. 2008 Jul;57(7):977-86.	**Excluded** due to different study topic;
48	A novel camptothecin analog with enhanced antitumor activity.	Yount G, Yang Y, Wong B, Wang HJ, Yang LX.	Anticancer Res. 2007 Sep-Oct;27(5A):3173-8.	**Excluded** due to different study topic;

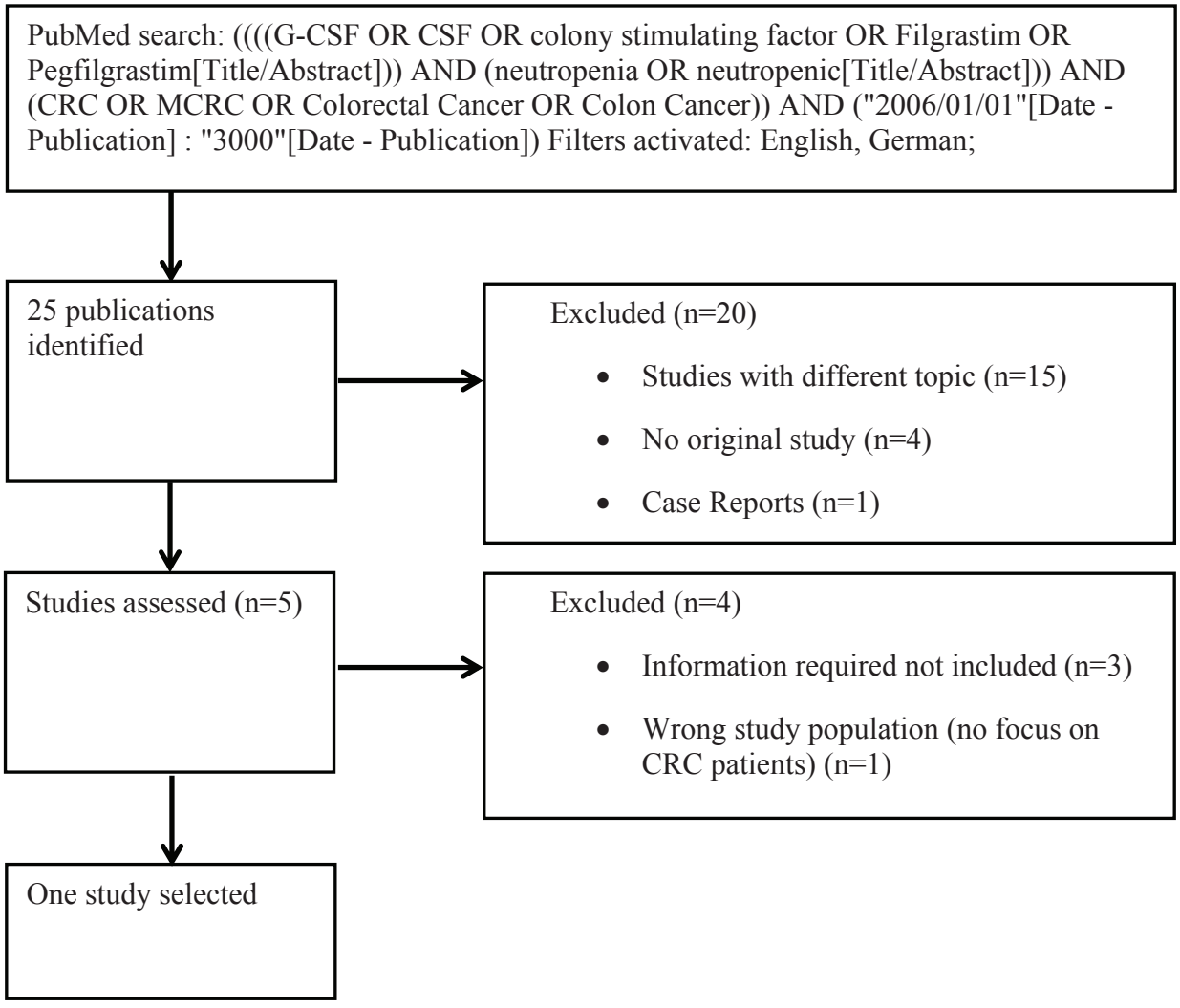
49	Pharmacodynamic study of the Saltz regimen for metastatic colorectal cancer in a hemodialyzed patient.	Akiyama S, Nakayama H, Takami H, Gotoh H, Gotoh Y.	Chemotherapy. 2007;53(6):418-21. Epub 2007 Oct 19.	**Excluded** due to different study topic;
50	Tritherapy with fluorouracil/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX): a phase II study in colorectal cancer patients with non-resectable liver metastases.	Ychou M, Viret F, Kramar A, Desseigne F, Mitry E, Guimbaud R, Delpero JR, Rivoire M, Quénet F, Portier G, Nordlinger B.	Cancer Chemother Pharmacol. 2008 Jul;62(2):195-201. Epub 2007 Sep 28.	**Excluded** due to different study topic;
51	Oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX-4) as salvage chemotherapy in patients with pretreated colorectal cancer.	Shitara K, Munakata M, Muto O, Kasai M, Okada R, Mitobe S, Sakata Y.	Gan To Kagaku Ryoho. 2007 Jul;34(7):1079-84.	**Excluded,** Japanese study;
52	Cost considerations in the treatment of colorectal cancer.	Jansman FG, Postma MJ, Brouwers JR.	Pharmacoeconomics. 2007;25(7):537-62. Review.	**Excluded** due to different study topic;
53	Adjuvant therapy for stage II and III colorectal cancer.	de Gramont A, Tournigand C, André T, Larsen AK, Louvet C.	Semin Oncol. 2007 Apr;34(2 Suppl 1):S37-40.	**Excluded** due to different study topic;
54	Planned treatment interruptions and chemotherapy-free intervals in the treatment of metastatic colorectal cancer: time to start stopping?	Saltz L.	Semin Oncol. 2006 Dec;33(6 Suppl 11):S28-32. Review.	**Excluded** due to different study topic;
55	Pharmacogenetics and irinotecan therapy.	Hahn KK, Wolff JJ, Kolesar JM.	Am J Health Syst Pharm. 2006 Nov 15;63(22):2211-7. Review.	**Excluded,** no original study
56	Single-agent irinotecan as second-line weekly chemotherapy in elderly patients with advanced colorectal cancer.	Rosati G, Cordio S.	Tumori. 2006 Jul-Aug;92(4):290-4.	**Excluded** due to different study topic;

57	Biweekly oxaliplatin plus irinotecan and folinic acid-modulated 5-fluorouracil: a phase II study in pretreated patients with metastatic colorectal cancer.	Comella P, Massidda B, Palmeri S, Putzu C, De Rosa V, Izzo F, Fiore F, Casaretti R, Sandomenico C.	Anticancer Drugs. 2006 Sep;17(8):985-92.	**Excluded** due to different study topic;
58	A phase II study of high-dose bevacizumab in combination with irinotecan, 5-fluorouracil, leucovorin, as initial therapy for advanced colorectal cancer: results from the Eastern Cooperative Oncology Group study E2200.	Giantonio BJ, Levy DE, O'dwyer PJ, Meropol NJ, Catalano PJ, Benson AB 3rd; Eastern Cooperative Oncology Group.	Ann Oncol. 2006 Sep;17(9):1399-403. Epub 2006 Jul 27.	**Excluded,** wrong study population: patients were treated with 125mgm-2 Irinotecan (reduced dose 100mgm-2). Usually FOLFIRI = 180mgm-2.
59	Randomized controlled trial of reduced-dose bolus fluorouracil plus leucovorin and irinotecan or infused fluorouracil plus leucovorin and oxaliplatin in patients with previously untreated metastatic colorectal cancer: a North American Intergroup Trial.	Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts S.	J Clin Oncol. 2006 Jul 20;24(21):3347-53.	**Excluded** due to different study topic;
60	The role of UGT1A1*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer.	Toffoli G, Cecchin E, Corona G, Russo A, Buonadonna A, D'Andrea M, Pasetto LM, Pessa S, Errante D, De Pangher V, Giusto M, Medici M, Gaion F, Sandri P, Galligioni E, Bonura S, Boccalon M, Biason P, Frustaci S.	J Clin Oncol. 2006 Jul 1;24(19):3061-8.	**Included;**
61	Inhibition of poly(ADP-ribose) polymerase prevents irinotecan-induced intestinal damage and enhances irinotecan/temozolomide efficacy against colon carcinoma.	Tentori L, Leonetti C, Scarsella M, Muzi A, Mazzon E, Vergati M, Forini O, Lapidus R, Xu W, Dorio AS, Zhang J, Cuzzocrea S, Graziani G.	FASEB J. 2006 Aug;20(10):1709-11. Epub 2006 Jun 29.	**Excluded** due to different study topic;

62	Irinotecan in combination with thalidomide in patients with advanced solid tumors: a clinical study with pharmacodynamic and pharmacokinetic evaluation.	Allegrini G, Di Paolo A, Cerri E, Cupini S, Amatori F, Masi G, Danesi R, Marcucci L, Bocci G, Del Tacca M, Falcone A.	Cancer Chemother Pharmacol. 2006 Nov;58(5):585-93. Epub 2006 May 6.	**Excluded** due to different study topic;
63	Individualizing chemotherapeutic treatment of colorectal cancer.	Crews KR.	Am J Health Syst Pharm. 2006 May 1;63(9 Suppl 2):S12-7.	**Excluded** due to different study topic;
64	Phase I/pilot study of SU5416 (semaxinib) in combination with irinotecan/bolus 5-FU/LV (IFL) in patients with metastatic colorectal cancer.	Lockhart AC, Cropp GF, Berlin JD, Donnelly E, Schumaker RD, Schaaf LJ, Hande KR, Fleischer AC, Hannah AL, Rothenberg ML.	Am J Clin Oncol. 2006 Apr;29(2):109-15.	**Excluded** due to different study topic;
65	A phase I and pharmacokinetic study of fixed-dose selenomethionine and irinotecan in solid tumors.	Fakih MG, Pendyala L, Smith PF, Creaven PJ, Reid ME, Badmaev V, Azrak RG, Prey JD, Lawrence D, Rustum YM.	Clin Cancer Res. 2006 Feb 15;12(4):1237-44.	**Excluded** due to different study topic;
66	[Reflexion on a good strategy of use of oxaliplatine with 5-fluorouracil and its derivatives in patients with advanced colorectal cancer].	Tournigand C, de Gramont A.	Bull Cancer. 2006 Feb 1;93 Suppl 1:S11-5. French.	**Excluded,** different language.
67	A Phase I study of escalating doses of the tyrosine kinase inhibitor semaxanib (SU5416) in combination with irinotecan in patients with advanced colorectal carcinoma.	Hoff PM, Wolff RA, Bogaard K, Waldrum S, Abbruzzese JL.	Jpn J Clin Oncol. 2006 Feb;36(2):100-3. Epub 2006 Jan 31.	**Excluded** due to different study topic;
68	Adjuvant therapy for colon cancer 2005: new options in the twenty-first century.	Leichman CG.	Surg Oncol Clin N Am. 2006 Jan;15(1):159-73. Review.	**Excluded** due to different study topic;
69	A pilot study on the safety of combining chrysin, a non-absorbable inducer of UGT1A1, and irinotecan (CPT-11) to treat metastatic colorectal cancer.	Tobin PJ, Beale P, Noney L, Liddell S, Rivory LP, Clarke S.	Cancer Chemother Pharmacol. 2006 Feb;57(3):309-16. Epub 2005 Jul 8.	**Excluded** due to different study topic;

1.6 Impact on side effects by growth factors

1.6.1 Flowchart of the structured literature search



Hecht et al. A randomized, placebo-controlled phase ii study evaluating the reduction of neutropenia and febrile neutropenia in patients with colorectal cancer receiving pegfilgrastim with every-2-week chemotherapy. Clin Colorectal Cancer. 2010 Apr;9(2):95-101.

1.6.2 List of identified studies.

((((G-CSF OR CSF OR colony stimulating factor OR Filgrastim OR Pegfilgrastim[Title/Abstract])) AND (neutropenia OR neutropenic[Title/Abstract])) AND (CRC OR MCRC OR Colorectal Cancer OR Colon Cancer)) AND ("2006/01/01"[Date - Publication] : "3000"[Date - Publication]) Filters activated: English, German; 21.05.2013; 25 studies;				
	Title	Author	Journal	Ex- or included
1	GM-CSF enhances tumor invasion by elevated MMP-2, -9, and -26 expression.	Gutschalk CM, Yanamandra AK, Linde N, Meides A, Depner S, Mueller MM.	Cancer Med. 2013 Apr;2(2):117-29.	**Excluded** due to different study topic;
2	Pegfilgrastim prophylaxis is associated with a lower risk of hospitalization of cancer patients than filgrastim prophylaxis: a retrospective United States claims analysis of granulocyte colony-stimulating factors (G-CSF).	Naeim A, Henk HJ, Becker L, Chia V, Badre S, Li X, Deeter R.	BMC Cancer. 2013 Jan 8;13:11.	**Excluded** due to different study topic;
3	Agranulocytosis from levamisole-adulterated cocaine.	Caldwell KB, Graham OZ, Arnold JJ.	J Am Board Fam Med. 2012 Jul;25(4):528-30.	**Excluded,** case report;
4	Chemotherapy patients with C. difficile colitis have outcomes similar to immunocompetent C. difficile patients.	Stewart DB, Yacoub E, Zhu J.	J Gastrointest Surg. 2012 Aug;16(8):1566-72.	**Excluded** due to different study topic;
5	Safety, pharmacokinetics, and activity of EZN-2208, a novel conjugate of polyethylene glycol and SN38, in patients with advanced malignancies.	Kurzrock R, Goel S, Wheler J, Hong D, Fu S, Rezai K, Morgan-Linnell SK, Urien S, Mani S, Chaudhary I, Ghalib MH, Buchbinder A, Lokiec F, Mulcahy M.	Cancer. 2012 Dec 15;118(24):6144-51.	**Excluded** due to different study topic;
6	The value of genetic polymorphisms to predict toxicity in metastatic colorectal patients with irinotecan-based regimens.	Lamas MJ, Duran G, Balboa E, Bernardez B, Candamio S, Vidal Y, Mosquera A, Giraldez JM, Lopez R, Carracedo A, Barros F.	Cancer Chemother Pharmacol. 2012 Jun;69(6):1591-9.	**Excluded,** information required not included;

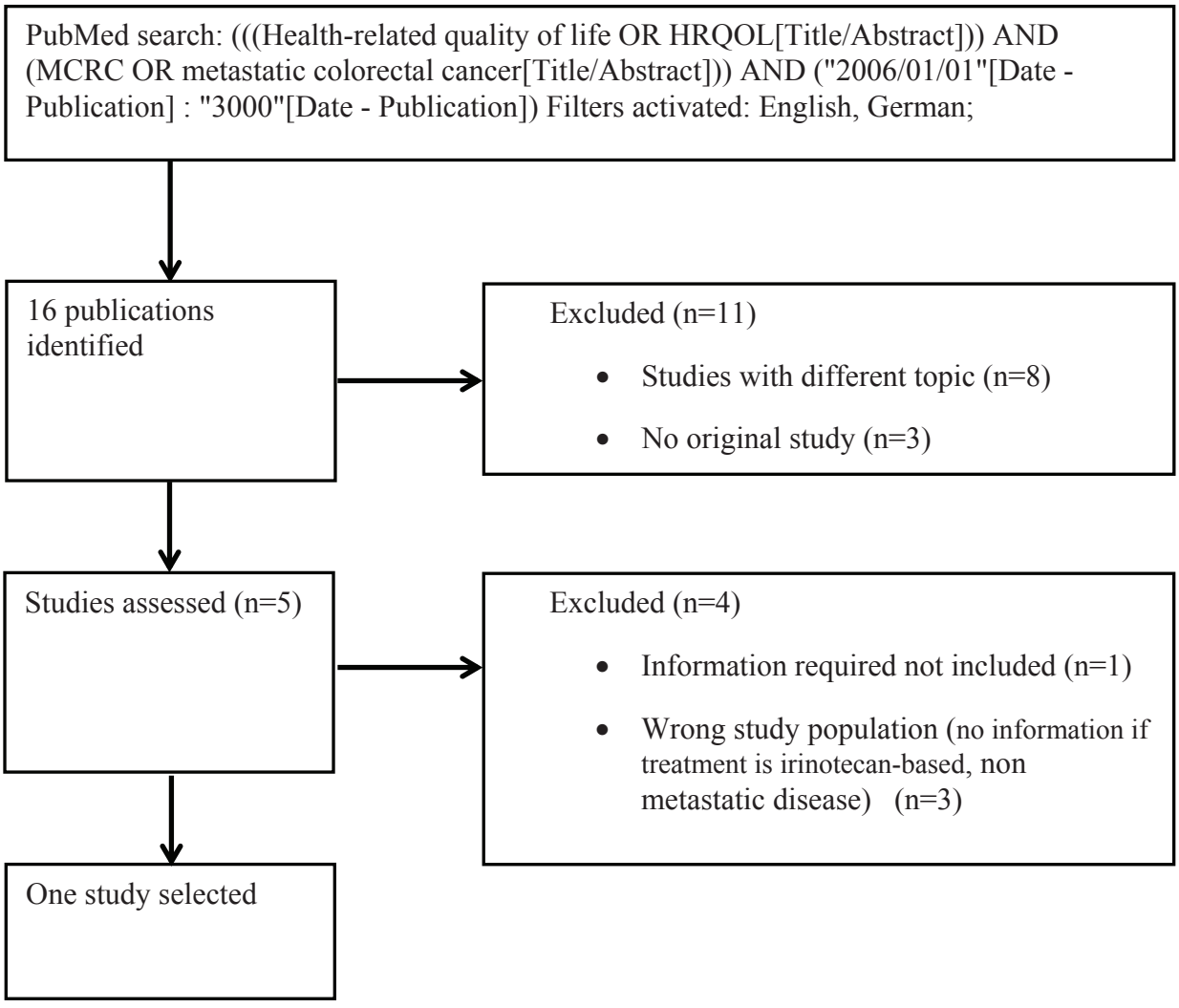
7	Colony-stimulating factor use and impact on febrile neutropenia among patients with newly diagnosed breast, colorectal, or non-small cell lung cancer who were receiving chemotherapy.	McCune JS, Sullivan SD, Blough DK, Clarke L, McDermott C, Malin J, Ramsey S.	Pharmacotherapy. 2012 Jan;32(1):7-19.	**Excluded,** information required not included;
8	Use of colony-stimulating factors with chemotherapy: opportunities for cost savings and improved outcomes.	Potosky AL, Malin JL, Kim B, Chrischilles EA, Makgoeng SB, Howlader N, Weeks JC.	J Natl Cancer Inst. 2011 Jun 22;103(12):979-82.	**Excluded** due to different study topic;
9	A pilot study evaluating a novel regimen comprised of carboplatin, paclitaxel, and bevacizumab for advanced-stage ovarian carcinoma.	Brown JV 3rd, Micha JP, Rettenmaier MA, Abaid LN, Lopez KL, Goldstein BH.	Int J Gynecol Cancer. 2010 Oct;20(7):1132-6.	**Excluded** due to different study topic;
10	Health care use and primary prophylaxis with colony-stimulating factors.	Sullivan SD, Ramsey SD, Blough DK, McDermott CL, Clarke L, McCune JS.	Value Health. 2011 Mar-Apr;14(2):247-52.	**Excluded,** wrong patient population (no focus on CRC);
11	Colony-stimulating factor prescribing patterns in patients receiving chemotherapy for cancer.	Ramsey SD, McCune JS, Blough DK, McDermott CL, Clarke L, Malin JL, Sullivan SD.	Am J Manag Care. 2010 Sep;16(9):678-86.	**Excluded** due to different study topic;
12	Trends in G-CSF use in 990 patients after EORTC and ASCO guidelines.	Falandry C, Campone M, Cartron G, Guerin D, Freyer G.	Eur J Cancer. 2010 Sep;46(13):2389-98.	**Excluded** due to different study topic;
13	A randomized, placebo-controlled phase ii study evaluating the reduction of neutropenia and febrile neutropenia in patients with colorectal cancer receiving pegfilgrastim with every-2-week chemotherapy.	Hecht JR, Pillai M, Gollard R, Heim W, Swan F, Patel R, Dreiling L, Mo M, Malik I.	Clin Colorectal Cancer. 2010 Apr;9(2):95-101.	**Included:** ca. 120 patients (FOLFIRI and FOIL), plus Placebo or Pegfilgrastim, OR=0,19 (FOLFIRI), OR=0,35 (FOIL) for severe neutropenia Pegfilgrastim versus Placebo

14	Development and validation of a prediction model for the risk of developing febrile neutropenia in the first cycle of chemotherapy among elderly patients with breast, lung, colorectal, and prostate cancer.	Hosmer W, Malin J, Wong M.	Support Care Cancer. 2011 Mar;19(3):333-41.	**Excluded** due to different study topic;
15	Plasma and cerebrospinal fluid pharmacokinetics of topotecan in a phase I trial of topotecan, tamoxifen, and carboplatin, in the treatment of recurrent or refractory brain or spinal cord tumors.	Morgan RJ, Synold T, Mamelak A, Lim D, Al-Kadhimi Z, Twardowski P, Leong L, Chow W, Margolin K, Shibata S, Somlo G, Yen Y, Frankel P, Doroshow JH.	Cancer Chemother Pharmacol. 2010 Oct;66(5):927-33.	**Excluded** due to different study topic;
16	Cost-effectiveness of UGT1A1*28 genotyping in preventing severe neutropenia following FOLFIRI therapy in colorectal cancer.	Pichereau S, Le Louarn A, Lecomte T, Blasco H, Le Guellec C, Bourgoin H.	J Pharm Pharm Sci. 2010;13(4):615-25.	**Excluded,** no original study;
17	Can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? An evidence-based review.	Palomaki GE, Bradley LA, Douglas MP, Kolor K, Dotson WD.	Genet Med. 2009 Jan;11(1):21-34.	**Excluded**, no original study;
18	Neutropenia in 6 ethnic groups from the Caribbean and the U.S.	Grann VR, Bowman N, Joseph C, Wei Y, Horwitz MS, Jacobson JS, Santella RP, Hershman DL.	Cancer. 2008 Aug 15;113(4):854-60.	**Excluded** due to different study topic;
19	High-dose irinotecan plus LV5FU2 or simplified LV5FU (HD-FOLFIRI) for patients with untreated metastatic colorectal cancer: a new way to allow resection of liver metastases?	Ducreux M, Raoul JL, Marti P, Merrouche Y, Tigaud JM, Rebischung C, Boige V.	Oncology. 2008;74(1-2):17-24.	**Excluded d**ue to different study topic;
20	Cost-effectiveness of UGT1A1 genotyping in second-line, high-dose, once every 3 weeks irinotecan monotherapy treatment of colorectal cancer.	Obradovic M, Mrhar A, Kos M.	Pharmacogenomics. 2008 May;9(5):539-49.	**Excluded**, no original study;

21	Risk and timing of neutropenic events in adult cancer patients receiving chemotherapy: the results of a prospective nationwide study of oncology practice.	Crawford J, Dale DC, Kuderer NM, Culakova E, Poniewierski MS, Wolff D, Lyman GH.	J Natl Compr Canc Netw. 2008 Feb;6(2):109-18.	**Excluded** due to different study topic;
22	Impact of neutropenia on delivering planned chemotherapy for solid tumours.	Khan S, Dhadda A, Fyfe D, Sundar S.	Eur J Cancer Care (Engl). 2008 Jan;17(1):19-25.	**Excluded** due to different study topic;
23	Dose intensity and hematologic toxicity in older cancer patients receiving systemic chemotherapy.	Shayne M, Culakova E, Poniewierski MS, Wolff D, Dale DC, Crawford J, Lyman GH.	Cancer. 2007 Oct 1;110(7):1611-20.	**Excluded,** required information not included;
24	Observational study of the prevalence of febrile neutropenia in patients who received filgrastim or pegfilgrastim associated with 3-4 week chemotherapy regimens in community oncology practices.	Morrison VA, Wong M, Hershman D, Campos LT, Ding B, Malin J	J Manag Care Pharm. 2007 May;13(4):337-48.	**Excluded** due to different study topic;
25	Role of colony stimulating factors (CSFs) in solid tumours: results of an expert panel.	Gridelli C, Aapro MS, Barni S, Beretta GD, Colucci G, Daniele B, Del Mastro L, Di Maio M, De Petris L, Perrone F, Thatcher N, De Marinis F.	Crit Rev Oncol Hematol. 2007 Jul;63(1):53-64.	**Excluded**, no original study;

1.7 Quality of life and colorectal cancer

1.7.1 Flowchart of the structured literature search



Bennett et al. Health-related quality of life in patients with metastatic colorectal cancer treated with panitumumab in first- or second-line treatment. Br J Cancer. 2011 Nov 8;105(10):1495-502.

1.7.2 List of identified studies.

(((Health-related quality of life OR HRQOL[Title/Abstract])) AND (MCRC OR metastatic colorectal cancer[Title/Abstract])) AND ("2006/01/01"[Date - Publication] : "3000"[Date - Publication]) Filters activated: English, German; 14.06.2013, 16 studies;				
	Title	Author	Journal	Ex- or included
1	Health-related quality of life in patients with metastatic colorectal cancer treated with panitumumab in first- or second-line treatment.	Bennett L, Zhao Z, Barber B, Zhou X, Peeters M, Zhang J, Xu F, Wiezorek J, Douillard JY.	Br J Cancer. 2011 Nov 8;105(10):1495-502.	**Included:** HrQoLfor FOLFIRI+panitumumab: 0,769, FOLFIRI: 0,762 (EQ5D HSI)
2	Personality variables as predictors of early non-metastatic colorectal cancer patients' psychological distress and health-related quality of life: a one-year prospective study.	Hyphantis T, Paika V, Almyroudi A, Kampletsas EO, Pavlidis N.	J Psychosom Res. 2011 May;70(5):411-21.	**Excluded,** wrong study population: non-metastatic
3	Quality of life after severe trauma: results from the global trauma trial with recombinant Factor VII.	Christensen MC, Banner C, Lefering R, Vallejo-Torres L, Morris S.	J Trauma. 2011 Jun;70(6):1524-31.	**Excluded** due to different study topic;
4	Health-related quality of life and colorectal cancer-specific symptoms in patients with chemotherapy-refractory metastatic disease treated with panitumumab.	Odom D, Barber B, Bennett L, Peeters M, Zhao Z, Kaye J, Wolf M, Wiezorek J.	Int J Colorectal Dis. 2011 Feb;26(2):173-81.	**Excluded,** wrong study population (no information if treatment is irinotecan-based);
5	Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer.	Whyte S, Pandor A, Stevenson M, Rees A.	Health Technol Assess. 2010 Oct;14(Suppl. 2):47-53.	**Excluded,** no original study;
6	Psychometric evaluation of the FACT Colorectal Cancer Symptom Index (FCSI-9): reliability, validity, responsiveness, and clinical meaningfulness.	Colwell HH, Mathias SD, Turner MP, Lu J, Wright N, Peeters M, Cella D, Devercelli G.	Oncologist. 2010;15(3):308-16. doi: 10.1634/theoncologist.2009-0034.	**Excluded** due to different study topic;

7	Circadian rhythm in rest and activity: a biological correlate of quality of life and a predictor of survival in patients with metastatic colorectal cancer.	Innominato PF, Focan C, Gorlia T, Moreau T, Garufi C, Waterhouse J, Giacchetti S, Coudert B, Iacobelli S, Genet D, Tampellini M, Chollet P, Lentz MA, Mormont MC, Lévi F, Bjarnason GA; Chronotherapy Group of the European Organization for Research and Treament of Cancer.	Cancer Res. 2009 Jun 1;69(11):4700-7.	**Excluded** due to different study topic;
8	Quality of life after intracerebral hemorrhage: results of the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial.	Christensen MC, Mayer S, Ferran JM.	Stroke. 2009 May;40(5):1677-82.	**Excluded** due to different study topic;
9	Association of progression-free survival, overall survival, and patient-reported outcomes by skin toxicity and KRAS status in patients receiving panitumumab monotherapy.	Peeters M, Siena S, Van Cutsem E, Sobrero A, Hendlisz A, Cascinu S, Kalofonos H, Devercelli G, Wolf M, Amado RG.	Cancer. 2009 Apr 1;115(7):1544-54.	**Excluded** due to different study topic;
10	Health-related quality of life impact of bevacizumab when combined with irinotecan, 5-fluorouracil, and leucovorin or 5-fluorouracil and leucovorin for metastatic colorectal cancer.	Kabbinavar FF, Wallace JF, Holmgren E, Yi J, Cella D, Yost KJ, Hurwitz HI.	Oncologist. 2008 Sep;13(9):1021-9.	**Excluded** due to different study topic;
11	Balancing risk and benefit for first-line treatment of metastatic colorectal cancer: a graphic communication tool for patients and physicians.	Sanatani MS, Vincent MD.	Support Cancer Ther. 2007 Jan 1;4(2):101-9.	**Excluded** due to different study topic;
12	Validation of patient's self-reported social functioning as an independent prognostic factor for survival in metastatic colorectal cancer patients: results of an international study by the Chronotherapy Group of the European Organisation for Research and Treatment of Cancer.	Efficace F, Innominato PF, Bjarnason G, Coens C, Humblet Y, Tumolo S, Genet D, Tampellini M, Bottomley A, Garufi C, Focan C, Giacchetti S, Lévi F; Chronotherapy Group of the European Organisation for Research and Treatment of Cancer.	J Clin Oncol. 2008 Apr 20;26(12):2020-6.	**Excluded,** wrong study population (no information if treatment is irinotecan-based);

13	Association of progression-free survival with patient-reported outcomes and survival: results from a randomised phase 3 trial of panitumumab.	Siena S, Peeters M, Van Cutsem E, Humblet Y, Conte P, Bajetta E, Comandini D, Bodoky G, Van Hazel G, Salek T, Wolf M, Devercelli G, Woolley M, Amado RG.	Br J Cancer. 2007 Dec 3;97(11):1469-74.	**Excluded,** information required not included;
14	Health-related quality-of-life assessment in gastrointestinal cancer: are results relevant for clinical practice?	Conroy T, Uwer L, Deblock M.	Curr Opin Oncol. 2007 Jul;19(4):401-6.	**Excluded**, no original study;
15	Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.	Tappenden P, Jones R, Paisley S, Carroll C.	Health Technol Assess. 2007 Mar;11(12):1-128, iii-iv.	**Excluded**, no original study;
16	Does a patient's self-reported health-related quality of life predict survival beyond key biomedical data in advanced colorectal cancer?	Efficace F, Bottomley A, Coens C, Van Steen K, Conroy T, Schöffski P, Schmoll H, Van Cutsem E, Köhne CH.	Eur J Cancer. 2006 Jan;42(1):42-9. Epub 2005 Nov 18. Erratum in: Eur J Cancer. 2007 Feb;43(3):633.	**Excluded d**ue to different study topic;

Supplementary Online Appendix 3: Parameters

Parameter	Base case estimate	SD	95% confidence interval	Distribution for the PSA	Source
Probabilities					
Prevalence of UGT1A1*28, wildtype	0.398	0.048	0.303-0.499	Dirichlet	Schulz et al. [1]
…, heterozygous	0.505	0.049	0.405-0.605	Dirichlet	Schulz et al. [1]
…, homozygous	0.097	0.029	0.048-0.171	Dirichlet	Schulz et al. [1]
Probability of severe neutropenia, wildtype	0.135	0.055	0.045-0.288	Beta	Côté et al. [2]
…, heterozygous	0.227	0.062	0.115-0.378	Beta	Côté et al. [2]
…, homozygous	0.5	0.167	0.157-0.843	Beta	Côté et al. [2]
Probability of severe diarrhoea, wildtype	0.232	0.056	0.131-0.350	Beta	Martinez-Balibrea et al. [3]
…, heterozygous	0.295	0.051	0.2-0.4	Beta	Martinez-Balibrea et al. [3]
…, homozygous	0.6	0.122	0.3541-0.823	Beta	Martinez-Balibrea et al. [3]
Probability of hospitalization due neutropenia	0.421	0.11	0.203-0.665	Beta	Shulman et al. [4]
Probability of death from hospitalized neutropenia	0	0.228	0-0.091	Beta	Schultheis et [5]
Probability of hospitalization due to diarrhoea	0.25	-	0-0.5	Triangular	Expert opinion
Probability of death from hospitalized diarrhoea	0	0.005	0-0.019	Beta	Rothenberg et al [6]
Overall survival	Stage dependent	Stage dependent	Not varied	Beta	Van Cutsem et al. [7]
Risk ratio for severe neutropenia, dose reduction	0.299	0.382	0.141-0.631	Normal	Toffoli et al. [8]
…, growth factors	0.313	0.450	0.129-0.754	Normal	Hecht et al. [9]

Risk ratio for severe diarrhoea, dose reduction	0.329	0.546	0.113-0.960	Normal	Toffoli et al. [8]
…, growth factors	1	-	Not varied	Not varied	Expert opinion
Utility weights					
Metastatic colorectal cancer	0.762	0.252	0.234-1	Beta	Bennett et al. [10]
Utility decrement , febrile neutropenia	0.112	0.042*	0.148-0.722	Beta	NICE Diagnostic Assessment Report [11]
…, neutropenia	0.073	0.027*		Beta	NICE Diagnostic Assessment Report [11]
…, diarrhoea	0.074	0.028*	0.029-0.137	Beta	NICE Diagnostic Assessment Report [11]
Costs (in €)					
Growth factors (costs per chemotherapy cycle)	1,437.76	539.16*	583.14-2,671.31	Gamma	Lauer-Taxe[12]
FOLFIRI full dose (costs per chemotherapy cycle)	1,211.85	454.44*	491.52-2,251.57	Gamma	Lauer-Taxe[12]
Subsequent chemotherapy (costs per chemotherapy cycle)	1,061.14	413.87*	530.57-2,122.27	Gamma	Assenburg et al. [13]
Lump sum for chemotherapy (costs quarterly)	145	54.38*	58.80-269.42	Gamma	German ambulatory fee schedule (EBM) [14]
UGT1A1 test (costs per test)	69.90	26.21*	28.35-129.87	Gamma	German ambulatory fee schedule (EBM) [14]

Hospitalization for severe neutropenia, recovery (costs per case)	3,227.93	1,210.47*	1,309.22-5,997.38	Gamma	German Diagnosis Related Groups (DRG) [15]
…, death (costs per case)	11,748.79	4,405.80*	4,765.17-21,828.87	Gamma	German Diagnosis Related Groups (DRG) [15]
Hospitalization for severe diarrhea (costs per case)	1,528.05	573.02*	764,02-3,056.10	Gamma	German Diagnosis Related Groups (DRG) [15]
Physician office visit, neutropenia (costs per case)	628.36	235.64*	254.85-1,167.48	Gamma	Lauer-Taxe[12]
…, diarrhea (costs per case)	39.03	14.67*	19.52-78.06	Gamma	Lauer-Taxe[12]

PSA probabilistic sensitivity analysis; SD standard deviation; *SD was approximated based on the following formula: ((mean value*2)-(mean value*0,5)/4)

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Supplementary Online Appendix 4: Costs of Chemotherapy

c_chemotherapy (status July 2013, source: Lauertaxe)							
Premedication							
Active substance	Product	Quantity	Dosage	Price	PZN	Manufacturer	Calculation
Granisetron	1mg/ml for solution for infusion	5x1	1 mg i.v.	102.73 €	02398490	Ratiopharm GmbH	20.55 €
Dexamethason	DEXA Ratiopharm solution for injection	10	4 mg i.v.	15.99 €	07720996	Ratiopharm GmbH	1.60 €
Atropin	Atropinum Sulfurium solution for injection	10x1ml	0,25 mg s.c.	15.34 €	00085798	Eifelfango GmbH & Co KG	1.53 €
Loperamid	Film-coated tablets	10	2 mg p.o.	12.29 €	04271629	Ratiopharm GmbH	1.23 €
Metoclopramid	MCP Ratiopharm SF vial with solution for injection	5	10mg/2ml i.v.	11.96 €	00509407	Ratiopharm GmbH	2.39 €
						Sum	27.30 €
Chemotherapy							
Active substance	Product	Quantity	Dosage	Price	PZN	Manufacturer	Calculation
Irinotecan	Irinotecan Kabi concentrate for solution for infusion	1	100mg	232.47 €	05497459	Fresenuis Kabi	
		1	300mg	677.50 €	05497471		
Fluorouracil	5 FU Hexal 50mg/ml	1	5000mg/100 ml	28.98 €	04213595	Hexal	
Calciumfolinat	Calciumfolinat Hexal 10mg/ml	1	100mg /10ml	53.38 €	01527554	Hexal	
		1	200mg/ 20ml	91.83 €	01527560		
		1	500mg/ 50ml	200.44 €	01527695		
Glukose 5%		500ml	-	5.20 €	07462850	AlleMan Pharma	
Natriumchlorid	Natriumchlorid solution for infusion	10x250ml	-	23.40 €	01555734	Berlin Chemie	

		250ml	-	2.34 €	Berechnung	AG	
		1000ml	-	9.36 €			
FOLFIRI			Female: 1,5 m2	Male: 2 m2	Female	Male	Mean value
Irinotecan	180mg /m2 in 500ml G5%	1 hour	270	360	682.70 €	915.17 €	810.56 €
Calciumfolinat	400mg/m2 in 250ml NaCl	2 hours	600	800	256.16 €	347.99 €	306.67 €
Fluorouracil	400mg/m2 in NaCl as bolus (10-20ml)	as bolus	600	800	28.98 €	28.98 €	28.98 €
Fluorouracil	2400mg/m2 in 1000ml NaCl%	48 hours	3600	4800	38.34 €	38.34 €	38.34 €
						Sum	1,184.55 €
FOLFIRI 75%			Female: 1,5 m2	Male: 2 m2	Female	Male	Mean value
Irinotecan	180mg /m2 in 500ml G5%	1 hour	202.5	270	470.14 €	682.70 €	587.05 €
Calciumfolinat	400mg/m2 in 250ml NaCl	2 hours	600	800	256.16 €	347.99 €	306.67 €
Fluorouracil	400mg/m2 in NaCl as bolus (10-20ml)	as bolus	600	800	28.98 €	28.98 €	28.98 €
Fluorouracil	2400mg/m2 in 1000ml NaCl%	48 hours	3600	4800	38.34 €	38.34 €	38.34 €
						Sum	961.03 €
Ambulant flat rate payment							
Quarterly	145 €						
Including premedication and ambnulant flat rate payment of 145€		Expressed as a fraction					
FOLFIRI	1,211.85 €						
FOLFIRI 75%	988.33 €	81.56%	Note: Although the model assumes that UGT1A1 carriers receive 75% of the full dose, costs of the reduced dose are approximately 80% of the full dose. This is because calculation of costs for FOLFIRI treatment is based on required package sizes and packages' unit costs and thus includes wastage.				