Role of pharmacogenomics in predicting efficacy and safety of thiopurines in inflammatory bowel disease: A systematic review and meta-analysis

**APPENDIX 1** 

## INDEX

Search strategy	.3
Studies included for #Objective 2	.8
Tables	.15
Figures	.35

#### Search strategy

Database: Ovid MEDLINE Completo - Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Search Strategy:

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1 exp Azathioprine/

2 azathioprine.mp.

3 (((mercaptopurine or puri-nethol or purimethol or purinethol or bw 57 323h or bw 57-323h or bw 57323h) adj1 1 methyl 4 nitro 5 imidazolyl) or mercaptopurine or Arathioprin or arathioprine or aza-q or azafalkazahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or azathiopine or azathioprim or azathioprin or azathioprine sodium or azathiopurine or azathiopsin or azatox or azathioprin or azopi or azoran or azothioprin or azathioprine or bw 57 322 or bw 57-322 or bw 57322 or bw57-322 or bw57322 or Colinsan or immuran or immurel or immuthera or imunen or imuprin or lmuran or imurane or imurek or imurel or imuren or nsc 39084 or nsc39084 or thioazeprine or Thioprine or transimune or zytrim).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

4 mercaptopurine\*.mp. or exp Mercaptopurine/

5 thiopurine\*.mp.

6 (6 mercapto purine or 6 mercaptopurin or 6 mercaptopurine or 6 mercaptopurine monohydrate or 6 mp or 6 purinethiol or 6 purinethiol hydrate or 6 thiohypoxanthine or 6 thiopurine or 6-mercaptopurine or classen or empurine or ismipur or leukerin or leupurin or leupurine or loulla or mercaleukin or mercaptopurin or mercaptopurina or mercapurene or mern or mycaptine or nsc 755 or nsc755 or puri nethol or puri-nethol or purine 6 thiol or purine thiol 6 or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol

3

supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

7 or/1-6

8 (gene\* adj1 mutation\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

9 (gene\* adj1 alteration\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

10 exp Mutation/ or exp Genetics/

11 polymorphism\*.mp. or exp Polymorphism, Genetic/

12 exp Genotype/ or genotyp\*.mp. or genogroup\*.mp.

13 or/8-12

14 exp inflammatory bowel diseases/ or exp colitis, ulcerative/ or exp crohn disease/

15 ((colitis adj1 (granulomatous or enteritis)) or ((crohn or crohn's or crohns) adj1 (disease or enteritis)) or ileocolitis or ((regional or terminal) adj1 (enteritis or ileitides or ileitis))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

16 ((colitis adj1 (gravis or ulcerative)) or idiopathic proctocolitis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

17 (inflammatory enteropathy or intestinal inflammation or intestine inflammation or cleron disease or Crohn's disease or Crohns disease or enteritis regionalis or intestinal tract, regional enteritis or morbus Crohn or regional enteritis or regional enterocolitis or chronic ulcerative

4

colitis or colitis ulcerative or colitis ulcerosa or colitis ulcerosa chronica or colitis, ulcerative or colitis, ulcerative or colitis, ulcerous or colon, chronic ulceration or histiocytic ulcerative colitis or mucosal colitis or ulcerative colorectitis or ulcerative procto colitis or ulcerative proctocolitis or ulcerous colitis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

18 14 or 15 or 16 or 17

19 7 and 13 and 18

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Database: Embase

Search Strategy:

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1 exp Azathioprine/

2 azathioprine.mp.

3 (((mercaptopurine or puri-nethol or purimethol or purinethol or bw 57 323h or bw 57-323h or bw 57323h) adj1 1 methyl 4 nitro 5 imidazolyl) or mercaptopurine or Arathioprin or arathioprine or aza-q or azafalkazahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or azathioprine or azathioprim or azathioprin or azathioprine sodium or azathiopurine or azathioprin or azatox or azathioprin or azopi or azoran or azothioprin or azathioprine or bw 57 322 or bw 57-322 or bw 57322 or bw57-322 or bw57322 or Colinsan or immuran or immurel or immuthera or imunen or imuprin or Imuran or imurane or imurek or imurel or imuren or nsc 39084 or nsc39084 or thioazeprine or Thioprine or transimune or zytrim).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

4 exp mercaptopurine/ or mercaptopurine\*.mp.

5 exp thiopurine methyltransferase/ or thiopurine\*.mp.

6 (6 mercapto purine or 6 mercaptopurin or 6 mercaptopurine or 6 mercaptopurine monohydrate or 6 mp or 6 purinethiol or 6 purinethiol hydrate or 6 thiohypoxanthine or 6 thiopurine or 6-mercaptopurine or classen or empurine or ismipur or leukerin or leupurin or leupurine or loulla or mercaleukin or mercaptopurin or mercaptopurina or mercapurene or mern or mycaptine or nsc 755 or nsc755 or puri nethol or puri-nethol or purine 6 thiol or purine thiol 6 or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

7 or/1-6

8 (gene\* adj1 mutation\*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

9 (gene\* adj1 alteration\*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

10 exp Mutation/ or exp Genetics/

11 polymorphism\*.mp. or exp genetic polymorphism/

12 exp genotype/ or genotyp\*.mp. or genogroup\*.mp.

13 or/8-12

((colitis adj1 (granulomatous or enteritis)) or ((crohn or crohn's or crohns) adj1 (disease or enteritis)) or ileocolitis or ((regional or terminal) adj1 (enteritis or ileitides or ileitis))).mp.
[mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

15 ((colitis adj1 (gravis or ulcerative)) or idiopathic proctocolitis).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

16 exp Crohn disease/ or exp inflammatory bowel disease/ or exp ulcerative colitis/

17 (inflammatory enteropathy or intestinal inflammation or intestine inflammation or cleron disease or Crohn's disease or Crohns disease or enteritis regionalis or intestinal tract, regional

6

enteritis or morbus Crohn or regional enteritis or regional enterocolitis or chronic ulcerative colitis or colitis ulcerative or colitis ulcerosa or colitis ulcerosa chronica or colitis, ulcerative or colitis, ulcerative or colitis, ulcerative or colon, chronic ulceration or histiocytic ulcerative colitis or mucosal colitis or ulcerative colorectitis or ulcerative procto colitis or ulcerative proctocolitis or ulcerative proctocolitis).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

18 or/14-17

19 7 and 13 and 18

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Database: Cochrane library

Search Strategy:

- ID Search Hits
- #1 MeSH descriptor: [Azathioprine] explode all trees
- #2 (azathioprine):ti,ab,kw
- #3 MeSH descriptor: [Mercaptopurine] explode all trees
- #4 mercaptopurine
- #5 thiopurine\*
- #6 #1 OR #2 OR #3 OR #4 OR #5
- #7 gene mutation
- #8 gene alteration
- #9 MeSH descriptor: [Mutation] explode all trees
- #10 MeSH descriptor: [Genetics] explode all trees
- #11 MeSH descriptor: [Polymorphism, Genetic] explode all trees
- #12 polymorphism\*
- #13 MeSH descriptor: [Genotype] explode all trees
- #14 genotyp\*
- #15 genogroup\*
- #16 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
- #17 MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
- #18 MeSH descriptor: [Colitis, Ulcerative] explode all trees
- #19 MeSH descriptor: [Crohn Disease] explode all trees
- #20 inflammatory bowel disease
- #21 ulcerative colitis
- #22 Crohn disease
- #23 Crohn's disease
- #24 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
- #25 #6 AND #16 AND #24

#### Studies included for #Objective 2

- Adam, L., Soma, P., & Phulukdaree, A. (2018). Identification of single-nucleotide polymorphisms in inflammatory bowel disease patients on azathioprine therapy. *South African Medical Journal*, *108*(8), 687. https://doi.org/http://dx.doi.org/10.7196/SAMJ.2018.v108i8.13516
- Akiyama, S., Matsuoka, K., Fukuda, K., Hamada, S., Shimizu, M., Nanki, K., ... Kanai, T. (2019). Long-term effect of NUDT15 R139C on hematologic indices in inflammatory bowel disease patients treated with thiopurine. *Journal of Gastroenterology and Hepatology*. https://doi.org/http://dx.doi.org/10.1111/jgh.14693
- Al-Judaibi, B., Schwarz, U. I., Huda, N., Dresser, G. K., Gregor, J. C., Ponich, T., ... Kim, R. B. (2016). Genetic predictors of azathioprine toxicity and clinical response in patients with inflammatory bowel disease. *Journal of Population Therapeutics and Clinical Pharmacology*, 23(1), e26–e36.
- Ansari, A., Arenas, M., Greenfield, S. M., Morris, D., Lindsay, J., Gilshenan, K., ... Sanderson, J. (2008). Prospective evaluation of the pharmacogenetics of azathioprine in the treatment of inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics*, 28(8), 973–983. https://doi.org/http://dx.doi.org/10.1111/j.1365-2036.2008.03788.x
- Asada, A., Nishida, A., Shioya, M., Imaeda, H., Inatomi, O., Bamba, S., ... Andoh, A. (2016). NUDT15 R139C-related thiopurine leukocytopenia is mediated by 6-thioguanine nucleotide-independent mechanism in Japanese patients with inflammatory bowel disease. *Journal of Gastroenterology*, *51*(1), 22–29.
- Ban, H., Andoh, A., Imaeda, H., Kobori, A., Bamba, S., Tsujikawa, T., ... Fujiyama, Y. (2010). The multidrug-resistance protein 4 polymorphism is a new factor accounting for thiopurine sensitivity in Japanese patients with inflammatory bowel disease. *Journal of Gastroenterology*, 45(10), 1014–1021.
- Banerjee, R., Ravikanth, V. V., Pal, P., Bale, G., Avanthi, U. S., Goren, I., ... Reddy, D. N. (2020). NUDT15 C415T variant compared with TPMT genotyping in predicting azathioprineinduced leucopenia: prospective analysis of 1014 inflammatory bowel disease patients in India. *Alimentary Pharmacology & Therapeutics*, 52(11–12), 1683–1694. https://doi.org/https://dx.doi.org/10.1111/apt.16137
- Bangma, A., Voskuil, M. D., Uniken Venema, W. T. C., Brugge, H., Hu, S., Lanting, P., ... Weersma, R. K. (2020). Predicted efficacy of a pharmacogenetic passport for inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*, 51(11), 1105– 1115. https://doi.org/https://dx.doi.org/10.1111/apt.15762
- Bourgine, J., Billaut-Laden, I., Colombel, J. F., & Broly, F. (2012). Evidence for a functional genetic polymorphism of the Rho-GTPase Rac1: Implication in azathioprine response? *Fundamental and Clinical Pharmacology*, 26 (SUPPL., 16–17. https://doi.org/http://dx.doi.org/10.1111/j.1472-8206.2012.01032.x
- Chao, K., Zhu, X., Cao, Q., Yang, H., Liang, J., Lin, L., ... Gao, X. (2017). Combined detection variants of NUDT15 could highly predict thiopurine-induced leukopenia in Chinese patients with inflammatory bowel disease: A multi-center analysis. *Journal of Crohn's and Colitis*, 11 (Supple, S125. https://doi.org/http://dx.doi.org/10.1093/ecco-jcc/jjx002.222

- Choi, R., Lee, M.-N., Kim, K., Baek, S.-Y., Kim, T. J., Hong, S. N., ... Lee, S.-Y. (2020). Effects of various genetic polymorphisms on thiopurine treatment-associated outcomes for Korean patients with Crohn's disease. *British Journal of Clinical Pharmacology*, *86*(11), 2302– 2313. https://doi.org/https://dx.doi.org/10.1111/bcp.14339
- Coelho, T., Andreoletti, G., Ashton, J. J., Batra, A., Afzal, N. A., Gao, Y., ... Ennis, S. (2016). Genes implicated in thiopurine-induced toxicity: Comparing TPMT enzyme activity with clinical phenotype and exome data in a paediatric IBD cohort. *Scientific Reports*, *6*, 34658. https://doi.org/https://dx.doi.org/10.1038/srep34658
- Cravo, M., Ferreira, P., Sousa, P., Moura-Santos, P., Velho, S., Tavares, L., ... Brito, M. (2014). Clinical and genetic factors predicting response to therapy in patients with crohn's disease. *United European Gastroenterology Journal*, 2(1), 47–56.
- De Ridder, L., Van Dieren, J. M., Van Deventer, H. J., Stokkers, P. C., Van der Woude, J. C., Van Vuuren, A. J., ... Hommes, D. W. (2006). Pharmacogenetics of thiopurine therapy in paediatric IBD patients. *Alimentary Pharmacology & Therapeutics*, *23*(8), 1137–1141.
- Demlova, R., Mrkvicova, M., Sterba, J., Bernatikova, H., Stary, J., Sukova, M., ... Valik, D. (2014). Augmenting clinical interpretability of thiopurine methyltransferase laboratory evaluation. Oncology (Switzerland), 86(3), 152–158.
- Dubinsky, M. C., Lamothe, S., Yang, H. Y., Targan, S. R., Sinnett, D., Theoret, Y., & Seidman, E. G. (2000). Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. *Gastroenterology*, 118(4), 705–713.
- Fangbin, Z., Xiang, G., Liang, D., Hui, L., Xueding, W., Baili, C., ... Pinjin, H. (2016). Prospective Evaluation of Pharmacogenomics and Metabolite Measurements upon Azathioprine Therapy in Inflammatory Bowel Disease: An Observational Study. *Medicine*, 95(15), e3326. https://doi.org/https://dx.doi.org/10.1097/MD.00000000003326
- Franca, R., Stocco, G., Favretto, D., Giurici, N., del Rizzo, I., Locatelli, F., ... Rabusin, M. (2020). PACSIN2 rs2413739 influence on thiopurine pharmacokinetics: validation studies in pediatric patients. *Pharmacogenomics Journal*, 20(3), 415–425. https://doi.org/10.1038/s41397-019-0130-0
- Gazouli, M., Pachoula, I., Panayotou, I., Mantzaris, G., Syriopoulou, V. P., Goutas, N., ... Roma-Giannikou, E. (2010). Thiopurine S-methyltransferase genotype and the use of thiopurines in paediatric inflammatory bowel disease Greek patients. *Journal of Clinical Pharmacy and Therapeutics*, 35(1), 93–97. https://doi.org/http://dx.doi.org/10.1111/j.1365-2710.2009.01041.x
- Gearry, R. B., Barclay, M. L., Burt, M. J., Collett, J. A., Chapman, B. A., Roberts, R. L., & Kennedy, M. A. (2003). Thiopurine S-methyltransferase (TPMT) genotype does not predict adverse drug reactions to thiopurine drugs in patients with inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*, 18(4), 395–400.
- Giudici, F., Cavalli, T., Luceri, C., Russo, E., Zambonin, D., Scaringi, S., ... Malentacchi, C. (2021).
   Long-Term Follow-Up, Association between CARD15/NOD2 Polymorphisms, and Clinical
   Disease Behavior in Crohn's Disease Surgical Patients. *Mediators of Inflammation, 2021*, 8854916. https://doi.org/https://dx.doi.org/10.1155/2021/8854916
- Grover, N., Bhatia, P., Kumar, A., Mandavdhare, H., Prasad, K., Samanta, J., ... Singh, M. (2020). Genetic polymorphisms in prediction of thiopurine related cytopenia in inflammatory

bowel disease: A prospective study. *Indian Journal of Gastroenterology*, *39*(SUPPL 1), S27. https://doi.org/http://dx.doi.org/10.1007/s12664-020-01133-9

- Hawwa, A. F., Millership, J. S., Collier, P. S., Vandenbroeck, K., McCarthy, A., Dempsey, S., ... McElnay, J. C. (2008). Pharmacogenomic studies of the anticancer and immunosuppressive thiopurines mercaptopurine and azathioprine. *British Journal of Clinical Pharmacology*, *66*(4), 517–528. https://doi.org/https://dx.doi.org/10.1111/j.1365-2125.2008.03248.x
- Heap, G. A., Weedon, M. N., Bewshea, C. M., Singh, A., Chen, M., Satchwell, J. B., ... Ahmad, T. (2014). HLA-DQA1–HLA-DRB1 variants confer susceptibility to pancreatitis induced by thiopurine immunosuppressants. *Nature Genetics*, 46(10), 1131–1134. https://doi.org/10.1038/ng.3093
- Hibi, T., Naganuma, M., Kitahora, T., Kinjyo, F., & Shimoyama, T. (2003). Low-dose azathioprine is effective and safe for maintenance of remission in patients with ulcerative colitis. *Journal of Gastroenterology*, *38*(8), 740–746.
- Hindorf, U., Lindqvist, M., Peterson, C., Soderkvist, P., Strom, M., Hjortswang, H., ... Almer, S. (2006). Pharmacogenetics during standardised initiation of thiopurine treatment in inflammatory bowel disease. *Gut*, *55*(10), 1423–1431. https://doi.org/http://dx.doi.org/10.1136/gut.2005.074930
- Hlavaty, T., Batovsky, M., Balakova, D., Pav, I., Celec, P., Gregus, M., ... Slovak, I. B. D. study group. (2013). The impact of thiopurine-S-methyltransferase genotype on the adverse drug reactions to azathioprine in patients with inflammatory bowel diseases. *Bratislavske Lekarske Listy*, 114(4), 199–205.
- Kakuta, Y., Kawai, Y., Okamoto, D., Takagawa, T., Ikeya, K., Sakuraba, H., ... Suzuki, Y. (2018).
   NUDT15 codon 139 is the best pharmacogenetic marker for predicting thiopurineinduced severe adverse events in Japanese patients with inflammatory bowel disease: a multicenter study. *Journal of Gastroenterology*, *53*(9), 1065–1078. https://doi.org/http://dx.doi.org/10.1007/s00535-018-1486-7
- Kakuta, Y., Naito, T., Onodera, M., Kuroha, M., Kimura, T., Shiga, H., ... Shimosegawa, T. (2016).
   NUDT15 R139C causes thiopurine-induced early severe hair loss and leukopenia in Japanese patients with IBD. *Pharmacogenomics Journal*, *16*(3), 280–285.
- Kang, B., Kim, T. J., Choi, J., Baek, S.-Y., Ahn, S., Choi, R., ... Choe, Y. H. (2020). Adjustment of azathioprine dose should be based on a lower 6-TGN target level to avoid leucopenia in NUDT15 intermediate metabolisers. *Alimentary Pharmacology & Therapeutics*, 52(3), 459–470. https://doi.org/https://dx.doi.org/10.1111/apt.15810
- Kim, H. S., Cheon, J. H., Jung, E. S., Park, J., Aum, S., Park, S. J., ... Lee, M. G. (2017). A coding variant in FTO confers susceptibility to thiopurine-induced leukopenia in East Asian patients with IBD. *Gut*, 66(11), 1926–1935.
- Kim, J. H., Cheon, J. H., Hong, S. S., Eun, C. S., Byeon, J. S., Hong, S. Y., ... Kim, W. H. (2010). Influences of thiopurine methyltransferase genotype and activity on thiopurine-induced leukopenia in Korean patients with inflammatory bowel disease: a retrospective cohort study. *Journal of Clinical Gastroenterology*, *44*(10), e242-8. https://doi.org/https://dx.doi.org/10.1097/MCG.0b013e3181d6baf5

Kim, M. J., Lee, S. Y., & Choe, Y. H. (2014). Monitoring thiopurine metabolites in Korean

pediatric patients with inflammatory bowel disease. *Yonsei Medical Journal*, 55(5), 1289–1296. https://doi.org/http://dx.doi.org/10.3349/ymj.2014.55.5.1289

- Koifman, E., Karban, A., Mazor, Y., Chermesh, I., Waterman, M., Almog, R., ... Chowers, Y. (2013). Thiopurine effectiveness in patients with Crohn's disease: A study of genetic and clinical predictive factors. *Inflammatory Bowel Diseases*, *19*(8), 1639–1644.
- Larussa, T., Suraci, E., Lentini, M., Nazionale, I., Gallo, L., Abenavoli, L., ... Luzza, F. (2012). High prevalence of polymorphism and low activity of thiopurine methyltransferase in patients with inflammatory bowel disease. *European Journal of Internal Medicine*, *23*(3), 273–277. https://doi.org/https://dx.doi.org/10.1016/j.ejim.2011.12.002
- Lee, J. H., Kim, T. J., Kim, E. R., Hong, S. N., Chang, D. K., Choi, L. H., ... Kim, Y. H. (2017). Measurements of 6-thioguanine nucleotide levels with TPMT and NUDT15 genotyping in patients with Crohn's disease. *PLoS ONE [Electronic Resource]*, *12*(12), e0188925. https://doi.org/https://dx.doi.org/10.1371/journal.pone.0188925
- Lee, M., Kang, B., Woo, S. Y., Kim, J., Lee, S., & Choe, Y. H. (2015). Impact of genetic polymorphisms on 6-thioguanine nucleotide levels and toxicity in pediatric IBD patients treated with azathioprine. *Clinical Chemistry and Laboratory Medicine*, 1), S781.
- Liu, Q., Wang, Y., Mei, Q., Han, W., Hu, J., & Hu, N. (2016). Measurement of red blood cell 6thioguanine nucleotide is beneficial in azathioprine maintenance therapy of Chinese Crohn's disease patients. *Scandinavian Journal of Gastroenterology*, *51*(9), 1093–1099. https://doi.org/http://dx.doi.org/10.3109/00365521.2016.1161068
- Lucafo, M., Stocco, G., Martelossi, S., Favretto, D., Franca, R., Malusa, N., ... Decorti, G. (2019). Azathioprine Biotransformation in Young Patients with Inflammatory Bowel Disease: Contribution of Glutathione-S Transferase M1 and A1 Variants. *Genes*, *10 (4) (no*(277). https://doi.org/http://dx.doi.org/10.3390/genes10040277
- Maeda, T., Sakuraba, H., Hiraga, H., Yoshida, S., Kakuta, Y., Kikuchi, H., ... Fukuda, S. (2021). Long-term efficacy and tolerability of dose-adjusted thiopurine treatment in maintaining remission in inflammatory bowel disease patients with NUDT15 heterozygosity. *Intestinal Research*. https://doi.org/https://dx.doi.org/10.5217/ir.2020.00133
- Mahasneh, S., Sharab, A., Al Shhab, M., Rashid, M., & Zihlif, M. (2020). AOX1 and XDH Enzymes Genotyping and its Effect on Clinical Response to Azathioprine in Inflammatory Bowel Disease Patients Among Jordanian Population. *Current Drug Metabolism*, *21*(2), 140–144. https://doi.org/https://dx.doi.org/10.2174/1389200221666200413125011
- Marinaki, A. M., Ansari, A., Duley, J. A., Arenas, M., Sumi, S., Lewis, C. M., ... Sanderson, J. D. (2004). Adverse drug reactions to azathioprine therapy are associated with polymorphism in the gene encoding inosine triphosphate pyrophosphatase (ITPase). *Pharmacogenetics*, *14*(3), 181–187.
- Mazor, Y., Koifman, E., Elkin, H., Chowers, Y., Krivoy, N., Karban, A., & Efrati, E. (2013). Risk factors for serious adverse effects of thiopurines in patients with Crohn's disease. *Current Drug Safety*, 8(3), 181–185.
- Mendoza, J. L., Urcelay, E., Lana, R., Martin, M. C., Lopez, N., Guijarro, L. G., ... Diaz-Rubio, M. (2007). MDR1 polymorphisms and response to azathioprine therapy in patients with Crohn's disease. *Inflammatory Bowel Diseases*, 13(5), 585–590. https://doi.org/http://dx.doi.org/10.1002/ibd.20044

- Mhanna, M., Gharaibeh, M. G., Rashid, M., Sharab, A., Shehab, M., & Zihlif, M. (2019). TPMT
  Genotype and Adverse Effects of Azathioprine among Jordanian Group. *Current Drug Metabolism*, 20(11), 889–897.
  https://doi.org/https://dx.doi.org/10.2174/1389200220666191021100953
- Naughton, M. A., Battaglia, E., O'Brien, S., Walport, M. J., & Botto, M. (1999). Identification of thiopurine methyltransferase (TPMT) polymorphisms cannot predict myelosuppression in systemic lupus erythematosus patients taking azathioprine. *Rheumatology*, 38(7), 640– 644.
- Niess, J. H., Klaus, J., Stephani, J., Pfluger, C., Degenkolb, N., Spaniol, U., ... von Boyen, G. B. (2012). NOD2 polymorphism predicts response to treatment in Crohn's disease-first steps to a personalized therapy. *Digestive Diseases & Sciences*, 57(4), 879–886. https://doi.org/https://dx.doi.org/10.1007/s10620-011-1977-3
- Odahara, S., Uchiyama, K., Kubota, T., Ito, Z., Takami, S., Kobayashi, H., ... Ohkusa, T. (2015). A Prospective Study Evaluating Metabolic Capacity of Thiopurine and Associated Adverse Reactions in Japanese Patients with Inflammatory Bowel Disease (IBD). *PLoS ONE* [*Electronic Resource*], 10(9), e0137798. https://doi.org/https://dx.doi.org/10.1371/journal.pone.0137798
- Palmieri, O., Latiano, A., Bossa, F., Vecchi, M., D'Inca, R., Guagnozzi, D., ... Annese, V. (2007). Sequential evaluation of thiopurine methyltransferase, inosine triphosphate pyrophosphatase, and HPRT1 genes polymorphisms to explain thiopurines' toxicity and efficacy. *Alimentary Pharmacology and Therapeutics*, 26(5), 737–745. https://doi.org/http://dx.doi.org/10.1111/j.1365-2036.2007.03421.x
- Park, S. K., Hong, M., Ye, B. D., Kim, K. J., Park, S. H., Yang, D. H., ... Yang, S. K. (2016). Influences of XDH genotype by gene-gene interactions with SUCLA2 for thiopurine-induced leukopenia in Korean patients with Crohn's disease. *Scandinavian Journal of Gastroenterology*, 51(6), 684–691.
- Reuther, L. O., Sonne, J., Larsen, N. E., Larsen, B., Christensen, S., Rasmussen, S. N., ... Schmiegelow, K. (2003). Pharmacological monitoring of azathioprine therapy. *Scandinavian Journal of Gastroenterology*, *38*(9), 972–977.
- Ribaldone, D. G., Adriani, A., Caviglia, G. P., Nicolo, A., Agnesod, D., Simiele, M., ... Astegiano, M. (2019). Correlation between Thiopurine S-Methyltransferase Genotype and Adverse Events in Inflammatory Bowel Disease Patients. *Medicina*, 55(8), 5. https://doi.org/https://dx.doi.org/10.3390/medicina55080441
- Schwab, M., Schaffeler, E., Marx, C., Fischer, C., Lang, T., Behrens, C., ... Kaskas, B. A. (2002). Azathioprine therapy and adverse drug reactions in patients with inflammatory bowel disease: Impact of thiopurine S-methyltransferase polymorphism. *Pharmacogenetics*, 12(6), 429–436. https://doi.org/http://dx.doi.org/10.1097/00008571-200208000-00003
- Shah, S. A. V, Paradkar, M., Desai, D., & Ashavaid, T. F. (2017). Nucleoside diphosphate-linked moiety X-type motif 15 C415T variant as a predictor for thiopurine-induced toxicity in Indian patients. *Journal of Gastroenterology and Hepatology (Australia), 32*(3), 620–624. https://doi.org/http://dx.doi.org/10.1111/jgh.13494
- Smith, M. A., Marinaki, A. M., Arenas, M., Shobowale-Bakre, M., Lewis, C. M., Ansari, A., ... Sanderson, J. D. (2009). Novel pharmacogenetic markers for treatment outcome in azathioprine-treated inflammatory bowel disease. *Alimentary Pharmacology and*

*Therapeutics*, *30*(4), 375–384. https://doi.org/http://dx.doi.org/10.1111/j.1365-2036.2009.04057.x

- Steponaitiene, R., Kupcinskas, J., Survilaite, S., Varkalaite, G., Jonaitis, L., Kiudelis, G., ... Kupcinskas, L. (2016). TPMT and ITPA genetic variants in Lithuanian inflammatory bowel disease patients: Prevalence and azathioprine-related side effects. *Advances in Medical Sciences*, 61(1), 135–140.
- Stocco, G., Martelossi, S., Barabino, A., Decorti, G., Bartoli, F., Montico, M., ... Ventura, A. (2007). Glutathione-S-transferase genotypes and the adverse effects of azathioprine in young patients with inflammatory bowel disease. *Inflammatory Bowel Diseases*, 13(1), 57–64. https://doi.org/http://dx.doi.org/10.1002/ibd.20004
- Stocco, G., Martelossi, S., Barabino, A., Fontana, M., Lionetti, P., Decorti, G., ... Ventura, A. (2005). TPMT genotype and the use of thiopurines in paediatric inflammatory bowel disease. *Digestive and Liver Disease*, 37(12), 940–945. https://doi.org/http://dx.doi.org/10.1016/j.dld.2005.08.003
- Stocco, G., Martelossi, S., Decorti, G., Ventura, A., Malusa, N., Bartoli, F., & Giraldi, T. (2004). Pharmacogenetics of thiopurines: Can posology be guided by laboratory data? *Radiology* and Oncology, 38(2), 101-109+157.
- Stocco, G., Martelossi, S., Sartor, F., Toffoli, G., Lionetti, P., Barabino, A., ... Ventura, A. (2006). Prevalence of methylenetetrahydrofolate reductase polymorphisms in young patients with inflammatory bowel disease. *Digestive Diseases & Sciences*, 51(3), 474–479.
- Sutiman, N., Chen, S., Ling, K. L., Chuah, S. W., Leong, W. F., Nadiger, V., ... Chowbay, B. (2018). Predictive role of NUDT15 variants on thiopurine-induced myelotoxicity in Asian inflammatory bowel disease patients. *Pharmacogenomics*, 19(1), 31–43. https://doi.org/https://dx.doi.org/10.2217/pgs-2017-0147
- Takatsu, N., Matsui, T., Murakami, Y., Ishihara, H., Hisabe, T., Nagahama, T., ... Yao, K. (2009).
  Adverse reactions to azathioprine cannot be predicted by thiopurine S-methyltransferase genotype in Japanese patients with inflammatory bowel disease. *Journal of Gastroenterology & Hepatology*, 24(7), 1258–1264.
  https://doi.org/https://dx.doi.org/10.1111/j.1440-1746.2009.05917.x
- van Dieren, J. M., van Vuuren, A. J., Kusters, J. G., Nieuwenhuis, E. E., Kuipers, E. J., & van der Woude, C. J. (2005). ITPA genotyping is not predictive for the development of side effects in AZA treated inflammatory bowel disease patients. *Gut*, *54*(11), 1664.
- Von Ahsen, N., Armstrong, V. W., Behrens, C., Von Tirpitz, C., Stallmach, A., Herfarth, H., ... Reinshagen, M. (2005). Association of inosine triphosphatase 94C>A and thiopurine Smethyltransferase deficiency with adverse events and study drop-outs under azathioprine therapy in a prospective Crohn disease study. *Clinical Chemistry*, 51(12), 2282–2288. https://doi.org/http://dx.doi.org/10.1373/clinchem.2005.057158
- Wang, H. H., He, Y., Wang, H. X., Liao, C. L., Peng, Y., Tao, L. J., ... Yang, H. X. (2018). Comparison of TPMT and NUDT15 polymorphisms in Chinese patients with inflammatory bowel disease. *World Journal of Gastroenterology*, 24(8), 941–948. https://doi.org/https://dx.doi.org/10.3748/wjg.v24.i8.941
- Weiss, B., Lebowitz, O., Fidder, H. H., Maza, I., Levine, A., Shaoul, R., ... Karban, A. (2010). Response to medical treatment in patients with Crohn's disease: the role of

NOD2/CRAD15, disease phenotype, and age of diagnosis. *Digestive Diseases & Sciences*, 55(6), 1674–1680. https://doi.org/https://dx.doi.org/10.1007/s10620-009-0936-8

- Wilson, A., Jansen, L. E., Rose, R. V, Gregor, J. C., Ponich, T., Chande, N., ... Kim, R. B. (2018).
   HLA-DQA1-HLA-DRB1 polymorphism is a major predictor of azathioprine-induced pancreatitis in patients with inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*, 47(5), 615–620. https://doi.org/https://dx.doi.org/10.1111/apt.14483
- Winter, J. W., Gaffney, D., Shapiro, D., Spooner, R. J., Marinaki, A. M., Sanderson, J. D., & Mills, P. R. (2007). Assessment of thiopurine methyltransferase enzyme activity is superior to genotype in predicting myelosuppression following azathioprine therapy in patients with inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*, 25(9), 1069– 1077.
- Wroblova, K., Kolorz, M., Batovsky, M., Zboril, V., Suchankova, J., Bartos, M., ... Bartosova, L. (2012). Gene polymorphisms involved in manifestation of leucopenia, digestive intolerance, and pancreatitis in azathioprine-treated patients. *Digestive Diseases & Sciences*, *57*(9), 2394–2401. https://doi.org/https://dx.doi.org/10.1007/s10620-012-2163-y
- Xu, Y., Qiao, Y.-Q., Li, H.-Y., Zhou, M., Cai, C.-W., Shen, J., & Ran, Z.-H. (2020). NUDT15 genotyping during azathioprine treatment in patients with inflammatory bowel disease: Implications for a dose-optimization strategy. *Gastroenterology Report*, 8(6), 437–444. https://doi.org/http://dx.doi.org/10.1093/gastro/goaa021
- Yang, S. K., Hong, M., Baek, J., Choi, H., Zhao, W., Jung, Y., ... Song, K. (2014). A common missense variant in NUDT15 confers susceptibility to thiopurine-induced leukopenia. *Nature Genetics*, 46(9), 1017–1020. https://doi.org/http://dx.doi.org/10.1038/ng.3060
- Zabala-Fernandez, W., Barreiro-de Acosta, M., Echarri, A., Carpio, D., Lorenzo, A., Castro, J., ... Barros, F. (2011). A pharmacogenetics study of TPMT and ITPA genes detects a relationship with side effects and clinical response in patients with inflammatory bowel disease receiving Azathioprine. *Journal of Gastrointestinal & Liver Diseases*, 20(3), 247– 253.
- Zabala, W., Cruz, R., Acosta, M. B., Chaparro, M., Panes, J., Echarri, A., ... Barros, F. (2015). Exome-wide pharmacogenomic analysis of response to thiopurines in inflammatory bowel disease patients. *Current Pharmacogenomics and Personalized Medicine*, *13*(1), 61–67. https://doi.org/http://dx.doi.org/10.2174/1875692113666150813151413
- Zabala, W., Cruz, R., Barreiro-de Acosta, M., Chaparro, M., Panes, J., Echarri, A., ... investigators, E. (2013). New genetic associations in thiopurine-related bone marrow toxicity among inflammatory bowel disease patients. *Pharmacogenomics*, *14*(6), 631– 640. https://doi.org/https://dx.doi.org/10.2217/pgs.13.38
- Zelinkova, Z., Derijks, L. J., Stokkers, P. C., Vogels, E. W., van Kampen, A. H., Curvers, W. L., ... Hommes, D. W. (2006). Inosine triphosphate pyrophosphatase and thiopurine smethyltransferase genotypes relationship to azathioprine-induced myelosuppression. *Clinical Gastroenterology & Hepatology*, 4(1), 44–49.

## <u>Tables</u>

#### Table S1. Study characteristics (objective 1)

Aut hor, yea r	Design	Unit of alloc ation	C e n t e r	Loca tion	Study period	A r m s	A n al ys is	Populat ion of interest , no.	Baseli ne imbal ances	Withdrawals, exclusions	Age, years	Sex, males, no. (%)	Race, no. (%)	Crohn Diseas e, no. (%)	Children, no. (%)	Analyze d genes	Thiopurine doses
Cha ng 202 0	RCT	Indiv idual	M C	Kore a	01/2016- 09/2018	2	IT T	182	Yes	Genotyping +: 15 exclusions, 9 loss to follow- up; genotyping -: 3 exclusions, 4 loss to follow- up	Genotyping +: 39.7±15.9; genotyping -: 37.7±17.1	98 (59.8%)	100% Asian	85 (51.8 %)	0	TPMT, NUDT15, FTO	Control: start with AZA 50 mg/day and increasing Heterozygous: 50 mg/
Cha o 202 1	RCT	Indiv idual	M C	Chin a	August 2016- November 2017	2	IT T	442	Yes	Intervention: 6 lost to follow-up Control: 13 lost to follow-up	Intervention: 26 (21-33) Control: 26 (22- 31)	Intervention: 150 (68.5%) Control: 164 (80.4%)	100% Chinese Han	442 (100% )	Unknown (Inclusion criteria 14- 75 years)	NUDT15	Control: AZA 2 mg/kg/day Heterozygous: 50% of the dose
Coe nen 201 5	RCT	Grou ps of 4	M C	The Neth erla nds	Recruitment: 10/2007- 12/2010	2	IT T	783	Yes	13	40.5 (SD: 15.8)	354 (45.2%)	NR	476 (60.8 %)	0	TPMT	Control: AZA 2- 2.5 mg/kg/day Heterozygous: 50% of the dose
Ne wm an 201 1	RCT	Indiv idual	M C	UK	10/2005- 12/2007	2	IT T	333	No	6	NR overall	165 (49.5%)	White: 303 (90.1%); Asian: 20 (6.0%); Black: 6 (1.85), Other: 4 (1.25)	140 (42.0 %)	333 (100%) ≥16 years	TPMT	Wild type: AZA 1.5-3 mg/kg/day Heterozygous: start with 25-50 mg/day and increasing
Wils on 202 0	Historic ally controll ed study	Indiv idual	U C	Cana da	03/2017 (control: 2012)- 02/2020 (control: 2017)	2	N A	972	No	0	Genotyping +: 42.4 (18-86); genotyping -: 41.3 (18-79)	Genotyping +: 150 (45.7%); genotyping -: 170 (45.6%)	NR	458 (65.3 %)	972 (100%) > 17 years	HLA DQA1- HLADRB 1*07:01 A.C	No information

AZA: azathioprine; ITT: intention to treat; MC: multicenter; NA: not applicable; NR: not reported; RCT: randomized controlled trial; SD: standard deviation

Author, year	Desig n	Cente r	Location	Study period	Populati on of interest	Baseline imbalances by genotype	Withdrawals , exclusions	Age, years	Sex, males, no. (%)	Race, no. (%)	Crohn Disease, no. (%)	Ulcerative colitis, no. (%)	Children, no. (%)	Population of interest is a subgroup of all study participants	Analyzed genes
Adam 2018	С	МС	South Africa	NR	40	NR	NR	NR	13 (33%)	Black: 4 (10%); White: 32 (80%); Coloured: 1 (2.5%); Indian: 3 (7.5%)	NR	NR	NR	Yes	ΤΡΜΤ
Akiyama 2019	С	MC	Japan	11/2014- 12/2015	83	No	17	35.1 (SD: 11.7)	47 (56.6%)	Japanese: 83 (100%)	54 (65.1%)	29 (34.9%)	0	No	TPMT, NUDT15
Al- Judaibi 2016	С	UC	Canada	2005-2010	53	NR	4	41 (Min: 19; Max: 80)	32 (60.4%)	Caucasian: 48 (90.6%); Other: 5 (9.4%)	35 (66.0%)	18 (34.0%)	0	No	TPMT, ITPA94, GSTP 313, GSTM1, GSTT1
Ansari 2008	С	MC	UK, Australia	NR	207	NR	8	40.3 (range: 18-80)	100 (48.3%)	NR	117 (56.5%)	90 (43.5%)	0	No	ТРМТ, ІТРА
Asada 2016	С	UC	Japan	Recruitment : 05/2015- 07/2015	161	NR	NR	UC: 37.0±1.4; CD: 32.3±1.2	97 (60.2%)	Japanese: 161 (100%)	72 (44.7%)	89 (55.3%)	NR	Yes	TPMT, NUDT15, ITPA, MRP4
Ban 2010	С	UC	Japan	NR	130	NR	4	Total trial population: 40.8 (range: 13-81)	Total trial population: 173 (62.0%)	Japanese: 130 (100%)	55 (42.3%)	75 (57.7%)	Some children. NR	Yes	TPMT, ITPA, MRP4
Banerje e 2020	С	UC	India	NR	1014	No	79	35.84±12.74	565 (60.4%)	Indian: 1014 (100%)	413 (40.7%)	506 (49.9%)	0	No	NUDT15

#### Table S2. Study characteristics (objective 2)

Bangma 2020	С	UC	The Netherla nds	01/1981- 12/2018	695	NR	NR	47 (IQR: 23)	286 (41.2%)	The Netherlands: 695 (100%)	404 (58.1%)	267 (38.4%)	NR	Yes	TPMT, NUDT15, HLA-DQA1*02:01- HLA-DRB1*07:01 (rs2647087), HLA- DQA1*05 (rs2097432)
Bourgin e 2011	С	UC	France	NR	128	NR	NR	NR	66 (51.6%)	Caucasian: 128 (100%)	103 (80.5%)	25 (19.5%)	0	Yes	TPMT, Rac1
Chao 2017	С	MC	China	07/2012- 11/2015	732	Yes	0	28 (4-68)	507 (69.3%)	Chinese Han: 732 (100%)	660 (90.2%)	60 (8.2%)	Some children. NR	No	TPMT, NUDT15
Choi 2020	С	UC	Korea	01/2014- 03/2015	131	NR	NR	33.0 (IQR: 26.3-40.0)	107 (81.7%)	Korean: 131 (100%)	131 (100%)	0	0	No	TPMT, NUDT15, ITPA, other 34 genes
Coelho 2016	С	UC	UK	NR	78	NR	NR	NR	41 (53%)	Predominantly Caucasian	49 (63%)	17 (22%)	78 (100%)	Yes	TPMT
Cravo 2014	С	MC	Portugal	NR	160	NR	NR	Total trial population: 39 (SD: 12.8)	Total trial population: 109 (45%)	NR	160 (100%)	0	NR	Yes	ABCB1, IL23R, CASP9, Fas, FasL, ATG16L1
Demlov a 2014	С	MC	Czech Republic, Bratislav a	01/2009. End NR	16	No	NR	NR	9 (56.3%)	NR	NR	NR	0	Yes	ТРМТ
De Ridder 2006	С	MC	The Netherla nds	11/2003- 04/2005	72	NR	0	12.5 (6.5- 17.5)	38 (52.8%)	Caucasian: 60 (83.3%); Black: 9 (12.55); Asian: 3 (4.2%)	57 (79.2%)	15 (20.8%)	72 (100%)	No	TPMT, ITPA

Dubinsk y 2000	С	UC	Canada	Recruitment : 1995-1998	92	NR	1	11.5 (range: 1-18)	41 (44.6%)	NR	79 (85.9%)	8 (8.7%)	92 (100%)	No	ΤΡΜΤ
Fangbin 2016	С	UC	China	08/2006- 08/2014	132	NR	NR	34 (18-72)	76 (57.6%)	Chinese: 132 (100%)	102 (77.3%)	30 (22.7%)	0	No	TPMT
Franca 2020	С	MC	Italy	NR	119	NR	7	15.1 (12.3- 16.9)	62 (52.1%)	White: 119 (100%)	67 (52.1%)	51 (42.9%)	119 (100%)	Yes	TPMT, PACSIN2
Gazouli 2010	С	UC	Greece	02/2007- 08/2008	97	NR	NR	11.25 (range: 3–16)	40 (41.2%)	NR	69 (71.1%)	17 (17.5%)	97 (100%)	No	ΤΡΜΤ
Gearry 2003	СС	MC	New Zealand	01/1996- 12/2002	100	NR	6	Cases: 40.6 (range: 17- 74)	27 (48.2%)	Caucasian: 100 (100%)	39 (67.0%)	NR	Some children. NR	No	ΤΡΜΤ
Grover 2020	С	UC	India	01/2019- 03/2020	119	No	15	36.8 (SD: 13.5)	61 (51.3%)	Indian: 119 (100%)	14 (11.8%)	105 (88.2%)	119 (100%) >12 years	No	TPMT, NUDT15
Giudici 2021	C	UC	Italy	01/2010- 12/2014	101	Yes	NR	Total trial population: At onset: 27 (IQR: 21.5- 38.5)	Total trial population: 110 (58%)	Caucasian: 101 (100%)	101 (100%)	0	0	Yes	CARD/NOD2
Hawwa 2008	С	MC	UK	NR	35	NR	NR	39 (15-73)	16 (46%)	NR	NR	NR	Some children of ≥15 years. NR	Yes	ТРМТ, ІТРА, ХО
Heap 2014	сс	мс	Internati onal.	03/2012- 12/2013	2207	NR overall	NR	NR	NR	NR	NR	NR	NR	No	TPMT, ITPA, HLA
Hibi 2003	С	UC	Japan	1985-1999	82	NR	59	NR	NR	Japanese: 82 (100%)	35 (42.7%)	47 (57.3%)	NR	No	TPMT
Hindorf 2006	С	MC	Sweden	Recruitment : 01/2002- 10/2003	60	NR	6	NR	32 (53.3%)	NR	33 (55%)	27 (45%)	0	No	TPMT, ITPA

Hlavaty 2013	С	MC	Slovakia	01/2009- 05/2009	220	NR	NR	37.1 (12.4)	119 (54%)	NR	NR	NR	NR	No	TPMT
Kakuta 2018	СС	MC	Japan	12/2015- 09/2017	1291	NR	NR	41.0 (3.84)	819 (63.4%)	Japanese: 1291 (100%)	548 (42.4%)	722 (55.9%)	Some children. NR	Yes	NUDT15
Kakuta 2016	С	UC	Japan	04/2002- 09/2004	135	No	7	Mean (SD): 35.3 (12.2)	98 (72.6%)	Japanese: 135 (100%)	111 (82.0%)	23 (17.0%)	0	No	NUDT15
Kang 2020	С	UC	Korea	01/2006- 08/2016	192	No	14	At AZA start: patients with leucopenia: Median 14.9 (IQR 12.8- 16.5); patients without leucopenia: 14.9 (IQR 13.0-16.1)	118 (70.7%)	Korean: 192 (100%)	134 (80.2%)	33 (19.8%)	192 (100%)	No	TPMT, NUDT15
Kim 2017	С	MC	South Korea, Japan	07/1998- 09/2015	331	NR	NR	NR	NR	East Asian: 331 (100%)	161 (48.6%)	107 (32.3%)	Some children. NR	Yes	TPMT, NUDT15
Kim 2014	С	UC	South Korea	03/2004- 10/2011	109	NR	NR	15.8 (range 3- 21)	75 (68.8%)	Korean: 109 (100%)	87 (79.8%)	22 (20.2%)	Some children. NR	No	ТРМТ
Kim 2010	С	MC	South Korea	06/1996- 09/2006	286	Yes	NR	25.7 (9.3%)	187 (65.4%)	Korean: 286 (100%)	228 (79.7%)	34 (11.9%)	NR	No	TPMT, ITPA
Koifman 2013	С	UC	Israel	01/2000- January 2011	156	NR	27	Mean: 22.8 (SD: 10.1). Range: 5-58. Median: 20.0	84 (53.8%)	Jewish: 148 (94.8%)	156 (100%)	0	Some children. NR	No	Rac1, Fas ligand, Caspase-9

Larussa 2012	С	UC	Italy	NR	27	NR	NR	NR	NR	Caucasian: 27 (100%)	NR	NR	0	Yes	ΤΡΜΤ
Lee 2017	С	UC	South Korea	01/2014- 03/2015	140	NR	NR	33.6 (8.8)	114 (81.4%)	NR	140 (100%)	NR	0	No	TPMT, NUDT15
Lee 2015	С	UC	South Korea	NR	132	NR	NR	17 (IQR: 15- 18)	95 (72.0%)	Asian: 132 (100%)	99 (75.0%)	33 (25.0%)	132 (100%) <19 years	No	TPMT
Liu 2015	С	UC	China	NR	112	NR	0	32±15.6.Rang e: 18-63	71 (63.4%)	Asian: 112 (100%)	87 (77.7%)	25 (22.3)	0	No	GSTM1, GSTT1, GSTP1, GSTA1
Lucafò 2019	С	UC	Italy	03/2004- 02/2015	111	NR	NR	NR	59 (53.2%)	Caucasian: 111 (100%)	61 (55.0%)	50 (45.0%)	Some children. NR	No	TPMT
Maeda 2021	С	UC	Japan	01/2015- 10/2018	210	Yes	72	UC: median 43 (IQR: 30- 59); CD: 38 (IQR: 26-45)	135 (64.3%)	Japanese: 210 (1005)	170 (51.0%)	103 (49.0%)	0	No	NUDT15
Mahasn eh 2020	С	UC	Jordan	NR	100	NR	NR	Range: 17-72	50 (50%)	Jordan: 100 (100%)	NR	NR	100 (100%) ≥17 years	No	AOX1, XDH
Marinak i 2004	СС	UC	UK	NR	130	NR	NR	Range: 12-82	54 (41.5%)	Caucasian: 130 (100%)	100 (76.9%)	28 (21.5%)	Some children. NR	No	TPMT, ITPA
Mazor Y 2013	C	UC	Israel	01/2000- 01/2011	176	No	0	28.8 (SD: 12.2) Range: 10-61	99 (56%)	Jewish descent: 167 (94.8%); Arab muslims: 6 (3.2%); Arab Christians: 2 (1%); Druze: 2 (1%)	176 (100%)	NR	24 (14%) <17 years	No	TPMT, GSTM1, GSTT1
Mendoz a 2007	С	UC	Spain	NR	76	NR	36	Total trial population: At diagnosis: median: 27;	36 (47.4%)	White: 76 (100%)	76 (100%)	0	Some children. NR	Yes	ABCB1

								mean: 33; range: 8-80							
Mhanna 2019	С	UC	Jordan	09/2015- 09/2016	149	NR	NR	39.9±15.2	67 (45.0%)	Jordanian: 149 (100%)	77 (51.7%)	65 (43.6%)	0	No	ТРМТ
Naughto n MA 1999	С	UC	UK	1992-1997	15	NR	0	NR	NR	NR	NR	NR	NR	No	ΤΡΜΤ
Niess 2012	C	NR	Germany	NR	68	NR	NR	Total trial population: At diagnosis: NOD2-/-: median: 30.1 (14-59); NOD2+/-: median: 26.4 (15-48); NOD2+/+: 18	Total trial population: 77 (41.6%)	NR	68 (100%)	0	Some children. NR	Yes	NOD2
Odahara S 2015	С	UC	Japan	03/2008- 06/2011	48	NR	2	34.2 ± 13.6	29 (60.4%)	Japanese: 48 (100%)	19 (39.6%)	29 (60.4%)	NR	No	TPMT, ITPA
Palmieri 2007	С	MC	Italy	NR	422 ( <i>ITPA</i> : 408)	NR	0	35±14 (CD); 43.5±15 (UC)	227 (53.8%)	Caucasian: 422 (100%)	250 (59.2%)	172 (40.8%)	NR	No	TPMT, ITPA, HPRT1
Park 2016	C	UC	Korea	06/1989- 07/2012	964	NR	950 patients XDH Genotype (p.Gly172Arg ) available. 940 patients XDH Genotype (p.Asn1109T	With early leukopenia: 27 (12-46); late leukopenia: 25 (15-74); without leukopenia: 24 (13-64)	693 (71.9%)	Koreans: 964 (100%)	964 (100%)	0	Some children. NR	No	ХDH

							hr) data available								
Reuther 2003	С	MC	Denmark	NR	71	NR	5	Median: 35 (range: 19-75 )	29 (48.8%)	White: 71 (100%)	71 (100%)	0	0	No	ΤΡΜΤ
Ribaldo ne 2019	С	UC	Italy	06/2015- 01/2016	200	NR	472 excluded	UC: 33 (13- 59); CD: 30.5 (16-67)	116 (58%)	White: 200 (100%)	120 (60%)	80 (40%)	Some children. NR	No	TPMT
Schwab 2002	С	UC	Germany	06/2015- 01/2016	93	NR	NR	UC: 42 (24- 60); CD: 40 (19-71)	45 (48.4%)	Caucasian: 93 (100%)	77 (82.8%)	16 (17.2%)	0	No	TPMT
Smith 2009	С	MC	Uk and Australia	NR	192	NR	23	Mean: 39 (range: 16- 84)	80 (41.7%)	Caucian: 178 (92.7%); Other: 14 (2.8%)	105 (54.7%)	86 (44.8%)	Some children. NR	No	XDH, MOCOS, AOX1
Stepona itiene 2016	С	MC	Lithuania	2011-2014	82	NR	NR	37.1 (SD: 10.1)	42 (51.2%)	White: 82 (100%)	39 (47.6%)	43 (52.4%)	0	Yes	TPMT, ITPA
Stocco 2007	С	MC	Italy	NR	70	NR	NR	Median: 16.17 (range: 1.61-44.66)	34 (49%)	NR	41 (59%)	29 (41%)	Some children. NR	No	TPMT, GST P
Stocco 2006	С	MC	Italy	06/2002- 06/2004	67	NR	NR	Total trial population: Median: 15 (range: 4–38)	Total trial population: 43 (46.7%)	NR	NR	NR	Some children. NR	Yes	MTHFR
Stocco 2005	С	MC	Italy	07/2002- 03/2004	70	NR	0	Mean: 14.2 (range: 0.8- 38.8)	34 (48.6%)	NR	38 (54.3%)	31 (44.3%)	Some children. NR	No	TPMT

Stocco 2004	С	UC	Italy	07/2002- 07/2003	44	NR	0	Mean: 16.4 (range: 4-38)	24 (54.5%)	NR	NR	NR	Some children. NR	No	ΤΡΜΤ
Sutiman 2018	С	UC	Singapur	NR	129	NR	0	42 (range: 17- 18)	87 (67.4%)	Asian: 129 (100%)	89 (69.0%)	40 (31.0%)	Some children. NR	No	TPMT, NUDT15
Takatsu 2009	С	UC	Japan	2000	117	NR	NR	NR	NR	Japanese: 117 (100%)	71 (60.7%)	44 (37.6%)	NR	No	ТРМТ
VanDier en 2005	С	UC	The Netherla nds	01/2003. End NR	109	NR	NR	NR	NR	NR	NR	NR	NR	No	TPMT, ITPA
von Ahsen 2005	С	MC	Germany	2000-2002	71	NR	13	Mean: 36 (SD: 11,6)	31 (43.7%)	Caucasian: 71 (100%)	71 (100%)	0	0	No	TPMT, ITPA
Wang 2018	С	UC	China	02/2016- 11/2017	80	No	NR	33.18 (SD: 11,31)	48 (60%)	Chinese: 80 (100%)	NR	NR	Some children. NR	Yes	TPMT, NUDT15
Weiss 2010	С	MC	Israel	1998-2005	148	NR	There were some. NR	Total trial population: 31.5 (SD: 14.7)	Total trial population: 118 (59.3%)	NR	148 (100%)	0	NR	Yes	NOD2/CARD15
Wilson 2018	C	UC	Canada	07/2012- 03/2017	373	No	NR	Aza-induced pancreatitis: mean: 46.15 (SD: 11.87); controls: mean: 41.25 (SD: 15.98)	170 (45.6%)	NR	245 (65.68%)	128 (34.31%)	0	No	HLA
Winter 2007	С	UC	UK	02/2003- 07/2006	130	NR	15	Mean: 45	70 (53.8%)	NR	69 (53.1%)	61 (46.9%)	NR	No	TPMT

Wroblov a 2012	С	MC	Czech Republic and Slovak republic	NR	188	NR	NR	37.3 (20-71)	107 (56.9%)	Caucasian: 188 (100%)	137 (72.9%)	41 (21.8%)	0	No	TPMT, ITPA, XDH
Xu 2020	С	UC	China	08/2016- 01/2017	159	Yes	5	32 (IQR: 27- 40)	113 (71.1%)	Chinese Han: 159 (100%)	131 (82.4%)	24 (15.1%)	0	No	NUDT15
Yang 2014	C	UC	Korea	Recruitment : 06/1989- 07/2012	978	NR	213	NR	704 (72.0%)	Korean: 978 (100%)	978 (100%)	0	Some children. NR	No	TPMT, NUDT15
Zabala 2015	CC	MC	Spain	NR	Initial C: 167; Replicati on C: 90	NR	NR	Initial C: 31 (8–65); replication C 44 (19–75)	Initial C: 82 (49.1%). Replication C: 39 (43.3%)	NR	Initial C 103 (61.7%). Replication C 55 (61.1%)	Initial C 64 (38.3%). Replicatio n C 35 (38.9%)	Some children. NR	No	TPMT, SNX9, OR13D1, SLAC2-B, ENSG0000197176 , CNGB1, STAB2, NUPL2, PION, OR13C5, APOL5, NAV1, HLA-DPB2, CSTL1, ZNF291, ZNF336, DDX27, OR10T1P, ZNF673 (FLJ20344), LRRC34
Zabala 2013	C	MC	Spain	07/2003- 10/2009	260	NR	NR	Initial C: 39 (8-69), replication: 34 (9-78)	Initial C: 84 (48.6%), replication C: 42 (48.3%)	NR	initial C: 107 (61.8%), replication C: 60 (69.0%)	initial C: 66 (38.2%), replication C: 27 (31.0%)	Some children. NR	No	TPMT, cSNPs related to ADH4 gene
Zabala- Fernánd ez 2011	CC	MC	Spain	NR	232	NR	NR	32.6 (range 8- 70)	115 (49.6%)	NR	156 (67.2%)	76 (32.8%)	Some children. NR	No	TPMT, ITPA

Zelinkov	С	UC	The	10/1995-	262	NR	NR	Mean: 39 (17-	103 (39.3%)	NR	195 (74.4%)	67 (25.6%)	0	No	TPMT, ITPA
a 2006			Netherla	09/2003				87)							
			nds												
Zhu	С	UC	China	07/2014-	411	NR	0	Median: 28	305 (74.0%)	NR	411 (100%)	0	Some children.	No	TPMT, NUDT15
2019				02/2017				(range: 12-					NR		
								70)							

C: cohort study; CC: Case-Control study; MC: multicenter; UC: unicenter; NR: not reported

#### Table S3. Risk of bias (RoB2) of randomized controlled trials (objective 1)

	Randomization process	Deviations form intended interventions	Missing outcome data	Measurement of the outcome	Reported results	Overall
Chang 2020	Low	Low	Low	Low	Unclear	Unclear
Chao 2021	Low	Low	Low	Low	Low	Low
Coenen 2015	Low	Unclear	Low	Low	Low	Unclear
Newman 2011	Low	Low	Unclear	Low	Low	Unclear

### Table S4. Risk of Bias assessment (ROBINS-I) of non-randomized studies (objective 1)

	Bias due	Bias in selection of	Bias in	Bias due to	Bias due	Bias in	Bias in selection	Overall bias
	confoundi ng	into the study	of	from intended interventions	to missing data	measurement of outcomes	reported result	
Wils on 2020	Moderate	Low	Low	Low	Low	Low	Low	Moderate

### Table S5. Risk of bias (Newcastle-Ottawa Scale) of non-randomized studies (objective 2)

	SELECTION				COMPARABILITY	C	DUTCOMES		
Cohort studies	1	2	3	4	1	1	2	3	TOTAL SCORE
Author, year									
Adam 2018	*	*	*	*		*	*	*	7/9
Akiyama 2019	*	*	*	*		*	*	*	7/9
Al-Judaibi 2016	*	*	*				*	*	5/9
Ansari 2008	*	*	*			*	*	*	6/9
Asada 2016	*	*	*		**	*		*	7/9
Ban 2010	*	*							2/9
Banerjee 2020	*	*	*	*	**	*	*	*	9/9
Bangma 2020	*	*	*		**	*		*	7/9

Bourgine 2011			*					*	2/9
Chao 2017	*	*	*			*		*	5/9
Choi 2020	*	*	*		**	*	*		7/9
Coelho 2016	*	*	*				*	*	5/9
Cravo 2014	*	*	*	*	**	*	*	*	9/9
Demlova 2014	*	*	*						3/9
De Ridder 2006	*	*	*			*	*	*	6/9
Dubinsky 2000	*	*	*	*		*	*	*	7/9
Fangbin 2016	*	*	*	*		*		*	6/9
Fangbin 2012	*	*	*				*		4/9
Franca 2020	*	*	*			*	*	*	6/9
Gazouli 2010	*	*	*			*	*	*	6/9
Giudici 2021	*	*	*	*			*		5/9
Grover 2020	*	*	*		**	*	*	*	8/9
Hawwa 2008	*	*	*	*			*		5/9
Hibi 2003	*	*	*				*		4/9
Hindorf 2006	*	*	*		**	*	*	*	8/9
Hlavaty 2013	*	*	*			*	*	*	6/9
Kakuta 2016		*	*	*		*	*	*	6/9
Kang 2020	*	*	*	*	**	*		*	8/9
Kim 2017	*	*	*			*	*		5/9
Kim 2014	*	*	*			*		*	5/9
Kim 2010	*	*	*	*			*	*	6/9
Koifman 2013	*	*	*	*	**	*	*	*	9/9
Larussa 2012	*	*	*	*		*		*	6/9
Lee 2017	*	*	*	*		*	*	*	7/9
Lee 2015	*	*	*	*	**	*		*	8/9
Liu 2015	*	*	*		**	*	*	*	8/9

Lucafò 2019	*	*	*			*	*	*	6/9
Maeda 2021	*	*	*			*		*	5/9
Mahasneh 2020	*	*	*	*		*			5/9
Mazor 2013	*	*	*			*	*	*	6/9
Mendoza 2007	*	*	*	*		*	*	*	7/9
Mhanna 2019	*	*	*						3/9
Naughton 1999	*	*	*						3/9
Niess 2012			*	*		*	*	*	5/9
Odahara S 2015	*	*	*	*			*	*	6/9
Palmieri 2007	*	*	*	*		*	*	*	7/9
Park 2016	*	*	*			*	*	*	6/9
Reuther 2003	*	*	*	*				*	5/9
Ribaldone 2019	*	*	*	*		*	*	*	7/9
Schwab 2002	*	*	*			*		*	5/9
Smith 2009	*	*	*			*	*	*	6/9
Steponaitiene 2016	*	*	*			*	*	*	6/9
Stocco 2007	*	*	*		**	*	*	*	8/9
Stocco 2006	*	*	*				*	*	5/9
Stocco 2005	*	*	*			*	*	*	6/9
Stocco 2004	*	*	*				*	*	5/9
Sutiman 2018	*	*	*	*			*	*	6/9
Takatsu 2009	*	*	*					*	4/9
VanDieren 2005	*	*	*	*			*	*	6/9
von Ahsen 2005	*	*	*	*		*		*	6/9
Wang 2018	*	*	*		**		*	*	7/9
Weiss 2010	*	*	*	*		*	*		6/9
Wilson 2018	*	*	*			*	*	*	6/9
Winter 2007	*	*	*	*		*		*	6/9

Wroblova 2012	*	*	*			*	*	*	6/9
Xu 2020	*	*	*	*	**	*	*	*	9/9
Yang 2014	*	*	*	*		*	*		6/9
Zabala 2013	*	*	*	*	**	*	*	*	9/9
Zelinkova 2006	*	*	*	*		*	*	*	7/9
Zhu 2019	*	*	*			*	*	*	6/9
		SELEC	TION		COMPARABILITY	l	EXPOSURE		
Case-control studies	1	2	3	4	1	1	2	3	TOTAL SCORE
Author, year									
Author, year Gearry 2003		*	*	*		*	*		5/9
Author, year Gearry 2003 Heap 2014	*	*	*	*	**	*	*		5/9 8/9
Author, year Gearry 2003 Heap 2014 Kakuta 2018	*	*	*	*	*	*	*	*	5/9 8/9 6/9
Author, year Gearry 2003 Heap 2014 Kakuta 2018 Marinaki 2004	*	* * *	*	*	**	*	* * * *	*	5/9 8/9 6/9 5/9
Author, year Gearry 2003 Heap 2014 Kakuta 2018 Marinaki 2004 Zabala 2015	*	* * * *	*	* * *	*	* * * *	* * * *	*	5/9 8/9 6/9 5/9 7/9

Table S6. Additional results for different comparisons of TPMT genotype for outcomes of interest

		TPM	T gen		TPMT*2		TPMT*3		
Outcome	No. mutated alleles vs wild- type	1	2	1	2	1-2	1	2	1-2
All-cause mortality	No. studies	0	0	0	0	0	0	0	0
Total SAE	No. studies	12	6	1	2	2	6	3	6
	OR (95%CI)	2.02	74.09	5776	13.02	25.19	2.53	75.73	5.74
		(1.05-3.88)	(12.25-448.24)	(0.00-1.7e+11)	(0.97-174.12)	(2.71-234.18)	(0.59-10.04)	(5.29-1083.88)	(1.99-16.61)
	l <sup>2</sup>	1%	0%	NA	0%	27%	0%	0%	0%
	Figure	S37	S45	-	S56	S59	S66	S74	S81
Total	No. studies	38	12	5	2	6	28	8	28
hematologic AE	OR (95%CI)	2.65	33.02	3.54	8.00	4.33	2.65	94.98	3.01
		(2.05-3.43)	(9.65-112.96)	(0.63-19.86)	(0.54-119.34)	(1.01-18.55)	(1.94-3.62)	(14.35-628.79)	(2.23-4.05)
	l <sup>2</sup>	48%	0%	0%	0%	0%	49%	0%	53%
	Figure	S38	S46	\$52	\$57	S60	S67	\$75	S82
Serious	No. studies	11	6	1	2	2	6	2	6
hematologic AE	OR (95%CI)	4.58	79.02	5776	26.58	51.29	2.63	9741.13	5.91
	-	(1.93-10.87)	(14.31-436.34)	(0.00-1.7e+11)	(1.53-462.41)	(4.14-635.21)	(0.61-11.33)	(0.12-8.2e+08)	(2.00-17.46)
	I <sup>2</sup>	0%	0%	NA	0%	14%	0%	0%	0%
	Figure	S39	S47	-	S58	S61	S68	S76	S83
Withdrawal due	No. studies	11	4	1	1	2	5	2	5
to AE	OR (95%CI)	3.21	6.36	0.01	132.37	1.39	3.71	1.18	3.49
	,	(1.91-5.41)	(1.28-31.48)	(0.00-3.0e+06)	(0.01-2.5e+06)	(0.15-12.79)	(1.91-7.22)	(0.08-17.79)	(1.83-6.64)
	ľ	0%	0%	NA	NA	5%	7%	0%	10%
	Figure	S40	S48	-	-	S62	S69	\$77	S84
Pancreatitis	No. studies	21	8	4	1	5	15	6	15
	OR (95%CI)	0.89	0.22	0.09	0.47	0.13	0.72	0.15	0.67
	12	(0.47-1.67)	(0.00-23.55)	(0.00-226.28)	(0.00-9346.89)	(0.00-57.63)	(0.28-1.86)	(0.00-108.55)	(0.26-1.72)
	l Figure	0%	0%	0%	NA	0%	0%	0%	0%
Henetetevisity	Figure	341	549	355	-	303	370	5/6	365
пераююлицу	OR (05%(CI)	0.69	0	4	202.00	2.02	0.79	0.16	17
	OK (55/6CI)	(0 31-1 48)	(0.21-12.06)	(0.00-382.50)	(0.01-5.8e+06)	(0.25=16.21)	(0.35-1.75)	(0.00-105.21)	(0.44-1.79)
	1 <sup>2</sup>	0%	0%	(0.00 362.50)	(0.01 5.0C 100)	0%	0%	0%	0%
	Figure	\$42	\$50	\$54	-	\$64	\$71	\$79	586
Gastrointestinal	No. studies	14	7	2	0	2	12	6	12
AE	OR (95%CI)	1.76	0.11	0.09	-	0.09	1.94	0.10	1.82
		(1.02-3.03)	(0.00-190.39)	(0.00-		(0.00-	(1.10-3.42)	(0.00-352.47)	(1.04-3.20)
				42594.45)		42594.45)			
	l <sup>2</sup>	0%	0%	0%	-	0%	0%	0%	0%
	Figure	S43	S51	S55	-	S65	S72	S80	S87
Change in disease activity	No. studies	0	0	0	0	0	0	0	0
Clinical	No. studies	8	1	1	0	1	5	1	5
Remission	OR (95%CI)	1.57	0.00	0.37	-	0.37	1.47	0.00	1.25
		(0.92-2.69)	(0.00-8.9e+08)	(0.03-4.12)		(0.03-4.12)	(0.75-2.86)	(0.00-8.9e+08)	(0.66-2.35)
	I <sup>2</sup>	29%	NA	NA	-	NA	37%	NA	45%
	Figure	\$44	-	-	-	-	\$73	-	S88

AE: adverse events; CI: confidence interval; NA: not applicable; OR: odds ratio; SAE: serious adverse events

Table S7. Sensitiv	ity analyses excludi	ng studies with high risk (	of bias	
Outcome	No. mutated alleles vs wild- type	<i>TPMT</i> gen	ITPA gen	NUDT15 gen
All-cause mortality	No. studies	0	0	0
Total SAE	No. studies	9	1	5
	OR (95%CI)	5.91 (2.87-12.19)	0.30 (0.00-127.69)	11.44 (7.36-17.77)
	l <sup>2</sup>	10%	NA	0%
	Figure	S89	-	S221
Total	No. studies	38	7	15
hematologic AE	OR (95%CI)	3.03 (2.36-3.88)	0.87 (0.59-1.26)	8.36 (5.71-12.23)
	l <sup>2</sup>	48%	42%	80%
	Figure	S90	\$155	S222
Serious	No. studies	10	1	6
hematologic AE	OR (95%CI)	8.76 (4.21-18.26)	0.30 (0.00-127.69)	12.83 (8.21-20.04)
	l <sup>2</sup>	0%	NA	0%
	Figure	S91	-	S223
Withdrawal due	No. studies	11	3	1
to AE	OR (95%CI)	3.28 (2.04-5.27)	1.11 (0.48-2.55)	2.08 (0.76-5.68)
	l <sup>2</sup>	0%	27%	NA
	Figure	S92	\$156	-
Pancreatitis	No. studies	21	4	4
	OR (95%CI)	0.92 (0.48-1.79)	0.70 (0.22-2.17)	0.28 (0.08-1.05)
	l <sup>2</sup>	0%	0%	0%
	Figure	S93	S157	S224
Hepatotoxicity	No. studies	22	5	3
	OR (95%CI)	0.73 (0.37-1.46)	0.72 (0.20-2.57)	0.63 (0.32-1.25)
	l <sup>2</sup>	0%	0%	0%
	Figure	S94	S158	S225
Gastrointestinal	No. studies	14	2	3
AE	OR (95%CI)	0.80 (0.40-1.59)	0.09 (0.00-4.12)	2.04 (1.34-3.08)
	l <sup>2</sup>	8%	0%	0%
	Figure	S95	\$159	S226
Change in disease activity	No. studies	0	0	0
Clinical	No. studies	7	2	1
Remission	OR (95%CI)	1.28 (0.76-2.17)	0.70 (0.40-1.21)	1.07 (0.47-2.46)
	l <sup>2</sup>	35%	0%	NA
	Figure	S96	S160	-

AE: adverse events; CI: confidence interval; NA: not applicable; OR: odds ratio; SAE: serious adverse events

Table S8. Additional results for different comparisons of ITPA genotype for outcomes of interest

		ITPA	gen		ITPA 94C>A			ITPA IVS2 + 21A>C	
Outcome	No. mutated	1	2	1	2	1-2	1	2	1-2
	alleles vs wild-								
	type								
All-cause	No. studies	0	0	0	0	0	0	0	0
mortality									
Total SAE	No. studies	1	0	1	0	1	0	0	0
	OR (95%CI)	0.30		0.30		0.30			
	.2	(0.00-127.69)		(0.00-127.69)		(0.00-127.69)			
		NA		NA		NA			
	Figure	-		-		-	-	-	<i>.</i>
lotal	No. studies	6	4	9	4	11	5	5	6
nematologic AE	OR (95%CI)	1.00	0.30	1.35	0.20	1.09	0.69	0.96	0.76
	12	(0.59-1.09)	(0.10-0.87)	(0.80-2.28)	(0.00-439.41)	(0.75-1.59)	(0.55-1.46)	(0.21-4.54)	(0.40-1.44)
	Figuro	44% \$117	5122	14/0 \$126	5122	13% \$12E	5142	5146	51E0
Sorious	Figure No. studios	1	0	1	0	3133	0	5140	3130
hematologic AF	OR (95%CI)	0.30	0	0.30	0	1 11	0	0	0
inclusion of the second	011 (55/001)	(0.00-127.69)		(0.00-127.69)		(0 13-9 60)			
	<sup>2</sup>	NA		NA		0%			
	Figure	-		-		\$136			
Withdrawal due	No. studies	2	1	2	1	3	1	1	2
to AE	OR (95%CI)	0.82	0.07	1.00	0.07	1.91	0.50	0.07	0.69
		(0.23-2.86)	(0.00-62.86)	(0.22-4.55)	(0.00-6878.45)	(0.73-4.95)	(0.06-4.36)	(0.00-3.8e+05)	(0.21-2.23)
	l <sup>2</sup>	13%	NA	0%	NA	21%	NA	NA	0%
	Figure	S118	-	S127	-	S137	-	-	S151
Pancreatitis	No. studies	4	2	7	2	8	4	4	5
	OR (95%CI)	0.74	0.16	0.92	0.16	0.86	1.40	0.15	1.37
		(0.24-2.34)	(0.00-138.00)	(0.40-2.14)	(0.00-9613.47)	(0.38-1.98)	(0.63-3.11)	(0.00-45.64)	(0.64-2.93)
	l <sup>2</sup>	0%	0%	14%	0%	7%	0%	0%	0%
	Figure	S119	S124	S128	S133	S138	S143	S147	S152
Hepatotoxicity	No. studies	5	2	8	2	10	4	4	5
	OR (95%CI)	0.73	0.73	1.19	0.52	0.84	0.37	0.21	0.54
		(0.20-2.61)	(0.00-715.62)	(0.48-2.95)	(0.00-	(0.35-1.99)	(0.07-2.10)	(0.00-55.25)	(0.14-2.03)
	.2				31889.34)				
	[ <sup>-</sup>	0%	0%	0%	0%	0%	0%	0%	0%
Castraintestinal	Figure	5120	5125	5129	5134	5139	5144	5148	5153
Gastrointestinai	NO. Studies	2	1	5	1	b 1 1 4	3	3	4
AL	OR (95%CI)	(0.09	(0.00-6.3e+14)	(0.72	(0.00-6.3e+14)	1.14	1.10	1.14	1.25
	I <sup>2</sup>	(0.00-4.15)	(0.00-0.3e+14)	34%	(0.00-0.3e+14)	22%	(0.30-2.83)	(0.13-0.31)	(0.30-2.70)
	Figure	5121	-	\$130	-	\$140	\$145	\$149	\$154
Change in	No. studies	0	0	0	0	0	0	0	0
disease activity	Norstaales	0	Ũ	Ũ	Ũ	Ũ	0	Ũ	0
Clinical	No. studies	2	1	3	1	3	1	1	1
Remission	OR (95%CI)	0.68	111.03	0.66	111.03	0.67	0.83	0.70	0.82
		(0.39-1.19)	(0.00-7.2e+17)	(0.41-1.05)	(0.00-7.2e+17)	(0.42-1.06)	(0.47-1.46)	(0.10-5.09)	(0.47-1.43)
	I <sup>2</sup>	0%	NA	0%	NA	0%	NA	NA	NA
	Figure	S122	-	\$131	-	\$141	-	-	-

AE: adverse events; CI: confidence interval; NA: not applicable; OR: odds ratio; SAE: serious adverse events

		NUDT	15 gen	NUDT15 R139C				
Outcome	No. mutated	1	2	1	2	1-2		
	alleles vs wild-							
	type							
All-cause	No. studies	0	0	0	0	0		
mortality		-						
I otal SAE	No. studies	5	3	4	3	4		
	OR (95%CI)	6.13	155.17	/.28	//.68	9.79		
	.2	(3.76-9.98)	(73.19-328.96)	(2.92-18.15)	(13.58-444.29)	(4.12-23.24)		
		0%	43%	14%	3%	5%		
	Figure	\$1//	\$184	\$190	\$197	\$200		
Total	No. studies	15	11	11	8	12		
nematologic AE	OR (95%CI)	5.83	159.26	6.80	200.91	6.83		
	.2	(4.22-8.06)	(66.44-381.74)	(4.46-10.38)	(45.09-895.18)	(4.25-10.98)		
		/2%	0%	70%	0%	/8%		
	Figure	\$178	\$185	\$191	\$198	\$201		
Serious	No. studies	6	4	6	4	6		
nematologic AE	OR (95%CI)	6.89 (4.24-11.22)	1/3.// (83.18-363.03)	5.66 (2.58-12.37)	(32.10-722.51)	9.79 (4.71-20.35)		
	l <sup>2</sup>	22%	28%	0%	25%	0%		
	Figure	S179	S186	S192	S199	S202		
Withdrawal due	No. studies	2	1	2	1	1		
to AE	OR (95%CI)	1.93	26.73 (4.40-	3.12	26.73 (4.40-	2.08 (0.76-		
		(0.89-4.20)	162.43)	(1.40-6.97)	162.43)	5.68)		
	l <sup>2</sup>	55%	NA	0%	NA	NA		
	Figure	S180	-	S193	-	-		
Pancreatitis	No. studies	4	2	2	1	2		
	OR (95%CI)	0.32	0.08 (0.00-	0.29 (0.01-	0.32 (0.00-	0.27 (0.01-		
		(0.09-1.18)	64.64)	11.79)	9953.97)	5.69)		
	.2	0%	0%	0%	NA	09/		
	F	070	- · · -	070	INA	0%		
	Figure	\$181	S187	\$194	-	5203		
Hepatotoxicity	Figure No. studies	5181 3	S187 2	S194 2	- 1	S203 2		
Hepatotoxicity	Figure No. studies OR (95%CI)	S181 3 0.66	\$187 2 0.48	S194 2 0.41 (0.06-	- 1 0.19 (0.00-	5203 2 0.39 (0.06-		
Hepatotoxicity	Figure No. studies OR (95%CI)	5181 3 0.66 (0.32-1.34)	S187 2 0.48 (0.07-3.41)	5194 2 0.41 (0.06- 2.68)	- 1 0.19 (0.00- 5720.91)	S203 2 0.39 (0.06- 2.54)		
Hepatotoxicity	Figure No. studies OR (95%CI)	5181 3 0.66 (0.32-1.34) 0%	S187 2 0.48 (0.07-3.41) 0%	5194 2 0.41 (0.06- 2.68) 0%	- 1 0.19 (0.00- 5720.91) NA	0% S203 2 0.39 (0.06- 2.54) 0%		
Hepatotoxicity	Figure No. studies OR (95%CI) I <sup>2</sup> Figure	5181 3 0.66 (0.32-1.34) 0% 5182	S187 2 0.48 (0.07-3.41) 0% S188	S194           2           0.41 (0.06-           2.68)           0%           S195	- 1 0.19 (0.00- 5720.91) NA -	0% S203 2 0.39 (0.06- 2.54) 0% S204		
Hepatotoxicity Gastrointestinal	Figure No. studies OR (95%CI) I <sup>2</sup> Figure No. studies	5181 3 0.66 (0.32-1.34) 0% 5182 3	5187 2 0.48 (0.07-3.41) 0% 5188 2	5194 2 0.41 (0.06- 2.68) 0% 5195 2	- 1 0.19 (0.00- 5720.91) NA - 1	0% S203 2 0.39 (0.06- 2.54) 0% S204 2		
Hepatotoxicity Gastrointestinal AE	Figure No. studies OR (95%CI) I <sup>2</sup> Figure No. studies OR (95%CI)	5181 3 0.66 (0.32-1.34) 0% 5182 3 1.96	\$187 2 0.48 (0.07-3.41) 0% \$188 2 2 2.52	5194 2 0.41 (0.06- 2.68) 0% 5195 2 1.02 (0.21-	- - 1 0.19 (0.00- 5720.91) NA - - 1 6.12 (0.60-	0% S203 2 0.39 (0.06- 2.54) 0% S204 2 1.40 (0.36-		
Hepatotoxicity Gastrointestinal AE	F Figure No. studies OR (95%CI) I <sup>2</sup> Figure No. studies OR (95%CI)	0% 5181 3 0.66 (0.32-1.34) 0% 5182 3 1.96 (1.26-3.04)	S187 2 0.48 (0.07-3.41) 0% S188 2 2.52 (1.10-5.81)	0.3 5194 2 0.41 (0.06- 2.68) 0% 5195 2 1.02 (0.21- 4.97)	- - 1 0.19 (0.00- 5720.91) NA - 1 6.12 (0.60- 62.55)	0% S203 2 0.39 (0.06- 2.54) 0% S204 2 1.40 (0.36- 5.55)		
Hepatotoxicity Gastrointestinal AE	I <sup>2</sup> Figure           No. studies           OR (95%CI)           I <sup>2</sup> Figure           No. studies           OR (95%CI)           I <sup>2</sup> Figure           No. studies           OR (95%CI)           I <sup>2</sup>	5781 3 0.66 (0.32-1.34) 0% 5182 3 1.96 (1.26-3.04) 0%	\$187           2           0.48           (0.07-3.41)           0%           \$188           2           2.52           (1.10-5.81)           0%	0% \$194 2 0.41 (0.06- 2.68) 0% \$195 2 1.02 (0.21- 4.97) 0%	- - 1 0.19 (0.00- 5720.91) NA - 1 6.12 (0.60- 62.55) NA	0% S203 2 0.39 (0.06- 2.54) 0% S204 2 1.40 (0.36- 5.55) 0%		
Hepatotoxicity Gastrointestinal AE	F Figure No. studies OR (95%CI) I <sup>2</sup> Figure No. studies OR (95%CI) I <sup>2</sup> Figure	0% S181 3 0.66 (0.32-1.34) 0% S182 3 1.96 (1.26-3.04) 0% S183	\$187 2 0.48 (0.07-3.41) 0% \$188 2 2.52 (1.10-5.81) 0% \$189	5194 2 0.41 (0.06- 2.68) 0% 5195 2 1.02 (0.21- 4.97) 0% 5196		0% S203 2 0.39 (0.06- 2.54) 0% S204 2 1.40 (0.36- 5.55) 0% S205		
Hepatotoxicity Gastrointestinal AE Change in disease activity	F Figure No. studies OR (95%CI) I <sup>2</sup> Figure No. studies OR (95%CI) I <sup>2</sup> Figure No. studies	0% 5181 3 0.66 (0.32-1.34) 0% 5182 3 1.96 (1.26-3.04) 0% 5183 0	\$187           2           0.48           (0.07-3.41)           0%           \$188           2           2.52           (1.10-5.81)           0%           \$189           0	5194 2 0.41 (0.06- 2.68) 0% 5195 2 1.02 (0.21- 4.97) 0% 5196 0		0% S203 2 0.39 (0.06- 2.54) 0% S204 2 1.40 (0.36- 5.55) 0% S205 0		
Hepatotoxicity Gastrointestinal AE Change in disease activity Clinical	F Figure No. studies OR (95%CI) I <sup>2</sup> Figure No. studies No. studies No. studies	0% 5181 3 0.66 (0.32-1.34) 0% 5182 3 1.96 (1.26-3.04) 0% 5183 0 1	\$187           2           0.48           (0.07-3.41)           0%           \$188           2           2.52           (1.10-5.81)           0%           \$189           0           0	5194 2 0.41 (0.06- 2.68) 0% 5195 2 1.02 (0.21- 4.97) 0% 5196 0		0% S203 2 0.39 (0.06- 2.54) 0% S204 2 1.40 (0.36- 5.55) 0% S205 0 1		
Hepatotoxicity Gastrointestinal AE Change in disease activity Clinical Remission	I°           Figure           No. studies           OR (95%CI)           I²           Figure           No. studies           OR (95%CI)           I²           Figure           No. studies           No. studies           OR (95%CI)	0% 5181 3 0.66 (0.32-1.34) 0% 5182 3 1.96 (1.26-3.04) 0% 5183 0 1.07 (0.47-	\$187           2           0.48           (0.07-3.41)           0%           \$188           2 <b>1.10-5.81</b> 0%           \$189           0	5.194 2 0.41 (0.06- 2.68) 0% 5.195 2 1.02 (0.21- 4.97) 0% 5.196 0 0 1 1.07 (0.47-		0% S203 2 0.39 (0.06- 2.54) 0% S204 2 1.40 (0.36- 5.55) 0% S205 0 1 1.07 (0.47-		
Hepatotoxicity Gastrointestinal AE Change in disease activity Clinical Remission	I°           Figure           No. studies           OR (95%CI)           I²           Figure           No. studies           OR (95%CI)           I²           Figure           No. studies           No. studies           OR (95%CI)	5781 5181 3 0.66 (0.32-1.34) 0% 5182 3 1.96 (1.26-3.04) 0% 5183 0 1 1.07 (0.47- 2.46)	\$187           2           0.48           (0.07-3.41)           0%           \$188           2           2.52           (1.10-5.81)           0%           \$189           0           0	5194 2 0.41 (0.06- 2.68) 0% 5195 2 1.02 (0.21- 4.97) 0% 5196 0 1 1.07 (0.47- 2.46)		0% \$203 2 0.39 (0.06- 2.54) 0% \$204 2 1.40 (0.36- 5.55) 0% \$205 0 1 1.07 (0.47- 2.46)		
Hepatotoxicity Gastrointestinal AE Change in disease activity Clinical Remission	I*           Figure           No. studies           OR (95%CI)           I²           Figure           No. studies           OR (95%CI)           I²           Figure           No. studies           OR (95%CI)           I²           Figure           No. studies           OR (95%CI)           I²	0% 5181 3 0.66 (0.32-1.34) 0% 5182 3 1.96 (1.26-3.04) 0% 5183 0 1 1.07 (0.47- 2.46) NA	\$187           2           0.48           (0.07-3.41)           0%           \$188           2           2.52           (1.10-5.81)           0%           \$189           0           -	5/34 5/194 2 0.41 (0.06- 2.68) 0% 5/195 2 1.02 (0.21- 4.97) 0% 5/196 0 1 1.07 (0.47- 2.46) NA		0% S203 2 0.39 (0.06- 2.54) 0% S204 2 1.40 (0.36- 5.55) 0% S205 0 1 1.07 (0.47- 2.46) NA		

Table S9. Additional results for different comparisons of NUDT15 genotype for outcomes of interest

Table S10. Additional results for different comparisons of NUDT15 genotype for outcomes of interest

		NUDT15*2				NUDT15*3			NUDT15*4			NUDT15*5			NUDT15*6	
Outcome	No. mutated	1	2	1-2	1	2	1-2	1	2	1-2	1	2	1-2	1	2	1-2
	alleles vs wild-															
	type															
Total SAE	No. studies	1	1	1	1	1	1	1	1	1	2	1	2	0	0	0
	OR (95%CI)	6.43 (2.54-	513.75	20.33 (9.84-	8.38 (3.86-	171.12	20.80 (10.65-	0.07 (0.00-	36946.44	16.31 (3.06-	2.59 (0.33-	3.00 (0.37-	2.28 (0.29-	-	-	-
		16.26)	(107.05-	41.99)	18.19)	(66.50-	40.61)	2.6e+07)	(0.00-	86.80)	20.17)	24.30)	17.68)			
			1465.46)			441.02)			3.1e+20)							
	l <sup>2</sup>	NA	NA	NA	NA	NA	NA	NA	NA	NA	0%	NA	0%	-	-	-
	Figure	-	-	-	-	-	-	-	-	-	S212	-	S216	-	-	-
Total	No. studies	2	2	2	3	3	3	1	1	1	4	2	4	2	1	2
hematologic AE	OR (95%CI)	5.57 (3.80-	222.34	7.96 (5.59-	3.41 (2.51-	143.64	5.45 (4.12-	1.47 (0.17-	6096.05	4.41 (1.08-	2.51 (1.18-	5.21 (2.18-	3.55 (1.85-	3.45 (1.39-	2932 (0.00-	3.89 (1.91-
		8.17)	(28.38-	11.34)	4.65)	(42.04-	7.20)	12.38)	(0.00-	18.01)	5.31)	12.45)	6.80)	6.82)	9.8e+22)	9.41)
			1741.81)			490.73)			5.1e+19)							
	l <sup>2</sup>	0%	0%	0%	0%	0%	0%	NA	NA	NA	0%	32%	0%	0%	NA	0%
	Figure	S206	S207	S208	S209	S210	S211	-	-	1	S213	\$215	S217	S219	-	S220
Serious	No. studies	1	1	1	1	1	1	1	1	1	2	1	2	0	0	0
hematologic AE	OR (95%CI)	6.43 (2.564-	20.33 (9.84-	20.33 (9.84-	8.38 (3.86-	171.25	20.80 (10.65-	0.07 (0.00-	36946.44	16.31 (3.06-	2.59 (0.33-	3.00 (0.37-	2.28 (0.29-	-	-	-
		16.26)	41.99)	41.99)	18.19)	(66.50-	40.61)	2.6e+07)	(0.00-	86.80)	20.17)	24.30)	17.68)			
						441.02)			3.1e+20)							
	l <sup>2</sup>	NA	NA	NA	NA	NA	NA	NA	NA	NA	0%	NA	0%	-	-	-
	Figure	-	-	-	-	-	-	-	-	-	S214	-	S218	-	-	-
AE: adverse events	s; CI: confidence inter	rval; NA: not applic	able; OR: odds ra	tio; SAE: serious a	dverse events											
*No studies report	ed data on the rest o	of the outcomes														

#### **Figures**



Fixed-effects Mantel-Haenszel model

Figure S1. Forest plot of comparison genotyping vs no genotyping, outcome: Total serious adverse events

Study	Gen Yes	otype No	No ger Yes	notype No				Risk Ra with 95%	tio CI	Weight (%)
RCT										
Chang 2020	1	86	1	94				– 1.09 [ 0.07,	17.19]	38.63
Newman 2011	0	163	1	158				0.33 [ 0.01,	7.92]	61.37
Heterogeneity: I <sup>2</sup>	= 0.0	0%, H	<sup>2</sup> = 1.00	C				0.62 [ 0.08,	4.59]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(	(1) = 0	).32, p	= 0.57							
Overall								0.62 [ 0.08,	4.59]	
Heterogeneity: I <sup>2</sup>	= 0.0	0%, H	<sup>2</sup> = 1.00	D						
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q	(1) = 0	).32, p	= 0.57		Higher in N	lo genotype	Higher in C	Genotype		
Test of group dif	ferend	ces: Q <sub>b</sub>	(0) = -0	0.00, p = .						
					1/64	1/8	1 8	_		

Fixed-effects Mantel-Haenszel model

Figure S2. Forest plot of comparison genotyping vs no genotyping, outcome: Serious hematologic adverse events



# Figure S3. Forest plot of comparison genotyping vs no genotyping, outcome: Withdrawal due to adverse events

Study	Gen Yes	otype No	No ger Yes	notype No	Risk Ratio with 95% Cl	Weight (%)
Historically controlled						
Wilson 2020	1	598	13	360	← ■ 0.05 [ 0.01, 0.3	6] 14.32
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00			0.05 [ 0.01, 0.3	3]
Test of $\theta_i = \theta_j$ : Q(0) = 0.00, p = .						
RCT						
Chao 2021	3	216	5	199		1] 4.63
Coenen 2015	106	283	84	281	1.18 [ 0.92, 1.5	2] 77.44
Newman 2011	1	162	4	155		3.62
Heterogeneity: $I^2 = 33.62\%$ , $H^2 = 1.51$					🔶 1.11 [ 0.87, 1.4	1]
Test of $\theta_i = \theta_j$ : Q(2) = 3.01, p = 0.22						
Overall					0.96 [ 0.76, 1.2]	1]
Heterogeneity: $I^2 = 77.32\%$ , $H^2 = 4.41$						
Test of $\theta_i = \theta_j$ : Q(3) = 13.23, p = 0.00					Higher in No genotype Higher in Genotype	
Test of group differences: $Q_b(1) = 9.08$ , p = 0.00						
					1/64 1/16 1/4 1	

Fixed-effects Mantel-Haenszel model


	Gen	otype	No ger	notype		Risk Ratio	Weight
Study	Yes	No	Yes	No		with 95% CI	(%)
RCT							
Chao 2021	7	212	8	196		0.82 [ 0.30, 2.21]	7.04
Coenen 2015	106	291	98	273	-#-	1.01 [ 0.80, 1.28]	86.08
Newman 2011	19	144	8	151		2.32 [ 1.04, 5.14]	6.88
Heterogeneity: I	<sup>2</sup> = 51	.84%,	$H^2 = 2.$	08	-	1.09 [ 0.87, 1.35]	
Test of $0_i = 0_j$ : Q	2(2) = 4	4.15, p	o = 0.13				
Overall					-	1.09 [ 0.87, 1.35]	
Heterogeneity: I	<sup>2</sup> = 51	.84%,	$H^2 = 2.$	08			
Test of $0_i = 0_j$ : Q	2(2) = 4	4.15, p	) = 0.13	Hig	her in No genotype Higher in	Genotype	
Test of group di	fferend	ces: Q	<sub>b</sub> (0) = 0	.00, p =			
					1/2 1 2	4	
Fixed-effects Mar	ntel-Ha	aensz	el mode	el			

#### Figure S5. Forest plot of comparison genotyping vs no genotyping, outcome: Hepatotoxicity

	Geno	otype	No ger	notype		<b>Risk Ratio</b>	Weight
Study	Yes	No	Yes	No		with 95% CI	(%)
RCT							ä.
Chao 2021	4	215	5	199			1.54
Chang 2020	18	69	24	71		0.82 [ 0.48, 1.40]	6.83
Coenen 2015	290	115	269	109		1.01 [ 0.92, 1.10]	82.88
Newman 2011	33	130	29	130		1.11 [ 0.71, 1.74]	8.74
Heterogeneity:	$ ^2 = 0.0$	0%, H	$^{2} = 1.0$	D	•	1.00 [ 0.91, 1.10]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : C	Q(3) = C	).96, p	= 0.81				
Overall					+	1.00 [ 0.91, 1.10]	
Heterogeneity: I	$ ^2 = 0.0$	0%, H	$ ^2 = 1.0$	D			
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : G	Q(3) = C	).96, p	= 0.81		Higher in No genotype Higher	in Genotype	
Test of group di	fferenc	es: Q	<sub>0</sub> (0) = 0	.00, p = .			
					1/4 1/2 1	2	

Fixed-effects Mantel-Haenszel model

# Figure S6. Forest plot of comparison genotyping vs no genotyping, outcome: Gastrointestinal side effects

	Μ	lut	Nor	n mut					Odds F	Ratio	Weight
Study	Yes	No	Yes	No					with 95	% CI	(%)
Case-control											
Gearry 2003	2	7	0	91				•	29.77 [ 2.26,	391.90]	2.67
Heterogeneity: I <sup>2</sup> =	0.00	%, H <sup>2</sup>	= 1.0	00					29.77 [ 2.26,	391.90]	
Test of $0_i = 0_j$ : Q(0)	= 0.0	00, p	= .								
Cohort											
Demlova 2014	0	4	0	12	←		-	$\rightarrow$	1.00 [ 0.01,	105.38]	7.48
Hibi 2003	4	4	0	74			-	-	83.00 [ 6.91,	997.66]	1.86
Larussa 2012	1	3	1	22			-	$\rightarrow$	7.33 [ 0.36,	150.71]	4.69
Mhanna 2019	0	7	4	138	<	-		$\rightarrow$	0.19 [ 0.00,	1703.31]	9.77
Mazor 2013	0	4	24	148	←			$\rightarrow$	0.03 [ 0.00,	15586.61]	23.85
Schwab 2002	3	5	11	74		_			4.04 [ 0.84,	19.31]	24.99
Sutiman 2018	0	3	6	120	←	-			0.13 [ 0.00,	54705.08]	6.80
Takatsu 2009	0	3	4	110	←			>	0.19 [ 0.00,	42566.46]	5.34
Van Dieren 2005	2	8	0	99					28.44 [ 2.19,	369.67]	2.80
Winter 2007	1	10	3	116		31 <del>-</del>	_		3.87 [ 0.37,	40.69]	9.75
Heterogeneity: I <sup>2</sup> =	5.69	%, H <sup>2</sup>	= 1.0	06			-		4.30 [ 2.05,	9.02]	
Test of $0_i = 0_j$ : Q(9)	= 9.5	54, p	= 0.3	9							
Overall							•		4.98 [ 2.49,	9.99]	
Heterogeneity: I <sup>2</sup> =	7.41	%, H <sup>2</sup>	= 1.0	08							
Test of $0_i = 0_j$ : Q(10)	)) = 1	0.80,	p = 0	).37	Higher in 1	non-mut	Higher in	mut			
Test of group differ	ence	s: Q <sub>b</sub>	(1) =	2.00, p = 0.16							
					1/64	1/4	4	64			
Fixed-effects Mantel	-Hae	nszel	l mod	el							

Figure S7. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Total serious adverse events

	Μ	lut	Nor	n mut					Odds F	Ratio	Weight
Study	Yes	No	Yes	No					with 95	% CI	(%)
Case-control											
Gearry 2003	2	7	0	91				$\rightarrow$	29.77 [ 2.26,	391.90]	4.06
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	= 1.0	00					29.77 [ 2.26,	391.90]	
Test of $0_i = 0_j$ : Q(0)	= 0.0	00, p	= .								
Cohort											
Demlova 2014	0	4	0	12	<──	_		$\rightarrow$	1.00 [ 0.01,	105.38]	11.36
Hibi 2003	4	4	0	74					83.00 [ 6.91,	997.66]	2.82
Hindorf 2006	0	8	1	51	<	-		$\rightarrow$	0.46 [ 0.00,	123.79]	15.71
Larussa 2012	1	3	0	23					10.21 [ 0.49,	213.30]	5.93
Mazor 2013	0	4	11	161	←			$\rightarrow$	0.08 [ 0.00,	35564.48]	17.36
Schwab 2002	3	5	2	83				$\rightarrow$	24.90 [ 3.36,	184.71]	6.90
Sutiman 2018	0	3	6	120	←				0.13 [ 0.00,	54705.08]	10.33
Takatsu 2009	0	3	3	111	←	-		$\rightarrow$	0.24 [ 0.00,	54181.44]	6.48
Van Dieren 2005	2	8	0	99				$\rightarrow$	28.44 [ 2.19,	369.67]	4.25
Winter 2007	1	10	3	116					3.87 [ 0.37,	40.69]	14.80
Heterogeneity: I <sup>2</sup> =	5.39	%, H <sup>2</sup>	= 1.0	06			-		6.96 [ 3.22,	15.05]	
Test of $0_i = 0_i$ : Q(9)	= 9.5	51, p	= 0.3	9							
10 <b></b>											
Overall							•		7.88 [ 3.80,	16.33]	
Heterogeneity: I <sup>2</sup> =	0.00	%, H <sup>2</sup>	= 1.0	00							
Test of <b>0</b> <sub>i</sub> = <b>0</b> <sub>j</sub> : Q(10	)) = 1	0.00,	p = 0	).44	Higher in r	non-mut	Higher in I	mut			
Test of group differ	ence	s: Q <sub>h</sub>	(1) =	1.12, p = 0.29							
<b>,</b>				nanonina in antipation and a	1/64	1/4	4	64			
Fixed-effects Mante	-Hae	nszel	l mod	el							

Figure S8. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Serious hematologic adverse events

Study	N Yes	lut No	Noi Yes	n mut No					Odds Rawith 95%	atio 6 Cl	Weight (%)
Case-control											(70)
Gearry 2003	6	3	44	47		_			2.14 [ 0.50,	9.07]	15.40
Heterogeneity: I <sup>2</sup> =	0.00	)%, H	l <sup>2</sup> = 1.	.00		-			2.14 [ 0.50,	9.07]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(0	) = 0.	00, p	= .								
Cohort											
Ansari 2008	15	4	66	122					6.93 [ 2.21,	21.74]	14.88
Coelho 2016	5	4	9	60					8.33 [ 1.88,	36.97]	5.39
De Ridder 2006	1	4	10	57	-				1.43 [ 0.14,	14.10]	6.48
Gazouli 2010	4	16	6	71		1			2.96 [ 0.75,	11.72]	11.55
Larussa 2012	2	2	3	20		9 <u></u>	-		6.67 [ 0.66,	66.84]	2.59
Naughton 1999	1	0	1	13				$\rightarrow$ 1	15.31 [ 0.04,	3.3e+05]	0.09
Ribaldone 2019	2	6	58	134	-		<u> </u>		0.77 [ 0.15,	3.93]	20.30
Schwab 2002	2	6	8	77					3.21 [ 0.55,	18.61]	6.02
Stocco 2004	2	2	12	28			-		2.33 [ 0.29,	18.55]	6.36
Stocco 2005	2	3	11	54			-		3.27 [ 0.49,	21.95]	5.50
Von Ahsen 2005	2	3	11	55			-		3.33 [ 0.50,	22.35]	5.42
Heterogeneity: I <sup>2</sup> =	0.00	)%, H	l <sup>2</sup> = 1.	.00			•		3.60 [ 2.20,	5.91]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1	0) = 7	7.83,	p = 0	.65							
Overall							•		3.38 [ 2.11,	5.41]	
Heterogeneity: I <sup>2</sup> =	0.00	)%, H	l <sup>2</sup> = 1.	.00							
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1	1) = 8	3.27,	p = 0	.69	Higher in no	n-mut	Higher in mut				
Test of group diffe	rence	es: Q	.(1) =	0.45, p	0.50						
					1/16	1/2	4 32	2			
Fixed-effects Mante	el-Ha	ensze	el mod	del							

Figure S9. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Withdrawal due to adverse events

	M	ut	Nor	n mut				Odds I	Ratio	Weight
Study	Yes	No	Yes	No				with 95	% CI	(%)
Case-control										
Gearry 2003	0	9	5	86	←		>	0.15 [ 0.00,	108.99]	5.46
Marinaki 2004	1	7	7	61				1.24 [ 0.13,	11.65]	6.69
Zabala-Fernández 2011	1	10	18	147			<b>—</b>	0.82 [ 0.10,	6.76]	10.61
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00				-		0.78 [ 0.18,	3.40]	
Test of $\theta_i = \theta_j$ : Q(2) = 0.42	, p = (	0.81								
Cohort										
Al-Judaibi 2016	0	5	0	48	←		$\longrightarrow$	1.00 [ 0.00,	868.79]	0.87
Ansari 2008	0	19	8	180	<			0.10 [ 0.00,	66.23]	8.44
De Ridder 2006	0	5	4	63	←		>	0.18 [ 0.00,	335.63]	3.50
Gazouli 2010	0	20	3	74	←			0.20 [ 0.00,	17.39]	8.03
Hlavaty 2013	0	15	6	199	←		>	0.13 [ 0.00,	250.83]	4.88
Larussa 2012	0	4	1	22	<	-		0.44 [ 0.00,	97.02]	2.75
Mhanna 2019	0	7	4	138	<	-	>	0.19 [ 0.00,	1703.31]	2.40
Mazor 2013	0	4	7	165	←		>	0.12 [ 0.00,	55052.90]	1.87
Palmieri 2007	0	29	16	377	←			0.05 [ 0.00,	95.53]	12.04
Ribaldone 2019	2	6	26	166				2.13 [ 0.41,	11.11]	8.09
Schwab 2002	0	8	3	82	<──		>	0.23 [ 0.00,	201.15]	3.46
Steponaitiene 2016	3	6	3	70				11.67 [ 1.92,	70.90]	2.28
Stocco 2004	0	4	2	38	<	-	>	0.30 [ 0.00,	236.54]	2.68
Stocco 2005	0	5	4	61	←	-	>	0.18 [ 0.00,	301.87]	3.60
Stocco 2007	1	4	6	59			-	2.46 [ 0.24,	25.69]	3.56
Takatsu 2009	0	3	0	114	←		>	1.00 [ 0.00,	2.6e+05]	0.26
Van Dieren 2005	1	9	5	94		<i></i>	-	2.09 [ 0.22,	19.88]	4.28
Winter 2007	0	11	1	118	←	-	>	0.47 [ 0.00,	476.21]	1.67
Wroblova 2012	0	16	2	170	←	-	>	0.31 [ 0.00,	288.45]	2.56
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00				<		0.94 [ 0.45,	1.97]	
Test of $\theta_i = \theta_i$ : Q(18) = 12.	40, p	= 0.8	3							
<i>2</i>										
Overall						-		0.90 [ 0.47,	1.75]	
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00								
Test of $\theta_i = \theta_j$ : Q(21) = 13.	08, p	= 0.9	1		Higher in I	non-mut	Higher in mut			
Test of group differences:	Q <sub>b</sub> (1)	= 0.0	05. p	= 0.83						
	- / /		2.6		1/64	1/4	4 64			

Figure S10. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Pancreatitis

	M	lut	Nor	n mut				Odds	Ratio	Weight
Study	Yes	No	Yes	No				with 9	5% CI	(%)
Case-control										
Gearry 2003	0	9	15	76	←			0.05 [ 0.00,	34.75]	13.13
Marinaki 2004	1	7	3	61			-	2.90 [ 0.26,	31.84]	2.70
Zabala-Fernández 2011	0	6	5	119	<	-		>0.15 [ 0.00,	1514.23]	2.53
Heterogeneity: I <sup>2</sup> = 25.65%	6, H <sup>2</sup>	= 1.34	4		-			0.48 [ 0.07,	3.26]	
Test of $\theta_i = \theta_j$ : Q(2) = 2.69	, p = (	0.26								
Cohort										
Al-Judaibi 2016	0	5	0	48	←			> 1.00 [ 0.00,	868.79]	0.78
Ansari 2008	0	19	8	180	←			0.10 [ 0.00,	66.23]	7.54
De Ridder 2006	0	5	0	67	←			> 1.00 [ 0.00,	2351.24]	0.59
Hlavaty 2013	1	14	23	182	-			0.57 [ 0.07,	4.50]	13.56
Larussa 2012	1	3	1	22		3	-	>7.33 [ 0.36,	150.71]	1.03
Mhanna 2019	1	6	3	139		_	•	- 7.72 [ 0.70,	85.65]	1.12
Mazor 2013	0	4	6	166	←			>0.14 [ 0.00,	63489.67]	1.46
Palmieri 2007	1	28	11	382				1.24 [ 0.15,	9.96]	6.76
Reuther 2003	0	4	0	62	←			> 1.00 [ 0.00,	3925.66]	0.52
Ribaldone 2019	0	8	24	168	←			>0.03 [ 0.00,	627.81]	9.20
Schwab 2002	0	8	3	82	←	-		> 0.23 [ 0.00,	201.15]	3.09
Steponaitiene 2016	0	9	5	68	←	-		0.14 [ 0.00,	57.46]	5.92
Stocco 2004	0	4	2	38	←	-		> 0.30 [ 0.00,	236.54]	2.40
Stocco 2005	0	5	6	59	←	-		>0.12[0.00,	204.70]	4.52
Stocco 2007	0	5	3	62	←	-		> 0.23 [ 0.00,	389.95]	2.56
Takatsu 2009	0	3	2	112	<──	-		> 0.32 [ 0.00,	74011.48]	0.70
Van Dieren 2005	0	10	5	94	<			> 0.15 [ 0.00,	102.43]	4.98
Winter 2007	1	10	8	111				1.39 [ 0.16,	12.24]	5.70
Wroblova 2012	1	15	3	169			-	3.76 [ 0.37,	38.37]	2.22
Zelinkova 2006	2	22	9	229		_		2.31 [ 0.47,	11.38]	7.00
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00				-		0.88 [ 0.44,	1.77]	
Test of $\theta_i = \theta_i$ : Q(19) = 10.	62, p	= 0.9	4							
Overall						•		0.81 [ 0.42,	1.56]	
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00								
Test of $\theta_i = \theta_j$ : Q(22) = 13.	27, p	= 0.9	3		Higher in r	ion-mut	Higher in mut	ĺ.		
Test of group differences:	Q <sub>b</sub> (1)	) = 0.3	34, p	= 0.56						
					1/64	1/4	4 6	4		

Figure S11. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Hepatotoxicity

	Μ	ut	Non mut			Odds Ratio		Weight
Study	Yes	No	Yes	No	1	with 9	5% CI	(%)
Case-control								
Gearry 2003	2	7	10	81		2.31 [ 0.42,	12.71]	6.65
Marinaki 2004	5	7	8	61		5.45 [ 1.39,	21.30]	6.56
Zabala-Fernández 2011	1	10	15	147		0.98 [ 0.12,	8.19]	8.23
Heterogeneity: I <sup>2</sup> = 0.00%,	$H^2 =$	1.00			-	2.76 [ 1.13,	6.76]	
Test of $\theta_i = \theta_j$ : Q(2) = 1.91,	p = 0	).39						
Cohort								
Ansari 2008	0	19	26	162	←	0.03 [ 0.00,	19.31]	23.34
Hlavaty 2013	0	15	7	198	← ■	→ 0.11 [ 0.00,	217.10]	5.11
Kim 2014	0	7	2	100	< • •	→ 0.31 [ 0.00,	806.28]	1.77
Mhanna 2019	1	6	20	122		1.02 [ 0.12,	8.90]	7.65
Palmieri 2007	0	29	9	384		→ 0.09 [ 0.00,	167.66]	6.46
Ribaldone 2019	0	8	2	190	< • •	→ 0.32 [ 0.00,	6339.69]	1.12
Schwab 2002	0	8	3	82	← ■	→ 0.23 [ 0.00,	201.15]	3.16
Steponaitiene 2016	0	9	5	68	< <b>.</b>	— 0.14 [ 0.00,	57.46]	6.06
Takatsu 2009	0	3	11	103	< ∎	→ 0.07 [ 0.00,	16268.11]	2.89
Van Dieren 2005	0	10	7	92	← ■	— 0.11 [ 0.00,	73.98]	6.83
Winter 2007	0	11	14	105	←	- 0.05 [ 0.00,	47.96]	11.89
Wroblova 2012	1	15	3	169		3.76 [ 0.37,	38.37]	2.27
Heterogeneity: $I^2 = 0.00\%$ ,	H <sup>2</sup> =	1.00			-	0.28 [ 0.08,	0.95]	
Test of $\theta_i = \theta_j$ : Q(11) = 7.12	2, p =	0.79						
Overall					•	0.81 [ 0.42,	1.57]	
Heterogeneity: $I^2 = 0.00\%$ ,	$H^2 =$	1.00						
Test of $\theta_i = \theta_j$ : Q(14) = 13.9	92, p	= 0.4	6		Higher in non-mut Higher in m	nut		
Test of group differences:	Q <sub>b</sub> (1)	= 8.8	81, p =	= 0.00				
					1/64 1/4 4	64		

Figure S12. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Gastrointestinal side effects



Figure S13. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Clinical remission



Test for Funnel Plot Asymmetry: z = 10.61, p < 0.001

Figure S14. Funnel plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Total serious adverse events



Test for Funnel Plot Asymmetry: z = 11.94, p < 0.001

Figure S15. Funnel plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: total hematologic adverse events



Test for Funnel Plot Asymmetry: z = 7.60, p < 0.001

Figure S16. Funnel plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Serious hematologic adverse events



Test for Funnel Plot Asymmetry: z = 4.42, p < 0.001

Figure S17. Funnel plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Withdrawal due to adverse events



Test for Funnel Plot Asymmetry: z = 4.61, p < 0.001

Figure S18. Funnel plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Pancreatitis



Test for Funnel Plot Asymmetry: z = 0.33, p = 0.7413

Figure S19. Funnel plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Hepatotoxicity



Test for Funnel Plot Asymmetry: z = 9.39, p < 0.001

Figure S20. Funnel plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Gastrointestinal side effects

	М	ut	Nor	n mut			Odds	Ratio	Weight
Study	Yes	No	Yes	No			with 95	% CI	(%)
Adults									
Demlova 2014	0	4	0	12	←	•>	1.00 [ 0.01,	105.38]	7.48
Larussa 2012	1	3	1	22		•	7.33 [ 0.36,	150.71]	4.69
Mhanna 2019	0	7	4	138	← ∎	>	0.19 [ 0.00,	1703.31]	9.77
Schwab 2002	3	5	11	74			4.04 [ 0.84,	19.31]	24.99
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	<sup>2</sup> = 1.0	00			3.08 [ 0.90,	10.56]	
Test of $0_i = 0_j$ : Q(3)	) = 1.(	02, p	= 0.8	0					
Mixed/NR									
Gearry 2003	2	7	0	91			29.77 [ 2.26,	391.90]	2.67
Hibi 2003	4	4	0	74		>	83.00 [ 6.91,	997.66]	1.86
Mazor 2013	0	4	24	148	←	>	0.03 [ 0.00,	15586.61]	23.85
Sutiman 2018	0	3	6	120	← ■	>	0.13 [ 0.00,	54705.08]	6.80
Takatsu 2009	0	3	4	110	← ■	>	0.19 [ 0.00,	42566.46]	5.34
Van Dieren 2005	2	8	0	99			28.44 [ 2.19,	369.67]	2.80
Winter 2007	1	10	3	116			3.87 [ 0.37,	40.69]	9.75
Heterogeneity: $I^2 =$	24.8	4%, H	$+1^2 = 1$	.33		-	6.67 [ 2.88,	15.46]	
Test of $0_i = 0_j$ : Q(6)	) = 7.9	98, p	= 0.2	4					
Overall						•	4.98 [ 2.49,	9.99]	
Heterogeneity: $I^2 =$	7.41	%, H <sup>2</sup>	<sup>2</sup> = 1.0	08					
Test of $0_i = 0_j$ : Q(10)	0) = 1	0.80,	p = 0	).37	Higher in non-mut	Higher in mut			
Test of group differ	rence	s: Q <sub>b</sub>	(1) =	1.03, p = 0.31	1/64 1/4	4 64			
Fixed-effects Mante	I-Hae	nsze	l mod	lel					

Figure S21. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Total serious adverse events. Subgroup analysis according to age

Study	N	lut No	Nor	Mo		C	dds Ra	atio	Weight
Adulto	163		165	NO		vv	111 957		(70)
Adults	2	2	5	42	_	5 72 [	0.76	42.001	0.06
Al-Judalbi 2016	2	14	2	196		22 21 [	5.00	42.99]	0.96
Ansan 2000	2	14	2	100		560 50 [	0.00	5 00+001	0.40
Fangbin 2016	2	0	24	100	-	1 00 [	0.00,	5.0e+09]	0.01
	2	0	0	44		1.03	0.31,	TU.75]	2.71
Larussa 2012	1	3	2	21		3.50 [	12.05	700.601	0.75
Reuther 2002	4	3	2	62		1 00 [	12.05,	2025 661	0.14
Reutilei 2003	0	4	0	02		1.00[	0.00,	104 71	0.19
Scriwad 2002	3	0	2	03		24.90	3.30,	2 5 0 0 5 1	0.30
Steponaltiene 2016	9	0	0	140	-	5 601	1.54,	2.50+05]	0.04
Verobiova 2012	0	0	20	140		5.62	1.94,	10.29]	3.75
Zelinkova 2006	4	20	。 。	230		5.75	1.59,	20.77]	2.07
Heterogeneity: $T = 36.7$ m	%, H	= 1.5	8		-	9.87 [	5.92,	16.46]	
Test of $\mathbf{U}_i = \mathbf{U}_j$ : Q(10) = 15.	.80, p	= 0.1	1						
Children									
De Ridder 2006	1	4	1	66	>	16.50 [	0.86,	315.19]	0.19
Dubinsky 2000	1	7	12	72		0.86 [	0.10,	7.60]	3.09
Gazouli 2010	4	16	3	74		6.17 [	1.26,	30.29]	1.68
Heterogeneity: I <sup>2</sup> = 37.929	%, H <sup>2</sup>	= 1.6	1		-	3.25 [	1.11,	9.47]	
Test of $\theta_i = \theta_j$ : Q(2) = 3.22	2, p =	0.20							
Mixed/NR									
Asada 2016	2	3	43	113		1.75 [	0.28.	10.851	2.71
Chao 2017	4	23	173	532		0.53 [	0.18	1 571	18 40
Gearry 2003	2	7	0	91		29 77 [	2.26	391,901	0.21
Grover 2020	1	4	32	82		0.64 [	0.07.	5.951	3.64
Hawwa 2008	0	4	3	28	<	0.21 [	0.00.	81.03]	1.46
Hibi 2003	7	1	5	69	$\longrightarrow$	96.60 [	9.85	947,701	0.21
Hlavaty 2013	11	4	21	184		24.10 [	7.04.	82,451	1.29
Kim 2010	5	2	111	168		3.78 [	0.72.	19.851	2.63
Kim 2014	3	4	21	81		2.89 [	0.60.	13.93]	2.61
Kim 2017	4	5	128	194		1.21 [	0.32.	4.601	6.55
Marinaki 2004	1	7	10	61		0.87 [	0.10.	7.861	3.00
Mazor 2013	0	4	24	148	$\leftarrow$	0.03 [	0.00.	15586.611	1.91
Naughton 1999	1	0	1	13	>	115.31 [	0.04	3.3e+051	0.03
Palmieri 2007	6	21	17	376		6.32 [	2.26	17.69]	2.88
Ribaldone 2019	0	8	6	186	<	0.13 [	0.00.	2541.911	0.94
Stocco 2004	0	4	13	27		0.04 [	0.00	32,901	4.19
Stocco 2005	0	5	7	58	••••••••••••••••••••••••••••••••••••	0.10 [	0.00.	175.091	1.89
Stocco 2007	0	5	3	62	$\leftarrow$	0 23 [	0.00	389.951	0.94
Sutiman 2018	0	3	10	116	<	0.08	0.00.	33361.89]	0.86
Takatsu 2009	1	2	18	96		2 67 [	0.23	30 991	1 04
Van Dieren 2005	3	7		90		4 29 [	0.94	19 521	1.96
Wang 2018	1	0	18	61	<	264 44 [	0.00	1 2e+10]	0.01
Winter 2007	1	10		116		3 87 [	0.37	40 691	0.78
Yang 2014	13	15	333	617		161	0.76	3 421	17 29
Zabala-Fernández 2011	.3	4	9	90		7 50 1	1 45	38 911	1 15
Zhu 2019	4	9	68	330		2 16 [	0.65	7 211	5.04
Heterogeneity: $I^2 = 51.40^\circ$	ч %. Н <sup>2</sup>	= 2 0	6	200		2 26 1	1.67	3 041	5.04
Test of $0_i = 0_i$ : Q(25) = 51.	.44, p	= 0.0	0			2.20[	,	0.04]	
Overall	172				•	3.18 [	2.49,	4.06]	
Heterogeneity: I <sup>2</sup> = 52.189	%, H <sup>2</sup>	= 2.0	9						
Test of $0_i = 0_j$ : Q(39) = 81.	.56, p	= 0.0	0		Higher in non-mut Higher in mut				

1/64

1/4

64

4

Fixed-effects Mantel-Haenszel model

Test of group differences:  $Q_b(2)$  = 23.85, p = 0.00

# Figure S22. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Total hematologic adverse events. Subgroup analysis according to age

	M	ut	Nor	n mut				Odds I	Ratio	Weight
Study	Yes	No	Yes	No				with 95	5% CI	(%)
Adults										
Demlova 2014	0	4	0	12	←			→ 1.00 [ 0.01,	105.38]	11.36
Hindorf 2006	0	8	1	51	←	_		→ 0.46 [ 0.00,	123.79]	15.71
Larussa 2012	1	3	0	23			-	→ 10.21 [ 0.49,	213.30]	5.93
Schwab 2002	3	5	2	83				<mark>→</mark> 24.90 [ 3.36,	184.71]	6.90
Heterogeneity: $I^2 =$	10.48	3%,⊦	H <sup>2</sup> = 1	.12				6.29 [ 1.70,	23.20]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(3)	= 3.3	5, p	= 0.3	4						
976 <b>v.4</b> 00050 [000										
Mixed/NR										
Gearry 2003	2	7	0	91				→ 29.77 [ 2.26,	391.90]	4.06
Hibi 2003	4	4	0	74				<b>8</b> 3.00 [ 6.91,	997.66]	2.82
Mazor 2013	0	4	11	161	←	-		→ 0.08 [ 0.00,	35564.48]	17.36
Sutiman 2018	0	3	6	120	←	-		→ 0.13 [ 0.00,	54705.08]	10.33
Takatsu 2009	0	3	3	111	←			→ 0.24 [ 0.00,	54181.44]	6.48
Van Dieren 2005	2	8	0	99				→ 28.44 [ 2.19,	369.67]	4.25
Winter 2007	1	10	3	116				3.87 [ 0.37,	40.69]	14.80
Heterogeneity: $I^2 =$	6.839	%, H <sup>2</sup>	= 1.0	07			-	8.94 [ 3.77,	21.19]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_i$ : Q(6)	= 6.4	4, p	= 0.3	8						
Overall							•	7.88 [ 3.80,	16.33]	
Heterogeneity: $I^2 =$	0.009	%, H <sup>2</sup>	= 1.0	00						
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(10)	) = 10	0.00,	p = 0	).44	Higher in r	ion-mut	Higher in mut			
Test of group differ	up differences: $Q_b(1) = 0.19$ , p = 0.66									
					1/64	1/4	4 6	4		

Fixed-effects Mantel-Haenszel model

Figure S23. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Serious hematologic adverse events. Subgroup analysis according to age

	М	ut	Nor	n mut						Odds Ra	atio	Weight
Study	Yes	No	Yes	No						with 95%	6 CI	(%)
Adults												
Ansari 2008	15	4	66	122						6.93 [ 2.21,	21.74]	14.88
Larussa 2012	2	2	3	20			-	-		6.67 [ 0.66,	66.84]	2.59
Schwab 2002	2	6	8	77				-		3.21 [ 0.55,	18.61]	6.02
Von Ahsen 2005	2	3	11	55				-		3.33 [ 0.50,	22.35]	5.42
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00				-		5.46 [ 2.47,	12.04]	
Test of $0_i = 0_j$ : Q(3)	) = 0.8	31, p	= 0.8	5								
Children												
Coelho 2016	5	4	9	60					_	8.33 [ 1.88,	36.97]	5.39
De Ridder 2006	1	4	10	57		-		-		1.43 [ 0.14,	14.10]	6.48
Gazouli 2010	4	16	6	71			<u></u>	-		2.96 [ 0.75,	11.72]	11.55
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00				-		3.77 [ 1.55,	9.15]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(2)	) = 1.9	90, p	= 0.3	9								
Mixed/NR												
Gearry 2003	6	3	44	47						2.14 [ 0.50,	9.07]	15.40
Naughton 1999	1	0	1	13					$\rightarrow$	115.31 [ 0.04,	3.3e+05]	0.09
Ribaldone 2019	2	6	58	134		-		<u> </u>		0.77 [ 0.15,	3.93]	20.30
Stocco 2004	2	2	12	28				-		2.33 [ 0.29,	18.55]	6.36
Stocco 2005	2	3	11	54				-		3.27 [ 0.49,	21.95]	5.50
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00			-			1.92 [ 0.86,	4.29]	
Test of $0_i = 0_j$ : Q(4)	) = 2.5	58, p	= 0.6	3								
Overall								•		3.38 [ 2.11,	5.41]	
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00								
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1	1) = 8	.27,	p = 0.	69	High	er in noi	n-mut	Higher in m	ut			
Test of group diffe	rence	s: Q <sub>b</sub>	(2) =	3.37, p = 0.19	9							
						1/16	1/2	4	32			

Figure S24. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Withdrawal due to adverse events. Subgroup analysis according to age

0	M	ut	Nor	mut		Odds I	Ratio	Weight
Study	Yes	NO	Yes	NO		With 95	9% CI	(%)
Adults		_						
Al-Judaibi 2016	0	5	0	48	<	1.00 [ 0.00,	868.79]	0.87
Ansari 2008	0	19	8	180	< <b></b>	0.10 [ 0.00,	66.23]	8.44
Larussa 2012	0	4	1	22	<	- 0.44 [ 0.00,	97.02]	2.75
Mhanna 2019	0	7	4	138	<	0.19 [ 0.00,	1703.31]	2.40
Schwab 2002	0	8	3	82	<	0.23 [ 0.00,	201.15]	3.46
Steponaitiene 2016	3	6	3	70		11.67 [ 1.92,	70.90]	2.28
Wroblova 2012	0	16	2	170	<	0.31 [ 0.00,	288.45]	2.56
Heterogeneity: I <sup>2</sup> = 12.04%	6, H <sup>2</sup>	= 1.1	4			1.38 [ 0.44,	4.38]	
Test of $\theta_i = \theta_j$ : Q(6) = 6.82	, p = (	0.34						
Children								
De Ridder 2006	0	5	1	63		0.18[0.00	335 631	3 50
	0	20	4	74			17 201	0.00
Gazouli 2010	U	20	3	74		0.20[0.00,	17.39]	8.03
Heterogeneity: $I = 0.00\%$	, н =	1.00				0.19[0.00,	9.06]	
lest of $\mathbf{U}_i = \mathbf{U}_j$ : $\mathbf{Q}(1) = 0.00$	, p = (	J.98						
Mixed/NR								
Gearry 2003	0	9	5	86	<	0.15 [ 0.00,	108.99]	5.46
Hlavaty 2013	0	15	6	199	<	0.13 [ 0.00,	250.83]	4.88
Marinaki 2004	1	7	7	61		1.24 [ 0.13,	11.65]	6.69
Mazor 2013	0	4	7	165	<	0.12 [ 0.00,	55052.90]	1.87
Palmieri 2007	0	29	16	377	←	- 0.05 [ 0.00,	95.53]	12.04
Ribaldone 2019	2	6	26	166		2.13 [ 0.41,	11.11]	8.09
Stocco 2004	0	4	2	38	< <b>•</b>	0.30 [ 0.00,	236.54]	2.68
Stocco 2005	0	5	4	61	< <b>-</b>	0.18 [ 0.00,	301.87]	3.60
Stocco 2007	1	4	6	59		2.46 [ 0.24,	25.69]	3.56
Takatsu 2009	0	3	0	114	<	1.00 [ 0.00,	2.6e+05]	0.26
Van Dieren 2005	1	9	5	94		2.09 [ 0.22,	19.88]	4.28
Winter 2007	0	11	1	118	<	0.47 [ 0.00.	476.21]	1.67
Zabala-Fernández 2011	1	10	18	147		0.82 [ 0.10.	6.76]	10.61
Heterogeneity: $I^2 = 0.00\%$	. H <sup>2</sup> =	1.00				0.86 [ 0.38.	1.98]	
Test of $0 = 0$ ; Q(12) = 4.0	5. p =	0.98				, ,		
	-, F							
Overall					•	0.90 [ 0.47,	1.75]	
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00				option MC	-	
Test of $\theta_i = \theta_j$ : Q(21) = 13.	08, p	= 0.9	1		Higher in non-mut Higher in mut			
Test of group differences:	Q <sub>b</sub> (2)	= 1.	12, p	= 0.57				
					1/64 1/4 4 64			

Figure S25. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Pancreatitis. Subgroup analysis according to age

	M	ut	Nor	n mut			Odds	Ratio	Weight
Study	Yes	No	Yes	No			with 95	5% CI	(%)
Adults									
Al-Judaibi 2016	0	5	0	48	<	•>	1.00 [ 0.00,	868.79]	0.78
Ansari 2008	0	19	8	180	← ■		0.10 [ 0.00,	66.23]	7.54
Larussa 2012	1	3	1	22		• • • • •	7.33 [ 0.36,	150.71]	1.03
Mhanna 2019	1	6	3	139	-	•	7.72 [ 0.70,	85.65]	1.12
Reuther 2003	0	4	0	62	<	•>	1.00 [ 0.00,	3925.66]	0.52
Schwab 2002	0	8	3	82	← ■	>	0.23 [ 0.00,	201.15]	3.09
Steponaitiene 2016	0	9	5	68	← ■		0.14 [ 0.00,	57.46]	5.92
Wroblova 2012	1	15	3	169	8	-	3.76 [ 0.37,	38.37]	2.22
Zelinkova 2006	2	22	9	229			2.31 [ 0.47,	11.38]	7.00
Heterogeneity: I <sup>2</sup> = 0.00%	, H <sup>2</sup> =	1.00			<		1.52 [ 0.60,	3.82]	
Test of $\theta_i = \theta_j$ : Q(8) = 5.27	', p =	0.73							
Children									
De Ridder 2006	0	5	0	67	<	•>	1.00 [ 0.00,	2351.24]	0.59
Heterogeneity: I <sup>2</sup> = 0.00%	, H <sup>2</sup> =	1.00					1.00 [ 0.00,	2351.24]	
Test of $\theta_i = \theta_j$ : Q(0) = 0.00	), p =	•							
Mixed/NR									
Gearry 2003	0	9	15	76	<		0.05 [ 0.00,	34.75]	13.13
Hlavaty 2013	1	14	23	182			0.57 [ 0.07,	4.50]	13.56
Marinaki 2004	1	7	3	61			2.90 [ 0.26,	31.84]	2.70
Mazor 2013	0	4	6	166	← ∎	>	0.14 [ 0.00,	63489.67]	1.46
Palmieri 2007	1	28	11	382			1.24 [ 0.15,	9.96]	6.76
Ribaldone 2019	0	8	24	168	←	>	0.03 [ 0.00,	627.81]	9.20
Stocco 2004	0	4	2	38	← ■	>	0.30 [ 0.00,	236.54]	2.40
Stocco 2005	0	5	6	59	← ∎	>	0.12 [ 0.00,	204.70]	4.52
Stocco 2007	0	5	3	62	← ■	>	0.23 [ 0.00,	389.95]	2.56
Takatsu 2009	0	3	2	112	<	>	0.32 [ 0.00,	74011.48]	0.70
Van Dieren 2005	0	10	5	94	← ■	>	0.15 [ 0.00,	102.43]	4.98
Winter 2007	1	10	8	111	( <del>**</del>	-	1.39 [ 0.16,	12.24]	5.70
Zabala-Fernández 2011	0	6	5	119	← ■	>	0.15 [ 0.00,	1514.23]	2.53
Heterogeneity: I <sup>2</sup> = 0.00%	, H <sup>2</sup> =	1.00			-		0.51 [ 0.20,	1.34]	
Test of $\theta_i = \theta_j$ : Q(12) = 4.7	′6, p =	= 0.97	'						
Overall							0.81 [ 0.42,	1.56]	
Heterogeneity: I <sup>2</sup> = 0.00%	, H <sup>2</sup> =	1.00							
Test of $\theta_i = \theta_j$ : Q(22) = 13.	.27, p	= 0.9	93		Higher in non-mut	Higher in mut			
Test of group differences:	Q.(2)	= 2 !	54, p	= 0,28		A535			
			., P	0.20	1/64 1/4	4 64			
					1/04 1/4	4 04			

Figure S26. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Hepatotoxicity. Subgroup analysis according to age

	Μ	ut	Nor	mut		Odds	Ratio	Weight
Study	Yes	No	Yes	No		with 95	5% CI	(%)
Adults								
Ansari 2008	0	19	26	162	←	0.03 [ 0.00,	19.31]	23.34
Mhanna 2019	1	6	20	122		1.02 [ 0.12,	8.90]	7.65
Schwab 2002	0	8	3	82	← ∎	→ 0.23 [ 0.00,	201.15]	3.16
Steponaitiene 2016	0	9	5	68	← ∎	— 0.14 [ 0.00,	57.46]	6.06
Wroblova 2012	1	15	3	169		— 3.76 [ 0.37,	38.37]	2.27
Heterogeneity: I <sup>2</sup> = 15.17%	6, H <sup>2</sup> :	= 1.18	3			0.44 [ 0.11,	1.66]	
Test of $\theta_i = \theta_j$ : Q(4) = 4.72	p = 0	).32						
Mixed/NR								
Gearry 2003	2	7	10	81		2.31 [ 0.42,	12.71]	6.65
Hlavaty 2013	0	15	7	198	< ∎	→ 0.11 [ 0.00,	217.10]	5.11
Kim 2014	0	7	2	100	<	→ 0.31 [ 0.00,	806.28]	1.77
Marinaki 2004	5	7	8	61		5.45 [ 1.39,	21.30]	6.56
Palmieri 2007	0	29	9	384	←	→ 0.09 [ 0.00,	167.66]	6.46
Ribaldone 2019	0	8	2	190	<	→ 0.32 [ 0.00,	6339.69]	1.12
Takatsu 2009	0	3	11	103	< •	→ 0.07 [ 0.00,	16268.11]	2.89
Van Dieren 2005	0	10	7	92	← ■	— 0.11 [ 0.00,	73.98]	6.83
Winter 2007	0	11	14	105	← ■	— 0.05 [ 0.00,	47.96]	11.89
Zabala-Fernández 2011	1	10	15	147		0.98 [ 0.12,	8.19]	8.23
Heterogeneity: $I^2 = 0.00\%$	$H^2 =$	1.00			-	1.09 [ 0.51,	2.35]	
Test of <b>0</b> <sub>i</sub> = <b>0</b> <sub>i</sub> : Q(9) = 8.42	p = 0	).49						
Overall					+	0.81 [ 0.42,	1.57]	
Heterogeneity: $I^2 = 0.00\%$	H <sup>2</sup> =	1.00						
Test of $\theta_i = \theta_j$ : Q(14) = 13.	92, p	= 0.4	6		Higher in non-mut Higher in	mut		
Test of group differences:	Q <sub>b</sub> (1)	= 1.3	86, p =	= 0.24				
					1/64 1/4 4	64		

Figure S27. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Gastrointestinal side effects. Subgroup analysis according to age

	M	ut	Non	mut					Odds R	atio	Weight
Study	Yes	No	Yes	No					with 95%	6 CI	(%)
Adults											
Al-Judaibi 2016	2	2	14	24			•		1.71 [ 0.22,	13.56]	5.22
Reuther 2003	4	0	60	2	<			$\rightarrow$	3.23 [ 0.00,	10706.13]	0.43
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00							1.83 [ 0.25,	13.39]	
Test of $\theta_i = \theta_j$ : Q(1) = 0.02	, p = (	0.88									
Children											
Dubinsky 2000	8	0	39	45				$\rightarrow$	106.98 [ 0.13,	86534.12]	0.29
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00							106.98 [ 0.13,	86534.12]	
Test of $\theta_i = \theta_j$ : Q(0) = 0.00	, p = .										
Lucafò 2019	8	0	62	34					58 28 [ 0 05	71507 111	0.36
Palmieri 2007	17	12	287	106					0.52[0.24	1 13	63 90
Stocco 2005	3	0	31	17	<			$\rightarrow$	29 21 [ 0 01	1 0e+05]	0.28
Zabala-Fernández 2011	8	7	125	92		-	<u> </u>		0.84 [ 0.29.	2.401	29.53
Heterogeneity: $I^2 = 27.35\%$	6. H <sup>2</sup> :	= 1.3	8			<			0.93 [ 0.52.	1.64]	
Test of $\theta_i = \theta_j$ : Q(3) = 4.13	, p = (	).25								Second a	
Overall									1 28 [ 0 76	2 171	
Heterogeneity: $I^2 = 35.44\%$	6 H <sup>2</sup> :	= 1.5	5						1.20[0.70,	2.17]	
Test of <b>A</b> = <b>A</b> : $Q(6) = 9.29$	n=(	) 16	•		Higher in n	on-mut	Higher in	mut			
T ( ( ) = 0, ( ) = 0.23	, μ = t	. 10	~~	0.05		5n-mut	ingrici in	mut			
lest of group differences:	Q <sub>b</sub> (2)	= 2.	29, p =	= 0.32	1/64	1/4	4	<b>C</b> 1			
Fixed-effects Mantel-Haens	zel m	odel			1/04	1/4	4	04			

Figure S28. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Clinical remission. Subgroup analysis according to age



Figure S29. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Total serious adverse events. Subgroup analysis according to race

	м	ut	Nor	mut				C	dds Ra	atio	Weight
Study	Yes	No	Yes	No				w	ith 95%		(%)
Asian											
Asada 2016	2	3	43	113				1.75 [	0.28,	10.85]	2.71
Chao 2017	4	23	173	532			_	0.53 [	0.18,	1.57]	18.40
Fangbin 2016	2	0	24	106	<		>	569.50 [	0.00,	5.0e+09]	0.01
Grover 2020	1	4	32	82		-		0.64 [	0.07,	5.95]	3.64
Hibi 2003	7	1	5	69			$\longrightarrow$	96.60 [	9.85,	947.70]	0.21
Kim 2010	5	2	111	168		-		3.78 [	0.72,	19.85]	2.63
Kim 2014	3	4	21	81		-		2.89 [	0.60,	13.93]	2.61
Kim 2017	4	5	128	194		_		1.21 [	0.32,	4.60]	6.55
Sutiman 2018	0	3	10	116	<		>	0.08 [	0.00,	33361.89]	0.86
Takatsu 2009	1	2	18	96				2.67 [	0.23,	30.99]	1.04
Wang 2018	1	0	18	61	<		>	264.44 [	0.00,	1.2e+10]	0.01
Yang 2014	13	15	333	617		-	-	1.61 [	0.76,	3.42]	17.29
Heterogeneity: I <sup>2</sup> = 45.22%	%, Η <sup>2</sup>	= 1.8	3				•	1.80 [	1.21,	2.69]	
Test of $\theta_i = \theta_j$ : Q(11) = 20.	08, p	= 0.0	4								
Other/Mixed/NR	_		_	10-						100.000	o / -
Ansari 2008	5	14	2	186			$\longrightarrow$	33.21 [	5.90,	186.87]	0.46
De Ridder 2006	1	4	1	55			>	10.50	0.86,	315.19]	0.19
Dubinsky 2000	1	1	12	72	-			0.86 [	0.10,	7.60]	3.09
Gazouli 2010	4	16	3	74	,	_		0.1/[	1.26,	30.29]	1.68
Hawwa 2008	0	4	3	28	<	•		0.21	0.00,	81.03]	1.46
Hindoff 2006	2	6	8	44		_	-	1.83	0.31,	10.75]	2.71
Hiavaty 2013	11	4	21	184	<i>.</i> -			24.10	7.04,	82.45]	1.29
Mazor 2013	1	4	24	148	<b>—</b>		~ ~ ~	0.03	0.00,	15586.61]	1.91
Naughton 1999	1	0	12	13			>	115.31	0.04,	3.30+05]	0.03
Stocco 2004	0	4	13	27				0.04	0.00,	32.90]	4.19
Stocco 2005	0	5	2	50				0.10[	0.00,	380.051	0.94
Van Dieren 2005	3	7	0	02				1 20 [	0.00,	10 521	1.96
Winter 2007	1	10	3	116			-	3.87 [	0.34,	19.02]	0.78
Zabala-Fernández 2011	3	10	۵ ۵	90				7 50 [	1.45	38 011	1 15
Zelinkova 2006	4	20	8	230				5 75 [	1.40,	20 771	2.07
Zeiiii 1000 2000	4	9	68	330				2 16 [	0.65	7 211	5.04
Heterogeneity: $I^2 = 38.56^{\circ}$	- 6 Н <sup>2</sup>	= 1.6	3	000				3 70 [	2 47	5 561	0.04
Test of $\mathbf{A} = \mathbf{A}$ : $O(16) = 26$	04 n	= 0.0	5					0.70[	2.47,	0.00]	
	с I, р	0.0									
White/Caucasian											
Al-Judaibi 2016	2	3	5	43		-		5.73 [	0.76,	42.99]	0.96
Gearry 2003	2	7	0	91			$\longrightarrow$	29.77 [	2.26,	391.90]	0.21
Larussa 2012	1	3	2	21		_		3.50 [	0.24,	51.46]	0.75
Mhanna 2019	4	3	2	140			$\rightarrow$	93.33 [	12.05,	722.62]	0.14
Marinaki 2004	1	7	10	61	-	-		0.87 [	0.10,	7.86]	3.00
Palmieri 2007	6	21	17	376				6.32 [	2.26,	17.69]	2.88
Reuther 2003	0	4	0	62	<		$\rightarrow$	1.00 [	0.00,	3925.66]	0.19
Ribaldone 2019	0	8	6	186	←•		$\rightarrow$	0.13 [	0.00,	2541.91]	0.94
Schwab 2002	3	5	2	83			$\longrightarrow$	24.90 [	3.36,	184.71]	0.36
Steponaitiene 2016	9	0	8	65			$\rightarrow$	615.16 [	1.54,	2.5e+05]	0.04
Wroblova 2012	8	8	26	146			-	5.62 [	1.94,	16.29]	3.75
Heterogeneity: I <sup>2</sup> = 36.23%	%, H <sup>2</sup>	= 1.5	7				•	7.77 [	4.76,	12.68]	
Test of $\theta_i = \theta_j$ : Q(10) = 15.	68, p	= 0.1	1								
o "								0.105	0.15		
	2		•				•	3.18 [	2.49,	4.06]	
Heterogeneity: I <sup>2</sup> = 52.18%	%, H⁴	= 2.0	9		1.8.1		1.0				
$1 \text{ est of } \mathbf{U}_i = \mathbf{U}_j$ : $\mathbf{Q}(39) = 81$ .	56, p	= 0.0	U		Higher in nor	n-mut	Higher in mut				
Test of group differences:	Q <sub>b</sub> (2)	= 20	.80, p	0.00 = 0.00	)	_					
					1/64	1/4	4 64				

# Figure S30. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Total hematologic adverse events. Subgroup analysis according to race

Study	M Ves	ut	Nor	n mut				Odds F with 95	Ratio	Weight
Asian	103	NO	103	NO				with 55	/0 01	(70)
	1	1	0	74				10 3 1 00 5	007 661	2 82
Sutiman 2018	4	4	6	120	/			0.13[0.00]	54705.081	10.33
Takatsu 2009	0	3	3	111	2			0.10[0.00,	5/181 //1	6.48
Heterogeneity: $I^2 = 3$	36 76	% н <sup>2</sup>	2 = 1 4	58				12 09 [ 3 19	45 781	0.40
Test of $\mathbf{A} = \mathbf{A} \cdot O(2)$ :	= 3 16	$h_{0,11}^{0,11}$	0.21					12.00 [ 0.10,	40.70]	
$ \mathbf{C}_{i}  = \mathbf{U}_{i} \cdot \mathbf{Q}_{i}(\mathbf{z})$	0.10	, р –	0.21							
Other/Mixed/NR										
Demlova 2014	0	4	0	12	←	_	→	1.00 [ 0.01,	105.38]	11.36
Hindorf 2006	0	8	1	51	←		<b></b>	0.46 [ 0.00,	123.79]	15.71
Mazor 2013	0	4	11	161	←	8	>	0.08 [ 0.00,	35564.48]	17.36
Van Dieren 2005	2	8	0	99				28.44 [ 2.19,	369.67]	4.25
Winter 2007	1	10	3	116		** <del></del>		3.87 [ 0.37,	40.69]	14.80
Heterogeneity: $I^2 = 0$	0.00%	5, <b>H</b> <sup>2</sup> :	= 1.00	)				3.12 [ 0.89,	10.90]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(4) =	= 3.88	3, p =	0.42							
White/Caucasian										
Gearry 2003	2	7	0	91				29.77 [ 2.26,	391.90]	4.06
Larussa 2012	1	3	0	23				10.21 [ 0.49,	213.30]	5.93
Schwab 2002	3	5	2	83				24.90 [ 3.36,	184.71]	6.90
Heterogeneity: $I^2 = 0$	0.00%	5, H <sup>2</sup> :	= 1.00	)				20.91 [ 5.11,	85.53]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(2) =	= 0.31	I, p =	0.85							
Overall							•	7.88 [ 3.80,	16.33]	
Heterogeneity: $I^2 = 0$	0.00%	5, H <sup>2</sup> :	= 1.00	)						
Test of $0_i = 0_j$ : Q(10)	= 10	.00, p	0 = 0.4	44	Higher in 1	non-mut	Higher in mut			
Test of group differe	ences	: Q <sub>b</sub> (2	2) = 4	.31, p = 0.12						
					1/64	1/4	4 64			

Fixed-effects Mantel-Haenszel model

Figure S31. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Serious hematologic adverse events. Subgroup analysis according to race

	M	ut	Nor	n mut				Odds R	atio	Weight
Study	Yes	No	Yes	No				with 959	% Cl	(%)
Other/Mixed/NR										
Ansari 2008	15	4	66	122				6.93 [ 2.21,	21.74]	14.88
Coelho 2016	5	4	9	60				8.33 [ 1.88,	36.97]	5.39
De Ridder 2006	1	4	10	57			-	1.43 [ 0.14,	14.10]	6.48
Gazouli 2010	4	16	6	71		-		2.96 [ 0.75,	11.72]	11.55
Naughton 1999	1	0	1	13				→ 115.31 [ 0.04,	3.3e+05]	0.09
Stocco 2004	2	2	12	28			-	2.33 [ 0.29,	18.55]	6.36
Stocco 2005	2	3	11	54		-	-	3.27 [ 0.49,	21.95]	5.50
Heterogeneity: $I^2 = 0$	0.00%	, H <sup>2</sup> :	= 1.00	)			•	4.67 [ 2.53,	8.60]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(6) =	= 3.68	8, p =	0.72							
White/Caucasian										
Gearry 2003	6	3	44	47		_	-	2.14 [ 0.50,	9.07]	15.40
Larussa 2012	2	2	3	20				— 6.67 [ 0.66,	66.84]	2.59
Ribaldone 2019	2	6	58	134	-		<u> </u>	0.77 [ 0.15,	3.93]	20.30
Schwab 2002	2	6	8	77			-	3.21 [ 0.55,	18.61]	6.02
Von Ahsen 2005	2	3	11	55				3.33 [ 0.50,	22.35]	5.42
Heterogeneity: $I^2 = 0$	0.00%	, H <sup>2</sup> :	= 1.00	)		5	<b></b>	2.08 [ 0.97,	4.44]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(4) =	= 2.88	8, p =	0.58							
Overall							•	3.38 [ 2.11,	5.41]	
Heterogeneity: $I^2 = 0$	0.00%	, H <sup>2</sup> :	= 1.00	)						
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(11)	= 8.2	27, p	= 0.69	9	Higher in no	n-mut	Higher in mut	t		
Test of group differe	nces:	Q <sub>b</sub> (1	) = 2.	.65, p =	0.10					
					1/16	1/2	4 32	2		
	202	22								

Figure S32. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Withdrawal due to adverse events. Subgroup analysis according to race

Mut Non mut Odds Rat	io Weight
Study Yes No Yes No with 95%	CI (%)
Asian	
Takatsu 2009 0 3 0 114 ← → 1.00 [ 0.00, 2	2.6e+05] 0.26
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$ 1.00 [ 0.00, 2	2.6e+05]
Test of $0_i = 0_j$ : Q(0) = 0.00, p = .	
	66 231 8 44
Ansair 2006         0         19         8         160         0         0         19         0         10         0         0         10         0         0         10         0         0         10         0         0         10         0         0         10         0         0         10         0         10         0         10         0         10         0         10         0         10         0         10         0         10         0         10         0         10         0         0         10         0         0         10         0         0         10         0         10         0         10         0         10         0         10         0         10         0         10         0         10         0         10         0         10         0         10         0         10         0         10         0         10         0         10 <th< td=""><td>225 621 2 50</td></th<>	225 621 2 50
	17 30] 8.03
Havaty 2013 0 15 6 199 0.23 [0.00]	250.831 / 88
Mazor 2013 0 4 7 165 0 12 [ 0.00, 55	250.05] 4.00 5052.90] 1.87
Storce 2004 0 4 2 38	236 541 2 68
Stocco 2005 0 5 4 61	200.04] 2.00 301.87] 3.60
Storco 2007 1 4 6 59 246 [ 0.24	25.601 3.56
Van Dieren 2005 1 9 5 94 2.49 [0.22]	10.881 / 28
Winter 2007 0 11 1 118	4.20 476 211 1 67
Zabela Ecraéndoz 2011         1         10         18         147         0.82 [ 0.10	6.76] 10.61
$\begin{array}{c} \text{Zabia-Fernandez 2011} & 1 & 10 & 18 & 147 \\ \text{Hotorogonaity: } 1^2 = 0.00\% \text{ H}^2 = 1.00 \\ \text{O} = 0.011 \text{ O} = 0.0011 \text{ O} = 0.00111 \text{ O} = 0.001111 \text{ O} = 0.0011111 \text{ O} = 0.00111111111111111111111111111111111$	1 70]
Therefore $P = 0$ : $O(10) = 3.50$ , $P = 0.96$	1.79]
$f = 0, \alpha(10) - 0.03, \beta = 0.30$	
White/Caucasian	
Al-Judaibi 2016 0 5 0 48 ← → 1.00 [ 0.00,	868.79] 0.87
Gearry 2003 0 9 5 86 ← ● → 0.15 [ 0.00,	108.99] 5.46
Larussa 2012 0 4 1 22 < 0.44 [ 0.00,	97.02] 2.75
Mhanna 2019 0 7 4 138 <  0.19 [ 0.00, 1	703.31] 2.40
Marinaki 2004 1 7 7 61	11.65] 6.69
Palmieri 2007 0 29 16 377 - 0.05 [ 0.00,	95.53] 12.04
Ribaldone 2019 2 6 26 166 2.13 [ 0.41,	11.11] 8.09
Schwab 2002 0 8 3 82 ← ● → 0.23 [ 0.00,	201.15] 3.46
Steponaitiene 2016 3 6 3 70	70.90] 2.28
Wroblova 2012 0 16 2 170	288.45] 2.56
Heterogeneity: I <sup>2</sup> = 0.00%, H <sup>2</sup> = 1.00	2.88]
Test of <b>0</b> <sub>i</sub> = <b>0</b> <sub>i</sub> : Q(9) = 8.14, p = 0.52	
Overall 0.90 [ 0.47,	1.75]
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$	
Test of $\mathbf{\theta}_i = \mathbf{\theta}_j$ : Q(21) = 13.08, p = 0.91 Higher in non-mut Higher in mut	
Test of group differences: $Q_{h}(2) = 1.02$ , $p = 0.60$	

Figure S33. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Pancreatitis. Subgroup analysis according to race

	M	lut	Nor	n mut				Odds	Ratio	Weight
Study	Yes	No	Yes	No				with 9	5% CI	(%)
Asian										
Takatsu 2009	0	3	2	112	<	•		→ 0.32 [ 0.00,	74011.48]	0.70
Heterogeneity: $I^2 = 0.00\%$	$, H^2 =$	1.00						0.32 [ 0.00,	74011.48]	
Test of $\theta_i = \theta_j$ : Q(0) = 0.00	, p =	•2								
Other/Mixed/NP										
Ansari 2008	0	10	8	180	4			010[0.00	66 231	7 54
De Ridder 2006	0	5	0	67	2			0.10[0.00,	2351 241	0.59
Havaty 2013	1	14	23	182		_		0.57[0.07	4 501	13 56
Mazor 2013	0	4	6	166	<	_		$\rightarrow 0.07 [0.07]$	63489 671	1 46
Stocco 2004	0	4	2	38	-	_		$\rightarrow$ 0.30 [ 0.00	236 541	2.40
Stocco 2005	0	5	6	59	È	_		$\rightarrow 0.00 [0.00]$	200.04]	4 52
Stocco 2007	0	5	3	62	←	_		$\rightarrow 0.23[0.00]$	389 951	2.56
Van Dieren 2005	0	10	5	94	<	-		$\rightarrow 0.15[0.00]$	102 43	4 98
Winter 2007	1	10	8	111				1 39 [ 0 16	12 24]	5 70
Zabala-Fernández 2011	0	6	5	119	←	-		$\rightarrow 0.15[0.00]$	1514 23]	2.53
Zelinkova 2006	2	22	9	229				2.31 [ 0.47.	11.38]	7.00
Heterogeneity: $I^2 = 0.00\%$	. H <sup>2</sup> =	1.00				<		0.69 [ 0.26.	1.81]	
Test of <b>0</b> = <b>0</b> : Q(10) = 3.7	5. p =	: 0.96						Ľ,		
1 1 1										
White/Caucasian										
Al-Judaibi 2016	0	5	0	48	←			→ 1.00 [ 0.00,	868.79]	0.78
Gearry 2003	0	9	15	76	<b>←</b>		-	0.05 [ 0.00,	34.75]	13.13
Larussa 2012	1	3	1	22		-	-	→ 7.33 [ 0.36,	150.71]	1.03
Mhanna 2019	1	6	3	139			-	— 7.72 [ 0.70,	85.65]	1.12
Marinaki 2004	1	7	3	61			-	2.90 [ 0.26,	31.84]	2.70
Palmieri 2007	1	28	11	382				1.24 [ 0.15,	9.96]	6.76
Reuther 2003	0	4	0	62	<			→ 1.00 [ 0.00,	3925.66]	0.52
Ribaldone 2019	0	8	24	168	<			→ 0.03 [ 0.00,	627.81]	9.20
Schwab 2002	0	8	3	82	<	-		→ 0.23 [ 0.00,	201.15]	3.09
Steponaitiene 2016	0	9	5	68	<──	-		— 0.14 [ 0.00,	57.46]	5.92
Wroblova 2012	1	15	3	169			-	- 3.76 [ 0.37,	38.37]	2.22
Heterogeneity: I <sup>2</sup> = 0.00%	, H <sup>2</sup> =	1.00				<		0.96 [ 0.39,	2.34]	
Test of $\theta_i = \theta_j$ : Q(10) = 8.6	5, p =	0.57								
Overall	2					-		0.81 [ 0.42,	1.56]	
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00						1997 <b>-</b> 1		
lest of $0_i = 0_j$ : Q(22) = 13.	27, p	= 0.9	3		Higher in r	ion-mut	Higher in m	nut		
Test of group differences:	Q <sub>b</sub> (2)	) = 0.2	27, p	= 0.87						
					1/64	1/4	4	64		

Figure S34. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Hepatotoxicity. Subgroup analysis according to race

	M	lut	Nor	n mut				Odds	Ratio	Weight
Study	Yes	No	Yes	No				with 95	5% CI	(%)
Asian										
Kim 2014	0	7	2	100	<	-		→ 0.31 [ 0.00,	806.28]	1.77
Takatsu 2009	0	3	11	103	←			→ 0.07 [ 0.00,	16268.11]	2.89
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00						0.16 [ 0.00,	118.74]	
Test of $\theta_i = \theta_j$ : Q(1) = 0.04	, p = (	0.84								
Other/Mixed/NR										
Ansari 2008	0	19	26	162	←			0.03 [ 0.00,	19.31]	23.34
Hlavaty 2013	0	15	7	198	$\leftarrow$			→ 0.11 [ 0.00,	217.10]	5.11
Van Dieren 2005	0	10	7	92	$\leftarrow$			— 0.11 [ 0.00,	73.98]	6.83
Winter 2007	0	11	14	105	←			- 0.05 [ 0.00,	47.96]	11.89
Zabala-Fernández 2011	1	10	15	147				0.98 [ 0.12,	8.19]	8.23
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00						0.19 [ 0.03,	1.07]	
Test of $\theta_i = \theta_j$ : Q(4) = 2.76	, p = (	0.60								
White/Caucasian										
Gearry 2003	2	7	10	81			•	2.31 [ 0.42,	12.71]	6.65
Mhanna 2019	1	6	20	122				1.02 [ 0.12,	8.90]	7.65
Marinaki 2004	5	7	8	61				5.45 [ 1.39,	21.30]	6.56
Palmieri 2007	0	29	9	384	← –			→ 0.09 [ 0.00,	167.66]	6.46
Ribaldone 2019	0	8	2	190	←	-		→ 0.32 [ 0.00,	6339.69]	1.12
Schwab 2002	0	8	3	82	←	-		→ 0.23 [ 0.00,	201.15]	3.16
Steponaitiene 2016	0	9	5	68	<			— 0.14 [ 0.00,	57.46]	6.06
Wroblova 2012	1	15	3	169		_	-	- 3.76 [ 0.37,	38.37]	2.27
Heterogeneity: I <sup>2</sup> = 0.00%	, H <sup>2</sup> =	1.00						1.75 [ 0.82,	3.76]	
Test of $\theta_i = \theta_j$ : Q(7) = 5.15	, p = (	0.64								
Overall						-		0.81 [ 0.42,	1.57]	
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00								
Test of $\theta_i = \theta_j$ : Q(14) = 13.	92, p	= 0.4	6		Higher in n	on-mut	Higher in n	nut		
Test of group differences:	Q <sub>b</sub> (2)	= 5.6	64, p	= 0.06						
					1/64	1/4	4	64		

Figure S35. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Gastrointestinal side effects. Subgroup analysis according to race

	M	ut	Non	mut					Odds R	tatio	Weight
Study	Yes	No	Yes	No					with 959	% Cl	(%)
Other/Mixed/NR											
Dubinsky 2000	8	0	39	45				$\rightarrow$	106.98 [ 0.13,	86534.12]	0.29
Stocco 2005	3	0	31	17	<			$\rightarrow$	29.21 [ 0.01,	1.0e+05]	0.28
Zabala-Fernández 2011	8	7	125	92			<b>—</b>		0.84 [ 0.29,	2.40]	29.53
Heterogeneity: I <sup>2</sup> = 57.44%	6, H <sup>2</sup> =	= 2.3	5			2	•		2.12 [ 0.89,	5.06]	
Test of <b>0</b> <sub>i</sub> = <b>0</b> <sub>j</sub> : Q(2) = 4.70	, p = 0	0.10									
White/Caucasian											
Al-Judaibi 2016	2	2	14	24					1.71 [ 0.22,	13.56]	5.22
Lucafò 2019	8	0	62	34	2			>	58.28 [ 0.05,	71507.11]	0.36
Palmieri 2007	17	12	287	106		-	-		0.52 [ 0.24,	1.13]	63.90
Reuther 2003	4	0	60	2	<			$\rightarrow$	3.23 [ 0.00,	10706.13]	0.43
Heterogeneity: I <sup>2</sup> = 21.56%	6, H <sup>2</sup> =	= 1.2	7			-			0.92 [ 0.48,	1.80]	
Test of <b>0</b> ; = <b>0</b> ; Q(3) = 3.82	, p = 0	0.28									
Overall									1.28 [ 0.76,	2.17]	
Heterogeneity: I <sup>2</sup> = 35.44%	6, H <sup>2</sup> :	= 1.5	5								
Test of <b>0</b> <sub>i</sub> = <b>0</b> <sub>j</sub> : Q(6) = 9.29	, p = 0	0.16			Higher in no	on-mut	Higher in r	nut			
Test of group differences:	Q <sub>b</sub> (1)	= 2.2	22, p =	= 0.14							
					1/64	1/4	4	64			
Fixed-effects Mantel-Haens	szel m	odel									

Figure S36. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Clinical remission. Subgroup analysis according to race

Study	Noi Yes	n mut No					Odds F with 95	Weight (%)			
Case-control				110					maroo		
Gearry 2003	1	7	0	91		-		$\rightarrow$	15.26 [ 0.85,	273.02]	1.28
Heterogeneity: I <sup>2</sup> =	0.00	)%, H	<sup>2</sup> = 1.	00		P			<del>15</del> .26 [ 0.85,	273.02]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(0)	) = 0.	00, p	= .								
Cohort											
Bangma 2020	4	46	34	509					1.30 [ 0.44,	3.83]	52.53
Demlova 2014	0	4	0	12	<			$\rightarrow$	1.00 [ 0.01,	105.38]	3.53
Hibi 2003	3	4	0	74					61.93 [ 4.89,	783.63]	0.90
Larussa 2012	0	2	1	22	←			>	0.46 [ 0.00,	623.29]	2.95
Mhanna 2019	0	6	4	138	←			$\rightarrow$	0.19 [ 0.00,	3417.97]	3.98
Mazor 2013	0	4	24	148	←-∎			$\rightarrow$	0.03 [ 0.00,	15586.61]	11.24
Schwab 2002	2	5	11	74					2.69 [ 0.46,	15.61]	11.91
Sutiman 2018	0	3	6	120	<			>	0.13 [ 0.00,	54705.08]	3.21
Takatsu 2009	0	3	4	110	<			$\rightarrow$	0.19 [ 0.00,	42566.46]	2.52
Van Dieren 2005	0	8	0	99	←			$\rightarrow$	1.00 [ 0.00,	1783.55]	1.37
Winter 2007	1	10	3	116		8	-		3.87 [ 0.37,	40.69]	4.60
Heterogeneity: I <sup>2</sup> =	0.00	)%, H	<sup>2</sup> = 1.	00		13	•		1.84 [ 0.93,	3.65]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(10)	D) = 9	9.42,	p = 0.	49							
Overall							•		2.02 [ 1.05,	3.88]	
Heterogeneity: I <sup>2</sup> =	1.03	3%, H	<sup>2</sup> = 1.	01							
Test of $0_i = 0_j$ : Q(1	1) = 1	11.11,	p = (	0.43	Higher in	non-mut	Higher in	n mut			
Test of group differ	rence	es: Q <sub>b</sub>	(1) =	1.95, p = 0.16							
					1/64	1/4	4	64			
Fixed-effects Mante	I-Hae	ensze	l moc	lel							

Figure S37. Forest plot of comparison heterozygous *TPMT* vs wild-type *TPMT*, outcome: Total serious adverse events

Staty         Test for 16         Test for 16         Test for 16         Test for 16         Test for 17         Test for 17         Test for 18         Test for 18 <thtest 18<="" for="" th=""> <thtest 18<="" for="" th=""> <tht< th=""><th>Study</th><th>M</th><th colspan="2">Mut Non mut Yes No Yes No</th><th>i mut</th><th></th><th></th><th colspan="2">Odds Ratio</th><th>Weight</th></tht<></thtest></thtest>	Study	M	Mut Non mut Yes No Yes No		i mut			Odds Ratio		Weight	
Casery 2003       1       7       0       91         Marinal 2004       1       7       10       61         Yang 2014       13       15       33       617         Zablat-Fernández 2011       3       4       9       90         Heterogeneity: $l^2 = 43.22\%, H^2 = 1.76$ Test of <b>9</b> 91       161       0.76       3.42       17.31         Zablat-Fernández 2011       2       3       5       43       91       91       195       1.04.       3.66         Asada 2016       2       3       4       175       10.28       10.85       2.72         Bangma 2020       6       3.6       2.3       43       1.75       12.82       0.53       10.18       1.57       18.42         De Ridder 2006       1       1       1       66       006.00       1.08       1.7       10.82       1.78       0.48       1.71       18.42         De Ridder 2006       1       1       1       66       006.00       1.00       1.13       1.15       1.15       1.15       1.15       1.15       1.15       1.15       1.15       1.15       1.15       1.15       1.15       1.15       <	<u>Case control</u>	103	NU	103	INO			with 50		(70)	
Granty 2003       1       7       0       61         Vang 2014       1       3       15       33       617         Zabala-Fernandrez 2011       3       4       9       90         Heterogeneticy: $l^{-1} = 43.32%, l^{-1} = 7.6$ 3.681       7.50 [1.45, 3.82]       7.50 [1.45, 3.82]         Cohort       Al-Judabi 2016       2       3       5       43       113         Assata 2016       2       3       43       113       1.55       1.95 [1.04, 3.66]       1.085       2.72         Bangma 2020       6       36       23       44       3.14 [1.20, 8.22]       5.62       Choots       1.15         Heitorgoneticy: Color       1       1       1.66       0.66 (0.12.0, 1.86, 1.77)       18.42       0.65 (0.10, 5.0e+09)       0.01         Pangbin 2016       2       0       2.4 (0.6       0.55 (0.00, 5.0e+09)       0.01         Hindor 2006       1       1       1.68       2.72       0.86 (0.12.20, 1.86, 1.76, 1.82, 2.90       0.86 (0.12.20, 1.86, 1.76, 1.82, 2.90       0.86 (0.10, 5.6, 1.91, 7.60, 1.80, 2.76       0.86 (0.10, 5.6, 1.91, 7.60, 1.80, 2.76       0.86 (0.10, 5.76, 1.76, 1.82, 9.76, 1.76, 1.82, 9.76       0.86 (0.10, 5.76, 1.76, 1.82, 9.76, 1.76, 1.82, 9.76       0.86 (0.13, 7.76, 7.60, 1.80, 9.76, 1.76, 1.82,	Case-control	4	7	0	01			15 06 10 95	070 001	0.00	
$\begin{array}{c} \text{Marking 2204} & 13 & 15 & 333 & 61 \\ \text{Zabala-Fernandez 2011} & 3 & 4 & 9 & 90 \\ \text{Hetergoeneity}; i^2 + 33.326, \text{H}^2 = 1.76 \\ \text{Tast of } \textbf{a} = \textbf{h}, Q(3) = 5.28 & 9 & 0.15 \\ \hline \textbf{Cohort} \\ \text{Al-Judabi 2016} & 2 & 3 & 5 & 43 \\ \text{Asada 2016} & 2 & 3 & 5 & 43 \\ \text{Asada 2016} & 2 & 3 & 5 & 43 \\ \text{Asada 2016} & 2 & 3 & 5 & 43 \\ \text{Asada 2016} & 2 & 3 & 5 & 43 \\ \text{Asada 2016} & 2 & 3 & 5 & 43 \\ \text{Asada 2016} & 2 & 3 & 5 & 43 \\ \text{Asada 2016} & 2 & 3 & 5 & 43 \\ \text{Asada 2016} & 2 & 3 & 43 & 113 \\ \text{De Ridder 2000} & 1 & 1 & 1 & 66 \\ \text{De Ridder 2000} & 1 & 1 & 1 & 66 \\ \text{De Ridder 2000} & 1 & 1 & 1 & 66 \\ \text{Mim 2010} & 5 & 2 & 111 & 168 \\ \text{Kim 2017} & 4 & 5 & 128 & 14 \\ \text{Mavaly 2013} & 10 & 4 & 21 & 118 \\ \text{Kim 2017} & 4 & 5 & 128 & 14 \\ \text{Kim 2017} & 4 & 5 & 128 & 144 \\ \text{Havary 2013} & 10 & 4 & 21 & 118 \\ \text{Kim 2017} & 4 & 5 & 128 & 144 \\ \text{Mazor 2013} & 0 & 4 & 11 & 108 \\ \text{Kim 2017} & 4 & 5 & 128 & 144 \\ \text{Mazor 2013} & 0 & 4 & 11 & 13 \\ \text{Markan 2019} & 3 & 3 & 2 & 140 \\ \text{Mazor 2013} & 0 & 4 & 11 & 13 \\ \text{Parkine 12007} & 4 & 23 & 17 & 376 \\ \text{Reuther 2005} & 0 & 5 & 7 & 58 \\ \text{Stocco 2004} & 0 & 4 & 13 & 27 \\ \text{Multim 2017} & 1 & 0 & 1 & 13 \\ \text{Parkine 12007} & 4 & 23 & 17 & 376 \\ \text{Reuther 2005} & 0 & 5 & 7 & 58 \\ \text{Stocco 2004} & 0 & 4 & 13 & 27 \\ \text{Ovanil} \\ \text{Ribaldone 2019} & 0 & 8 & 6 & 186 \\ \text{Takatsu 2009} & 1 & 2 & 18 & 96 \\ \text{Van Diren 2005} & 1 & 7 & 9 & 90 \\ \text{Wang 2018} & 1 & 0 & 18 & 61 \\ \text{Mimer 2007} & 1 & 10 & 9 & 110 \\ \text{Winder 2007} & 1 & 10 & 9 & 110 \\ \text{Winder 2007} & 1 & 10 & 9 & 110 \\ \text{Winder 2007} & 1 & 10 & 9 & 110 \\ \text{Winder 2007} & 1 & 10 & 9 & 110 \\ \text{Winder 2007} & 1 & 10 & 9 & 110 \\ \text{Winder 2007} & 1 & 10 & 9 & 110 \\ \text{Winder 2007} & 1 & 10 & 9 & 110 \\ \text{Winder 2007} & 1 & 10 & 9 & 110 \\ \text{Winder 2007} & 1 & 10 & 9 & 110 \\ \text{Winder 2007} & 1 & 10 & 9 & 110 \\ \text{Winder 2007} & 1 & 10 & 9 & 110 \\ \text{Winder 2007} & 1 & 10 & 9 & 110 \\ \text{Winder 2007} & 1 & 10 & 9 & 110 \\ \text{Winder 2007} & 1 & 10 & 9 & 110 \\ \text{Winder 2007} & 1 & 10 & 9 & 110 \\ \text{Winder 2007} & 1 & 10 & 9 & 110$	Gearry 2003	1	7	10	91		_	0.0710.10	Z73.02]	2.00	
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The terr definition of the second se	Zabala-Fernandez 2011	3	4	9	90			7.50 [ 1.45,	38.91]	1.15	
Cohort         Al-Judaibi 2016       2       3       5       3       5       5       5       5       5       5       5       5       3 <th cols<="" td=""><td>Heterogeneity: <math>I^{-} = 43.32\%</math></td><td>⁄₀, H⁻</td><td>= 1.7</td><td>6</td><td></td><td></td><td></td><td>1.95[1.04,</td><td>3.66]</td><td></td></th>	<td>Heterogeneity: <math>I^{-} = 43.32\%</math></td> <td>⁄₀, H⁻</td> <td>= 1.7</td> <td>6</td> <td></td> <td></td> <td></td> <td>1.95[1.04,</td> <td>3.66]</td> <td></td>	Heterogeneity: $I^{-} = 43.32\%$	⁄₀, H⁻	= 1.7	6				1.95[1.04,	3.66]	
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Al-Judaibi 2016       2       3       5       43         Ansari 2008       5       14       2       186         Asada 2016       2       3       43       113         Bangma 2020       6       3       62       13       13         Bangma 2020       6       36       23       43       113         De Ridder 2006       1       1       1       66       0.51       0.86       10.17       18.22         De Ridder 2006       1       7       12       72       0.86       60.00       5.09       0.00         Fangbin 2016       2       0       24       106       569.50       10.00       5.09       0.00         Hawaty 2013       10       4       21       184       22.00       6.31       76.02       1.30         Kim 2014       2       4       21       18.45       0.71       1.45       1.45       2.64         Kim 2014       2       2       2.10       0.83       1.12.5       2.64         Kim 2017       4       5       128       194       1.21       0.33       1.12.5       2.64         Kim 2017       4 <t< td=""><td>Cohort</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></t<>	Cohort										
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Dubinsky 2000       1       7       12       72         Fangbin 2016       2       0       24       106         Hawwa 2008       0       4       1       30         Hibi 2003       6       1       5       69         Hindorf 2006       2       5       8       44         Hiavaty 2013       10       4       21       184         Kim 2010       5       2       111       168         Kim 2017       4       5       128       194         Larussa 2012       0       2       2       21         Maaghton 1999       1       0       1       13         Palmieri 2007       4       23       17       376         Reuther 2003       0       4       0       62         Stocco 2005       0       5       7       58         Stocco 2007       0       5       3       62         Van Dieren 2005       1       7       9       90         Van Dieren 2005       1       7       9       90         Van Dieren 2005       1       7       9       90         Vand Dieren 2005 <t< td=""><td>De Ridder 2006</td><td>1</td><td>1</td><td>1</td><td>66</td><td></td><td>-&gt;</td><td>66.00 [ 2.20.</td><td>1984.211</td><td>0.05</td></t<>	De Ridder 2006	1	1	1	66		->	66.00 [ 2.20.	1984.211	0.05	
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Number of the original structure       Index (2006)       2       5       8       44         Hindorf 2006       2       5       8       44         Hindorf 2006       2       5       8       44         Hindorf 2010       5       2       111       168       220 [0.36, 13.37]       2.30         Kim 2010       5       2       111       168       3.78 [0.72, 19.85]       2.63         Kim 2017       4       5       128 194       1.21 [0.32, 4.60]       6.55         Larussa 2012       0       2       2       2.11       168       9.29 [0.00, 373.91]       0.76         Marna 2019       3       2       140       70.00 [8.37, 556.21]       0.14         Macro 2013       0       4       0       1       3 $\rightarrow$ 115.31 [0.04, 3.3e+65]       0.03         Naughton 1999       1       0       1       3 $\rightarrow$ 100 [0.00, 35564.48]       0.92         Naughton 2019       8       6       186       100       10.00, 135.621       0.03         Stocco 2007       0       5       3       62       3       92       90       90       90       92       92	Hibi 2003	6	1	5	69		->	82 80 [ 8 27	828 681	0.21	
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Inditive 201010421104Kim 201052111168Kim 201052111168Kim 201745128194Larussa 20120222Mhanna 2019332140Mazor 20130411161Marco 2013041161Marco 201304162Naughton 199910113Palmieri 200742317Reuther 2003040Stocco 20040413Stocco 2005057Stocco 2007053Stocco 2007053Stocco 2005179Sutiman 20181018Van Dieren 200517Stoco 200632082.61.46Van Dieren 20051799Wang 20181010910Vinter 20071109682.16 [0.65, 7.21]5.052.16 [0.65, 7.21]5.052.16 [0.65, 7.21]5.052.16 [0.65, 7.21]5.052.16 [0.65, 7.21]5.052.16 [0.65, 7.21]5.052.16 [0.65, 7.21]5.052.16 [0.65, 7.21]5.052.16 [0.65, 7.21]5.051.16 [1.2 ] =	Hlavaty 2013	10	4	21	184			21.20 [ 0.00,	76 021	1 30	
Nam 2010       3       2       11       100       1.93 [ 0.73, 11.25]       2.64         Kim 2017       4       5       128       194       1.93 [ 0.33, 11.25]       2.64         Kim 2017       4       5       128       194       1.21 [ 0.32, 4.60]       6.55         Larussa 2012       0       2       2       21       0.08 [ 0.00, 35564.48]       0.92         Naughton 1999       1       0       1       13       115.31 [ 0.04, 3.3e+05]       0.03         Palmieri 2007       4       23       17       376       3.85 [ 1.20, 12.37]       3.16         Reuther 2003       0       4       0       62       1.00 [ 0.00, 325.66]       0.19         Stocco 2004       0       4       13       27       0.04 [ 0.00, 32.90]       1.19         Stocco 2007       0       5       3       62       0.03 [ 0.00, 339.95]       0.94         Stocco 2007       0       5       3       62       0.03 [ 0.00, 339.95]       0.94         Van Dieren 2005       1       7       9       90       0.33 [ 0.16, 2.25]       2.00         Wang 2018       1       0       18       61       2.66 [ 1.94, 16.29]	Kim 2010	5	т 2	111	168			378[0.72	10.02	2.63	
Num 2014       2       4       21       61         Kim 2017       4       5       128       194       121       [0.32, 4.60]       6.55         Larussa 2012       0       2       2       21       4.61       6.55         Mhana 2019       3       3       2       140       70.00       [8.37, 585.21]       0.14         Mazor 2013       0       4       11       161       0.08       [0.00, 37564.48]       0.92         Naughton 1999       1       0       1       13 $\rightarrow$ 115.31       [0.04, 3.3e+05]       0.03         Palmieri 2007       4       23       17       376       3.85       1.20       [0.00, 32566]       0.09         Reuther 2003       0       4       0       6       186         Stocco 2007       0       8       6       186       3       1.12       2.04         Stocco 2007       0       5       3       62       3.6	Kim 2014	2	2	21	01			1.02[0.22	11 251	2.00	
Nmm 2017       4       3       128       194	Kim 2014	2	4	120	104			1.95[0.35,	4 601	2.04	
Latusa 2012       0       2       2       2       2       2       1         Mhanna 2019       3       3       2       140 $\rightarrow$ 70.00 [8.37, 585.21]       0.14         Mazor 2013       0       4       1       161 $\rightarrow$ 70.00 [8.37, 585.21]       0.14         Mazor 2013       0       4       1       161 $\rightarrow$ 70.00 [8.37, 585.21]       0.14         Maughton 1999       1       0       1       13 $\rightarrow$ 115.31 [0.04, 3.3e+05]       0.03         Palmieri 2007       4       23       17       376 $\rightarrow$ 3.85 [1.20, 12.37]       3.16         Reuther 2003       0       4       0       62 $\rightarrow$ 100 [0.00, 3925.66]       0.19         Ribaldone 2019       0       8       6       186 $\rightarrow$ 16.60 [1.92, 143.62]       0.37         Stocco 2004       0       4       13       27 $0.04$ [0.00, 32.90]       4.19         Stocco 2007       0       5       3       62 $0.23$ [0.00, 389.85]       0.94         Sutiman 2018       0       3       10       116 $$		4	2	120	21			0.20[0.02,	4.00J	0.55	
Minimiz 2019       3       3       2       140         Mazor 2013       0       4       11       161         Maughton 1999       1       0       1       13         Palmieri 2007       4       23       17       376         Reuther 2003       0       4       0       62         Kibaldone 2019       0       8       6       186         Schwab 2002       2       5       2       83         Stocco 2004       0       4       13       27         Stocco 2004       0       4       13       27         Stocco 2005       0       5       7       58         Stocco 2007       0       5       3       62         Van Dieren 2005       1       7       9       90         Van Dieren 2005       1       7       9       90         Wang 2018       1       0       18       61         Vrobiova 2012       8       8       26       146         Scice (104)       4       9       68       330         Heterogeneity: 1 <sup>2</sup> = 47.46%, H <sup>2</sup> = 1.90       2.84       2.16       0.05         Test of	Lalussa 2012	0	2	2	140		~	70.00 [ 0.00,	575.91]	0.70	
Mazghton 1999       1       0       1       16 $3364,46]$ $0.32$ Naughton 1999       1       0       1       13 $\rightarrow$ $115.31[0.04, 3.3e+05]$ $0.03$ Palmieri 2007       4       23       17       376 $\rightarrow$ $3.85[1.20, 12.37]$ $3.16$ Reuther 2003       0       4       0       62 $1.00[0.00, 3925.66]$ $0.19$ Ribaldone 2019       0       8       6       186 $\rightarrow$ $1.00[0.00, 3254.91]$ $0.94$ Schwab 2002       2       5       2       83 $\rightarrow$ $16.60[1.92, 143.62]$ $0.37$ Stocco 2004       0       4       13       27 $\rightarrow$ $0.04[0.00, 329.0]$ $1.99$ Stocco 2005       0       5       7       58 $\rightarrow$ $0.10[0.00, 175.09]$ $1.89$ Stocco 2007       0       5       3       62 $\rightarrow$ $0.267[0.23, 30.99]$ $0.94$ Sutiman 2018       0       10       18 $61$ $\rightarrow$ $2.67[0.23, 30.99]$ $1.04$ Van Dieren 2005       1       7       9 $90$ $4.31[1.06, 17.55$	Marar 2019	3	3	2	140		~	70.00[8.37,	265.21]	0.14	
Naugnton 1999       1       0       1       13 $\rightarrow$ 115.31 [0.04, 3.38+06]       0.03         Palmieri 2007       4       23       17       376 $\rightarrow$ 115.31 [0.04, 3.38+06]       0.03         Reuther 2003       0       4       0       62 $\rightarrow$ 1.00 [0.00, 3925.66]       0.19         Ribaldone 2019       0       8       6       186 $\rightarrow$ 16.60 [1.92, 143.62]       0.37         Schwab 2002       2       5       2       83 $\rightarrow$ 0.04 [0.00, 322.90]       4.19         Stocco 2005       0       5       7       58 $\rightarrow$ 0.04 [0.00, 3326.18]       0.38         Sutiman 2018       0       3       10       116 $\rightarrow$ 0.08 [0.00, 33361.89]       0.86         Takatsu 2009       1       2       18       96 $2.67$ [0.23, 30.99]       1.04         Van Dieren 2005       1       7       9       90 $2.64.44$ [0.00, 1.2e+10]       0.01         Winter 2007       1       10       9       10 $2.25$ [1.94, 16.29]       3.75         Zelinkova 2006       3       20       8       2.60 $4.31$ [1.06, 17.55]       2.08         Zhu 2019       4       9       68	Mazor 2013	0	4	11	161	< • •	$\rightarrow$	0.08 [ 0.00,	35564.48]	0.92	
Paimier 2007       4       23       17       376       3.85 $[1.20, 12.3]$ 3.16         Reuther 2003       0       4       0       62 $3.85$ $[1.20, 12.3]$ 3.16         Reuther 2003       0       4       0       62 $3.85$ $1.00$ $[0.00, 3925.66]$ $0.19$ Reuther 2004       0       4       13       27 $0.04$ $[0.00, 2541.91]$ $0.94$ Schwab 2002       2       5       2       83 $0.13$ $[0.00, 2541.91]$ $0.94$ Stocco 2004       0       4       13       27 $0.04$ $[0.00, 322.90]$ $4.19$ Stocco 2005       0       5       7       58 $0.010$ $[0.00, 3361.89]$ $0.86$ Sutiman 2018       0       3       10       116 $0.86$ $0.08$ $0.00$ $3.959$ $0.94$ Van Dieren 2005       1       7       9       90 $1.43$ $0.16$ $12.95$ $2.00$ Wang 2018       1       0       18       61 $0.62$ $1.22$ $0.14$ $0.65$ $7.21$ $5.62$ <td>Naughton 1999</td> <td>1</td> <td>0</td> <td>1</td> <td>13</td> <td></td> <td><math>\rightarrow</math></td> <td>115.31 [ 0.04,</td> <td>3.3e+05]</td> <td>0.03</td>	Naughton 1999	1	0	1	13		$\rightarrow$	115.31 [ 0.04,	3.3e+05]	0.03	
Returner 2003       0       4       0       62         Ribaldone 2019       0       8       6       186         Schwab 2002       2       5       2       83         Stocco 2004       0       4       13       27         Stocco 2005       0       5       7       58         Stocco 2007       0       5       3       62         Stocco 2007       10       110       116       0.08 [0.00, 33361.89]       0.86         Takatsu 2009       1       2       18       96       264.44 [0.00, 1.2e+10]       0.01         Winter 2007       1       10       9       110       1.22 [0.14, 10.65]       2.08         Zhu 201	Paimieri 2007	4	23	17	376			3.85 [ 1.20,	12.37]	3.16	
Hibaidone 2019       0       8       6       186         Schwab 2002       2       5       2       83         Stocco 2004       0       4       13       27         Stocco 2005       0       5       7       58         Stocco 2007       0       5       3       62         Sutiman 2018       0       3       10       116         Takatsu 2009       1       2       18       96         Van Dieren 2005       1       7       9       90         Winter 2007       1       10       9       10         Van Dieren 2006       3       20       8       26       146         Schwaize       2.65       1.94       16.29       3.75         Zelinkova 2006       3       2.08       2.30       2.84       2.16	Reutner 2003	0	4	0	62	<	$\rightarrow$	1.00[0.00,	3925.66]	0.19	
Schwab 2002 2 5 2 83 Stocco 2004 0 4 13 27 Stocco 2005 0 5 7 58 Stocco 2007 0 5 3 62 Sutiman 2018 0 3 10 116 Takatsu 2009 1 2 18 96 Van Dieren 2005 1 7 9 90 Wang 2018 1 0 18 61 Wroblova 2012 8 8 26 146 Zelinkova 2006 3 20 8 230 Zhu 2019 4 9 68 330 Heterogeneity: $l^2 = 47.96\%$ , $H^2 = 1.92$ Test of $9_i = 9_i$ : Q(37) = 70.42, p = 0.00 Overall Heterogeneity: $l^2 = 47.46\%$ , $H^2 = 1.90$ Test of $9_i = 9_i$ : Q(37) = 70.42, p = 0.00 Higher in non-mut Test of group differences: $Q_b(1) = 1.14$ , p = 0.29 t/64 - t/4	Ribaldone 2019	0	8	6	186	<	$\rightarrow$	0.13[0.00,	2541.91]	0.94	
Stocco 2004       0       4       13       27       0.04 [0.00, 32.90]       4.19         Stocco 2005       0       5       7       58       0.10 [0.00, 175.09]       1.89         Stocco 2007       0       5       3       62       0.23 [0.00, 389.95]       0.94         Sutiman 2018       0       3       10       116       0.08 [0.00, 33361.89]       0.86         Takatsu 2009       1       2       18       96       2.67 [0.23, 30.99]       1.04         Van Dieren 2005       1       7       9       90       1.43 [0.16, 12.95]       2.00         Wang 2018       1       0       18       61       264.44 [0.00, 1.2e+10]       0.01         Winter 2007       1       10       9       110       1.22 [0.14, 10.65]       2.35         Wroblova 2012       8       8       26       146       4.31 [1.06, 17.55]       2.08         Zhu 2019       4       9       68       330       2.16 [0.65, 7.21]       5.05         Heterogeneity: 1 <sup>2</sup> = 47.96%, H <sup>2</sup> = 1.92       2.84 [2.15, 3.77]       2.84 [2.15, 3.77]       2.84 [2.15, 3.43]         Heterogeneity: 1 <sup>2</sup> = 47.46%, H <sup>2</sup> = 1.90       Higher in non-mut       Higher in mut       4.14 <td>Schwab 2002</td> <td>2</td> <td>5</td> <td>2</td> <td>83</td> <td></td> <td><math>\rightarrow</math></td> <td>16.60 [ 1.92,</td> <td>143.62]</td> <td>0.37</td>	Schwab 2002	2	5	2	83		$\rightarrow$	16.60 [ 1.92,	143.62]	0.37	
Stocco 2005       0       5       7       58         Stocco 2007       0       5       3       62         Sutiman 2018       0       3       10       116         Takatsu 2009       1       2       18       96         Van Dieren 2005       1       7       9       90         Wang 2018       1       0       18       61         Winter 2007       1       10       9       110         Winter 2007       1       10       9       110         Winter 2007       1       10       9       10         Winter 2006       3       20       8       230         Zhu 2019       4       9       68       330         Heterogeneity: I <sup>2</sup> = 47.46%, H <sup>2</sup> = 1.92       2.84 [2.15, 3.77]       2.84 [2.15, 3.77]         Test of $\mathbf{\theta}_i = \mathbf{\theta}_i$ : Q(37) = 70.42, p = 0.00       Higher in non-mut       Higher in mut         Test of group differences: Q <sub>b</sub> (1) = 1.14, p = 0.29 $4.31$ $4.4$ <td>Stocco 2004</td> <td>0</td> <td>4</td> <td>13</td> <td>27</td> <td>&lt;</td> <td></td> <td>0.04 [ 0.00,</td> <td>32.90]</td> <td>4.19</td>	Stocco 2004	0	4	13	27	<		0.04 [ 0.00,	32.90]	4.19	
Stocco 2007       0       5       3       62 $\bullet$ 0.23 [0.00, 389.95]       0.94         Sutiman 2018       0       3       10       116 $\bullet$ 0.08 [0.00, 33361.89]       0.86         Takatsu 2009       1       2       18       96       2.67 [0.23, 30.99]       1.04         Van Dieren 2005       1       7       9       90       1.43 [0.16, 12.95]       2.00         Wang 2018       1       0       18       61 $\bullet$ 264.44 [0.00, 1.2e+10]       0.01         Winter 2007       1       10       9       110 $\bullet$ 1.22 [0.14, 10.65]       2.35         Wroblova 2012       8       8       26       146 $\bullet$ 5.62 [1.94, 16.29]       3.75         Zelinkova 2006       3       20       8       230 $4.31 [1.06, 17.55]$ 2.08         Zhu 2019       4       9       68       330 $\bullet$ 2.65 [2.05, 3.43]         Heterogeneity: I <sup>2</sup> = 47.46%, H <sup>2</sup> = 1.90 $\bullet$ 2.65 [2.05, 3.43] $\bullet$ 2.65 [2.05, 3.43]         Test of $0_i = 0_i$ : Q(37) = 70.42, p = 0.00       Higher in non-mut       Higher in mut $\bullet$ $\bullet$ $\bullet$ <td>Stocco 2005</td> <td>0</td> <td>5</td> <td>7</td> <td>58</td> <td>&lt;</td> <td><math>\rightarrow</math></td> <td>0.10 [ 0.00,</td> <td>175.09]</td> <td>1.89</td>	Stocco 2005	0	5	7	58	<	$\rightarrow$	0.10 [ 0.00,	175.09]	1.89	
Sutiman 2018 0 3 10 116 Takatsu 2009 1 2 18 96 Van Dieren 2005 1 7 9 90 Wang 2018 1 0 18 61 Winter 2007 1 10 9 110 Winter 2007 1 10 9 110 Wroblova 2012 8 8 26 146 Zelinkova 2006 3 20 8 230 Zhu 2019 4 9 68 330 Heterogeneity: $l^2 = 47.96\%$ , $H^2 = 1.92$ Test of $0_1 = 0_1$ : Q(33) = 63.42, p = 0.00 <b>Overall</b> Heterogeneity: $l^2 = 47.46\%$ , $H^2 = 1.90$ Test of $0_1 = 0_2$ : Q(37) = 70.42, p = 0.00 Higher in non-mut Test of group differences: $Q_b(1) = 1.14$ , p = 0.29 $1/24 = 1/4$ $d = \frac{6}{24}$	Stocco 2007	0	5	3	62	←	$\rightarrow$	0.23 [ 0.00,	389.95]	0.94	
Takatsu 2009       1       2       18       96         Van Dieren 2005       1       7       9       90         Wang 2018       1       0       18       61         Winter 2007       1       10       9       110         Wroblova 2012       8       8       26       146         Zelinkova 2006       3       20       8       230         Zhu 2019       4       9       68       330         Heterogeneity: $l^2 = 47.96\%$ , $H^2 = 1.92$ 2.84 [ 2.15, 3.77]         Test of $0_1 = 0_1$ : Q(37) = 70.42, p = 0.00       Higher in non-mut       Higher in mut         Utest of group differences: $Q_b(1) = 1.14$ , p = 0.29       Higher in non-mut       Higher in mut	Sutiman 2018	0	3	10	116	<	$\rightarrow$	0.08 [ 0.00,	33361.89]	0.86	
Van Dieren 2005       1       7       9       90       1.43 [0.16, 12.95]       2.00         Wang 2018       1       0       18       61 $264.44 [0.00, 1.2e+10]$ 0.01         Winter 2007       1       10       9       110       1.22 [0.14, 10.65]       2.35         Wroblova 2012       8       8       26       146 $5.62 [1.94, 16.29]$ 3.75         Zelinkova 2006       3       20       8       230 $4.31 [1.06, 17.55]$ 2.08         Zhu 2019       4       9       68       330 $2.16 [0.65, 7.21]$ 5.05         Heterogeneity: I <sup>2</sup> = 47.96%, H <sup>2</sup> = 1.92       2.84 [2.15, 3.77] $2.84 [2.15, 3.77]$ $5.05 [2.05, 3.43]$ Heterogeneity: I <sup>2</sup> = 47.46%, H <sup>2</sup> = 1.90 $4.9 = 0.29$ Higher in non-mut       Higher in mut         Test of group differences: Q <sub>b</sub> (1) = 1.14, p = 0.29       Higher in non-mut       Higher in mut	Takatsu 2009	1	2	18	96			2.67 [ 0.23,	30.99]	1.04	
Wang 2018       1       0       18       61         Winter 2007       1       10       9       110       9       110       9       110       9       110       9       110       9       110       9       110       9       110       9       110       9       110       9       110       9       110       9       110       1.22 [0.14, 10.65]       2.35         Wroblova 2012       8       8       26       146       5.62 [1.94, 16.29]       3.75         Zelinkova 2006       3       20       8       230       4.31 [1.06, 17.55]       2.08         Zhu 2019       4       9       68       330       9       2.84 [2.15, 3.77]       5.05         Heterogeneity: I <sup>2</sup> = 47.96%, H <sup>2</sup> = 1.92       2.65 [2.05, 3.43]       4.31 [1.06, 17.55]       2.08         Overall $\bullet$ 2.65 [2.05, 3.43]       4.31 [1.06, 17.55]       3.43 [1.06, 17.55]       3.43 [1.06, 17.55]       3.43 [1.06, 17.55]       3.43 [1.06, 17.55]       3.43 [1.06, 17.55]       3.43 [1.06, 17.55]       3.43 [1.06, 17.55]       3.43 [1.06, 17.55]       3.43 [1.06, 17.55]       3.43 [1.06, 17.55]       3.43 [1.06, 17.55]       3.43 [1.06, 17.55]       3.43 [1.06, 17.55]       3.43 [1.06, 17.55]       3.43 [1.06, 17.55]	Van Dieren 2005	1	7	9	90			1.43 [ 0.16,	12.95]	2.00	
Winter 2007       1       10       9       110       1.22 [0.14, 10.65]       2.35         Wroblova 2012       8       8       26       146       5.62 [1.94, 16.29]       3.75         Zelinkova 2006       3       20       8       230       4.31 [1.06, 17.55]       2.08         Zhu 2019       4       9       68       330        2.84 [2.15, 3.77]         Heterogeneity: $l^2 = 47.96\%$ , $H^2 = 1.92$ 2.84 [2.15, 3.77]       2.84 [2.15, 3.77]         Test of $0_i = 0_j$ : Q(37) = 70.42, p = 0.00       Higher in non-mut       Higher in mut         Test of group differences: Q <sub>b</sub> (1) = 1.14, p = 0.29       Higher in non-mut       Higher in mut	Wang 2018	1	0	18	61	<	$\rightarrow$	264.44 [ 0.00,	1.2e+10]	0.01	
Wroblova 2012       8       8       26       146         Zelinkova 2006       3       20       8       230         Zhu 2019       4       9       68       330         Heterogeneity: $1^2 = 47.96\%$ , $H^2 = 1.92$ 2.84 [ 2.15, 3.77]         Test of $0_1 = 0_1$ : Q(33) = 63.42, p = 0.00       2.65 [ 2.05, 3.43]         Weterogeneity: $1^2 = 47.46\%$ , $H^2 = 1.90$ Higher in non-mut         Test of $0_1 = 0_1$ : Q(37) = 70.42, p = 0.00       Higher in non-mut         Test of group differences: Q <sub>b</sub> (1) = 1.14, p = 0.29       Higher in non-mut	Winter 2007	1	10	9	110			1.22 [ 0.14,	10.65]	2.35	
Zelinkova 2006       3       20       8       230         Zhu 2019       4       9       68       330         Heterogeneity: $l^2 = 47.96\%$ , $H^2 = 1.92$ 2.16 [ 0.65, 7.21]       5.05         Test of $0_1 = 0_1$ : Q(33) = 63.42, p = 0.00       2.84 [ 2.15, 3.77]         Overall       2.65 [ 2.05, 3.43]         Heterogeneity: $l^2 = 47.46\%$ , $H^2 = 1.90$ Test of $0_1 = 0_1$ : Q(37) = 70.42, p = 0.00         Higher in non-mut         Test of group differences: Q <sub>b</sub> (1) = 1.14, p = 0.29	Wroblova 2012	8	8	26	146			5.62 [ 1.94,	16.29]	3.75	
Zhu 2019       4       9       68       330         Heterogeneity: $l^2 = 47.96\%$ , $H^2 = 1.92$ 2.16 [ 0.65, 7.21]       5.05         Test of $0_i = 0_j$ : Q(33) = 63.42, p = 0.00       2.84 [ 2.15, 3.77]         Overall         Heterogeneity: $l^2 = 47.46\%$ , $H^2 = 1.90$ Test of $0_i = 0_j$ : Q(37) = 70.42, p = 0.00       Higher in non-mut         Higher in mut       Test of group differences: Q <sub>b</sub> (1) = 1.14, p = 0.29	Zelinkova 2006	3	20	8	230			4.31 [ 1.06,	17.55]	2.08	
Heterogeneity: $l^2 = 47.96\%$ , $H^2 = 1.92$ Test of $0_i = 0_j$ : Q(33) = 63.42, p = 0.00 <b>Overall</b> Heterogeneity: $l^2 = 47.46\%$ , $H^2 = 1.90$ Test of $0_i = 0_j$ : Q(37) = 70.42, p = 0.00 Higher in non-mut Test of group differences: Q <sub>b</sub> (1) = 1.14, p = 0.29 1/64	Zhu 2019	4	9	68	330			2.16 [ 0.65,	7.21]	5.05	
Test of $0_{i} = 0_{j}$ : Q(33) = 63.42, p = 0.00         Overall         Heterogeneity: $l^{2} = 47.46\%$ , $H^{2} = 1.90$ Test of $0_{i} = 0_{j}$ : Q(37) = 70.42, p = 0.00         Higher in non-mut         Test of group differences: Q <sub>b</sub> (1) = 1.14, p = 0.29	Heterogeneity: I <sup>2</sup> = 47.96%	6, Η <sup>2</sup>	= 1.9	2		•		2.84 [ 2.15,	3.77]		
Overall $2.65 [ 2.05, 3.43]$ Heterogeneity: $l^2 = 47.46\%$ , $H^2 = 1.90$ Test of $0_i = 0_j$ : $Q(37) = 70.42$ , $p = 0.00$ Higher in non-mut         Higher in mut         Test of group differences: $Q_b(1) = 1.14$ , $p = 0.29$	Test of $\theta_i = \theta_j$ : Q(33) = 63.	42, p	= 0.0	0							
Overall       2.65 [ 2.05, 3.43]         Heterogeneity: $l^2 = 47.46\%$ , $H^2 = 1.90$ Higher in non-mut         Test of $0_i = 0_j$ : Q(37) = 70.42, p = 0.00       Higher in non-mut         Test of group differences: Q <sub>b</sub> (1) = 1.14, p = 0.29       Higher in non-mut	0							0.0510.05	0.401		
Heterogeneity: $I^{-} = 47.46\%$ , $H^{-} = 1.90$ Test of $0_{1} = 0_{1}$ : Q(37) = 70.42, p = 0.00 Test of group differences: Q <sub>b</sub> (1) = 1.14, p = 0.29 1/64		,2		•		•		2.65 [ 2.05,	3.43]		
Test of group differences: $Q_b(1) = 1.14$ , p = 0.29 Higher in non-mut Higher in mut	Heterogeneity: I <sup>+</sup> = 47.469	%, H <sup>≁</sup>	= 1.9	U							
Test of group differences: $Q_b(1) = 1.14$ , p = 0.29	lest of $\mathbf{U}_i = \mathbf{U}_j$ : Q(37) = 70.	42, p	= 0.0	U		Higher in non-mut Higher in m	ut				
1/04 1/4 4 04	Test of group differences:	Q <sub>b</sub> (1)	) = 1.	14, p	= 0.29	1/64 1/4 4	64				

# Figure S38. Forest plot of comparison heterozygous *TPMT* vs wild-type *TPMT*, outcome: Total hematologic adverse events

Study	n mut No						Odds Ratio with 95% Cl				
	100	110	100						with oo		(70)
Gearry 2003	1	7	0	91				$\rightarrow$	15 26 [ 0 85	273 021	4 25
Heterogeneity: $I^2 =$	0.00	% H <sup>2</sup>	= 1 (	00				-	15 26 [ 0 85	273 021	
Test of $0 = 0$ ; Q(0)											
		, p									
Cohort											
Demlova 2014	0	4	0	12	<del>&lt;</del>	_		$\rightarrow$	1.00 [ 0.01,	105.38]	11.67
Hibi 2003	3	4	0	74				-	61.93 [ 4.89,	783.63]	2.96
Hindorf 2006	0	7	1	51	←	-		$\rightarrow$	0.46 [ 0.00,	170.98]	14.47
Larussa 2012	0	2	0	23	<		-	$\rightarrow$	1.00 [ 0.00,	1575.21]	4.67
Mazor 2013	0	4	11	161	←			$\rightarrow$	0.08 [ 0.00,	35564.48]	17.84
Schwab 2002	2	5	2	83				$\rightarrow$	16.60 [ 1.92,	143.62]	7.16
Sutiman 2018	0	3	6	120	←			$\rightarrow$	0.13 [ 0.00,	54705.08]	10.61
Takatsu 2009	0	3	3	111	←			$\rightarrow$	0.24 [ 0.00,	54181.44]	6.66
Van Dieren 2005	0	8	0	99	←				1.00 [ 0.00,	1783.55]	4.52
Winter 2007	1	10	3	116				-	3.87 [ 0.37,	40.69]	15.21
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	= 1.0	00			-		4.11 [ 1.64,	10.28]	
Test of $0_i = 0_j$ : Q(9)	= 7.	99, p	= 0.5	3							
Overall									4.58 [ 1.93,	10.87]	
Heterogeneity: $I^2 =$	00										
Test of $\theta_i = \theta_j$ : Q(10) = 8.30, p = 0.60					Higher in r	non-mut	Higher in I	mut			
Test of group differ	0.72, p = 0.40										
					1/64	1/4	4	64			

Fixed-effects Mantel-Haenszel model

Figure S39. Forest plot of comparison heterozygous *TPMT* vs wild-type *TPMT*, outcome: Serious hematologic adverse events

-	М	ut	Nor	n mut						Odds Ra	atio	Weight
Study	Yes	No	Yes	No						with 95%		(%)
Case-control												
Gearry 2003	5	3	44	47						1.78 [ 0.40,	7.89]	18.34
Heterogeneity: I <sup>2</sup> =	00			-			1.78 [ 0.40,	7.89]				
Test of $0_i = 0_j$ : Q(0												
Cohort												
Ansari 2008	15	4	66	122					-	6.93 [ 2.21,	21.74]	17.55
Coelho 2016	5	4	9	60						8.33 [ 1.88,	36.97]	6.35
De Ridder 2006	1	1	10	57				-		5.70 [ 0.33,	98.75]	1.99
Larussa 2012	0	2	3	20		←	-	-	$\rightarrow$	0.21 [ 0.00,	259.81]	4.15
Naughton 1999	1	0	1	13					$\rightarrow$ 1	15.31 [ 0.04,	3.3e+05]	0.10
Ribaldone 2019	2	6	58	134				<u> </u>		0.77 [ 0.15,	3.93]	23.94
Schwab 2002	1	6	8	77			0	-		1.60 [ 0.17,	15.05]	7.18
Stocco 2004	2	2	12	28				-		2.33 [ 0.29,	18.55]	7.50
Stocco 2005	2	3	11	54				-	1	3.27 [ 0.49,	21.95]	6.49
Von Ahsen 2005	2	3	11	55				-	-	3.33 [ 0.50,	22.35]	6.39
Heterogeneity: I <sup>2</sup> =	0.00	%, H	l <sup>2</sup> = 1.	00				•		3.54 [ 2.03,	6.15]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(9)	) = 8.0	06, p	= 0.5	53								
Overall								•		3.21 [ 1.91,	5.41]	
Heterogeneity: I <sup>2</sup> =	0.00	%, H	l <sup>2</sup> = 1.	00								
Test of $\theta_i = \theta_j$ : Q(10) = 8.83, p = 0.55						Higher in	non-mut	Higher in	mut			
Test of group diffe	0.72, p	0 = 0.40										
						1/64	1/4	4	64			
Fixed-effects Mante	l-Hae	ensze	el mod	del								

Figure S40. Forest plot of comparison heterozygous *TPMT* vs wild-type *TPMT*, outcome: Withdrawal due to AE

	М	ut	Nor	n mut			Odds	Ratio	Weight		
Study	Yes	No	Yes	No		1	with 9	5% CI	(%)		
Case-control											
Gearry 2003	0	8	5	86	← ■	>(	0.15 [ 0.00,	157.69]	4.49		
Marinaki 2004	1	7	7	61	2		1.24 [ 0.13,	11.65]	6.11		
Zabala-Fernández 2011	1	10	18	147			0.82 [ 0.10,	6.76]	9.70		
Heterogeneity: I <sup>2</sup> = 0.00%,	$H^2 =$	1.00					0.80 [ 0.18,	3.48]			
Test of $\theta_i = \theta_j$ : Q(2) = 0.38	, p = (	0.83									
Cohort											
Al-Judaibi 2016	0	5	0	48	<	•> '	1.00 [ 0.00,	868.79]	0.80		
Ansari 2008	0	19	8	180	←	(	0.10 [ 0.00,	66.23]	7.72		
Bangma 2020	4	46	34	509			1.30 [ 0.44,	3.83]	25.01		
De Ridder 2006	0	2	4	63	<	>(	0.18 [ 0.00,	20666.95]	1.35		
Hlavaty 2013	0	14	6	199	← ■	>(	0.13 [ 0.00,	321.79]	4.19		
Larussa 2012	0	2	1	22	<	> (	0.46 [ 0.00,	623.29]	1.40		
Mhanna 2019	0	6	4	138	<	>(	0.19 [ 0.00,	3417.97]	1.89		
Mazor 2013	0	4	2	170	<	>(	0.32 [ 0.00,	1.6e+05]	0.64		
Palmieri 2007	0	27	16	377	←	> (	0.05 [ 0.00,	123.64]	10.30		
Ribaldone 2019	2	6	26	166	_	- :	2.13 [ 0.41,	11.11]	7.40		
Schwab 2002	0	7	3	82	< ∎	>(	0.23 [ 0.00,	308.96]	2.80		
Stocco 2004	0	4	2	38	← ■	> (	0.30 [ 0.00,	236.54]	2.45		
Stocco 2005	0	5	4	61	← ●	> (	0.18 [ 0.00,	301.87]	3.29		
Stocco 2007	1	4	6	59			2.46 [ 0.24,	25.69]	3.25		
Takatsu 2009	0	3	0	114	<	> '	1.00 [ 0.00,	2.6e+05]	0.23		
Van Dieren 2005	1	7	5	94			2.69 [ 0.27,	26.26]	3.10		
Winter 2007	0	11	1	118	←	>(	0.47 [ 0.00,	476.21]	1.53		
Wroblova 2012	0	16	2	170	<	>(	0.31 [ 0.00,	288.45]	2.34		
Heterogeneity: $I^2 = 0.00\%$ ,	$H^2 =$	1.00					0.91 [ 0.45,	1.84]			
Test of $\theta_i = \theta_j$ : Q(17) = 5.0	0, p =	1.00									
Overall							0.89 [ 0.47,	1.67]			
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$											
Test of $\theta_i = \theta_j$ : Q(20) = 5.5	0, p =	1.00			Higher in non-mut	Higher in mut					
Test of group differences:	Q <sub>b</sub> (1)	= 0.0	02, p	= 0.88							
second de			67 GI		1/64 1/4	4 64					

Figure S41. Forest plot of comparison heterozygous *TPMT* vs wild-type *TPMT*, outcome: Pancreatitis
Study       Yes       No       Yes       No         Case-control $Gearry 2003$ 0       8       15       76         Marinaki 2004       1       7       3       61       2.90 [ 0.26, 31.84]       3.26         Zabala-Fernández 2011       0       6       5       119 $0.15 [ 0.00, 1514.23]$ 3.05         Heterogeneity: $l^2 = 20.28\%$ , $H^2 = 1.25$ $0.52 [ 0.08, 3.55]$ $0.52 [ 0.08, 3.55]$	with 95% CI (%)
Case-control         Gearry 2003       0       8       15       76         Marinaki 2004       1       7       3       61         Zabala-Fernández 2011       0       6       5       119         Heterogeneity: $I^2 = 20.28\%$ , $H^2 = 1.25$ 0.52 [ 0.08, 3.55]       3.55]	
Gearry 2003       0       8       15       76 $0.05 [0.00, 50.41]$ 14.22         Marinaki 2004       1       7       3       61 $2.90 [0.26, 31.84]$ $3.26$ Zabala-Fernández 2011       0       6       5       119 $0.15 [0.00, 1514.23]$ $3.05$ Heterogeneity: $l^2 = 20.28\%$ , $H^2 = 1.25$ 0.52 [0.08, 3.55] $0.52 [0.08, 3.55]$	
Marinaki 2004       1       7       3       61         Zabala-Fernández 2011       0       6       5       119         Heterogeneity: $l^2 = 20.28\%$ , $H^2 = 1.25$ 0.52 [ 0.08, 3.55]       3.05         Test of $0_i = 0_j$ : Q(2) = 2.51, p = 0.29       0.52 [ 0.08, 3.55]	0.05 [ 0.00, 50.41] 14.22
Zabala-Fernández 2011       0       6       5       119 $\rightarrow$ 0.15 [ 0.00, 1514.23]       3.05         Heterogeneity: $l^2 = 20.28\%$ , $H^2 = 1.25$ 0.52 [ 0.08, 3.55]       0.52 [ 0.08, 3.55]         Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(2) = 2.51, p = 0.29       0.15 [ 0.00, 1514.23]       3.05	<b>2.90</b> [ 0.26, 31.84] 3.26
Heterogeneity: $I^2 = 20.28\%$ , $H^2 = 1.25$ 0.52 [ 0.08, 3.55] Test of $0_i = 0_j$ : Q(2) = 2.51, p = 0.29	→ 0.15 [ 0.00, 1514.23] 3.05
Test of $\theta_i = \theta_j$ : Q(2) = 2.51, p = 0.29	► 0.52 [ 0.08, 3.55]
Cohort	
Al-Judaibi 2016 0 5 0 48 ← → 1.00 [ 0.00, 868.79] 0.94	────→ 1.00 [ 0.00, 868.79] 0.94
Ansari 2008 0 19 8 180 < 0.10 [ 0.00, 66.23] 9.09	0.10 [ 0.00, 66.23] 9.09
De Ridder 2006 0 2 0 67 ← → 1.00 [ 0.00, 1.3e+05] 0.31	→ 1.00 [ 0.00, 1.3e+05] 0.31
Hlavaty 2013 1 13 23 182 0.61 [ 0.08, 4.87] 15.25	— 0.61 [ 0.08, 4.87] 15.25
Larussa 2012 0 2 1 22 <	→ 0.46 [ 0.00, 623.29] 1.65
Mhanna 2019         1         5         3         139	● ● ● 9.27 [ 0.81, 105.54] 1.13
Mazor 2013 0 4 6 166 <	────→ 0.14 [ 0.00, 63489.67] 1.76
Palmieri 2007 1 26 11 382	——
Reuther 2003 0 4 0 62 <	────→ 1.00 [ 0.00, 3925.66] 0.63
Ribaldone 2019         0         8         24         168         ←         →         0.03 [ 0.00, 627.81]         11.09	→ 0.03 [ 0.00, 627.81] 11.09
Schwab 2002         0         7         3         82         ►         >         0.23 [ 0.00, 308.96]         3.30	→ 0.23 [ 0.00, 308.96] 3.30
Stocco 2004 0 4 2 38 <	
Stocco 2005 0 5 6 59 $\leftarrow$ $\blacksquare$ $\rightarrow$ 0.12 [ 0.00, 204.70] 5.45	→ 0.12 [ 0.00, 204.70] 5.45
Stocco 2007 0 5 3 62 ← ● → 0.23 [ 0.00, 389.95] 3.09	→ 0.23 [ 0.00, 389.95] 3.09
Takatsu 2009         0         3         2         112         ←         ■         >         0.32 [ 0.00, 74011.48]         0.84	→ 0.32 [ 0.00, 74011.48] 0.84
Van Dieren 2005         0         8         5         94         ▲         →         0.15 [ 0.00, 208.61]         4.90	→ 0.15 [ 0.00, 208.61] 4.90
Winter 2007         1         10         8         111         Image: 1.39 [ 0.16, 12.24 ]         6.87	1.39 [ 0.16, 12.24] 6.87
Wroblova 2012 1 15 3 169 3.76 [ 0.37, 38.37] 2.67	<b>.</b> 3.76 [ 0.37, 38.37] 2.67
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$ $\bullet$ 0.72 [ 0.31, 1.69]	0.72 [ 0.31, 1.69]
Test of $0_{i} = 0_{j}$ : Q(17) = 8.36, p = 0.96	
Overall 0.68 [ 0.31, 1.48]	0.68 [ 0.31, 1.48]
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(20) = 10.79, p = 0.95 Higher in non-mut Higher in mut	gher in mut
Test of group differences: $Q_b(1) = 0.10$ , p = 0.75	
1/64 1/4 4 64	4 64

Figure S42. Forest plot of comparison heterozygous *TPMT* vs wild-type *TPMT*, outcome: Hepatotoxicity

	Μ	ut	Non	mut		Odds	Ratio	Weight
Study	Yes	No	Yes	No		with 9	5% CI	(%)
Case-control								
Gearry 2003	2	6	10	81		2.70 [ 0.48,	15.23]	7.28
Marinaki 2004	5	7	8	61		└──	21.30]	8.31
Zabala-Fernández 2011	1	10	15	147		- 0.98 [ 0.12,	8.19]	10.42
Heterogeneity: I <sup>2</sup> = 0.00%,	$H^{2} =$	1.00			-	2.89 [ 1.17,	7.10]	
Test of $\theta_i = \theta_j$ : Q(2) = 1.83	, p = 0	0.40						
Cohort								
Ansari 2008	8	11	26	162		— 4.53 [ 1.67,	12.32]	16.60
Hlavaty 2013	0	14	7	198	← ■	→ 0.11 [ 0.00,	278.59]	6.07
Kim 2014	0	6	2	100	← ■	→ 0.31 [ 0.00,	1446.30]	1.95
Mhanna 2019	1	5	20	122		— 1.22 [ 0.14,	10.99]	8.12
Palmieri 2007	0	27	9	384	← ■	→ 0.09 [ 0.00,	216.86]	7.66
Ribaldone 2019	0	8	2	190	← ■	→ 0.32 [ 0.00,	6339.69]	1.42
Schwab 2002	0	7	3	82	< <b>•</b>	→ 0.23 [ 0.00,	308.96]	3.55
Takatsu 2009	0	3	11	103	← ■	→ 0.07 [ 0.00,	16268.11]	3.66
Van Dieren 2005	0	8	7	92	← ■	→ 0.11 [ 0.00,	150.97]	7.05
Winter 2007	0	11	14	105	←	0.05 [ 0.00,	47.96]	15.05
Wroblova 2012	1	15	3	169		3.76 [ 0.37,	38.37]	2.88
Heterogeneity: $I^2 = 0.00\%$	H <sup>2</sup> =	1.00			-	1.37 [ 0.68,	2.74]	
Test of $\theta_i = \theta_j$ : Q(10) = 9.1	0, p =	0.52						
Overall					•	1.76 [ 1.02,	3.03]	
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00						
Test of $\theta_i = \theta_j$ : Q(13) = 10.	55, p	= 0.6	5		Higher in non-mut Highe	er in mut		
Test of group differences:	Q <sub>b</sub> (1)	= 1.6	67, p =	= 0.20				
					1/64 1/4 4	64		

Figure S43. Forest plot of comparison heterozygous *TPMT* vs wild-type *TPMT*, outcome: Gastrointestinal side effects

	Μ	ut	Non	mut					Odds R	atio	Weight
Study	Yes	No	Yes	No					with 959	% Cl	(%)
Case-control											
Zabala-Fernández 2011	8	7	125	92		_	-		0.84 [ 0.29,	2.40]	32.89
Heterogeneity: $I^2 = 0.00\%$	$H^{2} =$	1.00				-			0.84 [ 0.29,	2.40]	
Test of $\theta_i = \theta_j$ : Q(0) = 0.00	, p = .										
Cohort											
Al-Judaibi 2016	2	2	14	24		-	-	_	1.71 [ 0.22,	13.56]	5.81
Dubinsky 2000	8	0	39	45				$\rightarrow$	106.98 [ 0.13,	86534.12]	0.32
Lee 2017	5	0	90	45	←				71.25 [ 0.00,	2.4e+06]	0.20
Lucafò 2019	8	0	62	34					58.28 [ 0.05,	71507.11]	0.40
Palmieri 2007	17	10	287	106		-	-		0.63 [ 0.28,	1.41]	59.59
Reuther 2003	4	0	60	2	<			>	3.23 [ 0.00,	10706.13]	0.47
Stocco 2005	3	0	31	17	←			$\rightarrow$	29.21 [ 0.01,	1.0e+05]	0.31
Heterogeneity: I <sup>2</sup> = 43.10%	6, H <sup>2</sup> :	= 1.7	6				•		1.93 [ 1.02,	3.67]	
Test of $\theta_i = \theta_j$ : Q(6) = 10.54	4, p =	0.10									
Overall							•		1.57 [ 0.92,	2.69]	
Heterogeneity: I <sup>2</sup> = 28.94%	6, H <sup>2</sup> :	= 1.4	1								
Test of $\theta_i = \theta_j$ : Q(7) = 9.85	, p = 0	0.20			Higher in n	ion-mut	Highe	r in mut			
Test of group differences:	Q <sub>b</sub> (1)	= 1.	76, p =	= 0.18							
			10. 20		1/64	1/4	4	64			

Figure S44. Forest plot of comparison heterozygous *TPMT* vs wild-type *TPMT*, outcome: Clinical remission

	М	ut	Non	mut				Weight				
Study	Yes	No	Yes	No					with	95% (	CI	(%)
Case-control												
Gearry 2003	1	0	0	91	<				8649.00 [	0.00,	1.5e+12]	0.15
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	<sup>2</sup> = 1.0	00					8649.00 [	0.00,	1.5e+12]	
Test of $0_i = 0_j$ : Q(0)	= 0.0	)0, p	= .									
Cohort												
Hibi 2003	1	0	0	74	←			$\longrightarrow$	5776.00 [	0.00,	1.7e+11]	0.22
Larussa 2012	1	1	1	22		-		$\rightarrow$	22.00 [	0.72,	672.78]	52.13
Mhanna 2019	0	1	4	138	←				0.19 [	0.00,	3.2e+09]	45.19
Schwab 2002	1	0	11	74	<del>&lt;</del>			>	544.19 [	0.00,	4.8e+10]	2.06
Van Dieren 2005	2	0	0	99	<				10404.00 [	0.01,	1.4e+10]	0.25
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	<sup>2</sup> = 1.0	00					61.29 [	9.35,	401.87]	
Test of $0_i = 0_j$ : Q(4)	= 1.4	40, p	= 0.84	4								
Overall									74.09 [	12.25,	448.24]	
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	<sup>2</sup> = 1.0	00								
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(5)	= 1.7	73, p	= 0.88	3	Higher in n	on-mut	Higher	in mut				
Test of group differ	rence	s: Q <sub>b</sub>	(1) = (	0.26, p = 0.61								
etern T			101	88 YO	1/64	1/4	4	64				

Figure S45. Forest plot of comparison 2 mutant *TPMT* alleles vs wild-type, outcome: Total serious adverse events

	М	ut	Nor	n mut				Odds Ra	itio	Weight
Study	Yes	No	Yes	No				with 95%	CI	(%)
Case-control										
Gearry 2003	1	0	0	91	<		>	8649.00 [ 0.00,	1.5e+12]	0.03
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.0	00				8649.00 [ 0.00,	1.5e+12]	
Test of $0_i = 0_j$ : Q(0)	= 0.0	0, p	= .							
Cohort										
De Ridder 2006	0	3	1	66	<		>	0.48 [ 0.00,	7399.85]	24.64
Hibi 2003	1	0	5	69	←		>	888.47 [ 0.00,	2.4e+10]	0.31
Hindorf 2006	0	1	8	44	←		>	0.09 [ 0.00,	1.7e+05]	49.57
Hlavaty 2013	1	0	21	184	←		>	1741.02 [ 0.00,	3.1e+15]	0.15
Kim 2014	1	0	21	81	←		>	387.76 [ 0.00,	1.9e+11]	0.61
Larussa 2012	1	1	2	21		S-		10.50 [ 0.46,	239.78]	23.84
Mhanna 2019	1	0	2	140	←		>	6783.48 [ 0.00,	1.1e+14]	0.04
Palmieri 2007	2	0	17	376	←		>	8296.22 [ 0.00,	7.9e+15]	0.07
Schwab 2002	1	0	2	83	←		>	2445.14 [ 0.00,	2.2e+11]	0.12
Van Dieren 2005	2	0	9	90	←		>	929.84 [ 0.00,	1.1e+09]	0.57
Zelinkova 2006	1	0	8	230	←		>	6162.75 [ 0.00,	9.5e+16]	0.05
Heterogeneity: $I^2 =$	0.00	%, H	<sup>2</sup> = 1.0	00			$\langle \rangle$	30.08 [ 8.57,	105.61]	
Test of $\mathbf{\theta}_i = \mathbf{\theta}_i$ : Q(10)	0) = 2	.98, 1	o = 0.	98						
0. <b>.</b> 0.		10.2								
Overall								33.02 [ 9.65,	112.96]	
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.0	00						
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1	1) = 3	.39,	o = 0.	98	Higher in r	ion-mut	Higher in mut			
Test of group differ	ence	s: Q <sub>b</sub>	(1) =	0.34, p = 0.56						
59-2 55					1/64	1/4	4 64			

Figure S46. Forest plot of comparison 2 mutant *TPMT* alleles vs wild-type, outcome: Total hematologic adverse events



#### Figure S47. Forest plot of comparison 2 mutant *TPMT* alleles vs wild-type, outcome: Serious hematologic adverse events



Fixed-effects Mantel-Haenszel model

Figure S48. Forest plot of comparison 2 mutant *TPMT* alleles vs wild-type, outcome: Withdrawal due to adverse events

	M	lut	Nor	n mut					Odds I	Ratio	Weight
Study	Yes	No	Yes	No					with 95	5% CI	(%)
Case-control											
Gearry 2003	0	1	5	86	<	-		<b>→</b> 0.	16 [ 0.00,	2.6e+07]	8.71
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00				0.	16 [ 0.00,	2.6e+07]	
Test of $0_i = 0_j$ : Q(0)	) = 0.0	00, p	=.								
Cohort											
De Ridder 2006	0	3	4	63	←	_		<u>→</u> 0.	18 [ 0.00,	2623.75]	28.34
Hlavaty 2013	0	1	6	199	←	-		<mark>→</mark> 0.	14 [ 0.00,	2.5e+11]	4.57
Larussa 2012	0	2	1	22	←	-		→ 0.	46 [ 0.00,	623.29]	20.01
Mhanna 2019	0	1	4	138	←	-		<b>→</b> 0.	19 [ 0.00,	3.2e+09]	4.69
Palmieri 2007	0	2	16	377	←			→ 0.	06 [ 0.00,	5.4e+10]	11.61
Schwab 2002	0	1	3	82	←	-		→ 0.	24 [ 0.00,	2.1e+07]	6.20
Van Dieren 2005	0	2	5	94	←			<b>→</b> 0.	16 [ 0.00,	1.9e+05]	15.86
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.0	00				0.	22 [ 0.00,	28.12]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(6)	) = 0.0	05, p	= 1.0	0							
o "								0	001000	00 551	
Overall			· ·			1999 - 1999 - 2		0.	22 [ 0.00,	23.55]	
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>-</sup> = 1.0	00							
Test of $0_i = 0_j$ : Q(7)	) = 0.0	06, p	= 1.0	0	Higher in	non-mut	Higher in	mut			
Test of group diffe	rence	s: Q <sub>b</sub>	(1) =	0.00, p = 0.97							
					1/64	1/4	4	64			
-ixed-effects Mante	el-Hae	ensze	l mod	el							

Figure S49. Forest plot of comparison 2 mutant *TPMT* alleles vs wild-type, outcome: Pancreatitis

Study	M Yes	ut No	Nor Yes	n mut No					Odds F with 95	Ratio % CI	Weight (%)
Case-control											
Gearry 2003	0	1	15	76	<b>←</b>				0.05 [ 0.00,	8.4e+06]	27.74
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00					0.05 [ 0.00,	8.4e+06]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(0)	= 0.0	00, p	=.								
Cohort											
De Ridder 2006	0	3	0	67	<			$\rightarrow$	1.00 [ 0.00,	17069.95]	6.53
Hlavaty 2013	0	1	23	182	←			$\rightarrow$	0.04 [ 0.00,	6.5e+10]	18.70
Larussa 2012	1	1	1	22		-	-	$\rightarrow$	22.00 [ 0.72,	672.78]	6.45
Mhanna 2019	0	1	3	139	←	-			0.24 [ 0.00,	4.1e+09]	4.47
Palmieri 2007	0	2	11	382	←			$\rightarrow$	0.08 [ 0.00,	7.7e+10]	9.78
Schwab 2002	0	1	3	82	←	-			0.24 [ 0.00,	2.1e+07]	7.40
Van Dieren 2005	0	2	5	94	<			$\rightarrow$	0.16 [ 0.00,	1.9e+05]	18.92
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00		<			2.16 [ 0.27,	17.29]	
Test of <b>0</b> <sub>i</sub> = <b>0</b> <sub>i</sub> : Q(6)	= 2.1	15, p	= 0.9	1							
C.											
Overall									1.57 [ 0.21,	12.06]	
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00							
Test of $0_i = 0_j$ : Q(7)	= 2.7	70, p	= 0.9	1	Higher in r	non-mut	Higher in	mut			
Test of group differ	ence	s: Q <sub>b</sub>	(1) =	0.15, p = 0.70							
			an 1970)		1/64	1/4	4	64			
Fixed-effects Mantel	-Hae	nsze	l moc	lel							

Figure S50. Forest plot of comparison 2 mutant *TPMT* alleles vs wild-type, outcome: Hepatotoxicity

	N	lut	No	n mut					Odds F	Ratio	Weight
Study	Yes	No	Yes	s No					with 95	% CI	(%)
Case-control											
Gearry 2003	0	1	10	81	<			> (	0.08 [ 0.00,	1.3e+07]	20.23
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00				(	0.08 [ 0.00,	1.3e+07]	
Test of $0_i = 0_j$ : Q(0)	) = 0.	00, p	=.								
Cohort											
Hlavaty 2013	0	1	7	198	<			>(	0.12 [ 0.00,	2.1e+11]	6.61
Kim 2014	0	1	2	100	<	-		> (	0.32 [ 0.00,	1.6e+08]	4.92
Mhanna 2019	0	1	20	122	←			>(	0.04 [ 0.00,	6.7e+08]	24.96
Palmieri 2007	0	2	9	384	<	-		> (	0.10 [ 0.00,	9.3e+10]	8.64
Schwab 2002	0	1	3	82	←			> (	0.24 [ 0.00,	2.1e+07]	7.85
Van Dieren 2005	0	2	7	92	←			>(	0.11 [ 0.00,	1.4e+05]	26.79
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00				(	0.12 [ 0.00,	394.37]	
Test of $0_i = 0_j$ : Q(5)	) = 0.	02, p	= 1.0	0							
Overall								(	9.11 [ 0.00,	190.39]	
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00							
Test of $0_i = 0_j$ : Q(6)	) = 0.	03, p	= 1.0	0	Higher in	non-mut	Higher in	mut			
Test of aroun diffe	ronce	e. O	(1) =	0.00  n = 0.97							
rest of group diffe	rence	3. Q	5(1) -	0.00, p = 0.37	1/64	1/4	4	64			
					1/04	1/4	4	04			
Fixed-effects Mante	el-Hae	ensze	el mod	lel							

Figure S51. Forest plot of comparison 2 mutant *TPMT* alleles vs wild-type, outcome: Gastrointestinal side effects



## Figure S52. Forest plot of comparison *TPMT*\*2 heterozygous vs wild-type, outcome: Total hematologic adverse events



Fixed-effects Mantel-Haenszel model

Figure S53. Forest plot of comparison *TPMT*\*2 heterozygous vs wild-type, outcome: Pancreatitis

	Μ	lut	Non	mut				Odds	Ratio	Weight
Study	Yes	No	Yes	No				with 95	5% CI	(%)
Case-control										
Zabala-Fernández 2011	0	1	5	119	<			→ 0.16 [ 0.00,	5.8e+08]	9.93
Heterogeneity: I <sup>2</sup> = 0.00%	$H^2 =$	1.00						0.16 [ 0.00,	5.8e+08]	
Test of $\theta_i = \theta_j$ : Q(0) = 0.00	), p = .									
Cohort										
Ribaldone 2019	0	2	24	168	← -			→ 0.03 [ 0.00,	8.8e+06]	53.51
Stocco 2004	0	1	2	38	<	-	2	→ 0.31 [ 0.00,	1.1e+05]	14.80
Stocco 2005	0	1	6	59	←			→ 0.13 [ 0.00,	1.2e+06]	21.77
Heterogeneity: I <sup>2</sup> = 0.00%	, H <sup>2</sup> =	1.00						0.10 [ 0.00,	683.15]	
Test of <b>0</b> <sub>i</sub> = <b>0</b> <sub>j</sub> : Q(2) = 0.04	, p = (	0.98								
Overall								<del>0.1</del> 1 [ 0.00,	382.50]	
Heterogeneity: I <sup>2</sup> = 0.00%	, H <sup>2</sup> =	1.00								
Test of <b>0</b> <sub>i</sub> = <b>0</b> <sub>j</sub> : Q(3) = 0.04	, p = 1	1.00			Higher in n	on-mut	Higher in 1	mut		
Test of group differences:	$Q_{1}(1)$	= 0	00 n :	= 0.97						
rest of group differences.	~p(1)	0.	00, p	0.01	1/64	1/4	1	64		
					1/04	1/4	4	04		

Figure S54. Forest plot of comparison *TPMT*\*2 heterozygous vs wild-type, outcome: Hepatotoxicity



Fixed-effects Mantel-Haenszel model

Figure S55. Forest plot of comparison *TPMT*\*2 heterozygous vs wild-type, outcome: Gastrointestinal side effects



#### Figure S56. Forest plot of comparison TPMT\*2, 2 mutant alleles vs wild-type, outcome: Total serious adverse events

	M	ut	Non	mut					Odds Ra	atio	Weight
Study	Yes	No	Yes	No					with 95%	CI	(%)
Cohort											
Hibi 2003	1	0	5	69	<b>~</b>				888.47 [ 0.00,	2.4e+10]	0.87
Larussa 2012	0	1	2	21	<				0.30 [ 0.00,	5724.86]	99.13
Heterogeneity:	$ ^2 = 0.$	.00%	, H <sup>2</sup> =	1.00		-			8.00 [ 0.54,	119.34]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : G	2(1) =	0.72	, p = 0	0.40							
Overall						-		-	8.00 [ 0.54,	119.34]	
Heterogeneity:	$ ^2 = 0.$	.00%	, H <sup>2</sup> =	1.00							
Test of $0_i = 0_j$ : C	Q(1) =	0.72	, p = 0	0.40	Higher in	non-mut	Higher in	mut			
Test of group di	ifferer	ices:	$Q_{b}(0)$	) = 0.00, p = .							
				AA AD 9	1/64	1/4	4	64			

Fixed-effects Mantel-Haenszel model

#### Figure S57. Forest plot of comparison TPMT\*2, 2 mutant alleles vs wild-type, outcome: Total hematologic adverse events



# Figure S58. Forest plot of comparison *TPMT*\*2, 2 mutant alleles vs wild-type, outcome: Serious hematologic adverse events



Fixed-effects Mantel-Haenszel model

Figure S59. Forest plot of comparison mutated *TPMT*\*2 vs wild-type, outcome: Total serious adverse events



Figure S60. Forest plot of comparison mutated TPMT\*2 vs wild-type, outcome: Total hematologic adverse events



Fixed-effects Mantel-Haenszel model

Figure S61. Forest plot of comparison mutated TPMT\*2 vs wild-type, outcome: Serious hematologic adverse events

	M	ut	Nor	n mut					Odds Ra	atio	Weight
Study	Yes	No	Yes	No					with 95%	5 CI	(%)
Cohort											
Larussa 2012	1	0	3	20	~				132.37 [ 0.01,	2.5e+06]	1.04
Ribaldone 2019	0	2	58	134					0.01 [ 0.00,	3.0e+06]	98.96
Heterogeneity: I <sup>2</sup>	= 5.3	5%, H	H <sup>2</sup> = 1	.06					1.39 [ 0.15,	12.79]	
Test of $0_i = 0_j$ : Q(1	1) = 1	.06, p	o = 0.3	30							
							2.00				
Overall						<			1.39 [ 0.15,	12.79]	
Heterogeneity: I <sup>2</sup>	= 5.3	5%, H	H <sup>2</sup> = 1	.06							
Test of $0_i = 0_j$ : Q(1	1) = 1	.06, p	o = 0.3	30	Higher i	n non-mut	Higher in	mut			
Test of group diffe	erenc	es: C	a <sub>b</sub> (0) =	0.00,	p = .						
					1/64	1/4	4	64			
Fixed-effects Mant	el-Ha	ensz	el mo	del							

Figure S62. Forest plot of comparison mutated *TPMT*\*2 vs wild-type, outcome: Withdrawal due to AE

Study	M Yes	ut No	Non Yes	mut No			Odds R with 95°	atio % CI	Weight (%)
Case-control									
Zabala-Fernández 2011	0	2	18	147	←		0.05 [ 0.00,	3.0e+06]	31.11
Heterogeneity: I <sup>2</sup> = 0.00%	$H^2 =$	1.00				0	0.05 [ 0.00,	3.0e+06]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(0) = 0.00	), p = .								
Cohort									
Larussa 2012	0	1	1	22	<	> (	0.47 [ 0.00,	9346.89]	10.80
Ribaldone 2019	0	2	26	166	←		0.03 [ 0.00,	8.1e+06]	38.10
Stocco 2004	0	1	2	38	←		0.31 [ 0.00,	1.1e+05]	9.76
Stocco 2005	0	1	4	61	← ■	→ (	0.19 [ 0.00,	1.8e+06]	10.24
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00				0	0.16 [ 0.00,	110.48]	
Test of $\theta_i = \theta_j$ : Q(3) = 0.08	8, p = 0	).99							
Overall							0.13 [ 0.00,	57.63]	
Heterogeneity: $I^2 = 0.00\%$	$H^2 =$	1.00							
Test of $0_i = 0_j$ : Q(4) = 0.12	2, p = 1	1.00			Higher in non-mut	Higher in mut			
Test of group differences:	Q₀(1)	= 0.0	02, p =	= 0.90	1/64 1/4	4 64			
Fixed-effects Mantel-Haen	szel m	odel							

Figure S63. Forest plot of comparison mutated TPMT\*2 vs wild-type, outcome: Pancreatitis



#### Figure S64. Forest plot of comparison mutated TPMT\*2 vs wild-type, outcome: Hepatotoxicity



Figure S65. Forest plot of comparison mutated *TPMT*\*2 vs wild-type, outcome: Gastrointestinal side effects



Figure S66. Forest plot of comparison *TPMT*\*3 heterozygous vs wild-type, outcome: Total serious adverse events

Study	N Yes	lut No	Nor Yes	i mut No				Odds R with 95°	atio ⁄/ Cl	Weight
Case-control	100		100	110						(/0)
Gearry 2003	1	7	0	91			•••	15.26 [ 0.85,	273.02]	0.32
Marinaki 2004	1	7	10	61				0.87 [ 0.10,	7.86]	4.44
Heterogeneity: $I^2 =$	60.1	3%, I	$+^2 = 2$	.51		<		1.85 [ 0.38,	9.00]	
Test of $0_i = 0_i$ : Q(1)	= 2.5	51, p	= 0.1	1				•		
Cohort										
Al-Judaibi 2016	2	3	5	43		-		5.73 [ 0.76,	42.99]	1.42
Ansari 2008	5	14	2	186				33.21 [ 5.90,	186.87]	0.68
Chao 2017	4	23	173	532		_	-	0.53 [ 0.18,	1.57]	27.25
De Ridder 2006	1	1	1	66			>	66.00 [ 2.20,	1984.21]	0.07
Dubinsky 2000	1	7	12	72				0.86 [ 0.10,	7.60]	4.58
Fangbin 2016	2	0	24	106	←			569.50 [ 0.00,	5.0e+09]	0.01
Hawwa 2008	0	4	3	28	<	-		0.21 [ 0.00,	81.03]	2.17
Hindorf 2006	2	5	8	44		-		2.20 [ 0.36,	13.37]	3.40
Hlavaty 2013	10	4	21	184				21.90 [ 6.31,	76.02]	1.92
Kim 2010	5	2	111	168				3.78 [ 0.72,	19.85]	3.89
Kim 2014	2	2	21	81		_	•	3.86 [ 0.51,	29.01]	1.99
Kim 2017	4	5	128	194				1.21 [ 0.32,	4.60]	9.69
Mhanna 2019	3	3	2	140				70.00 [ 8.37,	585.21]	0.20
Palmieri 2007	4	23	17	376				3.85 [ 1.20,	12.37]	4.67
Reuther 2003	0	4	0	62	←		<u>↓                                    </u>	1.00 [ 0.00,	3925.66]	0.28
Ribaldone 2019	0	6	6	186	←	•	>	0.13 [ 0.00,	11034.22]	1.05
Stocco 2004	0	3	13	27	<			0.05 [ 0.00,	85.04]	4.76
Stocco 2005	0	4	7	58	←	•	>	0.11 [ 0.00,	398.45]	2.28
Sutiman 2018	0	2	10	117	<	•	>	0.08 [ 0.00,	6.1e+05]	0.85
Takatsu 2009	1	2	18	96		22-	•	2.67 [ 0.23,	30.99]	1.54
Van Dieren 2005	1	7	9	90				1.43 [ 0.16,	12.95]	2.95
Wang 2018	1	0	18	61	←		>	264.44 [ 0.00,	1.2e+10]	0.01
Winter 2007	1	10	9	110			<b>.</b>	1.22 [ 0.14,	10.65]	3.47
Wroblova 2012	8	8	26	146				5.62 [ 1.94,	16.29]	5.55
Zelinkova 2006	3	20	8	230				4.31 [ 1.06,	17.55]	3.07
Zhu 2019	4	9	68	330		-		2.16 [ 0.65,	7.21]	7.47
Heterogeneity: I <sup>2</sup> =	50.6	6%, ł	$H^2 = 2$	.03			•	2.69 [ 1.96,	3.70]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(25)	5) = 5	0.67	p = 0	.00			02			
Overall							•	2.65 [ 1.94.	3.621	
Heterogeneity: $I^2 =$	49.3	4%.1	$+1^2 = 1$	.97				L		
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(27)	7) = 5	3.29	p = 0	.00	Higher in	non-mut	Higher in mut			
Test of group differ	ence	s: Q <sub>b</sub>	(1) = (	0.21, p = 0.65						
					1/64	1/4	4 64			

Figure S67. Forest plot of comparison *TPMT*\*3 heterozygous vs wild-type, outcome: Total hematologic adverse events

	М	ut	Nor	i mut					Odds F	Ratio	Weight
Study	Yes	No	Yes	No					with 95	% CI	(%)
Case-control											
Gearry 2003	1	7	0	91		-	-		15.26 [ 0.85,	273.02]	8.14
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	2 = 1.0	00		-			<del>15</del> .26 [ 0.85,	273.02]	
Test of $0_i = 0_j$ : Q(0)	= 0.0	)0, p	= .								
Cohort											
Hindorf 2006	0	7	1	51	<			$\rightarrow$	0.46 [ 0.00,	170.98]	27.73
Sutiman 2018	0	2	6	121	<	-	-	$\rightarrow$	0.13 [ 0.00,	1.0e+06]	13.57
Takatsu 2009	0	3	3	111	<	-		$\rightarrow$	0.24 [ 0.00,	54181.44]	12.76
Van Dieren 2005	0	8	0	99	<	-		$\rightarrow$	1.00 [ 0.00,	1783.55]	8.66
Winter 2007	1	10	3	116				-	3.87 [ 0.37,	40.69]	29.14
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	2 = 1.0	00					1.51 [ 0.22,	10.29]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(4)	= 0.9	95, p	= 0.9	2							
Overall									2.63 [ 0.61,	11.33]	
Heterogeneity: I <sup>2</sup> =	0.00	%, H <sup>2</sup>	<sup>2</sup> = 1.0	00							
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(5)	= 2.2	21, p	= 0.8	2	Higher in r	non-mut	Higher in n	nut			
Test of group differ	ence	s: Q <sub>b</sub>	(1) =	1.71, p = 0.19							
			13 19495	86 72	1/64	1/4	4	64			

Figure S68. Forest plot of comparison *TPMT*\*3 heterozygous vs wild-type, outcome: Serious hematologic adverse events



Figure S69. Forest plot of comparison *TPMT*\*3 heterozygous vs wild-type, outcome: Withdrawal due to AE

	Ν	/lut	Nor	n mut				Odds	Ratio	Weight
Study	Yes	s No	Yes	No				with 9	5% CI	(%)
Case-control										
Gearry 2003	0	8	5	86	<			> 0.15 [ 0.00,	157.69]	8.38
Marinaki 2004	1	7	7	61				1.24 [ 0.13,	11.65]	11.41
Heterogeneity: I <sup>2</sup> =	0.00	)%, H <sup>2</sup>	<sup>2</sup> = 1.	00				0.78 [ 0.10,	6.11]	
Test of $0_i = 0_j$ : Q(1)	) = 0.	39, p	= 0.5	3						
Cohort										
Al-Judaibi 2016	0	5	0	48	<			<b>&gt;</b> 1.00 [ 0.00,	868.79]	1.48
Ansari 2008	0	19	8	180	$\leftarrow$	-		0.10 [ 0.00,	66.23]	14.40
De Ridder 2006	0	2	4	63	←	-		• 0.18 [ 0.00,	20666.95]	2.51
Hlavaty 2013	0	14	6	199	<	-	>	• 0.13 [ 0.00,	321.79]	7.81
Mhanna 2019	0	6	4	138	<	-		<b>&gt;</b> 0.19 [ 0.00,	3417.97]	3.53
Palmieri 2007	0	27	16	377	←			<b>→</b> 0.05 [ 0.00,	123.64]	19.22
Ribaldone 2019	2	4	26	166		-		3.19 [ 0.56,	18.32]	9.29
Stocco 2004	0	3	2	38	<──	-		> 0.30 [ 0.00,	601.84]	3.54
Stocco 2005	0	4	4	61	<──			• 0.18 [ 0.00,	684.88]	5.00
Takatsu 2009	0	3	0	114	<		;	> 1.00 [ 0.00,	2.6e+05]	0.44
Van Dieren 2005	1	7	5	94		-	-	2.69 [ 0.27,	26.26]	5.79
Winter 2007	0	11	1	118	<	-		× 0.47 [ 0.00,	476.21]	2.85
Wroblova 2012	0	16	2	170	<	-		> 0.31 [ 0.00,	288.45]	4.37
Heterogeneity: $I^2 =$	0.00	)%, H <sup>2</sup>	<sup>2</sup> = 1.	00		-		0.70 [ 0.24,	2.06]	
Test of $0_i = 0_i$ : Q(12)	2) = 5	5.52, p	o = 0.	94						
Overall						-		0.72 [ 0.28,	1.86]	
Heterogeneity: I <sup>2</sup> =	0.00	)%, H <sup>2</sup>	<sup>2</sup> = 1.	00						
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(14)	4) = 5	5.86, p	o = 0.	97	Higher in n	on-mut	Higher in mut			
Test of group differ	rence	es: Q <sub>b</sub>	(1) =	0.01, p = 0.93				_		
					1/64	1/4	4 64	ļ		

Figure S70. Forest plot of comparison *TPMT*\*3 heterozygous vs wild-type, outcome: Pancreatitis

	Ν	1ut	Nor	n mut	Odds Ratio	Weight
Study	Yes	No	Yes	No	with 95% Cl	(%)
Case-control						
Gearry 2003	0	8	15	76	<ul> <li>0.05 [ 0.00, 50.41]</li> </ul>	17.18
Marinaki 2004	1	7	3	61	<b>2</b> .90 [ 0.26, 31.84]	3.93
Heterogeneity: I <sup>2</sup> =	55.1	3%, H	$H^2 = 2$	2.23	0.58 [ 0.08, 4.19]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1)	= 2.	23, p	= 0.1	4		
Cohort						
Al-Judaibi 2016	0	5	0	48	← ■ → 1.00 [ 0.00, 868.79]	1.13
Ansari 2008	0	19	8	180	<ul> <li>0.10 [ 0.00, 66.23]</li> </ul>	10.98
De Ridder 2006	0	2	0	67	<> 1.00 [ 0.00, 1.3e+05]	0.37
Hlavaty 2013	1	13	23	182	0.61 [ 0.08, 4.87]	18.42
Mhanna 2019	1	5	3	139	<b>→</b> 9.27 [ 0.81, 105.54]	1.37
Palmieri 2007	1	26	11	382	<b>1.34</b> [ 0.17, 10.75]	9.19
Reuther 2003	0	4	0	62	← → 1.00 [ 0.00, 3925.66]	0.76
Ribaldone 2019	0	6	24	168	← ● 0.03 [ 0.00, 2735.20]	10.16
Stocco 2004	0	3	2	38	← ● → 0.30 [ 0.00, 601.84]	2.70
Stocco 2005	0	4	6	59	← ● → 0.12 [ 0.00, 465.51]	5.35
Takatsu 2009	0	3	2	112	← ● → 0.32 [ 0.00, 74011.48]	1.02
Van Dieren 2005	0	8	5	94	← ● → 0.15 [ 0.00, 208.61]	5.92
Winter 2007	1	10	8	111	1.39 [ 0.16, 12.24]	8.30
Wroblova 2012	1	15	3	169	<b>—</b> 3.76 [ 0.37, 38.37]	3.23
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	<sup>2</sup> = 1.0	00	0.84 [ 0.35, 2.01]	
Test of $0_i = 0_i$ : Q(13)	3) = 7	.09, p	o = 0.	90		
	,					
Overall					0.78 [ 0.35, 1.75]	
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	<sup>2</sup> = 1.0	00		
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(15)	5) = 9	9.22, p	o = 0.	87	Higher in non-mut Higher in mut	
Test of group differ	rence	es: Q <sub>b</sub>	(1) =	0.11, p =	0.74	
					1/64 1/4 4 64	

Figure S71. Forest plot of comparison *TPMT*\*3 heterozygous vs wild-type, outcome: Hepatotoxicity

	Ν	1ut	Nor	n mut					Odds	Ratio	Weight
Study	Yes	s No	Yes	No					with 9	5% CI	(%)
Case-control											
Gearry 2003	2	6	10	81		-	-	2.70	0.48,	15.23]	8.56
Marinaki 2004	5	7	8	61				- 5.45	[ 1.39,	21.30]	9.76
Heterogeneity: I <sup>2</sup> =	0.00	9%, H	<sup>2</sup> = 1.	00				4.16	[ 1.45,	11.93]	
Test of $0_i = 0_j$ : Q(1)	) = 0.	39, p	= 0.5	3							
Cohort											
Ansari 2008	8	11	26	162				4.53	[ 1.67,	12.32]	19.51
Hlavaty 2013	0	14	7	198	<			→ 0.11	[ 0.00,	278.59]	7.13
Kim 2014	0	4	2	100	<	-		→ 0.32	0.00,	8588.37]	1.56
Mhanna 2019	1	5	20	122			-	1.22	[ 0.14,	10.99]	9.54
Palmieri 2007	0	27	9	384	<			→ 0.09	[ 0.00,	216.86]	9.00
Ribaldone 2019	0	6	2	190	<──			→ 0.32	[ 0.00,	27331.15]	1.26
Takatsu 2009	0	3	11	103	$\leftarrow$			→ 0.07	[ 0.00,	16268.11]	4.30
Van Dieren 2005	0	8	7	92	<			→ 0.11	0.00,	150.97]	8.29
Winter 2007	0	11	14	105	←				[ 0.00,	47.96]	17.69
Wroblova 2012	1	15	3	169			-	- 3.76	[ 0.37,	38.37]	3.38
Heterogeneity: I <sup>2</sup> =	0.00	9%, H	<sup>2</sup> = 1.	00			•	1.44	[ 0.71,	2.90]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(9)	) = 8.	38, p	= 0.5	0							
Overall							•	1.94	1.10,	3.42]	
Heterogeneity: $I^2 =$	0.00	)%. H	<sup>2</sup> = 1.	00				2007-00-000A		-	
Test of $0_i = 0_i$ : Q(1)	1) = 8	3.86. 1	o = 0.	63	Higher in r	non-mut	Higher ir	n mut			
Toot of group diffe	,		(1) -	2.71  n = 0.40	0						
rest of group diffe	ence	:5. Qb	(1) =	z.r i, p = 0.10	4104	414	<u> </u>	04			
					1/64	1/4	4	64			
Fixed-effects Mante	I-Hae	ensze	I moc	lei							

Figure S72. Forest plot of comparison *TPMT*\*3 heterozygous vs wild-type, outcome: Gastrointestinal side effects

	M	lut	Non	i mut		Odds F	tatio	Weight
Study	Yes	No	Yes	No		with 95°	% CI	(%)
Cohort								
Al-Judaibi 2016	2	2	14	24		1.71 [ 0.22,	13.56]	8.76
Dubinsky 2000	8	0	39	45	$\rightarrow$	106.98 [ 0.13,	86534.12]	0.48
Lee 2017	5	0	90	45	<	71.25 [ 0.00,	2.4e+06]	0.30
Palmieri 2007	17	10	287	106		0.63 [ 0.28,	1.41]	89.75
Reuther 2003	4	0	60	2	<	3.23 [ 0.00,	10706.13]	0.71
Heterogeneity: I <sup>2</sup>	= 37.	27%	, H <sup>2</sup> =	1.59	•	1.47 [ 0.75,	2.86]	
Test of $\mathbf{\theta}_i = \mathbf{\theta}_j$ : Q(	4) = 6	6.38,	p = 0.	17				
Overall					-	1.47 [ 0.75,	2.86]	
Heterogeneity: I <sup>2</sup>	= 37	27%	, H <sup>2</sup> =	1.59				
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(	4) = 6	6.38,	p = 0.	17	Higher in non-mut Higher in mut			
Test of group diff	erend	ces: (	Q <sub>b</sub> (0) =	= 0.00,	=.			
					1/64 1/4 4 64			
Fixed-effects Man	tel-Ha	aensz	el mo	del				

Figure S73. Forest plot of comparison *TPMT*\*3 heterozygous vs wild-type, outcome: Clinical remission



Figure S74. Forest plot of comparison *TPMT*\*3, 2 mutant alleles vs wild-type, outcome: Total serious adverse events

	N	lut	Noi	n mut					Oc	lds Ra	tio	Weight
Study	Yes	No	Yes	No					wit	h 95%	CI	(%)
Case-control												
Gearry 2003	1	0	0	91	<			$\rightarrow$	8649.00 [	0.00,	1.5e+12]	0.13
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00					8649.00 [	0.00,	1.5e+12]	
Test of $0_i = 0_j$ : Q(0	) = 0.	00, p	= .									
Cohort												
De Ridder 2006	0	3	1	66	<			$\rightarrow$	0.48 [	0.00,	7399.85]	94.18
Hlavaty 2013	1	0	21	184	<			$\rightarrow$	1741.02 [	0.00,	3.1e+15]	0.58
Kim 2014	1	0	21	81	<			$\longrightarrow$	387.76 [	0.00,	1.9e+11]	2.32
Mhanna 2019	1	0	2	140	<				6783.48 [	0.00,	1.1e+14]	0.16
Palmieri 2007	2	0	17	376	←				8296.22 [	0.00,	7.9e+15]	0.26
Van Dieren 2005	2	0	9	90	<			$\rightarrow$	929.84 [	0.00,	1.1e+09]	2.18
Zelinkova 2006	1	0	8	230	<				6162.75 [	0.00,	9.5e+16]	0.18
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00			-		83.82 [	11.90,	590.38]	
Test of $0_i = 0_j$ : Q(6)	) = 1.0	60, p	= 0.9	5								
Overall									94.98 [	14.35,	628.79]	
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00								
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(7	) = 1.8	83, p	= 0.9	7	Higher in r	on-mut	Higher ir	n mut				
Test of group diffe	rence	s: Qt	(1) =	0.23, p = 0.63								
					1/64	1/4	4	64				
Fixed-effects Mante	el-Hae	ensze	el moc	lel								

# Figure S75. Forest plot of comparison *TPMT*\*3, 2 mutant alleles vs wild-type, outcome: Total hematologic adverse events

Study	Mu Yes	t No	Non Yes	mut No						Odds Ra with 95%	tio Cl	Weight (%)
Case-control												
Gearry 2003	1	0	0	91		<del>&lt;</del>				8649.00 [ 0.00,	1.5e+12]	37.77
Heterogeneity: $I^2 =$	0.00%	, H <sup>2</sup>	= 1.0	0						8649.00 [ 0.00,	1.5e+12]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(0)	= 0.00	), p =	■.									
Cohort												
Van Dieren 2005	2	0	0	99		←		-		10404.00 [ 0.01,	1.4e+10]	62.23
Heterogeneity: $I^2 =$	0.00%	, H <sup>2</sup>	= 1.0	0						10404.00 [ 0.01,	1.4e+10]	
Test of $0_i = 0_j$ : Q(0)	= 0.00	), p =	۰.									
Overall										9741.13 [ 0.12.	8.2e+08]	
Heterogeneity: $I^2 =$	0.00%	$H^2$	= 1.0	0								
Test of $0_i = 0_j$ : Q(1)	= 0.00	), p =	= 0.99	)	Hig	gher in n	on-mut	Higher	in mut			
Test of group differ	ences:	Q <sub>b</sub> (	1) = 0	0.00, p = 0.99								
						1/64	1/4	4	64			

Fixed-effects Mantel-Haenszel model

# Figure S76. Forest plot of comparison *TPMT*\*3, 2 mutant alleles vs wild-type, outcome: Serious hematologic adverse events



## Figure S77. Forest plot of comparison *TPMT*\*3, 2 mutant alleles vs wild-type, outcome: Withdrawal due to AE

Otivitie	M	ut	Nor	n mut					Odds F	Ratio	Weight
Study	Yes	NO	Yes	NO			E.		With 95	% CI	(%)
Case-control											
Gearry 2003	0	1	5	86	<	-		→ 0.	.16 [ 0.00,	2.6e+07]	11.81
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00				0.	.16 [ 0.00,	2.6e+07]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(0)	= 0.0	00, p	= .								
Cohort											
De Ridder 2006	0	3	4	63	<	_		<b>→</b> 0.	18 [ 0.00,	2623.75]	38.41
Hlavaty 2013	0	1	6	199	←	-	0	<u>→</u> 0.	.14 [ 0.00,	2.5e+11]	6.20
Mhanna 2019	0	1	4	138	<	-		→ 0.	19 [ 0.00,	3.2e+09]	6.36
Palmieri 2007	0	2	16	377	< <b>─</b> ∎	-		<b>→</b> 0.	.06 [ 0.00,	5.4e+10]	15.74
Van Dieren 2005	0	2	5	94	<			<b>→</b> 0.	16 [ 0.00,	1.9e+05]	21.50
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00				0.	15 [ 0.00,	167.34]	
Test of $\theta_i = \theta_j$ : Q(4)	= 0.0	01, p	= 1.0	0							
Overall								0.	.15 [ 0.00,	108.55]	
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00						-	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(5)	= 0.0	01, p	= 1.0	0	Higher in I	non-mut	Higher in	mut			
Test of aroup differ	ence	s' O	(1) =	0.00  p = 1.00							
		<b>_</b> 0	(.)		1/64	1/4	4	64			
Fixed-effects Mantel	-Hae	nsze	l mod	el			es <b>4</b>				

Figure S78. Forest plot of comparison *TPMT*\*3, 2 mutant alleles vs wild-type, outcome: Pancreatitis

	Μ	ut	Nor	n mut						Odds	Ratio	Weight
Study	Yes	No	Yes	No						with 9	5% CI	(%)
Case-control												
Gearry 2003	0	1	15	76		<			→ 0.0	5 [ 0.00,	8.4e+06]	32.21
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.0	00					0.0	5 [ 0.00,	8.4e+06]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(0)	= 0.0	0, p	= .									
Cohort												
De Ridder 2006	0	3	0	67		<		-	→ 1.0	0 [ 0.00,	17069.95]	7.58
Hlavaty 2013	0	1	23	182		←		0	→ 0.0	4 [ 0.00,	6.5e+10]	21.71
Mhanna 2019	0	1	3	139		←	-		→ 0.2	4 [ 0.00,	4.1e+09]	5.19
Palmieri 2007	0	2	11	382		$\leftarrow$			→ 0.0	8 [ 0.00,	7.7e+10]	11.35
Van Dieren 2005	0	2	5	94		<			<u>→ 0.1</u>	6 [ 0.00,	1.9e+05]	21.96
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.0	00					0.2	1 [ 0.00,	220.08]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_i$ : Q(4)	= 0.1	2, p	= 1.0	0								
Overall									0.1	6 [ 0.00,	105.21]	
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.0	00								
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(5)	= 0.1	7, p	= 1.0	0	H	Higher in r	non-mut	Higher in	mut			
Test of group diffe	ence	s: Qh	(1) =	0.02, p = 0	0.89							
5 ,						1/64	1/4	4	64			

Figure S79. Forest plot of comparison *TPMT*\*3, 2 mutant alleles vs wild-type, outcome: Hepatotoxicity

	M	ut	Nor	i mut				Odds I	Ratio	Weight
Study	Yes	No	Yes	No				with 95	5% CI	(%)
Case-control							V			
Gearry 2003	0	1	10	81	←			→ 0.08 [ 0.00,	1.3e+07]	21.95
Heterogeneity: $I^2 =$	0.00%	6, H <sup>2</sup>	<sup>2</sup> = 1.0	00				0.08 [ 0.00,	1.3e+07]	
Test of $0_i = 0_j$ : Q(0)	= 0.0	0, p	= .							
Cohort										
Hlavaty 2013	0	1	7	198	<──	-		→ 0.12 [ 0.00,	2.1e+11]	7.18
Kim 2014	0	1	2	100	←	-	0	→ 0.32 [ 0.00,	1.6e+08]	5.34
Mhanna 2019	0	1	20	122	< <b>──</b>			→ 0.04 [ 0.00,	6.7e+08]	27.08
Palmieri 2007	0	2	9	384	<del>&lt;</del>			→ 0.10 [ 0.00,	9.3e+10]	9.38
Van Dieren 2005	0	2	7	92	<			→ 0.11 [ 0.00,	1.4e+05]	29.07
Heterogeneity: $I^2 =$	0.00%	%, H <sup>2</sup>	<sup>2</sup> = 1.0	0000				0.10 [ 0.00,	909.71]	
Test of $0_i = 0_j$ : Q(4)	= 0.0	2, p	= 1.0	0						
Overall								<del>0.1</del> 0 [ 0.00,	352.47]	
Heterogeneity: $I^2 =$	0.00%	6, H <sup>2</sup>	<sup>2</sup> = 1.0	00						
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(5)	= 0.0	2, p	= 1.0	)	Higher in r	non-mut	Higher in m	ut		
Test of group differ	ences	s: Q <sub>b</sub>	(1) =	0.00, p = 0.98						
			a 950	66 TC	1/64	1/4	4	64		

Figure S80. Forest plot of comparison *TPMT*\*3, 2 mutant alleles vs wild-type, outcome: Gastrointestinal side effects



Figure S81. Forest plot of comparison *TPMT*\*3 vs wild-type, outcome: Total serious adverse events

Study	N Yes	lut No	Nor Yes	n mut No				C	Ddds Ra /ith 95%	atio 6 Cl	Weight
Case-control											()
Gearry 2003	2	7	0	91			$\longrightarrow$	29.77 [	2.26,	391.90]	0.31
Marinaki 2004	1	7	10	61				0.87 [	0.10,	7.86]	4.41
Heterogeneity: I <sup>2</sup> =	76.8	2%,	$H^2 = 4$	.31		-		2.80 [	0.71,	10.97]	
Test of $0_i = 0_j$ : Q(1	) = 4.	31, p	= 0.0	4							
2											
Cohort											
Al-Judaibi 2016	2	3	5	43		-		5.73 [	0.76,	42.99]	1.41
Ansari 2008	5	14	2	186			$\longrightarrow$	33.21 [	5.90,	186.87]	0.67
Chao 2017	4	23	173	532		-		0.53 [	0.18,	1.57]	27.06
De Ridder 2006	1	4	1	66			• >	16.50 [	0.86,	315.19]	0.28
Dubinsky 2000	1	7	12	72				0.86 [	0.10,	7.60]	4.55
Fangbin 2016	2	0	24	106	←		>	569.50 [	0.00,	5.0e+09]	0.01
Hawwa 2008	0	4	3	28	←	•		0.21 [	0.00,	81.03]	2.15
Hindorf 2006	2	6	8	44		-	-	1.83 [	0.31,	10.75]	3.98
Hlavaty 2013	11	4	21	184				24.10 [	7.04,	82.45]	1.90
Kim 2010	5	2	111	168		8 <del>.</del>		3.78 [	0.72,	19.85]	3.86
Kim 2014	3	2	21	81		8		5.79 [	0.91,	36.89]	1.95
Kim 2017	4	5	128	194			<b>.</b>	1.21 [	0.32,	4.60]	9.63
Mhanna 2019	4	3	2	140			$\longrightarrow$	93.33 [	12.05,	722.62]	0.20
Palmieri 2007	6	23	17	376				5.77 [	2.08,	16.02]	4.61
Reuther 2003	0	4	0	62	<		>	1.00 [	0.00,	3925.66]	0.28
Ribaldone 2019	0	6	6	186	←	•	>	0.13 [	0.00,	11034.22]	1.05
Stocco 2004	0	3	13	27	<			0.05 [	0.00,	85.04]	4.73
Stocco 2005	0	4	7	58	<	•	>	0.11 [	0.00,	398.45]	2.26
Sutiman 2018	0	2	10	117	←	•	>	0.08 [	0.00,	6.1e+05]	0.84
Takatsu 2009	1	2	18	96		0 <u></u>		2.67 [	0.23,	30.99]	1.53
Van Dieren 2005	3	7	9	90				4.29 [	0.94,	19.52]	2.88
Wang 2018	1	0	18	61	<		>	264.44 [	0.00,	1.2e+10]	0.01
Winter 2007	1	10	9	110				1.22 [	0.14,	10.65]	3.45
Wroblova 2012	8	8	26	146				5.62 [	1.94,	16.29]	5.51
Zelinkova 2006	4	20	8	230				5.75 [	1.59,	20.77]	3.04
Zhu 2019	4	9	68	330		-	-	2.16 [	0.65,	7.21]	7.41
Heterogeneity: I <sup>2</sup> =	53.2	7%,	$H^2 = 2$	2.14			•	3.02 [	2.22,	4.10]	
Test of $0_i = 0_j$ : Q(2	5) = 5	53.50	, p = C	0.00							
Overall							•	3.01 [	2.23,	4.05]	
Heterogeneity: I <sup>2</sup> =	= 53.3	0%,	$H^2 = 2$								
Test of $0_i = 0_j$ : Q(2	7) = 5	57.82	, p = C	).00	Higher in	non-mut	Higher in mut				
Test of group diffe	rence	es: Q	(1) =	0.01, p = 0.91							
					1/64	1/4	4 64				

Figure S82. Forest plot of comparison *TPMT*\*3 vs wild-type, outcome: Total hematologic adverse events



Figure S83. Forest plot of comparison *TPMT*\*3 vs wild-type, outcome: Serious hematologic adverse events



Figure S84. Forest plot of comparison TPMT\*3 vs wild-type, outcome: Withdrawal due to AE

Study	Mut Non mut						Odds Ratio			Weight
	res	NO	res	i nu				with 95	176 CI	(%)
Case-control	0	~	F	00		_		0.4510.00	400.001	0.00
Gearry 2003	0	9	5	86	<			> 0.15 [ 0.00,	108.99]	8.60
Marinaki 2004	1	1	1	61				1.24 [ 0.13,	11.65]	10.53
Heterogeneity: I <sup>2</sup> =	0.00	%, H'	= 1.	00				0.75 [ 0.10,	5.80]	
Test of $0_i = 0_j$ : Q(1)	= 0.4	43, p	= 0.5	1						
Cohort										
Al-Judaibi 2016	0	5	0	48	←			> 1.00 [ 0.00,	868.79]	1.37
Ansari 2008	0	19	8	180	<			0.10 [ 0.00,	66.23]	13.29
De Ridder 2006	0	5	4	63	←	-		> 0.18 [ 0.00,	335.63]	5.52
Hlavaty 2013	0	15	6	199	←	-		> 0.13 [ 0.00,	250.83]	7.69
Mhanna 2019	0	7	4	138	<	-		> 0.19 [ 0.00,	1703.31]	3.78
Palmieri 2007	0	29	16	377	←		v	- 0.05 [ 0.00,	95.53]	18.96
Ribaldone 2019	2	4	26	166				3.19 [ 0.56,	18.32]	8.58
Stocco 2004	0	3	2	38	<	-		> 0.30 [ 0.00,	601.84]	3.27
Stocco 2005	0	4	4	61	<		;	> 0.18 [ 0.00,	684.88]	4.61
Takatsu 2009	0	3	0	114	<			> 1.00 [ 0.00,	2.6e+05]	0.40
Van Dieren 2005	1	9	5	94			-	2.09 [ 0.22,	19.88]	6.74
Winter 2007	0	11	1	118	<	-		> 0.47 [ 0.00,	476.21]	2.63
Wroblova 2012	0	16	2	170	<	-		> 0.31 [ 0.00,	288.45]	4.03
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	<sup>2</sup> = 1.	00				0.65 [ 0.22,	1.89]	
Test of $0_i = 0_j$ : Q(12)	2) = 5	5.54, p	o = 0.	94						
Overall						-		0.67 [ 0.26,	1.72]	
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	<sup>2</sup> = 1.	00						
Test of $0_i = 0_j$ : Q(14)	l) = 5	5.92, p	o = 0.	97	Higher in	non-mut	Higher in mut			
Test of group differ	ence	es: Q <sub>b</sub>	(1) =	0.02, p = 0.	90			8		
					1/64	1/4	4 64	1		



Mut Non mut						Odds	Weight			
Study	Yes	s No	Yes	No			1	with 9	5% CI	(%)
Case-control										
Gearry 2003	0	9	15	76	< <b>─</b>			0.05 [ 0.00,	34.75]	16.46
Marinaki 2004	1	7	3	61			-	2.90 [ 0.26,	31.84]	3.39
Heterogeneity: I <sup>2</sup> =	58.8	89%, H	$+^2 = 2$	2.43				0.54 [ 0.08,	3.79]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1)	) = 2.	43, p	= 0.1	2						
Cohort										
Al-Judaibi 2016	0	5	0	48	<			→ 1.00 [ 0.00,	868.79]	0.97
Ansari 2008	0	19	8	180	←			— 0.10 [ 0.00,	66.23]	9.45
De Ridder 2006	0	5	0	67	<			→ 1.00 [ 0.00,	2351.24]	0.74
Hlavaty 2013	1	14	23	182	-	_		0.57 [ 0.07,	4.50]	16.99
Mhanna 2019	1	6	3	139		-		— 7.72 [ 0.70,	85.65]	1.40
Palmieri 2007	1	28	11	382				1.24 [ 0.15,	9.96]	8.47
Reuther 2003	0	4	0	62	<──			→ 1.00 [ 0.00,	3925.66]	0.65
Ribaldone 2019	0	6	24	168	$\leftarrow$			→ 0.03 [ 0.00,	2735.20]	8.74
Stocco 2004	0	3	2	38	←			→ 0.30 [ 0.00,	601.84]	2.32
Stocco 2005	0	4	6	59	←	-		→ 0.12 [ 0.00,	465.51]	4.61
Takatsu 2009	0	3	2	112	<	-		→ 0.32 [ 0.00,	74011.48]	0.88
Van Dieren 2005	0	10	5	94	<	-		→ 0.15 [ 0.00,	102.43]	6.24
Winter 2007	1	10	8	111				1.39 [ 0.16,	12.24]	7.14
Wroblova 2012	1	15	3	169			-	3.76 [ 0.37,	38.37]	2.78
Zelinkova 2006	2	22	9	229				2.31 [ 0.47,	11.38]	8.77
Heterogeneity: I <sup>2</sup> =	0.00	)%, H <sup>2</sup>	= 1.	00		<		0.97 [ 0.45,	2.06]	
Test of $0_i = 0_j$ : Q(14)	4) = 7	7.23, p	o = 0.	93						
Overall						<		0.88 [ 0.44,	1.79]	
Heterogeneity: I <sup>2</sup> =	0.00	)%, H <sup>2</sup>	= 1.	00						
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1)	6) = 9	9.54, p	o = 0.	89	Higher in r	ion-mut	Higher in m	ut		
Test of group diffe	rence	es: Q <sub>b</sub>	(1) =	0.31, p = 0.58	<u>-</u> 27					
					1/64	1/4	4	64		



Mut Non mut								Odds Ratio		
Study	Yes	No	Yes	No				with 95	5% CI	(%)
Case-control										
Gearry 2003	2	7	10	81		_		2.31 [ 0.42,	12.71]	9.28
Marinaki 2004	5	7	8	61				5.45 [ 1.39,	21.30]	9.17
Heterogeneity: $I^2 =$	%, H <sup>2</sup>	<sup>2</sup> = 1.	00				3.87 [ 1.37,	10.94]		
Test of $0_i = 0_j$ : Q(1)	= 0.	59, p	= 0.4	4						
Cohort										
Ansari 2008	8	11	26	162				4.53 [ 1.67,	12.32]	18.33
Hlavaty 2013	0	15	7	198	<			→ 0.11 [ 0.00,	217.10]	7.14
Kim 2014	0	5	2	100	<	-		→ 0.32 [ 0.00,	3076.38]	1.81
Mhanna 2019	1	6	20	122				1.02 [ 0.12,	8.90]	10.68
Palmieri 2007	0	29	9	384	←	-		→ 0.09 [ 0.00,	167.66]	9.03
Ribaldone 2019	0	6	2	190	<	-		→ 0.32 [ 0.00,	27331.15]	1.19
Takatsu 2009	0	3	11	103	←			→ 0.07 [ 0.00,	16268.11]	4.04
Van Dieren 2005	0	10	7	92	←			— 0.11 [ 0.00,	73.98]	9.54
Winter 2007	0	11	14	105	←			- 0.05 [ 0.00,	47.96]	16.61
Wroblova 2012	1	15	3	169		8.	-	3.76 [ 0.37,	38.37]	3.17
Heterogeneity: I <sup>2</sup> =	1.25	%, H <sup>2</sup>	<sup>2</sup> = 1.	01			•	1.36 [ 0.68,	2.73]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(9)	= 9.	11, p	= 0.4	3						
Overall							<b></b>	1.82 [ 1.04,	3.20]	
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	00						
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1	1) = 9	).77, p	o = 0.	55	Higher in n	on-mut	Higher in m	ut		
Test of group differ	ence	s: Q <sub>b</sub>	(1) =	2.69, p = 0.10						
					1/64	1/4	4	64		
				100						

Figure S87. Forest plot of comparison *TPMT*\*3 vs wild-type, outcome: Gastrointestinal side effects

	Mut Non mut				Odds Ratio	Weight
Study	Yes	No	Yes	No	with 95% Cl	(%)
Cohort						
Al-Judaibi 2016	2	2	14	24	<b>— — — — — — — — — —</b>	7.46
Dubinsky 2000	8	0	39	45	→ 106.98 [ 0.13, 86534.12]	0.41
Lee 2017	5	0	90	45		0.26
Palmieri 2007	17	12	287	106	0.52 [ 0.24, 1.13]	91.27
Reuther 2003	4	0	60	2	← 3.23 [ 0.00, 10706.13]	0.61
Heterogeneity: I <sup>2</sup> = 45.21%, H <sup>2</sup> = 1.83					1.25 [ 0.66, 2.35]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(	4) = 7	.30,	p = 0.	12		
Overall					1.25 [ 0.66, 2.35]	
Heterogeneity: I <sup>2</sup>	= 45.	21%	, H <sup>2</sup> =	1.83		
Test of $\theta_i = \theta_j$ : Q(4) = 7.30, p = 0.12					Higher in non-mut Higher in mut	
Test of group differences: $Q_b(0) = 0.00$ , p = .						
					1/64 1/4 4 64	
Fixed-effects Man	tel-Ha	aensz	el mo	del		



	Mut Non mut									Weight	
Study	Yes	No	Yes	No				with 95	with 95% CI		
Case-control							-				
Gearry 2003	2	7	0	91			<b>→</b>	29.77 [ 2.26,	391.90]	3.23	
Heterogeneity: I <sup>2</sup> =	0.00	%, H	<sup>2</sup> = 1.	.00				29.77 [ 2.26,	391.90]		
Test of $\theta_i = \theta_j$ : Q(0	) = 0.	.00, p	= .								
Cohort											
Hibi 2003	4	4	0	74				83.00 [ 6.91,	997.66]	2.25	
Larussa 2012	1	3	1	22		-	• • • • •	7.33 [ 0.36,	150.71]	5.67	
Mazor 2013	0	4	24	148	← 📕	-	>	0.03 [ 0.00,	15586.61]	28.82	
Schwab 2002	3	5	11	74		14		4.04 [ 0.84,	19.31]	30.19	
Sutiman 2018	0	3	6	120	<		>	0.13 [ 0.00,	54705.08]	8.22	
Takatsu 2009	0	3	4	110	< <u> </u>	-	>	0.19 [ 0.00,	42566.46]	6.46	
Van Dieren 2005	2	8	0	99				28.44 [ 2.19,	369.67]	3.38	
Winter 2007	1	10	3	116		0	-	3.87 [ 0.37,	40.69]	11.78	
Heterogeneity: I <sup>2</sup> =	11.2	8%, 1	$H^2 = $	1.13			$\diamond$	5.11 [ 2.37,	11.05]		
Test of $\theta_i = \theta_j$ : Q(7	) = 7.	.89, p	= 0.3	34							
Overall							•	5.91 [ 2.87,	12.19]		
Heterogeneity: I <sup>2</sup> =	10.0	6%, I	H <sup>2</sup> = 1	1.11							
Test of $\theta_i = \theta_j$ : Q(8)	) = 8.	.89, p	= 0.3	35	Higher in	non-mut	Higher in mut				
Test of group diffe	rence	es: Q <sub>b</sub>	(1) =	1.65, p = 0.20							
					1/64	1/4	4 64				

Figure S89. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *TPMT* vs wild-type, outcome: Total SAE

Mut Non mut						Odds Ratio			Weight
Study	Yes	No	Yes	No			with 95%	% CI	(%)
Case-control									
Gearry 2003	2	7	0	91		$\longrightarrow$	29.77 [ 2.26,	391.90]	0.21
Marinaki 2004	1	7	10	61			0.87 [ 0.10,	7.86]	3.00
Yang 2014	13	15	333	617	-	-	1.61 [ 0.76,	3.42]	17.32
Zabala-Fernández 2011	3	4	9	90			7.50 [ 1.45,	38.91]	1.15
Heterogeneity: I <sup>2</sup> = 59.82%	6, H <sup>2</sup>	= 2.4	9			<b></b>	2.10 [ 1.13,	3.88]	
Test of $\theta_i = \theta_j$ : Q(3) = 7.47	, p =	0.06							
Cohort									
Al-Judaibi 2016	2	3	5	43	-	•	5.73 [ 0.76,	42.99]	0.96
Ansari 2008	5	14	2	186		$\longrightarrow$	33.21 [ 5.90,	186.87]	0.46
Asada 2016	2	3	43	113	0-	-	1.75 [ 0.28,	10.85]	2.72
Chao 2017	4	23	173	532			0.53 [ 0.18,	1.57]	18.43
De Ridder 2006	1	4	1	66		·	16.50 [ 0.86,	315.19]	0.19
Dubinsky 2000	1	7	12	72			0.86 [ 0.10,	7.60]	3.10
Fangbin 2016	2	0	24	106	<	>	569.50 [ 0.00,	5.0e+09]	0.01
Gazouli 2010	4	16	3	74			6.17 [ 1.26,	30.29]	1.68
Grover 2020	1	4	32	82			0.64 [ 0.07,	5.95]	3.65
Hawwa 2008	0	4	3	28	<		0.21 [ 0.00,	81.03]	1.47
Hibi 2003	7	1	5	69		$\longrightarrow$	96.60 [ 9.85,	947.70]	0.21
Hindorf 2006	2	6	8	44	1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 -	•	1.83 [ 0.31,	10.75]	2.71
Hlavaty 2013	11	4	21	184			24.10 [ 7.04,	82.45]	1.29
Kim 2010	5	2	111	168	100		3.78 [ 0.72,	19.85]	2.63
Kim 2014	3	4	21	81	17		2.89 [ 0.60,	13.93]	2.61
Kim 2017	4	5	128	194	77	<b>.</b>	1.21 [ 0.32,	4.60]	6.56
Larussa 2012	1	3	2	21	- <del>3</del> -		3.50 [ 0.24,	51.46]	0.75
Mazor 2013	0	4	24	148	<- <b></b>	>	0.03 [ 0.00,	15586.61]	1.91
Palmieri 2007	6	21	17	376			6.32 [ 2.26,	17.69]	2.88
Reuther 2003	0	4	0	62	<	·>	1.00 [ 0.00,	3925.66]	0.19
Ribaldone 2019	0	8	6	186	<	>	0.13 [ 0.00,	2541.91]	0.94
Schwab 2002	3	5	2	83		$\longrightarrow$	24.90 [ 3.36,	184.71]	0.36
Steponaitiene 2016	9	0	8	65		$\rightarrow$	615.16 [ 1.54,	2.5e+05]	0.04
Stocco 2004	0	4	13	27	←∎		0.04 [ 0.00,	32.90]	4.19
Stocco 2005	0	5	7	58	< ∎	>	0.10 [ 0.00,	175.09]	1.89
Stocco 2007	0	5	3	62	< <b>•</b>	>	0.23 [ 0.00,	389.95]	0.94
Sutiman 2018	0	3	10	116	< .	>	0.08 [ 0.00,	33361.89]	0.86
Takatsu 2009	1	2	18	96	1 <u>21</u>	•	2.67 [ 0.23,	30.99]	1.04
Van Dieren 2005	3	7	9	90			4.29 [ 0.94,	19.52]	1.96
Wang 2018	1	0	18	61	<		264.44 [ 0.00,	1.2e+10]	0.01
Winter 2007	1	10	3	116	1		3.87 [ 0.37,	40.69]	0.78
Wroblova 2012	8	8	26	146			5.62 [ 1.94,	16.29]	3.75
Zelinkova 2006	4	20	8	230			5.75 [ 1.59,	20.77]	2.07
Zhu 2019	4	9	68	330	_	-	2.16 [ 0.65,	7.21]	5.05
Heterogeneity: I <sup>2</sup> = 46.26%	6, H <sup>2</sup>	= 1.8	6			•	3.28 [ 2.50,	4.31]	
Test of $\theta_i = \theta_j$ : Q(33) = 61.	41, p	= 0.0	00						
800 W 80 9897									
Overall						•	3.03 [ 2.36,	3.88]	
Heterogeneity: I <sup>2</sup> = 47.81%	6, H <sup>2</sup>	= 1.9	2						
Test of $\theta_i = \theta_j$ : Q(37) = 70.89, p = 0.00					Higher in non-mut	Higher in mut			

Test of group differences:  $Q_b(1) = 1.71$ , p = 0.19

1/64 1/4 4 64
## Figure S90. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *TPMT* vs wild-type, outcome: Total hematologic AE

	Ν	1ut	Nor	n mut				0	Odds Ratio		
Study	Yes	No	Yes	No				wi	th 95	5% CI	(%)
Case-control											
Gearry 2003	2	7	0	91				→ 29.77 [ 2	2.26,	391.90]	4.58
Heterogeneity: I <sup>2</sup> =	= 0.00	)%, H	<sup>2</sup> = 1.	00				29.77 [ 2	2.26,	391.90]	
Test of $\theta_i = \theta_j$ : Q(0	) = 0	.00, p	= .								
Cohort											
Hibi 2003	4	4	0	74			8.5	<b>83.00</b> [ 6	6.91,	997.66]	3.19
Hindorf 2006	0	8	1	51	<			→ 0.46[0	0.00,	123.79]	17.72
Larussa 2012	1	3	0	23				→ 10.21 [ (	).49,	213.30]	6.69
Mazor 2013	0	4	11	161	←			→ 0.08 [ 0	0.00,	35564.48]	19.59
Schwab 2002	3	5	2	83				→ 24.90 [ 3	3.36,	184.71]	7.78
Sutiman 2018	0	3	6	120	<		<	→ 0.13[(	0.00,	54705.08]	11.65
Takatsu 2009	0	3	3	111	<──	-		→ 0.24 [ (	0.00,	54181.44]	7.31
Van Dieren 2005	2	8	0	99				→ 28.44 [ 2	2.19,	369.67]	4.79
Winter 2007	1	10	3	116		Q <del>.</del>		- 3.87 [ 0	).37,	40.69]	16.70
Heterogeneity: I <sup>2</sup> =	= 3.55	5%, H	<sup>2</sup> = 1.	.04			$\diamond$	7.76 [ 3	3.56,	16.89]	
Test of $\theta_i = \theta_j$ : Q(8)	3) = 8	.29, p	= 0.4	11							
Overall							•	8.76 [ 4	4.21,	18.26]	
Heterogeneity: I <sup>2</sup> =	= 0.00	)%, H	<sup>2</sup> = 1.	00							
Test of $\theta_i = \theta_j$ : Q(9)	9) = 8	.64, p	= 0.4	47	Higher in	non-mut	Higher in r	nut			
Test of group diffe	rence	es: Q <sub>b</sub>	(1) =	0.96, p = 0.33							
					1/64	1/4	4	64			

Fixed-effects Mantel-Haenszel model

Figure S91. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *TPMT* vs wild-type, outcome: Serious hematologic AE



Figure S92. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *TPMT* vs wild-type, outcome: Withdrawal due to AE

	M	ut	Nor	n mut			Odds F	Ratio	Weight
Study	Yes	No	Yes	No			with 95	% CI	(%)
Case-control									
Gearry 2003	0	9	5	86	← ■	>	0.15 [ 0.00,	108.99]	5.60
Marinaki 2004	1	7	7	61			1.24 [ 0.13,	11.65]	6.85
Zabala-Fernández 2011	1	10	18	147			0.82 [ 0.10,	6.76]	10.87
Heterogeneity: $I^2 = 0.00\%$	5, H <sup>2</sup> =	1.00			<		0.78 [ 0.18,	3.40]	
Test of $\theta_i = \theta_j$ : Q(2) = 0.42	2, p =	0.81							
Cohort									
Al-Judaibi 2016	0	5	0	48	<	• >	1.00 [ 0.00,	868.79]	0.89
Ansari 2008	0	19	8	180	← ■		0.10 [ 0.00,	66.23]	8.65
De Ridder 2006	0	5	4	63	< ∎	>	0.18 [ 0.00,	335.63]	3.59
Gazouli 2010	0	20	3	74	<		0.20 [ 0.00,	17.39]	8.23
Hlavaty 2013	0	15	6	199	← ■	>	0.13 [ 0.00,	250.83]	5.00
Larussa 2012	0	4	1	22	← ■		0.44 [ 0.00,	97.02]	2.82
Mazor 2013	0	4	7	165	← ■	>	0.12 [ 0.00,	55052.90]	1.92
Palmieri 2007	0	29	16	377	←	1	0.05 [ 0.00,	95.53]	12.34
Ribaldone 2019	2	6	26	166	12		2.13 [ 0.41,	11.11]	8.29
Schwab 2002	0	8	3	82	← ■	>	0.23 [ 0.00,	201.15]	3.54
Steponaitiene 2016	3	6	3	70			11.67 [ 1.92,	70.90]	2.33
Stocco 2004	0	4	2	38	← ■	>	0.30 [ 0.00,	236.54]	2.75
Stocco 2005	0	5	4	61	← ■	>	0.18 [ 0.00,	301.87]	3.69
Stocco 2007	1	4	6	59		-	2.46 [ 0.24,	25.69]	3.64
Takatsu 2009	0	3	0	114	<	•	1.00 [ 0.00,	2.6e+05]	0.26
Van Dieren 2005	1	9	5	94	18: 		2.09 [ 0.22,	19.88]	4.39
Winter 2007	0	11	1	118	← ■	>	0.47 [ 0.00,	476.21]	1.71
Wroblova 2012	0	16	2	170	← ■	>	0.31 [ 0.00,	288.45]	2.62
Heterogeneity: I <sup>2</sup> = 0.00%	, H <sup>2</sup> =	1.00	1			•	0.96 [ 0.46,	2.02]	
Test of $\theta_i = \theta_j$ : Q(17) = 12	2.08, p	= 0.8	30						
Overall							0.92 [ 0.48,	1.79]	
Heterogeneity: $I^2 = 0.00\%$	5, H <sup>2</sup> =	1.00	í.						
Test of $\theta_i = \theta_j$ : Q(20) = 12	2.81, p	= 0.8	39		Higher in non-mut	Higher in mut			
Test of group differences:	Q <sub>b</sub> (1)	= 0.0	06, p	= 0.80					
					1/64 1/4	4 64			

Figure S93. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *TPMT* vs wild-type, outcome: Pancreatitis

	M	ut	Nor	n mut			Odds	Ratio	Weight
Study	Yes	No	Yes	No		72	with 9	5% CI	(%)
Case-control									
Gearry 2003	0	9	15	76	<-		0.05 [ 0.00,	34.75]	13.28
Marinaki 2004	1	7	3	61		-	2.90 [ 0.26,	31.84]	2.73
Zabala-Fernández 2011	0	6	5	119	← ■	;	0.15 [ 0.00,	1514.23]	2.55
Heterogeneity: I <sup>2</sup> = 25.65%	6, H <sup>2</sup>	= 1.3	4				0.48 [ 0.07,	3.26]	
Test of $\theta_i = \theta_j$ : Q(2) = 2.69	, p =	0.26							
Cohort									
Al-Judaibi 2016	0	5	0	48	<	• >	1.00 [ 0.00,	868.79]	0.79
Ansari 2008	0	19	8	180	<		0.10 [ 0.00,	66.23]	7.62
De Ridder 2006	0	5	0	67	<	• >	1.00 [ 0.00,	2351.24]	0.60
Hlavaty 2013	1	14	23	182			0.57 [ 0.07,	4.50]	13.71
Larussa 2012	1	3	1	22		• >	7.33 [ 0.36,	150.71]	1.04
Mazor 2013	0	4	6	166	← ∎	, ,	0.14 [ 0.00,	63489.67]	1.48
Palmieri 2007	1	28	11	382	<u></u>	<b></b>	1.24 [ 0.15,	9.96]	6.84
Reuther 2003	0	4	0	62	<	>	1.00 [ 0.00,	3925.66]	0.53
Ribaldone 2019	0	8	24	168	←		0.03 [ 0.00,	627.81]	9.31
Schwab 2002	0	8	3	82	← ■	;	0.23 [ 0.00,	201.15]	3.12
Steponaitiene 2016	0	9	5	68	< ∎		0.14 [ 0.00,	57.46]	5.98
Stocco 2004	0	4	2	38	← ∎		0.30 [ 0.00,	236.54]	2.42
Stocco 2005	0	5	6	59	← ∎	,	0.12 [ 0.00,	204.70]	4.57
Stocco 2007	0	5	3	62	← ∎		0.23 [ 0.00,	389.95]	2.59
Takatsu 2009	0	3	2	112	<		0.32 [ 0.00,	74011.48]	0.71
Van Dieren 2005	0	10	5	94	< ∎	,	0.15 [ 0.00,	102.43]	5.03
Winter 2007	1	10	8	111	12	-	1.39 [ 0.16,	12.24]	5.77
Wroblova 2012	1	15	3	169	1		3.76 [ 0.37,	38.37]	2.24
Zelinkova 2006	2	22	9	229			2.31 [ 0.47,	11.38]	7.08
Heterogeneity: I <sup>2</sup> = 0.00%,	, H <sup>2</sup> =	1.00					0.79 [ 0.38,	1.65]	
Test of $\theta_i = \theta_i$ : Q(18) = 8.1	4, p =	= 0.98	3				20 - 1995, H. D. D. D. M.		
	0.000								
Overall							0.73 [ 0.37,	1.46]	
Heterogeneity: $I^2 = 0.00\%$ ,	, H <sup>2</sup> =	1.00	6						
Test of $\theta_i = \theta_j$ : Q(21) = 10.	69, p	= 0.9	97		Higher in non-mut	Higher in mut			
Test of aroun differences:	0.(1)	= 0	22 n	= 0.64					
reat of group differences.	orp(1)	- 0.	εε, p	- 0.04	1/64 1/4		ŝ		
					1/04 1/4	4 04	0		

Figure S94. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *TPMT* vs wild-type, outcome: Hepatotoxicity

	M	ut	Nor	mut		Odds	Ratio	Weight
Study	Yes	No	Yes	No		with 9	5% CI	(%)
Case-control								
Gearry 2003	2	7	10	81		- 2.31 [ 0.42,	12.71]	7.20
Marinaki 2004	5	7	8	61		5.45 [ 1.39,	21.30]	7.11
Zabala-Fernández 2011	1	10	15	147		- 0.98 [ 0.12,	8.19]	8.91
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00				2.76 [ 1.13,	6.76]	
Test of $\theta_i = \theta_j$ : Q(2) = 1.91	l, p =	0.39						
Cohort					1.000			
Ansari 2008	0	19	26	162	< <b>•</b>	0.03 [ 0.00,	19.31]	25.27
Hlavaty 2013	0	15	7	198	< <b>-</b>	→ 0.11 [ 0.00,	217.10]	5.53
Kim 2014	0	7	2	100	< <b>•</b>	→ 0.31 [ 0.00,	806.28]	1.92
Palmieri 2007	0	29	9	384	< <b>•</b>	→ 0.09 [ 0.00,	167.66]	7.00
Ribaldone 2019	0	8	2	190	< • •	→ 0.32 [ 0.00,	6339.69]	1.21
Schwab 2002	0	8	3	82	← ■	→ 0.23 [ 0.00,	201.15]	3.42
Steponaitiene 2016	0	9	5	68	< <b>•</b>	0.14 [ 0.00,	57.46]	6.57
Takatsu 2009	0	3	11	103	<	→ 0.07 [ 0.00,	16268.11]	3.13
Van Dieren 2005	0	10	7	92	< ∎	0.11 [ 0.00,	73.98]	7.39
Winter 2007	0	11	14	105	←	0.05 [ 0.00,	47.96]	12.88
Wroblova 2012	1	15	3	169		3.76 [ 0.37,	38.37]	2.46
Heterogeneity: I <sup>2</sup> = 0.00%	, H <sup>2</sup> =	1.00				0.20 [ 0.05,	0.91]	
Test of $\theta_i = \theta_j$ : Q(10) = 6.6	69, p =	0.75	5					
Overall					+	0.80 [ 0.40,	1.59]	
Heterogeneity: I <sup>2</sup> = 7.74%	, H <sup>2</sup> =	1.08	È.					
Test of $\theta_i = \theta_j$ : Q(13) = 14	.09, p	= 0.3	37		Higher in non-mut Highe	er in mut		
Test of group differences:	Q₀(1)	= 8.	59, p	= 0.00				
					1/64 1/4 4	64		

Figure S95. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *TPMT* vs wild-type, outcome: Gastrointestinal side effects

	M	ut	Nor	n mut			Odds F	Ratio	Weight
Study	Yes	No	Yes	No			with 95	% CI	(%)
Case-control									
Zabala-Fernández 2011	8	7	125	92		-	0.84 [ 0.29,	2.40]	29.53
Heterogeneity: I <sup>2</sup> = 0.00%	, H <sup>2</sup> =	1.00	)				0.84 [ 0.29,	2.40]	
Test of $\theta_i = \theta_j$ : Q(0) = 0.00	), p =	•							
Cohort									
Al-Judaibi 2016	2	2	14	24		•	1.71 [ 0.22,	13.56]	5.22
Dubinsky 2000	8	0	39	45			▶ 106.98 [ 0.13,	86534.12]	0.29
Lucafò 2019	8	0	62	34		•:	> 58.28 [ 0.05,	71507.11]	0.36
Palmieri 2007	17	12	287	106			0.52 [ 0.24,	1.13]	63.90
Reuther 2003	4	0	60	2	< <u> </u>		> 3.23 [ 0.00,	10706.13]	0.43
Stocco 2005	3	0	31	17	←		> 29.21 [ 0.01,	1.0e+05]	0.28
Heterogeneity: I <sup>2</sup> = 50.29	%, H <sup>2</sup>	= 2.0	01			•	1.47 [ 0.80,	2.71]	
Test of $\theta_i = \theta_j$ : Q(5) = 10.0	06, p =	= 0.0	7						
Overall						•	1.28 [ 0.76,	2.17]	
Heterogeneity: I <sup>2</sup> = 35.44	%, H <sup>2</sup>	= 1.5	55						
Test of $\theta_i = \theta_j$ : Q(6) = 9.29	9, p =	0.16			Higher in non-mut	Higher in mut			
Test of group differences:	Q <sub>b</sub> (1)	= 0.	81, p	= 0.37			-		
					1/64 1/4	4 64	ł		
ixed-effects Mantel-Haen	szel m	odel							

Figure S96. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *TPMT* vs wild-type, outcome: Clinical remission

	Non	mut		Odds Ratio							
Study	Yes	No	Yes	No					with 959	% CI	(%)
Cohort											
Ban 2010	1	29	2	98				1	1.69 [ 0.15,	19.31]	58.59
Van Dieren 2005	0	12	2	95	<	_		→ (	0.30 [ 0.00,	127.69]	41.41
Heterogeneity: I <sup>2</sup> =	0.00	%, H <sup>2</sup>	<sup>2</sup> = 1.0	00				1	1.11 [ 0.13,	9.60]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1)	) = 0.2	29, p	= 0.5	9							
Overall								1	1.11 [ 0.13,	9.60]	
Heterogeneity: I <sup>2</sup> =	0.00	%, H <sup>2</sup>	<sup>2</sup> = 1.0	00							
Test of $0_i = 0_j$ : Q(1)	) = 0.2	29, p	= 0.5	9	Higher in	non-mut	Higher in	mut			
Test of group differ	rence	s: Q <sub>b</sub>	(0) = (	0.00, p	=.						
					1/64	1/4	4	64			
Fixed-effects Mante	I-Hae	nsze	l mod	el							

## Figure S97. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Serious hematologic AE



Fixed-effects Mantel-Haenszel model

Figure S98. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Withdrawal due to AE

Mut Non mut							Odds R	latio	Weight
Yes	No	Yes	No				with 959	% CI	(%)
0	7	0	46	*			→ 1.00 [ 0.00,	344.56]	2.81
0	18	4	50	<	-		0.15 [ 0.00,	8.46]	29.20
3	62	13	330				1.23 [ 0.34,	4.44]	49.25
0	12	6	91	*			0.12 [ 0.00,	48.14]	18.74
0.009	%, H <sup>2</sup>	= 1.0	00		-		0.70 [ 0.22,	2.17]	
= 1.6	6, p	= 0.65	5						
					-		0.70 [ 0.22,	2.17]	
0.009	%, H <sup>2</sup>	= 1.0	00						
= 1.6	6, p	= 0.65	5	Higher in r	non-mut	Higher in mu	t		
ences	s: Q <sub>b</sub> (	(0) = (	0.00, p = .						
			68 N	1/64	1/4	4 6	4		
	Min Yes 0 0 0 $0.00^{-9}$ $0.00^$	Mut Yes No 0 7 0 18 3 62 0 12 0.00%, H <sup>2</sup> 0 = 1.66, p 0 = 1.66, p	Mut Non Yes No Yes 0 7 0 0 18 4 3 62 13 0 12 6 0.00%, $H^2 = 1.0$ 0 = 1.66, p = 0.65 0.00%, $H^2 = 1.0$ 0 = 1.66, p = 0.65 rences: $Q_b(0) = 0$	Mut         Non mut           Yes         No         Yes         No           0         7         0         46           0         18         4         50           3         62         13         330           0         12         6         91           0.00%, H <sup>2</sup> = 1.00         =         1.66, p = 0.65           0.00%, H <sup>2</sup> = 1.00         =         =           0.00%, H <sup>2</sup> = 0.65         =         =	Mut       Non mut         Yes       No         0       7       0       46         0       18       4       50         3       62       13       330         0       12       6       91         0.00%, H <sup>2</sup> = 1.00	Mut Non mut Yes No Yes No 0 7 0 46 0 18 4 50 3 62 13 330 0 12 6 91 0.00%, $H^2 = 1.00$ 9 = 1.66, p = 0.65 0.00%, $H^2 = 1.00$ Higher in non-mut rences: $Q_b(0) = 0.00$ , p = . 1/64 $1/4$	Mut Non mut Yes No Yes No 0 7 0 46 0 18 4 50 3 62 13 330 0 12 6 91 0.00%, $H^2 = 1.00$ 9 = 1.66, p = 0.65 0.00%, $H^2 = 1.00$ Higher in non-mut rences: $Q_b(0) = 0.00$ , p = . 1/64 1/4 4 6	Mut       Non mut       Odds R         Yes       No       Yes       No         0       7       0       46 $(0,0,0,0)$ 0       18       4       50 $(0,15)$ $(0,00,0)$ 3       62       13       330 $(1,23)$ $(0,00,0)$ 0       12       6       91 $(0,12)$ $(0,00,0)$ 0.00%, H <sup>2</sup> = 1.00 $(0,00,0)$	Mut       Non mut       Odds Ratio         Yes       No       Yes       No         0       7       0       46 $(1,0)$ [ 0.00, 344.56]         0       18       4       50 $(1,2)$ [ 0.00, 8.46]         3       62       13       330 $(1,2)$ [ 0.00, 48.14]         0       12       6       91 $(12)$ [ 0.00, 48.14]         0.00%, H <sup>2</sup> = 1.00 $(0,70)$ [ 0.22, 2.17] $(0,70)$ [ 0.22, 2.17]         0.00%, H <sup>2</sup> = 1.00 $(1,6)$ p = 0.65       Higher in non-mut $(1,6)$ p = 0.65       Higher in non-mut       Higher in mut

#### Figure S99. Forest plot of comparison mutated ITPA vs wild-type ITPA, outcome: Pancreatitis

	Mut Non mut							Odds F	Ratio	Weight
Study	Yes	No	Yes	No				with 95	% CI	(%)
Cohort										
Al-Judaibi 2016	0	7	0	46				→ 1.00 [ 0.00,	344.56]	3.62
De Ridder 2006	0	18	0	54				— 1.00 [ 0.01,	95.32]	5.95
Odahara 2015	0	19	1	28		-		0.36 [ 0.01,	12.37]	20.03
Palmieri 2007	2	63	10	333		_		1.06 [ 0.23,	4.94]	49.71
Van Dieren 2005	0	12	5	92	<	-		- 0.14 [ 0.00,	57.38]	20.69
Heterogeneity: I <sup>2</sup> =	0.00	%, H <sup>2</sup>	² = 1.0	00				0.72 [ 0.20,	2.57]	
Test of $0_i = 0_j$ : Q(4)	= 0.6	9, p	= 0.9	5						
Overall						-		0.72 [ 0.20,	2.57]	
Heterogeneity: I <sup>2</sup> =	0.00	%, H <sup>2</sup>	<sup>2</sup> = 1.0	00						
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(4)	= 0.6	69, p	= 0.9	5	Higher in I	non-mut	Higher in mu	ut		
Test of group diffe	ence	s: Q <sub>b</sub>	(0) = (	0.00, p = .						
					1/64	1/4	4	64		

Fixed-effects Mantel-Haenszel model

Figure S100. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Hepatotoxicity

	Mut Non mut						Odds Ratio			
Study	Yes	No	Yes	No			with 95% CI	(%)		
Cohort										
Palmieri 2007	0	65	9	334	← _		0.08 [ 0.00, 11.83]	64.50		
Van Dieren 2005	0	12	7	90	←		0.10 [ 0.00, 41.34]	35.50		
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	<sup>2</sup> = 1.0	00			0.09 [ 0.00, 4.12]			
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1)	= 0.0	0, p	= 0.95	5						
Overall							0.09 [ 0.00, 4.12]			
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	<sup>2</sup> = 1.0	00						
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1)	= 0.0	0, p	= 0.95	5	Higher in non-mu	Higher in mu	t			
Test of group differ	ences	s: Q <sub>b</sub>	(0) = (	0.00, p	₹ 2					
		2		<i>x</i> •	1/64 1/8	1 8				

# Figure S101. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Gastrointestinal side effects

	Μ	ut	Non	mut		Odds Ratio	Weight
Study	Yes	No	Yes	No		with 95% CI	(%)
Cohort							
Al-Judaibi 2016	2	3	14	23		- 1.10 [ 0.16, 7.39]	6.95
Palmieri 2007	44	21	260	83		0.67 [ 0.38, 1.19]	93.05
Heterogeneity: I <sup>2</sup>	= 0.0	0%,	$H^2 = 1$	.00		0.70 [ 0.40, 1.21]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1	l) = C	).24,	p = 0.	63			
Overall						0.70 [ 0.40, 1.21]	
Heterogeneity: I <sup>2</sup>	= 0.0	0%,	$H^2 = 1$	.00			
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1	) = C	0.24,	p = 0.	63	Higher in non-mut Higher in mut		
Test of group diffe	erenc	es: (	Q <sub>b</sub> (0) =	= -0.00,	p = . 1/4 1/2 1 2 4	-	

Fixed-effects Mantel-Haenszel model

Figure S102. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Clinical remission



Figure S103. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Total hematologic AE. Subgroup analysis according to age



Fixed-effects Mantel-Haenszel model

Figure S104. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Serious hematologic AE. Subgroup analysis according to age



Figure S105. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Withdrawal due to AE. Subgroup analysis according to age



Figure S106. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Pancreatitis. Subgroup analysis according to age



Figure S107. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Hepatotoxicity. Subgroup analysis according to age

Study	M Yes	ut No	Non Yes	mut No				Odds Ra with 95%	atio o CI	Weight (%)
Mixed/NR										
Palmieri 2007	0	65	9	334	*			0.08 [ 0.00,	11.83]	64.50
Van Dieren 2005	0	12	7	90	<			0.10 [ 0.00,	41.34]	35.50
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	= 1.0	0				0.09 [ 0.00,	4.12]	
Test of $0_i = 0_j$ : Q(1)	= 0.0	0, p :	= 0.95	5						
Overall								0.09 [ 0.00,	4.12]	
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	= 1.0	0						
Test of $0_i = 0_j$ : Q(1)	= 0.0	0, p :	= 0.95	5	Higher i	n non-mut	Higher in mut			
Test of group differ	ences	s: Q <sub>b</sub> (	(0) = (	0.00, p =	28					
					1/64	1/8	1 8			

Fixed-effects Mantel-Haenszel model

Figure S108. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Gastrointestinal side effects. Subgroup analysis according to age



Fixed-effects Maritel-Haeriszer model

Figure S109. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Clinical remission. Subgroup analysis according to age



Figure S110. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Total hematologic AE. Subgroup analysis according to race



Figure S111. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Serious hematologic AE. Subgroup analysis according to race



Fixed-effects Mantel-Haenszel model

Figure S112. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Withdrawal due to AE. Subgroup analysis according to race



Figure S113. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Pancreatitis. Subgroup analysis according to race



Figure S114. Forest plot of comparison mutated ITPA vs wild-type ITPA, outcome: Hepatotoxicity. Subgroup analysis according to race



Figure S115. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Gastrointestinal side effects. Subgroup analysis according to race



Fixed-effects Mantel-Haenszel model

Figure S116. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Clinical remission. Subgroup analysis according to race

	M	ut	Non	mut					Odds R	Weight	
Study	Yes	No	Yes	No					with 95%	% CI	(%)
Cohort							2				
Al-Judaibi 2016	0	7	0	46	<b>~</b>				1.00 [ 0.00,	344.56]	2.81
De Ridder 2006	0	18	4	50	<	-			0.15 [ 0.00,	8.46]	29.20
Palmieri 2007	3	62	13	330		-			1.23 [ 0.34,	4.44]	49.25
Van Dieren 2005	0	12	6	91	<	-	0	-	0.12 [ 0.00,	48.14]	18.74
Heterogeneity: $I^2 =$	0.009	%, H <sup>2</sup>	= 1.0	00		-			0.70 [ 0.22,	2.17]	
Test of $0_i = 0_j$ : Q(3)	= 1.6	6, p	= 0.6	5							
Overall						<			0.70 [ 0.22,	2.17]	
Heterogeneity: $I^2 =$	0.009	%, H <sup>2</sup>	= 1.0	00							
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(3)	= 1.6	6, p	= 0.6	5	Higher in r	non-mut	Higher in m	nut			
Test of group differ	ences	s: Q <sub>b</sub>	(0) = (	0.00, p = .							
			2 100		1/64	1/4	4	64			

#### Figure S117. Forest plot of comparison heterozygous *ITPA* vs wild-type *ITPA*, outcome: Total hematologic adverse events



Fixed-effects Mantel-Haenszel model

Figure S118. Forest plot of comparison heterozygous *ITPA* vs wild-type *ITPA*, outcome: Withdrawal due to AE



Figure S119. Forest plot of comparison heterozygous *ITPA* vs wild-type *ITPA*, outcome: Pancreatitis



Fixed-effects Mantel-Haenszel model

Figure S120. Forest plot of comparison heterozygous *ITPA* vs wild-type *ITPA*, outcome: Hepatotoxicity

	M	ut	Non	mut			atio	Weight	
Study	Yes	No	Yes	No			with 95%	CI	(%)
Cohort									
Palmieri 2007	0	64	9	334	←		0.08 [ 0.00,	12.24]	64.20
Van Dieren 2005	0	12	7	90	←		0.10 [ 0.00,	41.34]	35.80
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	= 1.0	00			0.09 [ 0.00,	4.19]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1)	= 0.0	0, p :	= 0.95	5					
Overall							0.09 [ 0.00,	4.19]	
Heterogeneity: $I^2 =$	0.00	%, H <sup>2</sup>	= 1.0	00					
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1)	= 0.0	0, p :	= 0.9	5	Higher in non-mut	Higher in mut	l.		
Test of group differ	ences	s: Q <sub>b</sub> (	(0) = (	0.00, p =	2				
					1/64 1/8	1 8			

## Figure S121. Forest plot of comparison heterozygous *ITPA* vs wild-type *ITPA*, outcome: Gastrointestinal side effects



Fixed-effects Mantel-Haenszel model

### Figure S122. Forest plot of comparison heterozygous *ITPA* vs wild-type *ITPA*, outcome: Clinical remission

	Mut Non mut							Odds Ratio			
Study	Yes	No	Yes	No				with 95	5% CI	(%)	
Cohort							5				
Choi 2020	6	15	28	21				0.30 [ 0.10,	0.90]	90.66	
De Ridder 2006	0	5	1	53	<b>~</b>		, ,	0.47 [ 0.00,	484.48]	2.41	
Hawwa 2008	0	3	3	22	<	-		0.20 [ 0.00,	98.36]	6.09	
Palmieri 2007	0	1	18	325	<del>~ •</del>		;	0.05 [ 0.00,	3.2e+14]	0.83	
Heterogeneity: I <sup>2</sup>	= 0.00	)%, H	$+^2 = 1$	.00		-		0.30 [ 0.10,	0.87]		
Test of $0_i = 0_j$ : Q(3)	3) = 0.	.04, p	o = 1.0	00							
Overall								0.30 [ 0.10,	0.87]		
Heterogeneity: I <sup>2</sup>	= 0.00	D%, ⊦	$H^2 = 1$	.00							
Test of $0_i = 0_j$ : Q(3)	3) = 0.	.04, p	o = 1.0	00	Higher in I	non-mut	Higher in mut				
Test of group diff	erence	es: Q	$a_{b}(0) =$	0.00, p = .							
					1/64	1/4	4 64				
Fixed-effects Mant	el-Ha	ensz	el mo	del							

Figure S123. Forest plot of comparison 2 mutant *ITPA* alleles vs wild-type, outcome: Total hematologic adverse events



Fixed-effects Mantel-Haenszel model

Figure S124. Forest plot of comparison 2 mutant *ITPA* alleles vs wild-type, outcome: Pancreatitis

	M	ut	Nor	n mut			Odds I	Ratio	Weight
Study	Yes	No	Yes	No			with 95	% CI	(%)
Cohort						7			
De Ridder 2006	0	5	0	54	*		→ 1.00 [ 0.00,	1207.01]	70.53
Palmieri 2007	0	1	10	333	← _		→ 0.09 [ 0.00,	5.7e+14]	29.47
Heterogeneity: I <sup>2</sup>	= 0.00	)%, ł	$H^2 = 1$	.00			0.73 [ 0.00,	715.62]	
Test of $0_i = 0_j$ : Q(*	1) = 0.	.02, p	o = 0.8	39					
Overall							0.73 [ 0.00,	715.62]	
Heterogeneity: I <sup>2</sup>	= 0.00	)%, ł	$H^2 = 1$	.00					
Test of $0_i = 0_j$ : Q(2)	1) = 0.	.02, p	o = 0.8	39	Higher in non-m	ut Higher in mu	ıt		
Test of group diffe	erence	es: Q	₽ <sub>b</sub> (0) =	0.00,	p = .				
					1/64 1/4	4 6	54		
Fixed-effects Mant	el-Ha	ensz	el mo	del					

Figure S125. Forest plot of comparison 2 mutant *ITPA* alleles vs wild-type, outcome: Hepatotoxicity

Study	M	ut No	Non Yes	mut			Odds F with 95	Ratio % Cl	Weight
Case control	100	140	100	110			With 00	/0 01	(70)
Case-control									
Marinaki 2004	1	6	10	62			1.03 [ 0.11,	9.51]	6.81
Zabala-Fernández 2011	0	8	12	86	←∎		0.06 [ 0.00,	83.47]	8.66
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00					0.49 [ 0.07,	3.69]	
Test of $\theta_i = \theta_j$ : Q(1) = 0.75	, p = C	).39							
Cohort									
De Ridder 2006	0	4	2	64	←	>	0.31 [ 0.00,	1300.27]	1.49
Hawwa 2008	0	2	3	29	<	>	0.22 [ 0.00,	841.51]	2.02
Odahara 2015	7	12	3	26			5.06 [ 1.11,	23.01]	6.72
Palmieri 2007	5	59	18	325	_		1.53 [ 0.55,	4.28]	23.38
Van Dieren 2005	0	12	12	85	←		0.06 [ 0.00,	23.54]	12.60
Wroblova 2012	4	22	30	132		-	0.80 [ 0.26,	2.49]	31.46
Zelinkova 2006	4	25	8	224			4.48 [ 1.26,	15.94]	6.87
Heterogeneity: I <sup>2</sup> = 24.43%	6, H <sup>2</sup> =	= 1.3	2			•	1.51 [ 0.87,	2.61]	
Test of $\theta_i = \theta_j$ : Q(6) = 7.94	, p = C	).24							
Overall						•	1.35 [ 0.80,	2.28]	
Heterogeneity: I <sup>2</sup> = 14.19%	6, H <sup>2</sup> =	= 1.1	7						
Test of $\theta_i = \theta_j$ : Q(8) = 9.32	, p = 0	).32			Higher in non-mut	Higher in mut			
Test of group differences:	Q <sub>b</sub> (1)	= 1.1	11, p	= 0.29					
ě.	- ( )				1/64 1/4	4 64			

Fixed-effects Mantel-Haenszel model

Figure S126. Forest plot of comparison *ITPA* 94C>A heterozygous vs wild-type, outcome: Total hematologic adverse events



#### Figure S127. Forest plot of comparison *ITPA* 94C>A heterozygous vs wild-type, outcome: Withdrawal due to AE

Study	M	ut	Non	mut			Odds F	Ratio	Weight
Sludy	res	NO	res	NO			with 95	% CI	(%)
Case-control									
Marinaki 2004	3	6	5	62			6.20 [ 1.18,	32.56]	6.82
Zabala-Fernández 2011	0	17	19	140	←		0.04 [ 0.00,	22.71]	33.01
Heterogeneity: I <sup>2</sup> = 80.94%	ώ, Η <sup>2</sup> :	= 5.2	5				1.09 [ 0.32,	3.80]	
Test of $\theta_i = \theta_j$ : Q(1) = 5.25,	p = (	0.02							
Cohort									
Conort			_						
Al-Judaibi 2016	0	7	0	46	←	•	▶ 1.00 [ 0.00,	344.56]	1.94
De Ridder 2006	0	4	4	62	← ●		> 0.18 [ 0.00,	726.95]	4.81
Palmieri 2007	3	61	13	330	_	-	1.25 [ 0.35,	4.51]	33.64
Van Dieren 2005	0	12	6	91	← ■		0.12 [ 0.00,	48.14]	12.98
Wroblova 2012	0	26	2	160	← ∎	-	0.30 [ 0.00,	66.65]	6.80
Heterogeneity: $I^2 = 0.00\%$ ,	$H^2 =$	1.00					0.80 [ 0.25,	2.54]	
Test of $\theta_i = \theta_j$ : Q(4) = 1.09,	p = 0	0.90							
Overall							0.92 [ 0.40.	2.14]	
Hotorogonoity: $I^2 = 14.26\%$	<u>ц</u> 2.	- 1 1	7					]	
neterogeneity. 1 – 14.207	о, п -	- 1.1	1						
Test of $\mathbf{U}_{i} = \mathbf{U}_{j}$ : Q(6) = 7.00,	p = (	).32			Higher in non-mu	Higher in mut			
Test of group differences:	Q <sub>b</sub> (1)	= 0.1	13, p =	= 0.72					
					1/64 1/4	4 64	ŀ		

Fixed-effects Mantel-Haenszel model

Figure S128. Forest plot of comparison *ITPA* 94C>A heterozygous vs wild-type, outcome: Pancreatitis



Figure S129. Forest plot of comparison *ITPA* 94C>A heterozygous vs wild-type, outcome: Hepatotoxicity



Figure S130. Forest plot of comparison *ITPA* 94C>A heterozygous vs wild-type, outcome: Gastrointestinal side effects



Fixed-effects Mantel-Haenszel model

Figure S131. Forest plot of comparison *ITPA* 94C>A heterozygous vs wild-type, outcome: Clinical remission

	M	ut	Non	mut					Odds	Ratio	Weight
Study	Yes	No	Yes	No					with 9	5% CI	(%)
Cohort											
De Ridder 2006	0	2	2	64	<			→ 0.32	2 [ 0.00,	33544.59]	29.05
Hawwa 2008	0	1	3	29	<			→ 0.22	2 [ 0.00,	21301.09]	39.41
Palmieri 2007	0	1	18	325	<			→ 0.05	5 [ 0.00,	3.2e+14]	18.57
Zelinkova 2006	0	1	8	224	*	-		<b>→</b> 0.11	[ 0.00,	1.1e+12]	12.97
Heterogeneity: I <sup>2</sup> =	= 0.00	)%, F	$H^2 = 1$	.00				0.20	0.00,	439.41]	
Test of $0_i = 0_j$ : Q(3)	) = 0.	01, p	o = 1.0	00							
Overall								0.20	0.00,	439.41]	
Heterogeneity: I <sup>2</sup> =	= 0.00	)%, <b>⊦</b>	H <sup>2</sup> = 1.	.00							
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(3)	) = 0.	01, p	) = 1.0	00	Higher in	non-mut	Higher in I	mut			
Test of group diffe	rence	es: Q	<sub>b</sub> (0) =	-0.00, p =							
					1/64	1/4	4	64			

Figure S132. Forest plot of comparison *ITPA* 94C>A, 2 mutant alleles vs wild-type, outcome: Total hematologic adverse events



Fixed-effects Mantel-Haenszel model

Figure S133. Forest plot of comparison *ITPA* 94C>A, 2 mutant alleles vs wild-type, outcome: Pancreatitis

	М	ut	Non	mut			Odds Ratio			Ratio	Weight
Study	Yes	No	Yes	No					with 95	% Cl	(%)
Cohort											
De Ridder 2006	0	2	0	66	*	_		<u> </u>	0 [ 0.00,	1.2e+05]	46.89
Palmieri 2007	0	1	10	333	←			→ 0.0	9 [ 0.00,	5.7e+14]	53.11
Heterogeneity: I <sup>2</sup> =	= 0.00	D%, ⊦	$+^2 = 1$	.00				0.5	62 [ 0.00,	<del>318</del> 89.34]	
Test of $0_i = 0_j$ : Q(1	) = 0.	.02, p	o = 0.8	38							
Overall								0.5	2 [ 0.00,	<del>318</del> 89.34]	
Heterogeneity: I <sup>2</sup> =	0.00	D%, ⊦	H <sup>2</sup> = 1	.00							
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1	) = 0.	.02, p	o = 0.8	38	Higher in n	on-mut	Higher in r	nut			
Test of group diffe	rence	es: Q	$a_{b}(0) =$	0.00,	p = .						
					1/64	1/4	4	64			

# Figure S134. Forest plot of comparison *ITPA* 94C>A, 2 mutant alleles vs wild-type, outcome: Hepatotoxicity

Study	M Yes	ut No	Nor Yes	i mut No		Odds R with 95°	atio % CI	Weight (%)
Case-control								
Marinaki 2004	1	6	10	62		1.03 [ 0.11,	9.51]	2.99
Zabala-Fernández 2011	0	8	12	86	<-∎	0.06 [ 0.00,	83.47]	3.80
Heterogeneity: $I^2 = 0.00\%$	H <sup>2</sup> =	1.00				0.49 [ 0.07,	3.69]	
Test of $\theta_i = \theta_j$ : Q(1) = 0.75	, p = 0	.39						
Cohort								
De Ridder 2006	0	6	2	64	<>	0.30 [ 0.00,	313.56]	0.94
Hawwa 2008	0	3	3	29	<>	0.21 [ 0.00,	204.05]	1.28
Kim 2010	25	41	91	129	-	0.86 [ 0.49,	1.52]	51.32
Odahara 2015	7	12	3	26		5.06 [ 1.11,	23.01]	2.95
Palmieri 2007	5	60	18	325		1.50 [ 0.54,	4.21]	10.41
Steponaitiene 2016	2	5	16	59		1.48 [ 0.26,	8.32]	3.84
Van Dieren 2005	0	12	12	85	←∎	0.06 [ 0.00,	23.54]	5.53
Wroblova 2012	4	22	30	132		0.80 [ 0.26,	2.49]	13.81
Zelinkova 2006	4	26	8	224		4.31 [ 1.21,	15.29]	3.12
Heterogeneity: $I^2 = 26.66\%$	6, H <sup>2</sup> :	= 1.3	6		*	1.14 [ 0.77,	1.67]	
Test of $\theta_i = \theta_j$ : Q(8) = 10.9	1, p =	0.21						
Overall					*	1.09 [ 0.75,	1.59]	
Heterogeneity: I <sup>2</sup> = 14.69%	6, H <sup>2</sup> =	= 1.1	7					
Test of $\theta_i = \theta_j$ : Q(10) = 11.	72, p	= 0.3	0		Higher in non-mut Higher in mut			
Test of group differences:	Q <sub>b</sub> (1)	= 0.6	64, p	= 0.42				
					1/64 1/4 4 64			

Fixed-effects Mantel-Haenszel model

Figure S135. Forest plot of comparison mutated *ITPA* 94C>A vs wild-type, outcome: Total hematologic adverse events



Figure S136. Forest plot of comparison mutated *ITPA* 94C>A vs wild-type, outcome: Serious hematologic adverse events



Fixed-effects Mantel-Haenszel model

Figure S137. Forest plot of comparison mutated *ITPA* 94C>A vs wild-type, outcome: Withdrawal due to AE



Figure S138. Forest plot of comparison mutated *ITPA* 94C>A vs wild-type, outcome: Pancreatitis

	М	ut	Nor	n mut			Odds R	atio	Weight
Study	Yes	No	Yes	No		1	with 959	% Cl	(%)
Case-control									
Marinaki 2004	2	6	2	62			10.33 [ 1.23,	87.09]	2.82
Zabala-Fernández 2011	0	11	5	114	← ■	>	0.15 [ 0.00,	135.00]	8.40
Heterogeneity: I <sup>2</sup> = 54.85	%, H <sup>2</sup>	= 2.2	1		-		2.71 [ 0.54,	13.45]	
Test of $\theta_i = \theta_j$ : Q(1) = 2.27	1, p = (	0.14							
Cohort									
Al-Judaibi 2016	0	7	0	46	<	•>	1.00 [ 0.00,	344.56]	1.90
De Ridder 2006	0	6	0	66	<	•>	1.00 [ 0.00,	1261.20]	1.27
Odahara 2015	0	19	1	28			0.36 [ 0.01,	12.37]	10.52
Palmieri 2007	2	63	10	333			1.06 [ 0.23,	4.94]	26.11
Steponaitiene 2016	0	7	5	70	←	<b>&gt;</b>	0.14 [ 0.00,	129.75]	8.44
Van Dieren 2005	0	12	5	92	←		0.14 [ 0.00,	57.38]	10.87
Wroblova 2012	1	25	3	159		-	2.12 [ 0.21,	21.19]	6.75
Zelinkova 2006	0	30	11	221	←		0.07 [ 0.00,	24.22]	22.93
Heterogeneity: I <sup>2</sup> = 0.00%	6, H <sup>2</sup> =	1.00			-		0.60 [ 0.21,	1.74]	
Test of $\theta_i = \theta_j$ : Q(7) = 2.70	), p = (	0.91							
Overall							0.84 [ 0.35.	1.991	
Heterogeneity: $I^2 = 0.00\%$	6 H <sup>2</sup> =	1 00							
Test of $0_{i} = 0_{i}$ : Q(9) = 7.80	), p = (	0.55			Higher in non-mut	Higher in mut			
Toot of group differences	. 0 (1)	- 24	06 0	- 0 12	3	3			
rest of group differences	. ce <sub>b</sub> (1)	- 2.	50, p	- 0.12	1/6/ 1//	1 64			
					1/04 1/4	4 04			
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Figure S139. Forest plot of comparison mutated *ITPA* 94C>A vs wild-type, outcome: Hepatotoxicity

	M	ut	Non	mut		Odds Ratio	Weight
Study	Yes	NO	Yes	NO		with 95% CI	(%)
Case-control							
Marinaki 2004	3	6	10	62		3.10 [ 0.67, 14.44]	14.28
Zabala-Fernández 2011	1	17	15	140		0.55 [ 0.07, 4.42]	28.41
Heterogeneity: I <sup>2</sup> = 44.38%	6, H <sup>2</sup> =	= 1.8	0			1.40 [ 0.44, 4.45]	
Test of $\theta_i = \theta_j$ : Q(1) = 1.80	, p = 0	).18					
Cohort							
Palmieri 2007	0	65	9	334	← ■	0.08 [ 0.00, 11.83]	30.15
Steponaitiene 2016	1	6	4	71		2.96 [ 0.28, 30.85]	5.64
Van Dieren 2005	0	12	7	90	< ∎	0.10 [ 0.00, 41.34]	16.59
Wroblova 2012	2	24	2	160		- 6.67 [ 0.90, 49.58]	4.92
Heterogeneity: I <sup>2</sup> = 50.22%	6, H <sup>2</sup> =	= 2.0	1		-	0.94 [ 0.29, 3.02]	
Test of $\theta_i = \theta_j$ : Q(3) = 6.03	, p = C	).11					
Overall					+	1.14 [ 0.50, 2.57]	
Heterogeneity: I <sup>2</sup> = 32.52%	6, H <sup>2</sup> =	= 1.4	8				
Test of $\theta_i = \theta_j$ : Q(5) = 7.41,	, p = C	).19			Higher in non-mut Higher in mu	t	
Test of group differences:	Q <sub>b</sub> (1)	= 0.2	23, p =	= 0.63			
	. ,		10.5		1/64 1/8 1 8		

Figure S140. Forest plot of comparison mutated *ITPA* 94C>A vs wild-type, outcome: Gastrointestinal AE

	М	ut	Non	mut		Odds Ratio	Weight
Study	Yes	No	Yes	No		with 95% CI	(%)
Case-control							
Zabala-Fernández 2011	10	12	123	87		0.59 [ 0.24, 1.43]	30.67
Heterogeneity: $I^2 = 0.00\%$ ,	$H^2 =$	1.00				0.59 [ 0.24, 1.43]	
Test of $\theta_i = \theta_j$ : Q(0) = 0.00,	p = .						
Cohort							
Al-Judaibi 2016	2	3	14	23	•	— 1.10 [ 0.16, 7.39]	4.82
Palmieri 2007	44	21	260	83		0.67 [ 0.38, 1.19]	64.51
Heterogeneity: $I^2 = 0.00\%$ ,	$H^2 =$	1.00			-	0.70 [ 0.40, 1.21]	
Test of $\theta_i = \theta_j$ : Q(1) = 0.24,	p = 0	0.63					
Overall						0.67 [ 0.42, 1.06]	
Heterogeneity: $I^2 = 0.00\%$ ,	$H^2 =$	1.00					
Test of $\theta_i = \theta_j$ : Q(2) = 0.33,	p = 0	0.85			Higher in non-mut Higher in mu	t	
Test of group differences:	Q <sub>b</sub> (1)	= 0.1	10, p :	= 0.75			
					1/4 1/2 1 2 4		

Fixed-effects Mantel-Haenszel model

Figure S141. Forest plot of comparison mutated *ITPA* 94C>A vs wild-type, outcome: Clinical remission

	M	ut	Non	mut		Odds R	atio	Weight
Study	Yes	No	Yes	No		with 959	% CI	(%)
Case-control								
Marinaki 2004	1	10	10	55		0.55 [ 0.06,	4.78]	14.66
Zabala-Fernández 2011	3	27	9	65		0.80 [ 0.20,	3.19]	26.03
Heterogeneity: $I^2 = 0.00\%$	$H^2 =$	1.00			-	0.71 [ 0.22,	2.27]	
Test of $\theta_i = \theta_j$ : Q(1) = 0.08	, p = 0	).77						
Cohort								
De Ridder 2006	1	10	1	59		> 5.90 [ 0.34,	102.17]	1.57
Hawwa 2008	0	5	3	25	<	0.20 [ 0.00,	36.52]	6.31
Wroblova 2012	4	30	28	120		0.57 [ 0.19,	1.75]	51.42
Heterogeneity: I <sup>2</sup> = 20.65%	6, H <sup>2</sup> =	= 1.2	6		-	0.67 [ 0.25,	1.80]	
Test of $\theta_i = \theta_j$ : Q(2) = 2.52	, p = 0	).28						
Overall					-	0.69 [ 0.33,	1.46]	
Heterogeneity: $I^2 = 0.00\%$ ,	$H^{2} =$	1.00						
Test of $\theta_i = \theta_j$ : Q(4) = 2.59	, p = C	0.63			Higher in non-mut Higher in mut			
Test of group differences:	Q <sub>b</sub> (1)	= 0.0	)1, p =	= 0.94				
~ ~	0003 050		10 72		1/64 1/4 4 64	1		

Figure S142. Forest plot of comparison *ITPA* IVS2 + 21A>C heterozygous vs wild-type, outcome: Total hematologic adverse events

	Mut		Non mut			Odds Ratio		Weight
Study	Yes	No	Yes	No		with 95%	o CI	(%)
Case-control								
Marinaki 2004	1	10	7	55		0.79 [ 0.09,	7.10]	20.02
Zabala-Fernández 2011	8	46	11	109		1.72 [ 0.65,	4.56]	60.73
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$						1.49 [ 0.62,	3.58]	
Test of $\theta_i = \theta_j$ : Q(1) = 0.41,	, p = C	).52						
Cohort								
De Ridder 2006	0	11	4	56	<	0.16 [ 0.00,	26.70]	15.46
Wroblova 2012	1	33	1	147		- 4.45 [ 0.27,	73.06]	3.79
Heterogeneity: $I^2$ = 36.52%, $H^2$ = 1.58						1.01 [ 0.13,	7.71]	
Test of $0_i = 0_j$ : Q(1) = 1.58, p = 0.21								
Overall					-	1.40 [ 0.63,	3.11]	
Heterogeneity: $I^2 = 0.00\%$ ,	$H^{2} =$	1.00						
Test of $0_{i} = 0_{j}$ : Q(3) = 1.78,	, p = C	.62			Higher in non-mut Higher in mut			
Test of group differences: $Q_b(1) = 0.12$ , p = 0.73								
					1/64 1/4 4 6	r 4		

Fixed-effects Mantel-Haenszel model

Figure S143. Forest plot of comparison *ITPA* IVS2 + 21A>C heterozygous vs wild-type, outcome: Pancreatitis



Figure S144. Forest plot of comparison *ITPA* IVS2 + 21A>C heterozygous vs wild-type, outcome: Hepatotoxicity



Fixed-effects Mantel-Haenszel model

Figure S145. Forest plot of comparison *ITPA* IVS2 + 21A>C heterozygous vs wild-type, outcome: Gastrointestinal side effects



Figure S146. Forest plot of comparison *ITPA* IVS2 + 21A>C, 2 mutant alleles vs wild-type, outcome: Total hematologic adverse events

	Mut		Non mut				Odds	Odds Ratio	
Study	Yes	No	Yes	No			with 9	5% CI	(%)
Case-control									
Marinaki 2004	0	3	7	55	<		→ 0.11 [ 0.00,	1078.33]	50.73
Zabala-Fernández 2011	0	2	11	109	← _		→ 0.07 [ 0.00,	3.6e+05]	27.34
Heterogeneity: $I^2 = 0.00\%$ ,	$H^2 =$	1.00					0.10 [ 0.00,	261.47]	
Test of $\theta_i = \theta_j$ : Q(1) = 0.00, p = 0.97									
Cohort									
De Ridder 2006	0	1	4	56	← ∎		→ 0.18 [ 0.00,	9.5e+05]	11.28
Wroblova 2012	0	6	1	147	← ∎		→ 0.49 [ 0.00,	11393.35]	10.65
Heterogeneity: $I^2 = 0.00\%$ ,	$H^2 =$	1.00		0.33 [ 0.00,	1491.57]				
Test of $\theta_i = \theta_j$ : Q(1) = 0.01,									
Overall							0.15 [ 0.00,	45.64]	
Heterogeneity: $I^2 = 0.00\%$ ,	$H^2 =$	1.00							
Test of $\theta_i = \theta_j$ : Q(3) = 0.07	, p = 1	.00			Higher in non-mut	Higher in mu	ıt		
Test of group differences: $Q_b(1) = 0.04$ , p = 0.83									
			10. 10		1/64 1/4	4 6	54		

Fixed-effects Mantel-Haenszel model

Figure S147. Forest plot of comparison *ITPA* IVS2 + 21A>C, 2 mutant alleles vs wild-type, outcome: Pancreatitis


Figure S148. Forest plot of comparison *ITPA* IVS2 + 21A>C, 2 mutant alleles vs wild-type, outcome: Hepatotoxicity



Fixed-effects Mantel-Haenszel model

Figure S149. Forest plot of comparison *ITPA* IVS2 + 21A>C, 2 mutant alleles vs wild-type, outcome: Gastrointestinal side effects

	M	ut	Non	mut				Odds Ra	atio	Weight
Study	Yes	No	Yes	No				with 95%	6 CI	(%)
Case-control										
Marinaki 2004	1	13	10	55	_			0.42 [ 0.05,	3.61]	14.40
Zabala-Fernández 2011	3	29	9	65				0.75 [ 0.19,	2.96]	21.54
Heterogeneity: I <sup>2</sup> = 0.00%	, H <sup>2</sup> =	1.00						0.62 [ 0.20,	1.95]	
Test of $\theta_i = \theta_j$ : Q(1) = 0.19	, p = 0	0.66								
Cohort										
De Ridder 2006	1	11	1	59			<b>1</b>	- 5.36 [ 0.31,	92.32]	1.34
Hawwa 2008	0	7	3	25	<	-		0.19 [ 0.00,	18.24]	6.47
Steponaitiene 2016	2	7	16	57			<b></b>	1.02 [ 0.19,	5.39]	11.95
Wroblova 2012	6	34	28	120			<b>—</b>	0.76 [ 0.29,	1.98]	44.30
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00				-		0.84 [ 0.39,	1.82]	
Test of $\theta_i = \theta_j$ : Q(3) = 2.13	, p = 0	).55								
Overall						-		0.76 [ 0.40,	1.44]	
Heterogeneity: $I^2 = 0.00\%$	, H <sup>2</sup> =	1.00								
Test of $\theta_i = \theta_j$ : Q(5) = 2.57	, p = 0	).77			Higher in	non-mut	Higher in mut			
Test of group differences:	Q <sub>b</sub> (1)	= 0.2	20, p =	= 0.66						
					1/64	1/4	4 6	4		

#### Figure S150. Forest plot of comparison mutated *ITPA* IVS2 + 21A>C vs wild-type, outcome: Total hematologic adverse events



Fixed-effects Mantel-Haenszel model

Figure S151. Forest plot of comparison mutated *ITPA* IVS2 + 21A>C vs wild-type, outcome: Withdrawal due to AE

	Μ	ut	Non	mut		Odds Ra	atio	Weight
Study	Yes	No	Yes	No		with 95%	6 CI	(%)
Case-control								
Marinaki 2004	1	13	7	55		0.60 [ 0.07,	5.35]	22.13
Zabala-Fernández 2011	8	48	11	108		1.64 [ 0.62,	4.33]	55.75
Heterogeneity: $I^2 = 0.00\%$ ,	H <sup>2</sup> =	1.00			-	1.34 [ 0.56,	3.20]	
Test of $\theta_i = \theta_j$ : Q(1) = 0.67,	p = 0	0.41						
Cohort								
Conort			1			2 10 2 2 2 22		
De Ridder 2006	0	12	4	56	<	0.16 [ 0.00,	22.11]	14.68
Steponaitiene 2016	1	8	2	71		4.44 [ 0.36,	54.56]	3.61
Wroblova 2012	1	39	1	147		· 3.77 [ 0.23,	61.63]	3.83
Heterogeneity: $I^2 = 0.00\%$ ,	H <sup>2</sup> =	1.00				1.48 [ 0.32,	6.90]	
Test of $\theta_i = \theta_j$ : Q(2) = 1.94,	p = 0	).38						
Overall					•	1.37 [ 0.64,	2.93]	
Heterogeneity: $I^2 = 0.00\%$ ,	$H^2 =$	1.00				<u> </u>	-	
Test of $\theta_i = \theta_j$ : Q(4) = 2.74,	p = 0	0.60			Higher in non-mut Higher in mut			
Test of group differences:	Q <sub>b</sub> (1)	= 0.0	)1, p =	= 0.91				
					1/64 1/8 1 8			

Figure S152. Forest plot of comparison mutated *ITPA* IVS2 + 21A>C vs wild-type, outcome: Pancreatitis

Study	Mı Yes	ut No	Non Yes	mut No				Odds R with 95°	atio % Cl	Weight (%)
Case-control	CONTRACTOR -								1.160 Mer 9-104	
Marinaki 2004	0	13	4	55	←			0.16 [ 0.00,	18.09]	23.85
Zabala-Fernández 2011	1	39	4	86		_		0.55 [ 0.06,	5.09]	33.34
Heterogeneity: $I^2 = 0.00\%$ ,	H <sup>2</sup> =	1.00						0.39 [ 0.05,	2.80]	
Test of $\theta_i = \theta_j$ : Q(1) = 0.23,	p = 0	.63								
Cohort										
De Ridder 2006	0	12	0	60	←		•>	1.00 [ 0.01,	199.34]	3.81
Steponaitiene 2016	1	8	4	69		-		2.16 [ 0.21,	21.73]	10.84
Wroblova 2012	0	40	4	144	<──			0.16 [ 0.00,	12.48]	28.15
Heterogeneity: $I^2 = 0.00\%$ ,	H <sup>2</sup> =	1.00						0.74 [ 0.12,	4.44]	
Test of $\theta_i = \theta_j$ : Q(2) = 1.31,	p = 0	).52								
Overall								0.54 [ 0.14,	2.03]	
Heterogeneity: $I^2 = 0.00\%$ ,	$H^2 =$	1.00								
Test of $\theta_i = \theta_j$ : Q(4) = 1.99,	p = 0	).74			Higher in	non-mut	Higher in mut			
Test of group differences:	Q <sub>b</sub> (1)	= 0.2	23, p =	= 0.63						
					1/64	1/4	4 64			

Fixed-effects Mantel-Haenszel model

Figure S153. Forest plot of comparison mutated *ITPA* IVS2 + 21A>C vs wild-type, outcome: Hepatotoxicity



Figure S154. Forest plot of comparison mutated *ITPA* IVS2 + 21A>C vs wild-type, outcome: Gastrointestinal side effects



Fixed-effects Mantel-Haenszel model

Figure S155. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *ITPA* vs wild-type, outcome: Total hematologic AE



Figure S156. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *ITPA* vs wild-type, outcome: Withdrawal due to AE



Fixed-effects Mantel-Haenszel model

Figure S157. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *ITPA* vs wild-type, outcome: Pancreatitis

	M	Mut Non		mut		Odds F	Weight		
Study	Yes	No	Yes	No			with 95	% CI	(%)
Cohort									
Al-Judaibi 2016	0	7	0	46	<	•	• 1.00 [ 0.00,	344.56]	3.62
De Ridder 2006	0	18	0	54	a <del>.</del>	+	- 1.00 [ 0.01,	95.32]	5.95
Odahara 2015	0	19	1	28			0.36 [ 0.01,	12.37]	20.03
Palmieri 2007	2	63	10	333			1.06 [ 0.23,	4.94]	49.71
Van Dieren 2005	0	12	5	92	← ■		0.14 [ 0.00,	57.38]	20.69
Heterogeneity: I <sup>2</sup> :	= 0.00	%, H	<sup>2</sup> = 1.0	00	-		0.72 [ 0.20,	2.57]	
Test of $\theta_i = \theta_j$ : Q(4)	4) = 0.0	69, p	= 0.9	5					
Overall					-		0.72 [ 0.20,	2.57]	
Heterogeneity: I <sup>2</sup> :	= 0.00	%, H	<sup>2</sup> = 1.0	00					
Test of $\theta_i = \theta_j$ : Q(4)	4) = 0.0	69, p	= 0.9	5	Higher in non-mu	t Higher in mut			
Test of group diffe	rence	s: Q <sub>b</sub>	(0) = (	0.00, p =	e				
					1/64 1/4	4 64	1		
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Figure S158. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *ITPA* vs wild-type, outcome: Hepatotoxicity



Fixed-effects Mantel-Haenszel model

Figure S159. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *ITPA* vs wild-type, outcome: Gastrointestinal side effects

	M	lut	Non	mut				Odds Ra	atio	Weight
Study	Yes	No	Yes	No				with 95%	CI	(%)
Cohort										
Al-Judaibi 2016	2	3	14	23	1		-	- 1.10 [ 0.16,	7.39]	6.95
Palmieri 2007	44	21	260	83				0.67 [ 0.38,	1.19]	93.05
Heterogeneity: I <sup>2</sup>	2 = 0.0	0%,	$H^2 = 2$	1.00		-		0.70 [ 0.40,	1.21]	
Test of $\theta_i = \theta_j$ : Q	(1) =	0.24,	p = 0	.63						
Overall						-		0.70 [ 0.40,	1.21]	
Heterogeneity: I <sup>2</sup>	2 = 0.0	0%,	$H^2 = 4$	1.00						
Test of $\theta_i = \theta_j$ : Q	(1) =	0.24,	p = 0	.63	Higher in I	non-mut	Higher in mut			
Test of group dif	ferend	ces: (	Q <sub>b</sub> (0) =	= -0.00, p	=.					
					1/4	1/2	1 2 4	-0		

Figure S160. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *ITPA* vs wild-type, outcome: Clinical remission

Mut Non mut									Ratio	Weight		
Study	Yes	No	Yes	No						with 95	% CI	(%)
Case-control												
Kakuta 2018	71	253	17	941				-	ŀ	15.53 [ 8.99,	26.85]	61.86
Heterogeneity:	$ ^2 = 0.0$	00%,	$H^2 = f$	1.00				•		15.53 [ 8.99,	26.85]	
Test of $0_i = 0_j$ : C	2(0) =	0.00,	p = .									
Cohort												
Akiyama 2019	3	18	0	60						14.64 [ 1.11,	192.49]	3.00
Asada 2016	4	30	4	123						4.10 [ 0.97,	17.34]	13.74
Bangma 2020	0	11	38	544		←				0.02 [ 0.00,	42496.05]	13.31
Maeda 2021	6	46	2	156						10.17 [ 1.99,	52.12]	8.08
Heterogeneity:	$ ^2 = 0.0$	00%,	$H^2 = f$	1.00				-		4.79 [ 2.10,	10.92]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : C	2(3) =	2.10,	p = 0.	.55								
Overall								•		11.44 [ 7.36,	17.77]	
Heterogeneity:	$ ^2 = 0.0$	00%,	$H^2 = f$	1.00								
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : G	2(4) =	3.91,	p = 0.	.42		Higher in	n non-mut	Higher in	mut			
Test of group di	fferen	ces: (	Q₀(1) :	= 5.43,	p = 0.02							
						1/64	1/4	4	64			

Figure S161. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Total serious adverse events

	M	lut	Nor	n mut						Odds R	atio	Weight
Study	Yes	No	Yes	No						with 95%	% Cl	(%)
Case-control												
Kakuta 2018	71	253	17	941			-	-		15.53 [ 8.99,	26.85]	63.76
Heterogeneity: I <sup>2</sup>	= 0.0	00%, I	$H^2 = c$	1.00						15.53 [ 8.99,	26.85]	
Test of $0_i = 0_j$ : Q(	0) =	0.00,	p = .									
Cohort												
Akiyama 2019	3	18	0	60						14.64 [ 1.11,	192.49]	3.10
Asada 2016	4	30	4	123						4.10 [ 0.97,	17.34]	14.17
Kakuta 2016	5	23	1	106		-				23.04 [ 2.57,	206.69]	3.24
Maeda 2021	6	46	2	156			-		_	10.17 [ 1.99,	52.12]	8.33
Xu 2020	2	31	2	124						4.00 [ 0.54,	29.53]	7.41
Heterogeneity: I <sup>2</sup>	= 0.0	00%, I	$H^2 = c$	1.00			<			8.07 [ 3.66,	17.77]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(	4) = :	2.48,	p = 0.	.65								
Overall							-			12.83 [ 8.21,	20.04]	
Heterogeneity: I <sup>2</sup>	= 0.0	00%, I	$H^2 = c$	1.00								
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(	5) = (	4.54,	p = 0.	.47	Higher in non-mut	Higher	in mu	t				
Test of group diff	eren	ces: C	Q <sub>b</sub> (1)	= 1.79	, p = 0.18							
						1 4	1	16	64			

Fixed-effects Mantel-Haenszel model

Figure S162. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Serious hematologic adverse events





Study	N	lut No	Nor	n mut						Odds Ra	atio	Weight
Sludy	165	NU	res	INU						with 957		(70)
Case-control												
Kakuta 2018	9	315	38	920				-		0.69 [ 0.33,	1.45]	79.70
Heterogeneity:	$ ^{2} = 0$	.00%,	$H^2 =$	1.00				-		0.69 [ 0.33,	1.45]	
Test of $0_i = 0_j$ : C	2(0) =	0.00,	p = .									
Cohort												
Maeda 2021	0	52	4	154		<	-			0.15 [ 0.00,	8.88]	10.00
Xu 2020	1	32	6	120				-		0.63 [ 0.07,	5.38]	10.31
Heterogeneity:	$ ^{2} = 0$	.00%,	H <sup>2</sup> =	1.00						0.39 [ 0.06,	2.54]	
Test of $0_i = 0_j$ : C	Q(1) =	0.38,	p = 0	).54								
Overall								-		0.63 [ 0.32,	1.25]	
Heterogeneity:	$ ^{2} = 0$	.00%,	$H^2 =$	1.00								
Test of $0_i = 0_j$ : C	Q(2) =	0.52,	p = 0	).77		High	er in no	n-mut	Higher in	mut		
Test of group d	ifferer	nces:	Q <sub>b</sub> (1)	= 0.30	, p = 0.58							
0 1			-1 7		(T •)	1/64	1/8		1 8			

Fixed-effects Mantel-Haenszel model

Figure S164. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Hepatotoxicity



Figure S165. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Gastrointestinal side effects



Test for Funnel Plot Asymmetry: z = -4.28, p < 0.001

Figure S166. Funnel plot of comparison mutated *NUDT15* vs wild-type *NUDT15*, outcome: Total hematologic adverse events

Mut Non mut									Odds F	Ratio	Weight	
Study	Yes	No	Yes	No						with 95	% CI	(%)
Adults												
Akiyama 2019	3	18	0	60						14.64 [ 1.11,	192.49]	3.00
Maeda 2021	6	46	2	156					-	10.17 [ 1.99,	52.12]	8.08
Heterogeneity: I	<sup>2</sup> = 0.0	00%,	H <sup>2</sup> = 1	1.00						11.38 [ 2.87,	45.09]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q	2(1) =	0.05,	p = 0	.82								
Mixed/NR												
Acada 2016	4	20	4	100						4 40 5 0 07	17 241	12 74
Asada 2016	4	30	4	123						4.10[0.97,	17.34]	13.74
Bangma 2020	0	11	38	544		←		-	$\rightarrow$	0.02 [ 0.00,	42496.05]	13.31
Kakuta 2018	71	253	17	941						15.53 [ 8.99,	26.85]	61.86
Heterogeneity: I	<sup>2</sup> = 48	.08%	, H <sup>2</sup> =	1.93				•		11.44 [ 7.19,	18.21]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q	2(2) =	3.85,	p = 0	.15								
Overall								•		11.44 [ 7.36.	17.771	
Heterogeneity: I	<sup>2</sup> = 0.0	00%.	$H^2 = -$	1.00								
Test of $0_i = 0_j$ : Q	(4) =	3.91,	p = 0	.42		Higher in r	non-mut	Higher in m	ut			
Test of group di	fferen	ces: C	Q <sub>b</sub> (1)	= 0.00	, p = 0.99							
						1/64	1/4	4	64			

Figure S167. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Total serious adverse events. Subgroup analysis according to age



Figure S168. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Serious hematologic adverse events. Subgroup analysis according to age



Figure S169. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Pancreatitis. Subgroup analysis according to age



Fixed-effects Mantel-Haenszel model

Figure S170. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Hepatotoxicity. Subgroup analysis according to age

Mut Non mut			Odds Ratio	Weight
Study Yes No Yes No			with 95% CI	(%)
Adults				
Maeda 2021 2 50 5 153		•	1.22 [ 0.23, 6.51]	8.56
Xu 2020 1 32 2 124			— 1.94 [ 0.17, 22.05]	2.89
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$			1.40 [ 0.36, 5.55]	
Test of $\theta_i = \theta_j$ : Q(1) = 0.09, p = 0.76				
Mixed/NR				
Kakuta 2018 37 287 55 903			2.12 [ 1.37, 3.28]	88.54
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$		-	2.12 [ 1.37, 3.28]	
Test of $\theta_i = \theta_j$ : Q(0) = 0.00, p = .				
Overall		-	2.04 [ 1.34, 3.08]	
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$				
Test of $\theta_i = \theta_j$ : Q(2) = 0.39, p = 0.82	Higher in non-mut	Higher in mut		
Test of group differences: $Q_b(1) = 0.31$ , p =	0.58			
	1/4 1	4	16	

Figure S171. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Gastrointestinal side effects. Subgroup analysis according to age

	N	lut	Nor	mut				Odds	Ratio	Weight
Study	Yes	No	Yes	No				with 95	i% Cl	(%)
Asian										
Akiyama 2019	3	18	0	60				> 14.64 [ 1.11,	192.49]	3.00
Asada 2016	4	30	4	123				4.10 [ 0.97,	17.34]	13.74
Kakuta 2018	71	253	17	941			-	15.53 [ 8.99,	26.85]	61.86
Maeda 2021	6	46	2	156				10.17 [ 1.99,	52.12]	8.08
Heterogeneity: I <sup>2</sup>	= 0.00%	, H <sup>2</sup> =	= 1.00				<b>\</b>	13.19 [ 8.23,	21.14]	
Test of $\theta_i = \theta_j$ : Q(3)	3) = 2.9	7, p =	0.40							
White/Caucasian	n									
Bangma 2020	0	11	38	544	< <b>-</b>			> 0.02 [ 0.00,	42496.05]	13.31
Heterogeneity: I2	= 0.00%	, H <sup>2</sup> =	= 1.00					0.02 [ 0.00,	42496.05]	
Test of $\theta_i = \theta_j$ : Q(0	0) = 0.00	0, p =	•							
Overall							•	11.44 [ 7.36,	17.77]	
Heterogeneity: I <sup>2</sup>	= 0.00%	5, H <sup>2</sup> =	= 1.00							
Test of $\theta_i = \theta_j$ : Q(4)	4) = 3.9	1, p =	0.42		Higher in	non-mut	Higher in mut			
Test of group diffe	erences	Q <sub>b</sub> (1	) = 0.7	74, p = 0.3	9			<u>_</u>		
					1/64	1/4	4 64	1		

Fixed-effects Mantel-Haenszel model

Figure S172. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Total serious adverse events. Subgroup analysis according to race



Figure S173. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Serious hematologic adverse events. Subgroup analysis according to race



Figure S174. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Pancreatitis. Subgroup analysis according to race



Figure S175. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Hepatotoxicity. Subgroup analysis according to race



Fixed-effects Mantel-Haenszel model

Figure S176. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Gastrointestinal side effects. Subgroup analysis according to race

Mut Non mut Study Yes No Yes No		Odds Ratio with 95% Cl	Weight (%)
Case-control			
Kakuta 2018 33 242 17 941		7.55 [ 4.13, 13.78]	62.04
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$	•	7.55 [ 4.13, 13.78]	
Test of $\theta_i = \theta_j$ : Q(0) = 0.00, p = .			
Cobort			
Akiyama 2019 3 18 0 60			3.03
Acada 2016 2 30 4 123		2 05 [ 0 36 11 72]	14.03
Asada 2010 2 50 4 125		2.03 [ 0.30, 11.72]	12.40
Bangma 2020 0 11 38 544		→ 0.02 [ 0.00, 42496.05]	13.42
Maeda 2021 5 41 2 156		- 9.51[1.78, 50.81]	1.47
Heterogeneity: $I^2 = 5.05\%$ , $H^2 = 1.05$	-	3.81 [ 1.59, 9.11]	
Test of $0_i = 0_j$ : Q(3) = 3.16, p = 0.37			
<b>Overall</b> Heterogeneity: $l^2 = 0.00\%$ H <sup>2</sup> = 1.00	•	6.13 [ 3.76, 9.98]	
Test of $0 = 0$ : $O(4) = 2.25$ , $n = 0.52$	Higher in non mut Higher in m	+	
Test of $\mathbf{u}_i = \mathbf{u}_j$ . $Q(4) = 3.23$ , $\beta = 0.32$	righer in non-mat riigher in m	ut	
Test of group differences: $Q_b(1) = 1.60$ , p = 0.21	1/64 1/4 4	64	
Fixed-effects Mantel-Haenszel model			

Figure S177. Forest plot of comparison heterozygous *NUDT15* vs wild-type *NUDT15*, outcome: Total serious adverse events

	M	lut	Non	mut		Odds Ratio	Weight
Study	Yes	No	Yes	No		with 95% CI	(%)
Case-control							
Kakuta 2018	94	181	94	864		4.77 [ 3.44, 6.62]	9.77
Yang 2014	133	43	199	589		9.15 [ 6.26, 13.38]	9.45
Heterogeneity: <b>t</b> <sup>2</sup>	<sup>2</sup> = 0.1	18, I <sup>2</sup> :	= 84.5	6%, H <sup>2</sup> = 6.48	-	6.56 [ 3.47, 12.42]	
Test of $0_i = 0_j$ : Q(	1) = 6	5.48, p	o = 0.0	01			
Cohort							
Akiyama 2019	15	6	7	53		18.93 [ 5.52, 64.88]	4.22
Asada 2016	18	14	25	102		5.25 [ 2.30, 11.96]	6.37
Banerjee 2020	44	77	27	774		16.38 [ 9.61, 27.92]	8.39
Bangma 2020	4	4	24	466		19.42 [ 4.58, 82.39]	3.43
Chao 2017	82	110	79	445		4.20 [ 2.89, 6.10]	9.49
Choi 2020	18	7	44	62		3.62 [ 1.39, 9.41]	5.58
Kakuta 2016	10	13	19	88		3.56 [ 1.36, 9.32]	5.54
Kang 2020	13	17	26	108		3.18 [ 1.37, 7.35]	6.28
Kim 2017	33	23	96	176		2.63 [ 1.46, 4.73]	8.00
Maeda 2021	9	37	5	153		7.44 [ 2.36, 23.52]	4.58
Wang 2018	8	8	11	53		4.82 [ 1.49, 15.61]	4.46
Xu 2020	15	18	28	98		2.92 [ 1.31, 6.52]	6.51
Zhu 2019	33	32	35	307		9.05 [ 4.97, 16.46]	7.92
Heterogeneity: <b>T</b> <sup>2</sup>	= 0.3	30, I <sup>2</sup> :	= 68.1	3%, H <sup>2</sup> = 3.14	•	5.68 [ 3.88, 8.33]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(	12) =	39.47	7, p =	0.00			
Overall					•	5.83 [ 4.22, 8.06]	
Heterogeneity: <b>T</b> <sup>2</sup>	<sup>2</sup> = 0.2	25, I <sup>2</sup> :	= 71.5	64%, H <sup>2</sup> = 3.51			
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(	14) =	46.69	9, p =	0.00			
				Higher in non-mut	Higher in mut		
Test of group diff	erend	ces: C	₽ <sub>b</sub> (1) =	0.14, p = 0.70	2 4 8 16 32 64		

Random-effects REML model

# Figure S178. Forest plot of comparison heterozygous *NUDT15* vs wild-type *NUDT15*, outcome: Total hematologic adverse events



# Figure S179. Forest plot of comparison heterozygous *NUDT15* vs wild-type *NUDT15*, outcome: Serious hematologic adverse events





Fixed-effects Mantel-Haenszel model

Figure S180. Forest plot of comparison heterozygous *NUDT15* vs wild-type *NUDT15*, outcome: Withdrawal due to AE



Figure S181. Forest plot of comparison heterozygous *NUDT15* vs wild-type *NUDT15*, outcome: Pancreatitis



Fixed-effects Mantel-Haenszel model

Figure S182. Forest plot of comparison heterozygous *NUDT15* vs wild-type *NUDT15*, outcome: Hepatotoxicity



Figure S183. Forest plot of comparison heterozygous *NUDT15* vs wild-type *NUDT15*, outcome: Gastrointestinal side effects



Fixed-effects Mantel-Haenszel model

Figure S184. Forest plot of comparison 2 mutant *NUDT15* alleles vs wild-type, outcome: Total serious adverse events

	М	ut	Nor	n mut				Odds Ratio V	Veight
Study	Yes	No	Yes	No			1	with 95% CI	(%)
Case-control									
Kakuta 2018	45	4	94	864				ightarrow 103.40 [ 36.38, 293.88] 6	66.34
Yang 2014	14	0	199	589	<			→ 2368.99 [ 0.00, 6.6e+09]	0.77
Heterogeneity: I	$^{2} = 0.0$	00%,	$H^2 =$	1.00				<b>129.45</b> [ 42.70, 392.45]	
Test of $0_i = 0_j$ : Q	(1) = (	0.32,	p = 0	.57					
Cohort									
Asada 2016	2	0	25	102	<			→ 515.23 [ 0.00, 3.8e+09]	0.55
Banerjee 2020	10	3	27	774			8	<b>—— 9</b> 5.56 [ 24.87, 367.15] 1	17.68
Bangma 2020	1	0	24	466	<			→ 9191.27 [ 0.00, 7.0e+22]	0.02
Chao 2017	16	0	79	445				→ 3016.99 [ 0.03, 2.7e+08]	0.78
Kakuta 2016	5	0	19	88				→ 503.72 [ 0.04, 5.7e+06]	1.39
Kang 2020	3	0	26	108	←			→ 557.45 [ 0.00, 3.3e+08]	0.76
Maeda 2021	4	2	5	153				<b>──●</b> 61.20 [ 9.00, 416.15] 1	10.83
Kim 2017	3	0	96	176	<			→ 503.65 [ 0.00, 7.4e+10]	0.68
Zhu 2019	4	0	35	307	←			→ 2969.62 [ 0.00, 2.5e+11]	0.21
Heterogeneity: I	<sup>2</sup> = 0.0	00%,	$H^2 =$	1.00				<b>220.</b> 10 [ 53.72, 901.76]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_i$ : Q	(8) = 3	3.57,	p = 0	.89					
Overall								<b>15</b> 9.26 [ 66.44, 381.74]	
Heterogeneity: I	<sup>2</sup> = 0.0	00%,	$H^2 =$	1.00					
Test of $0_i = 0_j$ : Q	(10) =	2.81	l, p =	0.99	Higher in r	non-mut	Higher in I	mut	
Test of group di	fferen	ces:	Q <sub>b</sub> (1)	= 0.34, p = 0.56					
					1/64	1/4	4	64	
Fixed-effects Mar	ntel-Ha	aens	zel m	odel					

Figure S185. Forest plot of comparison 2 mutant *NUDT15* alleles vs wild-type, outcome: Total hematologic adverse events



Figure S186. Forest plot of comparison 2 mutant *NUDT15* alleles vs wild-type, outcome: Serious hematologic adverse events



Fixed-effects Mantel-Haenszel model

Figure S187. Forest plot of comparison 2 mutant *NUDT15* alleles vs wild-type, outcome: Pancreatitis



Figure S188. Forest plot of comparison 2 mutant *NUDT15* alleles vs wild-type, outcome: Hepatotoxicity



Fixed-effects Mantel-Haenszel model

#### Figure S189. Forest plot of comparison 2 mutant *NUDT15* alleles vs wild-type, outcome: Gastrointestinal side effects

	Mu	ut	Non	n mut					Odds Ra	atio	Weight
Study	Yes	No	Yes	No					with 95%	6 CI	(%)
Cohort											
Akiyama 2019	3	18	0	60			-		→ 14.64 [ 1.11,	192.49]	11.46
Asada 2016	2	30	4	123			-		2.05 [ 0.36,	11.72]	53.07
Maeda 2021	5	41	2	156			_		9.51 [ 1.78,	50.81]	28.27
Sutiman 2018	3	13	1	110		_		•	→ 25.38 [ 2.46,	262.22]	7.20
Heterogeneity: I	<sup>2</sup> = 14	.49%	, H <sup>2</sup> =	= 1.17		-			7.28 [ 2.92,	18.15]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q	(3) = 3	3.51,	p = 0	.32							
Overall									7.28 [ 2.92,	18.15]	
Heterogeneity: I	<sup>2</sup> = 14	.49%	, H <sup>2</sup> =	= 1.17						-	
Test of $0_i = 0_j$ : Q	(3) = 3	3.51,	p = 0	.32	Higher in non-mut	Higher	in mut				
Test of group dif	feren	ces:	Q <sub>b</sub> (0)	= 0.0	), p = .						
					1/2	2	8	32	_		

Figure S190. Forest plot of comparison *NUDT15* R139C heterozygous vs wild-type, outcome: Total serious adverse events



Random-effects REML model

Figure S191. Forest plot of comparison *NUDT15* R139C heterozygous vs wild-type, outcome: Total hematologic adverse events

	Μ	ut	Non	mut				Odds Rat	tio	Weight
Study	Yes	No	Yes	No				with 95%	CI	(%)
Cohort										
Akiyama 2019	3	18	0	60				→ 14.64 [ 1.11, 1	192.49]	7.64
Asada 2016	2	30	4	123		_		2.05 [ 0.36,	11.72]	35.40
Kakuta 2016	0	23	1	106	*	-		— 0.45 [ 0.00,	60.14]	15.01
Maeda 2021	5	41	2	156				— 9.51 [ 1.78,	50.81]	18.85
Sutiman 2018	3	13	1	110				→ 25.38 [ 2.46, 2	262.22]	4.80
Xu 2020	2	31	2	124		-		4.00 [ 0.54,	29.53]	18.29
Heterogeneity: I	$ ^2 = 0.0$	00%,	$H^2 =$	1.00			-	5.66 [ 2.58,	12.37]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : C	2(5) =	4.93,	p = 0	.42						
Overall							-	5.66 [ 2.58,	12.37]	
Heterogeneity: I	$ ^2 = 0.0$	00%,	H <sup>2</sup> =	1.00						
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : G	2(5) =	4.93,	p = 0	.42	Higher in	non-mut	Higher in n	nut		
Test of group di	fferen	ces:	$Q_b(0)$	= -0.00, p = .	•					
			1965 (15)		1/64	1/4	4	64		

# Figure S192. Forest plot of comparison *NUDT15* R139C heterozygous vs wild-type, outcome: Serious hematologic adverse events



Fixed-effects Mantel-Haenszel model

# Figure S193. Forest plot of comparison *NUDT15* R139C heterozygous vs wild-type, outcome: Withdrawal due to adverse events

	N	lut	Nor	n mut						Odds F	Ratio	Weight
Study	Yes	No	Yes	No						with 95	% CI	(%)
Cohort												
Maeda 2021	0	46	2	456		<u> </u>	_		,	0.31 [ 0.00,	227.64]	31.51
Xu 2020	0	33	2	124		<				0.28 [ 0.00,	24.54]	68.49
Heterogeneity	:   <sup>2</sup> =	0.00	%, H <sup>2</sup>	= 1.00						0.29 [ 0.01,	11.79]	
Test of $0_i = 0_j$ :	Q(1)	= 0.0	0, p =	0.98								
Overall								No. of Concession, Name		0.29 [ 0.01,	11.79]	
Heterogeneity	:   <sup>2</sup> =	0.00	%, H <sup>2</sup>	= 1.00								
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ :	Q(1)	= 0.0	0, p =	- 0.98	Н	igher in	non-mut	Higher	in mut			
Test of group	differ	ences	s: Q <sub>b</sub> (	0) = 0.00, p	ŧ.,							
						1/64	1/4	4	64	2		
Fixed-effects M	lantel	-Haei	nszel	model								

Figure S194. Forest plot of comparison *NUDT15* R139C heterozygous vs wild-type, outcome: Pancreatitis

Study	M Yes	ut No	Non Yes	mut No							Odds Ra with 95%	atio 5 CI	Weight (%)
Cohort													
Maeda 2021	0	46	4	154		<del>&lt;</del>	_			— 0	.16 [ 0.00,	10.94]	47.01
Xu 2020	1	32	6	120						0	.63 [ 0.07,	5.38]	52.99
Heterogeneity	$  ^2 = 0$	0.00%	6, H <sup>2</sup> :	= 1.00						0	.41 [ 0.06,	2.68]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ :	Q(1) =	= 0.3	4, p =	0.56									
Overall										0	.41 [ 0.06,	2.68]	
Heterogeneity	:   <sup>2</sup> = (	0.00%	6, H <sup>2</sup> :	= 1.00									
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ :	Q(1) :	= 0.3	4, p =	0.56		Higher	in non-	mut	Higher in	n m	ut		
Test of group	differe	ences	: Q <sub>b</sub> (0	0) = 0.00	), p = .								
						1/64	1/8	1		8			

Fixed-effects Mantel-Haenszel model

Figure S195. Forest plot of comparison *NUDT15* R139C heterozygous vs wild-type, outcome: Hepatotoxicity

	M	ut	Nor	n mut						Odds R	atio	Weight
Study	Yes	No	Yes	No						with 95%	6 CI	(%)
Cohort												
Maeda 2021	1	45	5	153						0.68 [ 0.08,	5.97]	73.26
Xu 2020	1	32	2	124		-				— 1.94 [ 0.17,	22.05]	26.74
Heterogeneity	': <b>I</b> <sup>2</sup> = (	0.00%	%, H <sup>2</sup>	= 1.00					-	1.02 [ 0.21,	4.97]	
Test of $0_i = 0_j$ :	Q(1)	= 0.4	0, p =	= 0.53								
Overall									-	1.02 [ 0.21,	4.97]	
Heterogeneity	r:  ² = (	0.00%	%, H <sup>2</sup>	= 1.00								
Test of $0_i = 0_j$ :	Q(1)	= 0.4	0, p =	= 0.53	Н	igher in I	non-mu	t Highe	r in mut			
Test of group	differe	ences	s: Q <sub>b</sub> (	0) = 0.00,	p = .							
						1/8	1/2	2	8			
Fixed-effects M	lantel-	Haer	nszel	model								

### Figure S196. Forest plot of comparison *NUDT15* R139C heterozygous vs wild-type, outcome: Gastrointestinal side effects



Fixed-effects Mantel-Haenszel model

Figure S197. Forest plot of comparison *NUDT15* R139C, 2 mutant alleles vs wild-type, outcome: Total serious adverse events

	Μ	ut	Nor	i mut						Oc	dds Ra	tio	Weight
Study	Yes	No	Yes	No						wit	:h 95%	CI	(%)
Case-control													
Yang 2014	14	0	199	589		<			>	2368.99 [	0.00,	6.6e+09]	2.39
Heterogeneity: I	$^{2} = 0.0$	00%,	$H^2 = $	1.00						2368.99 [	0.00,	6.6e+09]	
Test of $0_i = 0_j$ : Q	(0) =	0.00,	p = .										
Cohort													
Asada 2016	2	0	25	102		<			$\rightarrow$	515.23 [	0.00,	3.8e+09]	1.70
Banerjee 2020	10	3	27	774					_	95.56 [	24.87,	367.15]	54.87
Kakuta 2016	5	0	19	88					$\rightarrow$	503.72 [	0.04,	5.7e+06]	4.31
Kim 2017	3	0	96	176		<			$\rightarrow$	503.65 [	0.00,	7.4e+10]	2.11
Maeda 2021	4	2	5	153						61.20 [	9.00,	416.15]	33.62
Sutiman 2018	2	0	3	108		←			$\rightarrow$	3119.80 [	0.00,	8.6e+09]	0.34
Zhu 2019	4	0	35	307		←			$\rightarrow$	2969.62 [	0.00,	2.5e+11]	0.66
Heterogeneity: I	<sup>2</sup> = 0.0	00%,	H <sup>2</sup> =	1.00					<	147.72 [	38.32,	569.42]	
Test of <b>0</b> <sub>i</sub> = <b>0</b> <sub>j</sub> : Q	(6) =	1.59,	p = 0	.95									
Overall									<	200.91 [	45.09,	895.18]	
Heterogeneity: I	<sup>2</sup> = 0.0	00%,	H <sup>2</sup> =	1.00									
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q	2(7) = 3	3.03,	p = 0	.88		Higher in r	non-mut	Higher in	mut				
Test of group di	fferen	ces:	Q <sub>b</sub> (1)	= 0.13	, p = 0.72								
						1/64	1/4	4	64				
Fixed-effects Mar	ntel-H	aens	zel m	odel									

## Figure S198. Forest plot of comparison *NUDT15* R139C, 2 mutant alleles vs wild-type, outcome: Total hematologic adverse events

	M	ut	Non	mut					Oc	lds Rat	io	Weight
Study	Yes	No	Yes	No					wit	h 95%	CI	(%)
Cohort												
Asada 2016	2	0	4	123	←				3233.62 [	0.00,	2.4e+10]	0.94
Kakuta 2016	5	0	1	106				$\rightarrow$	6180.95 [	0.50,	7.7e+07]	1.22
Maeda 2021	1	5	2	156					15.60 [	1.21,	201.86]	97.35
Sutiman 2018	2	0	1	110	<				6382.47 [	0.00,	1.8e+10]	0.49
Heterogeneity:	l <sup>2</sup> = 25	5.40%	6, H <sup>2</sup>	= 1.34				<	152.29 [	32.10,	722.51]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : G	2(3) =	4.02	, p = (	0.26								
Overall								$\leq$	152.29 [	32.10,	722.51]	
Heterogeneity:	l <sup>2</sup> = 25	5.40%	6, H <sup>2</sup>	= 1.34								
Test of $0_i = 0_j$ : C	Q(3) =	4.02	, p = (	0.26	Higher in r	non-mut	Higher in n	nut				
Test of group di	ifferen	ces:	Q <sub>b</sub> (0)	= 0.00, p = .								
0.1			24 7	a (5 •0	1/64	1/4	4	64				

Fixed-effects Mantel-Haenszel model

# Figure S199. Forest plot of comparison *NUDT15* R139C, 2 mutant alleles vs wild-type, outcome: Serious hematologic adverse events



Figure S200. Forest plot of comparison NUDT15 R139C vs wild-type, outcome: Total serious adverse events



Random-effects REML model

Figure S201. Forest plot of comparison *NUDT15* R139C vs wild-type, outcome: Total hematologic adverse events



Figure S202. Forest plot of comparison *NUDT15* R139C vs wild-type, outcome: Serious hematologic adverse events



Fixed-effects Mantel-Haenszel model



	M	ut	Non	mut		Odds Ratio	Weight
Study	Yes	No	Yes	No		with 95% CI	(%)
Cohort							
Maeda 2021	0	52	4	154	<	0.15 [ 0.00, 8.88]	49.24
Xu 2020	1	32	6	120		— 0.63 [ 0.07, 5.38]	50.76
Heterogeneity	: <b>I</b> <sup>2</sup> = (	0.00%	6, Η <sup>2</sup> :	= 1.00		0.39 [ 0.06, 2.54]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ :	Q(1) :	= 0.3	8, p =	0.54			
Overall						0.39 [ 0.06, 2.54]	
Heterogeneity	:   <sup>2</sup> = (	0.00%	6, H <sup>2</sup> :	= 1.00			
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ :	Q(1) :	= 0.3	8, p =	0.54	Higher in non-mut Highe	er in mut	
Test of group	differe	ences	: Q <sub>b</sub> (0	0) = 0.00	p = .		
					1/64 1/8 1	8	

#### Figure S204. Forest plot of comparison NUDT15 R139C vs wild-type, outcome: Hepatotoxicity



Fixed-effects Mantel-Haenszel model

### Figure S205. Forest plot of comparison *NUDT15* R139C vs wild-type, outcome: Gastrointestinal side effects

Mut Non mut	Odds Ratio	Weight
Study Yes No Yes No	with 95% Cl	(%)
Case-control		
Kakuta 2018 31 48 71 626	<b>5</b> .69 [ 3.41, 9.52	] 52.69
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$	5.69 [ 3.41, 9.52	]
Test of $\theta_i = \theta_j$ : Q(0) = 0.00, p = .		
Cohort		
Chao 2017 28 29 79 445	5.44 [ 3.07, 9.63	] 47.31
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$	5.44 [ 3.07, 9.63	]
Test of $\theta_i = \theta_j$ : Q(0) = 0.00, p = .		
Overall	5.57 [ 3.80, 8.17	]
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$		
Test of $\mathbf{\theta}_i = \mathbf{\theta}_j$ : Q(1) = 0.01, p = 0.91 Higher in non-mut Higher in mut		
Test of group differences: $Q_b(1) = 0.01$ , p = 0.91	·	
	4 8	

## Figure S206. Forest plot of comparison *NUDT15*\*2 heterozygous vs wild-type, outcome: Total hematologic adverse events



Figure S207. Forest plot of comparison *NUDT15*\*2 2 mutant alleles vs wild-type, outcome: Total hematologic adverse events

	Mut	Non	mut				Odds R	atio	Weight
Study	Yes No	Yes	No				with 95%	6 CI	(%)
Case-control									
Kakuta 2018	50 49	71	626				 - 9.00 [ 5.66,	14.31]	52.87
Heterogeneity:	$I^2 = 0.00\%$	5, H <sup>2</sup> =	1.00				9.00 [ 5.66,	14.31]	
Test of $0_i = 0_j$ : C	Q(0) = 0.00	), p = .							
Cohort									
Chao 2017	35 29	79	445				 6.80 [ 3.93,	11.75]	47.13
Heterogeneity:	$I^2 = 0.00\%$	, H <sup>2</sup> =	1.00				6.80 [ 3.93,	11.75]	
Test of $0_i = 0_j$ : C	Q(0) = 0.00	), p = .							
Overall							7.96 [ 5.59,	11.34]	
Heterogeneity:	$I^2 = 0.00\%$	, H <sup>2</sup> =	1.00						
Test of $0_i = 0_j$ : C	Q(1) = 0.59	9, p = (	0.44						
Higher in no Test of aroup d	n-mut Hig	gher ir	mut = 0.59	9. p = 0.44					
3	I,	5( - 7			4	8	-		
						•			

### Figure S208. Forest plot of comparison *NUDT15*\*2 vs wild-type, outcome: Total hematologic adverse events



Fixed-effects Mantel-Haenszel model

#### Figure S209. Forest plot of comparison *NUDT15*\*3 heterozygous vs wild-type, outcome: Total hematologic adverse events






Figure S211. Forest plot of comparison NUDT15\*3 vs wild-type, outcome: Total hematologic adverse events



# Figure S212. Forest plot of comparison *NUDT15*\*5 heterozygous vs wild-type, outcome: Total serious adverse events

Study	Mu Yes	ut No	Nor Yes	n mut No				Odds Ratio with 95% Cl				Weight (%)
Case-control												
Kakuta 2018	4	13	71	626			-		2.	71 [ 0.86,	8.54]	38.62
Heterogeneity:	$ ^2 = 0.0$	00%,	H <sup>2</sup> =	1.00			1		2.	71 [ 0.86,	8.54]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : G	0(0) =	0.00,	p =									
Cohort												
Chao 2017	4	9	79	445			-		2.	50 [ 0.75,	8.33]	39.56
Kang 2020	2	3	26	108					2.	77 [ 0.44,	17.43]	16.77
Sutiman 2018	0	2	10	117		<	-		→ 0.	08 [ 0.00,	6.1e+05]	5.05
Heterogeneity:	<sup>2</sup> = 0.0	00%,	H <sup>2</sup> =	1.00					2.	38 [ 0.89,	6.38]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : C	(2) =	0.21,	p =	0.90								
Overall								-	2.	51 [ 1.18,	5.31]	
Heterogeneity:	<sup>2</sup> = 0.0	00%,	H <sup>2</sup> =	1.00								
Test of $0_i = 0_j$ : C	(3) =	0.21	p =	0.98		Higher in	non-mut	Higher in 1	nut			
Test of group di	fferen	ces:	Q <sub>b</sub> (1)	) = 0.03	, p = 0.86							
					1.12	1/64	1/4	4	64			

Fixed-effects Mantel-Haenszel model

Figure S213. Forest plot of comparison *NUDT15*\*5 heterozygous vs wild-type, outcome: Total hematologic adverse events



Figure S214. Forest plot of comparison *NUDT15*\*5 heterozygous vs wild-type, outcome: Serious hematologic adverse events

Mut Non mut Study Yes No Yes No			Odds Ra with 95%	tio CI	Weight (%)
Case-control					
Kakuta 2018 5 15 71 626			2.94 [ 1.04,	8.33]	99.92
Heterogeneity: $I^2 = 100.00\%$ , $H^2 = 1.00$		$\langle$	2.94 [ 1.04,	8.33]	
Test of $\theta_i = \theta_j$ : Q(0) = 0.00, p = .					
Cohort					
Chao 2017 4 0 79 445	<		2949.40 [ 0.00,	1.8e+13]	0.08
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$			2949.40 [ 0.00,	1.8e+13]	
Test of $\theta_i = \theta_i$ : Q(0) = 0.00, p = .					
Overall		-	5.21 [ 2.18,	12.45]	
Heterogeneity: $I^2 = 31.56\%$ , $H^2 = 1.46$					
Test of $\theta_i = \theta_j$ : Q(1) = 1.46, p = 0.23	Higher in non-mut	Higher in mut			
Test of group differences: $Q_b(1) = 0.36$ , p = 0.55					
	1/64 1/4	4 64			
Fixed-effects Mantel-Haenszel model					

Figure S215. Forest plot of comparison *NUDT15*\*5 2 mutant alleles vs wild-type, outcome: Total hematologic adverse events



Figure S216. Forest plot of comparison *NUDT15*\*5 vs wild-type, outcome: Total serious adverse events

Mut Non mut Study Xes No Xes No		Ratio % CI	Weight		
			With 55	/0 01	(70)
Case-control					
Kakuta 2018 5 15 71 626			2.94 [ 1.04,	8.33]	42.08
Heterogeneity: I <sup>2</sup> = 100.00%, H <sup>2</sup> = 1.00		-	2.94 [ 1.04,	8.33]	
Test of $\theta_i = \theta_j$ : Q(0) = 0.00, p = .					
Cohort					
Chao 2017 8 9 79 445			5.01 [ 1.88,	13.37]	37.23
Kang 2020 2 3 26 108			2.77 [ 0.44,	17.43]	15.90
Sutiman 2018 0 2 10 117	←		• 0.08 [ 0.00,	6.1e+05]	4.79
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$		-	3.99 [ 1.71,	9.27]	
Test of <b>0</b> <sub>i</sub> = <b>0</b> <sub>j</sub> : Q(2) = 0.59, p = 0.75					
Overall		•	3.55 [ 1.85,	6.80]	
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$					
Test of $\theta_i = \theta_j$ : Q(3) = 0.89, p = 0.83	Higher in non-mut	Higher in mut			
Test of group differences: $Q_{h}(1) = 0.20$ . p = 0.66					
	1/64 1/4	4 64			

Fixed-effects Mantel-Haenszel model

Figure S217. Forest plot of comparison *NUDT15*\*5 vs wild-type, outcome: Total hematologic adverse events



Figure S218. Forest plot of comparison *NUDT15*\*5 vs wild-type, outcome: Serious hematologic adverse events

Study	M Yes	ut No	Nor Yes	n mut No		Odds Ratio with 95% Cl					atio 5 Cl	Weight (%)
Cohort												
Chao 2017	7	13	79	445						3.03 [ 1.17,	7.84]	99.92
Kang 2020	1	0	26	108		<				549.15 [ 0.00,	4.7e+12]	0.08
Heterogenei	ty: I <sup>2</sup> =	= 0.0	0%, H	$1^2 = 1.00$						3.45 [ 1.39,	8.62]	
Test of $0_i = 0$	lj: Q(1	) = 0	.26, p	= 0.61								
								_				
Overall								-		3.45 [ 1.39,	8.62]	
Heterogenei	ty: I <sup>2</sup> =	0.0	0%, H	<sup>2</sup> = 1.00								
Test of $0_i = 0$	lj: Q(1	) = 0	.26, p	= 0.61	Н	igher in r	ion-mut	Higher in	mut			
Test of group	o diffe	renc	es: Q	o(0) = 0.00, p =	= .				21.27			
						1/64	1/4	4	64			

Fixed-effects Mantel-Haenszel model

# Figure S219. Forest plot of comparison *NUDT15*\*6 heterozygous vs wild-type, outcome: Total hematologic adverse events

Mut Non mut		Odds Ratio	Weight
Study Yes No Yes No		with 95% CI	(%)
Cohort			
Chao 2017 8 13 79 445		- 3.47 [ 1.39, 8.63]	99.92
Kang 2020 1 0 26 108	<	→ 549.15 [ 0.00, 4.7e+12]	0.08
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$	-	3.89 [ 1.61, 9.41]	
Test of $0_i = 0_j$ : Q(1) = 0.24, p = 0.62			
Overall	-	3.89 [ 1.61, 9.41]	
Heterogeneity: $I^2 = 0.00\%$ , $H^2 = 1.00$			
Test of $\theta_i = \theta_j$ : Q(1) = 0.24, p = 0.62	Higher in non-mut Highe	er in mut	
Test of group differences: $Q_b(0) = 0.00$ , p =			
	1/64 1/4 4	64	
Fixed-effects Mantel-Haenszel model			

Figure S220. Forest plot of comparison *NUDT15*\*6 vs wild-type, outcome: Total hematologic adverse events

	N	/lut	Nor	n mut				Odd	Odds Ratio		
Study	Yes	No	Yes	No				with	with 95% CI		
Case-control										15	
Kakuta 2018	71	253	17	941				15.53 [ 8.9	9, 26.85]	61.86	
Heterogeneity:	$ ^2 = 0.$	00%,	$H^2 =$	1.00			-	15.53 [ 8.9	9, 26.85]		
Test of $\theta_i = \theta_j$ : C	2(0) =	0.00,	p = .								
Cohort											
Akiyama 2019	3	18	0	60				→ 14.64 [ 1.1	1, 192.49]	3.00	
Asada 2016	4	30	4	123				4.10 [ 0.9	7, 17.34]	13.74	
Bangma 2020	0	11	38	544	<b>←∎</b>			→ 0.02[0.0	0, 42496.05]	13.31	
Maeda 2021	6	46	2	156				- 10.17 [ 1.9	9, 52.12]	8.08	
Heterogeneity:	$ ^2 = 0.$	00%,	H <sup>2</sup> =	1.00			-	4.79 [ 2.1	0, 10.92]		
Test of $\theta_i = \theta_j$ : C	2(3) =	2.10,	p = 0	).55							
Overall							•	11.44 [ 7.3	6, 17.77]		
Heterogeneity: I	$ ^2 = 0.$	00%,	H <sup>2</sup> =	1.00							
Test of $\theta_i = \theta_j$ : C	2(4) =	3.91,	p = 0	).42	Higher in n	on-mut	Higher in m	ut			
Test of group di	ifferen	nces: (	Q <sub>b</sub> (1)	= 5.43, p = 0.02							
					1/64	1/4	4	64			

Fixed-effects Mantel-Haenszel model

Figure S221. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Total SAE

	N	lut	Nor	n mut	Odds Ratio	Weight
Study	Yes	No	Yes	No	with 95% Cl	(%)
Case-control						
Kakuta 2018	139	185	94	864		9.05
Yang 2014	147	43	199	589		8.78
Heterogeneity: 1	$2^{2} = 0.$	04, I <sup>2</sup> =	= 58.0	07%, H <sup>2</sup> = 2.38	<b>*</b> 8.22 [ 5.66, 11.94]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q	(1) = 2	2.38, p	o = 0.	12		
Cohort						
Akiyama 2019	15	6	7	53	<b>18.93</b> [ 5.52, 64.88]	4.79
Asada 2016	20	14	25	102	5.83 [ 2.59, 13.12]	6.69
Banerjee 2020	54	80	27	774	——————————————————————————————————————	8.16
Bangma 2020	5	4	24	466	24.27 [ 6.12, 96.21]	4.25
Chao 2017	98	110	79	445	- 5.02 [ 3.49, 7.21]	8.84
Grover 2020	7	6	26	80	3.59 [ 1.11, 11.64]	5.01
Kakuta 2016	15	13	19	88	5.34 [ 2.19, 13.05]	6.28
Kang 2020	16	17	26	108	3.91 [ 1.75, 8.75]	6.71
Kim 2017	36	23	9	263	→ 45.74 [ 19.63, 106.55]	6.52
Maeda 2021	13	39	5	153	10.20 [ 3.43, 30.33]	5.37
Wang 2018	8	8	11	53	4.82 [ 1.49, 15.61]	5.01
Xu 2020	15	18	28	98	2.92 [ 1.31, 6.52]	6.72
Zhu 2019	37	32	35	307		7.81
Heterogeneity:	<sup>2</sup> = 0.	51, I <sup>2</sup> =	= 77.7	71%, H <sup>2</sup> = 4.49	8.38 [ 5.28, 13.30]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q	(12) =	52.06	6, p =	0.00		
Overall		-			8.36 [ 5.71, 12.23]	
Heterogeneity:	$1^2 = 0.3$	39, I <sup>2</sup> =	= 79.8	30%, H <sup>2</sup> = 4.95		
Test of $0_i = 0_j$ : Q	(14) =	54.46	6, p =	0.00		
				Higher in non-mut	Higher in mut	
Test of group dif	ferend	ces: Q	a <sub>b</sub> (1) =	0.00, p = 0.95	2 4 8 16 32 64	
Random-effects F	REML	mode	el			

Figure S222. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Total hematologic AE



Figure S223. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Serious hematologic AE

Study	Mut Non mut tudy Yes No Yes No									Odds with 95	Weight	
Case-control												()
Kakuta 2018	2	322	18	940				_		0.32 [ 0.07,	1.41]	69.58
Heterogeneity:	$ ^2 = 0.$	.00%,	$H^2 =$	1.00			-			0.32 [ 0.07,	1.41]	
Test of $\theta_i = \theta_j$ : (	Q(0) =	0.00,	p = .							15 80		
Cohort												
Bangma 2020	0	11	38	544		<del>~ 8</del>				0.02 [ 0.00,	42496.05]	11.11
Maeda 2021	0	52	2	156		<	-			0.27 [ 0.00,	16.68]	10.44
Xu 2020	0	33	2	124		<	-	-		0.28 [ 0.00,	24.54]	8.86
Heterogeneity:	$ ^2 = 0.$	.00%,	H <sup>2</sup> =	1.00		-	-	-		0.18 [ 0.01,	3.56]	
Test of $\theta_i = \theta_j$ : (	ຊ(2) =	0.15,	p = (	0.93								
Overall							-			0.28 [ 0.08,	1.05]	
Heterogeneity:	$ ^2 = 0.$	.00%,	H <sup>2</sup> =	1.00								
Test of $\theta_i = \theta_j$ : (	ຊ(3) =	0.15,	p = (	0.99		Higher in	non-mut	Higher ir	n mut			
Test of group d	ifferer	nces: (	Q₀(1)	= 0.12	p = 0.73	1/64	1/4	4	64	Ĩ		

Fixed-effects Mantel-Haenszel model

Figure S224. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Pancreatitis



Figure S225. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Hepatotoxicity



Figure S226. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Gastrointestinal side effects

#### **OTHER GENES**



Fixed-effects Mantel-Haenszel model





Fixed-effects Mantel-Haenszel model





Figure S229. Forest plot of comparison mutated GSTT1 vs wild-type, outcome: Total hematologic AE

	М	ut	Non	mut					Odds R	latio	Weight
Study	Yes	No	Yes	No					with 959	% CI	(%)
Cohort							0				
Al-Judaibi 2016	0	11	0	41	*				1.00 [ 0.01,	127.00]	6.53
Liu 2015	0	57	0	55				_	1.00 [ 0.02,	51.31]	9.88
Mazor 2013	0	48	7	121	<				0.09 [ 0.00,	4.11]	83.59
Heterogeneity: I <sup>2</sup>	= 0.0	0%, ł	$H^2 = 1$	.00	-				0.24 [ 0.03,	2.09]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(2)	2) = 1	.10,	p = 0.	58							
Overall							-		0.24 [ 0.03,	2.09]	
Heterogeneity: I <sup>2</sup>	= 0.0	0%, I	$+1^2 = 1$	.00							
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(2)	2) = 1	.10,	p = 0.	58	Higher in	non-mut	Higher in	mut			
Test of group diff	erenc	es: C	Q <sub>b</sub> (0) =	= 0.00, p	=.						
					1/64	1/4	4	64			
Test of group diff	erenc	es: C	Q <sub>b</sub> (0) =	= 0.00, p	= . 1/64	1/4	4	64			

Fixed-effects Mantel-Haenszel model

#### Figure S230. Forest plot of comparison mutated GSTT1 vs wild-type, outcome: Pancreatitis

	M	ut	Non	mut					Odds R	latio	Weight
Study	Yes	No	Yes	No					with 959	% CI	(%)
Cohort							0				
Al-Judaibi 2016	0	11	0	41	*				1.00 [ 0.01,	127.00]	13.89
Liu 2015	0	57	0	55				_	1.00 [ 0.02,	51.31]	21.02
Mazor 2013	3	45	3	125		_			2.78 [ 0.54,	14.27]	65.09
Heterogeneity: I <sup>2</sup>	= 0.0	0%,	$H^2 = 1$	.00		-			2.16 [ 0.52,	9.01]	
Test of <b>0</b> ; = <b>0</b> ;: Q(	(2) = 0	.33,	p = 0.	85							
Overall						-			2.16 [ 0.52,	9.01]	
Heterogeneity: I <sup>2</sup>	= 0.0	0%,	$H^2 = 1$	.00							
Test of <b>0</b> <sub>i</sub> = <b>0</b> <sub>j</sub> : Q(	(2) = 0	.33,	p = 0.	85	Higher in	non-mut	Higher in r	mut			
Test of group diff	ferenc	es: C	Q <sub>b</sub> (0) =	= 0.00, p = .							
			.,	10 <b>•</b>	1/64	1/4	4	64			
Fixed-effects Man	tel-Ha	iensz	zel mo	del							





Figure S232. Forest plot of comparison mutated GSTM1 vs wild-type, outcome: Total hematologic AE

	Μ	ut	Non	mut				Odds Ratio	Weight
Study	Yes	No	Yes	No				with 95% CI	(%)
Cohort									
Al-Judaibi 2016	0	27	0	25		-		- 1.00 [ 0.02, 52.44]	5.64
Liu 2015	0	59	0	53	3			– 1.00 [ 0.02, 51.57]	5.69
Mazor 2013	5	94	2	75		-		1.99 [ 0.38, 10.57]	24.58
Stocco 2007	2	39	5	24				0.25 [ 0.04, 1.37]	64.10
Heterogeneity: I <sup>2</sup>	= 0.0	0%, I	$H^2 = 1$	.00		-		0.76 [ 0.28, 2.07]	
Test of $0_i = 0_j$ : Q(	3) = 2	.98,	p = 0.	39					
Overall						-		0.76 [ 0.28, 2.07]	
Heterogeneity: I <sup>2</sup>	= 0.0	0%, I	$H^2 = 1$	.00					
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(	3) = 2	.98,	p = 0.	39	Higher in	non-mut	Higher in mut		
Test of group diff	erenc	es: C	Q <sub>b</sub> (0) =	= -0.00, p = .					
<b>U</b> .			/	65 <b>9</b> 3	1/32	1/4	2 16	_	
Fixed-effects Man	tel-Ha	iensz	el mo	del					



	M	ut	Non	mut					Odds Ra	tio	Weight
Study	Yes	No	Yes	No					with 95%	CI	(%)
Cohort											
Al-Judaibi 2016	0	27	0	25		-	-		1.00 [ 0.02,	52.44]	15.59
Liu 2015	0	59	0	53					1.00 [ 0.02,	51.57]	15.72
Mazor 2013	4	95	2	75				-	1.58 [ 0.28,	8.85]	68.69
Heterogeneity: I <sup>2</sup>	= 0.0	0%, ł	$+1^2 = 1$	.00					1.40 [ 0.33,	6.01]	
Test of $0_i = 0_j$ : Q(2)	2) = 0	.07,	o = 0.	96							
Overall						<			1.40 [ 0.33,	6.01]	
Heterogeneity: I <sup>2</sup>	= 0.0	0%, ł	$+1^2 = 1$	.00							
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(2)	2) = 0	.07, p	o = 0.	96	Higher in	non-mut	Higher	in mut			
Test of group diff	erenc	es: C	Q <sub>b</sub> (0) =	= 0.00, p = .							
					1/32	1/4	2	16			

### Figure S234. Forest plot of comparison mutated GSTM1 vs wild-type, outcome: Hepatotoxicity

	Μ	ut	Non	mut							Odds R	atio	Weight
Study	Yes	No	Yes	No							with 95%	6 CI	(%)
Cohort													
Hawwa 2008	1	5	2	27		-	_	-			— 2.70 [ 0.20,	35.75]	17.80
Wroblova 2012	3	8	31	146		3					1.77 [ 0.44,	7.04]	82.20
Heterogeneity: I <sup>2</sup>	= 0.0	0%,	$H^2 = 1$	.00			-				1.93 [ 0.57,	6.51]	
Test of $0_i = 0_j$ : Q(	(1) = 0	.08,	p = 0.	78									
Overall							-				1.93 [ 0.57,	6.51]	
Heterogeneity: I <sup>2</sup>	= 0.0	0%,	$H^2 = 1$	.00									
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(	(1) = 0	.08,	p = 0.	78	Higher	in non-r	nut	Highe	er in m	ut			
Test of group dif	ferenc	es: C	Q <sub>b</sub> (0) =	= 0.00,	p = .								
						1/4	1	l,	4	16			
Fixed-effects Man	tel-Ha	ensz	zel mo	del									

Figure S235. Forest plot of comparison XDH heterozygous vs wild-type, outcome: Total hematologic AE



Fixed-effects Mantel-Haenszel model

Figure S236. Forest plot of comparison mutated XDH rs17323225 vs wild-type, outcome: Clinical remission

	Μ	ut	Non	mut						Odds Ra	atio	Weight
Study	Yes	No	Yes	No						with 95%	6 CI	(%)
Cohort												
Mahasneh 2020	8	3	76	13					0.	46 [ 0.11,	1.95]	66.85
Smith 2009	6	2	65	42					— 1.	94 [ 0.37,	10.06]	33.15
Heterogeneity: I <sup>2</sup> =	= 41.1	9%,	$H^2 = f$	1.70					0.	95 [ 0.32,	2.76]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1	) = 0.1	9										
							_					
Overall									0.	95 [ 0.32,	2.76]	
Heterogeneity: I <sup>2</sup> =	= 41.1	9%,	$H^2 = c$	1.70								
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(1	) = 1.	70, p	) = 0.1	9	Hig	her in n	on-mut	Higher in mu	t			
Test of group diffe	rence	s: Q	<sub>b</sub> (0) =	0.00, p	= .							
page =2			nor d <b>i</b> li			1/8	1/2	2	8			

### Figure S237. Forest plot of comparison mutated XDH rs17011368 vs wild-type, outcome: Clinical remission



Fixed-effects Mantel-Haenszel model

Figure S238. Forest plot of comparison HLADQA1\*02:01-HLA-DRB1\*07-01 rs2647087 2 mutant alleles vs wild-type, outcome: Total SAE

	Μ	ut	Non	mut				Odds Ra	atio	Weight
Study	Yes	No	Yes	No				with 95%	CI	(%)
Cohort										
Bangma 2020	21	221	17	334				1.87 [ 0.96,	3.62]	96.22
Wilson 2018	0	182	0	190	2	•		1.00 [ 0.02,	50.71]	3.78
Heterogeneity: I <sup>2</sup>	$^{2} = 0.0$	00%,	$H^2 = 1$	.00		•		1.83 [ 0.96,	3.52]	
Test of $0_i = 0_j$ : Q(	(1) =	0.09,	p = 0.	76						
Overall								1.83 [ 0.96,	3.52]	
Heterogeneity: I <sup>2</sup>	<sup>2</sup> = 0.0	00%,	$H^2 = 1$	.00						
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : Q(	(1) =	0.09,	p = 0.	76	Higher in non-mut	Higher ir	n mut			
Test of group dif	feren	ces: (	Q <sub>b</sub> (0) =	= 0.00,	=.					
					1/32 1/4	2	16			

# Figure S239. Forest plot of comparison mutated HLADQA1\*02:01-HLA-DRB1\*07-01 rs2647087 vs wild-type, outcome: Total SAE

Study	M Yes	lut No	Nor Yes	n mut No						Odds F with 95°	atio % CI	Weight (%)
Cohort												
Bangma 2020	19	199	17	334			16			1.88 [ 0.95	3.69]	96.06
Wilson 2018	0	141	0	190						- 1.00 [ 0.02	52.96]	3.94
Heterogeneity:	$^{2} = 0.$	00%,	$H^2 = f$	1.00						1.84 [ 0.94	3.59]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : G	2(1) =	0.09,	p = 0	.76								
Overall										1.84 [ 0.94	3.59]	
Heterogeneity: I	$^{2} = 0.$	00%,	$H^2 = $	1.00								
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ : G	2(1) =	0.09,	p = 0	.76	Hig	gher in r	ion-mut	Highe	r in mut			
Test of group di	fferen	ces: (	Q <sub>b</sub> (0) :	= 0.00	p = .							
						1/32	1/4	2	16	-		

Fixed-effects Mantel-Haenszel model

Figure S240. Forest plot of comparison HLADQA1\*02:01-HLA-DRB1\*07-01 rs2647087 heterozygous vs wild-type, outcome: Total serious AE

	N	lut	Nor	mut			Odds R	atio	Weight
Study	Yes	No	Yes	No			with 95%	6 CI	(%)
Cohort									
Bangma 2020	19	199	17	334			1.88 [ 0.95,	3.69]	93.58
Wilson 2018	6	135	1	189	-			70.58]	6.42
Heterogeneity:	$ ^2 = 43$	3.43%	, H <sup>2</sup> =	1.77			2.29 [ 1.22,	4.30]	
Test of $\theta_i = \theta_j$ :	Q(1) =	1.77,	p = 0	.18					
Overall					-		2.29 [ 1.22,	4.30]	
Heterogeneity:	$ ^2 = 43$	3.43%	, H <sup>2</sup> =	1.77					
Test of $\theta_i = \theta_j$ :	Q(1) =	1.77,	p = 0	.18	Uishes in mut				
Test of group d	lifferer	nces: (	Q <sub>b</sub> (0)	= 0.00, p = .	Higner in mut				
					1 4	16	64		

Figure S241. Forest plot of comparison HLADQA1\*02:01-HLA-DRB1\*07-01 rs2647087 heterozygous vs wild-type, outcome: Pancreatitis



Random-effects REML model

# Figure S242. Forest plot of comparison HLADQA1\*02:01-HLA-DRB1\*07-01 rs2647087 2 mutant alleles vs wild-type, outcome: Pancreatitis

	N	lut	Nor	n mut						Odds Ra	atio	Weight
Study	Yes	No	Yes	No						with 95%	6 CI	(%)
Cohort												
Bangma 2020	21	221	17	334			-			1.87 [ 0.96,	3.62]	62.68
Wilson 2018	12	170	1	189				-	,	13.34 [ 1.72,	103.68]	37.32
Heterogeneity:	τ <sup>2</sup> = 1	.33, I <sup>2</sup>	= 68	75%,	$H^2 = 3.20$					3.89 [ 0.60,	25.09]	
Test of $\theta_i = \theta_j$ :	Q(1) =	3.20,	p = 0	0.07								
Overall										3.89 [ 0.60,	25.09]	
Heterogeneity:	τ <sup>2</sup> = 1	.33, I <sup>2</sup>	= 68	75%,	$H^2 = 3.20$							
Test of $\theta_i = \theta_j$ :	Q(1) =	3.20,	p = 0	).07Hiq	her in no	n-mut Hi	gher in m	ut				
Test of group d	ifferer	ices: (	Q <sub>b</sub> (0)	= 0.00	, p = .							
						1	4	16	64			
Random-effects	REML	. mod	el									

### Figure S243. Forest plot of comparison mutated HLADQA1\*02:01-HLA-DRB1\*07-01 rs2647087 vs wild-type, outcome: Pancreatitis



Fixed-effects Mantel-Haenszel model

Figure S244. Forest plot of comparison mutated AOX1 rs55754655 vs wild-type, outcome: Clinical remission

	M	ut	Non	mut		Odds Ra	atio	Weight
Study	Yes	No	Yes	No		with 95%	o CI	(%)
Cohort								
Giudici 2021	29	11	44	17		1.02 [ 0.42,	2.48]	45.30
Niess 2012	29	4	23	12		3.78 [ 1.08,	13.29]	12.79
Weiss 2010	50	8	82	8		0.61 [ 0.22,	1.73]	41.90
Heterogeneity	/:   <sup>2</sup> =	59.67	7%, H	<sup>2</sup> = 2.48		1.20 [ 0.67,	2.14]	
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ :	Q(2)	= 4.9	96, p =	= 0.08				
Ovorall						1 20 [ 0 67	2 1/1	
Overall	. 2			2		1.20[0.07,	2.14]	
Heterogeneity	/:  * =	59.67	7%, H	- = 2.48				
Test of $\boldsymbol{\theta}_i = \boldsymbol{\theta}_j$ :	Q(2)	= 4.9	96, p =	= 0.08	Higher in non-mut Higher in mut			
Test of group	differe	ence	s: Q <sub>b</sub> (	0) = 0.0	), p = .			
					1/4 1/2 1 2 4 8			
Fixed-effects M	lantel	Hae	nszel	model				

Figure S245. Forest plot of comparison mutated NOD2 vs wild-type, outcome: Clinical remission

	Mut Non mut							Odds Ra	atio	Weight	
Study	Yes	No	Yes	No					with 95%	6 CI	(%)
Cohort											
Choi 2020	8	3	48	61		-			- 3.39 [ 0.85,	13.47]	47.44
Lee 2015	17	55	16	16					0.31 [ 0.13,	0.75]	52.56
Heterogene	eity: τ <sup>2</sup>	= 2.5	52, I <sup>2</sup>	= 87.84%	$H^2 = 8.22$		-	-	0.96 [ 0.09,	10.03]	
Test of $\theta_i =$	θ <sub>j</sub> : Q(	(1) =	8.22,	p = 0.00							
Overall									0.96 [ 0.09,	10.03]	
Heterogene	eity: τ <sup>2</sup>	= 2.	52, I <sup>2</sup>	= 87.84%	5, H <sup>2</sup> = 8.22	2					
Test of $\theta_i =$	θ <sub>j</sub> : Q(	1) =	8.22,	p = 0.00		Higher in non-mut	Higher in	mut			
Test of grou	up diff	eren	ces: C	$Q_{\rm b}(0) = 0.0$	00, p = .				-0		
						1/4 1/2	124	8			

Random-effects REML model

Figure S246. Forest plot of comparison IMPDH1 heterozygous vs wild-type, outcome: Total hematologic AE

	M	ut	Non	mut							Odds Ra	atio	Weight
Study	Yes	No	Yes	No				~			with 95%	6 CI	(%)
Cohort													
Choi 2020	8	3	48	61			-				- 3.39 [ 0.85,	13.47]	47.14
Lee 2015	24	74	16	16			-				0.32 [ 0.14,	0.75]	52.86
Heterogene	eity: τ <sup>2</sup>	= 2.4	42, I <sup>2</sup>	= 87.73%, H <sup>2</sup> :	= 8.15				-	-	0.98 [ 0.10,	9.74]	
Test of $\theta_i$ =	θ <sub>j</sub> : Q(	(1) =	8.15,	p = 0.00			_						
Overall											0.98 [ 0.10,	9.74]	
Heterogene	eity: τ <sup>2</sup>	= 2.4	42, I <sup>2</sup>	= 87.73%, H <sup>2</sup> :	= 8.15								
Test of $\theta_i =$	θ <sub>j</sub> : Q(	1) =	8.15,	p = 0.00		Higher in non-m	ut	Higher	in n	nut			
Test of grou	up diff	eren	ces: C	$Q_{\rm b}(0) = 0.00,  {\rm p}$	= .								
						1/4 1/2	1	2	4	8			
Random-effe	ects R	EML	mode	el									

Figure S247. Forest plot of comparison mutated IMPDH1 vs wild-type, outcome: Total hematologic AE

Mut			Non	mut						Odds Ra	atio	Weight
Study	Yes	No	Yes	No						with 95%	CI	(%)
Cohort												
Choi 2020	18	26	41	34			1.11			0.57 [ 0.27,	1.22]	52.43
Lee 2015	11	33	6	62						3.44 [ 1.17,	10.15]	47.57
Heterogene	eity: τ <sup>2</sup>	= 1.3	38, I <sup>2</sup>	= 85.93%, H <sup>2</sup>	<sup>2</sup> = 7.10			-	-	1.35 [ 0.23,	7.78]	
Test of $\theta_i =$	θ <sub>j</sub> : Q(	(1) =	7.10,	p = 0.01								
Overall								-	-	1.35 [ 0.23,	7.78]	
Heterogene	eity: τ <sup>2</sup>	= 1.3	38, I <sup>2</sup>	= 85.93%, H <sup>2</sup>	<sup>2</sup> = 7.10							
Test of $\theta_i =$	θ <sub>j</sub> : Q(	1) =	7.10,	p = 0.01	Highe	r in non-mut	Higher in	mut				
Test of grou	up diff	eren	ces: C	$Q_{\rm b}(0) = 0.00,  \mu$	p = .							
						1/2	1 2	4	8			

Random-effects REML model

Figure S248. Forest plot of comparison SLC29A1 heterozygous vs wild-type, outcome: Total hematologic AE

	Mut Non mut						Odds R	atio	Weight	
Study	Yes	No	Yes	No			71	with 95%	6 CI	(%)
Cohort										
Choi 2020	1	5	41	34	70	-	-	0.17 [ 0.02,	1.49]	47.97
Lee 2015	4	5	6	62				- 8.27 [ 1.74,	39.31]	52.03
Heterogene	eity: τ <sup>2</sup>	= 6.	70, I <sup>2</sup>	= 87.65%, H <sup>2</sup> = 8.10			-	-1.27 [ 0.03,	58.25]	
Test of $\theta_i$ =	θ <sub>j</sub> : Q	(1) =	8.10,	p = 0.00						
Overall								-1.27 [ 0.03,	58.25]	
Heterogene	eity: τ <sup>2</sup>	= 6.	70, I <sup>2</sup>	= 87.65%, H <sup>2</sup> = 8.10	i.					
Test of $\theta_i =$	θ <sub>j</sub> : Q	(1) =	8.10,	p = 0.00	Higher in	n non-mut	Higher in mut			
Test of grou	up diff	eren	ces: C	$Q_{\rm b}(0) = 0.00,  p = .$				_		
					1/32	1/4	2 1 <sup>6</sup>			
Random-effe	ects R	EML	mode	el						

# Figure S249. Forest plot of comparison SLC29A1 2 mutant alleles vs wild-type, outcome: Total hematologic AE

Mut Non mut			mut							Odds Ra	atio	Weight	
Study	Yes	No	Yes	No							with 95%	6 CI	(%)
Cohort													
Choi 2020	19	31	41	34		14					0.51 [ 0.24,	1.05]	51.58
Lee 2015	15	38	6	62				13	_		- 4.08 [ 1.46,	11.42]	48.42
Heterogene	eity: τ <sup>2</sup>	= 1.9	96, I <sup>2</sup>	= 90.44%, H <sup>2</sup>	= 10.46				-		1.39 [ 0.18,	10.71]	
Test of $\theta_i =$	θ <sub>j</sub> : Q(	(1) =	10.46	6, p = 0.00									
Overall											1.39 [ 0.18,	10.71]	
Heterogene	eity: τ <sup>2</sup>	= 1.9	96, I <sup>2</sup>	= 90.44%, H <sup>2</sup>	= 10.46								
Test of $\theta_i =$	θ <sub>j</sub> : Q(	1) =	10.46	s, p = 0.00	Hi	igher in i	non-mut	Higher	in mut				
Test of grou	up diff	eren	ces: C	$Q_{\rm b}(0) = 0.00,  \mu$	=.								
						1/4	1/2	1 2	4	8			

Random-effects REML model

Figure S250. Forest plot of comparison mutated SLC29A1 vs wild-type, outcome: Total hematologic AE