Peer Review File

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Review Comments

Reviewer A

In this review Gmeiner provides an update of fluoropyrimidine pharmacogenetics with a focus on risk variants in DPYD. Overall, the manuscript is well written and informative. My main criticism is that the field has been extensively covered in the past and that it is difficult to see what this review adds on top of the pre-existing literature.

I thus provide some comments that might be considered to increase the novelty of the review that hopefully might contribute to distinguish the review:
- The work does not seem to be a systematic review. This is fine; however, a methods section is then not required.
I agree this is not a systematic review and I have removed the Methods Section

- The review focuses almost exclusively on the use of FPs for colorectal cancer. While I agree that this indication is the most common for FP use, FPs are also relevant in other solid tumors, such cancers of the upper GI tract, pancreatic cancer and basal cell carcinoma (as the author also correctly states). I would thus recommend to include also those cancers in the section "Patient populations for whom FP-based regimens are a preferred option" or to make clear that the review focuses specifically on CRC.
I agree and have added additional information on p. 4 lines 52-54, line 61, line 6, p. 5 lines 70,71; p.6 line 110-113 to address this.

- "An estimated 2 million cancer patients are treated with FP drugs annually (24)" – While this is likely correct, the reference is not adequate. Please exchange/update.
I agree and replace the reference with 3 new references (4-6) on p. 3 line 50.

- “certain populations such as African-Americans are at especially high risk to drug-induced toxicities” – suggest to rephrase to “individuals of African descent”, as the increase in toxicity risk will not be limited to America.

Change made as recommend on p. 7 line 145-146.

- Is the inverse also true, i.e. is the toxicity risk decreased in individuals of Asian descent? It would be informative if the author could provide an update.

I was unable to locate peer-review publications describing altered toxicity risk in Asian populations but added a citation form a 2015 meta-analysis indicating Asisan populations have an altered spectrum of DPYD polymorphisms on p. 7 lines 145-146.

- The author repeatedly highlights miR27 as an additional factor contributing to DPD variability. This is very interesting and valid. Are there other such examples?

Other factor of interest I could identify evidence for in the literature are p53, TYMS, ENOSF1 for which I added information and references p. 7-8 lines 149-156

- An additional short section providing an overview of other genetic factors beyond DPYD, such as TYMS and ENOSF1, would be interesting.

I added this information on p7-8 lines146-149.

- Please provide information regarding the current state of the implementation of DPYD genotyping in clinical practice. Where is pre-emptive testing adopted? At the level of hospitals or state/national healthcare programs?

National level intervention in the Netherlands and UK is implemented and further detail on p. 8 lines 163-172 while French guidelines are described on p. 12 line 261-262

Reviewer B

This manuscript describes the association between DPYD polymorphisms and the development of toxicities and summarizes methods for estimating patient phenotypes and the usefulness of TDM, but the new information defined in this review over

previous work is rather limited, evoking a low level of enthusiasm from this reviewer.

1. There are few descriptions about “genetic factors” compared to TDM. The author should describe the major guidelines for DPYD polymorphisms. The author cites the UK chemotherapy board as the recommendation of genetic screening for the four DPYD risk variants, but Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) guidelines should be mentioned.

I added a section on p. 8 lines 163-172 describing guidelines from the CPIC and DPWG and added additional information and citation related to guidelines for DPYD polymorphisms.

2. More explanation on the relation of miR27a polymorphism and development of toxicities should be mentioned.

I included additional information on p.7 lines 149-152.

3. In Table 1, DPYD*2A and DPYD*13 are defined as CPIC codes, but they are not defined as CPIC codes in the CPIC guidelines. The author should correct to the allele name.

I changed Table 1 heading to “DPYD variant” and NCBI SNP reference, which is in agreement with current references publishing similar information.