Reviewer’s report

Title: Genotyping Panel for Assessing Cancer Risk and Response to Chemotherapy

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Reviewer: Federico Innocenti

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This study has used a SNPlex platform to genotype 432 selected candidate SNPs in 160 genes implicated in the response to cancer chemotherapy and cancer risk. With this study, the authors demonstrate that about 95% of the SNPs can be genotyped with this platform. The authors also show that indels and other variants that cannot be detected with the SNPlex method are suitable to be genotyped with other methods. SNPlex and the other methods were used in patients enrolled in a phase I trial and in colorectal cancer patients. Several comments should be assessed by the authors.

1) The main purpose of this study is not entirely clear. It seems that several are the aims of this study, including 1) to create a platform suitable to genotype several variants, 2) to select variants that play a role in cancer pharmacogenetics and cancer risk from existing published data, 3) to identify variants that are associated with cancer risk (as a pilot study, as stated at page 20), or a combination of 1), 2), 3). The aim(s) should be clearly specified.

2) The inclusion of the genotyping data from 90 colorectal cancer patients and 39 phase I patients does not seem to provide useful information, for several reasons. First, this study is not designed to identify cancer risk genes, because is not prospectively designed, there is not a matched control arm and there is no control for variables of patient characteristics and environmental factors (diet, smoking etc.), which have not been reported in this study. Hence, the comparison of allele frequencies from SNPs reported in the CEPH HapMap (and other databases) should be removed from this manuscript. In addition, the genotyping information from 39 phase I patients treated with flavopiridol does not add useful information if the genotype-phenotypic association data will be published in a different publication (as stated at page 19). Instead of germline DNA collected from cancer patients, this platform should have been validated using unrelated HapMap samples. In this study, the use of germline samples from cancer patients serves purely to the purpose of determining the success rate of genotyping.

3) Hardy-Weinberg equilibrium should be analyzed for each SNP. Were positive control samples used for the alleles not included in the SNPlex?

4) In addition to the criteria used by the authors, a htSNP selection from the HapMap data should have been used from the 3 ethnic groups (taking into
account potential overlaps among SNPs in different ethnicity). The selection criteria in this paper do not utilize a haplotype-based approach, and this should be highlighted as a limitation of the study in the discussion. A combined approach of htSNPs and individual variants that are shown to be functional (at in vitro and/or clinical level) and not tagged by the htSNPs would accurately capture all important information from these genes.

5) For the selection of candidate SNPs, more information should be provided. For example, did the authors only choose studies that were independently replicated? Why the authors did not take advantage of the candidate genes from genome-wide studies of cancer risk? Concerning the SNPs selected from dbSNP, were they validated? Which transporter databases were used (PharmGKB is not a database for transporters)? How redundant SNPs (due the LD) were excluded before the inclusion in the final list?

6) The data in Fig. 3 and the discussion from pages 22 to 26 are suitable for a nice review paper, but not for the purpose of this publication.

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests