Reviewer's report

Title: Implementation of genotype-guided dosing of warfarin with point-of-care genetic testing in three UK clinics: a matched-cohort study

Version: 0 Date: 28 Feb 2019

Reviewer: Thomas M. Polasek

Reviewer's report:

This manuscript by Jorgensen et al. describes the results of implementing genotype-guided dosing of warfarin in UK clinics compared with traditional dosing, showing that on average, anti-coagulant control was superior using GGD and that, overall, the GGD approach was acceptable to patients and anti-coagulation nurses. The manuscript is well written. I have the following comments for the authors to address.

1. Methods, page 6 lines 4-6. Please show in brackets the eGFR cut-offs for stage 4 and 5 CKD.

2. Results, page 9, line 47. Start the sentence with the number 222 written-out.

3. Table 1, page 21 Baseline characteristics and page 6 lines 15-16. I am confused about where these patients have been referred from - directly from hospital, from the GP, or cardiologist? The baseline INRs in the table show that they are already anti-coagulated, but the referrals are for commencement of warfarin. Also, some patients have had DVTs and PEs, so their clinical journey to the anti-coagulant clinic is expected to be different to those newly diagnosed with AF i.e., they will have been treated in hospital I presume. Since the baseline INRs in table 1 show that patients were already anti-coagulated, some extra information on these points would be appreciated.

4. Methods, how many patients had previously been on a DOAC before the clinical decision was made to change to warfarin?

5. Results, page 12. Please define LGC.

6. Discussion - although the title and majority of the manuscript uses GGD, which I am happy to be left alone, the discussion would benefit from highlighting to readers that CYP2C9 and VKORC genotype are only two covariants used in the dosing algorithm to guide dosing. What are the contributions of genetic vs. non-genetic covariants to the
overall benefits i.e., if only on the non-genetic covariants were considered, how would this perform? This paper seems like a nice example of model-informed precision dosing because all the important covariants that influence warfarin PK/PD are used, so the branding as simply 'genotype-guided dosing' could be considered a little misleading. Please comment.

7. Discussion page 13, lines 41-45. This sentence on a future paper should be deleted since the paper is not accepted for publication.

8. Discussion page 14, lines 32-34. Again, please delete the last sentence on a possible future publication.

9. Reference 12 is not a proper reference. Please delete or provide the full citation.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

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I am able to assess the statistics

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