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Dear Professor Palmirotta

Thank you for reviewing our manuscript (ID 86616) titled: 'Clinical utilities and end-user experience of pharmacogenomics: 39 months of clinical implementation experience in an Australian hospital setting'. We have addressed the reviewer's specific comments as listed below;

I) Introduction needs to be more concrete (like last two paragraphs of your current introduction) in order to fit within the scope and aim.

✓ Refer to highlighted lines 74 – 80

In Australia, only two genotypes are covered by the national Medicare scheme, namely, *HLA-B*5701* for abacavir, and *TPMT* for thiopurine drugs. However, multigene panel pharmacogenomics testing is neither publicly-funded by Medicare nor covered by private health insurance schemes. Patient-pay testing can be requested by a specialist or a general practitioner. Most clinical genetics services in Australia, which are funded by State-operated public hospitals, do not routinely offer multigene panel pharmacogenomics testing, with the exception of St Vincent's Hospital Sydney which is the setting of our investigation.

II) Description of Australian setting in general (but with a special highlight on St Vincent's Hospital Clinical Genomics Centre) is needed as well as info on principle of referral to PGx and reimbursement as well.

✓ Refer to highlighted lines 74 – 80

In Australia, only two genotypes are covered by the national Medicare scheme, namely, *HLA-B*5701* for abacavir, and *TPMT* for thiopurine drugs. However, multigene panel pharmacogenomics testing is neither publicly-funded by Medicare nor covered by private health insurance schemes. Patient-pay testing can be requested by a specialist or a general practitioner. Most clinical genetics services in Australia, which are funded by State-operated public hospitals, do not routinely offer multigene panel pharmacogenomics testing, with the exception of St Vincent's Hospital Sydney which is the setting of our investigation.

III) Bearing the results obtained you need to discuss on what to do to make a change. Use it to tailor the stewardship activities and consider to propose a plan within your discussion section.

✓ Refer to highlighted lines 370 – 380

We identified a lack of education and training, and a lack of clinical decision aids and support as the major barriers to routine adoption of pharmacogenomics among our clinician cohort who was involved in the care of patients who underwent pharmacogenomics testing. The majority of our clinicians have not completed any formal training in pharmacogenomics; have expressed complexities of incorporating results in their patient care; and have expressed the need for support from trained health professionals to manage these results. Similar to initiatives in various healthcare settings in the United States[26-28], our findings could inform an interdisciplinary care model approach in Australia. Such an approach would incorporate the expertise of genetics professionals, clinical pharmacologists and pharmacists providing training and education to primary care providers, the patient's nominated specialist and/or pharmacist[29].

IV) Discuss on the role of clinical pharmacologists and pharamacogeneticists in your country when it comes to PGx interpretation as well as education (of other doctors) in general.

✓ Refer to highlighted lines 376 – 380

our findings could inform an interdisciplinary care model approach in Australia. Such an approach would incorporate the expertise of genetics professionals, clinical pharmacologists and

pharmacists providing training and education to primary care providers, the patient's nominated specialist and/or pharmacist[29].

V) Compare your commercial gene panel with relevant pharmacogenes (included in the guidelines) according to CPIC and DPWG. Consider to make a table comparison between your, CPIC and DPWG panels, etc.

- ✓ Refer to highlighted lines 106, 110 - 113.

This gene panel includes most pharmacogenes with high association evidence according to Clinical Pharmacogenetics Implementation Consortium, Dutch Pharmacogenetics Working Group and Pharmacogenomics Knowledgebase[18].

- ✓ The authors have considered the suggestion of a table comparison but decided it to be outside of the scope of this manuscript, which is a retrospective audit of the end-user experience rather than a prospective evaluation of pharmacogenomics gene panels.

VI) Did you validate the instrument used (survey)? Report the Cochrane alpha for the survey!

- ✓ Refer to highlighted lines 140 – 145, 407 – 409

Both surveys were pilot tested by a focus group of five laypeople randomly identified from investigator's peers and five clinicians who were randomly identified through St Vincent's Hospital network, who were representative of our intended survey respondents. Members of the focus groups were provided with written instructions on how to review and test the survey and their feedback was sought regarding clarity, comprehension, functionality of the branching logic and the duration of time taken to complete the survey.

As a Cronbach's Alpha Test was not performed to assess the reliability or internal consistency of the survey questions these surveys were not considered validated[34].

VII) Comment on response rate! Also have you performed the power analysis to determine the minimal sample size? Also rate your objectives on primary (used for power analysis) and secondary!

- ✓ Refer to highlighted lines 401 – 404

Our survey response rate of 31% from patients and 19% from clinicians in a sample size smaller than 500 can be considered sufficient to conclude estimates but is still below the average online survey response rate of 44.1% and is therefore best considered as observatory and exploratory

- ✓ This is a descriptive study on perceptions and attitudes and a power analysis was not required.

VIII) How many clinicians were invited to participate? Cite the response rate in order to present interest in PGx field indirectly. To comment, I believe that sample size for this concrete endpoint is to small and results are just observatory/exploratory unfortunately. Did you ask all clinicians (who referred their patient on PGx, analysed in your study, N=100)?

- ✓ Refer to highlighted lines 213 - 216, 401 - 404, Table 1

A total of 89 clinicians, including 29 subspecialist clinicians and 60 General Practitioners, involved in the care of the same patient cohort were identified and invited to participate in the clinician survey. Of those invited, 17 clinicians (19%) responded and completed the survey.

Our survey response rate of 31% from patients and 19% from clinicians in a sample size smaller than 500 can be considered sufficient to conclude estimates but is still below the average online survey response rate of 44.1% and is therefore best considered as observatory and exploratory

IX) If I were you, I would mention the characteristics and competencies for all 5 laypeople and 5 clinicians. Was some sort of training provided to reach the uniformity?

- ✓ Refer to highlighted lines 140 – 145

Both surveys were pilot tested by a focus group of five laypeople randomly identified from investigator's peers and five clinicians who were randomly identified through St Vincent's Hospital network, who were representative of our intended survey respondents. Members of the focus groups were provided with written instructions on how to review and test the survey and their feedback was sought regarding clarity, comprehension, functionality of the branching logic and the duration of time taken to complete the survey.

X) Within table 1 you should include N and % where applicable and also make the table components and subsections uniform!

- ✓ Refer to Table 1

XI) Did you use statistical package in Microsoft Excel or just a simple regular analysis package?

- ✓ Refer to highlighted 157 – 158

The survey data were exported from REDCap and analysed using a regular analysis Microsoft Excel (Microsoft Corporation, 2016, Version 16.0) package.

XII) Have you used KS test in order to check for normality of distribution?

- ✓ As a descriptive study the KS test was not required to check for normality of distribution

XIII) More strengths and limitations need to be stated within the discussion section.

- ✓ Refer to highlighted lines 370 – 375, 389 – 395, 401 - 404

We identified a lack of education and training, and a lack of clinical decision aids and support as the major barriers to routine adoption of pharmacogenomics among our clinician cohort who was involved in the care of patients who underwent pharmacogenomics testing. The majority of our clinicians have not completed any formal training in pharmacogenomics; have expressed complexities of incorporating results in their patient care; and have expressed the need for support from trained health professionals to manage these results.

To date, economic studies have suggested that pharmacogenomics testing can be cost-effective and that the cost of testing could be offset by its cost-savings from reduced time wastage on medication trial-and-error, enhanced therapeutic response, and mitigation of adverse drug reactions[30-32]. Future studies that explore the cost implications of pharmacogenomics-informed prescription should capture data on, not only individual patients, but also the overall healthcare system, to inform public funding for mainstream implementation in Australia.

Our survey response rate of 31% from patients and 19% from clinicians in a sample size smaller than 500 can be considered sufficient to conclude estimates but is still below the average online survey response rate of 44.1% and is therefore best considered as observatory and exploratory

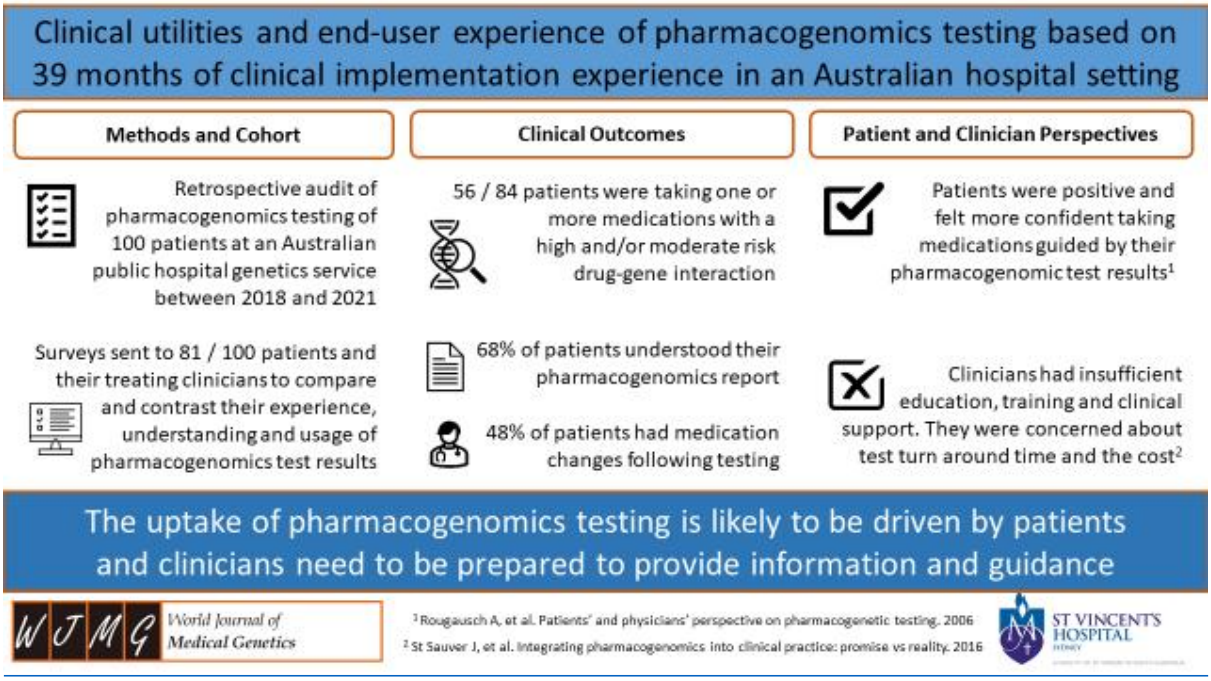
XIV) Also comment on your sample size as well on external validity (compare Australian and other settings - important!).

- ✓ Refer to highlighted lines 358 – 360

This is a valuable finding as there are no recent studies looking at the end users perception and understanding of pharmacogenomics using the current multi-variant testing technology.

XV) It would be nice if you could include the graphical abstract.

- ✓ Inserted at line 19



As requested the following documents are to be provided:

1. Revised manuscript
2. Biostatistics Review Certificate
3. Institutional Review Board Approval Form
4. Signed Informed Consent Forms
    a. Statement by the coordinating principal investigator regarding implied consent
    b. Patient Information Sheet
    c. Clinician Information Sheet

Please do not hesitate to contact me if you require any other information. I look forward to hearing the outcome of the review.

Yours sincerely,

Kathy Wu, MBBS, MMed, FRACP, HGSA (Clin Genet)