PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A transformative translational change programme to introduce genomics into healthcare: a complexity and implementation science study protocol
AUTHORS	Taylor, Natalie; Best, Stephanie; Martyn, Melissa; Long, Janet; North, Kathryn; Braithwaite, Jeffrey; Gaff, Clara

VERSION 1 – REVIEW

REVIEWER	Gabrielle Bertier Center for Genomics and Policy, McGill University Human Genetics Department, Montreal, Canada
REVIEW RETURNED	23-Jul-2018

GENERAL COMMENTS	- Abstract: Stage 2b and stage 3 could be briefly mentioned in the abstract. Right now it is mentioned only in the Discussion section and this can get the reader confused as to why authors focus on stage 2a only. The sentence: " Study stages '1' and '2a' represent Hybrid Model 1 and are the focus of this protocol. Nested within Hybrid Model 1 and applied across both stages [...]" is quite cryptic before reading the methods section. It should be simplified/clarified in the abstract. - Line 1 p. 5 : "The speed of scientific advances" I'm not sure it's the speed of the advances per se, rather than the complexity and uncertainties of scientific findings which causes an issue in implementation. - P. 11, line 13: "Given this is a test of diagnostic capability, as opposed to a treatment intervention" You mentioned p. 6 line 17 that "The first five Melbourne Genomics flagships have already undergone a formal evaluation to assess the effectiveness of genomic sequencing for the purposes of early detection, treatment and, where possible, prevention of major disease". Please clarify if treatment interventions resulting from genomic tests are considered in the implementation evaluation. - P.14 line 6: please provide more details on the expert resource group. How many participants from each stakeholder group? - p. 17 line 12: "Interview data will be audio recorded, fully transcribed and entered into NVivo 11 " it is unclear whether you will only recode existing interviews or perform new interviews in stage 1. Please clarify. You should also include a description of the limitations of recoding interviews performed several years ago, especially in this fast-evolving field.

	- More details should be included regarding: how many participants will be interviewed in each stakeholder group? How many participants in the focus groups? How will you ensure that all 29 Flagships are represented? What quantitative data will be collected? How will it be analysed ? Which statistical methods will be used? - Table 1, line 3: "Whilst the necessary steps must be taken to start and complete the process to finalise and communicate any given genetic diagnosis..." Which steps? Please specify. Grammar and ponctuation should be verified in this table. There are a few typos. - Will the Ethical approval and "Governance approvals" mentioned in the ETHICS AND DISSEMINATION section be available in annex / as supplementary materials? - Overall questions: Could you comment (maybe in the discussion section) on the generalizability of the results in health systems outside of Australia? Could you provide more details on the relationship of this study with the Actual Melbourne Genomics and Australian Genomics program ? Is this research embedded within the funded program? Although this information is detailed in Figure 1, More details should be provided in the text on the clinical contexts that the flagships focus on. The discussion section should include a descriptions of the limitations of this study. - Figure 1: What do the stars refer to? Please provide a timeline with dates for Stages 1-3 studies. - Figures 1, 4 and 5 seem to be taken from other sources/publications. How will you ensure copyright for this protocol publication? - Supplementary file 4: what do the XXX represent?

REVIEWER	Alex Ramsey Washington University School of Medicine, USA
REVIEW RETURNED	20-Aug-2018

GENERAL COMMENTS	This is a well-written study protocol outlining novel methodological approaches to examine 29 health systems in Australia integrating genomics into practice, and combining these data to co-design and test an implementation toolkit for translating genomics into healthcare. The use and integration of multiple theoretical frameworks is appropriate, and the incorporation of complexity, systems, and implementation science approaches are well-justified and important for the field of genomics translation. In general, the analytic plan reflects a sound mixed methods approach that is both comprehensive and rigorous. Despite the many strengths of the current manuscript, there are several issues that should be further addressed or improved, as follows: 1. The study protocol has implications for several broad approaches, such as "designing for dissemination" and "learning healthcare systems", which could be made more explicit in the manuscript. Relatedly, co-design with clinicians reflects an important approach to designing for dissemination. However, the manuscript would benefit from referencing literature about co-design and related approaches to intervention development in the Introduction.

	2. There needs to be consistency in terminology for key components of the study protocol. For instance, foundation intervention package, implementation toolkit, and implementation strategy to be co-designed are among the descriptors that may all be referencing the same thing. 3. There needs to be greater specification for the process by which data collected in earlier stages will inform the design of the implementation toolkit. The logic model in Figure 3 is emblematic of this issue. The set of activities reflect rigorous methods, and the outputs (e.g., identification of target behaviors for change, service provision pathways, and system and individual behavioral barriers and facilitators) are important; however, the outcomes remain at such a high level (i.e., evidence base to inform development of intervention package) that it becomes difficult to envision this developmental process. 4. It is somewhat unclear how the observation of these 29 Flagships will yield a generalizable model for organizations that are not early adopters, which characterize the bulk of organizations (and patients) that will eventually stand to benefit from genomic sequencing. What actions and assurances can be made to strengthen generalizability beyond the Flagships? 5. As reflected in the interview protocols, genomic innovations are ever-evolving as the evidence base advances rapidly. Some processes may be more non-linear than what is depicted in the Translation Phase model (Figure 5). Relevant concepts of adaptability and dynamic sustainability (Chambers et al., 2013) may be useful in supplementing more linear frameworks. 6. Although a limitation is listed in the bullet-pointed "strengths and limitations" section, limitations of the study protocol are largely omitted from the manuscript. As a specific potential limitation, the Stage 1 interview questions were apparently not grounded in the Theoretical Domains Framework, yet the coding tools were. The appropriateness of the TDF coding tools for these data should be addressed or acknowledged as a limitation. 7. The outcomes of the planned Stage 3 need to be stated more explicitly in the manuscript and Figure 1. 8. In Figure 2, how do each of the "principles of complexity" map on to the "broad elements of complexity" and the "frameworks to understand/respond to complexity"? 9. Quantitative data are said to be included as part the process mapping and clinical audit methods. In this case, detail is needed on statistical analyses planned for these data. 10. The StaRI checklist was mentioned once (on Page 13) but not depicted as a table or expanded upon in text. 11. As a minor point to consider, this reader was unfamiliar with the term "at the coal-face". 12. A general timeline of the study was found in Figure 1, but the dates of the study do not appear to be in the manuscript itself.

	13. For enhanced impact of this study, dissemination efforts outside of traditional academic forums should be considered. For instance, the Translational Science Benefits Model (Luke et al., 2018) could provide a very useful framework for attempting to maximize the health and societal benefits and impact of this study.

VERSION 1 – AUTHOR RESPONSE

Reviewer's comment	Response	Page
Reviewer 1: Gabrielle Bertier		
1. Please leave your comments for the authors below - Abstract: Stage 2b and stage 3 could be briefly mentioned in the abstract. Right now it is mentioned only in the Discussion section and this can get the reader confused as to why authors focus on stage 2a only.	Thank you for pointing this out. We have amended the abstract to address this request: *Study methods to simultaneously test the comparative effectiveness of genomic testing and the implementation toolkit (Stage 2b), and the refined implementation toolkit while simply observing the genomics intervention (Stage 3), are summarised.*	2 Line 22
2. The sentence: " Study stages '1' and '2a' represent Hybrid Model 1 and are the focus of this protocol. Nested within Hybrid Model 1 and applied across both stages [...]" is quite cryptic before reading the methods section. It should be simplified/clarified in the abstract	Thank you for raising this – we agree the sentence structure is confusing and have re-worded: *Stages '1' and '2a' (representing Hybrid Model 1) are the focus of this protocol. The Translation Science to Population Impact (TScImpact) framework is used to study policy decisions and service provision, and the Theoretical Domains Framework (TDF) is used to understand individual level behaviour change; both frameworks are applied across Stages 1 and 2a.*	2 Line 12
3. - Line 1 p. 5 : "The speed of scientific advances" I'm not sure it's the speed of the advances per se, rather than the complexity and uncertainties of scientific findings which causes an issue in implementation.	We agree the wording here could be refined and have incorporated the following: *The complex and unpredictable nature of scientific advances, however, has exceeded the ability of health systems to establish what the ideal conditions, systems, and behaviours ought to be for using genomics in complex healthcare settings.*	4 Line 6
4. - P. 11, line 13: "Given this is a test of diagnostic capability, as opposed to a treatment intervention" You mentioned p. 6 line 17 that "The first five Melbourne Genomics	We apologise for the confusion and have clarified wording on P.11 here:	11 Line 16

	flagships have already undergone a formal evaluation to assess the effectiveness of genomic sequencing for the purposes of early detection, treatment and, where possible, prevention of major disease". Please clarify if treatment interventions resulting from genomic tests are considered in the implementation evaluation.	*Given this is a test of diagnostic capability (which may lead to more personalised treatment interventions, as opposed to being a treatment intervention in of itself).* To clarify, the assessment of the impact of genomic testing on subsequent treatment decisions/interventions will be incorporated into the Stage 2b exploration of implementation outcomes (i.e., using the Proctor framework) and Stage 3 test of the implementation intervention. The general approaches taken to develop tools and formally measure implementation outcomes have been more explicitly detailed as part of this revision: *Quantitative and qualitative measures for assessing implementation effectiveness will be explored and developed[50] (Figure 1)…* And *…Following recommendations by Curran and colleagues,[25] summative outcomes – including adoption/uptake of the clinical intervention, process measures, and quality measures – will be assessed using data collection tools and approaches specifically designed for measuring implementation outcomes developed in Stage 2b[50] (see Figure 1).*	28 Line 8 Line 21
5.	- P.14 line 6: please provide more details on the expert resource group. How many participants from each stakeholder group?	We have incorporated information about the expert resource group and refer to an additional table for details: *Participant identification and data analysis will involve an expert resource group of multi-disciplinary research, clinical, and contextual expertise (Table 2) for interpretation and clarification of findings, consisting of experienced clinicians and researchers, each*	14 Line 11

	bringing academic and/or contextual knowledge from participating sites.	
6. - p. 17 line 12: "Interview data will be audio recorded, fully transcribed and entered into NVivo 11 " it is unclear whether you will only recode existing interviews or perform new interviews in stage 1. Please clarify. You should also include a description of the limitations of recoding interviews performed several years ago, especially in this fast-evolving field. - More details should be included regarding: how many participants will be interviewed in each stakeholder group? How many participants in the focus groups? How will you ensure that all 29 Flagships are represented? What quantitative data will be collected? How will it be analysed ? Which statistical methods will be used?	We apologise for the confusion here. Existing interviews will be recoded in stage 1. No new interviews will be undertaken in stage 1. All further interviews/focus groups undertaken will be associated with stage 2a. We have included a sentence noting the limitations of recoding interviews performed several years ago: *This study is not without limitations. First, recoding interviews undertaken in 2015 as part of Stage 1 may not remain entirely representative of stakeholder perceptions that exist at present. However, these views may be representative of individuals based at new sites which have not yet been exposed to genomic sequencing.* We have included some addition information in the text to indicate how many participants have been approached for the interviews in Phase 2a. *a) Service provision pathway participants: A total of 37 decision-makers and stakeholders (both clinical and administrative,) who play a key role in either flagship leadership, funding and financing strategies, genomic testing characteristics and costs, organisational and community factors or policy) who have been identified as fulfilling the inclusion criteria across the flagships and states will be invited to participate in an interview.* *b) Clinical process delivery participants: A total of 27 clinical non-genetics medical specialists (e.g., oncologists, neurologists,) who have been identified as fulfilling the*	29 Line 7 18

	inclusion criteria across the flagships and states will be invited to participate in an interview. *Across both participant groups, up to 12 people will be invited to participate a focus group to be held in each state (i.e., Victoria, Tasmania, New South Wales, and South Australia, and Western Australia). The participants invited will depend on the findings from the individual interviews.* With regards to quantitative data, the level of detail available in each site for clinical practice data is highly variable. Therefore, we plan to compute descriptive statistics, proportions, and timeframes between steps in clinical processes, and match this information, where available, to the relevant steps in the process map to highlight gaps or bottlenecks. We do not envisage a sophisticated statistical approach to the analysis of the clinical audit data. We have added this to the manuscript: *Clinical audit data analysis will consist of computation of descriptive statistics, proportions, and timeframes between steps in clinical processes. This information, where available, will be matched to the relevant steps in the process map to highlight gaps or bottlenecks.*	Line 21 25 Line 16
7. - Table 1, line 3: "Whilst the necessary steps must be taken to start and complete the process to finalise and communicate any given genetic diagnosis..." Which steps? Please specify. Grammar and ponctuation should be verified in this table. There are a few typos.	We apologise that this is confusing and have attempted to provide some context-specific examples to aid understanding. *Whilst the pathway that must be taken to complete the process for any given genetic test is generally linear, the interactions within and between each stage are non-linear (e.g., within the decision about which test is most appropriate for a patient, there is formal and informal discussion between clinicians and clinical geneticists about the appropriateness of genomic testing and the area of focus required), and iterative (e.g., first analysis of*	Table 1 Page 12

	the results may prompt re-examination of the clinical picture and alter decisions about the focus of the genomic analysis). Furthermore, the exploratory nature of Flagships under a research program introduces further ambiguity (e.g., around future funding or clinical utility of genomic testing in that condition) We have also been through the entire table and corrected grammar.	
8. - Will the Ethical approval and "Governance approvals" mentioned in the ETHICS AND DISSEMINATION section be available in annex / as supplementary materials?	We are happy to provide documentation regarding ethics approvals if this is standard procedure for the journal to publish. We have also clarified wording in relation to governance.: *Governance approval has been provided by Australian Genomics and Melbourne Genomics participating institutions.*	26 Line 23
9. - Overall questions: Could you comment (maybe in the discussion section) on the generalizability of the results in health systems outside of Australia? The discussion section should include a descriptions of the limitations of this study.	Thank you for encouraging us to elaborate on some of these important points. We have attempted to address some of these in the limitations section, which you recommend: We have included a limitations section, which now reads as: *This study is not without limitations. First, recoding interviews undertaken in 2015 as part of Stage 1 not remain entirely representative of stakeholder perceptions that exist at present. However, these views may be representative of individuals based at new sites which have not yet been exposed to genomic sequencing. Further to this, interview data from Stage 1a are being coded retrospectively using the TDF. While this will allow for identification of the issues most salient to interviewees, using the TDF to inform the interview schedule may have elicited information about barriers that are less spontaneously reported.[51] Moving forward beyond the original interviews, however,*	29 Line 7

Could you provide more details on the relationship of this study with the Actual Melbourne Genomics and Australian Genomics program ? Is this research embedded within the funded program? Although this information is detailed in Figure 1, More details should be provided in the text on the clinical contexts that the flagships focus on.	*interview schedules have been designed based on the TDF; this will not only enhance the evidence based by which information is collected, but may also allow for a comparison of answers provided by participants using both interview approaches. Finally, the study is based on the implementation of genomics into the Australian health system which, like any health system globally, has a unique composition and combination of idiosyncrasies in terms of infrastructure and funding. However, the varied nature of the Australian system (e.g., the combined private/public system) has its benefits in that it bares some resemblance with countries that have publicly funded (e.g., UK, Canada), but also with those operating insurance-based funding (e.g., Germany, USA). The novel approach taken here aims to enable the ability to identify generalisable interventions for addressing common challenges across contexts.* This study is embedded within and funded by the overarching Australian Genomics and Melbourne Genomics programs. We have included a new paragraph under 'Methods: Context" on the Australian health care system and made it more explicit that this research project is on the integration of genomics into the publicly funded hospitals. *Australian Healthcare and Genomics* *The Australian public health system is accessible to the public for free or at a lower cost through Medicare (funded by tax). The private system includes health service providers that are owned and managed privately, such as private hospitals, specialist medical and allied health, and pharmacies. The national health insurance scheme funded by the Australian Government currently funds few genetic and no genomic sequencing (whole exome/whole genome) tests. The largest expenditure in health - almost 40% - is on public hospital care, which includes some specialist genetic services and is the*	10 Line 17

	responsibility of the state governments. Genetic/genomic testing is funded through State government health budgets with availability of tests and funding varying across State. Governance structures exist to enable coordinated action and response to matters of national significance, such as genomics, across all Australian governments. Australian Genomics was established based on a national call from the National Health and Medical Research Council (NHMRC) for research on the application of genomics within the Australian public health system. Melbourne Genomics is funded by the Victorian Department of Health to support the integration of genomics in the Victorian health care system. The implementation science component of this work is embedded in the overall planned research program. *Flagships* *Under the Melbourne Genomics and Australian Genomics program of research, each of the 29 Flagships represents a test of the integration of genomics into the clinical settings within public hospital health care in parallel with usual (non-research funded) care, incorporating research consent processes into care processes delivered by genetic counsellors. The initial focus was on five conditions (childhood syndromes, neuropathies, hereditary colorectal cancer, focal epilepsy, acute myeloid leukaemia), with a total of 24 additional conditions planned for commencement over the following 2-3 years (Figure 1).*	
10. - Figure 1: What do the stars refer to? Please provide a timeline with dates for Stages 1-3 studies.	We apologise for the confusion. The stars were part of an earlier version of the diagram and have now been removed. We have further refined Figure 1 to add clarity on timeframes.	Figure 1
11. - Figures 1, 4 and 5 seem to be taken from other sources/publications. How will you ensure copyright for this protocol publication?	We have reviewed our figures and believe that we have applied research findings to generate our research plans, specifically: • Figure 1 refers to Curran's phases, but we apply it to our work. • Figure 4 (process map) is all our own work	Figures 1, 4, 5

	• Figure 5 refers to Spoth et al. but we apply it to our own work	
12. - Supplementary file 4: what do the XXX represent?	We apologise for the confusion. We have amended supplementary file 4 in the following ways: - Provided notes at the bottom of each table to explain what the 'XXX' represent. We have provided an additional table at the bottom of the clinician and service provision intervention development processes to show a hypothetical example of what resulting intervention strategies might look like based on using process mapping and focus group data to apply a theoretical approach to intervention design.	Supp file 4
Reviewer 2: Alex Ramsey		
This is a well-written study protocol outlining novel methodological approaches to examine 29 health systems in Australia integrating genomics into practice, and combining these data to co-design and test an implementation toolkit for translating genomics into healthcare. The use and integration of multiple theoretical frameworks is appropriate, and the incorporation of complexity, systems, and implementation science approaches are well-justified and important for the field of genomics translation. In general, the analytic plan reflects a sound mixed methods approach that is both comprehensive and rigorous. Despite the many strengths of the current manuscript, there are several issues that should be further addressed or improved, as follows:	We thank the reviewer for the positive comments on our manuscript.	
1. The study protocol has implications for several broad approaches, such as "designing for dissemination" and "learning healthcare systems", which could be made more explicit in the manuscript. Relatedly, co-design with clinicians reflects an important approach to designing for dissemination. However, the manuscript would benefit from referencing literature about co-design and related	Thank you for pointing out the need for additional evidence on co-design. We have attempted to address this comment by incorporating some of this literature into the introduction: *Furthermore, it has been argued that interventions to improve implementation of evidence into practice will be most effective*	5 Line 4

approaches to intervention development in the Introduction.	*when developed by those with local 'expertise' and tacit knowledge,[4-6] but which take account of evidence and external expertise.[7 8] In this paper, we outline a novel methodological approach, using complexity science, translation, and behaviour change frameworks, and co-design between healthcare professionals and stakeholders, and implementation and behavioural researchers, to study the integration of genomics into clinical practice as part of a national natural experiment, and develop a generalisable, evidence based package for implementation.*	
2. There needs to be consistency in terminology for key components of the study protocol. For instance, foundation intervention package, implementation toolkit, and implementation strategy to be co-designed are among the descriptors that may all be referencing the same thing.	Apologies for the confusion with these terms. We have amended the manuscript so that *'implementation toolkit'* is used throughout. Within the 'implementation toolkit' there will be *'implementation strategies'* and we have ensured this term is used in the relevant places in the manuscript.	
3. There needs to be greater specification for the process by which data collected in earlier stages will inform the design of the implementation toolkit. The logic model in Figure 3 is emblematic of this issue. The set of activities reflect rigorous methods, and the outputs (e.g., identification of target behaviors for change, service provision pathways, and system and individual behavioral barriers and facilitators) are important; however, the outcomes remain at such a high level (i.e., evidence base to inform development of intervention package) that it becomes difficult to envision this developmental process.	We apologise for the confusion. We have amended supplementary file 4 to provide an additional table at the bottom of the clinician and service provision intervention development processes to show a hypothetical example of what resulting intervention strategies might look like based on using process mapping and focus group data to apply a theoretical approach to intervention design. We have referred to this in the main text page 24 line 20.	Supp file 4
4. It is somewhat unclear how the observation of these 29 Flagships will yield a generalizable model for organizations that are not early adopters, which characterize the bulk of organizations (and patients) that will eventually stand to benefit from genomic sequencing. What actions and assurances can be made to strengthen generalizability beyond the Flagships?	Thank you for raising this. We have attempted to clarify our vision for the generalisable model we are aiming for: *The diversity of health professional disciplines, health care organisations, and clinical indications participating across the 29 Flagships (all of which are at different stages of implementation and involve a mixture of*	27 Line 18

	early, mid, and late adopters), will realise the ultimate goal of this work: to establish the 'ideal' and develop a generalisable model of implementation that future organisations can apply and tailor to their local contexts. The planned work for the remainder of this project will determine the finer details of this model, but the vision is for an interactive, theoretically underpinned, continuously refined toolkit informed by real-world data. This approach will enable diverse healthcare organisations at any stage of implementation to tailor their context-driven approach based on tried and tested intervention strategies used to address key challenges experienced by others.	
5. As reflected in the interview protocols, genomic innovations are ever-evolving as the evidence base advances rapidly. Some processes may be more non-linear than what is depicted in the Translation Phase model (Figure 5). Relevant concepts of adaptability and dynamic sustainability (Chambers et al., 2013) may be useful in supplementing more linear frameworks.	We would like to take an opportunity to explain the rationale for of our approach to the reviewer; we feel this may not be necessary to report in the manuscript: We used a participant-friendly version of the Spoth framework as part of the interview schedule as it was thought the complex diagram with many iterative loops may have been confusing or overwhelming for clinicians without any familiarity with these frameworks. We do acknowledge that processes are non-linear and the nature of the interview schedules allows for and encourages discussion about the iterative and convoluted nature of the processes being investigated. Furthermore, in our plans for analysis, we aim to take into account these factors. Whilst we have used the Spoth framework, we are open to assessing the relevance of other models, such as that of Chambers et al. (2013), to assist with interpretation and presentation of data, or to support intervention design by assessing the 'fit' across the practice setting and ecological system).	N/A
6. Although a limitation is listed in the bullet-pointed "strengths and limitations" section, limitations of the study protocol are largely omitted from the manuscript. As a specific potential limitation, the Stage 1 interview questions were apparently not	Thank you for pointing this out. We have added a limitations section, which includes the following information (in addition to two other key limitations suggested by reviewer 1): *Further to this, interview data from Stage 1a are being coded retrospectively using the TDF. While this will allow for identification of*	29 Line 11

grounded in the Theoretical Domains Framework, yet the coding tools were. The appropriateness of the TDF coding tools for these data should be addressed or acknowledged as a limitation.	*the issues most salient to interviewees, using the TDF to inform the interview schedule may have elicited information about barriers that are less spontaneously reported.[50] Moving forward beyond the original interviews, however, interview schedules have been designed based on the TDF; this will not only enhance the evidence based by which information is collected, but may also allow for a comparison of answers provided by participants using both interview approaches.*	
7. The outcomes of the planned Stage 3 need to be stated more explicitly in the manuscript and Figure 1.	Thank you for pointing this out. We have amended Figure 1 to incorporate some of this information. We have also included the following information in the text of the manuscript: *Following recommendations by Curran and colleagues,[25] summative outcomes – including adoption/uptake of the clinical intervention, process measures, and quality measures – will be assessed using data collection tools and approaches specifically designed for measuring implementation outcomes[50] (see Figure 1).*	28 Line 21
8. In Figure 2, how do each of the "principles of complexity" map on to the "broad elements of complexity" and the "frameworks to understand/respond to complexity"?	Thank you for allowing us to elaborate. We have added a note at the bottom of figure 2 to describe how the three columns relate: *The principles of complexity (column 2) overlap across all three broad elements of complexity (column 1). Using the proposed frameworks (column 3), we aim to understand the influence of, and interplay between, these principles across each broad element. More specifically, the effectiveness-implementation hybrid model is being applied to unpick the broad element of complexity related to clinical versus implementation effectiveness; the TSCimpact Model is being used to disentangle the broad element of complexity related to policy decisions and service provision; The TDF is being used to understand the broad element of complexity related to individual level behaviour change in a complex adaptive system.*	Figure 2

9. Quantitative data are said to be included as part the process mapping and clinical audit methods. In this case, detail is needed on statistical analyses planned for these data.	We apologise for the lack of clarity here. With regards to quantitative data, the level of detail available in each site for clinical practice data is highly variable. Therefore, we plan to compute descriptive statistics, proportions, and timeframes between steps in clinical processes, and match this information, where available, to the relevant steps in the process map to highlight gaps or bottlenecks. We do not envisage a sophisticated statistical approach to the analysis of the clinical audit data. We have added this to the manuscript: *Clinical audit data analysis will consist of computation of descriptive statistics, proportions, and timeframes between steps in clinical processes. This information, where available, will be matched to the relevant steps in the process map to highlight gaps or bottlenecks.*	25 Line 16
10. The StaRI checklist was mentioned once (on Page 13) but not depicted as a table or expanded upon in text.	We thank the reviewer for pointing this out. Given that the purpose of the STARI checklist is to encourage better reporting of the tests of implementation interventions, we have moved the reference to this tool to the outline of the plans for stage 2b presented in the discussion.	28
11. As a minor point to consider, this reader was unfamiliar with the term "at the coal-face".	We apologise for the confusion. After re-reading the sentence in the context of the paragraph, we thought the extra words were unnecessary so have removed them.	
12. A general timeline of the study was found in Figure 1, but the dates of the study do not appear to be in the manuscript itself.	We apologise for this oversight. We have made the timeframes in Figure 1 clearer, and have included timeframes in the sub-headings at the point that each study stage is introduced: ***Stage 1: Hybrid Model 1; post-implementation (2015-2017 timeframe)*** ***Stage 2a: Hybrid Model 1 pre, during, and post implementation (2018-2019 timeframe)*** ***Stage 2b; 2019-2020 timeframe*** ***Stage 3; 2020-2021 timeframe***	Various

13. For enhanced impact of this study, dissemination efforts outside of traditional academic forums should be considered. For instance, the Translational Science Benefits Model (Luke et al., 2018) could provide a very useful framework for attempting to maximize the health and societal benefits and impact of this study.	Thank you for flagging this recent model with us. We believe it is highly relevant to this work. This model provided us with another way to look at potential dissemination. Identifying benefits in this manner will open up more opportunities for dissemination. As a result, we have applied the key components of the model to the genomics context in Table 5 and referred to the model in the text in the abstract and ethics and dissemination section of the manuscript: Abstract: *Non-traditional academic dissemination methods (e.g., change in guidelines or government policy) will also be employed* Ethics and dissemination section: *In addition, the Translational Science Benefits Model[49] will be used to further understand the actual and potential value of genomics to society, and open up further opportunities for dissemination.* We also identified that this model would provide a useful link with Proctor's implementation outcomes, and have provided a hypothetical example of this, as outlined in the addition text: *Furthermore, these outcomes will be mapped against the TSBM[50] to demonstrate implementation outcomes across clinical, community, economy and policy contexts – a hypothetical example of this is provided in Table 5.*	3 Line 5 27 Line 4 28 Line 5

VERSION 2 – REVIEW

REVIEWER	Gabrielle Bertier Icahn School of Medicine at Mount Sinai Charles Bronfman Institute for Personalized Medicine, USA

REVIEW RETURNED	26-Oct-2018

GENERAL COMMENTS	The authors have addressed all comments and the article should now be ready for publication. I believe it will provide extremely valuable insights to the field and a great model to other sites who are implementing clinical genomics.

REVIEWER	Alex Ramsey Washington University School of Medicine, Department of Psychiatry St. Louis, MO 63110, United States
REVIEW RETURNED	03-Nov-2018

GENERAL COMMENTS	Thank you for addressing this reviewer's concerns in this revision.