nature portfolio

Peer Review File

Characterizing healthcare provider experiences delivering genomic testing in a Federally Qualified Health Center

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This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
Thank you for the authors for the opportunity to review their manuscript entitled “Characterizing healthcare provider experiences delivering polygenic risk scores (PRS) in a Federally Qualified Health Center.” The manuscript summarizes a mixed method approach employing surveys and interviews to characterize experiences of healthcare providers caring for low-resourced patients in a FQHC including in the provision of polygenic risk scores. Efforts to understand experiences of clinicians in low-resourced areas/clinics are necessary to understand strategies to implementing genomic medicine across the population. I have included comments below aimed at further strengthening this work. Comments are organized by section of the manuscript.

Introduction
1. The authors provide a useful description of FQHCs and then proceed to describe that “Research has also shown large racial and ethnic differences in levels of genomic-sequencing knowledge and trust in medical researchers (7).” Given there is not a discussion of the demographics of patients who seek care in FQHCs, this feels out of place. Further explanation and clarification would be useful.

2. Though not within FQHCs, there have been prior work examining healthcare provider experiences with PRS. It would be helpful for the authors to include that information as background.

Methods

3. I understand that interview guides are available upon request; however, it would be helpful to include the interview guides as a supplement. As described, it is not immediately clear how the questions incorporated genomic medicine or how the results flow from the question descriptions in the methods.

4. The authors note “The practice followed 20,474 active patients who receive care from 17 clinicians including physicians, nurse practitioners, physician assistants, and behavioral health providers.” Does this refer to eMERGE IV or the FQHC? I believe it is the former, but clarification could be useful to the reader. Further, if the former, how were only 17 clinicians engaged if 14 were recruited for this study from a single site? If that sentence does refer to the FQHC, then why is the number 100,000 patients in the study location section?

5. How were clinicians trained leading up to eMERGE IV and the implementation of PRS? This could have significant impacts on clinician experience. Though not the focus of this manuscript, description of the types of PRS results returned through eMERGE IV would also be useful in contextualizing the provider experience especially with relevance of results.

6. Study location – It would be helpful to provide additional details about the clinical population including the proportion who are LatinX, age range, sex, gender identity, etc.

7. In the Introduction, the authors note the limitations of PRS in non-European ancestral groups. How, if at all, was this considered when implementing PRS in a clinic population where were mostly LatinX?

8. The following sentence is difficult to follow: “Guided by Corbin and Strauss’ grounded theory approach (11), the study

interview transcripts using NVivo software according to a codebook (see Figure 1) identified in advance and iteratively updated.

9. In the results, clinicians discuss the use of monogenic results. Are monogenic results also provided via eMERGE IV or do clinicians have experience from prior efforts or clinical integration of testing? Describing this further in methods would be useful.

Results
10. It would be helpful to have clarity on the number of clinicians recruited for the study. Were all recruited and participating clinicians in internal medicine in the FQHC?

11. Do you have a sense of the number of PRS providers had received at the time of survey/interview? Understanding their adoption could be useful in contextualizing experience.
Are time constraints truly unique to the FQHC? This is a barrier across primary care.

Discussion
12. I am not convinced that the survey results convey an openness to PRS. They convey confidence in reviewing reports, value to care, and action for some patients among clinicians who were already integrating PRS into care due to eMERGE IV. They did not ask about acceptability or appropriateness of incorporating PRS or feasibility of doing so.

13. 3.5.3.4 – Illustrative quotes demonstrating "Results of PRS can complicate how providers are to provide
383 follow-up care, or not, to patients, particularly if results suggest that that care is
384 only offered outside of the FQHC" would be beneficial.

14. The discussion could benefit from further revisions to strengthen communication about the implications of these findings. For instance, what do clinician perspectives on utility tell us about PRS in general? Further, what does this mean for practices moving forward? The goal of this data collection is to inform implementation of genomic medicine across settings including those with low resources. How do the findings described advance that work?

15. Further how do these findings compare to other work characterizing provider perspectives (e.g., PMID: 39580561)? What is unique to a FQHC and what is not?

16. As for limitations, how do you think this work being conducted as part of eMERGE IV impacted the findings. Do you think they are generalizable to other FQHC?

Reviewer #2

(Remarks to the Author)
The authors present a nice study examining the experiences of healthcare providers in delivering polygenic risk scores to low-resourced diverse patients in a federally qualified health center. They make a strong case for why the work is needed, both due to a paucity of research into healthcare provider experiences but also the low-resource aspect. The work is well-conducted and reported and I believe offers some valuable insight into a timely issue.

Major concerns:
1. I'm not sure what the value is of a quantitative survey of 14 individuals. I would usually expect a mixed-methods study to recruit a much larger sample size to a survey to explore breadth of opinion or generalisable findings and then use the smaller interview cohort to probe deeper into more nuanced views and rich data. This is part of a larger study, why limit the survey just to the FQHC, it would be informative to see how these responses differ (or not) across the different settings of the study. If such an underpowered study is to be reported, I don't think it should form a headline finding in abstract for example that a majority are confident to guide health recommendations. This finding has too many caveats in this context.
2. It would be helpful to provide the interview guide. The brief description in methods seems to paint quite a one-sided picture of a negative line of questioning (ethical dilemmas, additional occupational burdens and potential moral injury) focussed only on challenges and barriers, however the codebook and indeed the results suggest a more balanced discussion.
3. Conflation between PRS and monogenic testing. The authors text and the participant quotes clearly demonstrate that there are some misunderstandings or lack of clarity around whether participants are discussing monogenic or PRS results. Some of the results text specifies PRS when the quotes themselves make no reference to this. How sure are the authors in each case that the participants do mean PRS? Perhaps the wider context makes this clear. The starkest example was the participant discussing reassurance in a patient with familial history of breast cancer. The description says that the provider explained how the PRS result provided emotional reassurance. If that's true, this is a significant misinterpretation of PRS clinical utility and possibly warrants more discussion (see point 4). However, if they are referring to the monogenic testing as the "clean genetic test" then that makes more sense but means PRS not discussed here. Given only 1 question on survey was specifically about PRS and the GIRA contains both mono and polygenic risk, I think more clarity is needed as to why this study only focusses on PRS and whether it's possible to disentangle
the two.
4. Related to the point above, the authors highlight in results and discussion about healthcare provider confidence in advising on healthcare recommendations. Given the conflation between mono and polygenic risk evident and the fact that

75% are confident to make recommendations despite 50% not being confident in their knowledge, I think more could be made in the discussion to highlight that self-rated confidence is not the same as competence. Many studies in genomics have asked healthcare professionals about their confidence in genomic knowledge and interpretation (almost always answered as high) but only when combined with questions assessing competence do we see that these are not well aligned.
5. The discussion is a little light on some of the underlying ethical considerations. Whilst highlighting participants concerns about financial barriers as well as only one participant being very confident these results would lead to healthcare changes and qualitative data pointing towards received results being largely already known, I was expecting a deeper discussion about cost-effectiveness and judicious use of resources. In fact, the authors suggest the generation of conversation itself, even if not about the genetic test may make this a promising tool particularly in low-resourced communities. I think that statement needs some unpacking. It may well be the case but it's not clear what the route to efficacy looks like to the reader. Also, the conflation here again between PRS and other genetic tests is unhelpful. Monogenic testing for highly penetrant conditions should not be evaluated alongside PRS for common conditions with more complex interventions. Also, the introduction raises the issue of European ancestry bias, the setting for this study is an FQHC which is described as being majority non-white European and yet none of the analyses or discussion points consider this issue. Some comment on this would strengthen the discussion further.

Minor concerns:

1. There are a number of acronyms which are not defined the first time they are used
2. eMERGE IV should be introduced and explained a little in the introduction.
3. RedCap needs citation if possible
4. In methods, the FQHC is described as having a majority of Latino patients, it would be helpful to quantify how many and what the breakdown is for other groups
5. It would also then be helpful to understand how the 20k people followed in eMERGE IV compare to the FQHC population demographically.
6. Over 10% double coded, with such small numbers it would be more informative to just say how many were double coded
7. Define GIRA reports
8. Numbering seems to have gone wrong in subsections
9. It would be helpful to attribute quotes to either pseudonyms, participant IDs or job roles. Job role was collected and is informative data for some of the viewpoints. As things stand, we have no idea whether 1 or all 14 participants have contributed to these exemplar quotes.
10. Underlining and spacing on sub-headings is inconsistent
11. Table 2 the survey has 100% of participants saying they went over GIRA with patients but next question has many reasons why they didn't, could the authors comment on this discrepancy?

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
Thank you for the opportunity to review the revised manuscript now titled "Characterizing healthcare provider experiences delivering genomic testing in a Federally Qualified Health Center." The manuscript summarizes a mixed method approach employing surveys and interviews to characterize experiences of healthcare providers caring for low-resourced patients in a FQHC including in the provision of polygenic risk scores. Efforts to understand experiences of clinicians in low-resourced areas/clinics are necessary to understand strategies to implementing genomic medicine across the population. The revised manuscript is much improved though there remain comments to further strengthen the manuscript.

1) The conclusion "The impact of genomic testing on families, particularly among the Latino patient population served at the FQHC, must also be considered before implementation." does not clearly flow from the exemplar quotes and results presented.
2) The introduction includes a summary of the study research findings that should be removed "Overall, providers reported feeling confident in their ability to deliver the intervention, all while relaying three major themes from their interviews. The three major themes that emerged were the unique context of a FQHC, providers' perceptions of genomic testing, and health systems management of genomic testing implementation."
3) The methods section could benefit from reorganization. Perhaps moving eMERGE and study location first in the methods followed by the remaining sections.
4) I appreciate the authors' careful consideration of reviewer comments and reworking the manuscript to focus on genomic medicine broadly. With that said, I think some additional edits may be helpful to further strengthen the manuscript.
- For example, it is clear that PRS is returned through eMERGE IV are monogenic results also returned? Without such context, this paper remains primarily a PRS manuscript with a few mentions of monogenic testing, but results may be most relevant to PRS. Provider experience with monogenic testing needs to be clear and the discussion should include further clarity that the results may primarily be representative of experience with PRS reports.
- What PRS are returned as part of eMERGE IV (e.g., obesity and breast cancer are mentioned)? Understanding what PRS

could be useful in contextualizing the utility results. For instance, a PRS for obesity may have less utility than other results.
- It would be helpful to understand whether themes occurred across PRS and monogenic testing. For example, only a single quote related to monogenic testing is noted for “Overall, providers did not report patient resistance to follow-up care plans resulting from genomic testing?
- Not all quotes include PRS vs monogenic context. This could be helpful to incorporate more fully (e.g., Provider 12 under Recommendations made by GIRA reports based on their patients PRS results can complicate how providers provide follow-up care when that care is offered outside of the FQHC. Some providers share how their shared decision making plays into effect here)
5) Did a single participant raise prior authorization concerns? If so, this is not sufficient for an included theme.

6) It is unclear how the following quote represents the described theme as it is a provider discussion of PSA. I would say like, I try to do my best on a lot of shared decision making with PSA, if we are going to order that or not. And so, I think I had someone the other day who’s had an increased risk of prostate cancer, and said his dad had prostate cancer, at what age, because you can be 95 and have prostate cancer, is that relevant or not? Oh, he’s in his sixties, ok this is relevant, you know being diagnosed with prostate cancer like in your sixties and that is your dad, so for sure, let’s order a prostate-specific antigen (PSA) test, keep an eye on it, you know, check for any issues with the urination. He said he has had no issues, it’s been helpful with that, in kind of solidifying reasoning for screenings, in that case. For prostate cancer, I am married to shared decision making. The patient asks me, “do you want me to take a PSA or not?” I explain what it is, and you know, what we were looking for, and so, it helps reinforce that”. (PRS) (Provider 14)

Other Minor Comments:
- “A provider expanded upon how, despite their patient receiving a positive monogenic result for PCSK19, follow-up care largely remained unchanged despite being referred to and seeing a cardiology for follow up” – I believe this is the PCSK9 gene. Also, gene names should be italicized.

Reviewer #2

(Remarks to the Author)
I commend the authors for the extremely thorough and diligent manner in which they have considered all reviewers' comments and the significant changes and clarifications they have made in response. As such, I think the manuscript is significantly improved.

Reviewers' comments:
Reviewer #1 (Remarks to the Author):

Thank you for the authors for the opportunity to review their manuscript entitled "Characterizing healthcare provider experiences delivering polygenic risk scores (PRS) in a Federally Qualified Health Center." The manuscript summarizes a mixed method approach employing surveys and interviews to characterize experiences of healthcare providers caring for low-resourced patients in a FQHC including in the provision of polygenic risk scores. Efforts to understand experiences of clinicians in low-resourced areas/clinics are necessary to understand strategies to implementing genomic medicine across the population. I have included comments below aimed at further strengthening this work. Comments are organized by section of the manuscript.

Introduction
1. The authors provide a useful description of FQHCs and then proceed to describe that "Research has also shown large racial and ethnic differences in levels of genomic-sequencing knowledge and trust in medical researchers (7)." Given there is not a discussion of the demographics of patients who seek care in FQHCs, this feels out of place. Further explanation and clarification would be useful.

Thank you for the comment. We agree that the sentence was out of place and distracted from the focus of the paragraph on the unique needs of patients who receive care at FQHCs. We have deleted that specific sentence and rephrased lines 72-76 accordingly "Patients who receive care at FQHCs often face challenges in obtaining primary health care, like inability to obtain health insurance, not able to afford the cost, and low health literacy. The unique needs of patients who receive care at FQHCs pose additional social determinants of health challenges to the integration of genomic medicine and testing in FQHCs (6-7)."

2. Though not within FQHCs, there have been prior work examining healthcare provider experiences with PRS. It would be helpful for the authors to include that information as background.

Thank you for the comment. We have added this sentence to the introduction section in setting up our study, on lines (78-80): "There has been growing research of healthcare provider experiences delivering genomic medicine (8,9), but limited research on provider experiences delivering genomic medicine in the primary care setting". The references we have also added in are:

Lewis, A. C., Perez, E. F., Prince, A. E., Flaxman, H. R., Gomez, L., Brockman, D. G., ... & Karlson, E. W. (2022). Patient and provider perspectives on polygenic risk scores: implications for clinical reporting and utilization. Genome Medicine, 14(1), 114.

Kerman, B. J., Brunette, C. A., Harris, E. J., Antwi, A. A., Lemke, A. A., & Vassy, J. L. (2023). Primary care physician use of patient race and polygenic risk scores in medical decision-making. Genetics in Medicine, 25(4), 100800
Methods

3. I understand that interview guides are available upon request; however, it would be helpful to include the interview guides as a supplement. As described, it is not immediately clear how the questions incorporated genomic medicine or how the results flow from the question descriptions in the methods.

Thank you for the suggestion. The provider interview guide has been added with the other supplementary materials along with details to highlight the incorporation of genomic medicine in the questions (see lines 130-142).

4. The authors note “The practice followed 20,474 active patients who receive care from 17 clinicians including physicians, nurse practitioners, physician assistants, and behavioral health providers.” Does this refer to eMERGE IV or the FQHC? I believe it is the former, but clarification could be useful to the reader. Further, if the former, how were only 17 clinicians engaged if 14 were recruited for this study from a single site? If that sentence does refer to the FQHC, then why is the number 100,000 patients in the study location section?

Thank you for pointing this out. We understand that sentence was extremely confusing. We decided that it ultimately was not relevant to include in this paper, and was distracting from the methods of our study, which was nestled in eMERGE IV. Accordingly, we have deleted the sentence mentioned above.

5. How were clinicians trained leading up to eMERGE IV and the implementation of PRS? This could have significant impacts on clinician experience. Though not the focus of this manuscript, description of the types of PRS results returned through eMERGE IV would also be useful in contextualizing the provider experience especially with relevance of results.

Thank you for this important point. Although provider training was not a part of this project (but rather occurred prior, during the setup of the eMERGE project in which this

project is nestled within), we have provided a brief explanation on what sort of training providers received regrading genomic medicine delivery. See lines: (108 – 112)

“Providers had varied levels of experience delivering genomic medicine in the past, with most having no experience at all. The eMERGE research coordination team at the FQHC provided training materials as directed by eMERGE IV, and regularly addressed questions that providers raised during monthly clinic-wide meetings. ”

6. Study location – It would be helpful to provide additional details about the clinical population including the proportion who are LatinX, age range, sex, gender identity, etc.

Thank you for your comment. We have added more information about the general population the clinic serves. Due to privacy considerations, we are unable to share specific demographics, including age, gender, etc. However, we believe the information we provided (see lines 165 – 171) provides relevant context to address this comment.

7. In the Introduction, the authors note the limitations of PRS in non-European ancestral groups. How, if at all, was this considered when implementing PRS in a clinic population where were mostly LatinX?

The study team built upon their previous research in this space and existing literature at the time of study design and execution on implementing PRS among non-European ancestral groups. We have added a sentence recognizing such in the introduction (lines 63 - 65).
“A growing body of research is focused on investigating genomic testing implementation in non-European ancestral groups (2-4). ”

8. The following sentence is difficult to follow: “Guided by Corbin and Strauss’ grounded theory approach (11), the study interview transcripts using NVivo software according to a codebook (see Figure 1) identified in advance and iteratively updated.

Thank you for pointing this out, the sentence has been reworded (lines 182 - 184) –
“The study team adapted Corbin and Strauss’ grounded theory approach (16) to code the interview transcripts using Nvivo software according to a previously designed and iteratively updated codebook (see Figure 1) .”

9. In the results, clinicians discuss the use of monogenic results. Are monogenic results also provided via eMERGE IV or do clinicians have experience from prior efforts or clinical integration of testing? Describing this further in methods would be useful.

Thank you for this comment. The research team thought extensively about this comment, and ultimately, we took this comment and reframed the entire paper. Now, the

paper is not focused on PRS vs. monogenic testing (we understand it was very confusing to have a paper focused on PRS, with significant results focused on monogenic testing). The paper is now titled “Characterizing healthcare provider experiences delivering genomic testing in a Federally Qualified Health Center”, of which PRS and monogenic testing are different types of genomic testing. We realized it was not important to emphasize the differences between PRS and monogenic testing for the purposes of this study (This study was not designed to differentiate between the two), so through this reframe we decentralized the specifics of PRS and monogenic testing, and refocus on what is most important: provider experiences delivering genomic testing, inclusive of PRS and monogenic testing. Now, the monogenic and polygenic results are integrated together, particularly in the section 3.3.2.1 “perceived utility”. The type of genomic test result referenced is mentioned for context.

Results

10. It would be helpful to have clarity on the number of clinicians recruited for the study. Were all recruited and participating clinicians in internal medicine in the FQHC?

Thank you for your comment. We made sure to clarify (see lines 112-114) that there was a total of 17 providers within the Internal Medicine clinic who of them, 14 were recruited to participate in an interview. We have also added Table 2 to provide specific individual participant profiles (sex, age, race, ethnicity, type of provider, total years working, years working at the FQHC). Table 1 shows the overall sample demographic makeup.

11. Do you have a sense of the number of PRS providers had received at the time of survey/interview? Understanding their adoption could be useful in contextualizing experience.
Are time constraints truly unique to the FQHC? This is a barrier across primary care.

Thank you for these questions. We do not have a sense of the number of PRS providers had received at the time of survey/interview; that was beyond the scope of our project design. We engaged with providers after they reported an experience delivering genomic medicine during our project period, and they could have had varied amounts of experience leading up to that point. We added clarification on this point accordingly, lines 124-128

“Additionally, this project did not track the number of GIRA reports providers had received at the time of survey/interview; that was beyond the scope project design. Recruitment of providers occurred after the a provider had an experience delivering genomic medicine during our project period. Accordingly, each provider had varied

amounts of experience doing so leading up to the point of recruitment, survey, and interview."

Time constraints are not truly unique to an FQHC setting, relative to other primary care environments, but they further exacerbate the challenges providers and patients face at a FQHC. We have added the following sentence as a result of this question, see lines 508 - 510:

"Time constraints are not unique to an FQHC setting, relative to other primary care environments, but they further exacerbate the challenges providers and patients face at a FQHC."

We also added the following citation (see line 491) that emphasizes the uniqueness of the FQHC setting: Nakamura, Y., Laberge, M., Davis, A., & Formoso, A. (2019). Barriers and strategies for specialty care access through federally qualified health centers: a scoping review. Journal of Health Care for the Poor and Underserved, 30(3), 910-933.

Discussion
12. I am not convinced that the survey results convey an openness to PRS. They convey confidence in reviewing reports, value to care, and action for some patients among clinicians who were already integrating PRS into care due to eMERGE IV. They did not ask about acceptability or appropriateness of incorporating PRS or feasibility of doing so.

Thank you for this clarification. The language has been changed accordingly, see lines 496-497: "Providers expressed a general confidence in reviewing PRS reports and PRS' value to care."

13. 3.5.3.4 – Illustrative quotes demonstrating "Results of PRS can complicate how providers are to provide
383 follow-up care, or not, to patients, particularly if results suggest that that care is
384 only offered outside of the FQHC" would be beneficial.

> *I do shared decision making with the patients. My personal opinion [that I share with the patient] is we only have to do this and this based on the genomic test result, just to see where you are at, because we have to keep an eye on it, but you know, what are your thoughts? You want to do it all? Know there's a cost associated, maybe we don't have to refer you to cardiology, because I can order a coronary calcium score, and those*

> *things, I think mostly I leave it out to the patient, because it's their money, if I don't think clinically it's an emergency and most of the genetic stuff isn't, then I just put it on the backburn.* (Provider 13)
>
> *That's kind of the approach I have taken, that, you know, there's going to be testing that's done that I didn't order, and the patient is going to do with that information what they will. My job is to inform them, offer next steps and guide them, and their job is to decide. They (the patients) are the medical decision-makers. I'm just here to inform, and so that's kind of the attitude I have taken with it, and I think it's been good, because no matter what, I have patients come in all the time and they'll say "my specialist ordered something and they've never dealt with me", and I'm now saddled with doing it anyways. If the patient trusts me enough to go over genomic test results and I trust them to decide what is best for them, given all the information, that's the deal we have struck with our patients and I'm ok with that. (PRS)* (Provider 2)

Thank you for the recommendation. We included quotes from providers (see lines 457 - 475) that highlighted how the recommendations from their patient's PRS results complicated their ability to provide follow up care. The conflict was associated more with how to minimize the need to see a specialist that is going to be an additional cost and the dynamic it plays in shared decision making.

14. The discussion could benefit from further revisions to strengthen communication about the implications of these findings. For instance, what do clinician perspectives on utility tell us about PRS in general? Further, what does this mean for practices moving forward? The goal of this data collection is to inform implementation of genomic medicine across settings including those with low resources. How do the findings described advance that work?

Thank you very much for your comment. We have removed the focus on polygenic scores in our paper, framing it instead as "genomic testing". Though they have clinical relevance, of course, our paper is focused on provider experiences delivering genomic testing. Yes, PRS vs. monogenic testing have their distinct implementation differences and characteristics, but this study was not focused on teasing out these distinctions. Rather, we engaged with providers after any test result was delivered – polygenic or monogenic. This study was focused on provider experiences, less on the test. Honing in on this distinction would be an interesting and important follow-up study!

15. Further how do these findings compare to other work characterizing provider perspectives (e.g., PMID: 39580561)? What is unique to a FQHC and what is not?

Thank you for this comment. We have integrated this paper into our discussion section and engaged with it at multiple points, see lines 488 - 493

“Prior research has investigated provider perspectives, attitudes, and experiences with genomic testing (specifically, PRS) (20), suggesting an overall feeling among providers of unpreparedness. Accordingly, this mixed-methods study is one of the first to investigate healthcare provider experiences delivering genomic testing in a FQHC serving a primarily Latino patient population”.

Additionally, see lines 498 - 504:

“Quantitatively, a majority expressed confidence in using genomic testing and communicating results to patients. This aligns with qualitative themes where several providers expressed openness and sometimes positive perceived utility of genomic testing in their practice. Such perceived utility was prominent when the genomic testing results had a potential positive impact on the patient’s family system. This finding consistent with existing literature (20), and particularly powerful among the FQHC’s primarily Latino patient population where the family system is a core value (21).”

16. As for limitations, how do you think this work being conducted as part of eMERGE IV impacted the findings. Do you think they are generalizable to other FQHC?

Thank you for your comment. We have added clarification of how being a part of eMERGE IV might have impacted findings, and whether or not findings are generalizable to other FQHCs, see lines 528-533:

“An additional limitation of the conclusions of this work is that it was conducted as a nestled study within eMERGE IV, a nation-wide study focused on clinical outcomes of genomic medicine, not on healthcare provider implementation of genomic medicine. Accordingly, findings of this work might be specific to the eMERGE IV context. This study was conducted in the only FQHC participating in eMERGE IV, and is another reason why findings may not be generalizable to other FQHCs.”

Reviewer #2 (Remarks to the Author):

The authors present a nice study examining the experiences of healthcare providers in delivering polygenic risk scores to low-resourced diverse patients in a federally qualified health center. They make a strong case for why the work is needed, both due to a paucity of research into healthcare provider experiences but also the low-resource aspect. The work is well-conducted and reported and I believe offers some valuable insight into a timely issue.

Major concerns:
1. I'm not sure what the value is of a quantitative survey of 14 individuals. I would usually expect a mixed-methods study to recruit a much larger sample size to a survey to explore breadth of opinion or generalizable findings and then use the smaller interview cohort to probe deeper into more nuanced views and rich data. This is part of a larger study, why limit the survey just to the FQHC, it would be informative to see how these responses differ (or not) across the different settings of the study. If such an underpowered study is to be reported, I don't think it should form a headline finding in abstract for example that a majority are confident to guide health recommendations. This finding has too many caveats in this context.

Thank you very much for your comment. Respectfully we would like to explain why our "smaller" sample size exists. Despite this study being nestled within the eMERGE network across the country, this FQHC was the only site in the nation that conducted interviews with providers delivery genomic medicine with a focus on their experiences and the ethics of delivery. This was made possible due to the involvement of the Arizona State University team and the Mayo-ASU funding in addition to the eMERGE funding. The other sites conducted surveys and interviews of providers, but not according to the same methods and interview guide. This is due to the bandwidth of the team at the FQHC as well as the bandwidth of the providers at the FQHC, who are limited in their time and resources in a different way than providers participating in the eMERGE study across the country. Additionally, this FQHC is the *only* FQHC and primary care setting that participated in eMERGE at this time, so it required different methods and approaches given the infrastructure available. All things considered, a sample size of 14 providers who completed both surveys and interviews within this smaller FQHC environment is significant and novel. With this in mind, we completely agree that we should not include a reference to "guiding health recommendations" in the abstract. Accordingly, we have deleted this reference from the abstract.

2. It would be helpful to provide the interview guide. The brief description in methods seems to paint quite a one-sided picture of a negative line of questioning (ethical dilemmas, additional occupational burdens and potential moral injury) focused only on challenges and barriers, however the codebook and indeed the results suggest a more balanced discussion.

Thank you for the comment. The provider interview guide has been added with the other supplementary materials along with a more well-rounded description of the topics covered in interviews (see lines 130-142).

3. Conflation between PRS and monogenic testing. The authors text and the participant quotes clearly demonstrate that there are some misunderstandings or lack of clarity around whether participants are discussing monogenic or PRS results. Some of the results text specifies PRS when the quotes themselves make no reference to this. How sure are the authors in each case that the participants do mean PRS? Perhaps the wider context makes this clear. The starkest example was the participant discussing reassurance in a patient with familial history of breast cancer. The description says that the provider explained how the PRS result provided emotional reassurance. If that's true, this is a significant misinterpretation of PRS clinical utility and possibly warrants more discussion (see point 4). However, if they are referring to the monogenic testing as the "clean genetic test" then that makes more sense but means PRS not discussed here. Given only 1 question on survey was specifically about PRS and the GIRA contains both mono and polygenic risk, I think more clarity is needed as to why this study only focusses on PRS and whether it's possible to disentangle the two.

Thank you for this comment. The research team thought extensively about this comment, and ultimately, we took this comment and reframed the entire paper. Now, the paper is not focused on PRS vs. monogenic testing (we understand it was very confusing to have a paper focused on PRS, with significant results focused on monogenic testing). The paper is now titled "Characterizing healthcare provider experiences delivering genomic testing in a Federally Qualified Health Center", of which PRS and monogenic testing are different types of genomic testing. We realized it was not important to emphasize the differences between PRS and monogenic testing for the purposes of this study (This study was not designed to differentiate between the two), so through this reframe we decentralized the specifics of PRS and monogenic testing, and refocus on what is most important: provider experiences delivering genomic testing, inclusive of PRS and monogenic testing. We do not mean to imply that there are no differences between PRS and monogenic testing clinical utility in this reframe. However, this study was not designed to make any claims about clinical utility of different genomic tests – rather, to emphasize the provider experiences delivering the genomic testing in a specific primary care setting (FQHC) to a unique population who generally is not offered genomic testing (Latino patients receiving care at a FQHC). Now, the monogenic and polygenic results are integrated together, particularly in the section "perceived utility". The type of genomic test result referenced is mentioned for context.

4. Related to the point above, the authors highlight in results and discussion about healthcare provider confidence in advising on healthcare recommendations. Given the conflation between mono and polygenic risk evident and the fact that 75% are confident to make recommendations despite 50% not being confident in their knowledge, I think more could be made in the discussion to highlight that self-rated confidence is not the

same as competence. Many studies in genomics have asked healthcare professionals about their confidence in genomic knowledge and interpretation (almost always answered as high) but only when combined with questions assessing competence do we see that these are not well aligned.

Thank you for this comment. We have considered it extensively and engaged with our community partners at length. As a result, we have decided to remove all statements about healthcare recommendations rooted in our data collected for this project from the discussion section. This project is focused on healthcare provider experiences delivering genomic medicine, and while we might have interesting qualitative statements, neither or project was designed nor our data robust enough to address healthcare provider confidence in advising healthcare recommendations. Providers commented on their familiarity and opinions towards genomic medicine, which is different.

The statements remain in the results of the KAP survey because that is what the KAP survey verbatim asked.

5. The discussion is a little light on some of the underlying ethical considerations. Whilst highlighting participants concerns about financial barriers as well as only one participant being very confident these results would lead to healthcare changes and qualitative data pointing towards received results being largely already known, I was expecting a deeper discussion about cost-effectiveness and judicious use of resources. In fact, the authors suggest the generation of conversation itself, even if not about the genetic test may make this a promising tool particularly in low-resourced communities. I think that statement needs some unpacking. It may well be the case but it's not clear what the route to efficacy looks like to the reader. Also, the conflation here again between PRS and other genetic tests is unhelpful. Monogenic testing for highly penetrant conditions should not be evaluated alongside PRS for common conditions with more complex interventions. Also, the introduction raises the issue of European ancestry bias, the setting for this study is an FQHC which is described as being majority non-white European and yet none of the analyses or discussion points consider this issue. Some comment on this would strengthen the discussion further.

Thank you very much for your comment. We agree that the ethical considerations of this work are extensive and worthy of lengthy discussion. Our discussion section is limited as we felt its length was appropriate for *Communications Medicine*. We would be happy to expand further at the recommendation of the editorial board, should they agree. To your second point, we have removed the distinction between monogenic and polygenic scores in our paper, framing the whole paper as "genomic testing" as to not focus in on the distinction. Though they have clinical relevance, of course, our paper is focused on

provider experiences delivering genomic testing. Yes, PRS vs. monogenic testing have their distinct implementation differences as well, but this study was not focused on teasing out these distinctions. Rather, we engaged with providers after any test result was delivered – polygenic or monogenic. Honing in on this distinction would be an interesting and important follow-up study!

Minor concerns:

1. There are a number of acronyms which are not defined the first time they are used

Thank you for the comment. All acronyms have been defined the first time they are introduced.

2. eMERGE IV should be introduced and explained a little in the introduction.

Thank you for the comment. eMERGE IV was added to the introduction, see lines 90 - 94.

3. RedCap needs citation if possible

Thank you for the suggestion. REDCap has been cited (please see 117-119), reference list #14 and #15.

4. In methods, the FQHC is described as having a majority of Latino patients, it would be helpful to quantify how many and what the breakdown is for other groups

Thank you for the comment. Please see lines 165 - 171 for racial/ethnic breakdown of the FQHC's clinical population.

5. It would also then be helpful to understand how the 20k people followed in eMERGE IV compare to the FQHC population demographically.

Thank you for the comment. We have decided to remove the reference to the 20k people followed in eMERGE IV, given it was distracting, confusing, and not very relevant to the focus of the study.

6. Over 10% double coded, with such small numbers it would be more informative to just say how many were double coded

Thank you for the suggestion, please see line #184 for this edit.

7. Define GIRA reports

Thank you for the comment. GIRA report has been defined, please see lines #217- 219:

“Genome Informed Risk Assessment (GIRA) reports informed patients if they were at high risk for any of the studied health conditions while also providing clinical recommendations for follow-up care (17,18)”

8. Numbering seems to have gone wrong in subsections

Thank you for the comment, numbering of subsections has been corrected.

9. It would be helpful to attribute quotes to either pseudonyms, participant IDs or job roles. Job role was collected and is informative data for some of the viewpoints. As things stand, we have no idea whether 1 or all 14 participants have contributed to these exemplar quotes.

Thank you for this comment. We have gone through and noted provider ID number per quote, so readers can cross-reference the provider profile in the individual participant profile table (Table 2), which is now included in the paper.

10. Underlining and spacing on sub-headings is inconsistent

Thank you for the comment, underlining and spacing has been corrected.

11. Table 2 the survey has 100% of participants saying they went over GIRA with patients but next question has many reasons why they didn’t, could the authors comment on this discrepancy?

Thank you for your comment. Providers had a range of patients who participated in the eMERGE study, and the survey question about reviewing the GIRA report referred to whether they had discussed it with any of their patients, not necessarily all. The following question asked about challenges or barriers in instances where they did not or could not review the report. Thus, the apparent discrepancy reflects that while all providers reviewed the GIRA report with at least one patient, some encountered situations where they were unable to do so with others. We have included this clarification in the paper, lines 225 – 227.