

Peer Review File

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Reviewer A

The authors have provided a narrative review on the topic of whether polygenic risk scores are ready for the cancer clinic. Overall it is well written and there are some good points (e.g. overdiagnosis and standardisation) but there are a few major points that need addressing:

We thank Reviewer A for taking the time to review our manuscript and for their favorable comments. Please find below our responses.

Comment 1: Page 2 Line 73: "A PRS can bring added value to an existing cancer risk model in the clinic if it presents information independent of established clinical, environmental or lifestyle risk factors, and therefore improves the predictive power more than incrementally." However, the citations used in the subsequent paragraphs demonstrate only incremental improvements of PRS when added to other additional risk factors e.g. C' index - Mars et al al. Prostate Cancer Clinical vs Clinical + PRS (0.840->0.866) and Kachrui et al Breast Cancer Clinical vs Clinical + PRS (0.572->0.635). It would therefore be helpful if the authors could provide an example where there is a greater than incremental improvement in PRS with citations or to clarify what they mean by incremental.

Reply 1: *We thank the reviewer for this important comment. As the reviewer noted, in the Kachrui UKBiobank study, the C-index improvements for breast cancer risk were relatively marginal. However, notable increases in the C-index were observed in other cancers, including those of the testes, thyroid, prostate, lymphocytic leukemia and melanoma. Supporting the findings on thyroid cancer, in a study on subsequent thyroid cancer in childhood cancer survivors, a risk prediction model that integrates the PRS with clinical factors showed better performance than the model considering only clinical factors (Cancer Epidemiol Biomarkers Prev. 2021 Aug 31;cebp.0448.2021). In the same UK Biobank study, for cancers with strong environmental risk factors, modeling the PRS in addition to established risk factors (including lung cancer in smokers), provided only marginal improvements. However, when the environmental risk factor is not present, such as in lung cancer in never smokers, the PRS may be more relevant. Furthermore, the UKBiobank study results suggest only marginal improvements in assessing breast cancer risk when combined with other risk factors, multiple recent studies have shown that in individuals with moderately penetrant pathogenic germline variants (e.g. BRCA1/2, PALB2, ATM), a PRS can provide significant benefit in identifying who is at higher breast cancer risk. PRS can be useful in those cases.*

Comment 2. The two above citations also use NRI which is has been suggested to be invalid (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4615606/>). It would be useful in this section on discriminatory power of PRS to discuss (briefly) appropriate methods of assessing

predictive power. Furthermore, it would be useful to place some of these measures in context with existing screening tests and their discriminatory power.

Reply 2: *We thank the reviewer for this valuable suggestion. As the reviewer kindly mentioned, NRI was used by the studies referenced by the reviewer. In our manuscript, we have not suggested the use of NRI to assess the predictive power of a PRS.*

Nevertheless, we have added the following paragraph (highlighted in yellow in manuscript starting on line 81): "In reporting the predictive power of a cancer PRS, the standard epidemiological literature should be consulted to consider the relative merits of different reporting metrics, as these essentially have the same issues as for any predictor of disease or trait. Typically, a regression model is performed on the target sample, with the PRS as a predictor of the target trait or outcome, and covariates are included as appropriate. The metric that is most sensible to use is based on the context and the question being asked. To make quantifying the difference with other published studies more consistent, most studies use the incremental R^2 , where the effect of the PRS is separate from the effect of other covariates. However, if the model includes many covariates, then the incremental R^2 may be higher because those other covariates will have explained a good fraction of the trait variance and thus some caution in this regard is warranted. For example, when a popular measure, the Net Reclassification Index (NRI)¹³ is calculated on a large test dataset, it is likely to be positive even when the addition of the PRS to an existing model has no predictive information. A good discussion on measurements of PRS analysis results, plots, interpretation, predictive accuracy and power, as well as avoidance of over-fitting is provided in a recent study by Choi et al (2020)⁹."

Comment 3. Page 2 Line 83: "In considering for which cancers a PRS may best discriminate germline genetic risk, the heritability of a cancer provides a natural upper limit to what can be solely achieved by a PRS. Twin studies may guide which cancers have sufficient genetic factors that a PRS could be of potential clinical utility." The upper limit can also be estimated from data from genome-wide association studies of cancer risk. This has been performed (<https://www.nature.com/articles/s41467-020-16483-3>). It would be useful to the reader if this was discussed particularly as the maximum AUCs are relatively low.

Reply 3. *We thank the reviewer for this valuable comment as it helps us clarify our perspective. PRS are typically estimated using summary statistics from GWAS, which have been historically based on array data, and thus only capture the combined impact of common variants on genetic risk. In contrast, twin studies capture the effect of all genetic variation, including rare variants that can be found in sequencing data but whose effects are missing in estimates of SNP heritability from microarray data. As we note in the manuscript, rare variants can have strong impact in the personal risk of an individual. We therefore recommend the development of reliable PRSs that capture common variants from GWAS, combined with rare variants of high impact that are deduced from burden or other analyses, to apply to target populations that have been low-depth sequenced.*

We have added the following to the manuscript: "Note that this natural upper limit is higher than what can be estimated from current genome-wide association studies of cancer risk, (<https://www.nature.com/articles/s41467-020-16483-3>), as it includes yet to be resolved genetic associations such as the inclusion of rare variants."

Comment 4. Paragraph on P3 Line 111. In this paragraph it would be helpful if the authors could discuss in further detail the expense and complexity of adding PRS to existing screening initiatives. Such an addition will be costly (blood sampling, DNA extraction, genotyping, data processing and storage, delivery of risk, counselling) and add complexity to existing screening which already has variable uptake.

Reply 4: *We have added the following: "From a cost perspective, even if WGS of every patient is necessary for the cancer PRS, this will be performed only once in a person's lifetime. As genetic sequencing becomes more common, these types of sequencing data will become available for screening for many different health outcomes. Hence, from the health system perspective, the cost will not be a major factor in utilizing PRSs at population level. We are already seeing efforts to that effect in research enterprises such as in the Million Veteran Program (MVP) that plans to sequence a million veterans; the UK Biobank that is sequencing individuals within the UK, and hospital-level efforts such as the BioMe Biobank of Icahn School of Medicine at Mount Sinai."*

Comment 5. Page 4 Para Line 141. a) The authors state there is limited behavioural studies to support their opinion that when individuals are confronted with their own genetic data and risk, they tend to take preventive action and make positive lifestyle changes. It would be helpful to provide such limited studies otherwise I would change this statement to be phrased as speculative.

Reply 5. *We thank the reviewer for these valuable comments as it helped us clarify this section.*

Reply 5 a) *Please note that we have now removed the Finnish study and instead added this paragraph: "So far, studies suggest that when individuals are confronted with their own genetic risk data, their preventive behavioral responses are impacted by multilevel sociocultural and policy-related factors, including race, ethnicity, culture, socioeconomic status, and available healthcare access, insurance coverage, and follow up care, in addition to trust in the health system³⁶. While limited, studies on communicating DNA-based disease risk estimates have reported little or no effect on smoking or physical activity, and a small effect on self-reported diet and on intentions to change behavior in the short term^{33,38}. However, users of direct-to-consumer of genetic testing services (who tend to self-select for individuals of higher educational levels), were reported to adopt long-term changes into healthier diets³⁹. In addition, a recent personalized genetically informed risk tool showed to promote progress towards smoking cessation⁴⁰. Furthermore, a recent melanoma clinical trial reported that while personal genomic risk information did not influence sun exposure patterns, it did improve some skin cancer prevention and early detection behaviors⁴¹."*

Finally, multiple studies have reported that personal risk information is potentially useful for shared and informed decision-making in the clinic⁴², and that individuals at high cancer risk tend to take preventive action. Of note, women's health behavior tended to change after receiving breast cancer risk estimates with tailored screening and prevention recommendations, highlighting the importance of effective risk communication⁴³."

Comment 5b) The same is true of the authors assertion that PRS for lung cancer risk will "likely" impact on future behaviour or indeed what effect a change in behaviour will be on cancer risk. There is evidence in cardiovascular disease that such changes in behaviour have limited impact on modifiable risk factors (<https://bmjopen.bmj.com/content/7/6/e015375>).

Reply 5b). *We have modified this sentence as: "Further research is needed in this area, on for example whether, a high PRS for lung cancer will impact young never-smokers' future smoking decisions, shifting focus from supporting smoking cessation to smoking prevention on high PRS individuals before they even start smoking."*

Comment 5c) Many of the modifiable risk factors are ones which arguably should be recommended for the entire population irrespective of their PRS e.g. exercise, diet, non-smoking. This should be mentioned.

We have actually mentioned this in the manuscript, however, now we have modified the specific sentence to clarify this: "We need to develop guidelines on how best to educate individuals and the medical community on what a PRS is: that a high score does not mean an individual will definitely develop cancer, and a low score does not mean freedom from disease; and that all individuals should adopt healthy habits such as eating less, exercising more, or quitting smoking, regardless of their personal PRS."

Comment 6. Page 5 Line 184. The authors are right to point out that many rare cancers are under represented. By definition many of these cancers occur at a low frequency in the population - therefore relative risk increases predicted through PRS have minimal effects on absolute risk. This should be included.

Reply 6. *We agree that for rare cancers, even a large relative risk translates into a small absolute risk. We now mention this after our discussion of rare cancers: "..., though the low frequency of these cancers means the benefit of population-level PRS screening would be reduced as there would be less cases to detect"*

Comment 7. Page 5 Line 206. Whilst systematic and unbiased assessment of RDVs is likely to be helpful, their incorporation into PRS for predictive purposes does not require such studies. It requires large population based sequencing studies such as this:
<https://www.nature.com/articles/s41586-021-03855-y>.

Reply 7: *While we agree that large population-based sequencing studies are needed to identify new genes that may play a role in cancer risk, variant interpretation of specific*

variants in ethan allen chairknown cancer risk genes is still a major problem. Solving both of these issues is necessary for RDVs to be used in the clinic. We have now rephrased the sentence to read "To incorporate RDVs into PRSs, large population-based sequencing studies for gene detection (PMID 34375979) we need new technology and algorithms for their systematic and unbiased functional assessment, in addition to a better understanding of their complex interplay with polygenic background."

Comment 8. P5 Line 217. Is there really a clear benefit for measuring a PRS earlier in life? Point 5 discusses behavioural/lifestyle risk factors (and concerns) in further detail but it is important to note that delivery of a PRS particularly if done with little support may be associated with harm and raises ethical issues too (which should be discussed).

Reply 8: Given that an individual's inherited risk variants are fixed at conception, a major strength of a PRS is that it can be applied to identify those individuals who are at elevated disease risk at an early stage in their lifecourse. Combined with the known benefits of early screening, detection and treatment of cancers, and their behavioral impact we outline in Reply 5, we anticipate that knowledge of a cancer PRS earlier in life will be beneficial to individuals, as it will enable interventions such as smoking prevention at an early stage in the lifecourse. However, we agree with the reviewer on the value of a discussion of potential harms and ethical concerns, and have therefore added the following to the paragraph: "In addition, benefits of measuring PRS early in life must be carefully balanced against the potential risks of stigmatization and discrimination, as well as implications for parents having this information for their children (<https://doi.org/10.1038/s41591-021-01549-6>).

Comment 9. P6 6 Paragraph 254. Whilst many resistant mechanisms to chemotherapy agents are not known, given are knowledge of somatic genetics and clonal evolution coupled with the fact there are few risk loci for aggressive cancers, it seems optimistic to suggest germline variants will be major determinants of response to cancer treatments.

Reply 9: While we agree that many factors other than germline variants influence response to treatment, we cannot discount the role that germline variants are already known to play. For instance, PARP inhibitors are approved for treatment based on **either** germline or somatic mutation in DNA repair genes. We now note this by saying "In support of the idea that germline genetic variation can influence treatment response, we note that PARP inhibitors are approved for several cancer indications on the basis of the presence of either a germline variant or a tumor mutation in DNA repair genes."

Comment 10. In the conclusion the authors state further genotyping and development of methods will overcome the challenges in the article. As mentioned in point 3 with the likely maximum AUCs, it is entirely plausible that the combination of low discrimination and the lack of low-toxicity, effective prevention and costly, complex and poor adherence to screening is likely to present insurmountable challenges to effective PRS implementation in the clinic.

Reply 10. *We need to try to get the PRS to the level as best as it can be so as to decide how we can use it in the clinic. Not everyone may adhere to it, but there will be a fraction of individuals who will adhere to it.*

Comment 11. Figure 1 does not capture the complexity of determining whether a PRS has utility. PRSs for cancer do have discriminatory power. The question is whether it is sufficient for a given intervention (with the costs, complexity, toxicity, efficacy) to be instituted at a population-wide level. Figure 1 should be revised.

Reply 11. *We have revised Figure 1.*

Comment 12. It would be useful to the reader if trials in PRS and cancer are discussed. Here is an example: <https://bjui-journals.onlinelibrary.wiley.com/doi/10.1111/bju.15535>. This study presents another problem with PRS which is the low uptake. This is a major drawback and attention to this for the reader would be of use.

Reply 12. *We agree this is an important point, though we are reluctant to read too much into uptake for a research study compared to a potential recommendation made by one's personal physician. We have now added this paragraph: "Fifth, the clinical success of PRS will depend on their uptake – both adoption by clinicians and acceptance by patients. To that end, a recent clinical trial on a prostate cancer PRS is informative (PMID 34214236). This study aimed to recruit men, measure them for a prostate cancer PRS, and perform intensive screening (MRI and biopsy) in those men with a PRS in the top decile. Interestingly, only 26% of men invited to participate by letter chose to participate, suggesting that uptake of PRS-based screening may be low. Further studies on this issue will be needed, however, as there is a difference between being invited to participate in a research study by letter and a screening recommendation made by your primary care physician in person."*

Reviewer B

The authors review the use of SNP PRS in targeting preventive measures in cancer. Whilst certainly an interesting and well constructed review (on the whole), I am not sure how much is being added over and above existing reviews referenced in (6) and (8). I think the 'actionability' aspect in this paragraph is the authors' attempt at formulating the information in a novel way. I think it would be good to explain more clearly the space the review is filling. Is it drawing on recent evidence not available when the previous pieces were published? Or is it taking an approach which has not been presented before? There is a lack of detail on how much a PRS can contribute in different cancers. A table showing this would be beneficial. Also the authors conflate prevention and early detection. Whilst some ED can prevent invasive cancers such as removing polyps in bowel screening or DCIS in breast screening most ED only downstages cancer and is thus secondary prevention as it does not reduce incidence. There is also a lack of detail on how a PRS can be incorporated into risk models and whether models already allow this and indeed if models are reasonably good at this. The authors should also provide a table showing the best existing risk models and whether SNP

PRS have been incorporated at least for the main cancers discussed -lung, prostate, breast colorectal

We thank the reviewer for their time and their valuable comments. Please note that while there are multiple recent studies on PRSs in complex disease, including (6), our focus is on PRSs in cancer. We have addressed the specific comments as below:

Comment 1. Figure 1; This figure doesn't seem to be adding much. Perhaps it could include details of what further research requirements would be warranted for a 'no' response? Or perhaps an example of these criteria in action?

Reply 1. *We have updated Figure 1.*

Comment 2. 'Just as numerous studies have shown that highly penetrant single germline rare pathogenic variants can lead to familial cancer syndromes that span cancers in multiple tissues, it is plausible to build PRSs that assess shared etiology across multiple cancer types⁹.' -Whilst reference (9) does contain information supporting this statement, the paper referenced is primarily a PRS tutorial. I think there are more fundamental papers which could be referenced here.

Reply 2. *We have now added other references from studies on cross-cancer shared heritability (Graff et al Nature Communication 2021; Rashkin et al Nature Communication 2020; Jiang et al Nat Communication 2019; Sampson et al, JNCI, 2015).*

Comment 3. 'A PRS can bring added value to an existing cancer risk model in the clinic if it presents information independent of established clinical, environmental or lifestyle risk factors, and therefore improves the predictive power more than incrementally.' -A PRS can still be used if there is some overlap with existing factors. For instance the CanRisk model attenuates the PRS score in the context of a family history of breast cancer.

Reply 3: *We thank the reviewer for their valuable comment. While the added value that a PRS brings is necessary for its utility, we agree that it is important to clarify that a PRS can still be used if there is some overlap with existing factors. Based on the reviewer's suggestion, we have now added the sentence "It is also worth noting that a PRS can still be used if there is some overlap with existing factors. For example, the CanRisk model attenuates the PRS score in the context of a family history of breast cancer ((PMID: 33335023, PMID: 30643217))."*

Comment 4. 'Similarly, in a study on germline genetic risk for 16 different cancers using UK BioBank data, PRSs have presented lower added value for cancers with strong modifiable risk factors (e.g. lung cancer risk in smokers), but higher in those without them (e.g. lung cancer risk in never-smokers)¹²,' – Whilst this is true, the paper (12) did add that there might be other metrics apart from basic discrimination which are still favorable (eg. non-event reclassification etc).

Reply 4: *We thank the reviewer for this comment. While using the net reclassification index as a measure, the authors note an improvement in 15 of the 16 cancers tested, the NRI is known to suffer from a problem whereby it gives a positive value even in the case of a random marker that is not associated with the condition of interest. Therefore, we have chosen to focus on the conclusion the authors derive from their primary analysis of the C-index.*

Comment 5. ‘Conversely, lower risk individuals could be screened less frequently, or removed from unnecessary screening’ -These benefits are being presented as options for PRS use even when heritability is low and competing variables are strong. This is true, but fundamentally, applicable to a PRS in a disease area with any level of heritability is it not? Surely the conclusion of this paragraph should be saying 'even when heritability is low and therefore added discriminatory ability from the PRS is limited, here is the evidence (...) that it could still save lives by adapting screening protocols.'

Reply 5. *We have removed this sentence.*

Comment 6. ‘One drawback to current PRSs is that their development is largely derived from individuals of European ancestry. This limits their applicability¹⁶ and precision¹⁷ for non-European populations.’ Should add that this also exacerbates health inequalities, although you do expand on this later’.

Reply 6: *We thank the reviewer for this valuable comment. We have added to the sentence: “this also exacerbates health inequalities.”*

Comment 7. ‘Predictive performance comparison to existing markers’ -This section really does not cover what its heading states. The lower part of the paragraph is what I assumed would be discussed based on the section header, but is preceded by what seems to be a discussion of testing practicalities. Furthermore, the section above discusses the difference between PRS use in smoker vs. non-smoker lung cancer prediction, which I would think belongs in this paragraph as is really dealing with the issue of competing existing markers. It might be appropriate to split this section into two: 1) Harm-benefit trade-off of PRS testing vs. standard of care. 2) Predictive improvement of PRS over existing predictors.

Reply 7. *We have now renamed this section “Potential utility of PRS in practice” to indicate that it covers both the practicalities of computing PRS on patients and how it compares with existing markers.*

Comment 8. ‘For example, in breast cancer, PRS thresholds would need to be highly stringent to undertake the preventive action of double mastectomy. However, in colon cancer, those at high-risk based on their PRS may simply undergo frequent screening and take a daily aspirin, affording less stringent thresholds²⁷.’ -This is too simplistic. There are other options for breast cancer including chemoprevention with SERMs or Aromatase inhibitors that are just as good as aspirin in CRC. This also makes it sound like radical intervention would be recommended based solely on PRS, without consideration of other clinical factors, family

history, patient preference etc. NICE guidelines in the UK do say that chemoprevention should be offered to highrisk women and that mastectomy should be discussed so the authors are making too much of this. Increased screening regimen would also be an option in breast cancer. There is therefore a false dichotomy set up in this paragraph.

Reply 8. *We thank the reviewer for this valuable comment. In this paragraph we aimed to emphasize that the stringency criteria of a PRS depends on the preventive actions that are available, which are cancer type specific. We absolutely agree that there are other options for women at high breast cancer risk, yet the decision to take aromatase inhibitors is not to be taken lightly as it can significantly impact bone density and other estrogen-dependent processes within the body, which needs a higher reliability threshold than the decision to take aspirin, which, while increases the risk of bleeding, in comparison, is an over-the-counter medicine. However, we have changed the paragraph based on the guidance of the reviewer.*

Comment 9. ‘For example, we anticipate that a high PRS for lung cancer is likely to impact young never-smokers’ future smoking decisions, shifting focus from supporting smoking cessation to smoking prevention on high PRS individuals before they even start smoking’ - This a very bold claim in light of the mixed evidence regarding impact of providing PRS to aid cessation, never mind preventing people starting in the first place!

Reply 9. *We thank the reviewer for their valuable comment. Please note that most smokers, even when presented with genetic information that puts them at high risk are unable to quit because they are already addicts, and a plethora of addiction studies have already established the difficulties in breaking an addiction. However, it is a completely different situation when individuals are presented with personalized high-risk information at a young age, before they start smoking, when addiction has not kicked in. Studies in breast cancer, for example, show that when individuals are faced with their own genetic risk information, take steps to decrease their risk. Clearly, this is an area where more research is needed.*

We have modified this sentence as follows: “Further research is needed in this area, on for example whether, a high PRS for lung cancer will impact young never-smokers’ future smoking decisions, shifting focus from supporting smoking cessation to smoking prevention on high PRS individuals before they even start smoking.”.

Comment 10. ‘While very limited, behavioral studies support our opinion that when individuals are confronted with their own genetic data and risk, they tend to take preventive action and make positive lifestyle changes. For example, in the GeneRISK study in Finland, providing a personalized cardiovascular disease risk score, based on a combination of traditional risk data and PRS motivated healthy behaviors, even for participants at lower risk²⁸’ -This may be very population and disease specific. There is important evidence contrary to this, both in informing someone of their PRS:

<https://pubmed.ncbi.nlm.nih.gov/20927756/>; <https://www.bmj.com/content/352/bmj.i1102> and in informing them of their risk score more generally: Usher-Smith JA, Silarova B, Sharp SJ, Mills K, Griffin SJ. Effect of interventions incorporating personalised cancer risk

information on intentions and behaviour: A systematic review and meta-analysis of randomised controlled trials. *BMJ Open*. 2018;8(1). Bayne M, Fairey M, Silarova B, Griffin SJ, Sharp SJ, Klein WMP, et al. Effect of interventions including provision of personalised cancer risk information on accuracy of risk perception and psychological responses: A systematic review and meta-analysis. *Patient Educ Couns*. 2020;103(1) These papers are all regarding cancer (the topic under discussion), whilst the reference in the paper is for another disease area.

Reply 10. We thank the reviewer for this important comment. We have referenced the GeneRISK study specifically, because it involves PRS related behavior response. The reviewer is pointing out to an important dimension of the clinical utility of a PRS, however, as understanding human behavior is key. Therefore, we have changed this section and removed the GeneRISK reference. Instead, we have expanded on this section as follows:

“So far, studies suggest that when individuals are confronted with their own genetic risk data, their preventive behavioral responses are impacted by multilevel sociocultural and policy-related factors, including race, ethnicity, culture, socioeconomic status, and available healthcare access, insurance coverage, and follow up care, in addition to trust in the health system³⁶. While limited, studies on communicating DNA-based disease risk estimates have reported little or no effect on smoking or physical activity, and a small effect on self-reported diet and on intentions to change behavior in the short term^{33,38}. However, users of direct-to-consumer of genetic testing services (who tend to self-select for individuals of higher educational levels), were reported to adopt long-term changes into healthier diets³⁹. In addition, a recent personalized genetically informed risk tool showed to promote progress towards smoking cessation⁴⁰. Furthermore, a recent melanoma clinical trial reported that while personal genomic risk information did not influence sun exposure patterns, it did improve some skin cancer prevention and early detection behaviors⁴¹. Finally, multiple studies have reported that personal risk information is potentially useful for shared and informed decision-making in the clinic⁴², and that individuals at high cancer risk tend to take preventive action. Of note, women’s health behavior tended to change after receiving breast cancer risk estimates with tailored screening and prevention recommendations, highlighting the importance of effective risk communication⁴³.”

Comment 11. ‘We will need considerable education of both the public and medical community on the interpretation of PRS results, and to integrate the patients into the discussions.’ -This is true, but presented as only applicable in a situation where someone lacks the ability to influence risk through lifestyle changes. This sort of education is required whenever a risk score is given to a patient.

Reply 11: *We agree with the reviewer and we have modified the sentence accordingly: “We will need considerable education of both the public and medical community on the interpretation of PRS results, and to integrate the patients into the discussions, whenever a risk score is to be given to an individual.”*

Comment 12. ‘For example, biological females clearly will not develop prostate cancer, no matter how high their PRS, and risk for all cancers increases with age.’ I’m not sure this is the best example to give here. Perhaps a more nuanced example where PRS needs to be carefully integrated with demographic and clinical factors, not just ‘PRS will be useless for prostate cancer in biological females’.

Reply 12: *We have changed this sentence to: “Third, genetic risk often depends on clinical, lifestyle and environmental risk factors, which should be carefully integrated with demographic and clinical factors.”*

Comment 13. ‘Towards this end, we need to continue genotyping large numbers of individuals at population or hospital-scale for all cancer types and ancestries, which will greatly aid in the development of new methods that will overcome the challenges described here.’ I think there is an opportunity here to comment more specifically as to what solutions to the challenges raised in the review might exist. Surely there are more detailed approaches than ‘genotype loads more people’?

Reply 13: *We modified the sentence as: “Towards this end, beyond continuing to genotype large numbers of individuals at population or hospital-scale for all cancer types and ancestries, we need to focus research on considering where PRS may be most discriminative and impactful at the population level.”*

Comment 14. There is a lack of detail on how much a PRS can contribute in different cancers. A table showing this would be beneficial.

Reply 14. *We agree that such a table would be beneficial on other contexts. However, this would be beyond the scope of our manuscript, which is a narrative review. Please note that as per TLCR guidelines, “a narrative view is less methodologically demanding than a systematic review, as it does not require a search of all literature in a field, nor does it necessarily require a rigorous appraisal on the included literature”.*

Comment 15. The authors should also provide a table showing the best existing risk models and whether SNP PRS have been incorporated at least for the main cancers discussed **-lung, prostate, breast colorectal.**

Reply 15. *We thank the reviewer for this comment. While we agree that a systematic review and a table of best existing PRS models in lung, prostate, breast and colorectal cancers would indeed be a useful study, this is beyond the scope of our current study, which is a narrative view.*