Is it just for a screening program to give people all the information they want?

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Abstract

Genomic screening at population scale generates many ethical considerations. One is the normative role that people's preferences should play in determining access to genomic information in screening contexts, particularly information that falls beyond the scope of screening. We expect both that people will express a preference to receive such results and that there will be interest from the professional community in providing them. In this paper, we consider this issue in relation to the just and equitable design of population screening programs like reproductive genetic carrier screening (RGCS). Drawing on a pluralistic public health ethics perspective, we claim that generating and reporting information about genetic variants beyond the scope of the screening program usually lacks clinical, and perhaps personal, utility. There are both pragmatic and ethical reasons to restrict information provision to that which fits the stated purpose of the program.

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Introduction

When genetic or genomic testing is used or trialed in clinical practice and population health, there is an increasing tendency to sequence a person's exome or genome. The scope of the test is then refined using bioinformatic pathways, such as reporting according to a curated variant list. This approach is considered more efficient and more flexible than alternatives like assembling a gene panel. However, the generation of exome or genome data also allows identifying and reporting information beyond the purpose of the initial intervention. In a clinical context, this is referred to as "opportunistic screening" for additional or secondary findings and involves looking for variants such as those recommended by the American College of Medical Genetics (Miller et al. 2021). Similar practices are also emerging in a research context, such as in cohort studies (Willis et al. 2022; Biesecker 2022).

There is a nascent literature that considers some of the practicalities and ethical issues that will arise in population genomic screening. By "population screening" we mean a public health intervention in which members of a target population (such as people of reproductive age) are offered the same test, and – if they agree to be screened – are subject to the same result generation pathway and the same test processes – there is no individual tailoring of a test offer.[1] To this end, a screening test offer is made without individual clinical workup, such as taking a family history. Screening is therefore a form of "filtering" to identify people at risk of a health condition, via an intervention that is aimed at a large population of people who are not previously known to be at risk of that health condition (Juth and Munthe 2011). Screening programs are set up with a defined goal, and their success is considered in terms of meeting that goal.

To our knowledge, there is little discussion of a practice akin to opportunistic screening in the context of population (public health) genomic screening. That is, there is no analysis of the ethical implications of looking for findings that fall beyond the goals of a population genomic screening program. Without

[1] We are writing this paper as scholars working in a setting where public health screening programs are generally publicly funded, and a publicly available carrier screening program is under consideration. However we recognise that in many other jurisdictions reproductive genetic carrier screening is only available through commercial providers to those who can pay. We intend that our analysis of what information is appropriate to provide in RGCS should be applicable to all contexts in which this intervention takes place. In a subsequent section, we offer justification as to why our arguments apply to screening that is not publicly funded.

specific analysis, there is a good chance that existing analyses of opportunistic screening in the clinical context will be applied to population health as well. This would be mistaken, not least because the different applications of genetic or genomic testing give rise to differences in the way that risks and benefits of such testing are framed, prioritized and addressed (Brothers, Vassy & Green, 2019).

In this paper, we use reproductive genetic carrier screening (RGCS) as a case in point to consider the issues arising from reporting and communicating results beyond the program's stated goal . While we acknowledge that screening for reproductive purposes has specific features that might not translate to all types of genetic screening, the consideration of a population health approach to RGCS may yield relevant insights. RGCS is a form of genomic screening offered with the goal of providing individuals or couples with information to inform their reproductive decision-making. Specifically, RGCS provides information about the chance of having children with certain serious genetic conditions (Rowe and Wright 2019). RGCS usually comprises screening for tens, even hundreds of conditions, depending on the mode of offer (individual testing or simultaneous/couples-based). It is distinguished from carrier testing, which is offered to those with a known family history of particular genetic conditions. Information obtained from RGCS can inform future reproductive decisions, including whether to use prenatal or preimplantation genetic testing.

The development and implementation of any genomic screening program gives rise to ethical issues. For RGCS, these include: whether to report individual carrier status or couples-based information, whether to report VUS in genes for recessive or x-linked conditions, whether to report variants for conditions of variable expressivity and/or variable penetrance, and how to engage with critiques that the wide offer of testing will impact which future children are born (Dive and Newson 2022). These factors show that the decision about which genetic findings to report in the context of screening is ethically complex (Dive, Archibald, and Newson 2021).

Given the nature of sequencing methods, it is possible to provide information beyond the scope of RGCS to people undergoing such screening. Results beyond the scope of the initial test can comprise information relevant to individual health, information of uncertain significance, or information not associated with severe genetic conditions. Two reasons for providing results beyond the scope of testing are: (1) interest in receipt of such information from screening participants, and (2) a desire to maximize the value of genomic sequencing for human health. We expect that such reasons will be offered more frequently as genomic screening programs such as RGCS are increasingly available, via either commercial providers or state-funded screening.

The question of whether we ought to provide results beyond the scope of screening is the central topic of this paper. This issue can be framed as: "is it just to give people information beyond the stated aims of screening?" At first glance, the answer seems obvious: if it is straightforward for a genetic pathologist or laboratory to look at the sequence data from a screening participant to determine whether they have, for example, variants on the secondary findings list recommended by the ACMG, then why would they not take this opportunity? In this paper, we demonstrate that answering this question is more complex than it may first appear. A secondary claim is that such questions should be answered with reference to the goals of population screening rather than clinical care, informed by public health pluralism. As we go on to describe, a pluralistic public health ethics perspective integrates ethical principles from public health with the more individually-oriented goals of RGCS. We draw on such a perspective in making our argument that the design of population genomic screening programs like RGCS must account for justice and equity considerations. These factors support a carefully curated gene list in the context of population screening to ensure both equitable access to the primary intervention as well as follow-up care if required.

After briefly outlining the goals of genomic screening, we first argue that reporting results from RGCS should be approached with reference to the aims of screening. We also claim that personal preferences have some normative weight but should be balanced against the utility of information provided, and the potential societal impacts of RGCS. Finally, we argue that if RGCS is to be offered at scale, there are compelling reasons to limit the information provided to that which is relevant to reproductive decision-making. Providing further genomic information in the context of RGCS lacks utility and has the potential to deepen existing health inequities. These considerations are relevant whether RGCS is offered as a public screening program or on a private user-pays basis; because RGCS still takes place within a healthcare system, and the findings from screening might have implications for people beyond those who access RGCS. A public health pluralistic approach carefully balances the potential benefits of RGCS with sustainability within healthcare systems more generally.

The goals of population genomic screening

In many health settings, a distinction can be made between clinical care and population (or public) health. This distinction is important because it has implications for what a test offer looks like, decision-making processes, how results are provided and what options follow. A key challenge with genomic testing is that aspects such as how a sample is taken and the way the test is performed in the laboratory

are similar in clinical care and population health. The similarity can make it difficult to distinguish clinical genomic sequencing from genomic screening undertaken as a population health intervention. However the care pathways before and after the test can vary significantly depending on whether sequencing is part of clinical care or screening. Screening typically takes place only when there is a strong population-wide evidence base to support the offer of information[2], whereas in clinical care there may be additional opportunity to weigh risks and benefits in the balance in the context of individual circumstances (Brothers, Vassy and Green, 2019). Elements that can differ include how pre-test information and counseling are structured and provided (including the opportunity for pre-test deliberation in conjunction with a provider), whether and which health professionals are involved, who is offered sequencing, as well as how (and which) results are reported. Access to healthcare services and support post-result can also differ substantially according to the setting in which the test is offered.

Screening programs are designed to improve the health of populations. In contrast to clinical care, there is a single standardized test offer, designed for use in a population with certain characteristics, often offered to thousands (if not hundreds of thousands) of people. As such, screening programs need to pay attention not simply to the health of individuals in a population, but also to the distribution of health and access to health care across a population. To this end, the way screening is offered needs to factor in considerations of equity and justice. In brief, screening programs should be responsive to, and take care not to exacerbate, existing health disparities and inequities in access to health care.

In the case of RGCS, therefore, it becomes clear that this is not the same as targeted carrier testing. RGCS needs to be designed and implemented with reference to the goals of public health. We have argued elsewhere that, given the nature of RGCS, a public health pluralistic approach is warranted (Dive and Newson 2021). Public health pluralism includes the goals of avoiding suffering, promoting mothers', newborns' and families' health, respecting autonomy (on a broad conception, acknowledging social influences and constraints on choice), reducing inequity, and recognizing and responding to social determinants and constructions of health including health disparities. On this view, an offer of carrier screening for reproductive purposes needs to provide information to support participants' reproductive decision making, but must also – deliberately and explicitly – foster plural public health goals.

[2] We say "offer of information" deliberately here, to recognise that in RGCS a more appropriate outcome measure for screening is wide access to an offer of testing, rather than wide uptake of that offer. We discuss this further elsewhere (Dive & Newson, 2021). We also recognise that determining what information can and should be offered as part of screening is contested and must be approached carefully (Dive, Archibald & Newson, 2021).

Reporting results in genomic screening

Given the technological capacity to return a wide range of information obtained through population genomic screening, it is important to consider what kinds of results should be provided in programs like RGCS. In this section we consider two aspects of this issue. First, we address the question of whether RGCS, as a screening program designed to inform reproductive decisions, should report results on a "simultaneous" or couples-based approach (i.e., combined carrier status), or whether individual carrier status should be reported. We argue that a combined results approach is justified given the goals of RGCS, especially when construed under public health pluralism. Second, we consider whether genomic information obtained in the context of a screening program with a specific purpose should be routinely utilized to offer information about other findings, such as individual carrier status, information about conditions that may impact the participant's own health, or other information such as variants of uncertain significance.[3] We argue that programs like RGCS should not, at least at this point in time, be viewed as an opportunity to return genetic information beyond the screening program's goals.

Individual or combined carrier status?

With several jurisdictions considering wider offers of RGCS, debate has ensued over which (and how many) conditions, genes or variants should be included in screening (Henneman et al. 2016; Kirk et al. 2020; Dive, Archibald, and Newson 2021). A key consideration is the potential to return either individual carrier results or combined carrier status (where information from the reproductive partners is combined to determine their chance of having a child with a condition screened for). If carrier status were to be returned on an individual basis, then every pathogenic variant associated with an autosomal recessive condition and (for genetically female reproductive partners) X-linked conditions, is reported to the individual who receives screening. If a large number of recessive conditions are screened for on an individual basis the detection rate will be higher, which could place significant strain on the healthcare system as carriers seek follow-up testing and support.

The alternative is to return carrier findings only when *both* reproductive partners are carriers for the same autosomal recessive condition, or when the genetically female partner carries a variant associated with an X-linked condition. Doing so will reduce the proportion of people reported as having an

[3] We consider the normative weight of screening participants' interest in receiving this information in the following section.

increased chance of having children with a rare genetic condition to between 1-2% (Ropers 2012). Only those whose results have implications for reproductive decision making will receive an "increased chance" result. Reporting combined carrier status reduces both the burden of analysis and the genetic counseling resources required (Kirk et al. 2020). Furthermore, health system resources are not being used to communicate and discuss a result beyond the scope of reproductive decision making – a key goal of RGCS. Reporting only a reproductive couple's joint carrier status also facilitates a wider range of conditions to be screened, while meeting the goals of public health pluralism. Empirical research shows that couples both understand and accept this combined approach (Plantinga et al. 2019; Schuurmans et al. 2019). It aligns RGCS with its primary goal, namely to support reproductive decision making. By contrast, individual carrier status alone is rarely relevant to reproductive decision making.[4]

Screening as an opportunity to provide wider genomic information?

A second consideration with respect to reporting results is whether genomic screening programs like RGCS should be treated as an opportunity also to offer participating individuals additional genomic information, beyond the program's stated goals. Claims in support of opportunistic screening have been made in the clinical context, including for prenatal testing (Bayefsky and Berkman 2021; Biesecker 2019; Esplin et al. 2019). However, even if these claims hold in clinical practice or research, they may not hold for population screening. Using screening as a gateway to wider population provision of genomic information risks becoming inequitable, for at least two reasons.

First, such widescale provision of further information will have flow-on implications. As Horton and Lucassen (2022) discuss, analyzing genomic data for findings beyond the scope of screening is time and resource intensive, requiring variant interpretation and potentially discussion regarding pathogenicity. They also note the potential health system impacts from further investigations and interventions, including diverting resources away from those with greater a priori risk (Horton and Lucassen 2022). It may be a sub-optimal use of resources given that the screening population will have a low background chance of having a variant of interest. For RGCS in particular, flow-on implications include the feasibility of providing adequate post-test support (Righetti et al. 2022). Restricting RGCS results to the primary goal of screening – namely, to provide information that is relevant to reproductive decision making – is

[4] A simultaneous or couples-based approach to screening has been considered in more depth elsewhere (e.g., Plantinga, Birnie, Schuurmans, et al, 2019) and endorsed on both normative and empirical grounds. While an in-depth defence of simultaneous screening is beyond the scope of this paper, we note that it is possible to accommodate different family types – for example, couples (of all genders) who are using donor gametes – in screening program design when simultaneous screening is used.

one way of ensuring that RGCS remains sustainable and scalable within a complex health system (Schuurmans et al. 2019).

Second, those who can afford to pay can access genetic information that is not available to others, creating inequity. This information may also have questionable utility in relation to achieving the goals of screening (especially while interpretation databases remain unrepresentative of population diversity), and/or generate a cascade of further tests or interventions, not all of which may be necessary (Horton and Lucassen 2022). At its most problematic end, wider provision of such information could lead to misleading results or overdiagnosis, in which individuals who are not actually at risk will be identified (Laberge and Burke 2017, Meagher and Berg 2018, Vogt et al. 2019, Brothers, Vassy & Green 2019).[5] In the context of information to inform reproduction, we have argued elsewhere that there are justice-based reasons for restricting access to fetal genetic information that lacks clinical utility, and that routinely widening the scope of prenatal testing impacts the socio-normative implications of increased fetal genetic testing (Dive et al. 2022). Restricting the scope of programs like RGCS (by only reporting information relevant to reproductive decision-making) helps ensure program sustainability in the context of a wide population offer.

Taken together, these claims suggest that providers of programs like RGCS must take into consideration the utility of providing genetic information superfluous to the goal of screening. It is widely accepted that the primary purpose of RGCS is to provide information relevant to reproductive decision making (Henneman et al. 2016; Gregg et al. 2021). For a population-wide offer of interventions such as RGCS there are pragmatic considerations such as the importance of access to follow-up care following screening (Delatycki, Laing, and Kirk 2019) and factors related to scalability and feasibility. Research drawing on ancestry-based carrier screening programs has shown that population-wide RGCS is more likely to be effective if the purpose of screening is well understood, and there is equity of access to screening (Holtkamp et al. 2017).

Further, we contend that these claims hold for both publicly funded and privately provided screening. People who undertake private screening may receive information both relevant to, and beyond, the stated goals of the test. If beyond, the provision of this information is more likely to generate confusion and more likely to funnel people back into other forms of health care. The success of any screening

[5] In the final section of this paper, we consider and discuss a counter-argument to this position, including the appropriateness of identifying individuals at risk of conditions caused by genes with demonstrated clinical utility and the equity considerations.

intervention will be optimized when there are clearly defined goals, clear boundaries around the intervention and adequate support for participants before, during and after screening.

Utility and personal preferences

Support for offering or providing genomic information beyond the scope of a screening program could also appeal to patient preferences, reflecting the value placed on patient autonomy. There are understandable reasons for such valuing: concerns around medical paternalism and health data ownership are significant and important to bear in mind when seeking social license for genomic screening.

However, several ethical considerations need to be addressed before offering people genomic information beyond the scope of a population genomic screening program like RGCS. Given the complexity and inherent uncertainty of genomic information (Newson et al. 2016), consideration must be given to the utility of the information provided. One approach to categorizing conceptions of utility is to distinguish between clinical utility and personal utility. Clinical utility is the measurement of risks and benefits *specific to health outcomes* as a result of using a test. When evaluating clinical utility professionals will take into account the analytic validity of a test – how accurately genetic characteristics are picked up – as well as the clinical validity of the test – how accurately a test identifies a health condition from these genetic characteristics (Burke 2014). Personal utility refers to the evaluation of risks and benefits *not* specific to health outcomes. For example, this kind of utility measures less clinically tangible benefits like increased choice or control over health or gaining self-knowledge which helps aid decision-making. (Kohler, Turbitt, and Biesecker 2017).

While no systematic account of personal utility has been agreed, Bunnik, Janssens, and Schermer (2015) propose that it describes benefits that are "personal in nature." They also draw a distinction between personal and perceived utility: personal utility reflecting the extent to which a test result can be useful, for example to inform decisions about reproduction. While some tests – particularly in genetics and genomics – are *perceived* to have utility, actually they are unlikely to be useful in terms of answering questions or guiding decisions. They claim that people can be mistaken about the usefulness of genetic information, so perceived utility does not always translate into personal utility.

While we remain ambivalent about the concept of perceived utility as distinct from personal utility, the motivation for drawing the distinction highlights an important characteristic of health information,

particularly genetic and genomic information: there are social norms that shape people's preferences and may lead them (mistakenly) to consider all information as inherently valuable. The preference for more information is grounded in a wider social and normative context. In social and healthcare settings, where technological progress and intervention are lauded, people will generally seek to know as much information as they can about their genetic profile when offered. However, personal preferences should be just one consideration when determining whether to offer genomic information. It is also important to consider whether the information will have utility. Determining the potential utility of a genomic test requires weighing the personal utility (or even the potential perceived utility) of this information against the fact that it may not have clinical utility when offered at population scale, at least at this point in time. Further, there are potential costs arising from providing such information, including equity of access to follow-on healthcare, as discussed above.

Programs like RGCS are intended to benefit population health in addition to supporting reproductive autonomy, which means their aims are grounded in trying to improve health outcomes – determined in accordance with public health pluralism – of a population at a large scale and over time. Applying models that are weighted towards concepts and principles more prevalent in clinical ethics (which tend to prioritize individual interests) could undermine the goals of population screening by focusing on individual reproductive choices and potentially neglecting the collective goals of promoting equitable access and just distribution of resources (Dive and Newson 2021). When considering what information is suitable to offer in the context of population screening, the criteria are different (Brothers, Vassy, and Green 2019) – personal utility or individual preferences might not be sufficient justification. Further, claims for giving individuals all the information they want need to be considered against a backdrop of the significant hype surrounding individualized healthcare, including emphases on maximal information and intervention under a rhetoric of empowerment.

RGCS, beyond supporting reproductive decision-making at an individual level, is also offered at a scale large enough that it must also support equitable access to health care and just distribution of healthcare resources. Even when offered commercially on a user-pays basis, providing information that lacks clinical utility – in other words, that does not contribute to the goals of screening – has the potential to exacerbate existing inequities in the distribution of healthcare resources. It is difficult to ask people to think about such benefits and harms at a collective level, as it involves stepping back from an individualized mindset that is pervasive in healthcare. Further, it is questionable to provide information with little or no relevance to reproductive decision making (since supporting reproductive decision

making is the purpose of RGCS), especially if it triggers follow-up or cascade testing and further interventions (and consumption of healthcare resources).

By tacitly implying that genomic information is always valuable no matter the clinical utility (i.e., that personal or perceived utility alone can justify giving people all the information they want), we risk exposing participants in screening programs such as RGCS to a kind of epistemic fatigue. This kind of fatigue, generated by the desire or requirement to gain knowledge and the associated over-exposure to information, can make it difficult to process more information, ultimately affecting one's capacity for autonomous decision-making. There are wide-reaching collective implications of epistemic fatigue that go beyond potential individual psychosocial harms. These include potential costs to healthcare systems as individuals seek to know more based on genomic information that is difficult to interpret, even by experts. The implied responsibilization of health (van der Hout et al. 2019) that comes with access to large amounts of genomic information may strain resources as people who can pay for further testing or interventions are encouraged to pursue them. When considering the normative weight of individual preferences for increasing quantities of genomic information it is crucial to balance those preferences against potential harms, whether to individuals or to the healthcare system.

Are we missing an opportunity?

It is not difficult to imagine a scenario in which some of the distinctions we have relied upon in this paper, such as the possibility of defining genomic screening programs as stand-alone entities, collapse. If we assume that our genomes remain more or less static over our lifespan,[6] programs are emerging in which a sequence is generated (for example, at birth) and then stored, to be interrogated across clinical, research or population health settings and throughout the individual's lifetime. Taken at its simplest, such an approach would just need a different variant curation pipeline depending on who was looking for what, and when.

If the prospect of genome-first care becomes more widespread and accepted, then some will argue that not only is looking beyond the core purpose of population genomic screening desirable, it is also a moral imperative. Such a view might be argued, for example, on the basis that information about actionable variants that have high penetrance for serious conditions could have a positive impact on a person's

[6] This is, in reality, likely to be a rebuttable presumption – at least insofar as epigenetic modifications of gene expression are concerned.

health, and may not otherwise be identified, reported, or returned. It could be argued on the grounds of equity that offering genomic screening via affordable, large-scale programs may provide an opportunity for less well-resourced people to access valuable health-related information. Some may also go further to argue that we should be routinely seeking and reporting genomic information (at least that pertaining to highly penetrant and actionable variants) regardless whether participants in screening were informed in advance. In other words: why wouldn't you?

This position provides what appears to be a compelling case for reporting all the genomic information that people such as those participating in RGCS may want. However, the wide generation and reporting of genomic information beyond the aims of population screening may not be as simple as it first appears, for at least five reasons. First, genomic prediction remains imperfect, particularly in diverse populations. We cannot presume uncritically that genomic information will always be valuable and caution is still urged in offering such findings even in clinical practice, where infrastructure to facilitate shared decision-making is better embedded (Brothers, Vassy, and Green 2019). Second, a position informed by a "*why wouldn't you?*" rhetoric neglects ongoing structural inequities in health and health literacy by assuming that anyone will be able to make a considered decision about receiving this information and have ready access to ongoing care. Third, health systems are not yet resourced to manage the influx of patients who will be identified with actionable variants from population genomic screening. Even if detection rates are low, with potentially hundreds of thousands of people being screened the additional burden of referrals may place substantial strain on resource-stretched services. Fourth, personalizing medicine can entrench the "individualization of risk", where a focus on personal risk factors distracts "public policy focus away from the upstream determinants of population health" (Taylor-Robinson and Kee 2019). While personal risk factors will be relevant to population health, they should not be emphasized at the expense of a more "nuanced complex systems perspective" on health and its distribution, in which it is recognized that structures of society and health care themselves determine health (Taylor-Robinson and Kee 2019). Fifth, not all sequencing is necessarily equal. An exome produced now may be less useful in 5-10 years when sequencing technology has progressed and may incorporate factors like epigenetic information. While further elucidating each of these points in detail is beyond the scope of this paper, we contend that all need to be actively considered before the prospect of returning genomic information beyond the goal of a population screening program is implemented. Population health focuses on the *distribution* of health as well as the level of health in individuals, and maintaining emphasis on equity is an important element of attending to justice.

With that said, we recognize that our argument pertains to the current status of genomic knowledge, the cost and accuracy of current sequencing technologies, the current status and funding of health systems and ongoing population health disparities. As such, steps might be taken within population genomic screening programs now to preserve the opportunity for subsequent generation and reporting of genomic information in the future, such as securely storing data over time with appropriate consent. This could allow – when the various resources permit – for future reanalysis, reinterpretation and population offer, for well-defined highly penetrant variants while at the same time preserving the proper focus of the screening program.

Conclusion

With the expansion of genomic screening programs like RGCS, it is important to consider whether such an intervention should be used as an opportunity to provide genomic information to the target population that falls beyond the particular program's scope. In the case of RGCS, the program is intended to inform reproductive decision making. We have argued that there is significant complexity in determining whether such information would have clinical, or even personal, utility for screening participants and for population health. Further, we have argued that providing information beyond the scope of a particular genomic screening offer is inequitable and has the capacity to exacerbate existing health inequalities. Some of these reasons are based in the current state of knowledge about the causal role of an individual's genome in their future health outcomes, and that could change over time. Our broader point is that it will always be important to design large-scale offers of genomic screening in ways that promote a just distribution of health benefits across the population.

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