Pharmacogenomics and Personalized Medicine

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REVIEW

Are We Ready for Whole Population Genomic Sequencing of Asymptomatic Newborns?

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Abstract: The introduction of genomic sequencing technologies into routine newborn screening programs in some form is not only inevitable but also already occurring in some settings. The question is therefore not "if" but "when and how" genomic newborn screening (GNBS) should be implemented. In April 2022, the Centre for Ethics of Paediatric Genomics held a one-day symposium exploring ethical issues relating to the use of genomic sequencing in a range of clinical settings. This review article synthesises the panel discussion and presents both the potential benefits of wide-scale implementation of genomic newborn screening, as well as its practical and ethical issues, including obtaining appropriate consent, and health system implications. A more in-depth understanding of the barriers associated with implementing genomic newborn screening is critical to the success of GNBS programs, both from a practical perspective and also in order to maintain public trust in an important public health initiative.

Keywords: bioethics, infants, consent, genomic sequencing

Introduction

Newborn screening (NBS) is one of the world's most successful population screening initiatives.[1] It aims to identify newborns with serious but treatable conditions prior to the onset of clinically detectable symptoms, in order to prevent irreversible damage or death.[2,3] When implemented successfully, NBS programs screen >99% of newborns and are delivered with high public trust. Yet while NBS programs have been implemented widely at a global level, coverage remains nascent in some settings. There is also variation in what conditions are screened for and whether consent to screening is gained.[4–6]

Traditional NBS programs mostly measure biochemical markers in blood collected onto blood spot cards within the first 48 hours of life. This method is highly accurate but limits the number of conditions that can be detected to those for which a biochemical marker will be detectable straight after birth. Advances in DNA sequencing technologies, together with improvements in variant curation and reduced costs, have led many countries to begin exploring the use of such methods in NBS. Using genomic sequencing could identify variants undetectable via biochemical screening that either will, or are likely to, cause disease.

The introduction of genomic sequencing technologies into established population newborn screening programs in some form is not only inevitable but also already occurring in some jurisdictions.[7] The question is therefore not "if" but "when and how" genomic newborn screening (GNBS) should be implemented. The answers to these questions are continuously evolving as the technology progresses. As such, further exploration of these questions is both warranted and timely.

Received: 8 February 2023
Accepted: 19 June 2023
Published: 1 July 2023

In April 2022, the Centre for Ethics of Paediatric Genomics, based at the Murdoch Children's Research Institute in Melbourne, held a one-day live virtual symposium exploring ethical issues relating to the use of genomic sequencing in a range of paediatric clinical settings. The symposium included a panel discussion exploring the question: "Are we ready for genomic newborn screening?" Panellists comprised bioethicists, Prof Julian Savulescu (University of Oxford), Prof Ainsley Newson (University of Sydney), Prof Lynn Gillam (University of Melbourne; Panel Chair), and expert researchers and laboratory scientists, Prof John Christodoulou (Murdoch Children's Research Institute) and Dr Meaghan Wall (Victorian Clinical Genetics Services).

This review article presents both the potential benefits of wide-scale implementation of genomic newborn screening, as well as the practical and ethical issues raised in the panel discussion, including obtaining appropriate consent, and health system implications.

Materials and Methods

The panel session was structured around a case study designed to prompt discussion about various issues relating to implementing genomics into NBS. The scenario described a situation where two new parents were offered the choice between conventional and GNBS for their baby, as well as being asked to choose between receiving results that only indicated treatable/preventable conditions with onset in childhood or also receiving results for childhood onset conditions that are untreatable/unpreventable. Panel members were asked to describe a range of factors, such as the difference between conventional NBS and GNBS and the limitations of both methods. The panel members were also asked to consider a situation where the father could not be contacted to be part of the decision-making process and so was not in a position to potentially give consent for the baby to receive GNBS, rather than conventional NBS.

The panel session was recorded and transcribed. As this paper does not report on research with human participants, ethics approval is not required. The issues discussed were collated and synthesised by DV. They fell into seven major categories, which are discussed below.

Discussion

What are the Benefits and Technical Limitations of Using GNBS Compared with Conventional NBS?

Conventional NBS, which measures various biochemical markers in the blood, is relatively straightforward. It currently assesses over two dozen analytes and provides very robust and well-understood results. It is effective, cheap, and has high sensitivity and specificity, meaning it is a good screening test and, for most conditions, gives few false-positive results. The consequences associated with the results of biochemical screening are well understood, such as prognostic confidence in the likely spectrum of outcomes for the babies screened. This is important because it enables parents to be given information about a set of well-characterised conditions. As with most screening, these markers serve as a first-line test. Subsequent diagnostic testing is usually required following an initial screen-positive result.

Genomic sequencing technologies (GS) have been revolutionary in the diagnostic setting by increasing the diagnostic yield across a range of genetic conditions and providing answers for previously undiagnosable patients. The benefit of using GS over both traditional (Sanger) sequencing and screening using biochemical markers is the fact that it can interrogate many genes at the same time. More recently, turnaround times for GS have decreased from months to weeks or even days in some laboratories,[8,9] which have made it suitable for time critical settings, such as clinical testing in critically ill children in acute care.[10–13] These improvements in the speed at which results can be delivered have also meant that GS can be suitable for population-based screening programs where time is an important factor, such as reproductive carrier screening and newborn screening.[14–16] However, any move from the use of GS in clinical care to its use in population health will be complex and multi-dimensional. While the sequencing technology is the same, its use in clinical diagnosis (with access to family history) and its large-scale population application are distinct.[17–19]

In one respect, it would be relatively easy to obtain DNA in order to do GNBS; it can be extracted from the dried blood spots currently collected for conventional NBS. However, genomic data cannot be generated and analysed as quickly as is the case for biochemical screening. Integrating genomic sequencing into NBS will also involve analysing

much more data, which includes sifting through the normal variation within our genomes. If variants are identified in genes associated with genetic conditions, in many cases the variants have never been seen before so we cannot be definitive in drawing links between the variant and a genetic condition. This is already challenging in the diagnostic setting where a patient has a phenotype that correlates with a gene in which the variants have been identified, but in a screening setting where any potential phenotype is not yet apparent, determining the significance of a variant is considerably more challenging. This can make it difficult to have a high degree of confidence about what the implications might be for that baby and their family. As such, for the current range of conditions screened for by conventional NBS, GNBS has nowhere near the sensitivity and specificity of biochemical screening.[20] To address this issue, a carefully curated gene and variant list will be required to implement GNBS at scale; only variants that are highly penetrant, well characterised, and where we can be confident about the pathogenicity of the variants identified in the absence of a phenotype would be included. Here, helpful lessons can be learned from other initiatives that have already trialled population-scale genomic sequencing, for example reproductive genetic carrier screening.[21]

One example where genomic sequencing will potentially be useful in the newborn period is as a second-tier test for conventional newborn screening. One of the panel members discussed how, in some instances, conventional NBS identifies conditions that can have multiple presentations that cannot be differentiated between based on the biochemical result. An example of this is very long-chain acyl-CoA dehydrogenase deficiency (caused by biallelic variations in *ACADVL*), which can either present in infancy with very severe cardiomyopathy and multi-organ failure or in adolescence or adulthood in an individual who is undergoing intensive exercise and develops rhabdomyolysis. However, because there are correlations between at least some changes in the gene and the likely clinical outcome that could be predicted, genomic sequencing could be used to guide whether this baby needs intensive management or can be monitored and advised as they get older to avoid the potential triggers for the rhabdomyolysis.

But can genomics ever be used to detect something that biochemical screening might not? The answer to this is yes and can include inborn errors of metabolism whose signature metabolites are not currently part of NBS programs (e.g., Smith-Lemli-Opitz syndrome, caused by biallelic mutations in *DHCR7*), or for disorders where there are no biochemical markers but for which there is a strong gene-condition association which is highly actionable (e.g., bilateral retinoblastoma caused by biallelic mutation in the *RB1* gene). Pilots in other screening contexts, such as reproductive carrier screening, that have used a genomic intervention as a first-line test have been very successful in indicating to a family that they might wish to consider a second-line intervention with a high degree of efficacy at a relatively low cost.[15,22]

Which Conditions Should We Screen for?

A major question that continues to arise when discussing implementation of GNBS is which conditions should be screened. Panel members raised that one conservative starting point could be to only include genes for which we have a biochemical correlate so we can refine what we know about the variants and how they relate to particular phenotypes. However, as mentioned previously, one of the benefits of using genomic sequencing technologies is that many genes can be sequenced and then analyzed at the same time. As such, it is tempting to adopt a "bigger is better" approach to screening programs that use this technology. However, the bigger the scope of screening, the more complex considerations regarding technical, psychosocial and ethical aspects become. Like any screening initiative, there should be established criteria about which conditions are both ethically and technologically appropriate to include.

In the past, the Wilson and Jungner criteria[23] developed by the World Health Organization (WHO) were the "gold standard" by which inclusion of conditions on NBS panels were measured. While helpful at the time, these criteria were developed with the intention that additions to screening panels could be made on a condition-by-condition basis. However, the fact that genomic sequencing can assess many genes at once, and the sheer number of gene-condition associations that are being identified, make the principles laid out by the WHO a poor fit for this new technology. More recently, these principles have been revisited and reinvigorated to adapt them to the genomic space[24–26] and have been used to help determine which conditions to screen in other settings, such as reproductive carrier testing.[21]

Another aspect to consider when determining which conditions to include for screening is public opinion. While this could be achieved using a number of methods, including surveys or interviews, Genomics England adopted a large-scale public deliberative approach in which they recruited 130 participants from the community across a range of different

socioeconomic backgrounds, religious backgrounds, and ethnicities. The participants were given some education on GNBS, how it could be helpful, and its potential implications, and then a number of questions were posed to them about whether and how GNBS should be implemented, including which conditions to screen for. The study showed that overall, the participants representing the general public were quite positively predisposed to the concept of genomic sequencing being implemented in newborn screening programs, particularly for potentially treatable childhood onset conditions.[27] This aligns with other studies assessing health professionals' perspectives.[28,29] In 2022, the Australian Government awarded $15M across five research projects to explore implementation of genomics into NBS programs, some of which will include engagement with members of the public. Understanding and incorporating public perspectives into decisions about GNBS will be critical to ensure public support for, and trust in, population health initiatives where high uptake is of such import. Public engagement will also go some way to addressing longstanding epistemic imbalances in describing genetic conditions, specifically the dominance of clinical perspectives.[30]

Of course, communities' perspectives can change over time. One panel member postulated that in the future, members of society may feel compelled to receive more information about childhood onset disorders that are not curable, but which can be managed. Once the accuracy of polygenic scores for conditions such as diabetes or hypertension increases, individuals may be more comfortable receiving predictive information about them. While some might question the utility of offering information about untreatable childhood onset conditions to parents about their newborns, there are compelling reasons as to why some parents might appreciate having this knowledge. One is to avoid a lengthy diagnostic odyssey when the child starts developing symptoms. Knowing a diagnosis in advance could remove the need for unnecessary and often invasive investigations, as well as potentially avoiding trialling inappropriate and ineffective interventions, such as medications or surgeries. Aside from the medical benefits, knowing about a serious and/or life-limiting condition in advance can help parents adjust to the information over time. They might want to make changes to their lifestyle to be able to care for their child once symptoms begin or take an extended period of time off work to spend time with their child if a shortened lifespan is predicted. It is also important to consider that if parents desire this information about their children and it is not offered via a public NBS program, those who can afford to do so will access it through private providers. Most importantly, such information could have reproductive implications and the decision to employ preimplantation genetic testing or prenatal testing in future pregnancies. However, it must be noted that including these types of conditions in screening for the 300,000 babies born in Australia a year would place a non-trivial burden on laboratories and have sizeable knock-on effects for the health system.

When and How Should We Inform (Prospective) Parents About Genomic Newborn Screening?

One major challenge is to determine at what time point it is best to approach parents, or prospective parents, to offer them GNBS. In a small number of countries, conventional NBS seeks consent or informed choice from parents at the time the blood spot is being collected. Good practice suggests that parents be informed about NBS in advance, for example via information provided at antenatal appointments and available online.[31] While the quality of this process has been debated,[32,33] newborn screening has high population coverage and high public trust. This information typically canvasses the rationale for screening, the process, some potential outcomes, and what happens next. The possible introduction of genomics to NBS raises the question as to whether and how the information provision and consent process for NBS should change. If GNBS was only looking for variants in the same genes as the conditions that are currently being screened for, then one could argue that the informational needs of parents being offered GNBS would be similar to current NBS programs. However, if implemented, GNBS is likely to test for many more conditions than conventional NBS, potentially in the hundreds. In addition, the nature of genomic sequencing means that there is also a chance of identifying incidental findings, even if analysis is limited to a set list of genes. Because the results from GNBS are genetic, compared to the biochemical methods used for the majority of conditions screened in current NS programs, they also may have more direct implications for other family members who may be at risk of carrying any genetic variants identified in the child, not to mention privacy concerns and the potential implications for the screened individual's ability

to obtain personally risk rated insurance products in the future. Questions around storage and sharing of the genomic sequence data will also arise, and existing questions around storage and secondary use of blood spot cards may intensify.

These additional complexities associated with GNBS compared to conventional NBS mean that consent processes will likely need to be augmented. Parents may also need more time to consider their choices. As such, and in keeping with current good practice, panel members proposed that prospective parents be informed about GNBS in advance, with enough time to allow critical reflection on their choice. It would also be important for this decision to be more than just a brochure in a bundle along with all the other material parents receive prior to the birth of their child. Ideally, it would involve a conversation with a health professional of some form, potentially their general practitioner, midwife, obstetrician or gynaecologist. However, if this is not feasible given the scale at which this would need to take place, a range of other tools can be used to help people clarify their values and understand their informational needs during pregnancy, such as online decision aids and videos. These types of interactive resources are being used in other settings, such as reproductive carrier screening and testing for secondary findings,[34,35] and are generally evaluated positively by the individuals using them to assist their decision-making.[36]

Another aspect to consider is that if testing for untreatable conditions was to be offered, when is the best time for that to take place? As discussed above, it makes sense for anything that is treatable to be tested for as soon as practicable to allow early intervention and mitigate any potential long-term negative sequelae. Yet, some panel members suggested it may be more appropriate to offer parents the option to receive information about untreatable conditions in their child slightly later, which would give them more time to reflect on their values in order to make a decision. This kind of staged approach has been used in other settings where GS is being used in time-critical settings to obtain a diagnosis and secondary information is offered a few months after the initial testing.[37]

However, we also need to keep in mind that GNBS is a public health intervention; it is a screening test, rather than a diagnostic one. The difficulty here is that a testing technology is being supplanted from the clinical setting to population health and being used in a similar way (ie, to "diagnose" an individual, even if they do not yet have symptoms). However, the use of genomic sequencing in population health will occur without the usual clinical accompaniments, such as performing a physical examination or taking a family history, that help make sense of any variants identified.[17,18] This makes decisions about which variants to report and how to do that at population scale very challenging. To combat this, panel members stated that we need to make sure that other resources are as useful as possible, such as ensuring the databases that we use to interpret these findings are representative of the population being screened, a point also noted by the participants in the public dialogue commissioned by Genomics England,[27] and that careful consideration is given to the health system impacts of wider screening.[38]

If GNBS is implemented, it will be because a group of experts collectively decided that it is in the population's interest to have this test and it is a cost-effective medical intervention. All newborns will be offered GNBS because early detection of a well-curated set of conditions will improve the life of those screened. In line with this, we need to move from a clinical paradigm to a population health paradigm, both in terms of infrastructure and ethical analysis. This will involve determining what the critical components are that need to be canvassed pre-test and what is best left to the post-test discussion for those who receive a positive result. This kind of pre-test engagement (which could be through a health professional, via online materials, or both) might involve explaining the principles behind the offer of GNBS, why it is being offered in the newborn period, the fact that it is optional, and describing, in broad terms, the kinds of conditions the test might detect.

So, what should an informed decision look like in a screening context? Panel members explained that the focus of pre-GNBS parental engagement would be on value clarification, which may include asking them about what it means to them to be a good parent to their child and unpacking the ways in which that can be socially constructed or individually determined. They should also be provided with enough information allowing them to make a decision they can live with, that is in accordance with their personal values and parenting ideals. However, the amount and nature of this information is likely to differ depending on the individual. Panel members suggested that, rather than a detailed discussion of the technology being used and a description of every condition that could be detected, parents should receive an explanation as to why they are being offered the testing and broad information about the spectrum of conditions that could be detected. They should also be made aware of the potential implications if something is found and that GNBS will not

detect everything. It would also be important to convey that because of the potential for harm to their baby if a treatable condition is not detected early, this (like conventional NBS) is something the parents should strongly consider taking up.[39]

Although there is no legal requirement for both parents to agree to NBS (and thus GNBS), several panel members felt that ideally it would be a decision that the parents make together. Of course, there are situations where this is not possible, for example, if one parent is uncontactable or incapable of being involved in the discussion. In the context of newborn screening, there is no emergency and therefore if one parent is not contactable but could be reached within a few hours, or even a day or two, it might be reasonable to delay the decision in order to have their perspective, provided this does not inject cost-ineffective inefficiencies at a system level. However, although technically feasible for DNA to be extracted from blood samples long after the initial collection, there are some conditions, like methylmalonic acidaemia, where delaying treatment for as little as a week can result in irreversible harm. As such, delaying the decision too long in order to include the second parent in the decision-making process is not advisable as it could have serious consequences for the baby's health. In addition, given the number of babies born each year, from an organizational sense, it would be difficult to manage a program where parents could elect how long they waited until they opted into GNBS (just as parents are not able to elect a timeframe of their choice for NBS now).

Should Parents Be Able to Choose Whether Their Child Has GNBS?

As noted above, whether consent should be sought for NBS versus mandatory participation is a long and globally debated topic.[39,40] Additionally, as also noted, in Australia, we engage parents directly about agreeing to NBS and, despite it not being mandatory, we have a >99% uptake and very high public trust in NBS programs. Maintaining that public trust will be critical to the ongoing success of any NBS program, including one that incorporates genomics.

So, why might parents not want GNBS for their child? Depending on how GNBS is funded, parents may not be willing to, or be able to afford to pay for GNBS and therefore may opt for conventional NBS. Some parents might have personal objections to probing the genome of their child and want to opt for biochemical analyses alone. This could be due to concerns about the kinds of predictive or incidental information that could be identified inadvertently, or about requirements to disclose genetic information to insurance companies, police, or other authorities accessing information about their child in the future (though the same information can be accessed from newborn blood spot cards). Other parents might consent to receiving GNBS for treatable childhood onset conditions but choose not to receive information about untreatable conditions, preferring not to know information about things they cannot change. Regardless of the rationale behind their choice, removing parents' rights to refuse a technology they may have fundamental concerns about may undermine the trust that is so critical to the success of our current NBS program.

But is there a point where GNBS is so beneficial to the health of a child that parents should not have the right to refuse testing? This might be even more relevant if we consider the potential benefits of sequentially interrogating the individual's genome across the lifespan, especially as polygenic scores for common conditions, such as diabetes, or propensity to obesity, become more widespread. To assess this, ethical approaches, such as the zone of parental discretion[41] could be used to analyse under which conditions it might be acceptable to override parents' decisions for their children regarding GNBS, as has been done in other (clinical) contexts.[42,43] One could argue that refusing to receive information about treatable childhood onset conditions would lead to harm for the child due to missed opportunities for early interventions that, in some instances, could cause permanent damage. On this view, screening for untreatable childhood onset conditions would come under the zone of parental discretion. This is because, despite the concerns raised about potential harm to the parent–child relationship and generating "patients-in-waiting", there is no solid evidence to suggest that testing would cause significant harm, nor that it would be so beneficial that not testing would constitute harm. Some might argue that the goal of health-focused initiatives should be increasing overall wellbeing, rather than just health.

However, with this said, there are some potential distinctions that should also be accounted for. First, GNBS is a population screening intervention and not clinical care, and the harm principle or the zone of parental discretion (both developed for clinical care) would need to account for this different setting. Second, we need to consider the relative potential health impact of GNBS compared to conventional NBS. We know that other public health interventions such as giving people access to

a range of healthy food options, opportunities to exercise and outdoors, and good education vastly outweigh genomics as a determinant of childhood health at a population level.[44] That is not to say that genomic information is unimportant; there are clearly cases where GNBS could be lifesaving. However, looking at this from a public health perspective, the relative impact is going to be comparatively minimal. Thus, for any particular child, the chance of picking up a treatable genetic condition, like PKU, is small, and some argue that parents have the right to expose their children to small risks of avoidable harm.

Third, as we noted earlier, we need to carefully consider the kind of ethical paradigms we employ in these discussions. When we think about clinical care, we tend to use ethics, values and concepts that come more from a clinical background, such as individual autonomy and individual values. Yet, when we think about public health and screening technologies, we start to shift our thinking towards concepts that link with population benefit, such as maximising population health and avoiding harm, but also bringing in approaches such as public health pluralism (which aims to reduce health inequity while also promoting autonomy).[17] If this process is not managed carefully, it could create a tension between caring for individuals versus populations.

How can this tension be resolved? GNBS will be a complex intervention, offered to a very large number of people who may not have any lived experience of any of the conditions that are being screened for. First, we need to carefully design the way the test is offered so that it facilitates genuine choice. Second, the test itself needs to be carefully designed to ensure that it is carefully justified and aligns with stakeholder expectations. A single test offer (or a small amount of choice, such as between treatable and untreatable conditions) may seem to override individual choices, and, in some ways it does, but that is because this approach adopts a population health paradigm, rather than a clinical paradigm; this is a key difference between offering a screening test at population scale compared to a clinically based test.

If as a society, we determine that parents should be allowed to choose which form of NBS their child receives, panel members felt that one thing to be mindful of is the way that offer is made. Studies conducted in other settings have raised concerns about parents feeling obliged to accept genomic testing for their child, even though they do not necessarily believe it is in their child's best interests, a concept referred to as the "inflicted ought".[45,46] By contrast, another study showed that parents expressed the greatest decisional regret when they selected the most limited genomic screening option for their child.[47] This could reflect that post-test they felt societal pressure to have done everything possible for their child and potentially reflects a wider societal phenomenon of priming individuals to believe that more information is better overall. Or it could reflect societal or other pressure not to employ genetic testing that they later regret. Therefore, if we are allowing parents to choose between NBS and GNBS, we need to be certain that we are offering it as a genuine choice which is free not only from coercion but also any subtle suggestions that not proceeding with GNBS is not a valid choice. However, this is difficult to achieve when the messaging around NBS programs is, and should be, that testing is in the population's best interests. Of course, we need to remember that, despite our best efforts to assist those making choices about GNBS, people may still regret their choice if they do not receive the desired outcome. Yet this does not mean that it was not in their best interests to make the choice.

How Do We Support Families Who Receive a Positive Test?

Using GNBS as a means of increasing the number of conditions screened for will also increase the number of newborns who receive a positive result. Using a population health paradigm, this is the point where more in-depth engagement with the family begins. If a baby is identified to have a positive GNBS result, they should be contacted by a genetic counsellor, go to a genetic service for an appointment, and receive referrals to any relevant clinical services for treatment if this is an option, or palliative care if that is deemed appropriate. At this time, parents are likely to feel upset, shocked and overwhelmed; most people who undergo screening generally do not expect to receive a positive finding about their, or their child's health status.[48,49] As such, parents will need support to come to terms with the new diagnosis. The "diagnostic shock" may be more pronounced than in clinical settings because, in most cases, babies will be asymptomatic at the time the result is delivered and they have not experienced the long, protracted series of investigations many parents face when receiving the diagnosis of a rare condition.[50] The feeling of being overwhelmed is likely to be exacerbated by the fact that they have a new baby, particularly if this is their first child.[51] As such, follow-up appointments should be made to ensure families feel adequately supported and have opportunities to ask questions and clarify information once

they have had time to get over the initial shock. It should be noted that existing NBS programs already have good structures in place to support families who receive a diagnosis. GNBS can utilise and build on those existing services.

Parents should also be informed of the other potential implications that result from the diagnosis, such as the potential for them to be carriers of the condition, depending on the condition's mode of inheritance, and the implications and what this means for their reproductive options in the future to potentially avoid having another affected child if they wish. The potential for cascade carrier testing in relevant blood relatives should also be mentioned.

What are the Funding Considerations?

As with any public health initiative, cost needs to be considered and the difference between conventional NBS and GNBS is sizable. Even though we are now almost at the point of being able to obtain a genome sequence for a $600 USD,[52] that does not take into consideration the costs associated with the analysis, nor data storage.[53] The development of automated technologies for analysis of sequencing data to minimise person hours required will be critical in reducing both the overall cost of the analysis and the time it will take to yield a result. Yet, even with automation, GNBS would still be at least 50 times more expensive than conventional NBS based on the cost of sequencing.

In addition, implementing anything like this kind of technology at scale requires a significant upfront investment in terms of having the right equipment, computational setup and bioinformatics, and workforce to enable end-to-end testing at the sort of speed required to implement it in a clinically useful manner for the community. Of course, some of these expenses diminish over time as one learns from the process and builds in efficiencies, and as the technologies used evolve and mature.

Furthermore, if the intention is to store the sequence data long term, panel members suggested we need to consider what data storage and management logistics would be required to do so. This includes ensuring adequate security, as well as cost-effectiveness, which will be challenging if we intend to store that data for the lifetime of the individual. The most feasible solution will be cloud-based storage that has all the necessary security measures in place to adequately protect the data.

What Other Longer-Term Opportunities Might GNBS Provide?

As noted, basing cost–benefit assessments of GNBS purely on the testing occurring in the newborn period will never show justification for using the technology over conventional NBS. Where genomic sequencing potentially could become more cost-effective is if sequencing data is stored and re-interrogated as new clinical questions arise over the lifetime of the individual. We refer to this as sequential interrogation. Say, for example, a child presents with seizures in infancy where we know that a) in half of cases it will have a genetic basis and b) identifying the genetic basis can dramatically influence how that child is managed. That is where having the option to go back to that information can not only improve the cost-effectiveness of the test but also increase the clinical utility of the test itself. Moreover, having the data stored means that the time it would take to generate the data is saved and a diagnosis can be identified more rapidly.

One panel member suggested that in the future, this knowledge bank could also, subject to appropriate consent and counselling, be reinterrogated to determine an individual's risk of developing a hereditary cancer or cardiac syndrome. It could also be used to assess more probabilistic risks, such as polygenic scores. However, care should be taken when attempting to apply clinical standards in a population health context and feasibility will require careful assessment. Regardless, if polygenic screening of common adult conditions began at birth, and targeted interventions could be employed, the public health benefits, and cost-effectiveness, could be highly favourable.

The successful implementation of a process like this in complex health and social systems needs significant scoping out and resourcing. Factors including storage costs and infrastructure and access to stored data across health settings need planning. Debate over reinterpretation and recontact following genomic sequencing remain ongoing (e.g.,[54]) and as yet there is no consensus as to how these questions should be resolved in the context of population screening. Additionally – and perhaps more importantly – population health literacy and buy-in, including plans for engaging with the child themselves once they are old enough, need careful consideration.[19,55]

Conclusion

So, are we ready for GNBS to be implemented? In short, not yet. As we have highlighted, there are many aspects that continue to need to be considered and resolved before GNBS can be successfully implemented. Although the context of this discussion has been Australian focused, these issues are, in most part, global. Clearly, determining which genes and conditions should be included, and under what criteria, is critical. Such a decision should incorporate both expert opinion and public engagement to maintain public trust. We need to ensure that parents are provided with sufficient information and support to be able to make genuine decisions about GNBS that are in line with their values. In order to achieve this, we need to consider GNBS within a population health paradigm and carefully design the program, particularly which types of conditions are offered and how much individualized choice this encompasses, to meet the demands of screening principles. We need to think about how a GNBS program will be resourced, including the potential for long-term health benefits to be realized, and ensure that it does not result in greater health inequities within the population. Finally, we need to ensure that using technology improves, rather than diminishes the NBS program's capabilities by focusing not just on what it could possibly identify but what are the attributes of the actual technology and why we are using it in this particular setting.

Acknowledgments

The research conducted at the Murdoch Children's Research Institute was supported by the Victorian Government's Operational Infrastructure Support Program. The Chair in Genomic Medicine awarded to JC is generously supported by The Royal Children's Hospital Foundation. This work was supported by the Australian Government through the Medical Research Future Fund, as part of the Genomics Health Futures Mission (Grant numbers 76749 and MRF2015937), and the Australian Research Council (Grant number DP190101547). We also thank Profs Lynn Gillam and John Massie, and Drs Fiona Lynch and Christopher Gyngell for their assistance in the planning and execution of the panel discussion.

Disclosure

Julian Savulescu is a Partner Investigator on an Australian Research Council Linkage award (LP190100841, Oct 2020-2023) which involves industry partnership from Illumina. He does not personally receive any funds from Illumina. Julian Savulescu presented at a Genomic Prediction-organised webinar (2021), but received no payment or other benefits from Genomic Prediction Ltd. Julian Savulescu is a Bioethics Committee consultant for Bayer. Julian Savulescu also reports grants from Wellcome Centre for Ethics and Humanities, Centre for Ethics of Paediatric Genomics, Murdoch Children's Research Institute, Chen Su Lan Research Funding, during the conduct of the study; and is an advisory panel member for the Hevolution Foundation, outside the submitted work. Professor Ainsley J Newson reports grants from Medical Research Future Fund, during the conduct of the study; and Ainsley Newson is a member of the New South Wales Newborn Screening Expert Advisory Group. The remaining authors declare no conflicts of interest in this work.

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