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"WE'VE OPENED PANDORA'S BOX, HAVEN'T WE?" CLINICAL GENETICISTS' VIEWS ON ETHICAL ASPECTS OF GENOMIC TESTING IN NEONATAL INTENSIVE CARE

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ABSTRACT

The increasing use of genomic testing in neonatal intensive care units (NICU) gives rise to ethical issues. Yet little is known regarding what health professionals implementing the testing think about its ethical aspects. We therefore explored the views of Australian clinical geneticists towards ethical issues in the use of genomic testing in the Neonatal Intensive care Unit (NICU). Semi-structured interviews with 11 clinical geneticists were conducted, transcribed and analysed thematically. Four themes were identified: 1) Consent: the craft is in the conversation, which encapsulated the challenges in the consent process, and with pre-test counseling; 2) Whose autonomy and who decides? This illustrates the balancing of clinical utility and potentially harms the test, and how stakeholder interests are balanced; 3) The winds of change and ethical disruption, recognizing that while professional expertise is vital to clinical decision-making and oversight of mainstreaming, participants also expressed concern over the size of the genetics workforce and 4). Finding Solutions – the resources and mechanisms to prevent and resolve ethical dilemmas when they arise, such as quality genetic counseling, working as a team and drawing on external ethics and legal expertise. The findings highlight the ethical complexities associated with genomic testing in the NICU. They suggest the need for a workforce that has the necessary support and skills to navigate the ethical terrain, drawing on relevant ethical concepts and guidelines to balance the interests of neonates, their careers and health professionals.

Keywords: whole genome sequencing; bioethics; qualitative research; intensive care, neonatal; paediatrics; genetics, medical.

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INTRODUCTION

Technical advances and cost reductions in genomic testing have facilitated increased access in research and clinical practice settings. [1, 2] Such testing can lead to an overall diagnostic yield of around 40% of cases and may also impact clinical management. [3-5] However, the diagnostic yield from genomic testing in neonatal intensive care units (NICU) appears to be higher (up to 70%), with management implications in up to 50-80% of diagnosed cases. [6-9] Nevertheless, genomic testing is not yet internationally recommended as a first-line test in NICU.[10]

Given the clinical need for prompt decisions, time-to-result is of special importance in the NICU. Studies have reported on the feasibility and performance of a "rapid turnaround" genomic testing model, [11] leading to decreases in both infant morbidity and cost of hospitalization. [12, 13] Emerging evidence regarding the cost-effectiveness of genomic testing in the NICU suggests that the use of such testing in this setting will continue to increase. [13-15]

Genomic testing can generate complex information, often subject to conflicting interpretations. [16, 17] Its use in children is subject to specific psycho-social and ethical considerations. [18, 19-21] When it is employed in the NICU setting, specific ethical issues also arise. [22-25] While issues arising in the NICU have parallels with those that can arise in other forms of paediatric genomic testing, this specialised setting also offers some more distinctive concerns, such as: ensuring appropriate consent at what can be an emotionally charged time, implications for bonding and treatment limitation (including considerations of disability), distributive justice in allocating scarce health resources to the test, whether to undertake targeted or broad testing (the latter of which may lead to increased identification of incidental findings or variants of uncertain significance), and whether directive counselling is appropriate in this context. Underpinning all of these

is the issue of genetic exceptionalism, namely whether a genomic test performed in the setting of NICU is just like any other diagnostic test, or whether it retains some of the properties that have typically led to additional safeguards and oversight for other clinical genetic tests.

Studies have described health professionals' views on genomic testing in paediatrics more generally, [26] and there is nascent literature examining the general views of health professionals on the use of genomic testing in the NICU. [27, 28] Little is yet known, however, about the views of the health professionals implementing the testing and the ethical issues arising from its application. This qualitative study aimed to explore the views of Australian clinical geneticists on the ethical issues surrounding genomic testing in the NICU setting. Results will inform the debate on the appropriate use of genomics in the care of the critically ill infants.

SUBJECTS AND METHODS

Recruitment

This was an exploratory qualitative study conducted via purposive recruitment. Clinical geneticists with experience in paediatrics were identified from existing professional networks and invited (by e-mail or face to face) to take part in the study by two members of the research team (KBS, DR). Recruitment continued until data saturation was reached.

Data Collection

Data was collected by way of telephone interviews (conducted by the author of this manuscript in the period of December 2017 – March 2018). Interviews were carried out using a semi-structured interview guide developed by the research team and reviewed by two independent experts and were iterative, building on information learned during the process and refined. The interview guide explored participants' experiences with genomic testing and their views on a number of ethical issues, reflecting the literature and the Investigators' clinical and bioethics expertise. There was a mix of focused and more open-ended questions. Interviews also utilised five short case vignettes, modified from Wilkinson et al.[24] (see Supplementary File 2) which were sent to the participants prior to the interview. Interviews lasted for 60-90 minutes.

Data analysis

Interviews were recorded, transcribed, de-identified and coded. Coding was managed in Microsoft Excel. To check for coding concordance, 3/11 interviews were assessed by three independent coders (KBS, JF and TA) with a concordance rate of >95%. The remaining eight interviews were coded by a single coder (TA). Thematic analysis using an inductive approach was used to identify themes. [29-31] This study was approved by the Human Research Ethics Committee at the University of Sydney, Australia (Reference: 2016/050).

RESULTS

In total, 32 Australian clinical geneticists were invited to participate. Of these, 25 expressed interest (and were provided with further information), and 12 gave consent to participate. Data saturation was reached after 11 interviews. Of the 11 participants, 7 were female, 9 were over the age of 50 years, 9 from New South Wales and 10 had more than 15 years' experience practicing mostly in paediatric and/or adult genetics, with experience in genomic testing. None of the participants' clinical practice was dedicated to genomic testing in the NICU.

Analysis of data led to four themes being identified: 1) Consent: the craft is in the conversation; 2) Whose autonomy and who decides? 3) The winds of change and ethical disruption; and 4) Finding solutions.

Consent. The craft is in the conversation

Participants acknowledged that achieving a meaningful consent process in the NICU may be challenging, given the complexity of genomic testing and the time pressures under which parents or caregivers need to make care decisions for a critically ill infant. These health professionals drew on their experiences to reflect on the strengths and limitations of the consent processes they were familiar with. While most participants agreed that obtaining consent for genomic testing is complex, some were more skeptical of achieving 'true' consent:

> "…given how early all this is, how difficult it is to really counsel informed consent to parents…" (Participant 7)

> "…do people understand what they are consenting for? No, they don't!" (Participant 6)

The consent process was often framed as being dictated by pro-forma materials provided by the relevant healthcare organisation, reflecting a tension between consent as a process or conversation and consent as a signature on a form. Some participants were concerned that every aspect of the discussion had to be documented:

> "If you try to incorporate all those possibilities [such as the possible findings and limits of the test] into your consent process, you end up with multiple pages of documentation, that no one reads or understands or wants to talk about." (Participant 4)

All participants spoke about the challenges arising from identifying incidental or secondary findings (when these are not masked) and the importance of this possibility being discussed with parents. While they felt the decision about whether to receive such findings should remain with parents, this may be difficult to rationalise in advance:

> "…it is up to the family to decide how they deal with this… It is a lot about consent." (Participant 1)

> "I think what informed consent about a secondary finding means is that you depend on them [parents] having imagination [...as to what it will be like...] and I find that's very challenging for people and parents [...], until it happens, the impact on them is not really felt…" (Participant 5)

Others appeared to express scepticism about a seemingly exceptional approach to genomic consent:

> "Just because something is genetic or genomic, we need to wrap it in multiple layers of complex consent and bureaucracy…" (Participant 4)

Nevertheless, most participants agreed that, at this point in time, consent to genomic testing in children remains necessary:

> "...the only time you don't need a consent is when it's a lifesaving thing in the NICU and you can't get parental consent ... There's no genetic test that is a lifesaving test so there'd never be a case when you'd do it without consent." (Participant 9)

> "I think the answer at the present time is no [to testing children without consent]. I think that – yeah, that's a really, really difficult question. [...] Yeah, we really opened the Pandora's Box..." (Participant 5)

All participants were of the view that parents should have the right to decide what kind of results from genomic testing are returned, although views diverged if a condition was identified where an intervention was available in childhood. Participants also agreed that it is important to have an open conversation about the test, and that genetic counseling is valuable. Conversations with parents should acknowledge the limitations of the test:

> "I think it's important when we are counseling patients and families, when we do this sort of testing, that it's not perfect and it's not always going to find the answer… people see this on television and they come and they talk about a test that can do everything… an answer test for everything…" (Participant 8)

> "…sitting there with people and watching them or listening as they work through the pros and cons and giving them time is really very valuable." (Participant 5)

Whose autonomy and who decides?

Participants spoke about the justification for genomic testing in unwell infants, describing that this necessitates balancing the benefits and harms and the (sometimes conflicting) interests of the various stakeholders involved. Most agreed that diagnostic genomic testing is justified when the clinical utility and potential benefits outweigh the potential risks:

> "… in these kinds of cases they are diagnostic tests, they are not predictive tests… [If] there is reasonable chance that we will find something … [that] would actually help either the managing doctors with treatment or prevent the child from having unnecessary investigations, … then I would be comfortable ordering a test." (Participant 8)

Most participants acknowledged the limitations of genomic testing and the potential for harm. One participant spoke of a case where a devastating condition was identified from a genomic test performed early in life:

> "I think we have seen harm done… [T]he consequences are more severe than we realised, and it's all been done in a bit of a rush and a hurry and the time when you really don't know very much about this baby..." (Participant 7)

Others raised concerns with the prevailing rhetoric of choice and autonomy in clinical medicine:

> "So, potentially we are causing harm by offering too much choice… [P]eople often think that, you know, choice equates to autonomy, and that is a good thing, but I do think this is a very complex area, and we can't assume that choice actually makes life better for the family." (Participant 4)

> "I think in our society we over-emphasise that [autonomy] in some contexts. And autonomy is to be valued very, very highly except when it isn't the most important thing…" (Participant 6)

Most participants extended the benefits from genomic testing to the parents and the family, and some participants balanced the child's purported right to future autonomy in the context of the potential benefits for the wider family:

> "… you have to think carefully about the family as a whole, rather than the child as an isolated autonomous being. I think you need to talk about the family genetics being a family matter that can be thought of as a different kind of autonomy." (Participant 6)

The 'winds of change' and ethical disruption

Participants spoke about how genomic testing is changing clinical practice, both for them and how they engage with other health professionals. Knowledge and norms of the use of genomic testing are still (rapidly)

emerging. At present, professionals are keen to expend a scarce resource wisely while generating evidence for future implementation:

> "So… for certain indications, it is very good, for others, there is very poor availability of testing. So, you know, definitely much better than 5 years ago when we weren't doing any, but still a long way to go… We are not really concerned about increased availability; we are concerned about sustainable models of funding and implementation." (Participant 4)

> "…we think very hard – we struggle about the decision about whether to do whole exome or whole genomes for a baby in the NICU for example … And this is evolving. It is even different from what we might do six months ago. We are changing." (Participant 6)

While all participants spoke about the important role genetics professionals have in managing the mainstreaming of genomic medicine, they expressed concerns about the lack of an adequately sized workforce:

> "…genomics is running ahead of workforce… We're doing better, but there is an ethical issue here: is having this type of information but not being able to deliver and support people in interpreting it and providing them with psychosocial, emotional support [acceptable]? …it is immoral that we do this unless we have a trained workforce…" (Participant 1)

Concerns were also raised about non-genetics specialists ordering testing:

> "… there are endocrinologists I know and other people who think it's very clever to order these genomic tests, that they have no idea what they're doing or how to interpret them, all the ethical issues behind it." (Participant 5)

> "I don't think that non-genetics professionals actually understand the full implications of testing…. They don't understand variants… the potential for incidental findings… So, it does worry me…" (Participant 3)

Others, however, took a more pragmatic approach:

> "I don't think geneticists have a monopoly necessarily on that, the principle really should be that people should only be ordering the test if they know what they are doing." (Participant 4)

Participants showed an affinity for what can been termed 'ethical disruption', caused by the introduction of a new technology. Responses to the case vignettes in particular suggests participants were concerned about 'moral distress', which occurs when a moral event (such as a moral tension, conflict, dilemma, uncertainty or constraint) brings concomitant psychological distress (such as frustration, feeling torn, regret and so on).[32]

> "… all of these [cases] are hard, I find them very difficult. If you ask me tomorrow, I'm not sure I'd give the same answers. I mean hopefully I would, but they're all fairly difficult…" (Participant 9)

> "…what really concerns me in all this… I still don't think we have the knowledge and wisdom that we think we have..." (Participant 5)

Participants were probed on their views on genetic exceptionalism, given that the advent of genomic testing has reinvigorated this debate. Some supported an exceptionalist framing:

> "I don't think it's just like any other test at all. Most of those [other] tests are looking for specific things and don't have such a chance of finding something unexpected. At the moment genomic testing is fairly new and even the people who have been doing it for some time still get surprised by the things that get reported..." (Participant 8)

Others rejected this approach:

> "It is not any different from any other information you might get… You may do a renal ultrasound and find that the baby's got no kidneys, which will have just the same impact. There is nothing special about genomic testing in that regard." (Participant 1)

Finding solutions

When engaging with the technical, clinical and ethical complexity that comes from genomic testing in the NICU, participants spoke about the importance of working with an interdisciplinary team and partnering with parents/caregivers.

> "I guess what we try to do in our unit is discuss it as a team and come up with a consensus to offer to parents." (Participant 7)

> "… that is a complex discussion with the family and the medical team, and genetics has a role in that […] [in] some cases you can't let the parents dictate the management, when you are dealing with something that will impact other cases that actually have a potential for a better outcome." (Participant 2)

When asked how they would resolve the ethical dilemmas in the case vignettes, most participants took a contextual approach, highlighting the need to consider individual circumstances:

> "We do it on a case by case basis. If we had concerns with that case, we wouldn't do it. So, we judge each case as it comes." (Participant 9)

In turn, some clinical geneticists acknowledged the need for developing guidelines to help harmonise practice:

> "…you'd have a range of opinions… and these are sort of questions for which there needs to be some kind of a consensus… uniformity across, I think nationally, with acceptable standards…" (Participant 2)

A few participants said they would seek help from a hospital clinical ethics committee or the legal system to resolve complex disagreements with parents, especially if there was uncertainty as to best practice.

DISCUSSION

This qualitative study is the first to specifically examine the views of clinical geneticists experienced with genomic testing in the NICU regarding the ethical issues generated by such testing. Participants considered genomic testing in an outcomes-focused fashion, weighing up potential benefits and harms. The main reason given in support of genomic testing was to establish a diagnosis and to inform future management. However, concerns over the child's future autonomy and the future sustainability of this kind of testing were also expressed. Some participants also pointed to the benefits from genomic testing being seen in the context of the family as a whole, including parental health and future reproductive choice.

In contrast to some other studies, [e.g. 27] participants thought that gaining parental consent for genomic testing in the NICU is usually necessary, although some appeared to express a desire to be able to get on with exercising their professional judgement – including around what variants to return. At the same time, they also generally supported the notion that parents should have a say in what kind of additional (incidental or secondary) results are returned following testing. It is worth noting that Australian practice is, in general, in line with more conservative approaches to returning secondary findings. If a result is genuinely incidental (unexpected), it tends to be reported. But the process of deliberately searching for secondary findings at the same time as seeking a diagnosis remains rare. As such, participants were more measured in their enthusiasm for the return of such findings than some other studies of paediatric genomic testing have shown.[26]

Participants also raised concerns regarding the potential for 'information overload' in the consent process and problems from reasoning around complex and potentially ambiguous information. Participants emphasised the need for ongoing conversations with parents, consistent with the idea of moving away from the traditional emphases on information and choice provision as sole facilitators of autonomy. [33]

This also suggests a more relational approach to autonomy, one which incorporates the social context of decision making, based on honesty, openness, and trustworthiness. [34]

When faced with challenging ethical dilemmas, particularly around the uncertain nature of genomic results, or the potential for genomic testing in the NICU to abruptly change the course of treatment, clinical geneticists appear to be at risk of moral distress. Similarly, Szego *et al* [26] identified a paradox when a sought-after new technology has unintended consequences. Unlike participants in a 2019 focus group study by Knapp *et al* [27], our participants did not mention that this kind of testing raises the prospect of eugenics. This apparent distress also draws on the fast-paced rollout of genomic testing in the NICU. We observe this against a wider background rapid mainstreaming of genomic medicine.

Participants' approaches to preventing or resolving complex clinical and ethical situations when testing in the NICU was nuanced. They focused on building partnerships with parents, engaging with the expertise of multidisciplinary teams and taking a 'case by case' approach with attention to local context.

Aware of the ongoing challenges and changes in the practice of clinical genetics brought by the introduction of genomic technologies in medicine, participants would welcome external advice, such as professional guidelines or access to clinical ethics support.

Australian clinical geneticists were unequivocal about the critical role genetic counseling has in both preventing and mitigating most of the ethical issues arising in the genomic testing of children, including in the NICU. This is achieved through the provision of necessary/required information and emotional support and also, by building ongoing trusting relationships with the parents and families. In line with other studies, [28] participants emphasised the pressing need to strengthen the existing genetics professional workforce to facilitate the mainstreaming of genomics.

This exploratory study is subject to some limitations. Participants were purposively invited and self- selected, and they mostly practiced in New South Wales. In addition, qualitative data is not intended to be representative of the views of clinical geneticists everywhere. While all participants had experience with genomic testing, not all had extensive hands-on experience with testing in an NICU setting. Interestingly, our study did not identify the ethical issue of unequal access to genomic testing due to financial and geographic constraints in Australia, perhaps explained by the publicly funded Australian healthcare system (with the assumption that NICU genomic testing is listed on the medical benefit scheme) and by the centralised way laboratory work is performed, allowing access to testing from any NICU unit in Australia (at the time of the study offered mostly on research basis).

Australian clinical geneticists supported the use of genomic testing in the NICU, balancing the potential benefits and harms and the interests of the child, the parents, and the clinical team. They emphasised the paramount role that careful genetic counseling plays in building a partnership with the parents and the growing need for building up the genetic workforce to adequately support the implementation of genomics into mainstream medicine in Australia.

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Declaration of Interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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