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Rapid challenges: ethics and genomic neonatal intensive care

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Abstract

Neonatal intensive care units (NICUs) are a priority implementation area for genomic medicine. Rapid genomic testing in the NICU is expected to be genomic medicine's 'critical application', providing such clear benefits that it drives the adoption of genomics more broadly. Studies from multiple centres worldwide have now demonstrated the clinical utility and cost-effectiveness of rapid genomic sequencing in this setting, paving the way for widespread implementation. However, the introduction of this potentially powerful tool for predicting future impairment in the NICU also raises profound ethical challenges. Developing models of good practice that incorporate the identification, exploration and analysis of ethical issues will be critical for successful implementation. In this paper, we analyse three such issues: 1) the value and meaning of gaining consent to a complex test in a stressful, emotionally-charged environment; 2) the effect of rapid diagnosis on parent-child bonding and its implications for medical and family decisions, particularly in relation to treatment limitation; and 3) distributive justice - whether the substantial cost and diversion of resources to deliver rapid genomic testing in the NICU can be justified.

Introduction

Genomic tests (such as whole genome sequencing (WGS) and whole exome sequencing (WES)) are improving the diagnosis of rare genetic disorders in pediatric patients, with substantially more patients receiving an accurate diagnosis than with conventional genetic testing.1–6 While studies in patients primarily recruited from neonatal intensive care units (NICUs)6–12 have consistently reported high diagnostic yields (30-73%) and high clinical

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utility, more recent studies suggest that the delivery of results in this setting with rapid turnaround times provides a further advantage.6,8,10–12 Standard WGS and WES typically return results after 3-6 months. In contrast, the current record for fastest turnaround time for rapid WGS stands at 19.5hrs,13 and turnaround times of 2-21 days are becoming routinely achievable through clinical laboratories, paving the way for wider implementation. Rapid genomic testing (RGT) in the NICU is expected to be genomic medicine's 'critical application', providing such clear benefit that it drives the adoption of genomics more broadly within healthcare systems.14

Providing treatment in an intensive care unit is expensive (US$3000 per patient, per day).15 RGT holds the prospect of enabling more specific and more effective treatment decisions. 6,8,10–12 For a small number of patients, a specific diagnosis can be life-saving. Increasingly, such a diagnosis can also provide the opportunity to access experimental treatments for rare diseases, some of which may not be accessible in the country of origin.16 For a much larger group, diagnosis can lead to a reduction in painful and invasive investigations, tailored management and surveillance for complications, and potentially improved longer-term outcomes. A specific diagnosis of a lethal or severely debilitating condition may mean earlier discussions about palliative care.

RGT poses significant clinical and laboratory challenges.10 Successful implementation necessitates many changes to established working patterns of all professionals involved, including intensivists, clinical geneticists, genetic counselors and laboratory scientists. It also costs around twice- to four-times as much as standard WGS and WES.

RGT also raises significant ethical challenges.17,18 Some of these are shared with other prognostic tests and technologies, and some are shared with perennial questions around the care of very unwell newborns.19 These include normative uncertainty, and the challenge of identifying when a prognosis is sufficiently poor that treatment may be withheld, or sufficiently good that it must not be (see hypothetical cases Box 1).19

In this paper, we focus on three specific ethical issues raised by RGT in acutely unwell babies with suspected underlying genetic disorders the NICU. After introducing some illustrative case studies, we discuss: (1) aspects around consent for rapid testing in the emotionally charged environment of the NICU; (2) the effects rapid testing can have on the child-caregiver bonding and the relevance this may have for medical decisions; and (3) issues of distributive justice raised by RGT.

Consent to rapid testing

1) Aspects of consent to RGT

Genomic information is characterized by its volume and that it may give rise to uncertain, probabilistic or unexpected results. Its meaning will also almost certainly change over time, as genomic research advances.20–22 Discussions of consent to genomic testing recognize these features. It is widely accepted that the 'traditional' paradigm of fully informed consent is unsuitable for genomics,23,24 because it is not feasible to explain each potentially identifiable condition in detail. To date, ways of managing this issue have focused on

changing how information is discussed, such as ‘binning’ conditions,25 adopting broad or generic consent,26 or taking a tiered approach27 to information provision. A list of minimal elements to consent, albeit one which remains focused on description and information, has also been proposed.28

A potential challenge to consent to RGT is that the perceived urgency of testing, as well as the rapidity of obtaining results, leaves little time for critical reflection by parents. They are also likely to be experiencing substantial emotional distress from their child’s illness. The allure of testing, especially a new test not available elsewhere, and the natural tendency to be information-seeking in times of uncertainty may mean that parents agree to a test without fully appreciating its implications. Concerns have already been raised about the overly positive portrayal of WGS and WES, and the danger of this creating unrealistic expectations among the public.29 Therefore, rather than focusing on whether information should be binned, tiered or something else, those obtaining consent to RGT should talk with parents to promote realistic expectations from testing. They should also engage them about the broad goal of the test, clarify parental values and hopes, canvass the possible impact of the test on bonding (see further below) and discuss potential misunderstandings.

2) Non-directiveness and refusals of testing

It is widely held that genetic testing in children should only occur with parental consent, and counselling around testing should be non-directive. However, RGT is arguably distinct from many other genomic tests because it is typically employed early in the diagnostic trajectory of a critically ill infant where there is a suspicion of an underlying genetic disorder and may have much greater clinical utility.6,8,10–12 The nascent use of genomic testing in healthy individuals has also led some to argue that directive genetic counseling – where a professional takes a more active role in providing advice, guidance or recommendations – can be condoned.30–32 We suggest that directive genetic counseling may also be appropriate for at least some RGT in the NICU. While parents need to be able to both understand the possible outcomes of the test and should have the chance to reflect critically on their decision to have RGT, the known clinical utility of these tests8,10–12 means that the test can frequently have direct implications for subsequent treatment. This could be said to make RGT more like the kinds of medical tests that are routinely performed in NICU without explicit parental consent. However, given the possible implications for other family members, potential for future discrimination, combined with often uncertain direct benefit, gaining explicit consent to RGT remains prudent. Further, any directive counseling should not amount to coercion. Instead, those obtaining consent should describe how the evidence to date demonstrates the value of the test and that testing may be in their infant’s best interests.

Some parents may refuse RGT, due to concerns such as future discrimination, fears about losing hope, or misunderstandings about what the test may tell them. While initial refusals can change once parents have had a chance to reflect further10, some parents may continue to refuse RGT even when there is clear evidence of clinical utility. If the test is being recommended to enable access to a particularly effective treatment (especially one that may be very expensive, such as transplantation), or to avoid a harmful or futile treatment, then

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exploring undertaking the test despite the parents' refusal may be appropriate.33 However, any refusal should be managed on a case-by-case basis, with careful engagement with parents. Uncertainty in the results will also continue to be relevant – at least in the short term – given the rarity of some of the conditions identified. Wider factors such as the ongoing therapeutic relationship and the clinical team's confidence in the value of the test should also be addressed, and clinical ethics consultation services should also be involved where available. In some jurisdictions, there could be a role for the law in the face of intractable disagreement between the care team and the baby's parents about whether testing would in the child's best interests.15,16

These claims about directive counseling and test refusal are also easier to defend if RGT is carried out in a particular way. RGT that actively masks secondary findings and does not separately analyze parental genomic data for additional findings will mitigate unanticipated information being disclosed (and lessen the implications of the test for the parents' own health) and will be easier to justify for a directive model of offer. Testing this way is also clearly oriented to looking for a cause for the unwell infant's condition, rendering the test more like other diagnostic tests in the NICU.

Effect of rapid genetic diagnosis on parent-child bonding and implications for medical and family decisions

One consideration that parents may not appreciate when they agree to testing is the potential for WGS and WES in the newborn period to interfere with family dynamics by influencing parent-child bonding.34 These concerns could be exacerbated in the cases of RGT in the NICU, given the short turnaround time. While parent-child bonding starts during pregnancy, it intensifies in the months after birth. 35 This means that RGT in the NICU will often return genomic results very early in the bonding process, whereas traditional (slower) testing in unwell infants will return results when bonding is established.

Infancy is a crucial time for a child's brain development.36 The infant brain generates approximately 40,000 new synapses every second.37 The early experiences an infant has with her caregivers heavily influence how synaptic connections are formed. Repeated interactions and communication with caregivers form neural pathways that effect a child's long-term capacity to form relationships with others.36 Evidence suggests that if a child fails to properly bond with her caregivers, this has long term adverse consequences.36 Longitudinal studies indicate that having an insecure attachment to caregivers significantly impairs a child's ability to form and maintain healthy relationships throughout life.38 Poor child-caregiver bonding also predisposes children to a range of mental health issues, including psychopathology.39 Bonding with caregivers very early in infancy is especially important for a child's future.

Studies looking at the consequence of returning results from newborn screening tests indicate that when parents receive results early in infancy, it can have long term consequences for the child. Parents of infants who receive false positive results from newborn screening remain anxious about their child's health, and treat the child differently to children who did not have an adverse finding, even after a result has been revealed as a false

positive.40,41 Mothers who receive false positive results from newborn screening tests are also significantly more likely to report needing extra parental support, and children who received false positive results are three times more likely to require hospitalization in the first 6 months.40 While these findings are made in otherwise healthy children and relate to a biochemical rather than genetic test, one potential explanation for these results is that receiving negative information about their child's health disrupts the bonding process.

These observations have direct implication for RGT in the NICU. RGT will return results in a few days to weeks, while parents are still actively bonding with their child. Receiving the diagnosis of a genetic condition from RGT could have a more disruptive effect on child-caregiver bonding than a similar diagnosis from a standard WGS and WES. RGT will thus be more similar to newborn screening tests in this regard than standard WGS and WES.

Consider case B above. If the diagnosis had been received through a standard WGS and WES, the parents may well have bonded with their child before receiving the diagnosis (as the family did in case C). They may not have chosen to place the child for adoption at this point. The process of bonding with its parents could be expected to have beneficial long-term outcomes for that child. In cases such as this, a diagnosis of a genetic condition may have a worse overall effect if it is delivered rapidly.

Yet in other cases, receiving a diagnosis rapidly may have benefits for parents and child. If genomic results indicate a lethal and untreatable condition for a child, it would arguably be better for that information to be communicated earlier in the NICU stay. For the infant, it could avoid painful and unnecessary interventions42 and it may be easier for the parents to discontinue treatment if they haven't yet bonded with their child.

One potential complication is that in more intermediate cases, the rapidity of diagnosis may introduce a conflict between the interests of parents and that of the child. In case A, the nature of the child's underlying genetic diagnosis and predicted impairment potentially means that it would be in A's best interests to survive.19,43 However, if the diagnosis is made at a point prior to his parents establishing a strong bond to him, it may be in his parents' interests to withhold life-prolonging treatment.

RGT in the NICU thus raises difficult questions about how information about a specific genetic diagnosis should influence parental and clinician decisions about withdrawing or limiting treatment. The classic paradigm for limiting treatment in children with an underlying genetic condition is Down syndrome; a congenital condition that can be diagnosed *rapidly* on clinical examination, with laboratory confirmation through fluorescent *in situ* hybridization (FISH) generally available within 24 hours. A diagnosis of Down syndrome used to be considered a reason not to offer potentially lifesaving cardiac surgery. 44 However, choosing to not proceed with surgery for infants with Down syndrome, when surgery would be performed for infants without Down syndrome, has been argued to be a form of discrimination and hence current standard practice is to offer the same opportunity for cardiac repair45 (although some have questioned this paradigm).46

RGT makes possible the rapid diagnosis of a vast range of other, much rarer life impairing genetic conditions. RGT will thus require clinicians to address difficult questions regarding

how the information about a specific diagnosis should be framed when decisions about providing and limiting treatment need to be made by parents and medical teams. There is emerging evidence that healthcare providers who must make high-stakes irrevocable treatment decisions involving genomic results are already experiencing moral distress.47 There is therefore a need to articulate practical procedures, underpinned by consistent normative principles and values, to help clinicians decide whether a diagnosis of rare life-impairing conditions should influence a particular treatment decision in the NICU; and whether Down syndrome should provide the paradigm for dealing with such decisions.

More empirical work is needed to examine the long-term effects on parents and children of receiving a diagnosis from a genomics test at different stages of child-caregiver bonding. The potential effects of RGT on child-caregiver bonding and decision-making will need to be carefully considered as RGT becomes more widespread in NICUs.

Distributive justice

RGT raises additional ethical challenges for institutions involved in the distribution of healthcare resources. WGS and WES remain resource-intensive, both in terms of the production of raw genomic information and its interpretation.48 There is wide variation in the cost of standard WGS and WES, with averages of USD$4,859 for trio WES, and USD $1,944 for singleton WES reported in a recent benchmarking study.49 The cost effectiveness of standard WGS and WES is yet to be established to the standard required by most healthcare systems,50 resulting in ongoing paucity of access. In addition to the lack of sustainable healthcare funding for genomic tests in general, most clinical and laboratory genomic services are in their infancy, and many lack the human resources to take on additional testing services. Against this backdrop of insufficient funding and insufficient capacity, the production of rapid genomic results is currently highly disruptive to usual clinical and laboratory processes, resulting in the diversion of scarce laboratory and clinical resources10 and costs two- to four-times as much as standard testing.

RGT thus requires resources (such as time, money, personnel, materials) and produces a novel resource (timely genomic information), which could be used to guide treatment in the NICU. This raises two different questions: first, whether insurers, healthcare systems or hospitals should distribute resources to RGT, away from other standard WGS and WES (and other types of medical testing), and second, who should get priority with the use of RGT?

1) Should insurers, healthcare systems or hospitals distribute resources to rapid genomic testing?

Performing genomic testing with rapid turnaround times costs two- to four times as much as does testing with standard turnaround times. Can this increased allocation of resources be justified? Or would we be better off to test a larger number of patients with standard turnaround times?

Earlier diagnosis could allow medical resources to be more equitably spread, for example through earlier limitation of treatment, when such a course of action is agreed with the family. For example, in the case of infant C, diagnosis soon after birth could have avoided

months of costly treatment in intensive care. This can save considerable money, time and materials – which could, in theory, then fund other genomic tests or other resources in the NICU.

However, existing evidence about the economic impact of testing is based on small case series of infants who were identified to have a high pre-test probability of a monogenic disorder.3,6,10 More widespread availability of RGT in the NICU would potentially lead to testing in a larger cohort of infants, many of whom will not receive a genetic diagnosis, or whose diagnosis will not change medical management. It is therefore possible that future studies will show RGT is not as economically advantageous as it currently appears. But, based on the evidence available to date, it seems like RGT is a more efficient use of medical resources than standard WGS and WES in the NICU setting, which will make it attractive to insurers, healthcare systems and hospitals.

Policy makers need to carefully consider the best models for implementing RGT. The majority of RGT programs reported to date have been based at single tertiary pediatric institutions.6,10–12 As the momentum for wider implementation increases, it raises the question of the optimum service delivery model to ensure equitable access, within limited healthcare resources: while local testing will potentially offer quicker turnaround times and the benefit of close clinical-laboratory integration in result interpretation, centralized models where RGT only occurs in a few centers that have sufficient throughput, dedicated infrastructure and workforce capacity and capability may be more efficient and less disruptive to the delivery of standard WGS and WES.

2) Who should get priority?

In the absence of sufficient capacity to offer RGT for all infants in the NICU who may potentially benefit, there will be a need to prioritize.

It is likely that in the early phase at least, RGT will be restricted to those infants with clinical features that are highly suggestive of an underlying genetic condition. However, a diagnosis in such infants will not always lead to a change of management, for example, in cases where the condition is non-lethal, and there is no specific treatment. In such cases, RGT may provide little immediate benefit to the infant or their parents.

An alternative approach would be to prioritize infants where the result of RGT is expected to be of high clinical utility, for example where a diagnosis would potentially help parents considering treatment limitation decisions, an expensive intervention such as transplantation, or in cases where parents are considering adoption. These are the ‘weightiest’ choices parents can make, and they should have access to useful information to help inform those decisions. This would potentially mean prioritizing early testing in infants like C, where the pre-test probability of a genetic condition being identified may not be as high, but where the impact of a diagnostic result would be significant. If rapid testing increased the number of infants being placed for adoption, it could raise similar issues to pre-adoption genetic testing.51,52

Quantifying the full costs and benefits from RGT remains an ongoing challenge. A genome sequence obtained in the NICU could continue to benefit a patient throughout their childhood, for example through yielding additional diagnoses in light of new gene discoveries.53,54 The benefits of receiving a faster diagnosis, perhaps from parents accessing better support earlier, may only be apparent in the long-term. The costs of disrupting bonding may also not be fully apparent until adulthood. Studies evaluating the long-term effects of RGT are needed to inform how it should be implemented and prioritized.

Conclusions

RGT in acutely unwell newborns with suspected genetic disorders represents the most critical application of genomic medicine. Both the opportunities and challenges of RGT are acute in the NICU. Before RGT is widely implemented, it is crucial for hospitals, clinicians, health systems, and insurers to consider its ethical implications.

RGT heightens the challenges of informed consent for genomic tests, as it is offered in a highly stressful environment with few opportunities for critical reflection on the information provided, while at the same time, the high clinical utility arguably favors more directive counseling models. It has the potential to negatively affect bonding between infant and caregiver at a very early stage with long-term adverse consequences for the infant, and short-term implications for family and medical decision-making, particularly in relation to treatment limitation. Finally, RGT also raises important questions of distributive justice. There is a need to prioritize RGT in the first instance to those infants and families who stand to benefit most from the results. There is also a need to investigate the implications for health systems of more widespread access to genomic intensive care.

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Abbreviations

RGT	Rapid genomic testing

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Box 1

Case vignettes

Case examples

Baby A - born at 36 weeks gestation with multiple dysmorphic features and complex congenital heart disease. At two weeks of age, a diagnosis of Coffin-Siris syndrome was made using RGT. This syndrome is typically associated with moderate intellectual disability, although intellect in the normal range and severe disability have also been described. The parents elected not to proceed with surgery; baby A was managed palliatively and died in infancy.

Baby B (born at term), was hydropic and developed seizures which responded well to medications. At ten days of age, a diagnosis of cardiofaciocutaneous (CFC) syndrome was made on RGT. CFC syndrome is typically associated with moderate to severe intellectual disability. Baby B's parents found this news difficult to accept and later decided to relinquish her for adoption.

Baby C was extremely premature (26 weeks gestation) with severe intra-uterine growth restriction (birth weight 502g). She had multiple complications during a prolonged neonatal intensive care stay, including severe chronic lung disease. At 4 months of age, baby C was considered for a tracheostomy. Some minor dysmorphic features were apparent, and RGT revealed Rubinstein-Taybi syndrome. Her parents were counselled that baby C would be likely to have long-term severe cognitive disability. They requested that tracheostomy and long-term ventilator support proceed as planned.

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Table of Contents Summary

We examine the ethical challenges of rapid genomic testing in neonatal intensive care; focussing on informed consent, child-caregiver bonding and distributive justice.