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The Future of Newborn Genomic Screening

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The Future of Newborn Genomic Screening

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Abstract: Genome sequencing (GS) provides exciting opportunities to rapidly identify a diagnosis in critically ill newborns and children with rare genetic conditions. Nevertheless, there are reasons to remain cautious about the use of GS. Studies to date have been mostly in highly selected populations of babies with unusual clinical presentations. GS leads to diagnoses in many such infants. More rarely, it leads to beneficial and changes in management. Parents and physicians whose babies meet these criteria and for whom GS is done both find these results useful. The concern is this: we don't know how useful such testing will be in the general population. We can speculate that a number of problems will arise as the US of GS expands. First, the percentage of cases in which a valid molecular diagnosis is made will likely go down. The number of ambiguous results or false positive will rise. Genetic counseling will become more complex and challenging. We don't know the relative cost-effectiveness of whole genome, whole exome, or targeted panels in different populations. We don't know the relative contribution of a molecular diagnosis to the decision to withdraw life support. We will have to carefully evaluate the use of such testing in order to understand whether it truly improves outcome and survival or reduces symptoms in babies who are tested. Each of these concerns will require careful study of both the technology and the ethical issues to allow us to harness the potential of these new technologies while avoiding foreseeable problems. Studies are underway to see how the tests are used in general populations. These studies should generate important information to guide clinicians and policymakers. In the meantime, parents should know that genetic results sometimes confirm an already suspected dismal prognosis and sometimes yield only ambiguous findings. Anticipatory discussions should try to give parents a realistic understanding of the likely impact of a genetic diagnosis. Both doctors and parents should recognize that the clinical usefulness of diagnostic genomic testing in newborns is a work in progress. We are only a decade into the age of true genomic medicine. We still have much to learn.

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Introduction

The human genome was first sequenced in 2003. Since then, tools have been developed to rapidly sequence whole genomes, whole exomes, or targeted genes. Genome sequencing (GS) may soon become the most expeditious way to screen infants for genetic diseases. However, experience with diagnostic genome sequencing suggests reasons for caution. As we learn about the complexities of interpreting GS results, we are uncovering new clinical and ethical issues associated with this powerful technology.

Past research on ethical, legal, and social issues (ELSI) in genomics has allowed careful study of this ethically complex technology. Early studies of ethical issues focused on the psychological sequelae of incidental findings. Bioethicists were especially concerned about testing that found variants of uncertain significance, worried that such results would be difficult for parents to understand and could lead to negative psychological sequelae.[1] Those fears turned out to be overblown. Studies showed that, with careful counseling and informed consent, most parents do not have negative psychological sequelae even when test results are disturbing or ambiguous. Instead, parents report that genomic results are useful even if they are non-diagnostic, ambiguous, or if they diagnose a disease for which there is no effective treatment.[2] With those issues largely resolved, we now face a set of second-generation ethical issues associated with GS for critically ill newborns. Three questions seem key. First, who should be tested. Second, how accurate are test results. And third, does testing actually lead to better outcomes.

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Who should be tested?

Most babies who are admitted to the NICU are not suspected to have genetic disease.[3] Instead, the most common diagnoses are prematurity, sepsis, or problems related to asphyxia during labor or at birth. Many other babies are admitted to NICUs with congenital anomalies. For these two groups, diagnosis and clinical care are relatively straightforward. A precise genomic diagnosis might help families make future reproductive choices but it is unlikely to influence the clinical care of the babies.

Occasionally, babies have metabolic abnormalities or unusual neurological findings. For these babies, a diagnosis is often made using standard biochemical or metabolic tests. Post-natal GS is reserved for the situations in which such testing does not lead to a clear diagnosis.

These epidemiological facts about neonatal care today are crucial to interpreting the results of NGS testing as it is used today and to inform decisions about how it should be used in the future.

So who should be tested? As noted, current studies focus on the highly selected groups of babies who are symptomatic but for whom standard diagnostic testing has not led to a specific diagnosis. At the other extreme, Francis Collins, former Director of the NIH, suggested that every baby should have their genome sequenced at birth and the results used to guide a lifetime of health interventions.[4]

GS, like all clinical testing, should only be done when, in the doctor's opinion, it is likely to yield valuable information that could help in the clinical management of the patient. With GS, the most likely scenario leading to clinical benefit is one in which such testing leads to the diagnosis of a disease that had not been suspected or confirmed. In such cases, GS may lead to beneficial treatment or preventive screenings. Estimates of how often GS leads to diagnoses or changes in management vary widely. There are at least three good reasons for the variation.

First, the rate of positive results depends heavily on the choice of patients who are tested. Many studies report results from cohorts of babies who are tested because they have symptoms suggesting a genetic disease. Such babies are obviously more likely to have positive test results than would babies who are asymptomatic. But we often don't know precisely how decisions are made about which babies to test. Put another way, the inclusion criteria for studies of the efficacy of GS are not well-defined or standardized.

Second, the rate of positive findings may also differ in different studies because the definition of a "genomic" or "molecular" diagnosis is somewhat imprecise. The phrase "molecular diagnosis" usually refers to a situation in which genome sequencing reveals a genomic variant that is "plausibly related" to a patient's symptoms. In most cases, however, the population prevalence of such variants is unknown. Thus, we don't know how many people have the variant and have no symptoms. As a result, the nature of the causality is often an imperfect estimate, based on biological plausibility and prior reports of an association between the variant and the phenotype.[5]

Finally, definitions of "change in management" also vary. GS is often done in infants with serious illness for whom changes in management are common with or without molecular diagnoses. It may be difficult to determine whether a particular change in management was the direct result of information from the GS testing or whether the change would have occurred anyway. In addition, with GS, many proponents claim benefits that are not, strictly speaking, clinical benefits for the patient. For example, testing may end the diagnostic odyssey for parents. It may inform future reproductive decisions.

Because of variations in the populations of babies being studied, the criteria for claiming that a molecular diagnosis has been made, and the measurement of clinical utility in reported outcomes, it is difficult to know whether or how frequently GS will be beneficial for patients and families in the NICU. A study from The Netherlands that looked at every patient in the NICU or PICU in one hospital illustrates the complexities of estimating benefit.[6] Over 2 years, 1254 children <1 year of age were admitted to the NICU or PICU at one Dutch hospital. Of those, 24 (2%) were considered appropriate for GS because of a complex illness and diagnostic uncertainty. 7/24 had a finding on GS that was thought to explain the patients' symptoms. The most frequent change in management that resulted from GS was to redirect care to comfort care. That occurred in 5/7 cases. There were no cases in which testing led to the provision of a new beneficial treatment.

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Callaghan and colleagues did a meta-analysis of similar studies. They report that there is no uniform definition of either change in management or clinical utility.[7] The variation in the ways that outcomes are reported make it difficult to compare studies.

These ambiguities in the reporting of results make it difficult to know who to test. We know that the results of studies of GS in select populations of critically ill babies are unlikely to be generalizable to a less highly selected group of babies. We recognize the ambiguities of results in cases where it was used. These problems suggest the need for more research before we can say when and how GS should be used.

Does GS improve outcomes?

The hope for NGS is that it will lead to unsuspected diagnoses of conditions for which treatments could improve important health outcomes. In most reported cohorts to date, that hope is rarely realized. Instead, when GS results lead to change in management, that change is often either 1) a redirection of care towards palliation, 2) the referral of a patient to specialists for further evaluations (which may sometimes lead to benefit but the outcomes of such referrals are usually not described in the papers), 3) a possible change in the parents future reproductive decisions (though the actual changes, too, are seldom described) or 4) the implementation of treatments that could, in many cases, have been implemented even without the genomic diagnosis. Each of these purported benefits raise ethical questions.

With regard to the redirection of care, the concern is whether the molecular diagnosis justifies a decision to provide comfort care instead of life prolonging care. For example, one study reported that a molecular diagnosis of Noonan Syndrome led to a decision to initiate palliative care.[13] In another study, a diagnosis of Coffin-Siris syndrome did the same.[8] [9] These conditions would not ordinarily lead to a decision to initiate palliative care, as babies with the syndromes frequently have a good quality of life and are quite functional. The decisions to redirect care may well have been appropriate for those individual children but were likely based on multiple factors other than simply the genetic diagnosis. Furthermore, for many molecular diagnoses, there is a wide range of phenotypic findings, and children with precisely the same molecular genetic abnormality can have very variable outcomes. Even identical twins with the same molecular defect may have different phenotypes.

Most studies performed so far provide relatively little detail on how decisions about redirection of care were reached. Clinical teams are typically thoughtful about the evaluation of genomic findings, disease severity, and family preferences before considering withdrawal of support in the NICU and PICU setting. Still, it would be important for future studies to provide additional granularity on how molecular results might play a role in decisions to withdraw life-support and to specify the relative contribution of the molecular diagnosis, as opposed to other clinical information, to the decision to withdraw life support.

The decision to withdraw life support after a molecular diagnosis also raises important questions about evaluations of cost-effectiveness. For example, the Baby Bear study analyzed the economics of GS and claimed that it was cost-saving. Much of the cost-saving was generated by 11 cases in which life support was withdrawn after the return of GS results.[10] These decisions were judged to have saved expenditures on potentially futile care for babies with fatal illnesses. Similarly, in a multicenter Australian study, molecular diagnoses led to decisions to initiate palliative care in 14/55 (25%) patients with such diagnoses.[11] In both studies, details about the process of decision making were sparse. We don't know the weight given to the molecular diagnosis compared to that given to other factors. In some of the cases, the molecular diagnosis alone did not seem sufficient to justify withdrawal of treatment. Withdrawal of life support can certainly reduce health care costs, but the economic benefits need to be weighed against the ethical considerations that should always be primary in such decisions.

Many studies report cases in which a child receives a treatment after a molecular diagnosis, the study claims that the initiation of treatment was a benefit of GS, but it seems that the child could and

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should have received the treatment based on clinical diagnsosis and that the molecular diagnosis was either unnecessary or merely confirmatory rather than essential. Examples abound.

In a recent case series, a child with renal failure was found to have a genetic variant associated with hyperoxaluria.[12] In the past, that diagnosis would have been made by testing renal function and metabolites in serum and urine. Such traditional metabolic testing would likely have been quicker, more accurate, and more cost-effective than GS.

Another infant in the same report was diagnosed with Dravet syndrome by NGS. This diagnosis has a major impact on the choice of anticonvulsant medications as some medications may worsen the seizures if the patient has Dravet syndrome. Usually, however, a genomic diagnosis is not essential. Instead, doctors adjust therapy by using continuous EEG and observing responses to therapy. That can be done far more quickly than genomic sequencing. Furthermore, even with a molecular diagnosis, it would be necessary to such testing and adjustments of treatment. The molecular diagnosis may not be precise. Genotype–phenotype correlations are not 100%.[13]

In another case series, the purported benefit of GS was "changing anticonvulsant medication" after the diagnosis of hypereflexia in a newborn infant with "exaggerated startle response, hypertonia and apnea."[14] Again, such medication adjustment would likely have taken place before genomic results were available and would have been based on prolonged video-EEG recording which would remain normal throughout the spells. GS results are neither necessary nor sufficient to make a clinical decision to stop anticonvulsant medications in those circumstances.

One study reported the case of a child with developmental delay, failure to thrive and abnormal hair. GS confirmed the diagnosis of Menkes' disease on GS and the patient was started on appropriate therapy. The diagnosis of Menkes' is generally made clinically. A trial of therapy is the standard approach. The GS results may have added some certainty to the diagnosis, but they should not have been the primary reason for changed management.

In a different report, an infant was diagnosed with Cornelia-De Lange Syndrome. The purported benefit was "referral to Endocrinology."[15] In another with a myasthenic disorder, the benefit was "commenced salbutamol." In both cases, the action should have been based on the infant's clinical findings rather than on their genetics.

In these reports, and in many others, researchers inappropriately assume that diagnostic modalities other than GS are insufficient. That is surely sometimes the case but, from present reports, we cannot usually tell how often.

GS is a diagnostic modality. It should be compared with other diagnostic modalities to determine whether it is sensitive, specific, cost-effective, and clinically useful.[16] If so, it should certainly be used. But because it is such a broad form of testing, and because many experts advocate its broad use, it is being used more indiscriminately than present results would warrant. In many cases, molecular diagnosis does not change management. For example, in progressive leukoencephalopathy, lacking a diagnosis has no impact on treatment options as none of the possible diagnoses currently has a therapeutic option. A precise diagnosis may have an impact on future pregnancies, or even potentially on genetic counselling for the extended family but should be considered on that basis rather than as a benefit for the infant.

Many mutations found on NGS are labelled as "likely pathogenic." Such results are the most difficult to interpret.[17] Although scientific advances in this area have been rapid, not all such likely pathogenic mutations lead to the same degree of confidence that the variant is causal. The problem is that we often do not know whether a positive genomic result in patient who does not have the symptoms that are associated with that genomic variant is a false positive test, incomplete penetrance and expressivity, or some other phenomenon.[18] Variable penetrance and expressivity of many genetic abnormalities are well known phenomena and must be taken into consideration when analyzing the value of NGS for an individual.

In many well studied conditions (e.g. CHARGE syndrome,[19] or autism[20]), patients with exactly the same genetic abnormality have different phenotypes. This is true even in identical twins. Because of this, we need to be wary of claims that finding a "likely pathogenic" variant is the same as making a diagnosis or altering treatment.

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The difficulty in interpreting genomic results leads to wildly differing estimates of the cost-effectiveness of NGS in different patient populations. A recent study of cost-effectiveness reported that, by finding a genomic variant associated with CHARGE syndrome, doctors were able to avoid doing a supraglottoplasty and thus saved money.[21] But supraglottoplasties should not be performed (or avoided) because of a precise genetic diagnosis but instead should be provided or avoided based on an assessment of the baby's clinical condition. Similarly, much of the "modelling" which claims to show the cost savings of NGS is based on the assumption that a genetic diagnosis determines the time of discharge of an infant, and thus the total costs of hospitalization. In reality, infants are discharged when they no longer require hospitalization regardless of molecular diagnosis. Such hyperbolic claims of benefit undermine the validity of cost-effectiveness evaluations and of the clinical utility of NGS.

Relying solely on the genetic diagnosis to determine treatments is not usually warranted. The clinical evaluation of the patient is still required to determine which interventions are likely to be helpful.[22] [23]

Assessing the benefits of NGS

GS can be beneficial even if it does not lead to better treatment of a particular baby. These benefits include a potentially useful information about prognosis. But prognostic information is always probabilistic. When GS is ordered in critical cases, parents may believe that GS will help them make life-and-death decisions. Often, however, GS leads to a diagnosis with an unclear prognosis. Parents may then decide that intensive care should continue and may find it harder to grieve since they have no specific diagnosis or explanation for why their baby is sick and may die or has died.

Incidental findings may also be a benefit of GS. In one study, 4.8% of pediatric patients who underwent NGS were found to have cancer susceptibility genes[24] Future studies must explore how the finding of such genes impacts the life of the individual, when and how to inform them, and whether enhanced surveillance is truly advantageous for each gene.

How often does GS harm families?

In some cases, delaying redirection of care while waiting for a result which turns out to be non-diagnostic could be harmful. Because the majority of NGS results are non-diagnostic, this may be the most frequent impact of GS. The more widespread the use of GS becomes, and the more it is used in general populations, the more frequent such non-diagnostic tests will become. Some parents hope that GS will reveal a curable condition. Many are disappointed. Others cling to false hopes such as, for example, that CRISPR will allow their baby's genome to be corrected by editing.

Others feel guilty that the condition was caused by inheritance of the parental genomes, and that "they made him this way."[25] Sometimes, a GS result leads to the erroneous conclusion that a baby will quickly die and prevents parents from bonding with their child. Reliance on GS could potentially lead to other harms, such as failure to perform more rapid, lower cost and more prognostically accurate investigations, such as renal biopsy. Incidental findings may also be harmful, if no changes to health care are indicated and the prognosis is poor, or if health care insurance is impacted.

GS tempts us to rely more on the sequence of bases in a child's DNA than on the child's clinical picture. Clinicians need to remember, and to tell parents, that the most important indicator of the child's diagnosis and prognosis is the child's clinical presentation and responses to therapy.

Instead of waiting for the genome, we should focus on the patient. We will cause harm if we lead families to believe that we need a genetic diagnosis in order to redirect care. Such an approach makes it very difficult to engage in discussions about palliative care, even though, in most cases, the genetic results are neither definite nor strongly associated with a clear prognosis for the condition. When a child is on maximal ventilator settings, continues to seize despite our best attempts to control the seizures, and has a catastrophic EEG, we must engage in difficult conversations with families and not to avoid this by waiting for (yet more) tests.

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An Ethics Research Agenda for Genome Sequencing in Newborns

Research on ethical, legal, and social issues (ELSI) in genomics has allowed careful study of this ethically complex technology. Early studies examined the psychological sequelae of incidental findings, especially those of uncertain significance, would lead to negative psychological sequelae.[26] They found that with careful counseling and informed consent, most parents do not have psychological sequelae and they find genomic results useful even if they are non-diagnostic or if there is not therapy for their child's disease.[27] With those issues largely resolved, we now face a set of second-generation ethical issues associated with GS for critically ill newborns. We will need to develop and test strategies for testing in different populations, We will need to better define the benefits, costs, and harms of testing. We will need to differentiate the harms of the testing itself (which are negligible) from the harms that may accrue from misuse of the results. We will need to better understand the way doctors, parents and patients use genomic information.

The likelihood of finding a genetic diagnosis will almost certainly be much lower when testing is done in healthy babies or even in all NICU infants rather than in critically ill babies with a suspected genetic disease. Expansion of GS to healthy newborns is likely to generate results similar to those found in the pioneering BabySeq study.[28] In that study, 7.8% of healthy newborns had genomic variants that were classified as pathogenic. None of those babies were symptomatic. We won't know the predictive value of such testing until that cohort is followed for many years. In a critically ill newborn population, such high rates of incidental findings are often balanced by the finding of helpful diagnostic abnormalities. The frequency of potentially beneficial findings in a population of healthy newborns will be much lower, but these children will likely have a similar frequency of incidental abnormalities as well as more VUSs and even variants classified as clearly pathogenic despite being asymptomatic. Thus, future research in less highly selected populations will have to carefully study the unique counseling challenges that will arise when most results are ambiguous. Studies should also examine whether, in health populations, interrogation of more limited sets of genes will decrease the chance of unexpected ambiguous findings.

Two large studies, one in the UK and one in the US, may soon give answers to at least some of these questions. The Genomics England study plans to enroll 100,000 newborns over two years.[29] They will return results for 200 diseases that are thought to be clinically actionable. The Guardian Study in New York City also plans to screen 100,000 children and to test for and return results for 160 treatable disease and 160 untreatable neurodevelopmental disorders. These studies will also, almost certainly, suggest new questions to be investigated in future studies.

The definition of benefits from GS remains ambiguous. The best-case scenario is that testing leads to better treatments and improved outcomes. By this criterion, the jury is still out. No study to date of diagnostic GS in children has shown improved survival or shorter length of hospital stay in babies who received a diagnosis compared to those who didn't.

Many studies choose different measures of benefit, including the above-mentioned surrogate endpoint of a change in management.[30] Future research should add precision to the somewhat vague notion of what counts as a meaningful COM. COM is a complicated and ambiguous endpoint for three reasons. First, as Barrington pointed out, these are critically ill babies in ICUs for whom COMs occur all the time.[31] It is methodologically difficult to determine the precise cause of any COM. Second, COMs that do not lead to improved clinical outcome or survival may not be medically appropriate. They may just indicate false positive tests or overuse of medical services. We know, for example, that false positive results in newborn screening often increase parental stress without any benefit for the family or baby beyond ruling out the disease indicated by the false positive test.[32]

Future studies might clarify two aspects of decision to initiate palliative care. First, they should examine whether a particular molecular diagnosis justifies the withholding of life-sustaining treatment. Second, they should examine whether decisions about withholding life-sustaining treatment are inappropriately delayed while awaiting genomic results in the belief that those results give certainty about prognosis. Often, prognostic estimates can be made, accurately, based on the child's clinical condition and hospital course.

Conclusions

GS provides exciting opportunities to rapidly identify a diagnosis in critically ill newborns and children with rare genetic conditions. But there are good reasons to remain cautious about the broad implementation of these strategies in babies and children. At best, rapid GS leads to diagnoses in many infants in highly selected populations. It sometimes leads to beneficial and changes in management. Parents and physicians both often find these results useful.[33]

We don't know how useful such testing will be in the general population. It is almost inevitable that genetic counseling will be more challenging in a more general population. We don't know how often GS helps improve outcome and survival or reduce symptoms in babies who receive a molecular diagnosis. We don't know the relative cost-effectiveness of whole genome, whole exome, or targeted panels in different populations. We don't know the relative contribution of a molecular diagnosis to the decision to withdraw life support.

Each of these concerns will require careful study of both the technology and the ethical issues to allow us to harness the potential of these new technologies while avoiding foreseeable problems.

Studies are underway to see how the tests are used in general populations. These studies should generate important information to guide clinicians and policymakers. In the meantime, parents should know that genetic results sometimes confirm an already suspected dismal prognosis and sometimes yield only ambiguous findings. Anticipatory discussions should try to give parents a realistic understanding of the likely impact of a genetic diagnosis. Both doctors and parents should recognize that the clinical usefulness of diagnostic genomic testing in newborns is a work in progress. We are only a decade into the age of true genomic medicine. We still have much to learn.

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