Clinical Stewardship of Genomic Information in Pediatric Critical Care: A Qualitative Interview Study

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Abstract

Background: As clinical use of genomic sequencing (GS) increases within pediatric critical care, a model of clinical stewardship of genomic information is needed. To better understand in depth the responsibilities and ethical considerations around clinicians' use of GS in the pediatric critical care context, we undertook this study.

Methods: We conducted semi-structured, in-person and telephone interviews of clinicians involved in the care of critically ill children at a high-volume pediatric heart center. We conducted qualitative analysis of transcribed interviews.

Results: 35 clinicians were interviewed. Three areas of concern emerged: 1) the costs of acquiring the GS information; 2) resource allocation decisions (medical and financial) that already exist but can be informed by GS findings; and, 3) patient privacy and protecting the genomic information itself in a healthcare context.

Conclusions: Three key elements are needed for a model of clinical stewardship of GS in pediatric critical care. First, clinicians using GS need to negotiate the cost burdens and non-financial costs to families and society from GS testing. Second, clinicians need to define how GS improves or alters decision making around scarce resources. Third, clinicians are entrusted with protecting the privacy and sensitivity of their patient's GS revealed information.

Background

Pediatric critical care clinicians envision the main benefit of genomic sequencing (GS), as changing how decisions involving rationing of scarce resources, declaration of futility and withdrawal of care are made.[1] Implementation studies of GS in pediatric critical care show that transition to palliative care is most often identified as the benefit of GS testing over other actions such as changes to medication, procedures or counseling.[2,3,4] However variant classification is evolving with growing recognition that re-evaluation and re-analysis over time is likely necessary, especially if significant clinical decisions are being made from GS-derived information.[5]

Consequently, critical care clinicians using GS in clinical contexts are caught in an ethical tension between several, difficult to negotiate, responsibilities. There is the need to strengthen GS findings and outcome associations to increase the clinical utility of GS and polygenic risk scores;[6] the need to protect patients from potential harms like risks to privacy and discrimination;[7] and, the potential that GS findings will be used in ways unexpected to families but fundamental to critical care decisions- to guide allocation of scarce clinical resources, like organs for transplantation, and to inform decisions of futility and withdrawal of care.[1] In their fiduciary role, clinicians are also expected to steward resources that impact on patient care.

Stewardship in clinical medicine is defined in several ways, none of which provide a complete model to guide the clinical use of GS. One definition is “taking good care of that with which they [clinicians] have been entrusted.”[8] More than just fiduciary duty, this view encompasses an idea of responsible use of medical resources in which a physician-steward uses “finite resources responsibly, keeping one eye on the needs of their patients and another on the needs of countless other patients.”[8] Such stewardship considerations of resource scarcity are relevant since clinicians already use genomic information to guide resource-allocating decisions.[1]

Another definition of stewardship focuses more intensely on cost containment, defining good stewardship as avoiding treatments with uncertain or ineffective efficacy and considering the costs to a patient of a clinical choice.[9] This is relevant to clinical use of GS since the decision to undergo GS testing can certainly lead to further financial and morbid costs through costs of testing, follow-up tests, evaluations and procedures.[1]

In bio-banking research, a model of GS stewardship has also emerged describing stewardship as both protecting genomic data and protecting the providers of genomic data from harms, such as discriminations and psychological burdens that might result from disclosure of genomic information outside of research use.[10,11] This has relevance for the responsibilities around protection of genomic data in a clinical context as well, though bio-banking stewardship models offer only limited guidance for protecting patients and genomic information in the clinical context and for clinical decisions informed by genomic findings, since they are focused on responsibilities and obligations to research participants not patients. Bio-banking stewardship also discusses data ownership, with the underlying idea that GS data can only reveal so much now, but might have greater importance later as interpretation improves.[11] This notion of limitations of what can be currently revealed by GS testing is certainly clinically relevant, while research linking GS to clinical outcomes is still ongoing.[6]

As GS clinical use increases, a model of clinical GS stewardship is needed to encompass all of these stewardship obligations: care of the patient, awareness of the scarcity of resources involved in care choices and the potential influence of GS information on allocation decisions, being cognizant of limitations of a family’s wherewithal, being cognizant of the limitations of genomic information (particularly its predictive power) and taking good care of the genomic data itself. To better understand these responsibilities and ethical considerations around clinicians’ use of GS in the pediatric critical care context, we undertook this qualitative, interview-based study.

Methods

Congenital Heart Disease (CHD) is the most common type of birth defect leading to critical illness in the United States[12,13] and the leading cause of birth defects associated with illness and death.[14] As GS is being implemented in this population and has the potential to have a profound impact on how these

difficult care decisions are made,[1,15,2,16] we focused our study on clinicians caring for critically ill children with CHD.

We used a qualitative approach, interviewing physicians, nurse practitioners and physician assistants at a high-volume pediatric heart center. This field site is an institution implementing a clinical GS service at the time of the interviews. Interviewees were initially approached via telephone or email and were selected with the idea of garnering interviews that reflected the distribution of clinicians (seniority, specialty area) at the heart center. Recruitment stopped after saturation was reached. We used one-on-one interviews, a technique which has been found to be productive in providing an intimate, private context for discussing sensitive topics (such as personal decision-making) and because this approach is well suited for exploratory research attempting to find a range of perspectives.[17,18,19,20,21,22,23] The study was approved by the IRB of the Stanford University School of Medicine

We used a semi-structured interview guide of open-ended questions on ethical struggles clinicians currently face with GS as well as issues they envisioned emerging with further clinical GS implementation (Table 1: Questions). Interviews were conducted either in person or over the telephone and were audio-recorded and transcribed. Transcripts were de-identified, uploaded into the qualitative analysis software Dedoose, (www.dedoose.com) and interview data was analyzed incorporating modified grounded theory.[24,25,26] Codes were generated inductively through a collaborative reading and analysis of a subset of interviews (DC,SL) and then finalized through successive iterations into categories and codes. At least one primary and one secondary coder independently coded each transcript. Differences were reconciled through consensus coding. The team collaboratively reviewed each code and discussed interpretation of themes in a series of consultations.[27] Emerging themes were identified, described and discussed by the research group.

Results

Study participants included 35 clinicians (Table 2: Demographics). Response was 100% to requests for participation. Interviews lasted from approximately 20 to 60 minutes. Three areas of concern emerged: 1) the costs of acquiring the GS information; 2) resource allocation decisions (medical and financial) that already exist but can be informed by GS findings; and, 3) patient privacy and protecting the genomic information itself in a healthcare context.

1) Costs of acquiring the GS information

Financial Costs of Testing

The monetary cost of GS testing itself was a concern. Among clinicians currently ordering genomic sequencing, many feared unreliable 3rd party payments:

I worry about it because it's very expensive. The companies we use it's probably been anywhere between $2,000 and $5,000…I'm sending it because there's a valid good reason and I think it's an important part of the workup of a patient. So I've followed with insurance companies about it, but I do worry because the last thing I want is for the patient to get a bill for $5,000. So it is definitely a concern. Every patient I worry about. (Cardiologist)

Other clinicians felt they were, "being limited in the appropriate application of this technology by reluctance from payers." (Cardiologist/Geneticist) Others felt GS simply had to prove itself. Then, insurers would be more willing to pay and costs would come down: "They [insurers] would see the economic sense in a valuable test like this once it's proven itself." (Cardiologist)

Cost Burden to Families of Testing

Clinicians felt that they were ignorant of the costs of healthcare they ordered and that ordering GS could stick families with large healthcare bills:

Sometimes I send patients for studies and they'll tell me, 'oh, it was really expensive.' I don't have a great way of knowing that until I actually hear from patients. So I wouldn't want to say, 'let's send you for this whole genome sequencing' and have them get a huge bill. (Surgeon)

Clinicians felt that they needed to take costs of GS into consideration as they do in other areas of clinical care. "Our pharmacist will come to us and say, look, these are the five most expensive drugs on the unit. So I will think twice before I use them." (intensivist)

Costs to Society

Interviewed clinicians articulated how GS could help contain healthcare costs, "one [vision] is a preventive model, trying to minimize the chances of adult onset diabetes. One is saving costs to care for a child with a devastating outcome, if the parents are willing to withdraw or withhold care." (Neonatologist) GS could

reduce overall healthcare costs by targeted preventive care, in the case of diabetes, or could allow early withdrawal in cases where a devastating, prolonged ICU course could be predicted.

Clinicians raised related concerns that predictions could be used by 3rd party payers to predict children requiring the most intensive (and costly) care and ration on financial grounds:

A lot complex cardiac diseases are costing a quarter of a million dollars, if everything goes right, in the first year of life. You can imagine that in kids for whom everything is not going right and every hospitalization is costing a quarter to half a million dollars, insurance companies may decide to put caps on that. (Intensivist)

Non-monetary Costs of Burden to Family and Society

Clinicians also saw results being used to predict the potential emotional and social burden of individual patients on families and society:

The weight that that child is going to have on the family, on itself, and on the system are very important to know to make decisions about whether the kid is something that you want to bring into the world. That's a responsible thing not only for families, for the person you're bringing into the world, but for the system at large because any resources you spend to one is resources taken from other. (Anesthesiologist)

2) Resource allocation decisions informed by GS findings

Clinicians saw utility and potential for GS to be used in high-stakes decisions:

If a child is stuck on a ventilator and can never come off and is going to die of a horrible respiratory disease within a few weeks, no parents want to put their child through that amount of suffering, so genomic sequencing can make a lot of hard decisions easier. (Neonatologist)

GS results might allow clinicians, patients and families to avoid the burden of futile therapies. In addition, GS results might provide certainty or reassurance in other difficult decisions, like whether or not to pursue complex heart surgery:

Should you operate on them now or just let them go natural history? A genome will probably tell you that, if you could get enough patients. This kid has the gene, he's going to be fine till age 70, leave him alone. Or, this kid has a gene, the RV's going to be done in two years. (Intensivist)

However, with the number and complexity of GS findings, "I don't know how easily we'll be able to pick stuff out that matters." (Intensivist) Interpreting GS findings into clinical use will require understanding the difference between clinically significant GS findings and findings that merely have statistical interest. "Say we could move the needle between 40% and 45% probability and we have a 10% confidence to do that. I don't believe there's any [clinical] utility knowing that information, but if you did know that there was a 20% chance of this fatal disease, then that's a very different equation." (Cardiologist/Geneticist)

3) Privacy and protecting the genomic information itself

Bedside clinicians articulated concerns about the need to protect the sensitive information revealed by GS:

I think we should be very concerned about data security given that we'll learn more and more about the implications of it [the genome] over time. There will be certain parties within healthcare, possibly the government, and certainly in the private sector, most of the insurance companies, that will be interested in that information [GS results] and so I think we will have to think through the implications of having this level of knowledge and how to best protect it and what to do with it. (Intensivist)

Clinicians expressed concerns if GS information was inadequately protected, "all the risks for future discrimination, either denial of health coverage or discrimination at work, or you could imagine all kinds of things that that information changes in terms of what the discrimination could be." (Intensivist) Interviewees expressed related concerns that guidance regarding privacy of GS results in research did not

easily apply to clinical use of GS since results become part of the widely accessible medical record. “If you know somebody’s got the Huntington’s gene and you’re diagnosing them at birth, and then it’s on their medical record, I think that they need to have some kind of protection.” (Intensivist)

Clinicians described perceived inadequate privacy protection causing families to be reluctant to agree to GS fearing both, “change in legislation [e.g. GINA] that now prevents employers and others from discriminating against people with identified genetic abnormalities,” and despite current protections, “in reality there may still be issues and stigma. I think that’s a huge hurdle for our patients.” (Cardiologist) Clinicians shared concerns about insurance implications for privacy protections, “I’m old enough to have lived through the AIDS epidemic and how people truly died because nobody wanted to cover them, never mind take care of them, but cover them, and I worry about this.” (Intensivist)

Others noted that discrimination from GS results could be lifelong, “As a society, if we’re going to start doing this with every child born, are you setting a child up at birth for discrimination? If they potentially have some gene for a pulmonary condition or a cardiac condition, are they not going to be able to try out for a competitive team?” (Anesthesiologist)

Related to these concerns about discrimination, clinicians articulated distrust in the medical system’s ability to protect sensitive information:

Genomic results are highly sensitive. Just like many other things are sensitive in our medical system and they’re not protected. There are biases, and notes go out unprotected. As a healthcare system we’ve not done well being honest with, say, an adolescent and protecting them -saying this part of the note will never go anywhere. The note does go places. (Intensivist)

Some clinicians wondered whether direct-to-consumer testing would offer better privacy protection or simply have financial agendas and uncertain validity. “I would be much more comfortable having it [WGS results] come from a university or government, or someone who’s actually in the business of health rather than in the business of making money. I know at some point we’re all businesses and you could argue the NIH is the same, but I don't know that I would trust the doctor making decisions on 23andMe.” (Intensivist) Other interviewees felt private sequencing was safer from a data security standpoint, asserting that, for their own family, “I would probably go with private and have that information just for myself and not being used for insurance.” (Nurse Practitioner)

Regarding storage of data, clinicians felt private industry was safer from theft. “That cloud provider has 300 people in a room who attack the servers all day long to try and find vulnerabilities. We do not at our hospital have 300 people trying to attack our servers!” (Geneticist) Others felt protecting data was only part of the issue. Data has to be interpreted for clinical use, and they questioned how well private industry could:

I have been asked to be an expert witness for one case that was a wrongful birth suit. They were suing one of these obstetrical centers which makes you pretty pictures of your fetus. Not a doc, not their obstetrician, they had gone to a place just to get a picture to put in their baby book and the images from that apparently showed that there was a [specific cardiac defect]. That’s the 23andMe analogy. There was no mechanism for that company that did that to report it to anybody. There’s where the direct-to-consumer stuff wasn’t helpful. (Geneticist)

Though private sequencing might protect theft better, whether results could be safely conveyed to treating physicians was unclear.

Clinicians expressed concern that providing GS results, before social supports and protections were in place for children who have significant needs, was irresponsible:

We’ve learned over the last 50 years that knowledge is power and it depends on whose hands it’s in. I am always thinking about being an advocate for a young child who doesn’t have that choice. That’s a choice made by adults around them. If we’re going to add fancy testing, then we ought to have fancy systems to plug them into. Otherwise it’s a burden to the family and the patient, ‘you have this exotic genetic thing, you’re never going to go to college, your IQ’s going to be 70, and we have nothing to offer you.’ Go to the public schools and good luck. That’s where the real ethical issue comes for me. (Intensivist)

Discussion

Three themes emerged from our results, defining three key elements for a model of clinical stewardship of GS for pediatric critical care.

First, clinicians using GS need to negotiate the cost burdens of GS testing. Clinicians had explicit concerns about the financial burden to patients/families from GS testing and their current inability to

protect patients from these costs. Unlike bio-banking models for genomic stewardship,[10,11] an unconsidered, but significant element of a clinical stewardship model will need to be cost control and clinician-patient/family partnering around the financial implications for the decision to undergo GS testing. There is very limited data on the cost-effectiveness of widespread use of GS in clinical practice.[28] Such data is difficult to obtain both because costs of sequencing approaches are in a dynamic development phase and, as care uses of GS are still being defined, are not easily generalizable to health economic interpretations.[28] Consequently, the burden of controlling such costs (or at least the decision to take on the costs of GS) will remain between the ordering clinician and the patient/family and will have to rely on individualized assessment of the benefits and burdens, rather than broader evidence. Unfortunately, variable costs and inconsistent insurance coverage for testing currently limit the clinical utility of GS.[29]

The potential for financially motivated rationing of healthcare resources from GS revealed information is concerning but similarly difficult to assess with only limited data.[28] In a healthcare system with finite resources and a cultural era with growing distrust in the benevolence of institutions, the cost rationing implications for GS testing, and concerns about such uses, need to be acknowledged and discussed.

Equally challenging are considerations of the non-financial costs to families and society from undergoing testing. Clinicians raised questions around the burdens and benefits of being able to anticipate, from GS findings, the potential extent of the challenges involved in caring for a child with critical illness. While there has been considerable focus on protecting a future adult's autonomy ('the right to an open future'), recognition is growing that families and society are also stakeholders in decisions made from predictive genomic information. The 'open' future is only one consideration to weigh against other considerations.[30] While these debates are not unique to the critical care context, the clinical decisions made in critical care are starker and more immediate than in other clinical areas. The number of geneticists and genetic counselors are inadequate to address GS results for all patients, particularly in the setting of the time-sensitive decisions that are often involved in critical care.[31,32] Discussions around interpreting and contextualizing results for individual children in decisions around withdrawal of care or limiting aggressiveness of care are likely to remain between the bedside clinician and the family for the near future.

Second, clinicians need to define how GS improves or alters decision making around scarce resources. The ethical and cognitive challenge of having to make high-stakes clinical decisions from GS data in context of the known limited understanding of the genome, limitations in clinicians' own understanding of WGS interpretation, and clinicians' concerns about potential harms that might results from GS misuse, is significant. A needed part of a model for clinical stewardship is transparency in communication about the current state of GS implementation: that GS is being implemented before the workings of the genome are fully understood, the efficacy of therapies and clinical decisions made from GS results are still unclear, and contextualizing results is falling on families and bedside clinicians, while knowledge and decision support approaches are still being developed.[33,34] How to incorporate GS into clinical decision-

making while evidence linking GS findings with outcomes is still forthcoming is unclear, but explicit and transparent acknowledgement that this is the current state of knowledge will be fundamental to clinical GS stewardship in pediatric critical care. Particularly challenging is the tension critical care clinicians must negotiate between the growing awareness that GS variant classification is dynamic with patient findings needing to be re-evaluated over time,[5] and the use of GS findings to inform irrevocable decisions like critical resource allocation (organs) and withdrawal of care.

Third, in stewarding patients through the decision to undergo GS testing and to use GS information in clinical decisions, clinicians are entrusted with protecting the privacy and sensitivity of their patient's GS revealed information. This is similar to the bio-banking model of stewardship. GS use needs to be conscientious about unintended social ramifications to children and families who undergo testing. In this, models of stewardship in bio-banking are more helpful since they do discuss obligations to bio-bank contributors over the 'life' of the specimens, the need to maintain relationships with the contributors, and responsibilities around incidental findings and obligations to notify donors as sequencing technologies and research on variant findings change.[11,35,36,37,38] However, unlike in bio-banking, far more people and institutions would have access to clinical GS information than do in bio-banking, heightening already present concerns that privacy is unobtainable in the current healthcare system.[39] In addition, all of the children in critical care have been confirmed to have actual illness, rather than an incidental finding suggesting the potential for future illness, with the increased vulnerability to discriminations actual illness confers.

With ongoing debate about genetic exceptionalism and whether genetic information needs to be considered and protected as different or special,[40] uncertainty regarding how to translate bio-bank privacy protections to clinical care,[34] and doubt among interviewed clinicians about healthcare institutions' ability to protect patient privacy, the need to gauge the importance of genomic privacy to individual families, and approaches to GS privacy protection need to be discussed between clinicians and families. That interviewed clinicians discussed whether patients undergoing private direct-to-consumer testing and families selectively revealing pertinent GS findings to their treating clinicians is an appropriate privacy protection, makes clear the responsibility clinicians already feel towards protecting patients' GS information and that clinicians and families are already considering withholding GS information from the medical record (though not from clinical care). In the absence of agreed upon healthcare culture-wide GS privacy approaches, the burden of protection of GS information privacy is being negotiated between the ordering bedside clinician and the patient/family.

Limitations

The interviewer for all collected interviews (DC) is a practicing clinician who works at the field site. This work may have introduced interviewer bias into the interview dynamic. However, this association may also have allowed for greater candor by interviewees than they might have revealed to an interviewer unfamiliar with their work. As with all qualitative studies there are limits to generalizability. This study's

field site is developing a genomics service, consequently, clinicians at this particular field site may have thought considered the uses and impacts of GS more than clinicians in other critical care settings.

Conclusion

A model of clinical stewardship of GS for pediatric critical care will need to involve assisting patients to negotiate the financial and personal cost burdens of GS testing, defining how GS results will improve or alter decision making around potentially scarce resources, and protecting the privacy and sensitivity of their patient's GS revealed information. Guidance on stewardship of GS is needed as GS increasingly becomes part of pediatric critical care.

List Of Abbreviations

GS: Genomic Sequencing

CHD: Congenital Heart Disease

Declarations

Ethics: The study was approved by the IRB of the Stanford University School of Medicine (IRB–35294). All participants consented verbally to study participation.

Consent for Publication: Not applicable

Availability of Data: The de-identified interviews used and analyzed for this study are available from the corresponding author on reasonable request.

Competing Interests: The authors declare that they have no competing interests

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Authors' Contributions: DC conducted all interviews and wrote the manuscript. DC and SL analyzed and interpreted the interview data. DM was a major contributor in conceptually structuring the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1: Sample Interview Questions

Do you use or encounter genetic testing currently as part of your clinical work? Does it impact your care? How?
Do you use or encounter GS currently as part of your clinical work? Does it impact your care? How?
GS is being piloted through several different approaches. Can you envision how you might use GS-derived information if GS were to:
-replace or supplement current neonatal screening tests?
-be used for children with complex, difficult to diagnose disease?
-be implemented for pre-natal screening?
-be marketed direct-to-consumer?
Do you envision or have you encountered any ethical challenges using GS in clinical care?
Do you envision legal or liability concerns about using GS results?
Do you have data safety or security concerns about storing GS results?
Do you have concerns about insurance, payment and GS?
Do you have any concerns about your knowledge or understanding of GS?
Do you have thoughts about GS education for clinicians?

Table 2: Demographics of Interviewees

Gender (%)	Women (44%); Men (56%)
Relative seniority (Years since completion of training)	12 Junior (10 years or less) 10 Mid-career (10-20 years) 13 Senior (20+ years)
Type of Clinician (#,%)	Anesthesiologist (4, 12%) Anesthesiologist/ICU (2, 6%) Cardiologist–echocardiography (1, 3%) Cardiologist-electrophysiology (2, 6%) Cardiologist-geneticist (3, 9%) Cardiologist/ICU-CVICU (3, 9%) Cardiologist-interventionalist (1, 3%) Intensivist-PICU (3, 9%) Neonatologist (3, 9%) Nurse Practitioner (NP)-ICU (1, 3%) NP-Perioperative care/ICU (4, 12%) NP-electrophysiology (1, 3%) NP-interventional cardiology (2, 6%) Physician assistant (PA)- ICU (1, 3%) PA-interventional cardiology (1, 3%) Surgeon, cardiothoracic (2, 6%) Surgeon, ENT-bronchial (1, 3%)