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Anticipating uncertainty and irrevocable decisions: provider perspectives on implementing whole-genome sequencing in critically ill children with heart disease

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Abstract

Purpose—To investigate the potential impacts of whole-genome sequencing (WGS) in the pediatric critical-care context, we examined how clinicians caring for critically ill children with congenital heart disease (CHD) anticipate and perceive the impact of WGS on their decision-making process and treatment recommendations.

Methods—We conducted semistructured in-person and telephone interviews of clinicians involved in the care of critically ill children with CHD at a high-volume pediatric heart center. We qualitatively analyzed the transcribed interviews.

Results—In total, 34 clinicians were interviewed. Three themes emerged: (i) uncertainty about the accuracy of WGS testing and adequacy of testing validation; (ii) the use of WGS to facilitate life-limiting decisions such as futility, rationing, and selective prenatal termination; and (iii) moral distress over using WGS with a lack of decision support.

Conclusion—Despite uncertainty about WGS testing, the interviewed clinicians were using, and anticipated expanding the use of, WGS results to justify declarations of futility, withdrawal of care, and rationing in critically ill children with CHD. This situation is causing moral distress in providers who have to make high-stakes decisions involving WGS results, with only partial understanding of them. Decision support for clinicians, and discussion with families of the risks of using WGS for rationing or withdrawal, is needed.

Keywords

critical care; futility; pediatrics; rationing; whole-genome sequencing

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DISCLOSURE

The authors declare no conflict of interest.

INTRODUCTION

Research into the ethical, legal, and social implications (ELSI) of implementing whole-genome sequencing (WGS) in pediatric clinical care has raised concerns about the risks genetic testing may pose for parental perceptions of child vulnerability, impact on parent–child bonding, and parental self- and partner blame for genetic findings.[1,2] ELSI scholarship has focused on protecting a child's "right to an open future"[3] and examined the impact of direct-to-consumer WGS testing on family health anxiety and health behaviors such as diet and exercise.[4,5] However, in certain pediatric contexts, such as among critically ill children, the risk of WGS testing may be death. In the high-stakes, high-pressure context of critical care, WGS results may be used to justify declarations of futility, withdrawal of care, or rationing of scarce resources (such as an organ for transplantation) from one patient to another.[6] A recent study of WGS implementation in the care of critically ill infants showed that initiation of palliative care was most often identified as the clinical utility of WGS testing, more than other actions such as changes to medication, procedures, or counseling.[7]

Expanded use of WGS will outpace the necessary support and resources to render its results useful. The number of geneticists and genetic counselors in North America will be inadequate to address WGS results for all patients who receive findings, even in the outpatient setting.[8] With the time pressures common in critical care, the burden of interpreting and contextualizing WGS results will fall on bedside intensive care unit (ICU) clinicians, despite the known limited knowledge and understanding of genetics and genetic testing by bedside clinicians.[9,10] This is similar to how ICU physicians have been required to make clinical decisions based on other complex diagnostic tests, such as computed tomography (CT) scans, without the benefit of radiology support, because of the clinical time pressures involved.[11]

Clinicians already use current genetic findings to ration scarce resources in ICU care.[12] Pediatric solid-organ transplant programs use genetic findings associated with future developmental delay, such as fragile X, to guide organ allocation.[12,13] When considering extracorporeal membrane oxygenation (ECMO), most clinicians would withhold in children with trisomy 13 or 18 and consider trisomy 21 a relative contraindication.[14] When considering high-risk surgeries, such as for hypoplastic left heart syndrome, clinicians similarly use the presence of chromosomal defects to steer care away from intervention.[15] By expanding the number and kind of available genetic findings, WGS results have the potential to significantly expand the genetic findings used to evaluate therapeutic choices in the face of uncertain outcomes and be used to justify withdrawal of care or rationing decisions.[16]

Congenital heart disease (CHD) is the most common type of birth defect leading to critical illness in the United States[17,18] and the leading cause of birth-defect-associated illness and death.[19] Given the complexity of disease and invasive and costly procedures required for children with CHD, the care of this patient population involves difficult clinical decisions, organ transplantation, and end-of-life care questions, as well as rationing discussions, among clinicians and families.[20] Clinicians and families must continually assess whether the invasive therapies offered are proving useful or prolonging needless suffering, weighing the

uncertainties of treatment success against the pain and suffering inflicted by the treatment choice.[21] WGS is being piloted in this population[22] and has the potential to have a profound impact on how these difficult decisions are made.[23]

To better understand the potential impacts of WGS in the pediatric critical-care context, we undertook this qualitative study examining how clinicians caring for critically ill children with CHD anticipate and perceive the impact of WGS on their decision-making process and treatment recommendations.

MATERIALS AND METHODS

We used a qualitative approach, interviewing physicians, nurse practitioners, and physician assistants involved in the care of critically ill children with CHD at a high-volume pediatric heart center and its main referral hospital, to investigate how clinicians anticipate and envision the impact of WGS on their work. This field site is an institution implementing a clinical WGS service at the time of the interviews and had already started pilot WGS testing in critically ill children with CHD. Interviewees were initially approached via telephone or e-mail and selected to reflect the distribution of clinicians (in terms of seniority and specialty area) at the heart center. Recruitment stopped after saturation was reached. Not all clinicians working in the heart center were interviewed. We used one-on-one interviews as this technique has been found to be productive for discussing sensitive topics (such as personal decision making) and is well suited for exploratory research attempting to find a range of perspectives.[24–30] The study was approved by the institutional review board of the Stanford University School of Medicine. Informed consent was obtained from all participants.

A semistructured interview guide of open-ended questions intended to elicit participants' perspectives about use of WGS-derived information in their clinical practice was piloted with five clinicians. Following these pilot interviews, explicit questions about liability, data safety, and insurance concerns were added to the interview guide. Questions included current and hypothetical clinical applications of WGS (Table 1). Interviews were conducted either in person or over the telephone, and were audiorecorded and transcribed. Although every effort was made to conduct interviews in person, phone interviews were also used to accommodate the busy schedules of some interviewees. No differences were noted in the nature of the responses to the phone interviews compared with the in-person interviews. The primary investigator (D.S.C.) provided initial contact to all potential participants and conducted all interviews. Transcripts were uploaded into the qualitative analysis software Dedoose (http://www.dedoose.com), and interview data were analyzed incorporating grounded theory.[31–33] Codes were generated inductively through a collaborative reading and analysis of a subset of interviews (D.S.C., S.S-J.L., and M.C.) and then finalized through successive iterations into categories and codes. As interviews were being conducted and analyzed, every effort was made by the multidisciplinary team (D.S.C., S.S.-J.L., and M.C.) to identify any potential bias by the interviewer (D.S. C.). At least one primary (D.S.C.) and one secondary coder (Alvan Ikoku) 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.[34] Emerging themes were

identified, described, and discussed by the research group. Interviews continued until saturation was achieved.

RESULTS

The study participants were 34 clinicians (Table 2) who were interviewed over 5 weeks in 2016. The response to requests for participation was 100%. Interviews lasted for approximately 20 to 60 minutes. Three themes emerged from thematic analysis (Table 3): (i) uncertainty about the accuracy of WGS testing and adequacy of testing validation; (ii) the use of WGS to facilitate life-limiting decisions such as futility, rationing, and selective prenatal termination; and (iii) moral distress over using WGS with a lack of decision support. These themes are discussed below.

Uncertainty about WGS testing accuracy

Interviewed clinicians expressed uncertainty about how WGS and WGS-revealed knowledge would influence bedside practice. One interviewee (a cardiologist) asserted that broad implementation of WGS "is like picking your nose in public. You might get a result but you won't know what to do with it," arguing that, for individual patients, more is still unknown than known about WGS, which makes it difficult to interpret the results.

Interviewees articulated doubt about the testing technology itself, noting that WGS still had not been validated as even non-inferior to current genetic testing methods:

> "In the modern world, we've moved towards exome and genome sequencing and been willing to accept a report on a gene if 90% of that gene is covered with 10 ×, in other words, 10 base pairs of coverage or more, which is an incredibly low bar. And to me that's the biggest single challenge for us technically when we get into the world of exome and genome sequencing is to apply which is standard in the rest of medicine the concept of non-inferiority. We're not going to accept the new test until it's non-inferior to the current test." (Cardiologist)

This interviewee commented that WGS has not yet been established as equivalent in utility to current genetic testing and that, without this equivalence, interpreting what WGS findings mean and, more importantly, whether they are clinically significant is still difficult. Even the assumptions in how we currently understand and describe genetic results may change. Another cardiologist (a clinician and researcher) noted offhand the idea of genetic penetrance: "Penetrance is the word that we use right now which is probably not going to even be used 10 years from now." How we conceptualize the genome and clinically significant expression of genetic variation is already beginning to change among researchers working on WGS and WGS results.

With uncertainty in WGS testing and analysis, clinicians were unsure about when WGS-derived information should be used to make day-to-day management decisions, such as drug selection and treatment strategies. One interviewee described using WGS for selecting and tailoring treatment:

> "What unfortunately often happens is we find a deletion or an addition or a balanced translocation that we don't know exactly how to counsel for and part of the reason is it doesn't get tested on every single person and so there's not enough data out there on what that particular deletion or addition means. If everyone got tested you could probably start forming a database of what's different about those patients. Because right now, we are often flying blind." (Intensivist)

Clinicians articulated concern that they were "flying blind," having to process WGS results or make decisions from genetic test findings without adequate data to fully understand the potential clinical implications of the findings.

Using WGS to make life-limiting choices

Despite this uncertainty, for many interviewees the most immediate potential benefit of WGS was to guide withdrawal of care and allow earlier declaration of futility. As one interviewee noted:

> "It's of great importance for us to learn sooner rather than later, for some of these babies, what they may have. Not only might it help us adjust therapies, but more importantly for babies who have what we know to be fatal conditions, we would not want to prolong their suffering by continuous futile intensive care support. So, for us, one of the more immediate benefits of whole-genome sequencing is we could have that discussion with the parents and change our goals of care to comfort, as opposed to prolongation with futile intensive care." (Neonatologist)

WGS results could be used to avoid invasive and ineffective interventions in critically ill children by allowing earlier discussions about the desirability of life-prolonging therapies. Clinicians viewed WGS results as similarly aiding decision making regarding the choice to pursue aggressive therapies, such as surgical repair of complex cardiac lesions:

> "We already know that about 25% of kids with DiGeorge syndrome [22q11 deletion] get schizophrenia and they get Tet/PA/MAPCAS [tetralogy of Fallot with pulmonary atresia and multiple aorto-pulmonary collaterals]. It's a horrible surgery that's probably not going to go very well. Wouldn't you want to know about the schizophrenia as early as possible before you do the surgery?" (Intensivist)

If WGS results are able to reveal potential neurocognitive or severe psychiatric illness, these findings may influence clinician recommendations about therapeutic options, particularly if the therapeutic benefit is not certain or the potential for adverse outcomes is high. Similarly, clinicians articulated struggles with risk assessment and the choice to provide lifesaving, but palliative, therapies to children with genetic diagnoses that suggested potential for increased risk of a poor outcome. An example given by one intensivist was the platelet disorder associated with Jacobsen syndrome, which increases a child's risk for an intracranial bleed after undergoing cardiac surgery for single-ventricle physiology: "We had a kid who had Jacobsen syndrome. Is it even ethical to do a Norwood procedure on a baby with Jacobsen syndrome?" WGS-revealed foreknowledge of the potential for an adverse outcome might guide different clinical choices than would currently be made, particularly before counseling a family to pursue a palliative (not curative) therapy for single-ventricle disease involving multiple staged surgeries.

The weight given to the potential for adverse events was even stronger when clinicians considered prenatal WGS. Despite acknowledging uncertainty in being able to predict overall outcome from WGS results, interviewees envisioned WGS results expanding the reasons to decide on selective termination of a pregnancy:

> "I think if my daughter were getting pregnant and had that screening and found that her fertilized egg carried the 22q11 [DiGeorge] deletion, I think I'd probably say, you know, why don't we try again, but with the understanding that that could be a totally normal kid." (Cardiologist)

The potential for an adverse outcome could guide clinicians to recommend selective termination, even when such an outcome is not certain. This is even true for decisions about adult-onset conditions. Other interviewees envisioned benefits from WGS-revealed findings associated with adverse events later in life, such as breast and ovarian cancer, guiding selective termination decisions:

> "This sounds more paternalistic, but knowing that your little girl who's in utero has the breast cancer gene, I mean maybe that is useful, maybe try again and you get a girl that doesn't have the breast cancer gene." (Cardiologist)

While it is unlikely that a cardiologist would be in a position to recommend selective termination based on *BRCA* findings alone, such WGS-revealed findings in the context of concomitant cardiac disease could influence recommendations about termination. Other interviewees felt that WGS could be a powerful tool in the challenge of balancing health-care costs and helping with rationing decisions at the systems level:

> "What this single child needs right now may be $10 million worth of care over the next 4 weeks, where another, oh, I don't know, 50,000 children could have used that for care for things that are higher yield in terms of their outcome. So, I think genetic sequencing could help in that respect." (Anesthesiologist)

Outcomes data (including care costs) associated with WGS testing results could provide guidance on how systems allocate scarce resources.

Moral distress over using WGS with a lack of decision support

Interviewees articulated greater anxiety associated with interpreting WGS than other diagnostic tests, since the information revealed was potentially much broader with many more potential clinical implications and it was not clear, when interpretations had to be made in a variety of clinical contexts, who the interpreting expert might be:

> "WGS is somewhat of a new world where we get, really, information on so many different diseases. I think often this metaphor or comparison with imaging is made. I think that's a relevant and helpful comparison to make, but I think genome sequencing goes further than that. I mean, typically, if the example is a chest X-ray or a CT scan and there's a nodule on the lung and you're looking at the heart, you know, that is true and accepted, but this is a situation where you're not just seeing an image of one other organ, you're getting an individual base-pair level sequence for every gene and, potentially, that could be relevant for every disease, every organ, every…I think that's a major challenge to process." (Cardiologist)

The issues of how to process the breadth of information potentially revealed by WGS, where to look for decision support, and on whom the burden of decisions made from the results rests, particularly in the context of acute-care decisions, are challenging and unclear. Interviewees likened WGS to CT scans, another broad diagnostic test whose results intensivists have had to interpret as the basis of decisions, often without decision support or an interpretation of the test results other than their own.

> "With the CT scans, I think the main problem with it is that every test has false positives and it can lead then to other tests and then you know how that cycle goes. There's some kind of ditzel on the kidney, and then you get a biopsy, and then you have a complication, and then you're in the hospital, and then you're infected… But I guess I don't know yet because I haven't had any experience with whole genomes. I haven't actually had any experience of knowing what comes out of it that I would have to worry about, whereas I've seen a ton of the CT scan things." (Intensivist)

Underlying much of the discussion of WGS, interviewees articulated struggling with deciding whether offered critical-care therapies were beneficial or merely prolonged suffering, describing what some children go through during prolonged intensive care as "painful to watch" (intensive care nurse practitioner) and "horrible" (anesthesiologist). Interviewees said that it is often not clear, when therapeutic decisions are made, which child will have an adverse outcome or receive little benefit from the chosen therapies. In cases of complex genetic disease, clinicians described being troubled by the suffering, significant morbidity, and waste of care resources associated with choosing an aggressive therapy for a child unlikely to receive benefit:

> "I have the dubious distinction of probably being the only person that put somebody with [genetic finding associated with poor neonatal outcome omitted so as not to identify the interviewee] on ECMO. It was a 6-month-old that had heart surgery and the heart surgeon called me up and said baby can't come off the pump, and I told the parents that you can do ECMO, which was true, and baby survived, went home, and a couple months later died of [finding], which is not a surprise to anybody, but the parents had gotten insurance to cover it and maybe it's not my position to say that those resources were wasted, but it concerns me that literally hundreds of thousands of dollars were spent and this child had a modest prolongation of life and a lot of suffering in the hospital, perhaps more for the parents' sake than for the child's sake." (Neonatologist)

In fact, the combination of the two tensions—possibly inflicting needless suffering and the possibility of misallocation of scarce resources—seemed to heighten clinician distress.

DISCUSSION

Critical-care clinicians continually face the ongoing clinical dilemmas of considering when suffering outweighs therapeutic benefit and how best to triage scarce resources. In our study, clinicians involved in the care of critically ill children with CHD anticipated a struggle with how to incorporate WGS into the context of these clinical dilemmas. They envisioned that the most immediate potential benefits of WGS implementation will be allowing earlier

declaration of futility and better guidance in decisions involving withdrawal and the rationing of scarce resources. This finding is consistent with preliminary implementation studies showing that transition to palliative care was more often cited as an example of the clinical usefulness of WGS testing than were other actions, such as changes to medication, procedures, or counseling.[7,35] Clinicians also envisioned using WGS findings to broaden the basis for decisions of withdrawal or rationing to include genomic prediction of certain bleeding disorders and schizophrenia, impacting decisions. For in utero WGS, interviewees envisioned that further expansion of genomic findings will influence discussions about selective termination, such as 22q11 deletion and *BRCA*. Underlying the discussion of critical-care therapeutic choices was an understanding that prolonged intensive care can be the cause of significant suffering to affected children and families, that many available therapeutic options are of uncertain benefit, and that many therapeutic interventions (such as ECMO) involve the use of scarce resources that need to be stewarded toward patients with the best likelihood for a beneficial outcome.[36,37] These demands, however, need to be balanced against using WGS findings before they have been analytically validated, clinically validated, and demonstrated to be ethically appropriate.

Clinicians also articulated concerns about the WGS technology and lacked confidence in the validity or utility of WGS results to select or tailor treatment strategies, such as drug selection. It is interesting that despite this uncertainty, clinicians still envisioned using WGS results to support such irrevocable decisions as termination or withdrawal of care. The anxiety and feeling of burden associated with making these high-stakes decisions based on WGS results were also expressed in the interviews. Clinicians described how they already have to make high-stakes decisions using technology (such as CT imaging) that they are not experts in. More than CT findings, WGS results may have implications for multiple organ systems. Even if an expert in the technology is available (such as a radiologist for CT scans), the understanding of the potential outcomes of therapies chosen on the basis of test results and the burden of the outcomes of the decisions made still rest with the bedside clinician. This will also be true of decisions based on WGS results.

The uncertainty of how to interpret WGS results and the high-pressure contexts in which these results are being used creates a situation of moral distress for many interviewed clinicians. Moral distress and burnout are close phenomena, burnout itself being associated with high-stakes care contexts, such as those surrounding patient death.[38] The rapid introduction of WGS to the care of critically ill children may have unintended implications for clinician burnout. This is important because WGS implementation is in an early stage. For WGS to be useful in the critical-care context, further research correlating genetic markers with outcomes is needed to validate the predictive power of WGS results. If WGS is incautiously introduced and creates a distressed care environment, the ability to complete this research is jeopardized.

It is unlikely that families understand that WGS testing could result in rationing, justification of futility, and triage of scarce resources. If families understand that WGS results of testing done in utero, at birth, or as part of a screening program might later be used to deny their child scarce resources should the child become critically ill, it is possible that fewer families will agree to such testing. Parents may be highly disturbed on finding out that WGS results

are being used in this way, and the alliance between clinicians and families may be strained. Concern has already been articulated that clinical use of WGS in the newborn period might exacerbate stigmatization and discrimination against disabled persons.[39]

Before implementing a widespread WGS testing program, the full potential use of WGS results in the care of critically ill children with CHD, such as the possibility that WGS results might be used to guide withdrawal of care or rationing of scarce resources, should be made explicit to potential participants. If a population-wide WGS screening program becomes a societal or health-care goal, open discussion about how the results might be used in the critical-care context is necessary.

With competing demands on clinicians' time and rapid progress in genetic knowledge, comprehensive supplemental education seems unrealistic. Machine learning has been proposed to support WGS clinical decision making and to provide knowledge from both genetic and related clinical disciplines,[40] since interpretation of the breadth of WGS findings may require both genetics and organ-system-specific knowledge. A vulnerable period will exist while data for databases that could support machine learning systems are being collected. Ongoing consultation between groups of specialty clinicians who can prioritize and rapidly interpret results and ongoing dialogue between clinicians and families will be needed.

Clinicians already struggle with the difficult dilemmas of weighing suffering against benefit and how to triage scarce resources. WGS results are not yet ready to resolve these dilemmas, although they are being used to justify decisions. In these early stages of WGS implementation, without frank discussion of the potential rationing uses of WGS results and without improved ICU WGS interpretation and decision support, introducing WGS technology to intensive care for critically ill children with CHD may simply accelerate clinician moral distress and burnout, strain clinician relationships with families, and ultimately jeopardize the potential benefits of WGS implementation.

Limitations

The interviewer (D.S.C.) is a practicing clinician who works at the field site. This may have introduced interviewer bias into the interview dynamic, but may also have allowed for greater candor by interviewees, such as expressing unguarded concerns and challenges they might not 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, with many clinicians involved in genetic research. Clinicians at this particular field site may have considered the uses and impacts of WGS more than clinicians in other settings.

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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 WGS currently as part of your clinical work? Does it impact your care? How?
•WGS is being piloted through several different approaches. Can you envision how you might use WGS-derived information if WGS were to:
-replace or supplement current neonatal screening tests?
-be used for children with complex, difficult-to-diagnose disease?
-be implemented for prenatal screening?
-be marketed direct to the consumer?
•Do you envision legal or liability concerns about using WGS results?
•Do you have data safety or security concerns about storing WGS results?
•Do you have concerns about insurance, payment and WGS?

WGS, whole-genome sequencing.

Table 2

Demographics of interviewees

Gender (%)	Women (44%), men (56%)
Relative seniority (years since completion of training)	12 Junior (10 years or less)
	9 Midcareer (10–20 years)
	13 Senior (20+ years)
Type of clinician (*n*, %)	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%)
	NP—ICU (1, 3%)
	NP—perioperative care/ICU (4, 12%)
	NP—electrophysiology (1, 3%)
	NP—interventional cardiology (1, 3%)
	PA—ICU (1, 3%)
	PA—interventional cardiology (1, 3%)
	Surgeon—cardiothoracic (2, 6%)
	Surgeon—ENT/bronchial (1, 3%)

CVICU, cardiovascular intensive care unit; ENT, ear, nose and throat; NP, nurse practitioner; PA, physician assistant; PICU, pediatric intensive care unit..

Table 3

Frequency of comments and themes

Question/theme	Example	No. of respondents (out of 34 interviewees)
Do you use or encounter WGS as part of your clinical work?	Yes: "You know, I've got a few patients who were tested at [another hospital]. I had one patient just a couple weeks ago who was managed here by the new clinic."	32
Is it currently helpful/does it change care?	Yes: "Whole-genome sequencing was really important in this child's care, as well as in counseling the family for future children."	14
Main themes raised:		
Uncertainty in WGS testing	"I think that if the technology progresses and you have the right controls then someone with an expert background might be able to decipher all this information into a take-home message as a clinician. But I think this stuff is going to be a lot messier and there's going to be a lot of nuance, and I'm concerned most clinicians are not going to have the aptitude to figure out what any of that stuff means."	33
Moral distress/need for decision support	"I'm not sure how to deal with it. You know, there are some kids that we await, you know, kids who are stuck on a ventilator and we find out they really have surfactant protein deficiency that can be proven genetically, then we can stop, but they just wait. They still depend on us to know which test to order."	32
Using WGS to ration care or decide futility	"If a child's stuck on a ventilator and it's just a matter of days, we'll wait, but if that child is 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 WGS can make a lot of hard decisions easier."	27
Desire for ongoing education about WGS	"Things are changing so rapidly that when I think I may have a basic understanding of what I need to know, within a few months it's changed. I don't know how exactly I need to learn about this…maybe a quarterly update."	27

WGS, whole-genome sequencing.