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Access to prenatal exome sequencing for fetal malformations: A qualitative landscape analysis in the US

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Abstract

Objective: There is increasing evidence supporting the clinical utility of next generation sequencing for identifying fetal genetic disorders. However, there are limited data on the demand for and accessibility of these tests, as well as payer coverage in the prenatal context. We sought to identify clinician perspectives on the utility of prenatal exome sequencing (ES) and on equitable access to genomic technologies for the care of pregnancies complicated by fetal structural anomalies.

Method: We conducted two focus group discussions and six interviews with a total of 13 clinicians (11 genetic counselors; 2 Maternal Fetal Medicine/Geneticists) from U.S. academic centers and community clinics.

Results: Participants strongly supported ES for prenatal diagnostic testing in pregnancies with fetal structural anomalies. Participants emphasized the value of prenatal ES as an opportunity for a continuum of care before, during, and after a pregnancy, not solely as informing decisions about

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest in connection with this article.

abortions. Cost and coverage of the test was the main access barrier, and research was the main pathway to access ES in academic centers.

Conclusion: Further integrating the perspectives of additional key stakeholders are important for understanding clinical utility, developing policies and practices to address access barriers, and assuring equitable provision of prenatal diagnostic testing.

1 | INTRODUCTION

There is increasing evidence supporting the clinical utility of prenatal next generation sequencing for identifying a fetal genetic disorder.[1] However, there are limited data on the demand for, and access to these tests, including current payer coverage in the prenatal context.

A study on US private payers' perspectives on insurance coverage found that while payers saw value in ES for pediatric patients, they did not see merit in its use for prenatal testing.[2] However, studies have demonstrated a high diagnostic yield of ES for fetal structural anomalies[3-9] with diagnostic rates ranging from 8.5% to 44%[10] depending in part on phenotypic sub-groups.[11] Given this high yield, several professional societies now recommend the consideration of ES in cases with multiple fetal structural anomalies or in which a genetic disease is strongly suspected.[12,13]

Although ES is increasingly available with decreasing costs, optimal clinical implementation in the prenatal setting is still being discussed. A “Center of Excellence” model in which sequencing and return of results to patients is provided at a number of academic medical centers with genetics expertise and has been beneficial in the initial early phase of implementation of prenatal ES.[2] However, it is unlikely that such centralization will be feasible as ES becomes more widely available. Inequitable access to genomic medicine including prenatal diagnosis and therapy continues to be a concern[14,15] given disparate insurance coverage, and uptake of ES demonstrates similar access disparities to those reported with the rollout of other technologies, such as cell-free DNA screening.[16] Factors outside the immediate patient-care realm, such as payers' willingness to cover ES, are also important considerations as clinical use of these tests increases.[17]

In the face of a rapidly changing genomic sequencing environment, it is important to understand the perspectives and practices of prenatal care providers broadly. The goal of this study was to explore perspectives on the utility of ES for fetal structural anomalies and barriers to equitable provision of genomic sequencing. Findings can inform the development of service provision models, insurance coverage policies, and best practices on how to equitably implement genomic technologies to benefit all patients.

2 | METHODS

For this qualitative exploratory study, we conducted two focus groups with 3–4 participants each and six semi-structured interviews with a total of 13 key informants. We used purposive sampling to capture differences in geography and context: seven focus group participants were clinicians with expertise in prenatal sequencing affiliated with U.S. academic centers

participating in the Fetal Sequencing Consortium (FSC).[18] The study was introduced to the Consortium at a monthly meeting and those interested in participation were asked to contact the study team. Focus groups were formed and scheduled based on the availability of participants. Purposive sampling with the snowball technique was used to recruit participants for the semi-structured interviews, and researchers reached out to colleagues who then referred others to the study. One-on-one interviews allowed in-depth discussion of the unique circumstances in community clinics.

Sessions were conducted through video conferencing between January–April 2023, and were facilitated by the study team (MN, BL, NNSH) using interview guides developed for this study (see Supporting Information S1). The guides were pre-tested with two prenatal GCs and modified accordingly. Guides included questions about the standard of care for pregnancies with structural anomalies, current practices for offering prenatal ES, payer coverage of the test, perspectives on clinical utility of ES, access to prenatal ES, and suggestions for improving equitable access. Verbal consent was obtained at the beginning of each session. Focus groups lasted 90 min and interviews lasted 30–60 min; all sessions were recorded and transcribed. A short online survey was sent to collect information on participant demographics.

For qualitative data analysis, the study team employed a well-established thematic analysis approach.[19-22] Initially, the team developed a set of conceptual domains based on exploratory research questions including What are testing pathways for ES?; What are perceptions about clinical utility of ES?; How do cost and coverage of the test impact equitable access?; How do providers think about broadening access to prenatal ES? An iterative process was followed to develop deductive codes within each domain. Facilitators held debriefing meetings after each focus group and interview to review the session, identifying specific points for further discussion and clarification and probes to explore more in depth in subsequent interviews. Transcripts from the first three interviews were independently coded by two study team members (NNSH/BL) and discussed to resolve differences in inter-coder reliability. Remaining transcripts were coded by one study team member (NNSH or BL) using Excel; quotes for preliminary themes were identified within each domain. Emerging themes were discussed, and illustrative quotes were reviewed by the study team until consensus was reached on how to frame the main findings. The study was reviewed by the UCSF Human Research Protection Program as exempt (22-37266).

3 | FINDINGS

Participants were from institutions based in California, New York, North Carolina, Ohio, Pennsylvania, and Texas. Of the 13 participants, 10 were prenatal GCs, one was a GC in a hospital send-out laboratory, and two were physicians with a board certification in Maternal Fetal Medicine and Clinical Genetics. Eleven described themselves as having “quite a bit” of experience with prenatal ES (Table 1).

Qualitative findings are presented in two main domains: clinical utility of ES and access to ES. Themes are summarized below with additional exemplary quotes in Table 2.

3.1 | Clinical utility of exomes in the prenatal context

Participants were asked how often and in what circumstances they offered or recommended prenatal ES. ES was favored for prenatal diagnostic testing for pregnancies with structural anomalies and a negative chromosomal microarray (CMA). Saving time by avoiding sequential testing approaches, lower overall cost, and increased diagnostic yield were cited as some of the advantages of ES over multi-gene panels. A few exceptions in favor of gene panel testing included specific phenotypes (e.g. skeletal dysplasias), or higher likelihood of being covered by insurance. ES was felt to be useful for guiding care rather than solely for abortion decisions, and a strong theme was prenatal ES providing an opportunity to improve care "before, during and after" a pregnancy (Table 2:D1.A1-A2). Providers described the utility of prenatal ES as extending into the neonatal period, and that the "fastest neonatal exome is the one prenatal".

A GC in the Central Valley in California described the challenges of providing care to an under-resourced patient population with generally low health literacy. When she explained the utility of ES for care during pregnancy as well as after birth, uptake of ES increased, which might have increased the likelihood of families receiving genetic services after birth:

> [O]ur patient population is less likely to make reproductive decisions based on the diagnostic results, but it can be so helpful for planning in the neonatal period…I'll spend quite a lot of time in explaining why I think that that information would be beneficial … [Then] the uptake is much higher, especially when it's [explained] as [how] you could use this information in preparing for your baby to be born, and knowing what specialists to loop you into, and ensuring that appropriate follow-up is happening. I was particularly passionate about it in the [Clinic] because our likelihood for getting that baby to come back in peds genetics can be so low…. There was more pressure on me to ensure that testing was completed in that moment… because I was so worried about them disappearing forever.
>
> (IDI-3)

Similarly, in a community clinic in Texas, a provider reported that patients valued additional diagnostic information through ES, regardless of their views on abortion and that uptake was high when offered to all patients:

> What I found even before we had laws in place was a lot of these patients weren't going to terminate any-way. These are patients who are coming because what they want to know is if there is a treatment …. And if there is, where do we go to get it? Or is this something that we think is medically futile? [If] so, we want to stay in our smaller area, but deliver on a palliative care line…. So, for fetal anomalies, if they're referred because of an abnormal ultrasound, that is something we discuss with everyone. Interestingly […] probably half of our patients want to do diagnostic testing with either CVS or amniocentesis. And then the other half are actually still wanting that testing, but delaying to cord blood testing.
>
> (IDI-2)

Despite the potential utility of ES, balancing optimal patient care with the cost of the test was described as a challenge by a send-out laboratory GC:

> I think the true genetic counselor in me is really for [prenatal ES] and I want to push for it. And I do think we make really interesting diagnoses that can extend our postnatal understanding of phenotypes into the prenatal setting. I also think you're kind of queuing a population we've never queued before […] and we [don't] know things about a gene that could be really important….The other part of me, the hospital administration part does recognize that the impact on clinical care can be limited…. So you're dancing around what's covered, what's not versus what ideally can we do to give our patients the best care that we can without bankrupting them.
>
> (IDI-4)

3.2 | Access to prenatal ES

Cost was reported as the single most important factor limiting access to prenatal ES. Patients who were clinically assessed as potentially benefiting from ES were often referred to clinical studies in academic centers, allowing them to access the test free of charge. Those without local access to ongoing research would often reach out to other centers to find out if their patients would qualify (Table 2:D2.A1-A3). Figure 1 shows decision-making pathways to access ES under different circumstances.

Insurance coverage is critical to access ES (Table 2:D2.I1-I3), and clinicians voiced deep frustration in dealing with insurance providers (Table 2:D2.C1-C3), spending disproportionate amounts of time and effort attempting to obtain ES coverage. Many shared personal experiences of trying to obtain prior authorization and appeals. Several insurance companies will only talk to physicians for peer-to-peer consults, which creates additional burden for both the GCs and MFMs. The overwhelming feeling was that it is usually a waste of time, and that "you can write appeals all day long," but "it never works" (FGD2-2). This "fighting the fight" (FGD1-2) with insurance providers was seen as a significant access barrier:

> I think for me that's the biggest systemic hurdle that we need to overcome. If you think about providers that are less familiar with this testing option and, feeling less comfortable even offering it, they're not going to jump through all these hoops to get it.
>
> (FGD1-1)

Participants reported mixed experiences when caring for publicly insured patients. In one academic Center in North Carolina, providers reported that managed Medicaid covered ES except in prenatal cases. Providers in other academic centers also mentioned challenges with Medicaid. In contrast, in three clinics (two in California, one in Texas) where most patients had Medicaid coverage, a contract with one commercial laboratory made it easy to order CMA as well as ES without billing the patients. This enabled providers to offer ES to the majority of their patients, especially when the GCs were savvy and knew how to "play the game" with the commercial laboratories to make the testing available to their patients (Table 2:D2.D1). Interestingly, patients with private "middle of the road insurance" were often described as the most disadvantaged group, creating a form of "reverse discrimination" (Table 2:D2.E1-E2).

"Who [patients] interact with in the prenatal pathway" (IDI-1) was identified as another access factor (Table 2:D2.F1-F2). Participants felt that those living in rural areas distant from academic centers without access to genetic counseling were less likely to be offered ES (Table 2:D2.G1-G3). Outside the large academic centers, patients are less likely to receive genetic counseling about further testing options for pregnancies with structural anomalies after a negative CMA. Prenatal providers' understanding of available tests, and what they communicate to their patients about these tests are important factors for access:

> Something I've run into here is the MFM and OB providers in this area, not really being aware of the availability of sequencing, [have] been sort of a barrier in itself. There was a patient whose fetus had multiple anomalies. We did a microarray. It was normal. And I actually got prenatal ES authorized by her insurance….I figured out how to do it with this lab where they'd have to submit some information for financial assistance… So all these conversations back and forth. And then she's like, "Well, my MFM told me at the appointment this morning there's nothing else that can be done. I just have to wait till after the baby's born." And I was… Anyway, she did not end up getting the prenatal exome sequencing, and I didn't think about that ahead of time as being such a barrier. […]
>
> (FGD2-4)

The concern that ES could open up a "black box," yielding too many variants of uncertain significance and incidental findings was also mentioned as a potential access barrier. Although participants felt that this fear was not justified, they believed it could prevent some providers from ordering ES, and may be used by insurance companies as a justification for not covering the test (Table 2:D2.J1).

Not having access to a clinical geneticist made one participant hesitant to order ES at a community clinic; she did not want to order ES outside of her scope and was concerned about delaying the patient's referral to a geneticist (Table 2:D2.K1).

Other access barriers, not necessarily specific to genomic testing, were thought to disproportionately affect community clinics (Table 2:D2.H1). These barriers include limited access to transportation, local health care, and quality prenatal screening for early detection of fetal anomalies. Additionally, it is a bigger task to offer ES to non-English speaking patients, especially in the research context when study consent are required. Respondents were concerned about the quality of communication with an interpreter for complex genetic information and their ability to adequately explain tests to low-literacy patients and families. The time it takes for referrals from a clinic to an academic center was also a barrier, making prenatal ES less of an option.

When asked about facilitators to broaden access to ES, several participants mentioned the importance of professional guidelines to provide clinical recommendations (Table 2:D2.H1); insurance coverage (Table 2; D2.I2; De.I3); and educating providers on the value of the test for patient management and counseling. Connecting clinicians practicing in the community with geneticists experienced in ES was also mentioned to provide clinical support and back-up (Table 2: D2.K1).

4 | DISCUSSION

There is increased evidence to support the utility of prenatal ES for the diagnosis and management of fetuses with congenital abnormalities.[23] This study provides clinician perspectives and insights on prenatal diagnosis with ES based on their day-to-day practice and experiences. Providers endorsed the clinical utility of prenatal ES, noting that patients appreciate additional information during pregnancy even when termination is not a consideration, in order to plan for the birth of their baby and to navigate the difficult circumstances of pregnancy with a structural fetal anomaly. Despite this, numerous barriers to accessing ES in the prenatal setting were identified, ranging from insurance coverage to provider understanding of genomic sequencing and logistical issues such as geographical distance from providers trained in genetics.

Providers saw themselves as advocates and were committed to obtaining ES for their patients for what they consider the best care for the fetus/child. This is consistent with other studies reporting parents' perspectives—that parents appreciate more information as new genetic technologies are being rolled out.[24-26] In a recent study, parents described wanting to pursue testing that has the potential to provide more information, despite a low probability of making a diagnosis and the potential for uncertain results.[26] Parents have unique considerations for prenatal sequencing as the results could expand the complexity of risk and reproductive decision making.[27] But simply trying to do something to gain knowledge is important to many, in their desire to try anything to reduce uncertainty regarding a fetal structural anomaly.[28] Furthermore, studies from the UK, Denmark, and the Netherlands reported similar findings[29-31]: that parents wanted to “receive all the information possible”[31]; appreciated increased knowledge in an “otherwise difficult situation” even after losing a child[29]; and that the test provided psychosocial benefits to parents despite the experiences of “emotional rollercoaster” and potential negative impacts on parents.[30] On the other hand, while parents may have multiple reasons to have the test done, and a desire to know, there is limited information on the downstream impact of ES results on families and relationship dynamics.[32]

Framing the utility of ES as guiding care before, during, and after a pregnancy is in contrast with the perspective that the main goal of prenatal diagnostic testing is for decision making about termination. Terminating a pregnancy based on prenatal testing is a utility in and of itself, and a negative as well as a positive ES result may guide families to decide to continue with their pregnancy.[3,33] Providers described the utility of ES among patient populations where termination is not an option due to cultural or religious reasons, as well as those living in states where abortion is restricted. Offering diagnostic testing only if abortion is considered an option can in effect introduce further bias in terms of who has access to testing.

The challenges of prenatal diagnostic ES are well defined,[34,35] and strategies such as building expertise among the broader provider community and increased access to providers with genetics training will help mitigate some of these challenges. Perspectives of participants in this study on the utility of ES, and their support of ES as a mainstream test, is in significant contrast to payer perspectives documented just a few years ago when payers

did not see merit for the test in the prenatal setting.[2] Rapid advances and new information in the fields of genomic medicine and Maternal-Fetal Medicine require continuous review and updates of coverage policies and professional guidelines.

An interdisciplinary approach to broadening the understanding of the utility of prenatal ES and improving access to this test is prudent, with the involvement of patients, clinicians, research funders, and payers.[36] Factors such as alleviation of guilt, pragmatic life planning, managing uncertainty, or even just the ability of genomic tests to provide information that is "good to know"[36] are increasingly being recognized as important elements of utility. New empirical evidence generated in the prenatal context can help expand the prenatal clinical utility framework,[2] incorporating detailed observation, measurement and reporting of experiences from personal and clinical aspects.[3,27,33,37,38] Advances in fetal therapies[39] also strengthen the case for prenatal utility, as these are likely to become more common in the future.

In this exploratory study, we found that prenatal ES is currently primarily accessible through studies and in some cases through commercial laboratories contracted with Medicaid. Clinical research is being conducted to generate evidence on the optimal use, safety, efficacy and utility of genomic sequencing and other novel diagnostic tests, but disparities in research participation with underrepresentation of minority populations in medical and genomic research is a concern.[40,41] Research being one of the main pathways to access prenatal ES may exacerbate inequities, when most studies are concentrated around academic medical centers and not equally accessible to all who may benefit from their services.[42]

Strengths of this study include Applying qualitative methodology to understand use and barriers to prenatal ES, including providers from diverse settings, and providing information to guide the next steps of implementation. This study also has limitations: Findings are from a relatively small group of clinicians, most of whom have expertise or familiarity with prenatal genomic testing and cannot be generalized to other contexts. While we assert that the two interviewers (MN, BL) as members of the FSC might have influenced respondents' comfort level, mainly through enabling them to share perspectives that they would not have otherwise; we can't rule out potential influence in the opposite direction, making participants less likely to share views perceived to be contrary. A comprehensive review of Medicaid coverage policies for prenatal ES, and the role of commercial laboratories is beyond the scope of this study. The participants in this study are self-selected professionals who are advocating for their patients and are likely to be biased toward the utility of ES. We were able to explore access to ES from the perspective of the providers only after the patients made it to their clinics. As such, this study cannot provide information about access upstream, starting from the point when a structural anomaly is first identified.

5 | CONCLUSION

Sitting at the juncture of research and clinical care, advancing the science and utility of prenatal ES is only possible with wider access to testing in all settings. Rapid advances in genomic medicine are finding their way into clinical practice, although professional guidance and coverage policies lag behind. Further integrating the perspectives of additional

key stakeholders is an important next step for developing policies and practices that will address barriers to equitable provision of prenatal diagnostic testing and care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

I can confirm that I (NNSH) have full access to all the data in the study and responsibility for the integrity of the data and the accuracy of the data analysis. The datasets from which excerpts are presented in this article are not readily available as a condition of the study is that raw data will not be shared outside the research team. Upon request, sections of the data may be provided for specific research requests after the permissions of the participants are requested and received. Requests to access the datasets should be directed to nuriye.sahin-hodoglugil@ucsf.edu.

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Key Points

What is already known about this topic?

- Prenatal exome sequencing (ES) can identify a diagnosis in up to one third of pregnancies with fetal structural anomalies and a non-diagnostic chromosomal microarray.
- There are disparities in access to genomic technologies, including prenatal diagnostic testing.

What does this study add?

- We report on the perspectives of clinicians from academic centers and community clinics on the utility of and access to prenatal ES.
- A goal of prenatal ES is to guide clinical care, rather than solely for decision-making regarding abortion.
- In academic centers, access to ES is primarily through studies; cost, lack of insurance coverage, and knowledge of genomic sequencing among non-genetics providers are major barriers to access.

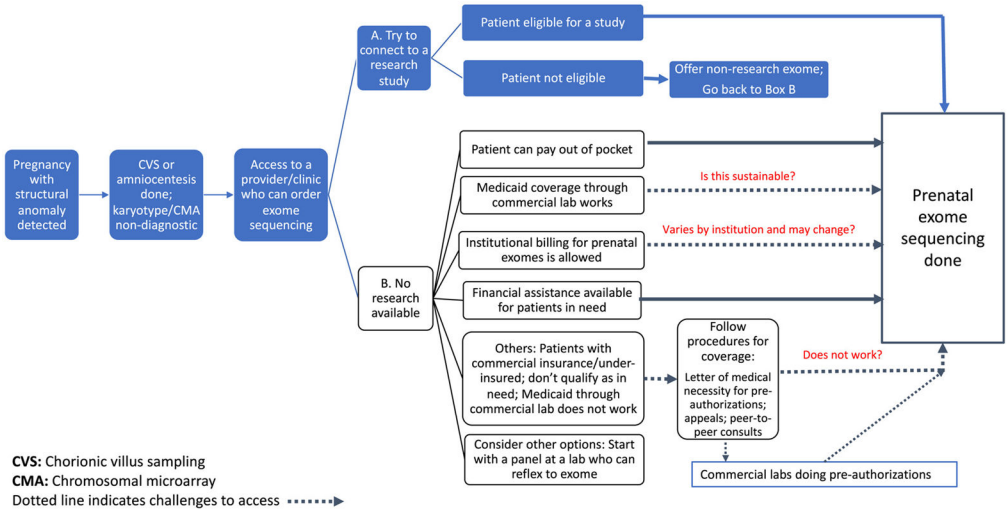

FIGURE 1.
Access pathway to prenatal exome sequencing.

TABLE 1

Participant characteristics (n = 13).

Characteristics	Number
Participants of	
Focus group discussions	7
One-on-one interviews	6
Race/ethnicity	
White European	9
White European & Hispanic/Latino(a)	1
Asian	1
Prefer not to answer	2
Gender identity	
Female	12
Male	1
Age group	
20–29	2
30–39	8
40–49	1
50+	2
Profession	
Genetic counselor	11
MD geneticist	2
Years of experience	
1–5 years	3
6–10 years	4
More than 10 years	6
Experience with exome sequencing	
Some experience	2
Quite a bit experience	11
Orders prenatal sequencing	13
Refers patients somewhere else for prenatal sequencing	2
State (responding for the site experience)	
CA	3
Texas	3
Ohio	2
North Carolina	3
Pennsylvania	1
New York	1
Clinic is a site for exome sequencing study	7
Opinion about utility of prenatal exome sequencing	
Prenatal ES has high clinical utility in all settings	9
Prenatal ES may have some clinical utility	4

TABLE 2

Additional exemplary quotes highlighting themes under each domain.

Domain 1: Clinical utility of prenatal exome sequencing (ES)	
A. Prenatal diagnosis supports continuum of care from pregnancy through neonatal and pediatric care	(D1.A1) There's no difference really between the fetus's medical management plan, long-term… between when it's a fetus and when it's a baby. I joke sometimes, I do inside babies and outside babies because almost all of my patients continue and I see them in [pediatrics] (IDI-3) (D1.A2) [When prenatal ES was diagnostic] there's not a scramble between the NICU trying to figure out what's going on or what diagnostics need to be done. They're sitting there with a diagnosis knowing what the next steps are. And it helped the family because now they know what's going on, they know what to expect as they're going through this care process… It answers our current question, guided care, which was very intense, baby ended up passing away, but nothing beyond what would've been appropriate was done, which the family felt good about. And then now this is a patient who's pregnant again, … and now we can test subsequent pregnancies. [F]or them, the utility was before, during, and after, and continues to be valuable what we got from exome. (IDI-2)
B. Prenatal ES is the only opportunity for cases that never get to pediatric setting	(D1.B1) "A lot of babies with serious anomalies die. They don't ever get to the pediatric setting. And so, none of those families have the opportunity for sequencing and for recurrence risk information if they don't do it prenatally. I think all of those things could be incorporated into an argument of clinical utility for sure." (FGD2-2)
C. Patients are interested in diagnostic information even when they may not want invasive diagnostic procedures	(D1.C1) There's a difference between being opposed and not feeling like the diagnostic procedure is the right choice for them, but that does not automatically equate that they're not interested in diagnostic level information. … It's just the way that we have to obtain that prenatally is maybe not something they're comfortable with. (FGD1-1)
Domain 2: Access to prenatal ES	
A. Research studies are one key access pathway for prenatal ES	(D2.A1) We have more research options than prenatal sequencing alone. […] And so basically any patient that has anomalies can be offered sequencing through some protocol in our center. It really has removed an entire layer of barriers […] We do have patients that don't want to do research, and sometimes we prefer clinical testing for a variety of reasons, or just doing a panel, but that's definitely the exception rather than the goal. (FGD1-3) (D2.A2) There's very few people who have been interested in clinical exome that haven't qualified for a research study at our institution. (FGD2-2) (D2.A3) I offer sequencing for fetuses with anomalies. I got connected with the sequencing study. I mean, we're not a site of it, but I could refer patients down to [the research center]…So then I started being able to offer prenatal sequencing more broadly and had a bunch of patients who enrolled in the study. (FGD2-4)
B. Cost is a major barrier for ES, causing clinicians to look for other options	(D2.B1) So depending on what's going on, and how much time we have… If I think that exome or genome is the right test, and the patients have time, we're not considering an intervention; we have weeks and weeks until delivery…. We'll try to pre-authorize the exome or genome first, and if that gets denied we'll back off to a panel. If it's more of a time-based thing that the patient really wants or needs quicker answers, we'll start with a targeted panel for their anomaly, but at a lab who then can reflex to exome. So, we might start with the CDH panel, and then, if that's negative, reflex to exome from there, because then usually the insurance will cover the panel…usually… And patients may be able to pay out of pocket, or we have some funding in the fetal care center that can help with patients who have insurance difficulties… But it's limited, so it's easier if their insurance has already covered the panel, and then we can pay that gap between reflexing to an exome, or the patient can pay it out of pocket, or whatever it is. (FGD1-3) (D2.B2) I'm in a place where we normally don't have any research money to be able to cover [ES]. So we're trying to work within the practicalities… we're balancing, cost and diagnostic yield, and sometimes a panel is going to thread that needle well enough… It's lovely to be able to offer research and have research funding to offer what you think is the best test across the board to everyone. But that's not realistic at scale. […] If we're taking cost, insurance, all that out of it, I would not be doing panels, I would be doing exome all the time. (FGD1-1) (D2.B3) We get very creative and try to find good ways to have it done. So, for patients who have a need, if the patient is under poverty level, there are some ways that we can get funds to help cover that. If patients have resources themselves and they're willing to pay out of pocket, it can be done. I'd say personally where sometimes I might fall into some difficulties, where you've got the patient in the middle where they don't necessarily qualify for need, but it's still an expense, and so then we just have to get creative on how we can try to get it covered or see if there's a way it can be reduced. The other option might be, let's say this is not going to influence decisions in pregnancy, then maybe they'll wait till after delivery to consider doing the testing. So I'll say sometimes cost does become a barrier to patients deciding to do it. (FGD2-3)
C. Clinicians are frustrated dealing with insurance coverage	(D2.C1) We don't have the staff for pre-authorizations (PA) right now. That's true, it is very frustrating…Making PA calls can take an hour. And that is not time that we have in our day to spend on the phone for a test that might ultimately not even be covered. (IDI-5)

	(D2.C2) Even the commercial insurance is like, if they say no, they say, “oh, do a peer-to-peer, write an appeal letter”. Then you write an appeal letter. I end up spending literally months on this process, and it never works. And you end up talking to somebody on the phone. Who's a geneticist or someone else who ends up saying, “You have a great argument. I completely agree with it. However, my hands are tied. This is our policy. I can't say yes.” Why would you even offer me this option to talk to you if your answer is always going to be “No”? (FGD1-3)
	(D2.C3) [Some commercial insurance companies cover prenatal exomes]. But honestly it's a crap shoot based on the policy -and this is for commercial insurance. We have a huge Medicaid population, and it's hardly even worth doing a letter of medical necessity, because it's going to be a categorical “No”. It's hard enough to get panels done through the Medicaid. (FGD1-1)
D. One Needs to figure out which commercial laboratory will accept public insurance at a given time	(D2.D1) I've always worked with largely Medi-Cal populations, and that's always the game, is figuring out which commercial lab is making the risk and doing that for now. And they do it for a few years and then they stop and you're desperate to find another one and then you use the other one. And that's part of the game that's played. (IDI-3)
E. There may be “reverse discrimination” for those with commercial insurance	(D2.E1) Honestly, I worry a little bit more sometimes about my commercial families because they're probably going to be paying toward that deductible and they may or may not want to do that at that point. Really sometimes I think it's almost easier with your Medicaid families to work things through with agreements and coverage. (IDI-2)
	(D2.E2) I have a lot of concerns. And the concern, actually is primarily for the insured patients where they're not going to get this test paid for. I think we're getting it from Medi-Cal…but I'm trying to think why did these patients refuse and they were privately insured? In fact, this one family, I'm thinking about with the GLE2, they're both nurses at the community hospital….Yes, it is [reverse discrimination], and it's totally that way in the outpatient setting. I can get anything I want on a Medi-Cal patient, and I have to jump through all kinds of hoops if they're private. (IDI-1)
F. The providers on the prenatal pathway are important whether a pregnant individual will get offered ES or not	(D2.F1) That was part of the reason I came out is because there was no genetic coverage in this area and it was very needed. I think the biggest bottleneck that we find to getting access to testing this is getting referred to the right place. So the first year that I was here, that was the biggest battle to fight is actually getting a patient into MFM so they could see me and have genetic testing done. So I think that remains a big barrier. Once you get to someone who knows how to order testing, I mean, to me, you're home free at that point. So if you're somewhere rural or you're far away from the medical center or a provider that offers that, you're going to be less likely to be able to access that kind of testing. […] (IDI-2)
	(D2.F2) I think, though, that the other barrier is that patient in South Dakota with a fetal anomaly- are they going to get counseling about the option of sequencing? My guess is there may not be a genetic counselor there in South Dakota. There's certain states, there aren't. And so, that's also an access issue in certain parts of the country based on who is reading their scan and counseling them that they may never get offered that option. (FGD2-1)
G. Access to ES is likely be more challenging in community clinics	(D2.G1) I think about the time it takes to coordinate an exome and a prenatal exome and to do it correctly and make sure the results are returned in a timely manner. And I see a lot of logistical barriers like that. I imagine community clinics being very busy with a high patient population and you're just making sure that you're getting the right nutrition counseling or that they're making sure to take their diabetes medication and it seems like it would be difficult to find the personnel to do all these things. (FGD2-3)
	(D2.G2) I do think the community places, though, are probably also not equipped to deal with trying to tackle the insurance components. So, it all kind of goes in tandem. So it's like, maybe even if they were comfortable ordering it, they might not know how to actually get it covered, so that's sort of what the Tertiary Care center is accustomed to doing is fighting that fight. (FGD1-2)
	(D2.G3) [T]here are some genetic counselors and some genetics teams that don't have the capacity or potentially the willingness to continue searching for laboratories that will actually be able to accept this testing or are unaware that this testing is available. And as such, their patients are obviously not offered these services…It's something that's sometimes politically and socially really difficult to navigate. You have to be very well networked to stay on top of everything because it's not like it's published anywhere. And so it's understandably a very difficult thing. And especially imagining a genetic counselor in Mississippi, for example, where there's one or two prenatal counselors and she sees like 30 patients a week, and she's dealing with the political, everything that's happening there right now. Does she also need to be contacting the 10 or so different labs that I'm in frequent contact with to see what they're doing? Like, how do you know…? (IDI-3)
H. In resource-limited settings, access to novel technologies may be superfluous as compared to primary care	(D2.H1) That's where I view the role of guidelines is to say… to level the playing field in what we consider as a field the standard of care, and not, having patients need to rely on “If I go to this physician and if it's their special interest, I'm more likely to get it”. There's at least kind of a baseline agreement that this is the appropriate step for this group of patients. Now there's other hurdles still…and you know, I think you have the same…when we're talking about, barriers to equitable health care access with…let's say, less resource patients, lower SE patients, English-not-as-a-first-language patients… The same barriers to me the same barriers that are there, on the patient access side, where you know: “Are we going to go to this high level? If I can't even get my patient to come in for a general wellness check or basic sickness care plan…If you're the provider in those types of clinics….Again, if most of the fight that you're fighting is to get access and give care on those more basic levels… then you're not gonna have a lot of resources left at the end of the day to fight the fight for a very high level, very specialized genetic test. (FGD1-1)

I. Professional society guidelines and insurance coverage is critical to broaden access to ES	(D2.I1) I do know that there are too many patients that are not getting [ES] because of money. (IDI-1) (D2.I2) In terms of broadening access to molecular testing, including exome and genome sequencing, the biggest thing that we need honestly are guidelines and insurance policy coverage updates. Those are the main things that are keeping access restricted because -even if a patient can get to a Tertiary Care Center, where we offer it, where we're comfortable with it- that's what's tying our hands and actually being able to do it for patients. (FGD1-1) (D2.I3) I mean,… the critical crux of the matter here is insurance coverage to a large degree because if it gets covered by insurance, then labs will be more likely to offer it to more people and eat cost every once in a while. And then there would be labs that would be the go-to labs for prenatal, which would increase access dramatically, I think. And so how do we get insurance companies on board to…… pay and to see the value of it. I mean, a lot of that comes from society recommendations and statements and standard of care established by those societies. […] So I mean, I guess we can push that. (FGD2-2)
J. The fear that ES can open a “black box” with too many variants of unknown significance (VUS) can be an access barrier	(D2.J1) And insurance companies and other providers, too that I talked to, who are uncomfortable ordering exome themselves also bring up incidental findings, VUSs. That's why they don't want to order exome or genome. “We don't want to deal with those things” …And I think there's this level of fear that people have. Because there's this black box, maybe they think that they're opening, but it's like you've already opened it. (FGD1-3)
K. Not having access to a geneticist can make providers at community clinics hesitant to order the test	(D2.K1) One other consideration that we always keep in mind when doing exome testing is we do not have a geneticist at our hospital system. […] That is a limitation of us feeling comfortable broadly offering it, even if cost wasn't the consideration. It is just the lack of resources potentially to follow up on these results. Or the delay in being able to go from, “Here's the result,” to, “Here's your additional referral.” That I think is why a lot of patients maybe don't get… Or we are not as comfortable offering it to patients who haven't gone through the Fetal Center yet. Once they go through the Fetal Center, they're plugged in …. But it's the potential, yes, that we order a test and get a result that we either don't feel comfortable with or qualified to counsel about, and know that we need to include yet another specialist for the patient. So that is a bit of a barrier. (IDI-5)