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US private payers' perspectives on insurance coverage for genome sequencing versus exome sequencing: A study by the Clinical Sequencing Evidence-Generating Research Consortium (CSER)

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Ethics Declaration

The University of California San Francisco Institutional Review Board approved an exemption for interviews conducted. This exemption included the ability to verbally consent participants. Written consent was not required.

Conflict of Interest

Dr. Phillips receives consulting income from Illumina, Inc, not related to this manuscript. Mr. Douglas receives consulting income from Illumina, Inc, not related to this manuscript. Dr. Slavotinek receives consulting income from UptoDate, Inc and income for editorial duties from John Wiley & Sons, Inc. All other authors: declare no conflicts of interest.

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Abstract

Purpose: There is limited payer coverage for genome sequencing (GS) relative to exome sequencing (ES) in the U.S. Our objective was to assess payers' considerations for coverage of GS versus coverage of ES and requirements payers have for coverage of GS. The study was conducted by the NIH-funded Clinical Sequencing Evidence-Generating Research Consortium (CSER).

Methods: We conducted semi-structured interviews with representatives of private payer organizations (payers, $N = 12$) on considerations and evidentiary and other needs for coverage of GS and ES. Data were analyzed using thematic analysis.

Results: We described four categories of findings and solutions: demonstrated merits of GS versus ES, enhanced methods for evidence generation, consistent laboratory processes/sequencing methods, and enhanced implementation/care delivery. Payers see advantages to GS vs. ES and are open to broader GS coverage but need more proof of these advantages to consider them in coverage decision-making. Next steps include establishing evidence of benefits in specific clinical scenarios, developing quality standards, ensuring transparency of laboratory methods, developing clinical centers of excellence, and incorporating the role of genetic professionals.

Conclusion: By comparing coverage considerations for GS and ES, we identified a path forward for coverage of GS. Future research should explicitly address payers' conditions for coverage.

Introduction

Genome sequencing (GS) and exome sequencing (ES) are becoming more widely used for diagnosing suspected genetic disorders.[1,2] While payer coverage of both GS and ES in the U.S. has been increasing, there is relatively less coverage of GS, and coverage varies across payers.[3–7] Half of insured individuals have coverage only for ES, 37% have no coverage for GS or ES, and 12% have coverage for both GS and ES.[4,5]

Our objective was to assess payers' decision-making considerations for coverage of GS versus coverage of ES

We obtained data from payers and coverage experts on decision-making considerations ($N = 12$). Our study is novel because: (1) although prior research considered payers' perspectives on ES,[6] no studies have examined considerations for GS vs. ES, and (2) prior research has found that payers do not cover GS,[8] but has not examined what opportunities payers perceive for advancing coverage of GS in addition to coverage of ES. Results of this study will be useful in guiding further research activities to generate evidence that meets payers' coverage decision-making needs.

Materials and Methods

Payer interviews

The study was approved by the University of California San Francisco (UCSF) Institutional Review Board. We used a modified framework approach of qualitative research to obtain and analyze input from payers. Data collection was conducted by facilitating a semi-structured group interview ("focus group") with payers, supplemented by interviews with individuals unable to join the group session.

Payer sample

Payers were recruited into the study from the UCSF Center for Translational and Policy Research on Personalized Medicine (TRANSPERS) Payer Advisory Board. The Board has been an ongoing advisory body to TRANSPERS since 2007 and includes senior executives from private health plans and national experts in Medicare and Medicaid coverage and large payer associations. Of the ten private health plans on the Board, representatives of nine health plans participated in our study (six large national plans and three regional plans) along with two experts. Together, these health plans cover 162 million enrollees. All health plan representatives had expertise and decision-making roles in coverage policy for genomic medicine at their respective organizations. We refer to all participants from the Board as "payers."

We developed the interview guide, which provided a summary background (key differences between GS and ES and the current state of insurance coverage for GS and ES), and three sections of questions (Table 1). The background was informed by literature, expert interviews, and input from CSER researchers, who completed surveys on whether the interview guide included factors that they believed were relevant from a research and clinical perspective. This enabled us to adapt the interview guide to reflect the "front-line" perspectives of researchers and clinicians.

Interviews and data analysis

The group interview was conducted on 1/15/2021 via an online video session (one hour, audio-recorded). The interview guide was emailed to all participants in advance. Participants were not paid. We conducted individual phone interviews with one representative from a health plan and one national expert using the same interview guide.

Interview recordings were transcribed verbatim and used in thematic analyses. The analyses were conducted by two investigators (MD and JT) and reviewed by a third investigator (KP). Disagreement was resolved by discussion and consensus.[9,10]

Results

We summarized themes from payers' input on advantages, challenges and opportunities to advance coverage of GS, along with their input on solutions (Table 2).

(1) Payers' feedback on postulated advantages of GS and solutions for incorporating advantages in in coverage decisions

Payers noted that the three postulated advantages related to the superior performance of GS compared to ES will be important considerations in coverage, but only if evidence proves both an advantage in performance and that this advantage has clinical significance. This included not only proving that GS produces more accurate and less variable results than ES but also demonstrating clinical significance of that differential, such as a change in clinical decisions and course of care. Likewise, payers considered the improvement in diagnostic yield an important factor, but as one of a number of factors in their decision-making. They also noted that the diagnostic yield needs to lead to a meaningful contribution to diagnosis and/or information influencing medical management. Evidence is also needed both to prove that GS may be substantially more effective than ES plus chromosome microarray (CMA) in ending patients' diagnostic odyssey and to articulate how this incremental improvement, such as faster diagnosis, contributes to clinical decisions or management. We asked whether the ability of GS to replace ES+CMA would be one of the factors in payers' decision-making. Payers shared that if the performance advantages of GS are proven and experts recommend GS to replace current testing, payers may consider this substitution an attractive factor in coverage. However, they will need assurance from testing laboratories that replacement will not entail challenges for clinicians and patients, such as dealing with additional variants of unknown significance (VUS). Payers also agreed that GS may enable more effective future re-analyses of the same samples as more genes are determined clinically significant. Payers want evidence of effective implementation, such as establishing registries that will help identify patients indicated for re-analyses.

(2) Payers' feedback on postulated challenges for coverage of GS and solutions for considering these challenges in coverage decisions

While payers acknowledged technical advantages of GS, they also discussed challenges related to GS performance. Variability of variant classification systems and interpretation across laboratories was described by payers as a considerable concern and obstacle to coverage. Payers indicated that they may address these concerns with individual laboratories during contracting but needed relevant professional societies to develop clear quality standards for GS that could be stipulated and managed via lab contracts. Payers' opinions varied regarding another technical challenge of GS – a higher number of VUS than that of ES. Payers who were less concerned reported that they have implemented policies for other sequencing tests allowing effective mitigation of the impact of VUS in the clinical setting,[11] which they will apply to GS as relevant. Some payers were concerned that a higher number of VUS will cause unwarranted downstream testing and care and suggested that the use of relevant registries may help address this impact over time. Similarly, payer perspectives varied on whether a higher GS cost compared to ES+CMA was a concern for coverage. Some payers stated they are less worried because they do not directly consider reimbursement in coverage decisions, while others conveyed concern with cost, noting that economic modeling will help them in addressing this concern. At least one payer intends to use internal claims data for such modeling. Conversely, payers broadly agreed that another challenge – the lack of knowledge by clinicians on the use of GS over ES – represents a concern and must be addressed. They suggested that requiring the use of genetic specialists in non-ICU settings and establishing standard clinical protocols will help address this concern.

(3) Payers' feedback on potential opportunities to advance GS coverage and solutions to realize these opportunities them

Payers agreed that establishing clinical centers of excellence for GS ordering and subsequent care may present an opportunity to realize GS advantages while mitigating challenges and thus provide payers with confidence GS will be used as medically necessary and appropriate. To realize this opportunity, payers will need relevant medical societies and organizations to develop concrete criteria for medical centers pursuing this designation to follow, and for payers to evaluate and monitor. Criteria may include standard clinical protocols and approaches for shared patient-clinician decision-making on ordering GS and acting on results. Payers noted that the center of excellence designation should entail using laboratories with demonstrated and transparent testing quality, and collecting real-world outcomes data.

Payers were more skeptical about an opportunity to use the model of Coverage with Evidence Development (CED, achieved by granting provisional coverage during evidence generation) to provide insurance for GS. Payers stated that CED arrangements are often cumbersome, challenging to implement, difficult to rescind if unsatisfactory, and conflict with the payers' mandate not to fund research. However, payers suggested that the concept of CED may have application in emerging models of value-based contracts. Reacting to another potential opportunity, payers agreed that determining evidentiary requirements for coverage may help generate relevant information. To that end, they conveyed that while evidence of clinical outcomes of using GS is optimal, intermediate endpoints may be acceptable as well, especially for diseases with prolonged progression and distant outcomes. In those cases, a projection and timing of clinical outcomes should accompany evidence. Evidence from clinical trials, not only from real-world practice, will be needed. Additionally, payers stated that evidence should be generated in the context of specific clinical scenarios, as coverage will be only considered for those clinical scenarios and not for broad use of GS across diseases and settings.

Discussion

We found that payers see several potential advantages to GS over ES and are increasingly willing to cover GS and/or ES for suspected genetic diseases (primarily in children vs. adults). However, they also perceived challenges to coverage of GS and shared views on solutions that could address challenges and help fulfill the opportunities. Importantly, we reported on payer perspectives as described by the payers themselves. We did not examine whether these perceptions are accurate as this was not the purpose of the study. Rather, by understanding payer perspectives as they exist, researchers and policymakers can consider how to best move forward.

This study builds on our previous examination of payer coverage decision-making for ES only.[6] We found that most private payers are willing to cover pediatric ES but not prenatal ES for structural anomalies. However, this previous study did not consider how payers view ES vs. GS. While other research has explored coverage policies and payers' decision-making for other genomic technologies,[6–8,12–14] we are unaware of any other

studies with representatives of payer organizations that focused specifically on comparing payer considerations for ES vs. GS. Thus, this study provides a look at coverage questions that will become increasingly salient as the routine use of clinical GS increases.

Our study addressed not only advantages and challenges of ES relative to GS, but also potential opportunities to advance coverage of GS as perceived by payers. The suggestions and recommendations need to be further examined for relevance and feasibility. For example, it may not be feasible to develop required registries in the foreseeable timeframe or avoid any challenges posed by transition from ES to GS to ordering physicians. However, these suggestions represent an initial and necessary step towards identifying what is needed for coverage. There are existing studies that compare ES and GS that provide some evidence of net benefit in certain clinical scenarios, including an RCT of diagnostic yield[2] and a meta-analysis of diagnostic yield and clinical management.[1] However, our study points out the need to more directly integrate payer evidence needs with evidence generation throughout the research process. Ideally, before a study or Consortium examining clinical and economic outcomes begins, it would be helpful to assess current coverage policies and obtain information from payers on what they perceive as key considerations and evidence needs. Then, future studies could directly take these considerations into account. For example, our findings indicate that direct comparisons of ES vs. GS (preferably randomized clinical trials) are needed to provide a comprehensive assessment for payers, which could be achieved by future research.

Our study has limitations. First, payers' perspectives are limited to the individuals who participated in the interviews. However, the individuals involved were in senior decision-making roles regarding coverage for genomic tests in their respective organizations. Because of the qualitative nature of our study, we involved a limited number of payers, but these payers cover 162 million members and therefore their input is representative relative to the US population of privately insured individuals. Also, we could not quantitatively describe our findings given our data collection approach. Future studies should focus on more granular examination of payer feedback, e.g., by payer characteristics or percentage of payers who agree or disagree with specific perspectives. Second, Medicaid is especially relevant to coverage for pediatric and prenatal disorders, but we were unable to examine Medicaid policy decision-making in this study. Engaging Medicaid payers in direct interview studies has been a challenge for researchers, given that these are state-level programs, and each state has different policies and documentation. Third, we explored a spectrum of factors in payers' decision-making, but did not examine any factor in detail. The influence of cost-related considerations in payers' weighing GS vs. ES will have particular relevance in the future and should be investigated in future studies. Additionally, future studies should utilize other methods of research to elucidate factors impacting coverage, *e.g.*, review of coverage policies relative to the perspectives shared by payers or to evidence reviews.

Conclusions

Our study compared payer decision-making considerations for GS to those for ES, and provided next steps on moving the path to GS coverage forward. These next steps will be

useful to guide further studies in developing evidence and incorporating such evidence into payer coverage decision-making for GS and ES across different clinical scenarios.

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Data Availability

Aggregate data and materials can be accessed individually upon request to corresponding author.

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Table 1

Payer Interview Guide

1. Feedback on postulated advantages of GS vs. ES a. Postulated benefits: • Superiority in accuracy, lower variability • Higher diagnostic yield • More effective in ending diagnostic odyssey • GS: one test vs. two (e.g., GS=CMA + ES); may replace other tests • GS is more effective for future re-analyses of same samples b. Questions regarding postulated benefits: • Do you agree/disagree with these benefits? • What are the conditions that are needed for these benefits to be considered in insurance coverage of GS?
2. Feedback on postulated challenges related to coverage of GS vs. ES a. Postulated challenges and concerns about GS vs ES • Varying, non-transparent testing quality across labs • GS may produce more VUS than ES, but same number of reportable VUS • Higher cost for GS than for ES • Lack of clinician knowledge when/how to use GS vs ES b. Questions regarding postulated challenges and concerns • Do you agree/disagree with these points? • What may be the solutions to these concerns?
3. Feedback on postulated opportunities to advance coverage of GS a. Postulated opportunities: • Establish clinical centers of excellence • Implement the CED model • Determine the types of evidence needed for coverage b. Questions regarding postulated Opportunities: • Do you agree or disagree that these may be opportunities to advance coverage? • What other opportunities do you see? • What are the solutions that will allow to fulfill these opportunities?

Notes: We use the term “postulated” to indicate that the advantages, challenges, and opportunities discussed with payers were those postulated by authors and informed by literature.[1–7]

GS, Genome sequencing; ES, Exome sequencing; VUS, variants of unknown significance; CED, coverage with evidence development. Under CED, a promising but unproven medical technology is granted provisional insurance coverage contingent on concurrent generation of evidence sufficient for definitive coverage. If evidence is not generated according to CED conditions, a negative coverage decision follows.[8]

CMA, chromosomal microarray

Table 2.

Payers' perspectives on advantages, challenges and opportunities to advance coverage of GS

Postulated aspect	Proposed solutions that would consider advantages in coverage, address concerns, or fulfill opportunities	Category of solution			
		Demonstrated merits of GS vs. ES	Enhanced methods for evidence generation	Consistent lab processes & sequencing methods	Enhanced implementation & care delivery
Advantages of GS vs ES					
Superiority in accuracy, lower variability	• Evidence of GS superiority in these aspects • Evidence that superiority is clinically significant	✓			
Higher diagnostic yield	• Evidence that genetic difference results in better diagnosis or actionable information	✓			
Better in ending diagnostic odyssey	• Proof of additive value of ending diagnostic odyssey	✓			
GS may replace current ES + CMA testing	• Ensure no increase in reportable VUS by using GS			✓	
GS is more effective for future re-analysis of same samples	• Build registries to identify patients for re-analyses				✓
Challenges for coverage of GS					
Varying, non-transparent testing quality across labs	• Develop quality standards; payers will use them in contracting with labs			✓	
Higher number of VUS	• Payers can implement policies mitigating impact of VUS • Require the use of registries			✓	✓
Higher cost	• Modeling the cost impact	✓			
Lack of clinician knowledge when/how to use GS vs ES	• Require the use of genetic specialists (for non-ICU) • Develop standard clinical protocols; best practices				✓
Potential opportunities to advance coverage of GS					
Establish clinical centers of excellence	• Establish and implement concrete excellence criteria • Collect real-world evidence	✓	✓	✓	✓
Implement the CED model	• CED may have application in value-based contracts	✓	✓		✓
Determine the types of evidence needed for coverage	• Clinical outcomes optimal, but intermediate outcomes may suffice if accompanied by a projection of clinical outcomes • Need evidence from trials, not only real-world evidence		✓		
Show GS advantages in specific clinical scenarios	• Generate evidence for specific clinical scenarios	✓	✓		

Notes: "Postulated aspect" is what was postulated by experts when developing the interview guide, and then presented to payers for feedback.

GS, Genome sequencing; ES, Exome sequencing; VUS, variants of unknown significance; CED, coverage with evidence development; CMA, chromosomal microarray