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ORIGINAL RESEARCH

Clinical and Counseling Experiences of Early Adopters of Whole Exome Sequencing

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Abstract Currently, there are limited data regarding the practice of genetic counseling for whole exome sequencing (WES). Improved understanding of how genetic counselors and other providers are educating, counseling, and communicating results may identify practice trends, and patient or provider needs. Between April 2013 and December 2014, we surveyed providers who ordered WES testing from GeneDx, a CLIA-certified laboratory. Forty-nine respondents completed the survey; 41 % of participants reported board certification in genetic counseling. Pre-test and post-test counseling was completed in all but one case each. Pre-test counseling lasted less than 1 h for 53 % of cases and 1 to 2 h for 43 %. Topics discussed with all patients included consent for testing, and incidental findings; other topics were variable. In contrast to pre-test counseling, 59 % reported post-test counseling lasting 1 to 2 h and 33 % less than an hour; post-testing counseling was significantly longer in cases with a definitive diagnosis than those without (p=0.0129). The survey findings indicate some variability regarding the amount of time spent on counseling and the topics discussed during pre-test counseling. Additional exploration, patient and provider educational resources, and potentially more specific guidelines regarding counseling for WES may be warranted.

Keywords Genetic counseling · Whole exome sequencing

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Introduction

Whole genome sequencing (WGS) and whole exome sequencing (WES) have garnered substantial interest as tests for diagnosable genetic conditions (Biesecker and Green 2014). An increasing number of reports have been published regarding the clinical use of WGS and WES, demonstrating a 25–31 % success rate in identifying disease-causing genetic changes (Atwal et al. 2014; Dewey et al. 2014; Farwell et al. 2014; Jacob et al. 2013; Lee et al. 2014; McCarthy et al. 2013; Strom et al. 2014; Taylor et al. 2015; Yang et al. 2013, 2014). Several diagnostic laboratories nationwide now offer next generation sequencing, including WGS and WES, as clinical tests.(Ashley et al. 2010; Choi et al. 2009; Ku et al. 2011)

Like many other new genomic tests, WES/WGS raises questions about its clinical utility (Johansen Taber et al. 2014), particularly given the high cost at this time (though anticipated to continue to decline). Published case reports may reflect publication bias of clinical examples where WES/WGS has found a causative mutation and this information led to improved health outcomes. The clinical value may be somewhat difficult to estimate at this time given its limited use (Berg et al. 2011) and some providers' wariness of the clinical utility, particularly in areas of practice like prenatal and cancer genetics (Machini et al. 2014).

In contrast to the concern of clinical utility of WES, the delivery of WES has remained largely unexplored. WES/WGS is often used in pediatric genetic specialty clinics, and so provision of genetic counseling is likely to occur. However, the novelty of testing has resulted in limited provider experiences. For example, a survey of genetic counselors found that most genetic counselors have not offered WGS or WES to patients; but of those who offered testing, 75 % worked in a pediatric setting (Machini et al. 2014). Although some counseling experiences were discussed in this survey study

(Machini et al. 2014), no specific information about the content of pre- or post-test counseling was described.

Thus, the amount of time for pre-testing and post-testing required for counseling (if provided), patient comprehension, the actionability of results, and the need for follow-up testing remain uncertain (Machini et al. 2014). To gather more data regarding the testing process, we conducted a survey of providers that have ordered WES. These data describe a group of users of WES, their counseling practices, and the outcomes of testing.

Methods

Participants

An invitation was included with all WES test report results sent to ordering physicians, typically via fax, who received WES results from GeneDx between April 2013 and December 2014. The invitation described the purpose of the study, risks, and benefits and instructions on how to access the secure online survey website. If the physician ordered WES more than once within the study period, we asked them to complete the survey only once, although they may have received the invitation multiple times. To maintain confidentiality, we did not acquire a list of ordering providers and thus, were not able to send survey reminders, nor were we able to verify that respondents were the ordering physician and intended recipient of the results and survey invitation.

Instrumentation

To ascertain experiences with clinical use of WES, we conducted a survey of providers who ordered WES from GeneDx, a CLIA-certified DNA-based diagnostic testing laboratory in Gaithersburg, MD (USA). Based on a review of the literature of the uses of WES and evidence of clinical utility for other genetic tests, we developed a 24-item survey to explore the clinical use of whole exome sequencing for physicians. We aimed initially to survey ordering physicians, including those who do not work in a specialty clinic with genetic counselors. The survey included questions pertaining to respondent characteristics, purpose of testing, pre- and post-test counseling, and anticipated/actual clinical outcomes based on test results. Responses were multiple choice or Likert response scales (e.g., on a scale of 1 to 5, respondents were asked to indicate level of agreement with 5 being "strongly agree"). All questions included an answer option of "Prefer not to answer." The survey questions were reviewed by five genetic counselors from Duke University Medical Center to evaluate understandability, credibility (e.g., believability of questions/appropriateness to practice), and interpretation of questions as intended. In particular, reviewers were asked to note confusing questions and ambiguous terms, and report confidence in answering questions accurately. The survey instrument was revised accordingly. This study was approved by the Duke University Medical Center's Institutional Review Board.

Data Collection

The online survey tool Qualtrics (http://www.qualtrics.com) was used to design and administer the pilot survey and the final survey. No private health information was collected; all responses were anonymous.

Data Analysis

Surveys received between April 2013 and December 2014 were reviewed for completion. Surveys were excluded from analysis if more than 25 % of questions were unanswered, as uncompleted surveys did not provide enough data for analysis. Frequency counts and percentages were generated for each question. The effective sample size for analyses varied depending on the size of the subsample that completed the relevant section(s) of the survey. Pearson's Chi-square analyses were performed to test for associations in categorical responses. A threshold of 0.05 was used to determine statistical significance.

Results

Characteristics of Survey Respondents

A total of 54 surveys were initiated; 49 were completed in full and comprised the final dataset for analysis. The majority of respondents were board-certified medical geneticists ($n=19$), genetic counselors ($n=20$), and pediatricians ($n=13$) (Table 1). Respondents spanned a 45-year period of graduation from medical school and genetic counseling programs (1969–2014). The majority of the newly practicing providers were genetic counselors: 13 of the 20 who had graduated since 2003 were genetic counselors (65 %).

Twenty-eight of the respondents (57 %) indicated that they learned about WES through attendance at a professional meeting. Prior experience with WES varied greatly, with respondents reporting to have ordered between 1 and 51 tests; one respondent indicated ordering 90 tests but this response was dropped from analysis as an outlier (mean of 12.05; median of 8.5; mode of 4). No significant difference in number of WES tests ordered (compared to the median) was found with respect to practice setting (non-academic or academic) ($p=0.3827$) or board certification (physician vs. genetic counselor) ($p=1.00$).

Table 1 Respondent demographics

Demographics	n (%)
Board certification	
Genetic counseling	20 (41 %)
Medical genetics	19 (39 %)
Pediatrics	13 (27 %)
Neurology	6 (12 %)
Other	4 (8 %)
In medical training	2 (4 %)
Practice setting	
Academic medical center	26 (53 %)
Hospital-based specialty care	19 (39 %)
Community-based specialty care	2 (4 %)
Hospital-based primary care	1 (2 %)
Other	1 (2 %)
Year of graduation	
1969–1980	3 (6 %)
1981–1990	8 (16 %)
1991–2000	6 (12 %)
2001–2010	19 (39 %)
2011–2014	5 (10 %)
Prefer not to answer	8 (16 %)

Board certification total does not equal 100 % as respondents could select multiple responses

Testing Process

The majority of WES tests were ordered for children (n=43; 88 %); five tests were ordered for adults (one could not recall the age of the patient). Of minors tested, the majority of tests were ordered for children 5 and under (n=26; 60 %). All but two providers reported that the primary reason for ordering WES was to diagnose or identify the cause of disease; the other two providers reported ordering WES to inform reproductive decision-making. Several additional factors were reported to impact the decision to order WES including exhaustion of all other options for diagnosis, the perceived cost-effectiveness of WES, perceived utility, insurance coverage, and patient or family interest (Table 2). Almost half of respondents reported that 2 to 3 genetic tests had been ordered for the patient prior to ordering WES (n=23; 47 %); six respondents (12 %) indicated that 12 or more genetic tests had been ordered for the patient prior to WES. Thirty-three of 37 respondents who answered the question regarding reimbursement (89 %) reported that testing was covered by insurers (the 12 who did not respond were either unsure or declined to answer).

In all but one case, pre-test counseling was conducted prior to WES. In most cases, pre-test counseling was completed in one session (n=39/48; 81 %) and nine reported that pre-testing counseling occurred over two appointments (19 %). Pre-test counseling was provided by physicians or genetic counselors (n=19 and n=28, respectively); one respondent reported an unspecified colleague conducted pre-test counseling. Pre-test counseling was reported to take less than an hour in 25 cases (53 %), 1–2 h in 20 cases (43 %), 2–3 h in one case, and more than 5 h in one case. There was no observable relationship between the number of genetic tests previously ordered and the length of pre-test counseling. No significant difference in time was observed between genetic counselors and physicians (p=1.079)

Of the respondents who conducted the pre-test counseling for patients themselves (n=38), all reported discussing informed consent and the possibility of secondary/incidental findings with patients. Pre-test counseling also included discussion about payment/reimbursement for testing, the possibility of not finding a diagnosis, a technical description of the test, implications of findings for other family members, which incidental findings would be reported, the possibility of testing revealing non-paternity, and the risk of genetic discrimination (Table 3). A total of nine respondents reported discussing all of these topics. Of those nine who discussed all talking points, 5 were genetic counselors and 4 were physicians. Seven of those nine respondents indicated that pre-test counseling lasted more than 1 hour. Write-in responses included discussion of how results would be provided to the family, limitations of the testing, and the possibility of identifying a variant of unknown significance.

Test Outcomes & Follow-Up

WES resulted in a new, definitive diagnosis for 27 patients (55 %). No definitive result was found in the other 21 patients (one provider declined to respond); however, a *possible* cause was reported in eight of those cases. In the survey question, a definitive diagnosis referred to a result "that had not been made prior to testing." Thirteen of the 27 definitive diagnoses led to a change in clinical management (10 did not, and four providers declined to respond), such as referral to additional specialists (cardiology, neurology), preventative care and additional testing (cardiology, brain MRI), consideration of a new unconsidered medication, consideration of dietary changes (after ruling-out a metabolic condition), enrollment in clinical trials, and follow-up genetic testing for family members. No plans for confirmatory follow-up testing were anticipated in 36 of the cases (one declined to respond). The other health care providers who did plan for additional follow-up confirmation testing considered additional testing for the following reasons: to validate the clinical significance of heterozygous findings by segregation analysis in other affected family members, exploration of the possibility of mosaicism, additional single gene sequencing to find a second mutation, or confirmation of a biochemical abnormality.

Table 2 Reasons for ordering WES for their patient (n=49)

Reason for ordering WES	n (%)
Exhausted all other possibilities to diagnose patient	43 (88 %)
Cost effectiveness of WES compared to numerous single gene/panel tests	36 (73 %)
Patient/family interest	31 (63 %)
Perceived utility	24 (49 %)
Insurance coverage	20 (41 %)
Other (e.g., analysis for genetic heterogeneity and due to worsening of patient's medical status)	2 (4 %)

Total does not equal 100 % as respondents could select multiple responses

Forty-six respondents indicated that post-test counseling had been conducted; 1 stated no counseling was completed and 2 declined to answer. Post-test counseling was conducted either by the physician (n=23) or genetic counselor (n=22), or in one case, both. Results of WES were discussed during a single appointment in most cases (n=40; 87 %). Post-test counseling lasted 1 to 2 h in the majority of cases (n=27; 59 %), others reported spending less than an hour (n=15; 33 %); one reported post-test counseling lasting 5 h or longer. Eleven of the 21 cases without an identified disease-causing mutation involved less than an hour of post-test counseling (one declined to answer), whereas only 4 of the 27 patients with a definitive diagnosis had post-test counseling lasting less than an hour (5 declined to answer) (p=0.0129). As with the pre-test counseling, there was no significant difference in time between counseling by a genetic counselor and physician (p=0.7474). Of interest, of 34 respondents who provided counseling and indicated the time to complete the pre- and post-testing sessions, a total of 11 indicated that each session took less than an hour.

Discussion

The clinical use of WES has garnered substantial attention and interest, with several case reports and reviews highlighting the successful use of the test to provide a definitive diagnosis, ending a diagnostic odyssey for patients, and sometimes informing treatment decisions. In our study, more than half of respondents (55 %) reported that WES resulted in a definitive diagnosis. This is much higher than the positive rate of 30.1 % of all patients tested by WES at the GeneDx laboratory (Neidich et al. 2014) or the reported rates of 25–31 % of other groups (Atwal et al. 2014; Dewey et al. 2014; Farwell et al. 2014; Jacob et al. 2013; Lee et al. 2014; McCarthy et al. 2013; Strom et al. 2014; Taylor et al. 2015; Yang et al. 2013, 2014). This discrepancy likely is due in part to our small population size and biased participation in the study. We also find that the counseling provided to patients is somewhat variable, with respect to the provider performing counseling, length of time, and topics discussed. This lack of consistency warrants additional exploration, and suggests that both provider and patient educational resources may help improve consistency of test information discussed. In addition to the current guidelines regarding test interpretation, consent and reporting of incidental findings (ACMG Board of Directors 2013; NSGC 2013), a talking points guide or similar tool may also be helpful. Indeed, additional guidance on consent for clinical WES is currently under development by the Genetic Counseling and the Informed Consent and Governance Working Groups of the Clinical Sequencing Exploratory Research (CSER) Consortium (Sarah Scollon, personal communication).

Table 3 Topics discussed with patient during pretest counseling (n=38)

Topics	n (%)
Informed consent[a]	38 (100 %)
Secondary/incidental findings[a]	38 (100 %)
Possibility of not finding a diagnosis	37 (97 %)
Implications of findings for family members[a]	35 (92 %)
What secondary/incidental findings would be reported[a]	32 (84 %)
Payment/reimbursement for testing	31 (82 %)
Technical description of the test	29 (76 %)
Possibility of revealing non-paternity	28 (74 %)
Risk for genetic discrimination/GINA	19 (50 %)

[a] Topics that correspond to ACMG guidelines

Given the complexities of WES, including potentially complicated test outcomes like incidental findings and variants of unknown significance, as well as few publications describing clinical practices with WES, we were particularly interested in the content of the counseling sessions. The National Society of Genetic Counselors (NSGC) has recommended that pre-test counseling for WES include development of a plan for return of results and to "establish clear expectations" regarding the types of results that will be returned, namely regarding incidental findings (NSGC 2013). Similarly, the American College of Genetics and Genomics (ACMG) recommends that pre-testing counseling include discussion of the possibility of incidental findings, anticipated outcomes and what type of results will be returned, benefits, risks and limitations of WES, implications for family members, and policies for re-contact (ACMG Board of Directors 2013). The

recommendations from NSGC and ACMG were published after the development of our survey, so we were not able to include all aspects of those recommendations in our survey; however, there was some overlap (Table 3). As recommended by ACMG, all or a majority of survey respondents indicated completing the informed consent process, and discussing incidental findings and implications for family members.

As the scope of WES differs from that of gene-specific (or disease-specific) tests with which patients may be more familiar, patients and families undergoing WES may have different expectations and more questions/concerns; hence, the length of counseling sessions may vary considerably. In addition, the informed consent process is complicated (Tomlinson et al. 2015), and explaining the range of potential results and uncertainty of results may require additional time. Indeed, we found that longer pre-test counseling times appeared to be associated with a higher number of topics discussed. Eighty-two percent of our respondents reported that pre-test counseling was completed in one visit, with about half of respondents indicating that it took less than an hour, comparable to data reported by Machini et al. (2014), where 71 % of counselors reported completed pre-test consent in one visit. Post-testing counseling sessions tended to be longer, lasting 1 to 2 h for the majority of cases, but comparable to the reported amount of time (120 min) previously reported to be reserved for WGS follow-up counseling (Dewey et al. 2014). As there was a significant difference in post-test counseling time between those who reported finding a new diagnosis and those who did not, the longer post-testing counseling times may be attributed to discussion of the specific results as well as incidental findings. Overall, approximately 2–3 h of counseling time was provided to each patient. While this appears to be comparable to previously reported counseling times (McPherson et al. 2008; Pritzlaff et al. 2014; Sobol et al. 1999; Wham et al. 2010), the content of the counseling sessions are likely to be distinct (e.g., unlikely that a family history/pedigree would be obtained in a WES counseling session) barring any meaningful comparison. The shorter counseling times may be cause for concern if key information is not discussed.

Study Limitations

Some limitations should be noted about this study. The survey used was developed specifically for this study and was not a validated survey. Further, we initially intended for only ordering physicians to complete the survey, since they are the individuals who are most likely authorized to order testing; however, many genetic counselors who work with the ordering physicians responded to the survey, likely because genetic counselors are often an integral part of a team of professionals that reviews WES testing results with patients (Machini et al. 2014). Though responses from genetic counselors turned out to be very informative regarding the counseling process, some of the responses were unclear or not answered by the genetic counselor. For example, we asked "What year did you graduate from medical school" and some genetic counselors skipped this question as most genetic counselors complete a Master's program and do not attend medical school. Additionally the questions about who conducted pre- and post-testing counseling were multiple-choice with two of the options being "counseling was conducted by the ordering physician (yourself)" and "counseling was conducted by a genetic counselor." Lastly, the survey only captures providers' experiences with the WES counseling and testing experience and does not take into account any other previous genetic counseling.

Research Recommendations

Our data and others' (e.g., Machini et al. 2014; Dewey et al. 2014) suggest there is some variability in the provision of counseling for WES with respect to provider, time, and content. Although some variability is anticipated with the use of a new application, additional research is needed to better understand counseling practices for WES, specifically what factors may attribute to the variability observed in our survey. Though NSGC and ACMG have provided some recommendations and guidelines for counseling associated with WES, given the relatively recent integration of WES testing into clinical practice, additional resources, particularly for ordering physicians who do not work with genetic counselors or have no specific training in genetics, may help standardize the information provided to patients. For example, a checklist may help physicians and genetic counselors ensure that all key discussion-points have been addressed during the pre or post-testing sessions. The standardization of information collected from and conveyed to patients may also benefit WES clinical testing laboratories and reduce effort required to obtain family history, prior tests performed, and clinical symptoms essential for test interpretation. It is important to continue research in this area, and to develop patient educational resources to supplement counseling as well as continuing education opportunities and other resources for providers.

Practice Implications

We find that many survey respondents that provided genetic counseling for WES appear to follow current guidelines set out by the ACMG and NSGC, though some variability exists among providers. Although some variability in counseling is expected with the use of a new application and to address the unique circumstances and concerns for each patient, it is important to further explore the differences regarding the recommended information to be conveyed to patients, specifically

for some patients that may require additional time or types of information for counseling (e.g., those with limited health literacy, those that have not previously met with a genetic counselor). The variability in counseling provided by genetic counselors and other providers could be minimized with best-practices guidelines, educational resources for providers, or patient hand-outs or decision aides. Given the extent of information to be discussed with a patient, including consent, the potential for incidental findings and what results would be returned, pre-test counseling should be made available to all patients for which WES is considered. In order to maintain standards of information, genetic counselors should continue to take a leading role in developing professional and patient educational resources, and partnering with other providers who offer WES but do not routinely have access to genetic counselors, potentially through tele-counseling or phone-based counseling. Counselors can also serve as liaisons with the WES laboratories to ensure proper interpretation and communication of results to the patient.

Conflict of Interest S Arora, E Haverfield, G Richard, SB Haga, and R Mills declare they have no conflict of interest.

Human Studies and Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all participants for being included in the study.

Animal Studies No animal studies were carried out by the authors for this article

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