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PROFESSIONAL ISSUES

Genetics Professionals' Opinions of Whole-Genome Sequencing in the Newborn Period

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Abstract Newborn screening (NBS) programs have been successful in identifying infants with rare, treatable, congenital conditions. While current programs rely largely on biochemical analysis, some predict that in the future, genome sequencing may be used as an adjunct. The purpose of this exploratory pilot study was to begin to characterize genetics professionals' opinions of the use of whole-genome sequencing (WGS) in NBS. We surveyed members of the American College of Medical Genetics and Genomics (ACMG) via an electronic survey distributed through email. The survey included questions about results disclosure, the current NBS paradigm, and the current criteria for adding a condition to the screening panel. The response rate was 7.3 % (n=113/1549). The majority of respondents (85 %, n=96/113) felt that WGS should not be currently used in NBS, and that if it were used, it should not be mandatory (86.5 %, n=96/111). However, 75.7 % (n=84/111) foresee it as a future use of WGS. Respondents felt that accurate interpretation of results (86.5 %, n=83/96), a more extensive consent process (72.6 %, n=69/95), pre- (79.2 %, n=76/96) and post-test (91.6 %, n=87/95) counseling, and comparable costs (70.8 %, n=68/96) and turn-around-times (64.6 %, n=62/96) to current NBS would be important for using WGS in NBS. Participants were in favor of disclosing most types of results at some point in the lifetime. However, the majority (87.3 %, n=96/110) also indicated that parents should be able to choose what results are disclosed. Overall, respondents foresee NBS as a future use of WGS, but indicated that WGS should not occur within the framework of traditional NBS. They agreed with the current criteria for including a condition on the recommended uniform screening panel (RUSP). Further discussion about these criteria is needed in order to better understand how they could be utilized if WGS is incorporated into NBS.

Keywords Whole-genome sequencing · Newborn screening · Public health

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Introduction

Newborn screening (NBS) is a public health program to identify newborns with rare but treatable conditions. Each year, over four million newborns in the United States are screened through this mandatory program. Of these, approximately 12,500 are diagnosed with one of the currently targeted conditions (CDC 2012). Original assays were developed in the 1960s by Dr. Robert Guthrie for phenylketonuria, maple syrup urine disease, and galactosemia (P. A. Levy 2010). The use of tandem mass spectrometry (MS/MS) since the early 2000s now permits expanded NBS for multiple conditions in one test (Zytkovicz et al. 2001). Requirements for parental consent and ability to refuse screening vary by state; nearly all programs utilize an opt-out model, whereby

screening is performed on all newborns unless parents specifically refuse it (Mandl et al. 2002). Historically, although individual states' methods varied, each state utilized a set of criteria developed by the World Health Organization as well as local legislative input to determine whether a disorder should be included in NBS (Wilson and Jungner 1968). The national Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (DACHDNC) now evaluates requests for addition of disorders to a recommended uniform screening panel (RUSP), which currently includes 31 conditions. Evaluation for additions to the RUSP is based on a set of criteria that includes the natural history of the condition, availability of screening and diagnostic tests, potential treatment, and cost-effectiveness, as well as the analytic validity (test accuracy), clinical validity (ability of the test to predict disease), and clinical utility (ability of the test to lead to improved outcomes) of the screening method used for each condition (Calonge et al. 2010). Some foresee that as costs for next-generation sequencing technologies decrease (Wetterstrand 2011), use of large-scale sequencing may expand to NBS (Clayton 2010; Goldenberg and Sharp 2012). The National Human Genome Research Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development are currently funding pilot projects to investigate the utility of whole-genome (WGS) and whole-exome sequencing (WES) as part of the NBS process (NIH 2012). To date, limited research has been performed to assess opinions of using WGS/WES in the newborn period. One recent Canadian study found that support for targeted whole-genome or exome sequencing to identify known and treatable conditions during NBS was higher than for untargeted whole-genome or exome sequencing (Bombard et al. 2014). In a survey of parents, most reported high interest in WGS for a hypothetical future newborn, either through state-run NBS or through pediatricians' offices (Goldenberg et al. 2013).

While WGS has the potential to provide a vast amount of information about an individual's genome, it can also miss important information, and may reveal uncertain or unwanted secondary findings. When, by whom, and even whether these results should be disclosed is uncertain. Berg et al. (2011) have proposed a disclosure system for the clinical diagnostic setting that separates findings into groups based on clinical utility, validity, and implication of each specific result. Clinical use of WGS in pediatric patients has also involved separating clearly pathogenic secondary findings into four categories based on age of onset and ability to take medical action in response to each finding. Parents then are given the option to choose the results that they would like to receive based on category (Bick and Dimmock 2011).

A 2012 survey of sixteen medical geneticists' opinions of return of secondary findings from hypothetical clinical WGS/WES situations indicated that specialists are generally in favor of disclosing incidental pathogenic mutations in both adults and children, and many are in favor of disclosing unknown variants when they are presumed or predicted to be pathogenic (Green et al. 2012). Information about opinions of hypothetical results disclosure from WGS performed during NBS is currently lacking.

In 2013, a set of recommendations from the American College of Medical Genetics and Genomics (ACMG) encouraged clinical laboratories to seek and report actionable findings from a list of 56 genes when performing clinical exome and genome sequencing in patients and adults, regardless of patient choice (ACMG 2013a; Green et al. 2013). In April 2014, these recommendations were updated to recommend providing patients with an "opt out" option for these actionable findings during pre-test counseling (ACMG 2014). Notably, these guidelines were developed for symptomatic patients. Recommendations do not currently exist for results disclosure for population-wide WGS.

Concerns have been raised about the potential impact of WGS on NBS (Clayton 2010; Goldenberg and Sharp 2012; Knoppers et al. 2014; Tarini and Goldenberg 2012). However, little is known about expert opinion of its use in this setting, which may be helpful for future research and policy development. The purpose of this study was to assess genetics professionals' views of the potential use of WGS during traditional NBS, including circumstances surrounding results disclosure. We also sought to determine if genetics professionals feel that the current criteria for NBS would continue to be applicable in the setting of WGS (Calonge et al. 2010).

Methods

This was a descriptive, cross-sectional pilot study with no prior hypotheses.

Study Population

A convenience sample of participants was recruited via email from the membership of the ACMG with active email accounts. The ACMG works to promote, increase access to, and advocate for genetics services and genetics education. The membership is composed of clinical and laboratory geneticists, genetic counselors, and other healthcare providers with involvement in genetics (ACMG 2013b). All members were eligible to participate in the survey. Upon its closure, three participants were randomly selected to each receive a $50 Amazon.com gift card.

Instrumentation

A survey was developed specifically for this study based on the binning categories compiled by Berg et al. (2011). The survey was piloted among a small group of family practice

providers for input regarding clarity, and changes were incorporated based on their feedback. Participants were given a brief description of WGS and NBS and a summary of the aims of the study. The survey consisted of multiple choice, yes/no, and Likert scale questions, in addition to text free response sections for contributing additional information, if desired.

Questions assessed general opinions about the use of WGS in NBS, including how WGS might be implemented in NBS, what aspects of the current paradigm would need to change if WGS was implemented and, if so, how these would change. Participants were given hypothetical WGS results categories, chosen based on age of onset and actionability of the condition. They were asked to decide if these results should be disclosed to parents, when during the lifetime they should be disclosed, and which type of healthcare provider should disclose them. Finally, we asked participants whether the current criteria for including a condition on the RUSP would remain applicable in the setting of WGS (Calonge et al. 2010). We collected demographic information including gender, age, years of practice, current role (research, teaching, clinical, administrative), profession type, degree(s) held, work setting, and past or current involvement in NBS.

Procedures

The survey was created and distributed online using the survey hosting website Survey Monkey, and took approximately 15 minutes to complete. The email included an invitation to participate in the survey, a brief description of the research aims, incentive information, and an electronic link to the survey. The survey was open for data collection from November 21st, 2012 through December 30th, 2012. A reminder email was not able to be sent due to ACMG email policies. This study was considered exempt and approved by the Northwestern University Institutional Review Board.

Data Analysis

Upon closure of the survey, data were compiled, coded, and analyzed statistically using SPSS version 20.0. Descriptive statistics were reported for each question, including frequencies, means, and number of respondents. The Likert scale responses "strongly disagree" and "disagree" were combined for analysis, as were "strongly agree" and "agree." Demographic factors including profession, degree(s) held, and age were also combined. Comparisons were made between different demographic variables to determine if they were associated with specific outcomes. Chi-square analysis and Fisher's exact tests were used to compare groups based on past or current involvement in NBS, clinical or non-clinical roles, and degree type. Analysis was performed post hoc and was not based on prior hypotheses. Statistical significance was considered if the p-value was less than or equal to 0.05.

Results

Demographic Characteristics

One thousand, five hundred forty-nine members of the ACMG were sent the email containing the survey. One hundred thirteen people began the survey, which provided a response rate of approximately 7.3 %. Some participants did not answer all questions, so the sample size for individual items varies (Figs. 1, 2, 3, 4, 5, 6 and 7). The demographic characteristics of respondents are summarized in Table 1. Fifty-nine percent of participants (n=56/95) were over 50 years old and 54.3 % (n=51/94) have been practicing for more than 20 years. Sixty point four percent (n=58/96) see patients and, of those who see patients, 65.5 % (n=38/58) spend 50 % or more of their time in this role (data not shown).

A demographic breakdown of the ACMG membership was not available for comparison with the study population to assess whether the characteristics of those who took the survey are representative of ACMG. However, the characteristics of the geneticists in the study population are similar to those of American Board of Medical Genetics-certified medical geneticists gathered in a recent survey (Cooksey et al. 2005).

Familiarity with WGS and Opinions About its use in NBS

Participants were asked to self-rate their familiarity with WGS, on a scale of 1 to 5 (with 1 being the least familiar and 5 the most familiar; see Fig. 1). In general, participants felt relatively familiar with this technology; 89.4 % (n=101/113) ranked themselves at a 3 or greater for their familiarity with WGS.

Respondents were asked whether WGS should currently be used as an adjunct to NBS. Most (85 %, n=96/113) indicated that WGS should not be used at the present time. Clinicians who currently see patients (p=0.011), clinicians who have been involved in NBS (p=0.015), and medical doctors (p=0.025) were more likely to say that WGS should not currently be used as an adjunct to NBS than clinicians who do not see

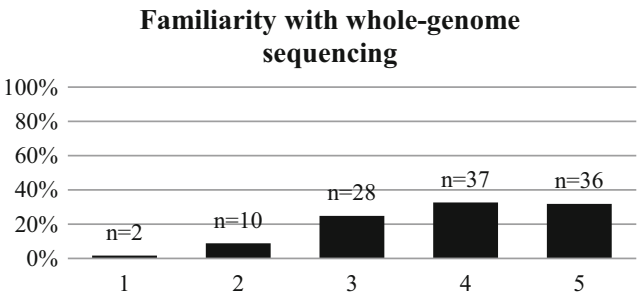

Fig. 1 Participants' self-rated familiarity with whole-genome sequencing, on a scale of 1 to 5 (with 1 being the least familiar and 5 being the most familiar) (n=113)

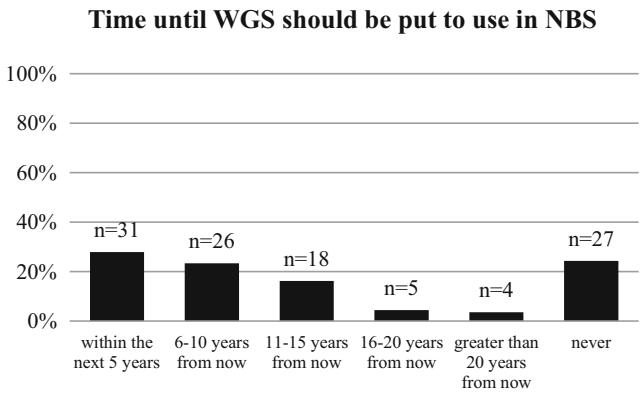

Fig. 2 Participants' opinions of whether/when whole-genome sequencing should be used adjunct to newborn screening (n=111)

patients, clinicians who have not been involved in NBS, and those without a medical degree, respectively. About half of participants (51.4 %, n=57/111) felt that WGS should be used as an adjunct to NBS within the next 10 years, and about one-quarter of participants (24.3 %, n=27/111) felt that WGS should never be used as an adjunct to NBS (Fig. 2).

Participants were asked to rate the importance of potential issues or challenges that may arise in the context of WGS as an adjunct to NBS (Fig. 3). The majority indicated that each proposed issue is very important or of utmost importance. The exception to this was participants' opinions of the importance of the ability to sequence 100 % of the genome, about which there was no majority opinion.

Questions about the process of NBS were asked in order to determine whether or not participants felt that the current NBS paradigm would need to change to accommodate implementation of WGS. These questions involved the mandatory nature of NBS, the consent process, pre- and post-test counseling, results disclosure, cost, turn-around-time, and if anti-discrimination laws should be in place in the areas of life insurance and long-term disability (Fig. 4).

The majority of participants (86.5 %, n=96/111) felt that WGS for NBS should not be mandatory in the same way that current NBS is mandatory. Medical doctors (p=0.034), those who see patients (p=0.029), and those who have been involved in NBS (p=0.040) were more likely to feel it should not be mandatory than non-physician care providers, those who do not see patients, and those without past or current involvement in NBS.

In the areas of consent and counseling, 98.2 % (n=109/111) agreed or strongly agreed that parents should be informed prior to testing about potential results of their child's WGS; 87.3 % (n=96/110) agreed that parents should be able to choose what types of results they would like to receive; 93.7 % (n=104/111) agreed that parents should be required to provide consent in order for their child's genome to be

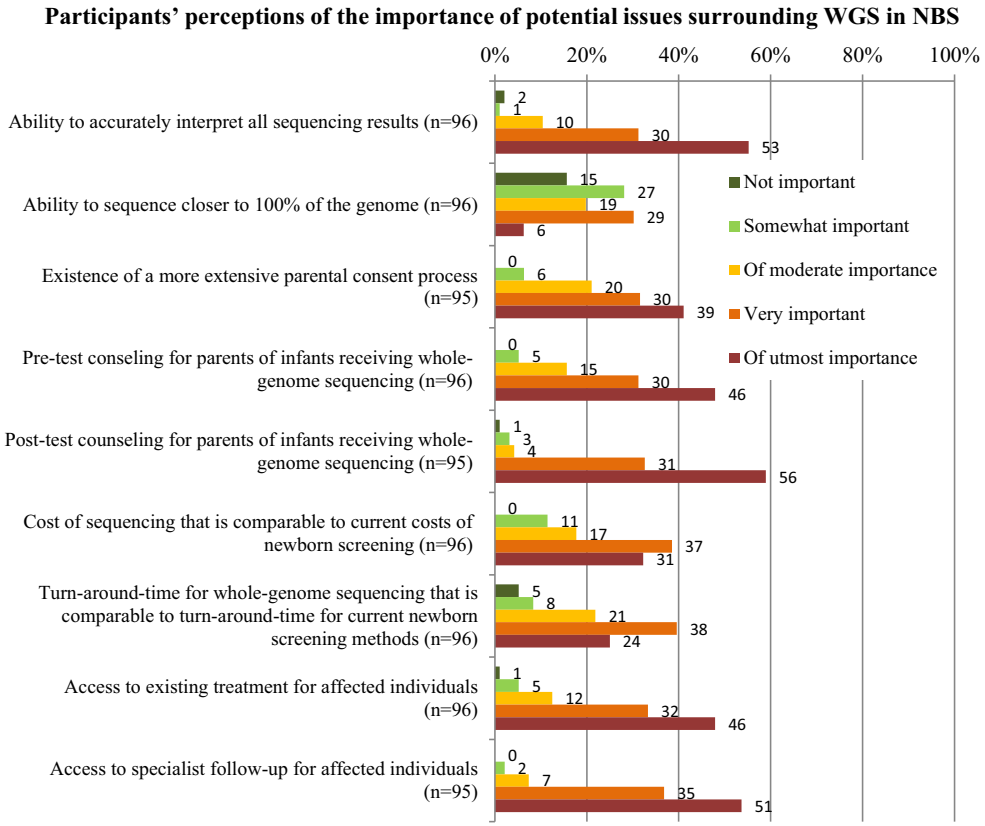

Fig. 3 Participants' perceptions of the importance of potential issues surrounding whole-genome sequencing in newborn screening (with n value included to the right of each response option)

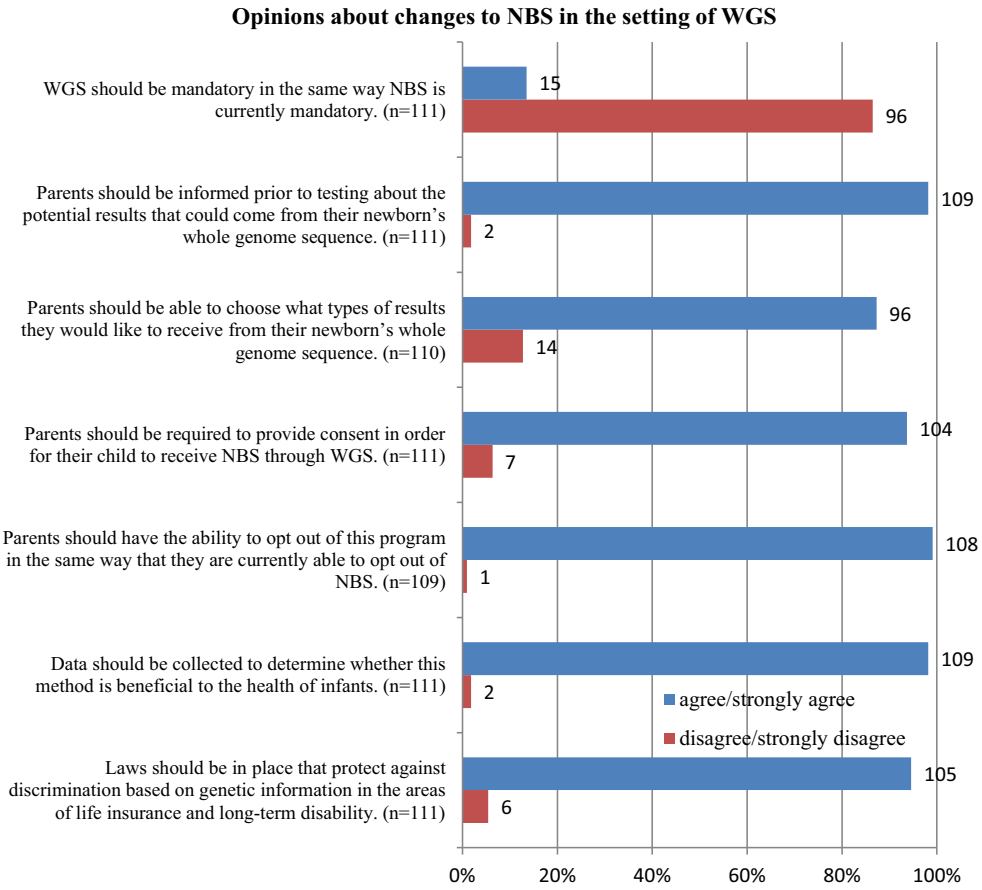

Fig. 4 Opinions of hypothetical changes to NBSin the setting of WGS (with n value included to the right of each response option)

sequenced during NBS; and 99.1 % (n=108/109) agreed that parents should have the ability to opt out of the program in the same way that they are currently able to opt out of NBS.

Participants were given potential NBS result scenarios and asked to decide whether and when each result should be disclosed, as well as by whom. For timing of the return of results, participants could choose either during the newborn period, during childhood (between infancy and age 6, between the ages of 7 and 12, between the ages of 13 and 18), upon onset of clinical symptoms, after age 18, or never (Fig. 5).

The majority of participants (97.2 %, n=104/107) indicated that disclosure for a condition on the current RUSP should occur at birth. The most frequent choices for disclosure of carrier status for a recessive condition were at birth (32.1 %, n=34/106) and after age 18 (33.0 %, n=35/106). Men were significantly more likely than women to indicate that carrier status should never be disclosed (p=0.033). Participants were also generally in favor of disclosing, at birth, sequencing results indicating that the newborn would develop a childhood-onset disorder, regardless of actionability. For scenarios involving adult-onset conditions and single nucleotide polymorphism (SNP) association results, the most common disclosure preferences were "at birth" and "after age 18," also regardless of actionability. Men were significantly more likely than women to feel that SNP results should never be disclosed (p=0.039). The majority of respondents (53.3 %, n=56/105) indicated that sequence variants of unknown significance should never be disclosed.

Participants were asked to specify which healthcare provider should disclose results from each category. They could choose from: primary care provider, physician geneticist, genetic counselor, or specialist in the condition detected (Fig. 6). For most hypothetical situations, physician geneticist was selected as the preferred provider to disclose the result. The two exceptions to this were (1) if the newborn is a carrier for a recessive condition, and (2) if the newborn has SNPs which indicate an increased risk for an adult onset-disease such as diabetes or heart disease. Forty-four point two percent of participants (n=46/104) chose genetic counselors to disclose carrier status identified through WGS, while 33.7 % (n=34/101) indicated that the patient's primary care provider should disclose SNP results.

Participants were asked whether the current guidelines for inclusion of a condition on RUSP should be considered if WGS was utilized in NBS (Fig. 7). The criteria "there are benefits associated with the use of the screening and diagnostic tests and the treatment" and "there are harms associated with screening, diagnosis, and treatment" were combined on

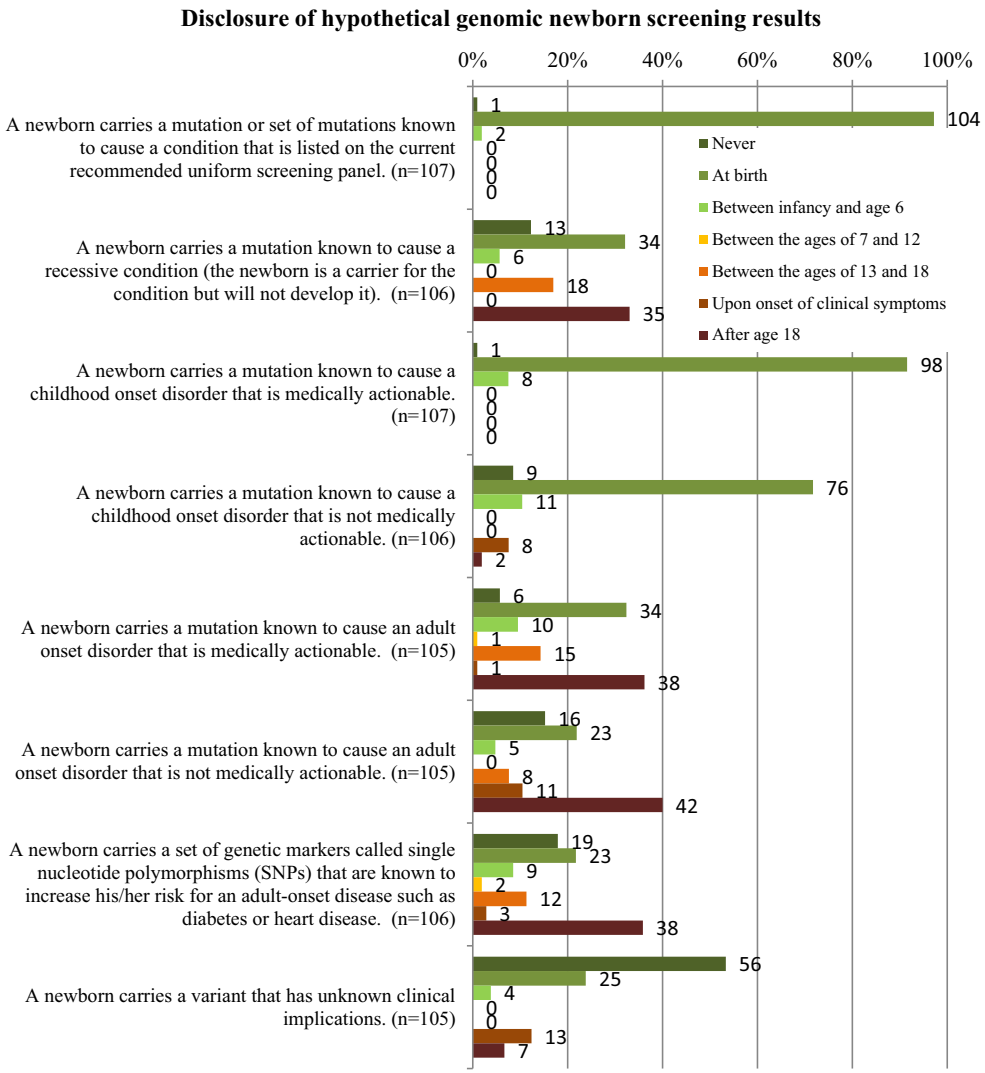

Fig. 5 Opinions regarding disclosure of hypothetical genomic newborn screening results (when the result should be disclosed, if ever) (with n value included to the right of each response option)

the survey in error and asked as one question. Thus, they were excluded from analysis. The majority of participants reported agreement or strong agreement for each of the current criteria.

Participants had the option to provide free text responses regarding the importance of the proposed issues of NBS in the setting of WGS as well as overall thoughts at the end of the survey. Themes identified in the text responses included concerns surrounding results interpretation, storage of results, disclosure of non-actionable conditions, and ethical concerns about utilizing WGS in the newborn period. Respondents also expressed concerns about a potential shortage of genetics professionals if this was implemented, as well as non-genetics clinicians' knowledge of genetics and concerns about their ability to effectively counsel about genetic test results.

Further statistical analyses were performed to compare additional response and demographic categories, and significant associations were not found.

Discussion

Logistical Challenges and Changes to NBS

The goal of this pilot study was to provide an initial glimpse of the opinions of genetics healthcare providers and specialists on the use of WGS as an adjunct to NBS. Respondents' self-reported high familiarity with WGS suggests that they are an appropriate group to survey regarding its use in the setting of NBS. The majority of respondents indicated that WGS should not currently be used as part of mandatory NBS. However, approximately three-fourths indicated that it should be used as an adjunct to NBS in the future, sooner (within in the next 10 years) rather than later (greater than 10 years from now). One-fourth of respondents indicated that WGS should never be utilized in the setting of NBS. Therefore, there is no clear consensus regarding whether or when WGS should be incorporated into NBS.

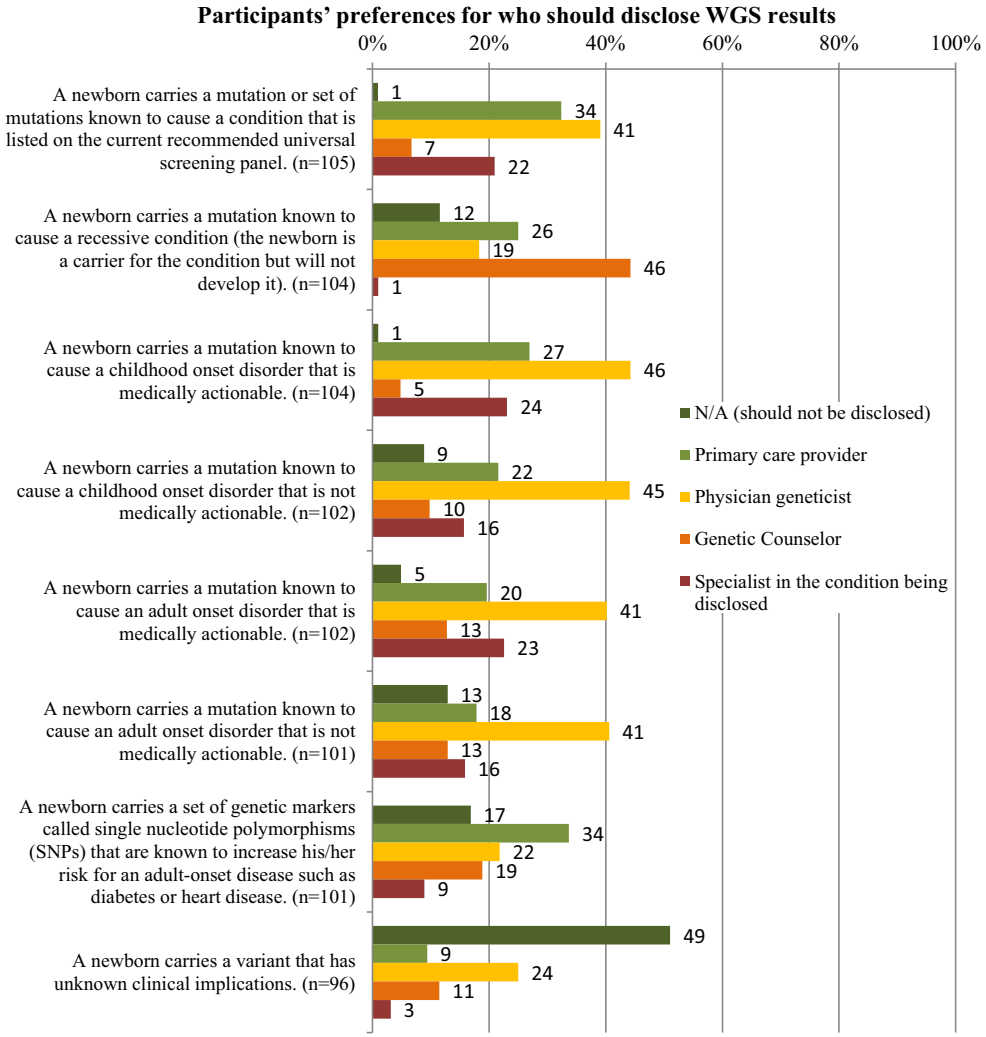

Fig. 6 Participants' preferences for who should disclose WGS results (with n value included to the right of each response option)

Participants felt there would be many challenges in the implementation of WGS in NBS, including pre- and post-test counseling, results interpretation, and access to follow-up. They also felt that parents should be able to choose what types of results they would like to receive, that consent should be required, that opting out should be an option, and that laws should be in place to protect against discrimination in the areas of life insurance and long-term disability. These issues have also been brought up by others (Landau et al. 2014; Levy 2014), who highlight not only these logistical challenges, but also the ethical, legal, and social implications of implementing WGS during NBS. For example, both note the possibility that parents may opt out entirely from NBS because of concerns about genetic screening, which would put at risk children who have a treatable condition that is otherwise identifiable through current NBS.

The ability for parents to select secondary results, widely supported by respondents, is offered by many clinical laboratories currently performing WES for symptomatic patients (Jamal et al. 2013). This option is in contrast to the initial ACMG recommendation that laboratories mandatorily seek and report actionable secondary findings identified by WES/WGS (ACMG 2013a; Green et al. 2013), regardless of patient choice. Feedback after the release of these guidelines led to the subsequent update to the recommendations, which now recommends providing patients with an opt-out option during pre-test counseling (ACMG 2014). Notably, the original recommendations were released subsequent to our data collection, and are also tailored for symptomatic patients rather than newborns.

Participants also placed importance on accurate results interpretation, which illustrates the need for continued improvement of data interpretation and data sharing among clinical laboratories.

Implementing informed consent would represent a departure from the current NBS paradigm, in which consent is typically not required for testing. The challenges of consent and counseling for WGS in NBS have been raised by others (Landau et al. 2014; H. L. Levy 2014; Sharp 2011; Tarini and Goldenberg 2012). For example, there would not be enough

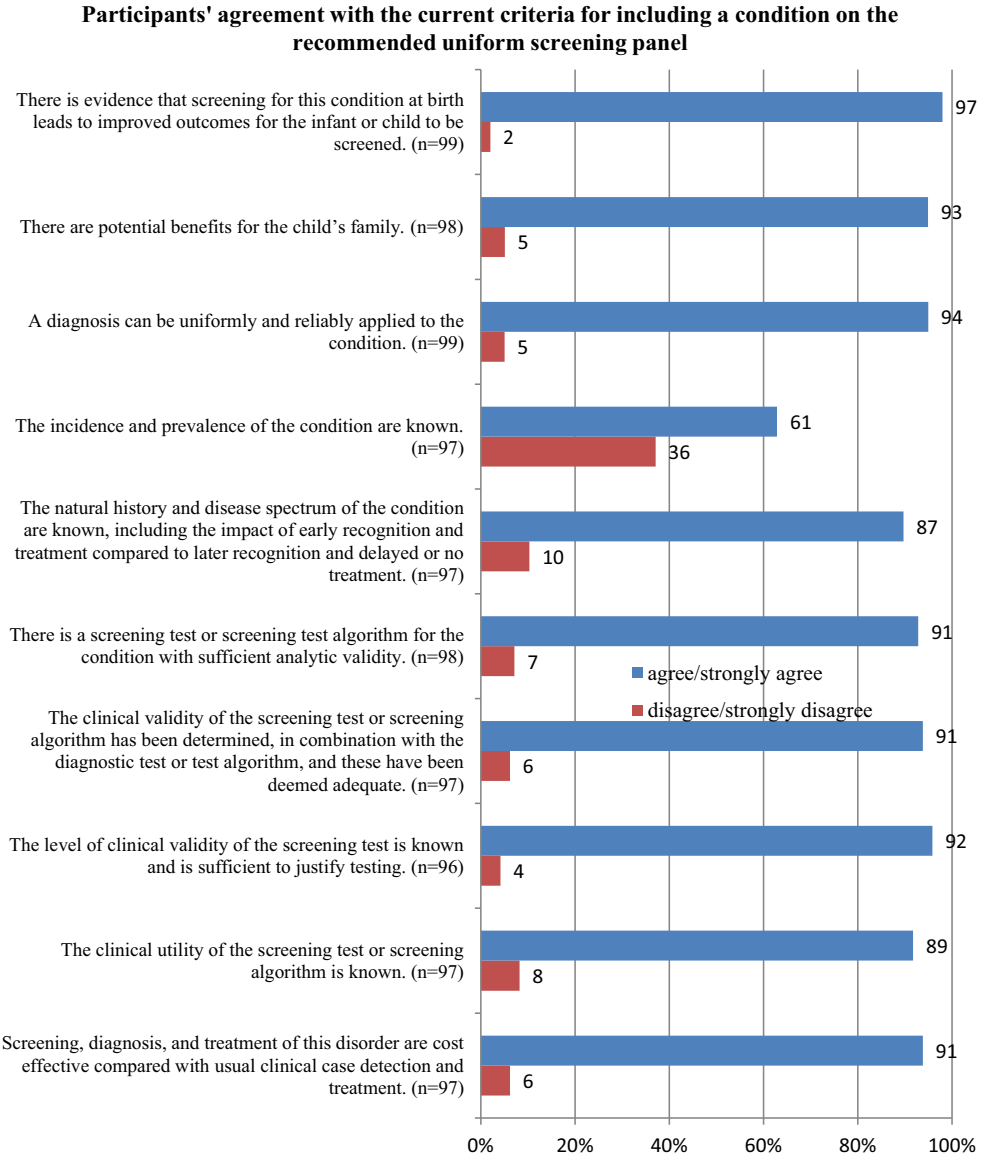

Fig. 7 Participants' agreement with the current criteria for including a condition on the recommended uniform screening panel (with n value included to the right of each response option)

genetics-trained providers to obtain consent from the families of each newborn, and a substantial amount of time would be needed to adequately educate each family about testing. Due to the vast array of potential results, the consent process would differ from consenting for traditional single-gene testing. Perhaps this could resemble consent for whole exome sequencing (WES), which is routinely performed in the clinical setting.

Respondents felt that WGS should not be a mandatory aspect of NBS. Medical doctors, those who see patients, and those who have been involved in NBS were most likely to feel this way. Possibly, providers with closer clinical ties to the NBS process can more readily envision challenges that would be associated with WGS in the newborn period, and feel that these challenges would make a non-mandatory program more appropriate.

The Genetic Information Nondiscrimination Act (GINA) protects individuals from discrimination based on genetic information in areas of health insurance and employment, but not in the areas of life insurance, long-term care insurance, or long-term disability (HHS 2009). Respondents indicated that it would be important to gain protection for these areas should WGS be implemented in NBS.

Based on participants' responses, a new counseling paradigm would be necessary for implementation of WGS in NBS. This would involve a non-mandatory program where parents receive pre- and post-test counseling, are required to provide consent, and are given options for which results to receive from their newborn's whole-genome sequence. It would also be provided in a setting of additional public policy protection from genetic discrimination. The current NBS paradigm does not require informed consent or pre-test

Table 1 Respondents' demographic characteristics

Gender	% (*n*)
Male	45.4 (44)
Female	54.6 (53)
Age	% (*n*)
20–29 years	3.1 % (3)
30–39 years	22.1 % (21)
40–49 years	15.8 % (15)
50–59 years	33.7 % (32)
60–69 years	25.3 % (24)
Years in practice	% (*n*)
0–9 years	26.6 % (25)
10–19 years	19.1 % (18)
20–29 years	31.9 % (30)
30–39 years	21.3 % (20)
40–49 years	1.1 % (1)
Sees patients currently	% (*n*)
Yes	60.4 % (58)
No	39.6 % (38)
Primary role	% (*n*)
Clinical	72.4 % (42)
Research	20.7 % (12)
Administration	5.2 % (3)
Teaching	1.7 % (1)
Profession (check all that apply)	% (*n*)
Biochemical/Cyto/Molecular Geneticist	60.8 % (59)
Clinical Geneticist (M.D.)	47.4 % (46)
Medical Geneticist (Ph. D.)	7.2 % (7)
Genetic counselor	12.4 % (12)
Other	5.0 (5)
Degree(s) held (check all that apply)	% (*n*)
PhD	38.1 % (37)
MD	58.8 % (57)
MS/MPH/MA	33.0 % (32)
BS/BA	20.6 % (20)
DO	1.0 % (1)
JD	1.0 % (1)
MBA	1.0 % (1)
Involvement in newborn screening	% (*n*)
Ever involved	72.9 % (70)
Never involved	27.1 % (27)
Currently involved (% of those ever involved)	60.6 % (43)
Practice setting	% (*n*)
Urban	74.7 % (71)
Suburban	20.0 % (19)
Rural	5.3 % (5)

counseling. Therefore, the infrastructure that would be needed to incorporate these changes may necessitate that management of NBS be moved from state public health departments to a new setting, and may require workforce development and education for state newborn screening programs.

Disclosure of Results

Participants were asked about the types of results that should be disclosed from WGS. These categories were based on the incidental findings categories used by Bick and Dimmock (2011) as well as those used by Berg et al. (2011) in their proposals for implementing WGS/WES in the clinical setting. Respondents almost universally agreed that conditions on the RUSP should be disclosed in the newborn period. Opinions about disclosure of carrier status among respondents were split between disclosure at birth and disclosure after age 18, which may reflect differing opinions about the benefits of learning carrier status in the newborn period and the implications for other family members (Bombard et al. 2012).

Respondents were generally in favor of disclosure of child-onset conditions at birth, regardless of the condition's actionability, while most chose "at birth" or "after age 18" for disclosure of adult-onset actionable or non-actionable conditions as well as SNP results. The opinions of those in favor of disclosure of adult-onset conditions before age 18 are in contrast to current guidelines for genetic testing for these conditions in minors (ASCO 2003; ASHG/ACMG 1995; NSGC 1997), and may reflect varied opinions of the benefits of disclosing these results and of the definition of "action ability". The majority of respondents indicated that variants of unknown significance should never be disclosed.

Overall, participants' choices for the types of results to disclose were similar to and expand upon those of Green et al. (2012), whose study sought to explore concordance or discordance among sixteen genetics professionals' opinions regarding disclosure of incidental findings from clinical WGS or WES in children and adults. The results are also similar to those of Berg et al., who proposed disclosure of actionable sequencing results, that clinically valid results with limited actionability should be disclosed only if chosen by the patient, and that variants of uncertain significance should not be disclosed because of their lack of clinical relevance and potential burden on the healthcare system (Berg et al. 2011).

Participants were asked to select which healthcare provider should disclose each potential result. This was an unexplored area for which no data currently exists. There was no majority preference for any of the result categories, suggesting a lack of consensus for who should handle results disclosure. However, the most frequent choice for disclosure of most results was physician geneticist, while primary health care provider was the most common choice for disclosure of SNP results and the second most common choice for the majority of the remaining categories. For disclosure of carrier status, genetic counselors were chosen most frequently.

The infrastructure that would be needed if physician geneticists were to be heavily involved in results disclosure in the setting of NBS would be lacking, as the number of physicians entering the field of genetics is in decline (Cooksey et al. 2005). Respondents may have felt that genetic counselors are more suited to disclose carrier status because this constitutes a reproductive risk assessment rather than an immediate health risk or a specific diagnosis. Research has shown that primary care providers may benefit from more education about genetics and the utility of genetic testing (Baars et al. 2005; Bernhardt et al. 2012). Placing the responsibility for disclosure of SNP results or other genetic testing results on primary care providers may burden those who may lack the knowledge and time to provide counseling to patients.

Agreement with Current Criteria for Including a Condition on the RUSP

Participants were asked about their opinions of the current criteria for adding a condition to the RUSP in the context of WGS during NBS. Opinions of these criteria in this setting have not previously been assessed, and one objective was to determine if participants' opinions were consistent with their choices for results disclosure. Respondents broadly agreed that nearly all of the current criteria for inclusion of a condition on the RUSP, with the exception of the importance of knowledge of the incidence and prevalence of the condition, should continue to be utilized when determining what conditions to add to the existing panel.

Respondents who disagreed that this specific criterion should be utilized in the setting of genomic NBS may feel that knowledge of incidence and prevalence of a condition are not as important because the cost for sequencing the genome is not dependent on a condition's incidence. However, downstream costs of early diagnosis of a rare condition would need to be considered as well. For example, cost analysis of NBS for severe combined immunodeficiency (SCID) has demonstrated that this is cost-effective and results in improvements in duration and quality of life for affected infants (Chan et al. 2011). However, screening for other rare conditions may not result in the same cost-effective outcomes, and knowledge of incidence of a condition would be necessary to determine this.

There is a discrepancy between participants' agreement with continued use of the current criteria and their choices for what should be disclosed if WGS would be implemented adjunct to NBS. For example, although they agreed that known clinical utility should be an important consideration in the context of WGS in the newborn period, respondents also supported disclosure of non-actionable conditions and SNPs for common complex disease. For these results, the argument could be made that there is no clear evidence of clinical utility, and therefore, these wouldn't be eligible for inclusion on the RUSP when considered under the current criteria. Similarly, respondents indicated that screening, diagnosis, and treatment of a disorder identified through WGS should provide increased value when compared with usual clinical case detection and treatment. While it is possible that for some conditions WGS could eliminate the need for an otherwise expensive diagnostic odyssey, for others, early diagnosis may be more costly than usual case detection if it prompts additional referrals or extra screening. Thus, while respondents agree with these criteria, they may not necessarily apply them when making decisions about which results should be disclosed.

Participants widely agreed with the criteria currently used to determine if a condition should be added to the RUSP. However, if WGS was introduced in this setting, the volume of potential results may make it impossible to continue to evaluate conditions on an individual basis, which would make continued utilization of these criteria difficult. Some have called for a revision of traditional screening guidelines to accommodate for changes in screening practices, such as for metabolic diseases in NBS (Forman et al. 2013). Others have proposed new guidelines for screening in the genomic era (Andermann et al. 2008). Perhaps new criteria will be necessary in the future that will be more applicable for WGS in the specific setting of NBS.

Practice Implications

These results begin to fill a gap in knowledge by providing a preliminary assessment of opinions of genetics specialists regarding the prospect of WGS in conjunction with NBS. Knowledge of the opinions of this specialized group is important, given that they would be expected to be heavily involved should WGS be used in this setting in the future. Given the complexity of the topic, the results suggest that the current implementation of WGS/NBS in the research setting will serve as the best starting point for future discussions to help guide the development of public policy regarding this issue.

Study Limitations

This is a pilot study, and the survey was not formally validated. In addition, because we surveyed only a sub-population of genetics professionals, their opinions do not represent the viewpoint of all of the stakeholders in the NBS process. The opinions of the small subset of respondents who chose to take the survey may not reflect opinions of the wider population of genetics specialists, although demographically our population is comparable to AMBG-certified medical geneticists (Cooksey et al. 2005). Despite the limited response rate, the skewed nature of some responses, such as agreement with parental choice for results disclosure, may be representative of more widely held opinions, as demonstrated in the discussion

surrounding the ACMG recommendations for mandatory reporting.

Future Research

Despite the limited response rate in this study, the data provide valuable insight on opinions of this topic, especially given that research projects are currently underway to study WGS in the newborn period. Future research should include surveying additional NBS stakeholders to assess their opinions of using WGS during NBS. In addition, an assessment of other healthcare providers' opinions of the criteria for including a condition on the NBS panel would provide more comprehensive information about whether these are still considered applicable, either in the setting of current NBS or WGS.

If the categories that respondents have chosen for disclosure were implemented in clinical practice, research would be needed to assess their economic impact. For example, these disclosures could prompt additional referrals as well as increased screening. Additional research would be necessary to determine if disclosure of these results resulted in improved outcomes and, if so, at what cost.

Given the discrepancy between participants' reported agreement with the criteria and their choices for result disclosure, conducting a qualitative study of genetics professionals may shed light on the reasons behind these apparent contradictions. Finally, development of a model based on the survey results with an assessment of the resources necessary to implement this technology may provide information about the downstream costs and economic impact of population-wide WGS during NBS.

Conclusions

When asked to consider a situation where WGS is used as an adjunct to typical NBS, genetics professionals agreed with retaining current criteria used to determine whether conditions should be added to the RUSP. They indicated that WGS should not occur within the same framework as traditional NBS; instead, it should take place in the setting of pre- and post-test counseling, should require parental consent, and should not be mandatory. In addition, they felt that parents should be able to choose which results they would like to receive from the test and that medical geneticists may be best suited to disclose most results. However, when given examples of potential results to disclose, respondents were generally in favor of disclosure of most results at some point in the lifetime, regardless of whether the current NBS criteria are met. Further understanding of these criteria and additional consideration of results disclosure in the genomics era, for which there are no current recommendations for NBS, are needed in order to better understand how WGS would be incorporated in this setting.

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Conflict of Interest The authors declare that they have no conflicts of interest.

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