Genetics in Medicine Open (2024) 2, 101885

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Genetics in Medicine OPEN
An Official Journal of the ACMG

www.journals.elsevier.com/genetics-in-medicine-open

ARTICLE

Genetic counselors' perspectives on genomic screening of apparently healthy newborns in the United States

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ARTICLE INFO

Article history:
Received 9 May 2024
Received in revised form
30 July 2024
Accepted 30 July 2024
Available online 7 August 2024

Keywords:
Ethical considerations
Genetic Counseling
Newborn screening
Newborn sequencing

ABSTRACT

Purpose: There is growing international interest in using genomic sequencing to screen newborns and children for treatable genomic conditions. Although recent research has demonstrated increasing support for using genomic sequencing to screen newborns and children for treatable genomic conditions among various stakeholders, little is known about the perspectives of genetic counselors (GCs) in the United States, who are frequently engaged in the disclosure of positive newborn screening results and coordination of follow-up testing and management.
Methods: This study utilized a cross-sectional 3-section survey to explore GCs' perspectives on the benefits, limitations, and ethical and practical considerations of genomic sequencing in newborns as an adjunct screen to standard newborn screening (NBS). Additionally, we evaluated GCs' views on specific genes that could be added to NBS via sequencing.
Results: Of 176 GCs who participated in the study, most endorsed the addition of NBSeq for conditions that typically manifest in childhood and have a well-defined treatment or management protocol. Some perspectives, such as attitudes toward health inequity, varied by practice region. Most respondents endorsed 13 of 25 specific genetic conditions for inclusion in NBSeq.
Conclusion: Our findings demonstrate GCs' support for the expansion of NBS using genomic sequencing in the United States and the need for ongoing investigation of ethical and practical concerns related to its implementation.

The Article Publishing Charge (APC) for this article was paid by Robert C. Green.

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doi: https://doi.org/10.1016/j.gimo.2024.101885

Introduction

Newborn screening (NBS) is a successful international public health program that identifies infants with actionable disorders shortly after birth. NBS primarily uses tandem mass spectrometry to identify biomarkers of disorders that are childhood onset and have clinically available treatments that can be implemented in infancy to prevent disease progression.[1,2] In the United States, the Recommended Uniform Screening Panel is a list of disorders that the Secretary of the US Department of Health and Human Services[3] recommends that states include in their universal NBS panels. Final determinations are made by the individual state or regional-level NBS program.[3] Although the criteria developed by Wilson and Junger[4] have set a precedent for the types of disorders that should be included in the recommended uniform screening panel (RUSP), the addition of disorders with attenuated or adult-onset forms, such as late-onset Pompe disease or adrenomyeloneuropathy, have challenged this paradigm.[5]

Over 30 international studies are exploring the potential utility of genomic sequencing of newborns and children (NBSeq).[6-9] NBSeq has the potential to expand the scope of screening in many ways, such as by identifying genetic conditions that lack specific laboratory biomarkers,[10] providing information about disease carrier status, or variants associated with adult-onset disorders that may affect relatives of an infant.[11,12] Stakeholders in NBS in the United States and internationally, including parents, medical geneticists, and clinical researchers, have demonstrated overall positive views of NBSeq.[12-23] Across studies, the majority of stakeholders show support for expanding NBSeq for treatable childhood disorders.[12] However, the perspectives of genetic counselors, who are often involved in discussions of positive NBS results and coordination of confirmatory testing and subsequent care, have not yet been systematically assessed.[24]

A survey study by Gold et al[14] demonstrated that medical geneticists and other pediatric specialist physicians broadly support the utilization of genomic sequencing for NBS. A majority of the 238 respondents in that report also indicated that over 400 specific genes and conditions should be screened by that method. Other stakeholders have expressed support for NBSeq but agree that it should only be implemented after careful consideration of impacts on the current health care system, cost and laboratory capabilities, patient accessibility, patient and provider understanding, and ethical considerations.[1,25,26] Although some studies from the past decade have investigated the possible impacts of NBSeq on families and genetic counselors, we revisited genetic counselors' perspectives on NBSeq now that the implementation of this technology has become a focus of international research.[12,27-30] In this study, we assessed the perspectives of genetic counselors in the United States on potential benefits, limitations, ethical considerations, and practical considerations NBSeq, which may be used to inform future guidance related to its implementation.

Materials and Methods

This survey, developed in Qualtrics (Qualtrics), was designed to assess US genetic counselors' perspectives on NBSeq. This study utilized a cross-sectional survey, which was determined to be exempt by the Boston University Medical Campus Institutional Review Board, (Protocol ID: H-44192). The introductory page of the survey notified participants that clicking forward would imply consent to participate. Participants who completed the survey were offered the option to provide their email address in a separate survey link to be entered in a raffle for 1 of 2 $50 gift cards.

Survey design

This survey contained 3 sections of questions, regarding (1) attitudes about the benefits, limitations, and ethical considerations of NBSeq, (2) the inclusion of genes associated with individual childhood-onset treatable genetic conditions to NBS, and (3) participant demographics.

Section 1 of the survey evaluated participants' attitudes about types of conditions that could be screened for with NBSeq, societal impact, and practical considerations of NBSeq using 26 Likert-scale questions. These questions were based on prior questions used in surveys published by De Simone et al[27] and Gold et al.[14] Participants were asked to respond to these questions using 1 of 5 response options (strongly agree, agree, unsure, disagree, and strongly disagree). Response reminders for these questions were included via Qualtrics survey design settings to encourage responses for all questions in this section, although responses were not required to proceed in the survey. Four optional free-text response options assessing additional perspectives on benefits, limitations, ethical considerations, and practical considerations were included at the end of Section 1.

Section 2 evaluated participants' views on whether 25 specific genes and corresponding genetic conditions with the highest concordance among participants who responded to the survey described by Gold et al[14] should be added to newborn screening via genomic sequencing. Genes were presented in the same order for all participants and were grouped by clinical area (urea cycle disorders, mucopolysaccharidoses, glycogen storage diseases, other metabolic conditions, hematology, endocrinology, neurology, oncology, and gastroenterology). Responses in this section were required by Qualtrics to proceed in the survey and response options included "yes," "no," "unsure," and "I don't know enough to answer."

Section 3 elicited demographic information on participants' age, gender, race, ethnicity, years practicing, years in a patient-facing role, primary practice setting, National Society of Genetic Counselors (NSGC) practice region divisions[31] practice area, and prior NBS counseling experience. Responses were required for all questions in this

section to complete the survey. Missing values were recoded and excluded from analysis.

Data from this survey were stored securely in Qualtrics and a Google Drive managed by Boston University.

Participants

Board-certified or board-eligible genetic counselors in the United States who are currently or were formerly working in a direct patient-facing role within the past 10 years were invited to complete the survey. All participants were anonymous. Study investigators were excluded from participation.

Invitations to participate in this survey were distributed to genetic counselors across the United States through the NSGC and the American Board of Genetic Counselors listservs. Survey invitations were initially sent to prospective participants on October 11, 2023, and left open for 3 months. One reminder email was sent to the NSGC listserv 2 weeks after the initial invitation. The survey was also posted to discussion boards for several NSGC special interest groups. These emails and posts included a brief description of the study, a hyperlink to the anonymous online survey, and contact details for the primary investigator.

We aimed to survey 200 participants, which constitutes approximately 10% of the genetic counselors who reported their involvement in direct patient-facing roles in the 2023 Professional Status Survey, administered by the NSGC.[32]

Data analysis

Survey data were downloaded from Qualtrics (Qualtrics) as a Microsoft Excel file and then imported into IBM's SPSS Statistics (Version 29.0.2.0) for analysis. Descriptive statistics were analyzed for all questions. Percentages were calculated using Microsoft Excel (Version 2202). We predicted that the northeast and west coast, as hubs of genetic resources, may feel differently than other regions. Other hypotheses included that attitudes would significantly differ by years practicing, prior experience returning positive NBS results, and practice area. χ^2 analyses were also used to determine whether demographic variables were associated with respondents' attitudes toward genomic newborn screening. Logistic regression analyses were performed to determine associations between respondents' years in practice and attitudes toward NBSeq.

For logistic regression analyses, responses to Likert-scale questions were dichotomized into 2 categories: Agree (including responses for "Strongly Agree" or "Agree") and did not agree (including responses for "Strongly disagree," "Disagree," and "Unsure"). Practice site and primary specialty information further specified by respondents were grouped by the investigator into broader categories for analysis. Responses regarding genetic counselors' recommendations for each of the 25 genetic conditions were tabulated, and rates of concordance were calculated and expressed as percentages.

A content analysis process was developed by the study team and performed on optional, free-text, qualitative responses provided by respondents to evaluate the patterns and frequencies of different topics.[33,34] A master list of codes was inductively developed by the first author (M.C.D.). Categories were created and the incidence of each category was recorded to determine additional barriers, concerns, ethical considerations, and practical considerations of genomic newborn screening not otherwise captured in the survey questions. The frequency of each category was tabulated. M.C.D. completed the initial analysis, which was then reviewed by other study investigators (K.S., J.S., N.B.G., and S.C.) for consistency. Respondents had the opportunity to indicate consent for their free-text responses to be used verbatim in publications. Illustrative quotes for which respondents provided consent were selected to add depth to respondents' views of NBSeq.

Results

Respondent characteristics

A total of 203 individuals accessed the survey, of which 176 met the study inclusion criteria and participated in the survey. One hundred and sixty-four individuals (164) completed the entire survey. The remaining 12 respondents partially completed surveys ($n = 12/176$; 6.8%), which were included in the analysis for the questions that had been answered. There was attrition between survey sections. Because responses in Section 1 were requested but not required, denominators for each statement vary. Because responses in Sections 2 and 3 were required, denominators for all questions are consistent within each section.

All respondents were board-certified or board-eligible genetic counselors who currently practice in the United States. Regression analysis was not conducted for respondent race or ethnicity as predictors given the homogeneity of the sample, aligning with data from the 2023 NSGC Professional Status Survey.[32] The majority of respondents ($n = 158/176$, 96%) were currently in a patient-facing role, whereas the remaining respondents had formerly been in a patient-facing role within the past 10 years. Most respondents reported that they worked at academic hospitals as their primary practice site ($n = 102/164$, 62%). More than half of respondents (84/164, 51%) had between 0 and 5 years of experience. Although the most frequently reported primary areas of practice were pediatric ($n = 56/164$, 34%) and prenatal ($n = 43/164$, 26%), most respondents had not provided counseling about positive newborn screening results in a current or prior role ($n = 98/164$, 60%). All 6 US NSGC practice regions[31] were represented by respondents (Table 1).

Table 1 Participant demographics (n = 164)

Additional Visual Delineation	n (%)
Gender	
Female	153 (93.3)
Male	9 (5.5)
Non-Binary	1 (0.6)
Prefer not to say	1 (0.6)
Race	
Asian	7 (4.3)
Black or African American	3 (1.8)
Middle Eastern or Northern African	1 (0.6)
Native Hawaiian or Pacific Islander	1 (0.6)
White	141 (86.0)
More than one race	6 (3.7)
Prefer not to say	5 (3.0)
Ethnicity	
Hispanic or Latino	4 (2.4)
Non-Hispanic or Latino	159 (97.0)
Prefer not to say	1 (0.6)
Practice Region	
I provide care for patients all over the country	2 (1.2)
NSGC Region 1: CT, MA, ME, NH, RI, VT	38 (23.2)
NSGC Region 2: DC, DE, MD, NJ, NY, PA, VA, WV, PR, VI	38 (23.2)
NSGC Region 3: Al, FL, GA, KY, LA, MS, NC, SC, TN	12 (7.3)
NSGC Region 4: AR, IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, OK, SD, WI	47 (28.7)
NSGC Region 5: AZ, CO, MT, NM, TX, UT, WY	13 (7.8)
NSGC Region 6: AK, CA, HI, ID, NV, OR, WA	14 (8.5)
Years Practicing	
Less than 1 year	21 (12.8)
1-4 years	63 (38.4)
5-9 years	44 (26.8)
10 or more years	35 (21.3)
Practice Setting	
Academic Hospital	103 (62)
Commercial Laboratory	10 (6)
Community Hospital	33 (20)
Shared Primary Setting	8 (4.9)
Other	7 (4.3)
Primary Area of Practice	
Adult/General Genetics	8 (4.9)
Cancer Genetics	33 (20.1)
Pediatric Genetics	56 (34.1)
Prenatal Genetics	43 (26.2)
Subspecialty Clinic	15 (9.1)
Preconception Genetics	9 (5.5)
Prior Experience Counseling for Newborn Screening	
Yes	67 (40.9)
No	97 (59.1)

Support for NBSeq

Respondents largely agreed about the inclusion of genes associated with disorders that are treatable in childhood in NBSeq. Approximately 93% (n = 153/176) of respondents agreed that expanded NBS should include conditions that are treatable but not currently on the RUSP. Most respondents also endorsed the addition of treatable conditions that can be confirmed through nonmolecular studies (n = 152/176, 86.4%) and conditions that are not treatable but have established guidelines for management or surveillance (n = 111/176, 63.1%) (Figure 1A).

Respondents also demonstrated a high level of agreement about several potential benefits of NBSeq. Most respondents agreed that expanding newborn screening using genomic sequencing will lead to expanded reproductive options (n = 108/176, 61.2%) and allow for parents to be proactive and take control of their children's health (n = 141/176, 80.1%). The vast majority of respondents also reported that expanded newborn screening using genomic sequencing would provide useful data for further research on rare conditions (n = 151/176, 85.8%), inform family planning (n = 155/176, 88.1%), identify more at-risk individuals allowing for early detection and/or prevention of conditions in the infant/childhood period (n = 161/176, 91.5%), and benefit individuals who have a genetic condition that would have been missed on standard newborn screening (n = 161/176, 91.5%).

Limitations and concerns about the implementation of NBSeq

Respondents also had a high level of agreement regarding several potential limitations, ethical concerns, and practical considerations surrounding the implementation of NBSeq. Most respondents agreed that misinterpretation of results by nongenetic specialists would lead to inappropriate clinical management (n = 134/176, 76.1%) (Figure 1B). Given this concern for the implementation of expanded NBS, respondents also shared high levels of support for the idea that there is a need for educational resources for providers regarding new conditions added to the newborn screening panel (169/175, 96.6%). An additional 85% (n = 150/176) of respondents agreed that legal regulations and protections regarding privacy and storage of genetic data should be in place before expanded newborn screening is implemented. In tandem with this high level of concern for privacy and data storage, most respondents endorsed that additional protections to prevent genetic discrimination (such as life insurance and disability insurance protections) should be in place before expanded newborn screening is implemented (n = 116/176, 65.9%).

Although respondents agreed with the addition of most types of conditions evaluated in this survey, 71% (n = 125/176) of respondents disagreed with including actionable and adult-onset conditions in NBSeq. One participant who disagreed with including adult-onset conditions noted: "We are taking away the child's right as to whether they want to learn about some of these adult-onset conditions." Most respondents also disagreed with the addition of conditions with childhood onset for which there are no established therapies or expert management guidelines (n = 101/176, 57.4%).

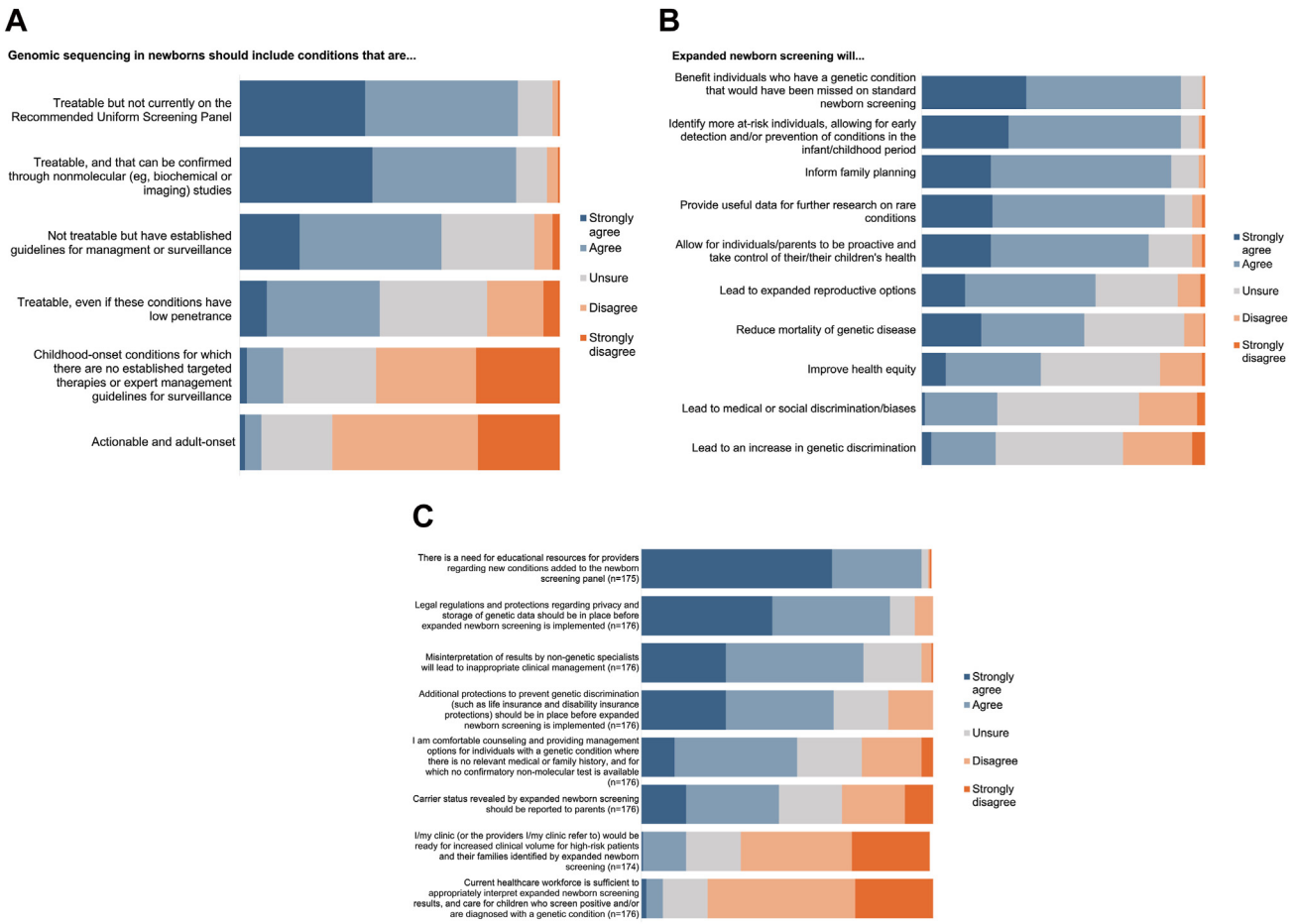

Figure 1 Genetic counselors' perspectives on important aspects of genomic sequencing of newborns. A. Genetic counselors' perspectives on types of conditions to be added to newborn screening using genomic sequencing (n = 176). B. Genetic counselors' perspectives on the societal impact of genomic sequencing of newborns and children (n = 176). C. Genetic counselors' perspectives on practical considerations of genomic sequencing of newborns and children.

Respondents expressed low levels of confidence that both their clinic (or practice site) and the broader health care workforce infrastructure would be equipped to handle the implementation of expanded NBS. Overall, 77.3% (n = 146/176) of respondents disagreed that they, their clinic, or the providers they/their clinic refer to would be ready for increased clinical volume for high-risk patients and their families identified by expanded newborn screening. Additionally, 65.5% of respondents (n = 114/174) disagreed that the current health care workforce is sufficient to appropriately interpret expanded newborn screening results, and care for children who screen positive and/or are diagnosed with a genetic condition (Figure 1C).

Regional differences in attitudes toward NBSeq

The 2 respondents who indicated that they provided genetic counseling services for more than 1 NSGC region were excluded from analyses comparing region and attitudes. Respondents in NSGC region 1 (CT, MA, ME, NH, RI, and VT) agreed that NBSeq should "include conditions that are treatable, even if those conditions have low penetrance" more than other regions, χ^2 (5, 162) = 11.23, P =.047. Respondents from NSGC regions 1 and 2 (DC, DE, MD, NJ, NY, PA, VA, WV, PR, and VI) had a higher level of agreement with the statement "expanding NBS will reduce mortality of genetic disease" than other regions, χ^2 (5, 162) = 12.73, P =.026. Regarding agreement with the statement "expanding NBS will improve health equity," respondents from region 2 agreed more than other regions, and respondents from regions 4 (AR, IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, OK, SD, and WI) and 5 (AZ, CO, MT, NM, TX, UT, and WY) disagreed more than other regions χ^2 (5, 162) = 11.24, P =.047.

Association of other demographic characteristics and views on NBSeq

There were no significant differences in the level of agreement with the following 7 statements and respondents' prior experience counseling about newborn screening or years practicing as a genetic counselor: (1) including conditions that are treatable, even if those conditions have low penetrance, (2) expanding NBS will reduce mortality of genetic

disease, (3) expanding NBS will improve health equity, (4) I am comfortable counseling and providing management options for individuals with a genetic condition where there is no relevant medical or family history, and for which no confirmatory non-molecular test is available, (5) carrier status revealed by NBSeq should be reported to parents, (6) lead to medical or social discrimination/biases, and (7) lead to an increase in genetic discrimination (all χ^2 = ns).

Respondents' endorsement of individual genes for NBSeq

Each of the 25 gene-disease pairs were endorsed by 20% to 80% of the 165 respondents. In total, 13 of the 25 genes (*OTC, DMD, F9, F8, GALNS, G6PC, ARSB, SLC37A4, RB1, SMPD1, GUSB,* and *CYP11B1*) were each endorsed by more than half of the respondents to be added to NBS with genomic sequencing (Figure 2). The gene with the highest level of support was *OTC*, associated with ornithine transcarbamylase deficiency. Overall, most genes supported by a majority of respondents were related to metabolic conditions, specifically those related to mucopolysaccharidoses and glycogen storage diseases. Both hematologic conditions, hemophilia A and hemophilia B, had 65.5% and 66% support, respectively. The genes with the least support were *SLC26A3*, associated with congenital secretory chloride diarrhea, *SLC7A7*, associated with lysinuric protein intolerance, and *GATM*, associated with cerebral creatine deficiency syndrome 3. The clinical area with the least support was gastroenterology, with the one disease in this area receiving only 20% support. Of note, most participants indicated that they did/did not have enough information to indicate whether or not they agreed with the inclusion of the 25 genes in this section in NBSeq.

Free-text responses

Several categories related to potential benefits emerged from these responses, including the ability to identify at-risk siblings or relatives, the increased representation in our genomics knowledge base, the usefulness of providing carrier status information for family planning, and the reduction of time to diagnosis for affected individuals.

Categories related to potential limitations of NBSeq included increased parental anxiety and distress, lack of autonomy or informed consent process, uncertainty related to variability in phenotype and onset, undefined reporting standards for variants of uncertain significance, and costs associated with personnel and laboratory capabilities.

The categories identified related to ethical, legal, and societal implications considerations primarily concerned the need for an informed consenting process, concern surrounding potential increase in disparities in which populations would get the most accurate data, and concern for increased disparities in access based on cost and insurance considerations. Regarding practical considerations, respondents most frequently brought up concerns in clarity related to variant reporting procedures, and privacy and data storage practices (Table 2).

Discussion

Using genomic sequencing to expand NBS would have downstream implications for both patients and health care professionals, including genetic counselors. In this study, genetic counselors' perspectives regarding the benefits, limitations, ethical considerations, and practical implications of NBSeq are largely concordant. Some perspectives, specifically those related to the impact on mortality and health equity were found to vary by NSGC practice region.

Respondents overwhelmingly agreed that genomic sequencing in newborns should include conditions that are treatable in childhood, including conditions that have low penetrance, are not currently on the RUSP, and can also be confirmed using nonmolecular methodologies. Additionally, most respondents agreed that NBSeq should be used to identify conditions that do not have a treatment but do have guideline-based screening and management recommendations associated. These responses reflect existing attitudes in the field based on the NSGC genetic counseling Code of Ethics principles that emphasize actionability, beneficence, and autonomy.[35] Additional comments made by respondents clarified that, although generally being in agreement with adding treatable conditions, the definitions of treatability must be more formally established to make inclusion criteria more concrete. These results generally reflect perspectives in the greater NBSeq literature, although interpretations of traditional Wilson and Junger criteria related to treatability and prevalence vary within each genomic screening project.[12,18-23]

Respondents from NSGC regions 1 and 2, which predominantly represent the northern half of the East Coast of the United States, had higher levels of agreement that NBSeq via genomic sequencing will reduce mortality and help increase health equity compared with other regions. Respondents in region 1, which represents New England, also had a significantly higher agreement than all other regions that conditions that are treatable but have low penetrance should be added to NBSeq in the United States. This agreement may correspond with additional factors such as the density of academic medical centers, access to genetic counselors or genetics services, or regional health care policies[24] in these areas. Additionally, most states in these 2 regions have less restrictive policies related to reproductive health, which may affect respondents' perspectives toward the impact of NBSeq.[36] These findings may also relate to variations in public health priorities including a high number of conditions currently included on NBS panels for states in these regions compared with other regions, which may influence perspectives in the implementation of NBSeq.[24] Respondents from region 5 were significantly less likely

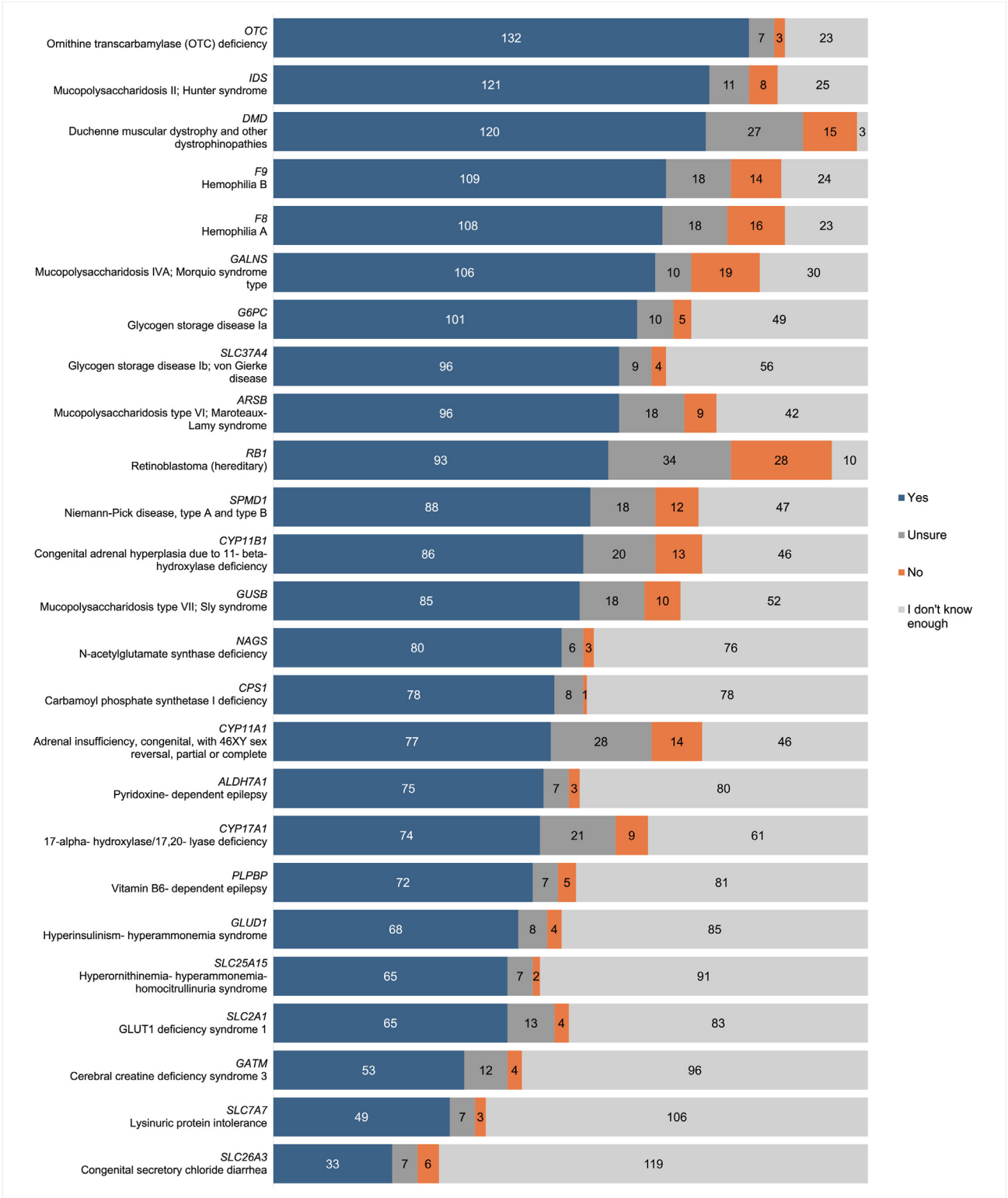

Figure 2 **Genetic counselors' endorsement of genes to include with genomic sequencing of newborns and children (n = 165).**

to agree that NBSeq will improve health equity, compared with other regions. This region includes states that have more limited NBS programs and restrictive health care policies related to reproductive health. It is possible that respondents from this area have less infrastructure to support care after expanded screening for additional conditions or resources for implementation, which may increase health inequities for that region.[37] Surprisingly, responses did not

Table 2 Selected categories and quotations from free-text responses

Category	Quotation
Benefits of NBSeq	
Identification of at-risk siblings and relatives	"[There is a benefit in identifying] affected siblings (especially for conditions with mild presentations) for whom expanded NBS was not available."
Increasing representation in our genomics knowledge base	"We are learning about more expanded phenotypes than were once reported. We … [would] also [be] getting genomic data on groups that have been underrepresented by biobank data since this is population-based screening."
Utility in providing carrier status for family planning	"[Expanded NBS would facilitate] more discussion about future family planning and family education"
Reduction in diagnostic odyssey for affected individuals	"[Expanded NBS would] reduce diagnostic odyssey, provide earlier diagnoses for possible development of earlier treatments, [and] would allow for further delineation of the spectrum and penetrance of genetic conditions"
Limitations of NBSeq	
Increased parental anxiety and distress	"[Expanded NBS would create] stress and psychological distress in what would otherwise be a happy newborn period"
Lack of autonomy and informed consent process for the child	"[NBSeq would create concern for] Autonomy related to adult-onset conditions and whether that baby would want to know that information as they get older."
Uncertainty related to variability in onset and phenotype	"Newborn screening has expanded our understanding of diseases like Pompe disease. However, it's also created a lot of uncertainty about when/whether some patients will be symptomatic. When I think about genome sequencing being used for NBS, I'm concerned about the number of other conditions for which we may not know the full spectrum of disease, and therefore will not be able to offer good guidance for patients who are asymptomatic."
Undefined reporting standards for VUS and pathogenic/likely pathogenic variants	"Labs still vary in their interpretation of variants, so the lab used by the state will potentially have a large impact on NBS results… if VUS are reported or conditions with limited treatment/management are reported. Provider/parental misunderstanding of what testing was/wasn't performed which could impact future testing/referrals to Genetics (i.e. will someone not be referred because they think the NBS would have picked up a condition of interest?)"
Costs associated with laboratories and personnel	"[NBSeq would increase] cost to the healthcare system/society to perform expanded testing."
ELSI Considerations	
A need for informed consent processes for parents	"[NBSeq would require] proper parental consent and making sure that they are truly aware of what is being tested and what it would mean."
Increase in disparities for different populations	"Individuals of underrepresented backgrounds in genomic research are more likely to have novel variants, possibly still classified as VUS… There could be health inequity if White patients with a genetic condition are more likely to be picked up than non-White patients with the exact same condition."
Increase in disparities in access based on cost and insurance	"[Expanded NBS would create] disparities due to differences in health insurance coverage (extent, policies, what constitutes as asymptomatic to warrant treatment)"
Practical Considerations	
Concerns about clarity related to variant reporting procedures	"What does [an NBSeq] report look like - does it need to look more like a report from a reference lab than the NBS report currently does? Where/how is this information stored in the chart for reference potentially years down the road?"
Concern about privacy and data storage practices	"How is all of this data going to be stored? Where is the data going to go? It's not only a matter of whether the testing can or should be done with this. It's also a matter of whether a healthcare institution can handle storage of such large amounts of data in the event that future reanalysis is needed."

ELSI, ethical, legal, and societal implications; *NBS*, newborn screening; *NBSeq*, newborn sequencing; *VUS*, variants of uncertain significance.

significantly differ by years practicing as a genetic counselor, prior NBS counseling experience, or primary area of practice. These results suggest that attitudes toward NBSeq are generally consistent and generalizable across genetic counselors in the profession.

Our findings demonstrate alignment between genetic counselor respondents in this study and the physician respondents to the survey on which this study was modeled.[14] In both studies, there was high concordance regarding the inclusion of conditions that are treatable but may have low penetrance and those that are not treatable but have established guidelines for management and surveillance, although genetic counselors from this survey had slightly higher percentages of agreement than rare disease experts, from their survey. Similarly, respondents in this survey and from Gold et al[14] both displayed a high degree of

disagreement with adding conditions that are childhood onset but have no treatment or management guidelines.

A notable difference in findings from this survey of genetic counselors and the prior survey of primarily rare disease physicians[14] was that physicians were more likely than genetic counselors to support adding treatable adult-onset conditions to NBS. Overall, 37.2% of respondents from the Gold et al[14] survey endorsed the inclusion of these conditions, compared with 6.8% of genetic counselors in this survey. This discrepancy in agreement between providers could be related to ethical and practical considerations that are distinct to genetic counselors. More specifically, genetic counselors may be less likely to support testing for adult-onset conditions compared with medical geneticists because of the field's conventional stance to defer testing of minors until age 18 to preserve autonomy unless immediately medically necessary.[38–40] Guidelines established by the American College of Medical Genetics and Genomics and the American Society of Human Genetics offer broader definitions for the appropriate use of predictive clinical testing for minors regarding medically actionable adult-onset conditions than the position statements made by the NSGC.[39–42] Some genetic counselors, through free-text responses, qualified that their disagreement with including treatable adult-onset conditions reflected concerns from parents about the need to preserve patient autonomy and avoid unnecessary parent anxiety that may affect how the child is raised.[38,43] Parents in both the United States and internationally, have recently demonstrated interest in learning about treatable adult-onset conditions with newborn sequencing practices,[15,18,19,44] which may cause genetic counselors' views to evolve in the future.

Regarding the inclusion of 25 specific gene-disease pairs in NBSeq, we found a wide range of concordance among respondents. Similar to the Gold et al[14] survey, ornithine transcarbamylase deficiency (OTC) was the most highly endorsed gene, with 80% of genetic counselors agreeing that it should be added to NBS through genomic sequencing. It is possible that this gene received the highest endorsement because it has already been piloted by several states using biochemical screening.[45] Of note, biochemical screening for OTC deficiency is not highly sensitive for affected females and can also produce high rates of false positive results, 2 issues which may be improved upon by genomic screening methods. For the 9 conditions with the lowest endorsement, the majority of responses indicated that respondents did not know enough to answer rather than "no" or "unsure," and for conditions with higher levels of endorsement, disagreement was more evenly distributed between "no," "unsure," and "I do not know enough to answer." It therefore seems plausible that genes that received higher endorsements reflect the level of exposure to these conditions and awareness among genetic counselors for those specific conditions, possibly within genetic counseling graduate courses.

Among the free-text responses, the most frequently reported category was concern related to variant classification and reporting, especially related to variants of uncertain significance. For the purposes of this survey, we asked respondents to consider that only well-established, known pathogenic and likely pathogenic variants would be reported for these conditions, although concerns about disparities related to classification and reclassification still emerged. Additionally, respondents frequently mentioned concerns related to possibly increasing disparities given the existing genomic knowledge base. Although one of the suggested potential benefits NBSeq may be to increase in the representation of genomic information from traditionally underrepresented groups, a parallel limitation is that it may not be equally beneficial across all racial, ethnic, and ancestral groups given our current limited understanding of variants in different ancestries.[26,46]

This study had several limitations. Genes that received less than 50% agreement had between 26% to 68% of respondents indicating that they did not know enough about the condition to answer. Limited awareness of certain conditions appears to account for the primary lack of endorsement rather than disagreement or unsureness. This result is likely related to variation in genetic counselor specialization. Because less than half of our respondents currently work primarily in a pediatric or metabolic clinic, and only 40.9% of respondents have provided counseling for positive NBS results in a current or prior position, the majority of our sample did not specialize in an area where they would have had frequent exposure to counseling for many of these metabolic conditions.

Additionally, there may have been recruitment bias because this survey was only reaching those willing to read the NSGC and American Board of Genetic Counselors listserv emails. Because not all genetic counselors could be reached through these recruitment methods, and only genetic counselors willing to take the survey self-selected do so, the survey population may not be representative of perspectives of the genetic counseling field as a whole. Although representative of the current genetic counseling field, the homogeneity of participant race and ethnicity in this sample did not represent a diversity of perspectives from groups traditionally underrepresented in biomedical research. Lastly, because of the limited sample size, some of the statistical analysis may have been underpowered for some of the tests that had more than 2 categorical variables.

This study suggests several important directions for future research. Importantly, most respondents from this study did not believe that they or their clinic would be ready for increased clinical volume for high-risk patients and their families identified by NBSeq. This points toward the need for targeted needs assessments addressing specific concerns and barriers to implementing NBSeq and what resources are needed to anticipate a future expansion of methodology. Perspectives of international genetic counselors regarding ethics of NBSeq and particular conditions for screening with NBSeq should also be explored because genomic researchers in other countries, including the United Kingdom and Australia, have begun prospectively investigating NBSeq as a replacement or adjunct NBS

methodology.[12,44,47] Additionally, NBS laboratory capabilities on a state by state should be investigated to assess readiness to scale service for NBSeq.

Taken together, findings from this survey demonstrate that US genetic counselors largely support NBSeq. Most respondents agreed that conditions that are childhood onset and either have clear treatment or management and screening guidelines should be considered for NBSeq. Although attitudes toward the potential benefits, limitations, ethical, and practical considerations are generally consistent among respondents, some attitudes did vary by practice region, with those in higher-resource areas demonstrating more enthusiasm for NBSeq. Our findings also align with prior research of physician perspectives on NBSeq[14] that supports endorsement of specific genetic conditions that are treatable or are actionable via targeted surveillance but do not have a biomarker that can be detected easily in the general population. The perspectives of genetic counselors, who are frequently engaged in the disclosure of positive NBS results and coordination of follow-up testing and management, will continue shape the implementation of NBSeq as it evolves.

Data Availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials; raw data files and qualitative data can be provided by the authors upon request.

Acknowledgments

The authors thank Brooke McGinley (Boston University) for her assistance in consulting on statistical analysis. The authors also thank Zachary Digena-Segal (IBM) for his assistance with the design of tables and figures in this manuscript. This work was completed, in part, to meet the requirements of a genetic counseling program.

Funding

N.B.G. reported receiving grants K08HG012811-01 and TR003201 from the National Institute of Health. M.C.D. received a $150 stipend from the Boston University Genetic Counseling program.

Author Contributions

Conceptualization: M.C.D., K.B.S., S.C., J.S., N.B.G.; Data Curation: M.C.D.; Formal Analysis: M.C.D.; Investigation: M.C.D; Methodology: M.C.D., K.B.S., S.C., J.S., N.B.G.; Project Administration: M.C.D.; Supervision: K.B.S., N.B.G., S.C., J.S.; Visualization: M.C.D.; Writing-original draft: M.C.D., N.B.G.; Writing-review and editing: M.C.D., K.B.S., S.C., J.S., R.C.G., N.B.G.

Ethics Declaration

This study was conducted at Boston University and determined exempt by the Boston University Institutional Review Board on September 29, 2023 (H-44192), and completion of the survey was taken to constitute consent to participate.

Conflict of Interest

Nina B. Gold is an occasional consultant to RCG Consulting and has received honoraria from Ambry Genetics. Jennifer Schwab was also an employee of Color Health at the time this work was conducted. Robert C. Green receives compensation for advising the following companies: Allelica, Atria, Fabric, Genomic Life and Juniper Genomics; and is cofounder of Genome Medical and Nurture Genomics. All other authors declare no conflicts of interest.

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