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Knowledge of Carrier Status and Barriers to Testing among Mothers of Sons with Duchenne or Becker Muscular Dystrophy

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Abstract

Our study objective was to survey female carriers for Duchenne and Becker muscular dystrophy to identify barriers to carrier testing and the impact of carrier risk knowledge on cardiac and reproductive health management. We surveyed women who have or had biological sons with Duchenne or Becker muscular dystrophy and were enrolled in the US DuchenneConnect patient registry, with questions assessing knowledge of carrier status and recurrence risk, knowledge of care standards for carriers, and barriers to testing. Of the 182 eligible respondents, 25% did not know their carrier status and 14% incorrectly classified themselves as not at risk. Cost of testing was the most commonly identified barrier to testing. Women reporting unknown carrier status were 13 times as likely to express uncertainty regarding their recurrence risk compared to women reporting positive carrier status. 37% of women at an increased risk for cardiomyopathy had never had an echocardiogram. Women who were certain of their positive carrier status were twice as likely to have had an echocardiogram in the last five years compared to women with unknown carrier status. Future research on reducing barriers to counseling and carrier testing, such as cost, may improve care standard adherence.

Keywords

Becker Muscular Dystrophy; Carrier Care Standards; Carrier Testing; Duchenne Muscular Dystrophy; Genetic Counseling; Genetic Testing

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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1. INTRODUCTION

Duchenne and Becker muscular dystrophy (DBMD) are a spectrum of X-linked muscular dystrophies caused by mutations in the dystrophin gene *DMD*. The Duchenne male phenotype typically exhibits progressive muscle weakness starting around ages 3–5 with loss of ambulation before age thirteen and associated cardiomyopathy and respiratory insufficiency, with an average lifespan of 25.3 years; the Becker phenotype is variable but milder [1,2]. Women who carry a dystrophin mutation can rarely present with a severe phenotype as the result of skewed X-inactivation [3] but more typically exhibit mild weakness, and cardiac abnormalities that range from asymptomatic mild left ventricle dilatation to severe cardiomyopathy requiring transplantation or causing death [4–6]. Based on these findings, surveillance guidelines published in 2005 recommend that women who are carriers for Duchenne or Becker muscular dystrophy should be counseled about their risk to develop cardiomyopathy and should receive complete cardiac evaluation every five years [7]. Carrier testing also has important ramifications on reproductive health management, including frequency of pregnancy terminations, reduction in number of pregnancies in at-risk women compared to control populations, percent of women who avoided pregnancies and limited their family size due to their risk, and rates of tubal ligation before and after genetic counseling in at-risk women [8–11]. Thus, determining carrier status has implications for personal and reproductive health management; however, limited research exists regarding risk awareness among carriers or women at risk to be carriers. Our study objectives were three-fold: first, we sought to estimate the rate of carrier testing in an engaged population of women in the United States with a son with Duchenne or Becker muscular dystrophy. Second we assessed respondents' understanding of their risk to have another child with DBMD and of their personal risk of cardiac disease. Third, we evaluated the barriers to carrier testing and risk awareness to identify future research needs and possible solutions to improve healthcare in this at-risk population.

2. PATIENTS AND METHODS

In this prospective cross-sectional survey study, we distributed a 31-item anonymous survey via web link to 1229 individual accounts registered with the US DuchenneConnect patient registry (web link to survey: https://www.surveymonkey.com/r/Preview/?sm=6XWmfhFet3OrqhPrkU3DRrQVJgZgDNpuqb7tNIhHL7o_3D). The study information and survey link was emailed twice: first as a component of a monthly newsletter, and second as part of an email blast sent a month later to registered participants. Only female respondents who have or had biological sons with DBMD and answered a mandatory question about whether or not they knew their carrier status, and if they knew, whether their status was negative or positive, were eligible for the study and were included in the analysis. The survey assessed: (a) knowledge of the participants' own carrier status, (b) accuracy and certainty regarding their recurrence risk, (c) understanding of carrier cardiac risks and their personal screening history for these risks, and (d) dissemination of information among family members. Incomplete surveys, where the respondent failed to answer the mandatory question regarding their carrier status, were excluded. Participants answered questions regarding knowledge of their carrier status, the reasons they had not had carrier testing, their impression and uncertainty of their recurrence and cardiac risks, their cardiac screening

history, their ability to have more children, their family history of DBMD, and their number of biological sisters.

2.1. Standard Protocol Approvals, Registrations, and Patient Consents

Institutional Review Board-Health Sciences and Behavioral Sciences at the University of Michigan reviewed the protocol and designated it as exempt from review.

2.2. Standardized assessments

We collected the following data: demographic variables (age range, race and ethnicity, and highest educational level attained), family history (if they had a brother with DBMD, more than one son with DBMD, or a family history of DBMD prior to the birth of their first affected son, with open text options), participants' assessment of their risk to have another child with DBMD, and qualify, if applicable, whether they were less than 100% sure about their assessment, and their knowledge of cardiac care standards (risk of cardiomyopathy in carriers, and whether or not they had seen a cardiologist, had an EKG, or had an echocardiogram within the last five years). Participants were also asked whether or not they were physically able to have more children. Participants were asked whether they had full biological sisters and whether they had shared carrier risk information with their sisters. Those who had not shared carrier information with their sisters were asked to identify any applicable reasons why they may have not shared information with open-text options. Participants who indicated they had a family history of DBMD prior to their first affected pregnancy were also asked whether they felt they understood their risk to have a child with DBMD before becoming pregnant.

2.3. Statistical Analysis

Obligate carriers were defined as women with two or more sons with DBMD, a brother with DBMD, a maternal uncle with DBMD, a father with BMD, or a mother, sister, or daughter who is a confirmed carrier. Classification as an obligate carrier via family structure was then cross-referenced against participants' self-reported carrier status to identify individuals who were not aware or not correct about their carrier status. The proportion of at-risk mothers who did not know their carrier status was estimated based on participants' self-reported carrier status with 95% confidence intervals. All respondents were classified as being at risk for recurrence (greater than population risk) unless they physically were no longer able to have more children due to menopause, a tubal ligation, hysterectomy, husband's vasectomy, other medical condition, or a personal age of ≥ 55 . Respondents were classified as being at increased risk to develop cardiomyopathy unless they self-reported that they were not carriers. Open entry responses were reviewed for family history information and thematic content related to psychosocial impacts of carrier testing or educational gaps in genetic counseling. We calculated associations between knowledge of carrier status and uncertainty in recurrence risk, knowledge of cardiac care standards, and sharing of risk information with their sisters, using two-tailed Fisher exact probability. Estimates of magnitude of correlations were performed using odds ratio (OR) and relative risk (RR) calculations. Finally, each open entry response was reviewed for (a) responses that revealed or discussed insufficient or unsatisfactory genetic counseling for carriers or women at risk to be carriers,

(b) responses that revealed potential inaccuracies in recurrence or cardiac risk determination, and (c) responses that revealed or discussed psychosocial impacts of carrier testing.

3. RESULTS

3.1. Patient demographics and characteristics

Of 197 survey responses received, 182 met criteria for inclusion in data analysis.

Respondents were excluded for the following reasons: did not meet inclusion criteria ($n = 3$); never had a son with DBMD ($n = 6$); did not complete a sufficient number of survey questions ($n = 6$). Table 1 lists the demographic data.

3.2. Participant's knowledge of own carrier status

Of 182 included respondents, 137 (75%) knew their carrier status and 45 (25%) did not.

55% of respondents who did not know their carrier status cited financial cost as a reason they had not pursued carrier testing (Table 2).

3.3. Confidence and accuracy of participant's assessment of carrier status and recurrence risk

Among 109 women classified as having a recurrence risk, 15 (14%) indicated with certainty that they were not at risk to have another affected child (95% CI: 7–20%). 32 women were identified as being obligate carriers based on responses to questions in the survey that addressed family history. Of these, 27 had self-identified as being carriers for DBMD, but 3 indicated they were unsure of their status and 2 had indicated that they were not carriers. Women who did not know their carrier status had the highest frequency of uncertainty in rating whether or not they had a chance to have another child with DBMD (68%), compared to women with negative carrier status (44%) and women with positive carrier status (5%). Women with unknown carrier status were 13 times as likely to express uncertainty regarding their recurrence risk compared to women with positive carrier status ($p < 0.001$, [RR]: 12.7, 95% CI: 4.1–39.2). Women with negative carrier status were also significantly more likely to express uncertainty about their recurrence risk compared to the same group ($p < 0.001$, [RR]: 8.2, 95% CI: 2.5–26.9).

3.4. Understanding of personal health risks and screening history for cardiomyopathy

86% of all women who were classified to be at risk to develop dystrophinopathy-related cardiomyopathy accurately identified that carriers of DBMD have an increased risk for this condition, but only 63% of the same group had ever had an echocardiogram, and only 45% had had an echocardiogram in the last five years. 21% of at-risk women had never had an echocardiogram, nor an EKG, nor seen a cardiologist. Known carriers were twice as likely to have had an echocardiogram in the last five years compared to women with unknown carrier status ($p = 0.0021$, [RR]: 2.0, 95% CI: 1.2–3.4), but no difference was detected between these groups in their ability to accurately report that carriers had an increased risk for cardiomyopathy ($p = 0.07$). Additionally, women whose youngest affected son was diagnosed 10 or more years ago, which predates the cardiac surveillance guidelines, were not found to be more or less likely to have had an echocardiogram than women whose sons were diagnosed more recently ($p = 0.13$).

3.5. Dissemination of information among family members

Of 26 women who had a family history of DBMD prior to their first affected pregnancy, 11 (42%) disagreed with the statement that they understood their risk to have an affected child before they became pregnant. Of respondents who were carriers or at-risk to be carriers, 84 (60%) reported having at least 1 full biological sister. 67 (80%) of women with full biological sisters indicated they had told their sisters they were at risk to be carriers, while 3 (4%) indicated they had informed their sisters they were not at risk, and 8 (10%) indicated they had not shared information with their sisters. The remaining 7% were not sure of how to answer the question. Of women who reported having full biological sisters, known carriers were more likely to have informed their sisters they were at risk to be carriers compared to women with unknown carrier status ($p=0.0014$, [OR]: 6.5, 95% CI: 2.1–20.7). Of the 8 women who had not shared information with their full sisters, belief that their full biological sisters were not at risk to be carriers was the most common reason they had not shared carrier information (Table 3).

3.6. Themes of open-entry text responses

Four respondents directly commented that knowledge of their carrier status altered their reproductive decisions. Three respondents made comments that revealed or discussed educational gaps in the genetic counseling for carriers or women at risk to be carriers, four respondents made comments that reflect obstacles to accurate risk construction, and three respondents made comments that revealed or discussed psychosocial impacts of carrier testing for DBMD. These comments are thematically reviewed in supplemental Table 4.

4. DISCUSSION

Our study demonstrates that a significant portion of women in the United States do not know their carrier status, and that not knowing ones carrier status predicted lower rates of cardiac screening and higher rates of uncertainty regarding recurrence risk. Though we report positive findings in the majority of our participants related to knowledge and access to genetic testing (most women have undergone carrier testing and most seem to appreciate the significance of the results, including the increased risk of cardiac outcomes), the findings have implications for improving both clinical interventions and for advocacy efforts. For example, despite only 14% of respondents reportedly not understanding their increased risk of cardiac disease, over a third of respondents, specifically 37% of women at an increased risk for cardiomyopathy had never had an echocardiogram, which is concerning. In the advocacy realm, Parent Project Muscular Dystrophy has conducted a series of parent engagement activities to nuance and extend the findings of this study. These efforts have contributed to the planning of a series of carrier-focused educational efforts and a longer-term data collection approach through the DuchenneConnect registry.

Limitations to our study include our participant population, which may not be representative of the average woman with a son with DBMD. However, as we expect that a person with sufficient disease awareness to participate in a patient registry such as DuchenneConnect would be more likely to be aware of their carrier status and risks, we predict that the likely outcome of this bias is that our results are conservative regarding the percentage of women

who may lack information about their health risks. We did not ascertain which patient had Becker and which had Duchenne in the survey; responses would clearly vary depending on the answers.

Consistent with one previous study evaluating heart screening in at-risk women, women with unknown carrier status are less likely to get heart screening [12]. Our study also evaluated adherence specifically to the 5-year window recommended by the American Academy of Pediatrics for heart screening, and found that nearly 10 years following these recommendations, even a sizeable portion of women who knew their carrier status (45%) had not had an echocardiogram in the last five years. Thus, not knowing ones carrier status is not the only barrier for at-risk women to receive cardiac screening. Interestingly, only a small percentage of at-risk women were unaware that carriers were at increased risk for heart problems (14%), and a difference in knowledge could not be detected between women who knew their carrier status and those who did not.

When asked whether or not they were at risk to have another affected child, women who knew their positive carrier status expressed significantly more certainty in stating that they were at risk to have another affected child. Although it may seem obvious that women with known carrier status are more certain about recurrence risk than women with unknown status, this is important because of the impact the risk has on reproductive choices. If women with known carrier status are more certain about this risk, then perhaps improving frequency of carrier testing could improve quality of life and reduce financial burden for at-risk families.

Additionally, our study reveals a genetic counseling need for women with negative carrier testing. Because our study evaluated the responses only for those women who were biologically capable of having more children, in theory, all respondents analyzed had a recurrence risk due to the fact that women with negative carrier status remain at increased risk due to germline mosaicism. Given that more women in the negative carrier status group were uncertain about their risk compared to women with positive carrier status, and that 12% of this group stated with certainty that they were *not* at risk to have another affected child, improving awareness of germline mosaicism may help this group better understand their risk and in turn impact their future reproductive choices.

Although this study included only mothers of affected sons, we were also interested in collecting data regarding transmission of information in families, as other family members may be at-risk to be carriers as well. Our study found that women with unknown carrier status are less likely to communicate information about carrier risk to their sisters, which was echoed by the sentiment that 42% of those with previous family history disagreed that they understood risk before their own affected pregnancy. Compared to mothers of sporadic cases of DBMD, this group is unique in that family information was available that could have alerted them to their risk, demonstrating that barriers to family communication are also important targets for improving healthcare in DBMD families.

Many factors can impact the decision to communicate: a recent paper identified familial implications, age and maturity, and the need for autonomy as important variables affecting

the decision to discuss and undergo carrier testing with at-risk females [13]. Our open-entry responses reveal that risk construction may play a role in why family risk information is not communicated. Two individuals indicated in open-entry responses that they did not communicate risk information to their sisters because their sisters did not have any affected boys; this reasoning fails to recognize that daughters can also inherit a DBMD mutation and in turn also be at risk to have an affected child. This reasoning also suggests that increased awareness of cardiac risk or screening guidelines may improve testing uptake, as also evidenced by respondents who personally indicated they had not had carrier testing because they had completed childbearing.

Carrier status impacts risk understanding and cardiac screening; therefore, it is important to understand why women who do not know their carrier status have not had testing. Cost was selected as the number one reason why women had not had carrier testing, but further research is needed to determine whether or not it is the actual cost, based on current lab offerings and insurance reimbursement rates, or rather the perception of a high cost of genetic testing that is deterring women. As evidenced by respondents who indicated that did not understand the benefit of knowing their carrier status, that they “did not know it was an option” or that they “would like to but don’t know how,” educational barriers also seem to play a role in preventing women from learning this critical piece of health information. Importantly, several respondents’ open text responses revealed that carrier testing has psychological impacts for at least some individuals, indicating an ongoing need for genetic counseling as a component of the carrier testing process.

5. CONCLUSION

A significant portion of at-risk DBMD carrier women do not know their carrier status; even among those who do, many have not had appropriate cardiac screening. Cost of testing and lack of appropriate genetic counseling were the most frequent barriers to testing cited. Women who knew their carrier status were more certain about their recurrence risk, more likely to share carrier risk information, and more likely to receive appropriate cardiac screening. Parent Project Muscular Dystrophy has formally launched a Carrier Initiative to focus on the needs of female carriers. Also, DuchenneConnect will continue to provide genetic counseling support for women who are carriers or at-risk to be carriers, and explore methods to improve access to carrier testing. This includes identifying ways to subsidize the cost of carrier testing. These efforts may ensure that more women can access all their healthcare options, as well as improve screening adherence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We surveyed 182 women with son(s) with Duchenne/Becker Muscular Dystrophy
- 39% didn't know or incorrectly classified their carrier risk status
- 37% of women at increased risk for cardiomyopathy had never had an echocardiogram
- Inadequate counseling and cost of testing are critical barriers for this population

Table 1

Respondent Demographics

		Percent of respondents
Respondent age n=177	18 – 24	0.00%
	25 – 34	16.38%
	35 – 44	42.37%
	45 – 54	33.90%
	55 – 64	6.21%
	65 or older	1.13%
Respondent ethnicity n=172	Hispanic/Latino	6.40%
	Non-Hispanic/Latino	93.60%
Respondent race n=175	American Indian/Alaska Native	0.57%
	Asian	4.00%
	Black or African American	1.71%
	Native Hawaiian or Other Pacific Islander	0.57%
	White or Caucasian	93.14%
Respondent highest education level n=145	Some high school	4.14%
	Graduated high school	13.79%
	Some college	19.31%
	Technical diploma	2.07%
	Bachelor's degree	37.24%
	Master's degree	20.00%
	Doctorate or other professional degree	3.45%

Table 2

Reasons why women with unknown carrier status have not had carrier testing

Are any of the following reasons why you have not had carrier testing? Select all that apply	% of respondents, n=44
I am concerned about the financial cost of carrier testing	54.5% (24)
I do not think knowing my carrier status will be beneficial to me	15.9% (7)
I plan to pursue carrier testing, but my test has not been ordered yet	13.6% (6)
I am not sure what the purpose of carrier testing is	6.8% (3)
I do not want to know my carrier status	2.3% (1)
I am waiting for the results of my carrier testing	2.3% (1)
Total question responses	44

Table 3

Reasons why women have not discussed carrier risk information with their full sisters

Please share why you have not discussed carrier information with your full sisters. Select all that apply.	Number of responses
I do not think they are at risk	3
I am worried the information will upset them	2
It makes me too upset to discuss it with them	1
I think they already understand their carrier risk	1
They told me they already understand their carrier risk	1
We are not close/do not speak	0
We haven't had time to talk about it	0
I am worried I will get the information wrong	0
They told me they didn't want to know the information	0
They have already had carrier testing	0
Total question responses	8

Note: limited to women whose full sisters are at risk to be carriers based on the respondents positive or unknown carrier status.