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ORIGINAL RESEARCH

Attitudes Toward Genetic Testing for Celiac Disease

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Abstract HLA molecular typing for celiac disease (CD) is a genetic test with a high negative predictive value. The aim of this study is to explore knowledge of and attitudes towards genetic testing (GT). A 25-item questionnaire was developed by a multidisciplinary team and distributed to members of CD support groups across the United States. Respondents (n=1835) were mainly female (88 %), married (76 %), and college-educated (55 %), with a median age range of 31–50 years. Those who were married (82 vs 75 %, p=0.002), had children (82 vs 74 %, p<0.001), and had pursued education beyond high school (81 vs 68 %, p=0.004) were more likely to be aware of the availability of GT. On multivariable analysis, adjusting for age, sex, education, marital status, region of residence, and having children, college-education (OR 2.05, 95 % CI: 1.33–3.16) and having children (OR 1.56, 95 % CI: 1.15–2.11) remained significant predictors of GT awareness. A majority of patients with a personal or family history of CD planned GT for their children, and the most common concerns regarding GT were cost and impact on health care and/or insurance. In conclusion, awareness of GT is high among CD support group members. Efforts should be made to increase knowledge of GT in those with a lower educational level, and healthcare professionals should attempt to address concerns regarding GT cost and the impact of results on health care and insurance status.

Keywords Celiac disease · Genetics · Genetic testing · Attitudes · Knowledge · Awareness · Education · HLA · Survey · Support groups

Introduction

Celiac disease (CD) is an autoimmune disorder that is triggered in genetically predisposed individuals by the ingestion of gluten—a protein derived from wheat, barley, and rye (Green 2003). CD is characterized by small bowel mucosal inflammation, villous atrophy, and crypt hyperplasia which results from exposure to dietary gluten and improves with the removal of gluten from the diet (Kagnoff 2006). Although it was originally thought to be a rare malabsorption syndrome of childhood, CD is now known as a condition that can affect multiple organ systems and can be diagnosed at any age (Green 2007).

Screening studies estimate that CD affects approximately 1–2 % of the population in Europe and North America (Catassi 2010, Lohi 2007, Mäki 2003, Rubio-Tapia 2009). Although the prevalence of CD has been increasing over the last 50 years—nearly fourfold in the United States (US)—population based studies suggest that only a small proportion of CD cases are clinically recognized (Mustalahti 2010, Rubio-Tapia 2009). The difficulty in accurately detecting CD arises from its heterogenous clinical picture, with symptoms ranging from "classic" gastrointestinal malabsorption (with diarrhea at the time of diagnosis seen in only 50 % of patients) to only atypical presentations (Barker 2008).

Based on the current guidelines by the American College of Gastroenterology (ACG), the initial diagnostic work up for

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CD involves serologic testing for antibodies to anti-tissue transglutaminase (TTG) and deamidated gliadin peptides (DGPs). The confirmation of the diagnosis relies on small bowel biopsy and histological analysis for evidence of intestinal damage (Rubio-Tapia 2013).

Although CD has a known genetic predisposition—with the Human Leukocyte Antigen (HLA) DQ2 or DQ8 present in almost all patients—genetic testing is not recommended to be routinely used in the initial diagnosis of CD. Genetic testing has a very low positive predictive value given that HLA DQ2/DQ8 is present in 25–40 % of the US population. However, since HLA-DQ2/DQ8 genotyping has a negative predictive value>99 %, current guidelines by the ACG state that genetic testing (GT) for CD is useful for the exclusion of disease in selected clinical situations: equivocal small bowel biopsy in patients with negative serologies; patients adhering to a gluten free diet (GFD) without previous serologic testing; patients with discrepant CD serology and histology; patients with an unclear initial diagnosis who may have developed refractory CD; and high risk populations such as patients with Down's syndrome (Rubio-Tapia 2013).

Despite not being a current choice for initial testing, GT for CD has been proposed as a possible first-level test if population screening were to be implemented. The rising prevalence of CD combined with the current rates of under-diagnosis have resulted in an ongoing debate about the possible advantages of mass screening. After a recent study demonstrated that apparently asymptomatic patients with CD benefit histologically, serologically, and symptomatically from serologic screening and subsequent GFD, there has been increased support for active screening of persons at risk of CD (Kurppa 2014). In fact, an updated strategy for population screening has been proposed using GT as a first-line test—as it will exclude a large proportion of the population from further testing (Catassi 2014).

Whether GT is used for large scale population screening or in the selected clinical scenarios currently recommended, it is very important for health care providers to gauge patients' awareness of and attitudes towards GT so that appropriate pre-test counseling can be offered. With the rapid advances that have been made in the field of genetics over the last decades, several studies have been undertaken to assess patients' knowledge, attitudes, and expectations of GT in a variety of medical fields, including oncology, renal disease, and Parkinson's disease (Blanchette 2014, Freedman 2013, Gupte 2015). To our knowledge, patient views on GT for CD have not been previously investigated. The objective of the current study was to explore knowledge of and attitudes towards genetic testing by creating and distributing a survey to members of CD support groups in the US.

Methods

Participants

A self-administered questionnaire (detailed below) was distributed electronically to patients with CD cared for at the Celiac Disease Center at Columbia University (Department of Medicine at Columbia University Medical Center; New York, NY). Paper and electronic versions of the survey were subsequently distributed to CD support groups in Westchester, NY, and Long Island, NY. Lastly, leaders of national support groups were used to distribute the link to the online survey to CD support and advocacy group members across the US.

Instrumentation

A survey to evaluate patients' knowledge, attitudes, and expectations of GT was created based on review of relevant literature and clinical experience from patient discussions regarding GT. A series of meetings by a multidisciplinary team including three physicians and a genetic counselor at the Celiac Disease Center at Columbia University as well as a privately-employed clinical molecular geneticist were conducted to refine the questionnaire. No questions from previously validated questionnaires were used.

The final questionnaire contained 25 items and was composed of five sections: demographics (7 items); information regarding CD diagnosis (7 items); family history (3 items); knowledge regarding GT (3 items); and attitudes and expectations regarding GT (5 items). The final questionnaire was printed for distribution at medical offices of the Celiac Disease Center and support group meetings, and an online version was created using the *SurveyMonkey*® program (Survey Monkey, Inc., USA) for electronic distribution to support groups. The study design and final questionnaire were approved by the Columbia University Institutional Review Board.

Data Analysis

Survey responses were collected in a secure, de-identified database for a 5 month period: April 2011 through August 2011. Consent was implied by completion and submission of the questionnaire to protect the anonymity of the participants. Responses from patients under the age of 18 years and those not answering all demographic items were excluded from the analysis.

Univariate analysis (chi-square tests and Fisher's exact tests, as appropriate) was used to assess demographics. Multivariate logistic regression models were constructed to test the association between demographic factors (sex, age, education, marital status, region of residence, and children) and awareness of GT. Analyses were performed for all respondents as well as for those reporting a biopsy-proven diagnosis of CD. Descriptive statistics were used to summarize patient

attitudes towards GT. Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

Patient Characteristics

In total, 2022 survey responses were collected from April 2011 through August 2011. Of these, 1835 (91 %) responses met the inclusion criteria: complete demographic data with respondent age>18 years. Ninety-seven percent of responses were completed online.

Overall patient characteristics are reported in Table 1. The study population consisted of 88 % females (n=1620), with a median age range of 31–50 years (n=805). There were respondents from each of the 50 states in the US, and the most common region of residence was the Northeast (48 %, n=858). Ninety-three percent of respondents (n=1717) had at least college-level education, with 38 % (n=705) reporting a graduate or professional degree. Seventy-six percent (n=1403) of patients were married at the time of survey completion, and 73 % (n=1340) had at least one child.

Sixty-seven percent (n=1238) of respondents reported a diagnosis of CD. Only 76 % (n=939) of these patients reported having undergone small bowel biopsy as part of their CD diagnosis. Similar to the overall population, these patients were predominantly female (85 %), college-educated (92 %), married (72 %) with children (67 %), with a median age range of 51–70 years (44 %). Thirty-five percent of respondents with biopsy proven CD reported having at least one family member with CD.

Table 1 Overall study population characteristics (n=1835)

Patient characteristic	No. of patients (%)
Sex	
Male	215 (12)
Female	1620 (88)
Age	
18–30	173 (9)
31–50	805 (44)
51–70	735 (40)
71+	122 (7)
Education	
High school graduate and below	118 (6)
Some or complete college	1012 (55)
Graduate or professional degree	705 (38)
Marital status	
Married	1403 (76)
Not married	432 (24)
Region residence	
Northeast	858 (48)
Midwest	209 (12)
South	487 (27)
West	226 (13)
Having children	1340 (73)
Self-reported diagnosis of celiac disease	1238 (67)

Patients' Awareness of Genetic Testing

Seventy-nine percent of the respondents (n=1442) reported being aware of the availability of GT for CD. Respondents who were married (82 vs 75 %, p=0.002), had children (82 vs 74 %, p<0.001), and had pursued education beyond high school (81 vs 68 %, p=0.004) were more likely to be aware of the availability of GT (Table 2). On multivariable analysis (Table 3), college-education (OR 2.05, 95 % CI: 1.33–3.16) and having children (OR 1.56, 95 % CI: 1.15–2.11) remained significant predictors of GT awareness after adjusting for age, sex, marital status, and region of residence (Nagelkerke's R^2=0.03).

Of patients with reported biopsy-proven CD, 78 % (n=730) were aware of CD genetic testing. Respondents who were older than 30 years (79–83 vs 67 %, p=0.028),

Table 2 Impact of demographics on awareness of genetic testing availability (n=1804)

Patient characteristic	No. of patients aware of genetic testing (%)	Significance (chi-square, p-value)
Sex		0.223
Male	162/211 (77)	
Female	1280/1593 (80)	
Age		0.079
18–30	125/172 (80)	
31–50	648/796 (81)	
51–70	577/720 (80)	
71+	92/116 (79)	
Education		0.004
High school graduate and below	78/115 (68)	
Some or complete college	805/997 (81)	
Graduate or professional degree	559/692 (81)	
Marital status		0.002
Married	1122/1375 (82)	
Not married	320/429 (75)	
Region of residence		0.977
Northeast	676/846 (80)	
Midwest	160/203 (79)	
South	381/476 (80)	
West	178/225 (79)	
Children		<0.0001
Yes	1080/1312 (82)	
No	362/492 (74)	

Table 3 Multivariate analysis: predictors of genetic test awareness among overall population

Variable	OR	95 % Cl	*P*-value
Sex			
Male	1		
Female	1.19	0.84–1.69	0.33
Age			
18–30	1		
31–50	1.01	0.65–1.56	0.97
51–70	1	0.64–1.56	0.99
71+	0.99	0.54–1.85	0.99
Education			
High school graduate and below	1		
Some or complete college	2.05	1.33–3.16	0.001
Graduate or professional degree	2.04	1.31–3.2	0.001
Marital status			
Not married	1		
Married	1.2	0.88–1.63	0.25
Region of residence			
Northeast	1		
Midwest	0.92	0.63–1.35	0.67
South	0.98	0.74–1.30	0.88
West	0.98	0.68–1.42	0.91
Children			
No	1		
Yes	1.56	1.15–2.11	0.005

married (81 vs 73 %, p=0.006), had children (82 vs 71 %, p<0.001), and had family members (84 vs 75 %, p= 0.002) and particularly children with CD (85 vs 77 %, p=0.014) were more likely to be aware of the availability of GT. On multivariable analysis, college education (OR 1.82, 95 % CI: 1.03–3.24) and having children (OR 1.81, 95 % CI: 1.19–2.73) remained significant predictors of GT awareness after adjusting for age, sex, marital status, and region of residence (Nagelkerke's R^2=0.04).

Knowledge of Genetic Testing and Previous or Planned Utilization of Genetic Testing

Of the 1442 respondents who were aware of GT, 46 % (n= 663) had been informed by a healthcare professional and 42 % (n=605) learned of the testing through media sources (television, internet, newspapers, or magazines). Nineteen percent (n=178) of biopsy-proven CD patients had undergone GT, and 55 % (n=516) planned to have their children tested. Similarly, among respondents having relatives with CD (n= 356, of whom 339 had first-degree relatives with CD), 83 % reported wanting to know if they were at risk of developing CD, 64 % considered GT, and 34 % underwent GT.

Attitudes Toward Genetic Testing: Perceived Advantages

The most common reasons selected by respondents for wanting to pursue GT were: to learn about children's risk of CD (94 % of respondents agreeing), to determine personal risk of CD (92 %), and to further research (91 %). Less common reasons for wanting genetic testing included pursuing a gluten free diet (72 %) or periodic blood testing (76 %) if test results were positive. When asked about the potential benefits of GT, nearly all respondents agreed that either positive or negative test results would be beneficial for their personal and children's health. Figures 1 and 2 show the full responses.

Attitudes Toward Genetic Testing: Perceived Disadvantages

Among respondents aware of but not having undergone GT, the most common concerns regarding GT were cost (64 % of respondents) and impact on health care and/or insurance (46 %). A majority of respondents did not agree with the statements that genetic testing would cause strained family relations (88 %), personal anxiety about developing CD (79 %), stress about dietary restrictions (70 %), and guilt about

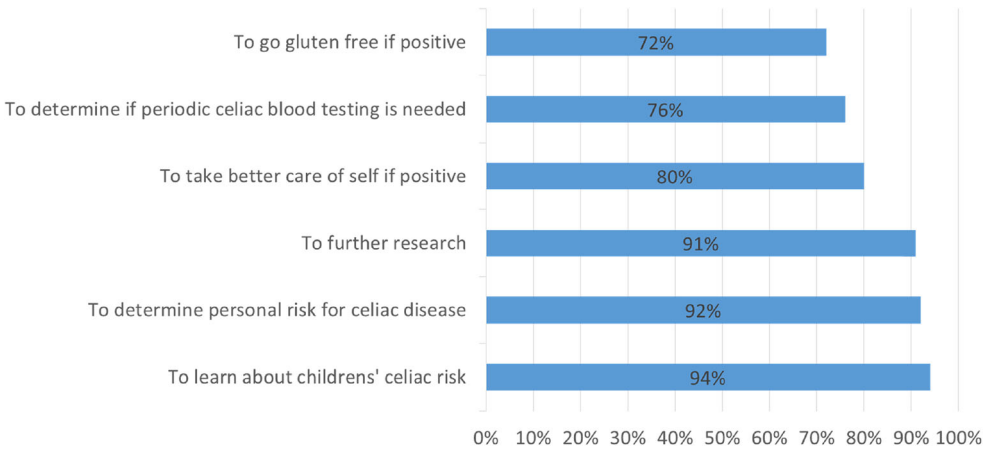

Fig. 1 Reasons for wanting genetic testing: all respondents (n=1835)

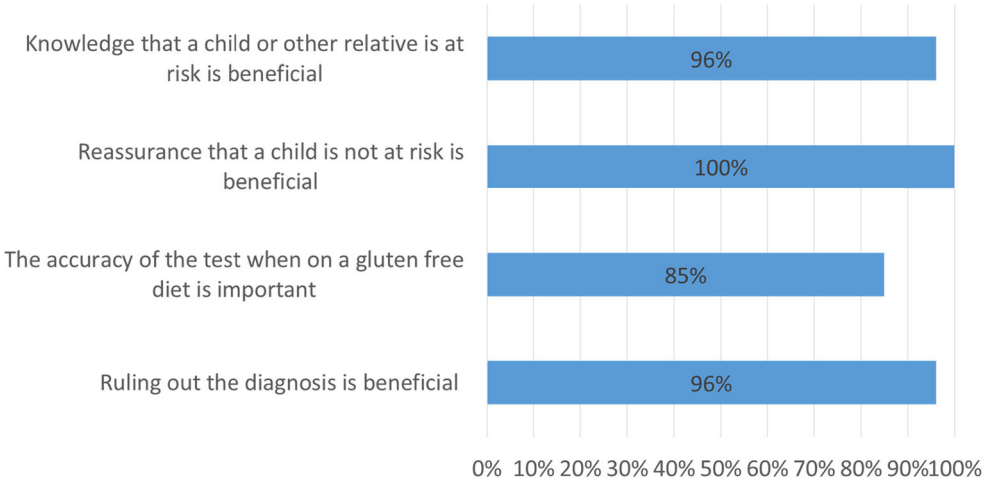

Fig. 2 Attitudes towards potential benefits of genetic testing: all respondents (n=1835)

passing along predisposing genes to offspring (67 %). Fig. 3 shows the full responses.

Attitudes Toward Genetic Testing: Implications of Results

With regards to the ultimate utility of test results, 83 % of respondents felt that GT results would allow them to make better informed decisions about their own medical care, and 72 % stated that they would inform family members of test results. A minority of respondents stated that their employer (19 %) or insurance company (38 %) could have access to test results. Figure 4 shows the full responses.

Discussion

Practice Implications

To our knowledge, this is the first study investigating patients' direct knowledge of and attitudes towards GT for CD. Our study shows that in a population of motivated, information-seeking, and well-educated CD support group members and those attending the Celiac Disease Center—both with and without biopsy proven CD—a large proportion (>75 %) are aware of the availability of GT for CD. This was the case for the general study population as well as the respondents for whom GT is currently recommended—individuals with first-degree relatives with CD. However, knowledge of GT was more prevalent for groups with higher educational status (at least college-level). This falls in line with previous studies that have shown that groups with reduced educational levels report that a lack of general knowledge about CD is a significant barrier to appropriate diagnosis and treatment (Barbero 2014). The results of this study suggest that efforts should be made on the part of health care providers to increase awareness of GT in those with a lower level of education.

Similar to educational level, our findings show that having children is associated with awareness of GT. This in itself is not surprising, especially considering that nearly all of the survey respondents (94 %) reported that one of the most important reasons for pursuing genetic testing was to learn about children's risk for CD. Taken one step further, however, more than half of respondents with biopsy proven CD planned to have their children undergo GT for CD. This is a significant observation that should be noted by gastroenterologists and pediatricians. Current pediatric guidelines support CD screening in children having first degree relatives with CD (Husby 2012). Our study suggests that a large proportion of parents

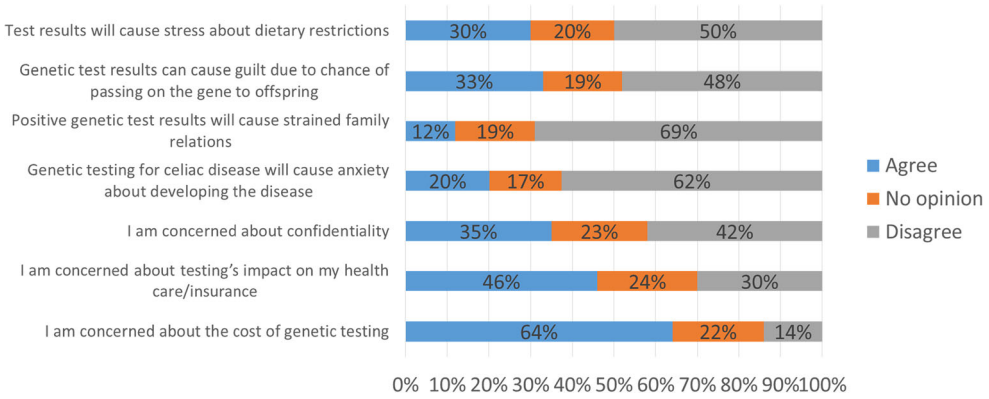

Fig. 3 Concerns: respondents aware of genetic testing but not tested (n=998)

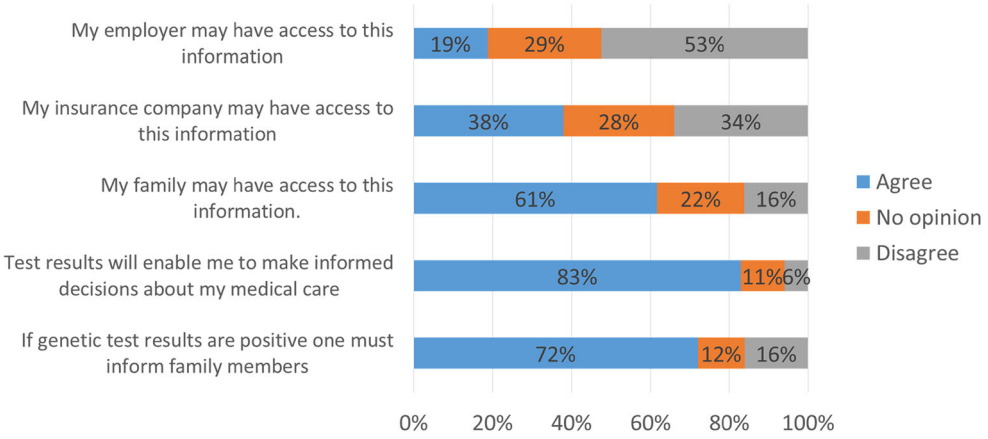

Fig. 4 Utilizing genetic testing results: all respondents (n=1835)

with CD are in favor of such screening using GT, and this test should certainly be discussed and offered in an attempt to increase current diagnosis rates of CD—especially diagnosis at a young age when many of the long-term morbidities and mortality from untreated CD can be effectively reduced with the implementation of a GFD. In addition, GT can exclude the diagnosis of CD in these high risk groups if results are negative, and the gene dosage information gained from positive results can help determine the risk of disease development in children with a family history of CD—a concept which has been proven in several recent studies (Lionetti 2014; Liu 2014; Vriezinga 2014).

Although most of the respondents in our study were aware of GT, an interesting finding was that about half of those surveyed reported being informed by a health care professional. In fact, nearly equal numbers reported receiving GT information from media sources as from health care providers. Part of this finding can likely be explained by the fact that our study population—predominantly members of CD support groups—are much more likely than the general public to be exposed to CD-related media. However, our findings do seem to suggest that steps can be taken by health care providers to increase the general level of knowledge and understanding about CD genetics and GT. Multiple studies in the realm of oncology have shown that improved patient education and counseling from health care professionals regarding GT can increase knowledge, decrease anxiety, and improve clinical decision making (Lerman 1997; Lobb 2004; Mancini 2006; Printz 2012; Sivell 2007). However, physicians need to be aware of the value and limitations of GT in CD. While CD is underdiagnosed especially in the US (Rubio-Tapia 2012), studies have shown that the rate of CD diagnosis increases after specific physician education (Collin 2007).

Of respondents having relatives with CD, a majority reported wanting to know if they were at risk of developing CD (83 %) and had considered GT (64 %). While mass screening for CD is not recommended, targeting at risk groups for diagnosis is recommended (Husby 2012). The frequency of CD is significantly increased in patients who have a first degree relative affected with CD—up to 20 % in siblings and 10 % in other first degree family members (Rubio-Tapia 2008). Our study suggests that relatives of patients with CD may often be amenable to GT to determine their personal or children's risk of CD. This testing certainly has benefits, and health care givers should consider offering it after careful discussion with the patient.

When looking at perceived benefits of GT, nearly all respondents agreed that either positive or negative test results would be beneficial for their personal and children's health (96–100 %). A majority of patients, in fact, reported that they would take better care of themselves in light of a positive GT. Further, nearly 75 % of respondents stated that they would inform family members of test results. These findings are consistent with what has been reported in other fields with regards to sharing results of GT with relatives. A recent study evaluating perceptions of GT in populations at risk for nephropathy reported that 89–92 % of patients would be likely to inform their family members of positive test results (Freedman 2013). Prior to ordering GT, health care providers should ensure that patients will understand the results and make wise health decisions as a consequence of testing. Our findings offer reassurance that many patients are motivated to make appropriate changes in response to positive GT, and this is in line with a recent study showing that people in the general population respond to hypothetical genetic risk information by wanting to take action—particularly related to self and family health (Almeling 2014).

While by far the majority of responses to our survey demonstrate knowledge of the value and significance of GT in CD, one very alarming fact was that 72 % of patients claimed they would adopt a gluten-free diet if the genetic test was positive—a therapeutic strategy that is not appropriate in the context of isolated GT results (without considering serologies or small bowel histology). Given that HLA DQ2/DQ8 positivity is not diagnostic of CD and the true utility of GT lies in its negative predictive value, patients must understand that

dietary modifications are not warranted by positive test results. Interestingly, there was no difference in response between those who learned of testing from health care professionals compared to those who learned from media sources. This yet again emphasizes the importance of well-educated providers offering patients relevant and accurate information regarding the interpretation of and appropriate response to GT results. As shown in a recent systematic review evaluating the role of genetic counselling in a variety of medical subspecialties (Skirton 2015), the expertise of genetic counselors is valuable in the education of both patients and healthcare providers. Working in conjunction with other team members of celiac disease centers and patient support groups, genetic counselors can be of great benefit in the genetic evaluation of CD.

The most important factors that might discourage GT were cost and impact on health care and health insurance. Accordingly, very few respondents agreed with allowing their employer or insurer to have access to GT results. Perhaps these factors account for the fact that despite clear interest in GT, only a minority of respondents with biopsy-proven CD or with CD-affected family members had actually undergone GT. Several studies assessing patient attitudes towards GT in a variety of medical specialties have identified the potential for insurance discrimination as a major barrier influencing the decision to pursue GT (Blanchette 2014; Freedman 2013; Gupte 2015). This seems to hold true in CD as well. Our study suggests that health care professionals should make a specific effort to address this particular concern—especially given that current legislation in the US (the Genetic Information Nondiscrimination Act) prevents employers and insurance companies from discriminating based on GT (Hudson 2008; Offit 2007). Similarly, physicians and genetic counselors should educate patients about the true costs of GT based on their particular insurance plans and personal circumstances—another valuable piece of information that may help assuage patient concerns so that well-informed GT decisions can be made.

Study Limitations

Several limitations of this study are worth noting. First, the study population was predominantly members of CD support and advocacy groups across the US. Although respondents resided in each of the 50 states, they shared several key demographics—with a majority being female, middle-age, college educated, and married with children. Although some of these characteristics are typical of CD, the extent of heterogeneity in our study population likely reflects the membership demographics of CD support group members, limiting the generalizability to the wider public. For example, although several studies have found the diagnosis of CD in the US to be more common among college-educated individuals (Riddle 2012; Shah 2014), the rate of college-education in our respondents (93 %) was even higher than in previous study populations. Furthermore, support group membership offered additional resources to our respondents which influenced their knowledge of and attitudes towards GT—information that is often not as readily available to the general population. There was likely an overestimation of the true awareness of GT in our study, and its results may not be generalizable to the population as a whole. Second, we acknowledge the selection bias that exists when collecting limited numbers of responses to a very widely distributed survey, and the inherent difficulties with interpreting survey data in the field of CD. Given that our survey was broadly distributed to support groups across the US, it was not possible to determine the exact number of individuals who received the survey. An exact response rate, therefore, could not be determined. Using our survey alone, it was impossible to specifically characterize each self-reported CD patient with regards to the exact type of practice setting in which they were diagnosed and ultimately managed—factors that would certainly impact their knowledge of GT. Further, there were no means by which to verify the diagnosis of CD. Similarly, we did not have specific family information about self-reported relatives of patients with CD. These were the two groups (CD-patients and family) to whom GT would be most pertinent. There was also a very small group of respondents who neither had CD themselves nor in their family (6 % of the study population), and the information provided by these individuals is very difficult to interpret. These patients were not excluded, however, given that the purpose of our study was to determine general awareness regarding GT for CD. Third, although our multivariable regression models identified several key factors predictive of GT awareness, the statistical measures of how close the data were to the fitted regression were relatively low: Nagelkerke's R^2=0.03–0.04. While we acknowledge that higher R^2 values generally indicate a better fit of the model and data, the goal of our analysis was simply to determine which predictors were statistically significant—not to produce precise predictions. Thus, the R^2 should not affect how relationships are interpreted. Further, in studies such as ours which evaluate human behavior, low R^2 values are expected. Fourth, although our study aimed to assess patients' awareness of GT, our survey did not evaluate whether patients have accurate knowledge regarding GT methods, results, reporting, and clinical implications. Some responses to our survey suggest that there may be common misconceptions about CD GT—including the high percentage of patients who reported that a reason for pursing GT was to follow a GFD if results are positive. Oncologic studies have been conducted to specifically assess patient knowledge of cancer genomics (Blanchette 2014), and similar studies should be pursued in CD as they may offer valuable information to help guide patient education efforts.

Overall, our study demonstrates that awareness of GT is high among CD support group members. However, efforts

should be made to increase knowledge of GT in those with a lower educational level. Since a majority with a personal or family history of CD plan for GT themselves or for their children, healthcare professionals should attempt to address concerns regarding GT cost and the impact of results on health care and insurance status. Education of health care personnel about GT in CD may be the best way to educate the patients.

Compliance with Ethical Standards

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

Human studies and Informed Consent This study was approved by the Columbia University Institutional Review Board. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

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