

The Iceberg and the Helix: Investigating the role of genetic testing and genetic counselors in the  
diagnosis and management of Celiac Disease

Master's Thesis

Presented to

The Faculty of the Graduate School of Arts and Sciences  
Brandeis University  
Department of Life Sciences  
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by  
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## **ABSTRACT**

The Iceberg and the Helix: Investigating the role of genetic testing and genetic counselors  
in the diagnosis and management of Celiac Disease

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Graduate School of Arts and Sciences  
Brandeis University  
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By Victoria E. Duke

Celiac Disease is an autoimmune disorder characterized by an aberrant immune response to the ingestion of gluten, found in wheat, barley, and rye, that causes various intestinal and extra-intestinal symptoms. One in 133 Americans is affected with CD; however, only one in seven affected individuals is diagnosed - an issue termed “The Celiac Iceberg”. CD predisposition is associated with the presence of Human Leukocyte Antigen (HLA) alleles DQ2 and/or DQ 8 and genetic testing can rule out CD in individuals with neither CD-associated allele. Genetic counseling is recommended for individuals electing genetic testing for CD, yet consensus is lacking regarding which health care professionals should provide these genetic services.

The purpose of this study was to assess genetic counselors’ knowledge of and experience with CD and to ascertain genetic counselors’ current practices regarding

genetic testing and counseling for patients with CD. This was accomplished using an anonymous online survey of 155 genetic counselors recruited through the NSGC listserv. Approximately 65% of respondents had seen a patient with CD in the past year, however fewer than 6% had seen patients with a primary indication of CD frequently. A majority (84%) correctly identified the multifactorial mode of inheritance of CD. Respondents with the most experience with CD were more likely to complete seven counseling aims integral to genetic counseling; four of these were related to patients' family members.

Our respondents were most knowledgeable about the multifactorial mode of inheritance of CD and encountered CD most frequently as a secondary indication or incidental finding. There was a consensus on a working "standard of care" on counseling for CD among those respondents most experienced with CD that included counseling aims related to patients' family members. Given their scope of practice, we propose genetic counselors have potential to shrink the Celiac Iceberg.

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## INTRODUCTION

Celiac Disease (CD) is an autoimmune disorder characterized by an aberrant immune response to the ingestion of gluten, a protein found in wheat, barley, and rye (Schuppan, Junker, & Barisani, 2009). For individuals with CD, ingestion of gluten causes a variety of intestinal and extra-intestinal symptoms (Tack, et al., 2010). The clinical spectrum of CD is broad and includes four subtypes – typical, atypical, latent, and silent – based on clinical definitions (Catassi, Fornaroli, & Fasano, 2002). Table 1 below highlights typical and atypical signs and symptoms of CD. For individuals with any subtype of CD, prolonged exposure to gluten over a lifetime can cause complications, including changes in fertility (Freeman, 2010) and development of non-Hodgkin lymphoma (Smedby et al., 2005).

Table 1. Clinical presentation of CD (adapted from (Tack, et al., 2010)).

<b>Typical signs and symptoms</b>	<b>Atypical signs and symptoms</b>	
Abdominal distension	Alopecia areata	Esophageal reflux
Abdominal pain	Anemia (iron deficiency)	Hepatic steatosis
Anorexia	Aphthous stomatitis	Infertility, recurrent miscarriage
Bulky, sticky and pale stools	Arthritis	Isolated hypertransaminasemia
Diarrhea	Behavioral changes	Late-onset puberty
Flatulence	Cerebellar ataxia	Myelopathy
Failure to thrive	Chronic fatigue	Obesity
Muscle wasting	Constipation	Osteoporosis/osteopenia
Steatorrhea	Dental enamel hypoplasia	Peripheral neuropathy
Vomiting	Dermatitis herpetiformis	Recurrent abdominal pain
Weight loss	Epilepsy	Short stature

CD is inherited in a multifactorial manner, as both genetic and environmental components influence its development. Hereditary predisposition to CD is associated

with the presence of Human Leukocyte Antigen (HLA) alleles DQ2 and/or DQ8. Approximately 30-35% of individuals in the general population in the United States have either the DQ2 or DQ8 allele, while only 2-5% of gene carriers go on to develop CD. Virtually all individuals affected with CD have one of these two CD-associated alleles (Schuppan, et al., 2009). Genetic testing for DQ2 and DQ8, which is also called HLA-typing, can determine the presence or absence of these alleles.

Current clinical practice utilizes a combination of assessment of symptoms, serologic testing, intestinal biopsy, and clinical follow-up to make a diagnosis of CD. It is important that diagnostic workup be undertaken before initiation of a gluten-free diet because positive serologic results and abnormal intestinal biopsy depend upon the presence of gluten in the diet. Genetic testing to determine if both HLA-DQ2 and HLA-DQ8 are absent is considered clinically useful for excluding CD in symptomatic individuals and at-risk relatives of individuals diagnosed with CD according to the American Gastroenterology Association (AGA) Institute Medical Positions Statement (Kagnoff, 2006).

Historically, the reported prevalence of CD has ranged from one in 300 to one in 10,000 and varied considerably with the population studied (Wong et al., 2003). However, recent investigation of the prevalence of CD in an American population found a prevalence of one in 133 (Fasano et al., 2003). Investigation of the prevalence of known and undiagnosed CD in Italian school children showed that the ratio of known to undiagnosed cases of CD was 1:7 (Catassi et al., 1996). This has been coined “The Celiac Iceberg”, a term that captures the discrepancy between the number of individuals diagnosed with CD and those affected who remain undiagnosed. The visible tip of the

iceberg represents the small number of diagnosed cases, while the large mass of ice beneath the surface represents the large number of undiagnosed cases. The large proportion of individuals who have CD but remain undiagnosed highlights the need for improved methods of ascertainment of individuals affected with CD.

The role of genetic testing for CD in the context of a CD diagnosis has been addressed in previous literature. Genetic testing for CD has been described as beneficial in the contexts of: (1) certain clinical parameters, such as a patient's reluctance to undergo an intestinal biopsy after positive serologic testing (Wong, et al., 2003), (2) stratifying the risk for an individual to develop CD (Wong, et al., 2003), and (3) screening at-risk relatives as a cost effective method to decrease the need for invasive endoscopic procedures performed by gastroenterologists (Chang & Green, 2009). A new diagnostic approach has been proposed that includes the presence of CD-associated alleles as one of five diagnostic criteria (Catassi & Fasano, 2010). Practice guidelines do not yet reflect this usage of genetic testing for CD, as the AGA Medical Positions Statement states that genetic testing for CD is useful when the diagnosis based on other tests is not clear and genetic testing for CD may be used to exclude a diagnosis of CD (Kagnoff, 2006).

The AGA Positions Statement stipulates that “when using HLA testing in the context of disease susceptibility in families, one must have the resources available to provide genetic counseling,”(Kagnoff, 2006, p. 1979). The issue of which health care professional(s) should provide genetic services for CD is not addressed in this document or any peer-reviewed literature. A pamphlet created by the University of Chicago Celiac Disease Center identifies the gastroenterologist as the provider who will order genetic

testing for CD ("Genetic Screening for Celiac Disease," 2011) but we could identify no references that directly pointed to a role for genetic counselors.

Genetic counselors have a potentially important role to play in providing genetic services to individuals with CD and their families. Genetic counselors have specific training and skills in risk assessment, risk communication within families, interpretation of complex genetic testing results, and psychosocial assessment and support in the care of individuals with genetic conditions and their family members (A Guide to Genetic Counseling, 2009). We hypothesize that thorough risk assessments in families affected by CD could help to identify more individuals who should receive clinical evaluations for CD. Such assessment may include elicitation of a complete family history with a focus on symptoms and complications of untreated CD in all family members, discussion of recurrence risk estimate, and facilitation of risk communication within families. This would increase the proportion of diagnosed individuals; thus, shrinking the submerged portion of the Celiac Iceberg. The public health value to increasing the diagnosis is substantial given the high risk for serious complications associated with untreated CD.

Treatment with a gluten-free diet is noted to be a "substantial social burden" (Tack, et al., 2010, p. 209), so psychosocial assessment and support, especially regarding adjustment and adherence to the gluten-free diet, may serve to improve treatment compliance by giving individuals with CD a counseling setting in which they can share their thoughts, feelings, and potential frustrations. Again, genetic counselors have the appropriate background to address these issues and make appropriate referrals.

Because genetic counselors have the skills and background necessary to help shrink the Celiac Iceberg by increasing the proportion of diagnosed individuals and

potentially improving treatment compliance, incorporating genetic counselors in the context of the diagnosis and management of individuals with CD is likely to be beneficial. Therefore, it is important to add to the literature regarding genetic counselor involvement in counseling for CD. The present study used an anonymous online survey to gain insight into genetic counselors' role in this area. The two specific aims for the study were to: (1) assess genetic counselors' knowledge of and experience with CD and (2) ascertain genetic counselors' current practices of genetic testing and genetic counseling for patients with CD.

## METHODS

### *Study design*

In order to learn about the role genetic counselors play in counseling patients with CD, we designed an anonymous online survey instrument (Appendix B). Topics addressed in the survey were: participant knowledge of the genetics of CD, opinion regarding the clinical utility of genetic testing for CD and experience offering genetic testing for CD. Genetic counselor practice surrounding genetic testing and counseling of patients with CD was assessed based on ten counseling aims for patients with CD (Appendix B) that we adapted from the genetic counseling literature (*A Guide to Genetic Counseling*, 2009). The counseling aims included actions related to patient care (including providing relevant resources and referrals and counseling about psychosocial issues related to a new diagnosis and/or adoption of a gluten free diet) as well as actions involving patients' extended family (such as, gathering a family history, completing a risk assessment, identifying at-risk relatives, facilitating discussion with at-risk relatives, and providing relevant resources and referrals for at-risk relatives). Participants rated how often they completed each counseling aim on a 5 point Likert scale (1= "Never", 2= "Rarely", 3= "Sometimes", 4= "Often", 5= "Always"). Questions were not forced choice. Some questions gave respondents an opportunity to select more than one answer. We provided participants with an opportunity to comment with open-ended questions as well.

This study received exempt status from the Brandeis University Institutional Review Board (IRB Protocol #12084).

### *Sample and recruitment*

An electronic recruitment notice (Appendix A) was distributed through the National Society of Genetic Counselors (NSGC) E-Blast Announcement. This sent the notice in an email to all NSGC members. All non-student NSGC members were eligible to participate.

### *Data collection*

The survey was designed using the online survey host “Qualtrics.” The initial E-blast announcing the availability of the survey was sent on February 13, 2012 followed by a second reminder announcement ten days later. The survey was open for one month in early 2012.

### *Data analysis*

SPSS (Statistic Package for the Social Sciences) software version 19 was used for statistical analysis. Not all questions were forced response, so not every participant responded to every question. For data analyses that depended on participants’ responses to multiple questions, we included only answers from respondents who had answered all pertinent questions. Open-ended questions were analyzed qualitatively using a thematic approach.



## RESULTS

### *Demographics*

One hundred fifty-five genetic counselors completed the survey. The majority of participants were female (96%). Reported years of experience ranged from 0.5 to 37 years.

Eighty-eight percent (136/154) of survey participants were seeing patients at the time of the survey. Of the 147 respondents who reported the nature of their patient population, 65% (96/147) reported primarily seeing adult patients, while 20% (30/147) and 14% (21/147), respectively, reported seeing primarily pediatric patients and equal numbers of adult and pediatric patients. Respondents' reported primary specialty areas were spread across prenatal (26%; 40/153), pediatric (16%; 25/153), cancer (33%; 51/153), and other specialties (24%; 37/153).

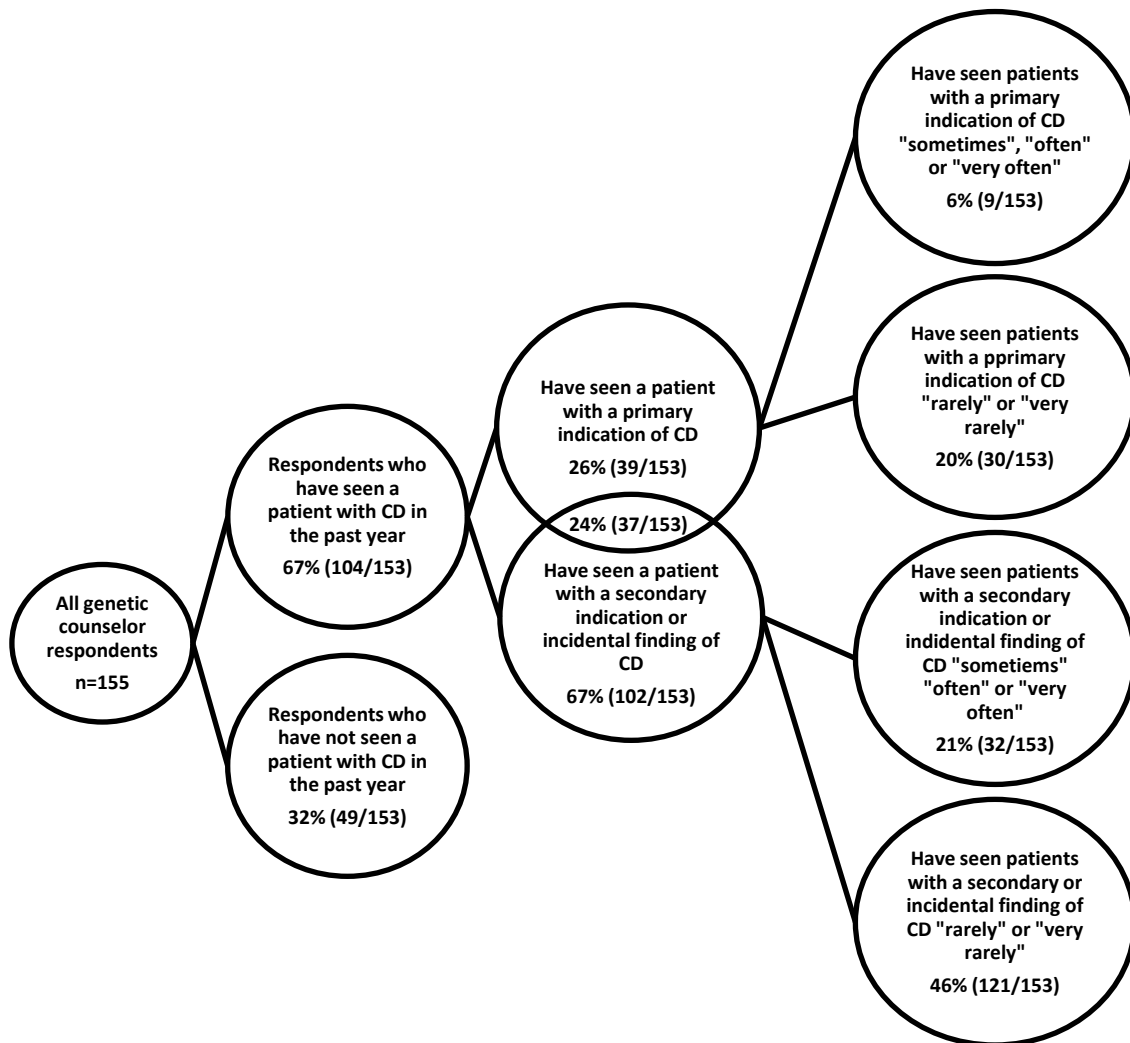
### *Experience with CD*

Respondents were asked how often in the past year they have seen patients with a primary indication of CD or patients with a secondary indication or incidental finding of CD (Figure 1). A majority, 67% (104/153), of respondents had seen a patient with CD (either as a primary or secondary indication or incidental finding) in the past year. A smaller number, 32% (49/153), had "never" seen a patient with a primary or secondary indication or an incidental finding of CD in the past year.

A minority of genetic counselor respondents, 26% (39/153), had seen a patient with a primary indication of CD in the past year and an even smaller percent, 6% (9/153),

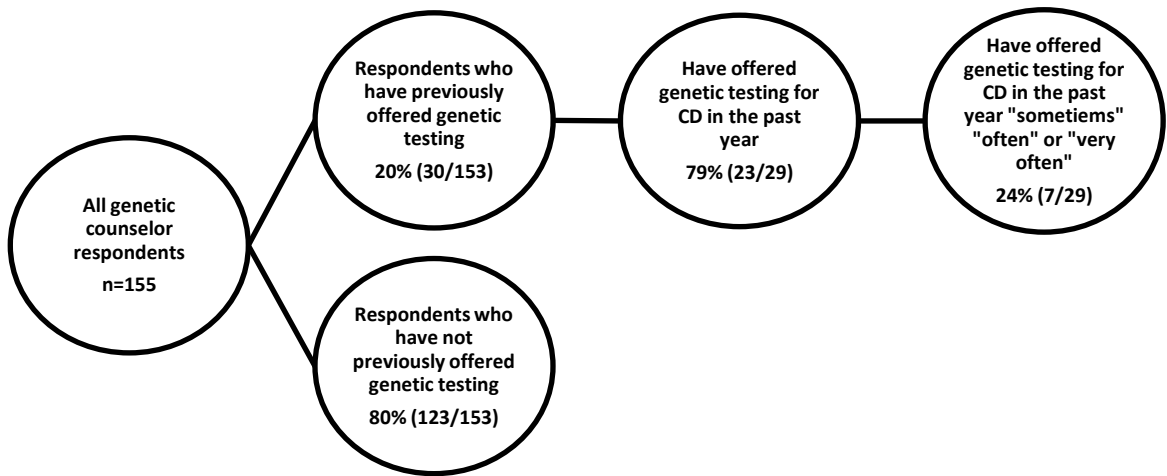
reported doing so “sometimes” “often” or “very often”. Two in three respondents, 67% (102/153), saw a patient with a secondary indication or incidental finding of CD in the past year and 21% (32/153), reported doing so “sometimes” “often” or “very often” in the past year. We can deduce that a majority of individuals who had seen a patient with a primary indication of CD (95%, 37/39) also had seen patients with a secondary indication or incidental finding of CD.

Figure 1. Proportion of genetic counselor respondents who have seen a patient with a primary or secondary indication or incidental finding of CD in the past year.



Genetic counselors were asked if they had ever offered genetic testing for CD and, if so, how often (Figure 2). One in five respondents, 20% (30/153), had previously offered genetic testing for CD. Of those who had offered genetic testing for CD, the majority, 79% (23/29), had done so in the past year. A smaller number, 24% (7/29), reported offering it “sometimes” “often” or “very often” in the past year.

Figure 2. Proportion of genetic counselor respondents who have previously offered genetic testing.



### *Knowledge of CD*

Genetic counselor respondents answered questions regarding how they would best describe the inheritance of CD to a patient, the name of the primary gene associated with a predisposition for CD, and the clinical utility of genetic testing for CD. Participants were able to select more than one answer for the former two questions. The distributions of responses to the three questions are summarized in Figures 3, 4, and 5.

The majority of respondents, 84% (126/155), correctly identified the inheritance pattern of CD as “multifactorial – an inherited predisposition” (Figure 3). Nearly half, 49% (76/155), correctly indicated that the primary gene associated with CD is “Human

Leukocyte Antigen (HLA) class II gene”, while another 47% (72/155) “didn’t know” the gene associated with an inherited predisposition for CD (Figure 4). Most respondents, 70% (109/155), indicated that genetic testing for CD may be used to “support a suspected diagnosis of CD”; few, 22% (34/155), correctly indentified genetic testing as being able to “rule out CD” (Figure 5). Of the 7% (10/155) of genetic counselors who reported genetic testing for CD has “other” uses, eight correctly specified the use to be related to risk assessment.

Figure 3. Frequency of how respondents would best describe the inheritance of CD to a patient.

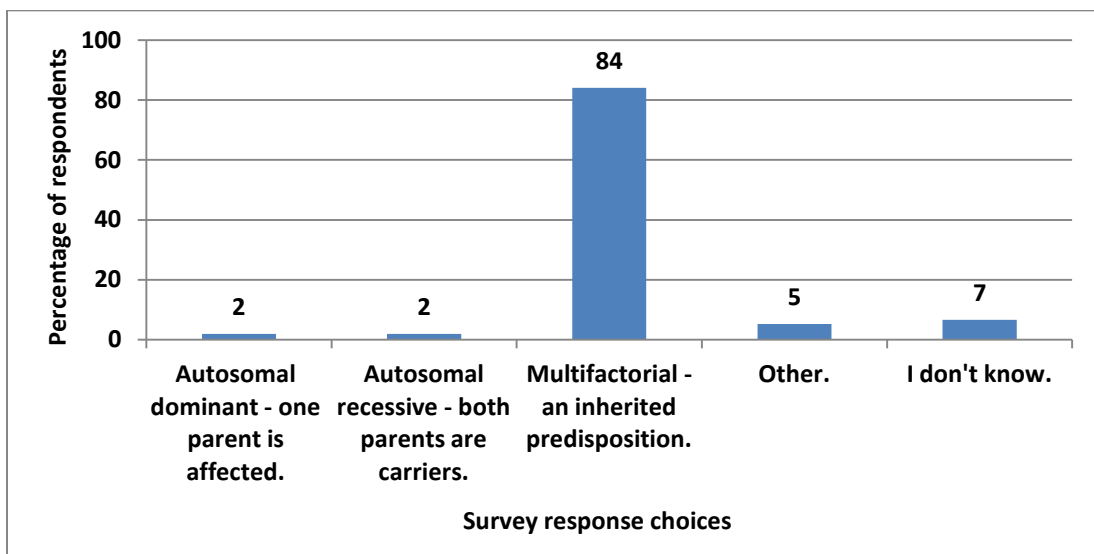


Figure 4. Frequency of genes respondents selected as associated with an inherited predisposition for CD.

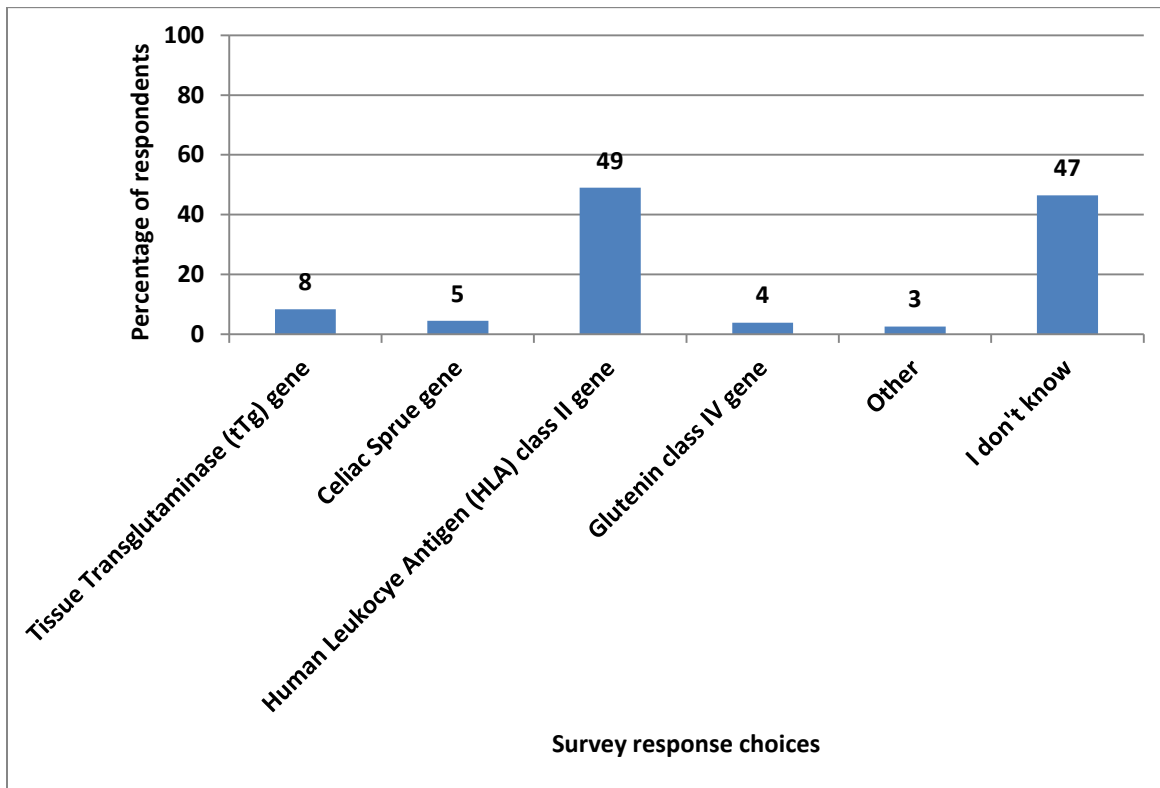
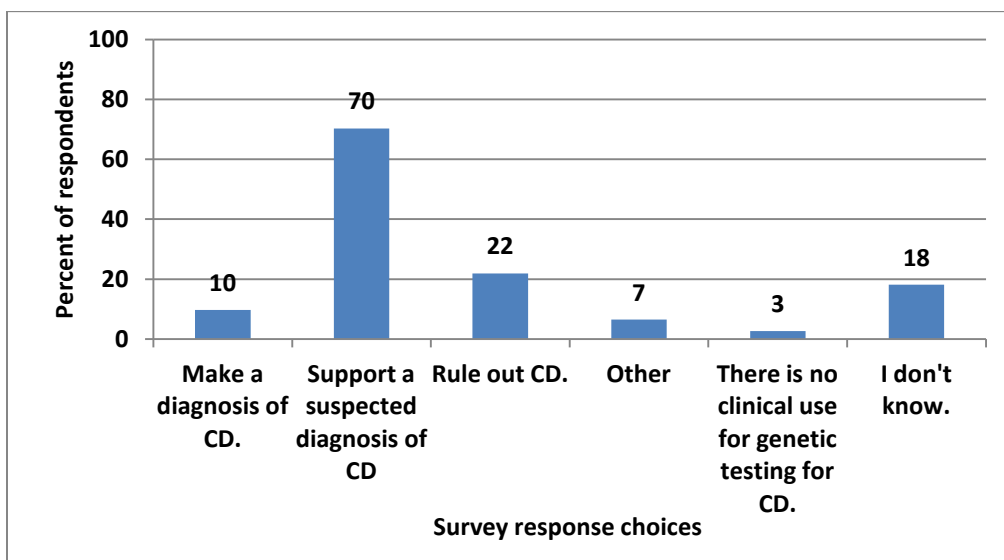


Figure 5. Frequency of what respondents identified as utility of genetic testing for CD.



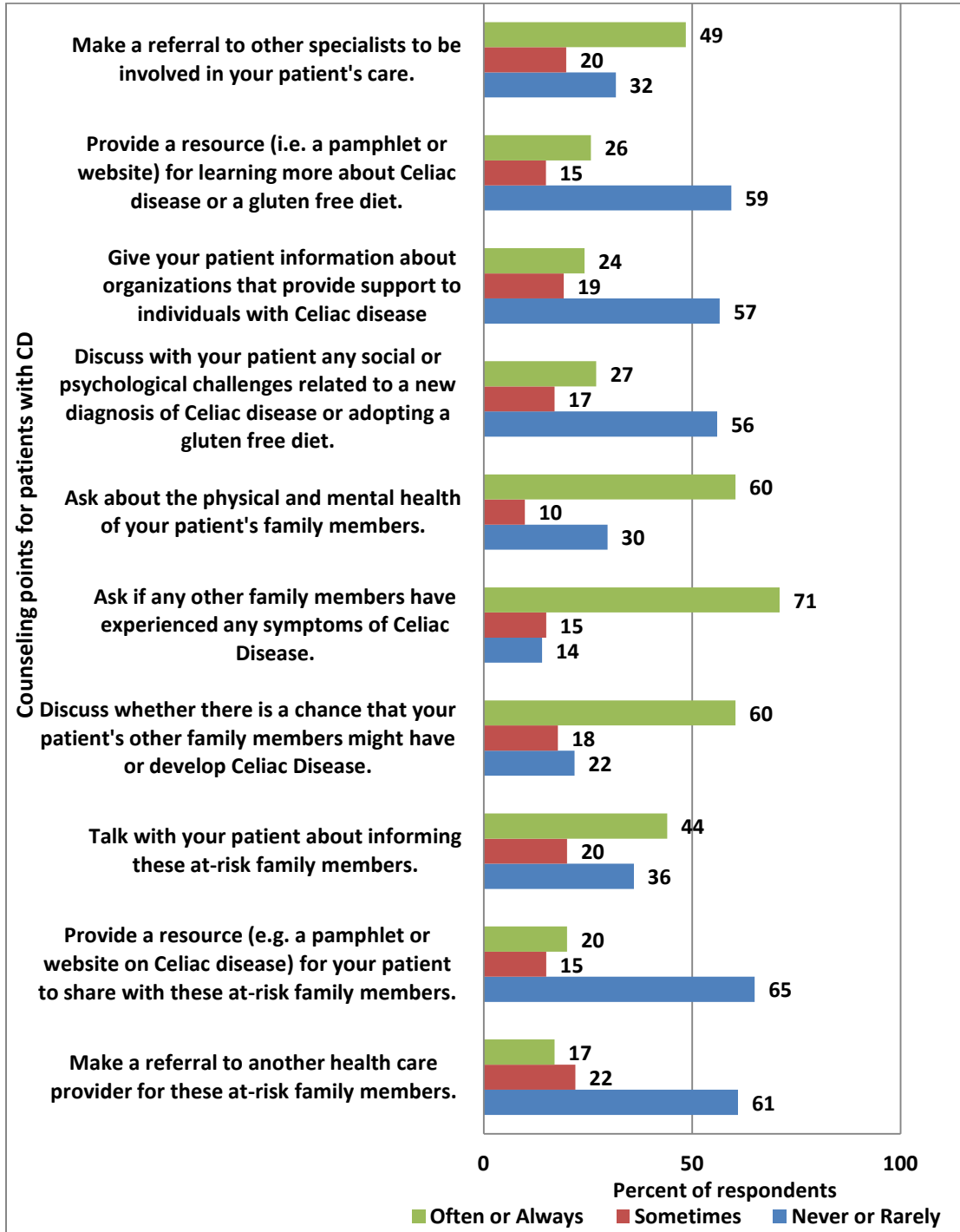
Respondent knowledge scores were calculated as the sum of correct answers for the aforementioned knowledge questions. A small number of respondents, 7% (11/150) answered no questions correctly. The majority of respondents, 77% (115/150), answered one or two questions correctly. Sixteen percent of respondents (24/150) answered all three questions correctly.

#### *Counseling practices for patients with CD*

Respondents who had seen a patient with a primary indication, secondary indication, or incidental finding of CD in the past year (n=99-101) were asked to rate how often they completed ten specific counseling aims (Appendix B) on a 5-point Likert scale where 1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Often, and 5 = Always.

Responses were grouped as “Often or Always”, “Sometimes”, or “Never or Rarely.” Figure 6 summarizes the distribution of responses. Genetic counselors were most likely to complete one out of the four counseling aims related directly to the patient’s care and four out of the six counseling aims related to the presenting patient’s relatives (Figure 6). The counseling aim related to the patient was making a referral, while the counseling aims related to the patient’s extended family included asking about extended family member’s physical and mental health, asking if any have symptoms of CD, discussing the chance that extended family members might have or develop CD, and talking about informing at-risk relatives.

Figure 6. Reported frequencies of completing counseling aims for respondents who have seen a patient with a primary or secondary indication or incidental finding of CD in the past year.



Participants who had not seen a patient with CD in the past year were asked to rate how often each of the ten counseling aims (listed in Appendix B) *should* be completed. Responses were grouped as “Often or Always,” “Sometimes,” or “Never or Rarely.”

Genetic counselors most often responded that all ten counseling aims should “Often or Always” be completed and infrequently responded that any of the aims should “Never or Rarely” be completed (data not shown).



## DISCUSSION

### *Demographics*

In 2010, there were 2,316 full NSGC members. Nearly 7% of the full NSGC members (155/2,316) responded to our survey. A comparison of our study respondent demographics with those reported in the NSGC 2010 Professional Status Survey (PSS) is listed in Table 2. The majority of participants (96%) were female, consistent with the gender demographics reported by the NSGC 2010 PSS. Counselors specializing in prenatal and “other” specialties are underrepresented in the present sample compared with the NSGC membership as a whole, while those specializing in pediatric and cancer are overrepresented.

Table 2. Comparison of respondent demographics from this study to NSGC 2010 PSS demographics.

<b>Demographic</b>	<b>Study Respondents</b>	<b>NSGC 2010 PSS</b>
<b>Gender</b>		
<b>Female</b>	96%	95%
<b>Male</b>	5%	5%
<b>Primary Specialty</b>		
<b>Prenatal</b>	26%	32%
<b>Pediatric</b>	16%	14%
<b>Cancer</b>	33%	22%
<b>Other</b>	24%	32%

### *Genetic counselor respondents' experience with CD*

This study assessed genetic counselors' experiences counseling about CD by asking them how often they have seen patients with a primary or secondary indication of CD or an incidental finding of CD in the past year, and if they have ever offered genetic testing for CD. Additionally, we assessed genetic counselors' knowledge of the inheritance of CD, the gene associated with an inherited predisposition for CD, and the clinical utility of CD genetic testing.

We found that a small proportion (26%) of genetic counselors have seen patients with a primary indication of CD in the past year, while 67% have seen patients with a secondary indication or incidental finding of CD in the past year.

One participant indicated that, apart from a genetic counselor in a gastroenterology specialty, the most common circumstances for genetic counselors to encounter CD is as part of taking a family history:

*“Celiac disease typically comes up as a part of family history review, but not as a primary indication for genetic counseling, at least outside of a GI setting.”*

This idea supports our finding that genetic counselors more commonly see CD as a secondary indication or incidental finding. However, this comment also suggests that CD may be a primary indication for genetic counseling in a GI setting. One respondent who noted his or her primary specialty as “other” wrote in “Celiac Disease.”

We used a Fischer's exact significance test to analyze how often genetic counselors in each sub-specialty see patients with a primary indication, secondary indication, or incidental finding of CD. Responses were grouped as “less often” (“Never, Very Rarely, or Rarely”) and “more often” (“Sometimes, Often, Very Often”). The

percentage of genetic counselors who saw patients with a primary indication of CD “less often” compared to “more often” significantly differed by respondent primary specialty ( $p = 0.038$ ). A very small number of respondents who indicated their primary specialty areas as prenatal (5%, 2/40), pediatric (0%, 0/25), or cancer (2%, 1/51) reported seeing patients with a primary indication of CD “more often”, while a larger number of respondents who indicated their primary specialty area as “other” (17%, 6/35) reported seeing patients with a primary indication of CD “more often”. Given that the “other” specialty category apparently included respondents with considerable experience counseling for CD, this difference in percentage of respondents who see patients with a primary indication of CD “more often” is not surprising. A respondent in this “other” category specified “Celiac Disease” as his/her specialty and another reported that s/he “speak[s] with many patient's about the results of their Celiac DNA test results.” The group of respondents who indicated their specialty as “other” includes individuals who specialize in CD and thus would see more patients with a primary indication of CD compared to respondents who indicated a prenatal, pediatric, or cancer specialty.

By comparison, the percentage of genetic counselors who saw patients with a secondary indication or incidental finding of CD “less often” compared to “more often” did not differ by primary specialty ( $\chi^2(3, N = 151) = 0.561, p = 0.905$ ). Approximately 20% to 25% of respondents in all specialty sub-categories reported seeing seeing patients with a primary indication of CD “more often”.

Overall, our data suggests that CD is generally not a primary indication for genetic counseling but is more commonly a secondary indication or incidental finding;

however, there is a small subset of genetic counselors who frequently see patients with CD as the primary indication.

In keeping with the AGA Institute Medical Positions Statement advising having the “resources available to provide genetic counseling” when using genetic testing for CD “in the context of disease susceptibility in families,” (Kagnoff, 2006), we expected that genetic counselors would have offered genetic testing for CD. We found that nearly one in five respondents had offered genetic testing for CD. Of those who had offered genetic testing for CD, only a minority offered it often in the past year. These results indicate that a small number of respondents offer genetic testing for CD, while the majority do not.

Though peer-reviewed literature fails to specify a set of providers appropriate for ordering genetic testing for CD, a patient pamphlet created by the University of Chicago Celiac Disease Center, identifies the gastroenterologist as the ordering provider (“Genetic Screening for Celiac Disease,” 2011). This is echoed in one genetic counselor’s open-ended response which offers his/her perception that patients with CD are generally offered genetic testing by a gastroenterologist:

*“I believe that genetic testing for Celiac disease is usually offered through my patients’ gastroenterologists who follow them.”*

Our unpublished data based on a survey of 165 individuals who have CD or a child with CD supports this idea. We found that 24% (39/165) of respondents who have CD or a child with CD had genetic testing for CD. Of those who completed genetic testing, most, 52% (16/31), accomplished this through a gastroenterologist. For others, the ordering provider for genetic testing was a primary care physician or pediatrician, 23% (7/31) or “other” 26% (8/31). None reported genetic counselor involvement in genetic testing.

These data indicate that gastroenterologists were more likely to be involved with genetic testing for CD than any other provider and that genetic counselors generally are not involved in testing.

In addition to the traditional provider-ordered mode, genetic testing for CD is also available direct-to-consumer (DTC). Many patients are aware of this testing and may ask their providers about it or even access it without a provider. One respondent who reported speaking with many patients about the results of their Celiac DNA test results observed a pattern of patient-driven genetic testing for CD:

*“Many of them [patients] also reported that their doctors are not the ones requesting the test, but the patient is the one bringing up the testing to their providers.”*

Our unpublished data from a survey of CD patients and parents indicate that of those who had genetic testing for CD, two-thirds went through a health care provider and most of the remaining third used a DTC company (a few were unsure of how their testing was ordered).

These data suggest that individuals with CD are accessing genetic testing through providers and DTC companies. As a result, some genetic counselor respondents may have counseled about CD without having the opportunity to offer genetic testing. This idea is supported by open-ended responses by genetic counselors indicating that when they are involved in CD cases, it is often *after* genetic testing has occurred.

### *Knowledge of CD*

We asked how genetic counselor respondents would best describe the inheritance of CD to a patient. A majority of genetic counselors correctly chose “multifactorial – an inherited predisposition.” This was the knowledge question that the greatest percentage of

genetic counselors answered correctly. The inheritance of CD is likely to be among the most important and relevant factors about the disease for genetic counselors, as it may be necessary for a family history risk assessment.

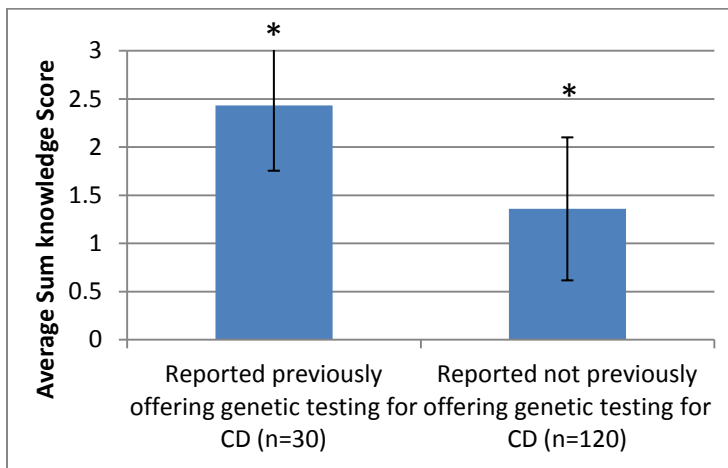
The second knowledge question asked respondents to identify the primary gene associated with CD. About half of genetic counselors correctly indicated the primary gene associated with CD to be a “Human Leukocyte Antigen (HLA) class II gene” and a similar proportion responded “I don’t know.” This divide between respondents who correctly identified the primary gene association and those who did not is not surprising in light of the disparity in genetic counselors’ experience with CD discussed above. Apparently, most genetic counselors encounter CD as a secondary indication or incidental finding and in these contexts, specific knowledge of the primary gene association is not necessary.

The final knowledge question asked respondents about the clinical utility of genetic testing for CD. The AGA Positions Statement defines the clinical utility of genetic testing for CD to be limited to “Excluding a diagnosis of CD” (Kagnoff, 2006), which corresponds to the survey response choice “rule out CD.” Only 22% (34/155) of respondents answered that genetic testing for CD can “rule out CD.” Another 70% (109/155) of respondents indicated that genetic testing for CD can be used to “support a suspected diagnosis of CD.” Given the new diagnostic approach incorporating genetic testing results as one criteria (Catassi & Fasano, 2010), it is possible that clinical practice has expanded the accepted utility of the testing from the AGA guidelines to include “support[ing] a diagnosis of CD” and respondent answers are reflecting this disparity between the guidelines and new diagnostic approach.

An overall respondent knowledge score was calculated as the sum of correct answers for the aforementioned knowledge questions. A one-way ANOVA was used to compare the mean knowledge scores for respondents in all four sub-specialties. There were no significant differences in mean knowledge scores among genetic counselor respondents in prenatal, pediatric, cancer, and “other” sub-specialties ( $F(3,144) = 1.370$ ,  $p = 0.254$ ).

An independent samples t-test was used to compare the mean knowledge scores of respondents who had offered genetic testing for CD with those who had not. Respondents who had previously offered genetic testing scored significantly higher ( $M=2.433$ ,  $SD=0.679$ ) compared with those who had not previously offered genetic testing ( $M=1.358$ ,  $SD=0.742$ ) ( $t(148)=7.210$ ,  $p=0.000$ ) (Figure 7)

Figure 7. Average sum knowledge scores for genetic counselor respondents who had and had not previously offered genetic testing for CD.



The data suggest that there is room for improvement in knowledge of CD for genetic counselors without experience counseling for CD. In particular, it would be beneficial for genetic counselors in all specialties to have better knowledge of the primary gene associated with CD and the utility of genetic testing for families affected

with CD, which could be accomplished through webinars and other continuing education programming.

#### *Current practices in genetic counseling for patients with CD*

Respondents who had seen a patient with CD reported completing five counseling aims “Often or Always.” Of these five counseling aims, one related directly to the patient (make a referral) and the remaining four related to the patient’s family (discuss the physical and mental health of extended family members, symptoms of CD in family members, and risk of CD for family members, and facilitating the informing of at-risk family members).

This result suggests that respondents with experience counseling for CD have developed an informal consensus of what the standard of care should include when counseling for CD.

A one-way ANOVA was used to compare the average frequencies of completing each of the counseling aims for patients with CD based on respondent specialty: prenatal (n=29), pediatric (n=20), cancer (n=30), and other (n=20). There was a significant difference in the average reported frequency of discussing symptoms of CD in family members ( $F(3, 95) = 2.861, p=0.041$ ). Counselors with a primary specialty in prenatal ( $M = 4.31, SD = 1.004$ ) had a higher average reported frequency of completion of this counseling aim compared to counselors with a primary specialty in cancer ( $M = 3.40, SD = 1.499$ ). Genetic counselors with a primary specialty in cancer focus the majority of the family history on gathering information about at cancer diagnosis, type of cancer, and treatments. When meeting with a patient with a strong family history of cancer this history supersedes other diagnoses, such as CD. However, this result is surprising when



considering the increased risk of cancer due to untreated CD, as this risk is pertinent to cancer risk assessment.

For all genetic counselor respondents who had seen a patient with CD in the past year and indicated their experience offering genetic testing for CD (101/155), independent samples t-tests were used to compare the average frequencies of completing each of the counseling aims based on having previously offered genetic testing for CD. Counselors who had offered genetic testing for CD had a significantly higher average reported frequency of completion for seven out of ten counseling aims compared to counselors who had not offered genetic testing for CD ( $p < 0.05$ ) (data not shown).

Those respondents who have previously offered genetic testing for CD are the most experienced with genetic testing and counseling for CD. The data suggest that the working “standard of care” among these respondents includes at least seven counseling aims. Three of these seven are related to patient care, including discussing psychosocial issues related to CD or a gluten free diet, providing resources for a patient about CD or a gluten free diet, and providing information about support organizations. The remaining four are related to the patient’s family, including asking about symptoms of CD in family members, discussing the risk of CD in family members, facilitating the informing of at-risk family members, and providing resources about CD for at-risk family members.

Counseling aims that did not significantly differ between respondents who had offered genetic testing and those who had not included: making a referral for a patient, taking a family history, and making a referral for family members. This result suggests that genetic counselors both with and without experience offering genetic testing for CD make referrals to specialists for patients and their family members and ask about the

physical and mental health of a patient's family members at approximately equal frequencies. It is not surprising that regardless of experience offering genetic testing for CD genetic counselors reported completing them with equal frequencies, as these are integral genetic counseling roles. Although these roles are integral for genetic counselors, they differ from the practice of other health care professionals who may focus less on the health or care of patients' family members.

### *The Celiac Iceberg*

The AGA Institute Medical Positions Statement clearly describes one of the roles of genetic testing for CD as assessing disease susceptibility in families. This position statement states that "one must have the resources available to provide genetic counseling," when assessing disease susceptibility in families (Kagnoff, 2006, p. 1979). Neither this positions statement, nor any other peer-reviewed literature to our knowledge specify which professional(s) should provide genetic counseling or order genetic testing for CD.

Based on the one in 133 prevalence of CD in the United States and the fact that genetic counseling is recommended when genetic testing for CD is completed, we assessed genetic counselor knowledge of and experience with CD and ascertained genetic counselors' current practices of genetic testing and genetic counseling for patients with CD. We found that genetic counselor respondents more commonly saw patients with a secondary indication or incidental finding of CD than a primary indication. Our study also showed a niche (likely in the gastroenterology setting) where a small proportion of genetic counselors see patients with a primary indication of CD and thus have sessions

focused on counseling for CD. Overall, our data suggest that genetic counselors may be underutilized in counseling and testing for CD.

If not genetic counselors, who is providing genetic services for CD? Is genetic counseling being provided at all? Genetic counselors are uniquely trained to address complex genetic test results, patients' diagnoses and implications for their families, and resulting psychosocial issues. This is accomplished by asking about the physical and mental health of family members, discussing whether any family members have symptoms of CD, assessing risk to family members, and facilitating the informing of at-risk relatives. Although these practices are integral parts of genetic counseling, they may be less common to the practice scope of other providers. Our unpublished data from a survey of individuals with CD or a child with CD indicated that health care professionals other than genetic counselors are providing genetic services. If genetic services for CD are being predominantly provided by providers other than genetic counselors, future studies should also examine the nature and extent of counseling for CD by various providers who order genetic testing for CD.

While the answers to these questions await future studies, they are important to addressing the problem of the "Celiac Iceberg." We postulate that with a stronger foundation of knowledge of CD and the practices integral to genetic counseling (such as asking about the physical and mental health of family members, discussing symptoms of CD in family members, assessing risk to family members, and facilitating the informing of at-risk relatives) genetic counselors would serve to shrink the submerged part of the Celiac Iceberg by increasing the number of diagnosed family members of individuals with CD. Therefore, expanding the field of genetic counseling to include more

specialized counseling in the gastroenterology setting may be one approach to shrinking the Celiac Iceberg.

Our unpublished data surveying individuals with CD or a child with CD showed that most genetic testing for CD was accessed through non-genetic counselor health care providers and DTC companies. Considering the public health goal of increasing the number of diagnosed family members of individuals with CD it is important that individuals with CD be educated about CD risk to family members, rather than relying on referrals from gastroenterologists, other health care providers, or DTC companies.

#### Study Limitations

One of the limitations of our study is the limited sample population. Participants were recruited through NSGC E-blasts, which does not represent the entire population of genetic counselors in the United States and Canada. As a result, the sample does not necessarily represent a random sample of genetic counselors in North America. There may also have been a selection bias among all genetic counselors, as those most interested in and/or educated about the topic may have been more likely to participate.

Our study focused on a sample of genetic counselors and did not include other health care professionals who may provide genetic testing to patients with CD, including gastroenterologists, geneticists, and primary care physicians. Additionally, the survey did not explicitly ask whether genetic counselors had a primary specialty in gastroenterology or CD. This may have skewed results of the assessment of knowledge of CD.

Another limitation of our study is related to the assessment of respondent knowledge of CD. We considered the answer “Support a diagnosis of CD” to the knowledge question about utility of genetic testing for CD as incorrect given the AGA

Positions Statement (Kagnoff, 2006). However, there is a new diagnostic approach that considers genetic testing for CD as one criterion to support a diagnosis of CD (Catassi & Fasano, 2010). The 70% of respondents who indicated that genetic testing for CD can “support a diagnosis of CD” may not be wrong in light of this new diagnostic approach. Consequently, our overall knowledge scores are likely an underestimate of respondents’ knowledge due to this disparity in accepted use of genetic testing for CD between the AGA Positions Statement and the new diagnostic approach.

An additional limitation is that in the survey questions asking respondents to rate how often the ten counseling aims either were or should be completed on a 5-point Likert scale composed of Never, Rarely, Sometimes, Often, or Always, there is a possibility that participants may have differing perceptions of “Rarely,” “Sometimes,” or “Often” on the Likert scale, which would have potential to affect participant frequency ratings. This is also true when respondents assessed how often they saw patients with CD in a year.

Another limitation of this study relates to the ten counseling aims we adapted from A Guide to Genetic Counseling (2009), as we only queried respondents on these ten counseling aims. There may have been other counseling aims that respondents often complete that were not captured by this portion of the survey.

Finally, the survey did not ask whether respondents’ patient populations included individuals with Down syndrome. Individuals with Down syndrome have at least a five-fold higher risk of developing CD than the general population (Kagnoff, 2006). It is possible that respondents with a pediatric primary specialty may have been referring in part to patients with Down syndrome in their survey responses. Since individuals with Down syndrome are often already in the care of geneticists and genetic counselors, they

may be more likely to receive genetic testing for CD through a geneticist or genetic counselor than individuals in the general population, or maybe do not receive genetic testing at all since their risk for CD is so high. In addition, a diagnosis of CD in an individual with Down syndrome may not have the same implications of risk of CD for family members; thus, the “Celiac Iceberg” may not apply to the population of individuals with CD and Down syndrome. For the purpose of this study it might have been helpful to have asked whether genetic counselors were working with a patient population that was primarily individuals with Down syndrome.

## CONCLUSION

We assessed genetic counselor knowledge of and experience with CD and ascertained genetic counselors' current practices of genetic testing and genetic counseling for patients with CD.

The data regarding genetic counselor experience with CD showed that the majority of genetic counselor respondents had seen a patient with CD (as a primary or secondary indication or an incidental finding). Few respondents had seen a patient with a primary indication of CD; yet, a small number often saw patients with a primary indication of CD. Most respondents saw a patient with CD as a secondary indication or incidental finding. The data also demonstrate that a minority of respondents had offered genetic testing for CD, while an even smaller number offer genetic testing for CD often. Overall, respondents were far more likely to encounter patients with CD as a secondary indication than as a primary indication. It appears that, with the exception of specialist gastroenterology settings, CD is generally not a primary indication for genetic counseling.

Most respondents correctly answered one or two knowledge questions. Overall, respondents were most knowledgeable about the inheritance of CD as a multifactorial condition and somewhat less so about the specific alleles associated with CD predisposition. Respondents were least familiar with the accepted use of genetic testing for CD to exclude a diagnosis of CD. Genetic counselors' knowledge of the primary gene

associated with CD and the utility of genetic testing for CD may be expanded through webinars and other continuing education forums.

Our data suggest that a set of seven counseling aims may be part of a working standard of care for those respondents who had offered genetic testing for CD. This subset was made up of three counseling aims related to patient care and four to the patient's extended family. The three counseling aims related to patient care included discussion of psychosocial issues related to CD or a gluten free diet, providing resources about CD or a gluten free diet, and providing support organization information. The four counseling aims related to the patient's extended family included asking about symptoms of CD in family members, discussing the chance of CD in family members, talking about informing at-risk family members, and providing resources about CD for family members.

The training and skill set of genetic counselors include practices that connect a genetic diagnosis and implications for family members, which may be less common in the practices of other health care professionals. Assuming an improved knowledge of CD, this training and skill set make genetic counselors ideally situated to provide care to CD patients and their families. Given that genetic counseling is recommended for individuals who elect genetic testing for CD, and that neither the AGA Positions Statement nor any peer-reviewed literature specify which professional(s) should provide genetic services, future research should examine the extent and nature of genetic services for those who elect genetic testing for CD.



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## APPENDIX A: Recruitment Notice

### Do you see patients with Celiac Disease?

My name is Victoria Duke and I am a graduate student in the Genetic Counseling program at Brandeis University. I am seeking health care professionals to participate in a research project. The goal of this study is to explore current practices and opinions of the diagnosis and management of Celiac Disease as a genetic condition.

**All health care professionals are encouraged to participate, regardless of previous clinical experience with Celiac Disease.** Participants will fill out a brief online survey. The survey should take approximately 10 minutes to complete and all data collected will remain anonymous. Participation in this study is voluntary and can be discontinued at any time for any reason.

As a thank you for participating in the survey, you will have the option to enter into a raffle for **one of three \$50 gift cards to Amazon.com.**

**If you are interested in participating in this study, please visit the following**

**link:** [https://brandeis.qualtrics.com/SE/?SID=SV\\_0JaY7lcSeAY1CDy](https://brandeis.qualtrics.com/SE/?SID=SV_0JaY7lcSeAY1CDy)

I appreciate your willingness to participate in this study. If you have any questions or comments, please feel free to contact me by email at [vduke@brandeis.edu](mailto:vduke@brandeis.edu), or the Brandeis University faculty advisor, Judith Tsipis, at [tsipis@brandeis.edu](mailto:tsipis@brandeis.edu).

Sincerely,

Victoria Duke  
Brandeis University Genetic Counseling Program, Class of 2012

## APPENDIX B: Survey

Q1 Thank you for choosing to participate in this research project, The iceberg and the helix: Assessing the role of genetic testing and genetic counselors in the diagnosis and management of Celiac Disease. The purpose of this study is to gain insight into the role of genetic testing and genetic counseling for patients with Celiac Disease. You will be asked to complete a brief online survey. The survey should take approximately 10 minutes to complete and all data collected will remain anonymous. Your participation is voluntary and you may choose to stop the survey at any time. As a thank you for your participation, at the end of the survey you will be offered an entry into a raffle for one of three \$50 Amazon.com gift cards. The risks associated with participating in this study are minimal, as data collected will remain anonymous. Although there is no direct benefit associated with participating in this study, I hope that in the future the information obtained from this study will help us gain a better understanding of the role of genetic testing and genetic counseling in the diagnosis of CD and analyze current usage of genetic testing and counseling as a method of ascertaining undiagnosed individuals. This study has been reviewed by the Brandeis University Institutional Review Board. If you have questions about your rights as a research subject please contact the Brandeis Institutional Review Board at irb@brandeis.edu or 781 736 8133. If you have any other questions or comments regarding this study, please feel free to contact Victoria Duke at vduke@brandeis.edu or Faculty Advisor, Judith Tsipis, at tsipis@brandeis.edu. By completing this survey, you indicate that you are over the age of 18 and are consenting to participation in this research project.

Q2 Please indicate your profession:

- Gastroenterologist (1)
- Geneticist (2)
- Genetic Counselor (3)
- Primary care physician (4)
- Nurse (5)
- Other, please specify: (6) \_\_\_\_\_

Q3 Do you primarily see adult or pediatric patients?

- Adult (1)
- Pediatric (2)
- Approximately equal numbers of each (3)

Answer If Please indicate your profession: Genetic Counselor Is Selected

Q4 Please indicate your primary specialty area.

- Prenatal (1)
- Pediatric (2)
- Cancer (3)
- Other, please specify: (4) \_\_\_\_\_

Answer If Please indicate your profession: Genetic Counselor Is Selected

Q5 Are you currently seeing patients?

- Yes (1)
- No (2)

Q6 How many years have you been in practice?

Q7 What is your gender?

- Male (1)
- Female (2)

Q8 In which state do you currently practice?

- Alabama (1)
- Alaska (2)
- Arizona (3)
- Arkansas (4)
- California (5)
- Colorado (6)
- Connecticut (7)
- Delaware (8)
- District of Columbia (9)
- Florida (10)
- Georgia (11)
- Hawaii (12)
- Idaho (13)
- Illinois (14)
- Indiana (15)
- Iowa (16)
- Kansas (17)
- Kentucky (18)
- Louisiana (19)
- Maine (20)
- Maryland (21)
- Massachusetts (22)
- Michigan (23)
- Minnesota (24)
- Mississippi (25)
- Missouri (26)
- Montana (27)
- Nebraska (28)
- Nevada (29)
- New Hampshire (30)
- New Jersey (31)
- New Mexico (32)
- New York (33)
- North Carolina (34)
- North Dakota (35)
- Ohio (36)
- Oklahoma (37)
- Oregon (38)
- Pennsylvania (39)
- Puerto Rico (40)
- Rhode Island (41)
- South Carolina (42)
- South Dakota (43)
- Tennessee (44)
- Texas (45)

- Utah (46)
- Vermont (47)
- Virginia (48)
- Washington (49)
- West Virginia (50)
- Wisconsin (51)
- Wyoming (52)
- I do not practice in the United States (53)

Q9 How often have you seen patients with a primary indication of Celiac Disease in the past year?

- Never (1)
- Very rarely (2)
- Rarely (3)
- Sometimes (4)
- Often (5)
- Very often (6)

Q10 How often have you seen patients with any primary indication and a secondary indication or incidental finding of Celiac Disease in the past year?

- Never (1)
- Very rarely (2)
- Rarely (3)
- Sometimes (4)
- Often (5)
- Very Often (6)

Q11 Have you ever offered genetic testing for Celiac Disease?

- Yes (1)
- No (2)

Answer If Have you ever offered genetic testing for Celiac Disease? Yes Is Selected

Q12 How often have you offered genetic testing for Celiac Disease in the past year?

- Never (1)
- Very rarely (2)
- Rarely (3)
- Sometimes (4)
- Often (5)
- Very Often (6)

Answer If Have you ever ordered genetic testing for Celiac Disease? Yes Is Selected

Q13 How do you usually inform a patient of his or her genetic test result (choose all that apply)?

- In person. (1)
- By a phone call from me. (2)
- In writing. (3)
- A member of my staff calls the patient. (4)
- Other, please specify: (5) \_\_\_\_\_

Q14 How would you best describe the inheritance of Celiac Disease to a patient?

- Autosomal dominant - one parent is affected (1)
- Autosomal recessive - both parents are carriers (2)
- Multifactorial - an inherited predisposition (3)
- Mitochondrial - inherited from the mother (4)
- Other, please specify: (5) \_\_\_\_\_
- I don't know. (6)

Q15 Which of the following genes is associated with an inherited predisposition for Celiac Disease (choose all that apply)?

- Tissue transglutaminase (tTg) gene (1)
- Celiac Sprue gene (2)
- Human Leukocyte Antigen (HLA) class II gene (3)
- Glutenin class IV gene (4)
- Other, please specify: (5) \_\_\_\_\_
- I don't know. (6)

Q16 In your opinion, the genetic testing for Celiac Disease can be used to (choose all that apply):

- Make a diagnosis of Celiac Disease (1)
- Support a suspected diagnosis of Celiac Disease (2)
- Rule out Celiac Disease (3)
- Other, please specify: (4) \_\_\_\_\_
- There is no clinical use for genetic testing for Celiac Disease (5)
- I don't know. (6)



Answer If How often have you seen patients with a primary indicatio... Never Is Not Selected  
 Or How often have you seen patients with any primary indicat... Never Is Not Selected

Q17 When you see a patient with an indication (or diagnosis) of Celiac Disease, how often do you do any of the following?

	Never (1)	Rarely (2)	Sometimes (3)	Often (4)	Always (5)
Make a referral to other specialists to be involved in your patient's care. (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Provide a resource (i.e. a pamphlet or website) for learning more about Celiac disease or a gluten free diet. (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Give your patient information about organizations that provide support to individuals with Celiac disease (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Discuss with your patient any social or psychological challenges related to a new diagnosis of Celiac disease or adopting a gluten free diet. (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ask about the physical and mental health of your patient's family members. (5)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ask if any other family	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

<p>members have experienced any symptoms of Celiac Disease. (6)</p> <p>Discuss whether there is a chance that your patient's other family members might have or develop Celiac Disease. (7)</p> <p>Talk with your patient about informing these at-risk family members (8)</p> <p>Provide a resource (e.g. a pamphlet or website on Celiac disease) for your patient to share with these at-risk family members. (9)</p> <p>Make a referral to another health care provider for these at-risk family members. (10)</p>	○	○	○	○	○
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Answer If How often have you seen patients with a primary indicatio... Never Is Selected  
 And How often have you seen patients with any primary indicat... Never Is Selected

Q18 For patients with an indication (or diagnosis) of Celiac Disease, how often do you think each of the following should be done?

	Never (1)	Rarely (2)	Sometimes (3)	Often (4)	Always (5)
Make a referral to other specialists to be involved in your patient's care. (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Provide a resource (i.e. a pamphlet or website) for learning more about Celiac disease or a gluten free diet. (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Give your patient information about organizations that provide support to individuals with Celiac disease (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Discuss with your patient any social or psychological challenges related to a new diagnosis of Celiac disease or adopting a gluten free diet. (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ask about the physical and mental health of your patient's family members. (5)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ask if any other family	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

members have experienced any symptoms of Celiac Disease. (6)					
Discuss whether there is a chance that your patient's other family members might have or develop Cecliac Disease. (7)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Talk with your patient about informing these at-risk family members (8)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Provide a resource (e.g. a pamphlet or website on Celiac disease) for your patient to share with these at-risk family members. (9)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Make a referral to another health care provider for these at-risk family members. (10)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q19 If you have any information or comments you wish to share about any topics covered in this survey, please include them below.

Q20 Thank you for your participation! If you would like to be entered for a chance to win one of three \$50 Amazon.com gift cards, please send an email to [CeliacDiseaseSurvey@gmail.com](mailto:CeliacDiseaseSurvey@gmail.com) with "Gift Card" as the subject line. Your email will in no way be tied to your survey responses.