I, Sarah K Walterman, hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled:
Genetic Testing Practices of Physicians for Primary Immunodeficiency Diseases

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Committee member: Rebecca Arehart Marsh, M.D.

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Genetic Testing Practices of Physicians
for Primary Immunodeficiency Diseases

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Master of Science

in the Program of Genetic Counseling
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by

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Abstract

Background

Primary immunodeficiency diseases refer to a heterogeneous group of genetic disorders involving an inborn defect in the immune system leading to an increased susceptibility to infections. An estimated 1 in 1,200 persons in the United States have a diagnosed primary immunodeficiency disease. The goal of this study was to describe current genetic testing practices of physicians of patients with primary immunodeficiency diseases and to determine if there are unmet patient needs that could potentially be met by genetic counseling services.

Methods

Members of the Clinical Immunology Society and the Histiocyte Society completed a paper or web-based survey designed to assess the demographics, frequency genetic testing is ordered, most common tests ordered, reasons for testing, perceived disadvantages and barriers to genetic testing, and frequency of genetic counseling referrals. Descriptive statistics were used to summarize the study population’s demographic characteristics and genetic testing practices. The Cochran-Armitage trend test was performed to assess associations between a binary variable and an ordinal variable. The relationship between two ordinal variables was also tested using linear-by-linear association tests.

Results

Ninety-six of the 125 returned surveys met study criteria and were used for data analysis. Results indicate that CVID was the most common primary immunodeficiency respondents treated in the past year (n=77, 80%), and SCID was the most common primary immunodeficiency for which respondents ordered genetic testing (n=43, 45%). However, CVID was indicated as one of the three most common diseases genetic testing was ordered for by only
15% (n=14) of respondents. Forty-seven percent (n=45) of respondents indicated ordering genetic testing for only 1-20% of patients with clinically suspected primary immunodeficiencies, and 40% (n=38) of respondents indicated ordering genetic testing for 1-20% of patients with clinically confirmed primary immunodeficiencies. Establishing a diagnosis was the most common (n=76, 79%) reason respondents ordered genetic testing. A majority of respondents indicated that genetic testing occasionally (n=49, 51%) or frequently (n=20, 21%) changed management for patients. Remarkably, forty-one percent (n=39) of respondents indicated referring 0% of their patients to genetic counseling before ordering genetic testing. Approximately half (54%, n=50) of respondents indicated that they always provided posttest counseling.

Conclusions

This study highlights unmet genetic testing and counseling needs of patients with or suspected to have primary immunodeficiency diseases. Despite recent advances in genetic testing and the large proportion of respondents that indicated genetic test results occasionally or frequently change management for patients, approximately half of respondents ordered genetic testing for 20% or less of their patients. The disparity between the most common diseases treated by respondents and the most common diseases genetic testing was ordered for and the lack of pretest genetic counseling illustrate a need for increased collaboration between primary immunodeficiency disease providers and genetic counselors. This will allow providers to better determine appropriate candidates for genetic testing, utilize genetic testing to better establish diagnoses, and share the burden of interpreting uncertain test results and providing counseling to patients with genetics professionals.
Keywords: Primary immunodeficiency diseases, genetic testing, rare diseases, allergist, immunologist, genetic counseling, CVID, SCID
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Introduction

Primary immunodeficiencies encompass a variety of genetic disorders that involve inborn defects of the immune system. While the majority of these disorders are considered rare, collectively, an estimated 1 in 1,200 persons in the United States have a diagnosed primary immunodeficiency disease (Boyle & Buckley, 2007). The specific symptoms and symptom onset vary for each primary immune deficiency and within each primary immune deficiency. Therefore, the prognosis for individuals with primary immunodeficiency diseases varies widely, from mildly affected patients with normal life expectancies to severely affected patients with life expectancies of just a few years or less. Proper management and treatment can improve the prognosis for many affected individuals.

Due to the complexity of primary immunodeficiency diseases and associated management needs, care teams for affected patients are often large and multidisciplinary. In addition to allergy/immunology and hematology/oncology specialists, nurses, pharmacists, nutritionists, and other specialists (e.g. pulmonologists, cardiologists, and gastroenterologists) are commonly involved. Many have noted the critical role of genetic counselors in the management of primary immunodeficiency diseases (Ameratunga et al., 2011; Ameratunga, Woon, Neas, & Love, 2010; Buckley, 2009; de Vries, 2006). In particular, the Immune Deficiency Foundation notes the importance of genetic counseling in the comprehensive care of patients with primary immunodeficiency diseases, pointing out that genetic counselors are skilled at presenting complex information in a way that is unbiased and understandable (Buckley, 2009). In addition to exploring psychosocial factors associated with a genetic disease diagnosis, it is recommended that genetic counselors discuss the genetic nature and inheritance patterns of primary immunodeficiency diseases, as well as the benefits and limitations of genetic testing with
Currently, approximately 200 genetic defects associated with more than 200 known primary immunodeficiency diseases have been identified (Al-Herz et al., 2011; Parvaneh, Casanova, Notarangelo, & Conley, 2013). In contrast, in 2007, approximately only 100 associated genetic defects had been identified (Guzman et al., 2007; Samarghitean, Valiaho, & Vihinen, 2007). As more genetic defects have been discovered, the need for clinical genetic testing has increased, and as a result clinical genetic testing has become more widely available for primary immunodeficiency diseases (Lehman, Hernandez-Trujillo, & Ballow, 2008). Ameratunga et al. have stated that molecular genetic testing is critical for patient management and should be regarded as the standard of care because of its benefits (Ameratunga et al., 2010). A practice parameter developed by Bonilla et al. includes multiple algorithms for initial evaluation, laboratory screening testing, and further evaluation of patients with suspected primary immunodeficiency diseases. According to this practice parameter, a molecular diagnosis is desirable in most cases in order to provide a definitive diagnosis, allow for accurate genetic counseling, allow for planning of future pregnancies, and better define genotype-phenotype correlations (Bonilla et al., 2005). Definitive diagnoses also help providers select the most appropriate treatments, and genotypes can help identify those who may benefit from gene therapy (Ameratunga et al., 2011; Ameratunga et al., 2010).

Genetic testing for primary immunodeficiency diseases can additionally benefit clinical research in several ways. Analysis has helped to classify primary immunodeficiency disease, further elucidate genotype-phenotype correlations, and further develop primary immunodeficiency disease management guidelines and will continue to do so. Molecular analysis of primary immunodeficiency diseases will also be important in identifying affected
genes, modifier genes, and pathways for multifactorial primary immunodeficiency diseases like CVID (Ameratunga et al., 2011; Ameratunga et al., 2010). Information from molecular genetic analysis for primary immunodeficiency diseases will help to further increase awareness of primary immunodeficiency diseases and to improve future patient management (Ameratunga et al., 2011; Ameratunga et al., 2010; McGrath, 2004).

However, there may also be perceived disadvantages to genetic testing. One of the most commonly cited associated disadvantages of genetic testing for primary immunodeficiency diseases is the uncertainty of test results in regards to both interpretation and accuracy (Ameratunga et al., 2011; Morra et al., 2008). An increase in the number of unclear test results for primary immunodeficiency disease diagnoses may result from the increased availability of genetic testing and the use of whole genome or whole exome analysis (Ameratunga et al., 2011).

Genetic testing also has associated psychosocial disadvantages. A child’s genetic diagnosis can stress family relationships, leaving parents with feelings of guilt and anxiety and with altered perceptions of their child (Ameratunga et al., 2010; Fanos, Davis, & Puck, 2001). In addition, an individual with a genetic diagnosis may have an altered self-image and altered expectations for himself (Fanos et al., 2001).

In addition to the perceived disadvantages to genetic testing, barriers to molecular testing for rare genetic diseases also exist, and can include the large number of genetic diseases, the low number of individuals affected by each disease, the technology needed for analysis, and the high cost of testing, which together may be impeding the widespread adoption of genetic testing for primary immunodeficiency diseases (Willems, 2008). Morra et al. discuss four additional impediments specific to primary immunodeficiency disease genetic testing: testing costs and insurance coverage concerns, difficulties identifying an appropriate clinical laboratory,
turnaround time, and the lack of clinical standardization at the laboratory level (Morra et al., 2008).

To our knowledge there are no studies that have assessed the current genetic testing practices for primary immunodeficiency diseases. Doing so will not only provide more information about the frequency of primary immunodeficiency disease genetic testing but will also provide information about the reasons for ordering primary immunodeficiency genetic testing and information about which medical professionals are currently involved in the genetic counseling process.

Here we report the results of a large-scale survey of the clinical genetic testing and counseling practices of primary immune deficiency physicians.

**Methods**

**Participants**

Organizations expected to include members who treat patients with primary immune deficiencies were contacted. These included the Clinical Immunology Society, the Histiocyte Society, the American Society of Pediatric Hematology/Oncology, and the American Academy of Allergy Asthma and Immunology. The Clinical Immunology Society and the Histiocyte Society agreed to participate in the study. Members of the Clinical Immunology Society were mailed paper surveys. The first mailing was sent on November, 18, 2013. A second mailing was sent on January 13, 2014 to those members of the Clinical Immunology Society who had not previously responded. Members of the Histiocyte Society received an electronic version of the survey created using REDCap via email. Emails were first sent on January 13, 2014, and reminder emails were sent on January 20, 2014 to those members of the Histiocyte Society that had not previously responded. Those who had seen patients with primary immunodeficiency
diseases within the past year were included, and those who had not seen any patients with primary immunodeficiency diseases within the past year were excluded from the study. This study was approved by the Institutional Review Boards of Cincinnati Children’s Hospital Medical Center and the University of Cincinnati.

Survey

A 26-question survey was developed to describe physicians’ current genetic testing practices for primary immunodeficiency diseases. The only required question was the first one asking participants to indicate the number of patients with or suspected to have primary immunodeficiency diseases they had seen in the past year. Those who indicated “0” were thanked for their time and informed that they did not meet the study’s eligibility requirements. The survey was made up of two components designed to gather information about demographics and genetic testing practices.

*Demographic Information*

Physicians’ training background, practice setting, experience with genetics and primary immunodeficiency diseases, and access to genetic counselors were hypothesized to be potential confounders for genetic testing practices. Therefore, information for each of these was collected. Participants were asked to indicate their subspecialties to provide information about training background. Participants were asked to indicate the type, location, and referral center classification of their practice institutions. Information about experience with primary immunodeficiency diseases was gathered by asking participants to indicate their primary patient population, the number of years of experience working with patients with primary immunodeficiency diseases, the number of patients with or suspected to have a primary immunodeficiency disease they had seen in the past year, and the three most common primary
immunodeficiency diseases they had seen in the past year. Finally, information about access to genetic counselors was gathered by asking participants to indicate whether or not there are genetic counselors at their practice institutions, whether or not there are genetic counselors within a 60-mile radius of their institutions, and whether or not they have contacted genetic counselors at testing laboratories.

*Genetic Testing Practices*

Genetic testing practices include the frequency with which testing is ordered, the most common genetic tests ordered, the reason genetic testing is ordered, the perceived disadvantages and barriers to genetic testing, and the frequency of genetic counseling referrals. Questions were included to assess each component of genetic testing. Participants were asked to indicate the percentage of patients with suspected primary immunodeficiency diseases in the past year for whom they had ordered genetic testing, as well as the percentage of patients with confirmed primary immunodeficiency diseases in the past year for whom they had ordered genetic testing. Participants were also asked to list the three most common primary immunodeficiency diseases for which they ordered genetic testing in the past year and to indicate whether or not they have considered ordering whole genome analysis for diagnosing primary immunodeficiency diseases. Participants were asked to indicate the reason genetic testing is ordered in most cases. To provide additional information about reasons genetic testing is ordered participants were asked to indicate the frequency genetic testing results change patient treatment or management. Study participants were asked to indicate which factor associated with primary immunodeficiency disease genetic testing they consider to be the greatest disadvantage. In order to gather information on the perceived barriers to genetic testing, participants were asked to indicate what they consider to be the biggest barrier to genetic testing. Participants were asked to indicate the
percentage of patients they referred to genetic counseling before ordering genetic testing and for those who are not referred to genetic counseling, how often they conducted pretest and posttest counseling in the past year. Finally, participants were asked to indicate what topics they had discussed with patients when conducting pretest and/or posttest counseling.

Data Analysis

Descriptive statistics were used to summarize the demographic characteristics and the genetic testing practices of the study population. Frequency (percentage) was reported for categorical variables. Some categorical variables were nominal variables while other categorical variables were ordinal variables using a Likert scale. Mean and standard deviation were reported for continuous variables. The Cochran-Armitage trend test was performed to assess possible associations between a binary variable and an ordinal variable. It tested for trends in binomial proportions across the levels of a single variable. The relationship between two ordinal variables was assessed using linear-by-linear association tests. The analysis was performed in R (www.r-project.org).

Results

Of the 1,074 surveys sent out, a total of 125 surveys were returned for an overall response rate of 12% (38 of the 1,074 surveys sent out were returned to sender). Ninety-six of the returned surveys met study criteria (indicated experience with primary immune deficiency patients) and were used for analysis. It should be noted that more than one response was allowed for certain questions.

Demographics

Participants’ years of experience working with patients ranged from 1 to 45 years (mean = 16.06, standard deviation (SD) =13.28). The 96 respondents that met study criteria were from 69 unique institutions distributed across all geographic regions of the United States. Thirty-two
percent of respondents (n=31) worked at institutions in the Northeast, 32% (n=31) worked at institutions located in the Midwest, 18% (n=17) worked in the West, 14% (n=13) worked in the Southeast, and 4% (n=4) worked in the Southwest. Detailed demographic data are reported in Table 1.

Frequency of Genetic Testing

Common variable immune deficiency (CVID) was the most common primary immunodeficiency disease respondents treated in the past year (n=77, 80%), followed by chronic granulomatous disease (CGD) (n=20, 21%), and DiGeorge syndrome (n=19, 20%). Forty-seven percent (n=45) of respondents indicated ordering genetic testing for 1-20% of patients with clinically suspected primary immunodeficiency diseases, and 40% (n=38) of respondents indicated ordering genetic testing for 1-20% of patients with clinically confirmed primary immunodeficiency diseases (Figure 1). Severe combined immune deficiency (SCID) was the most common primary immunodeficiency disease for which respondents ordered genetic testing (n=43, 45%), followed by CGD (n=34, 36%), and X-linked agammaglobulinemia (XLA) (n=30, 32%). Whole exome sequencing was ordered by 47% (n=45) of respondents for the purpose of diagnosing primary immunodeficiency diseases, and another 41% (n=39) of respondents reported having considered ordering whole exome sequencing for this purpose (Figure 2).

Potential Factors Influencing Frequency of Genetic Testing

Respondents who indicated allergy as a subspecialty were less likely to order genetic testing for patients with suspected primary immunodeficiency diseases (Cochran-Armitage trend test, P=0.043). Those who indicated oncology as a subspecialty were more likely to order genetic testing for patients with suspected primary immunodeficiency diseases (Cochran-Armitage trend test, P=0.013). They were also more likely to order testing for patients with confirmed primary
immunodeficiency diseases (Cochran-Armitage trend test, P=0.021). Respondents who indicated hematology as a subspecialty were more likely to order genetic testing for patients with confirmed primary immunodeficiency diseases (Cochran-Armitage trend test, P=0.025). Respondents who indicated CVID as one of the three most common diseases treated in the past year were less likely to have ordered genetic testing for patients with suspected primary immunodeficiency diseases compared to respondents who did not indicate CVID as one of the three most common diseases (Cochran-Armitage trend test, P=0.0043). CVID was indicated as one of the three most common diseases genetic testing was ordered for by only 15% (n=14) of respondents. Respondents who indicated having a primarily pediatric clinical population were more likely to order genetic testing for patients with confirmed primary immunodeficiency diseases compared to those respondents with a primarily adult clinical population (Cochran-Armitage trend test, P=0.032). There were no statistically significant associations between respondents’ self-reported genetics knowledge level and the frequency with which genetic testing was ordered for patients with suspected (linear-by-linear association test, P=0.064) or confirmed (linear-by-linear association test, P=0.33) primary immunodeficiency diseases.

A high percentage (n=76, 79%) of respondents indicated establishing a diagnosis as a primary reason for ordering genetic testing, followed by confirming a diagnosis (n=60, 63%), and for research purposes (n=22, 23%) (Figure 3). Approximately three fourths of respondents indicated that genetic testing occasionally (n=49, 51%) or frequently (n=20, 21%) changed the course of treatment or management for patients (Figure 4).

**Perceived Disadvantages and Barriers to Genetic Testing**

Uncertainty of test result interpretation was indicated as the greatest perceived disadvantage associated with genetic testing for primary immunodeficiency diseases by 36%
Of the 38% (n=36) of respondents who chose “other” for this question, more than half (n=21, 58%) described cost and/or insurance coverage as the greatest disadvantage, indicating that 22% of all respondents identified these issues as the greatest disadvantage (Figure 5). Cost of testing was indicated by 44% (n=42) of respondents as the biggest barrier to genetic testing for primary immunodeficiency diseases. This was followed by insurance coverage concerns (n=30, 31%) (Figure 6).

Genetic Counseling

Genetic counselors were present at 85% (n=80) of respondents’ practice institutions, and 97% (n=93) of respondents indicated that genetic counselors were available within a 60 mile radius. More than half (n=56, 58%) indicated that they had contacted genetic counselors at a laboratory.

Forty-one percent (n=39) of respondents did not refer any patients to genetic counseling before genetic testing was ordered. For those patients who were not referred for genetic counseling before testing was ordered, 40% (n=37) of respondents indicated that they always provided pretest counseling. Approximately one fourth (n=24, 26%) of respondents referred 1-20% of patients to genetic counseling after receiving genetic testing results. For those patients who were not referred for genetic counseling after receiving test results, 54% (n=50) of respondents indicated that they always provided posttest counseling. Refer to Figures 7 and 8 for detailed information on genetic counseling referrals and frequency of respondent (physician) counseling. All of the counseling topics we surveyed were discussed with patients by more than half of respondents when they did provide counseling. Respondents most commonly discussed testing options for other family members (n=79, 82%), followed by inheritance patterns (n=78, 81%) and health implications (n=75, 78%) (Figure 9).
Respondents who indicated establishing a diagnosis as a reason for ordering genetic testing were less likely to refer to genetic counseling before ordering testing (Cochran-Armitage trend test, P=0.013). There were no statistically significant associations between respondents’ self-reported knowledge of genetics and the frequency with which genetic counseling referrals were made before genetic testing was ordered (linear-by-linear association test, P=0.13) or after receiving genetic test results (linear-by-linear association test, P=0.76). There were also no statistically significant associations between whether or not respondents had ordered exome sequencing and the frequency with which genetic counseling referrals were made before genetic testing was ordered (linear-by-linear association test, P=0.94) or after receiving genetic test results (linear-by-linear association test, P=0.71).

**Discussion**

Over the last decade there has been a profound increase in the number of genetic defects discovered to be associated with primary immune deficiency disorders. These advances, along with the new availability of whole-exome sequencing, give physicians the opportunity to now make definitive diagnoses in many more patients. These advances additionally place a significant burden on care providers with regard to interpretation of results and pre- and post-test counseling of patients. This descriptive summary of survey responses provides a snapshot of primary immune deficiency genetic testing practices from the perspective of physicians in 2013. Interestingly, we found that despite the advances in diagnostic genetic testing, approximately half of respondents ordered genetic testing for 20% or less of their patients with suspected primary immune deficiencies, and 40% of respondents ordered genetic testing for 20% or less of their patients with clinically confirmed primary immune deficiencies. As expected, the frequency of ordering genetic testing seemed to be related in part to the particular disease classification
group. The three most common primary immunodeficiency diseases treated by respondents in the past year were CVID, CGD, and DiGeorge syndrome, but the three most common diseases respondents ordered genetic testing for were SCID, CGD, and XLA.

CVID was the most common primary immunodeficiency disease that respondents indicated treating in the past year, but only 15% of respondents indicated CVID as one of the three most common diseases for which genetic testing was ordered. While the diagnosis and treatment of CVID does not require an identified genetic cause, it has been suggested that certain molecular genetic defects should be ruled out in patients who meet diagnostic criteria for CVID (Bonilla et al., 2005). Respondents who indicated CVID as one of the three most common diseases treated in the past year were less likely to have ordered genetic testing for patients with suspected and confirmed primary immunodeficiency diseases. These data indicate that providers may not be ordering genetic testing for patients who are appropriate candidates. This disparity suggests that the genetic testing needs for primary immunodeficiency diseases are not being met and that providers may not see the value in the results of currently available genetic tests. Study data suggest this could be because the results do not always change the course of treatment or management for patients, the possibility of uncertain results interpretations, the availability of the tests, and the accumulated cost of these tests.

When ordering genetic testing to establish a diagnosis for disorders with genotypic and phenotypic heterogeneity like CVID and other primary immunodeficiency diseases, broader genetic testing, such as multi-gene sequencing panels and whole exome sequencing, may be more clinically useful and more cost effective due to the ability to simultaneously examine many genes. The whole exome approach also has the potential to identify novel candidate genetic defects. These tests are currently not as clinically available for primary immunodeficiency
diseases as are single gene sequencing tests. Future expansion of these genetic testing options for primary immunodeficiency diseases will facilitate incorporation into clinical practice and will also help to further characterize disease pathologies and elucidate genotype-phenotype correlations. The collective information gained by genetic diagnostics in larger groups of patients may help providers select the most appropriate treatments for particular genetic groups. As gene therapy approaches entering clinical practice in the coming years, genetic testing will be crucial to identify patients who may benefit from gene therapy. This benefit may also increase how often providers perceive that genetic test results change the course of treatment for patients with primary immunodeficiency diseases. In this study, only approximately one fifth of respondents indicated that genetic test results frequently impact patients’ care, which may explain the small proportion of respondents ordering genetic testing for a majority of their patients.

While there are obvious benefits of genetic sequencing when analyses clearly indicate a positive or negative result, variants of uncertain significance occur in all types of genetic testing. They can be especially problematic in multi-gene panels and whole exome sequencing approaches (Domchek & Weber, 2008). This may be a burden on providers who have to distinguish relevant clinical information and determine how to present it to patients. In fact, uncertainty of test result interpretation was most commonly indicated by respondents as the greatest perceived disadvantage associated with genetic testing. This may be due to the burden of interpreting uncertain results and the associated increase in issues related to patient education and counseling.

Like other groups of genetic disorders, the increase in the clinical availability of genetic testing for primary immunodeficiencies has not only led to challenges in interpreting and delivering test results, it may also play a part in the evolution of physician practices. For
example, genetic tests for primary immunodeficiency diseases have been historically used for confirming diagnoses rather than establishing them (Morra et al., 2008). While 63% of respondents indicated confirming a diagnosis as a primary reason for ordering genetic testing, an even higher percentage, 79%, indicated establishing a diagnosis as a primary reason for ordering testing. Also, genetic testing has now been included as a key component in several practice parameters and guidelines for the diagnosis and management of primary immunodeficiency diseases (Bonilla et al., 2005; de Vries, 2006). The increasing importance of genetic tests in routine patient care creates an increased need for patient education regarding the implications of genetic testing.

Interpreting and delivering results of broad genetic testing, which includes multi-gene panels and whole exome sequencing, can often be complex. Based on this, it was expected that providers ordering whole exome sequencing would be more likely to utilize genetic counselors’ expertise to interpret results and provide patient education and counseling. However, the frequency of genetic counseling referrals was not influenced by whether or not whole exome sequencing was ordered, or self-reported knowledge of genetics.

This suggests that additional education is needed to increase awareness of counseling issues associated with genetic testing among primary immunodeficiency diseases providers. The vast majority of respondents indicated that genetic counselors are available at their practice institutions. This availability suggests that genetic counselors may be the ideal healthcare professionals to provide education and counseling to patients given both their availability and focus of practice. Genetic counselors work to help patients understand and adapt to the medical, psychological, and familial implications of the genetic contributions to disease (National Society of Genetic Counselors' Definition Task et al., 2006). Genetic counseling has been shown to
promote the well-being and reduce the anxiety of patients in the general clinic setting (Davey, Rostant, Harrop, Goldblatt, & O'Leary, 2005). While data specific to primary immunodeficiency diseases is not available, genetic counseling for hereditary breast cancer has demonstrated decreases in anxiety and improved accuracy of perceived risk (Meiser & Halliday, 2002). Study data also suggest that cost and insurance coverage concerns continue to be a barrier to genetic testing, which is not unique to primary immunodeficiency diseases. Education by genetic counselors may not change this, but it may be able to help providers better weigh the benefits and limitations against the cost of genetic testing for their patients.

Before non-urgent genetic testing, physicians are encouraged to refer patients for genetic counseling so that the advantages and disadvantages of genetic testing can be discussed and psychosocial issues can be explored (Ameratunga et al., 2011). We found that respondents who indicated establishing a diagnosis as a primary reason for ordering genetic testing were less likely to refer patients for genetic counseling before ordering testing. This was expected based on the primacy of patients’ health and stability over additional information provided by genetic test results.

The Immune Deficiency Foundation recommends that genetic counseling for primary immunodeficiency diseases should be conducted by an immunologist or a genetic counselor who has experience with primary immunodeficiency diseases (Buckley, 2009). Approximately 60% of respondents referred patients to genetic counseling before testing was ordered, but about 40% of respondents did not refer any patients to genetic counseling before ordering genetic testing. In addition approximately 90% of respondents referred patients to genetic counseling after receiving test results, and about 10% of respondents did not refer any patients to genetic counseling after receiving test results.
These data indicate that while providers for primary immunodeficiency diseases are often referring patients to genetic counseling when genetic testing is indicated, there is a lack of counseling, specifically pretest counseling, by genetic counselors for many of these patients. However, 40% of respondents indicated that they always provide pretest counseling to patients not referred to genetic counseling before genetic testing was ordered, and more than half of respondents indicated always providing posttest counseling to patients not referred to genetic counseling after receiving test results. More than half of respondents discussed the genetic testing process, health implications, inheritance patterns, recurrence risk, and testing options for other family members with and provided resources for patients when conducting counseling.

While these data suggest that genetic counseling is being conducted by primary immunodeficiency providers or genetic counselors for a number of patients as recommended by the Immune Deficiency Foundation, previous evidence suggests that patients better understand genetic information provided by genetic counselors compared to medical, non-genetics staff (O'Shea et al., 2011).

This study highlights the need for increased involvement of genetic counselors in the care of patients with or suspected to have primary immunodeficiency diseases. There is currently a lack of genetic counseling, mainly pretest counseling, for many of these patients. As broad genetic testing for primary immunodeficiencies becomes more clinically available and increasingly integrated into practice, the number of results with variants of uncertain significance will rise. Genetic counselors could share the burden of interpreting uncertain test results and providing pretest and posttest counseling to patients. Genetic counselors could also provide education to providers about genetic testing and its associated counseling issues. This will allow providers to better determine which patients are appropriate candidates for genetic testing.
Increased collaboration between primary immunodeficiency disease providers and genetics professionals will allow providers to utilize genetic testing to better establish diagnoses, which will ultimately provide more information about primary immunodeficiency diseases that could lead to improved patient care in the future.
References


### Tables and Figures

**Table 1. Participant Demographic Characteristics**

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**Figure 1.** Frequency genetic testing was ordered for clinically suspected and clinically confirmed primary immunodeficiency diseases

**Figure 2.** Utilization of whole exome sequencing for the purpose of diagnosing primary immunodeficiency diseases
Figure 3. Primary reasons genetic testing was ordered

Figure 4. The frequency with which genetic test results change the course of treatment or management for patients
Figure 5. Greatest perceived disadvantage associated with genetic testing for primary immunodeficiency diseases

Figure 6. Biggest barrier to genetic testing for primary immunodeficiency diseases
**Figure 7.** Proportion of patients referred to genetic counseling

**Figure 8.** Frequency with which respondents provide counseling for patients who are not referred to genetic counseling
Figure 9. Topics discussed by respondents when providing counseling.
Appendix A: Survey

1. Please indicate the number of patients with or suspected to have primary immunodeficiency diseases you have seen in the past year.
   - 0*
   - 1-10
   - 11-20
   - 21-30
   - 31-40
   - >40

*If you have selected 0 as the answer for question 1, thank you for your time and interest, but you do not meet the eligibility requirements for this study.

2. Please indicate your gender.
   - Male
   - Female

3. Please indicate your subspecialty (Check all that apply).
   - Allergy
   - Hematology
   - Immunology
   - Oncology
   - Rheumatology
   - Infectious Diseases
   - Other:________________

4. Please indicate which best describes your primary practice institution.
   - Academic
   - Private
   - Research
   - Other:________________

5. Please indicate which best describes the location of your practice institution.
   - Metropolitan
   - Rural

6. Which type of referral center do you consider your institution to be?
   - Primary
   - Secondary
   - Tertiary

7. Please indicate your primary clinical patient population.
   - Pediatric
   - Adult

8. Please indicate the number of years of experience you have working with patients with primary immunodeficiency diseases.
   _______

9. Please list the 3 most common primary immunodeficiency diseases you saw in the past year (with 1 being the most common).
   1. ________________
   2. ________________
   3. ________________

10. Are there genetic counselors within a 60-mile radius of your practice institution?
   - Yes
   - No
   - Do not know

11. Are there genetic counselors at your practice institution?
   - Yes
   - No
   - Do not know

12. Have you ever contacted genetic counselors at any labs?
   - Yes
   - No

13. How would you describe your knowledge of genetics?
   - Poor
   - Fair
   - Good
   - Very good
   - Excellent

14. In the last year, what percentage of patients with clinically suspected primary immunodeficiency diseases have you ordered genetic testing for?
   - 0%
   - 1-20%
   - 21-40%
   - 41-60%
   - 61-80%
   - 81-100%
15. In the last year, what percentage of patients with clinically confirmed (certain) diagnoses of primary immunodeficiency diseases have you ordered genetic testing for?
   o 0%
   o 1-20%
   o 21-40%
   o 41-60%
   o 61-80%
   o 81-100%

16. Please list the 3 most common primary immunodeficiency diseases you ordered genetic testing for in the past year (with 1 being the most common).
   1. ______________________
   2. ______________________
   3. ______________________

17. Have you considered ordering whole genome/exome analysis for the purpose of diagnosing a primary immunodeficiency disease?
   o Have not considered
   o Have considered
   o Have ordered

18. In general, what is your primary reason for ordering genetic testing? (Check all that apply)
   □ Confirm a diagnosis
   □ Establish a diagnosis
   □ Presymptomatic testing
   □ Prenatal diagnosis
   □ Research purposes
   □ Other:____________________

19. How often do genetic testing results for primary immunodeficiency diseases change the course of treatment or management for patients?
   o Never
   o Rarely
   o Occasionally
   o Frequently
   o Always

20. Indicate which factor associated with genetic testing for primary immunodeficiency diseases you perceive to be the greatest disadvantage.
   o Uncertainty of test result interpretation
   o Possibility of inaccurate test results
   o Possibility of psychosocial burden for patient and family
   o Other:____________________

21. Indicate what you perceive to be the biggest barrier to genetic testing for primary immunodeficiency diseases.
   o Cost of testing
   o Insurance coverage concerns
   o Difficulty identifying clinical laboratory
   o Turnaround time
   o Lack of clinical laboratory standardization
   o Other:____________________

22. When genetic testing is indicated, what percentage of patients do you refer for genetic counseling before testing is ordered?
   o 0%
   o 1-20%
   o 21-40%
   o 41-60%
   o 61-80%
   o 81-100%

23. If patients are not referred for genetic counseling before genetic testing is ordered, how often do you provide pretest counseling?
   o Never
   o Rarely
   o Occasionally
   o Frequently
   o Always

24. When genetic testing is indicated, what percentage of patients do you refer for genetic counseling after receiving genetic testing results?
   o 0%
   o 1-20%
   o 21-40%
   o 41-60%
   o 61-80%
   o 81-100%

25. If patients are not referred for genetic counseling after genetic testing is ordered, how often do you provide post-test counseling?
   o Never
   o Rarely
   o Occasionally
   o Frequently
   o Always

26. In general, if you conduct pretest and/or post-test counseling what do you discuss with or provide to patients? (Check all that apply)
   □ Genetic testing process
   □ Health implications
   □ Inheritance patterns
   □ Recurrence risk
   □ Testing options for other family members
   □ Resources