Cystic Fibrosis Carrier Screening:
Current Practices and Challenges in Genetic Counseling

Master’s Thesis
Presented to

The Faculty of the Graduate School of Arts and Sciences
Brandeis University
Department of Biology, Genetic Counseling Program
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In Partial Fulfillment
of the Requirements for

Master’s Degree

by

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May 2012
ACKNOWLEDGEMENTS

I would like to thank my project advisor, Kate Kramer, for her support, encouragement, and feedback throughout this project. Additional thanks go to my committee members, Elinor Langfelder-Schwind and Elaine Sugarman for their time, expertise, and valuable perspective.

Many thanks to Ted Cross for his statistical assistance, and to Leslie Mandel for her direction in conducting and analyzing the interviews.

To Judith Tsipis, Beth Rosen Sheidley, Gretchen Schneider, and Missy Goldberg for their continuous inspiration, guidance and logistical support.

Thank you to all those who made this project possible: the genetic counselors who shared their knowledge and insight through the survey and interviews; the NSGC Cystic Fibrosis and Prenatal Special Interest Groups for recruitment assistance; and Cindy Ellis and Mulberry Studio, Inc. for transcription services. This work has been supported by the Jane Engelberg Memorial Fellowship Student Research Award, provided by the Engelberg Foundation to the National Society of Genetic Counselors, Inc.; and by the Brandeis University Graduate School of Arts and Sciences Master’s Research Fund.

Finally, to my classmates, friends and family: I am forever grateful for all of your love and support.
ABSTRACT

Cystic Fibrosis Carrier Screening: Current Practices and Challenges in Genetic Counseling

A thesis presented to the Department of Biology, Genetic Counseling Program

Graduate School of Arts and Sciences

Brandeis University

Waltham, Massachusetts

By Erica J. Wellington

Professional practice guidelines for cystic fibrosis (CF) carrier screening recommend the use of a 23 mutation panel that identifies couples at risk of having a child with classic CF while minimizing ambiguous test results. This study evaluated specific genetic counseling challenges that can arise from the use of expanded mutation panels and sequencing for CF carrier screening, and the strategies genetic counselors use to manage these challenges. We surveyed 129 genetic counselors to evaluate current practices. Of those surveyed, six counselors also participated in semi-structured telephone interviews during which they described a challenging case involving CF. The majority of counselors surveyed offer an expanded panel for routine CF carrier testing and order sequencing for at least one clinical
indication. Study participants identified cost-effectiveness, high detection rate, and utility in specific clinical situations as benefits of these tests. However, counselors also felt that expanded panels and sequencing increase the genetic counseling challenges associated with CF carrier testing. Factors described as contributing to counseling challenges included the practices of referring providers, availability of many testing options, complex case management, and ambiguity related to the identification of mild mutations, complex alleles and variants of uncertain significance. Management strategies that counselors found helpful for complicated CF carrier cases included consultation with colleagues, review of the literature, use of professional and laboratory resources, and having specific approaches to counseling. Overall, genetic counselors acknowledge a role for expanded panels and sequencing in CF carrier screening, but would like to see more education for non-genetics professionals, guidelines to create more consistency in test offerings, professional resources for continuing genetic counselor education, and additional research on genotype-phenotype correlation. Especially with regard to genotype-phenotype correlation, future work should focus on clinically useful and realistic goals, including further educating genetic counselors about the ambiguity inherent in CF counseling.

Keywords: cystic fibrosis; carrier screening; mutation panels; sequencing; genotype-phenotype correlation; genetic counseling challenges; professional guidelines
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INTRODUCTION

Cystic fibrosis (CF) is a multisystem disorder characterized in its classic form by persistent pulmonary infection, pancreatic insufficiency, male infertility, and increased salt excretion from the sweat glands. It occurs in one in every 2000 to 3000 Caucasian births, making it one of the most common recessive genetic diseases in this population (Welsh, Ramsey, Accurso, & Cutting, 2001). The disease is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR), which undergoes ATP hydrolysis to transport chloride ions across epithelial apical membranes (Riordan et al., 1989; Welsh et al., 2001). Defects in the protein impair this function, leading to dysfunctional electrolyte transport in the affected systems and the resulting clinical manifestations (Welsh et al., 2001).

More than 1900 pathological mutations have been reported in the CFTR gene (Cystic Fibrosis Mutation Database, 2012), and extensive investigation into the molecular and genetic basis of CF has revealed a high level of allelic, biochemical and phenotypic heterogeneity. CFTR mutations have been classified based on their functional effects: Classes I-III are considered “severe” CF alleles that produce no functional CFTR protein and can lead to the classic CF phenotype. Classes IV-V reduce the level of functional CFTR protein and typically result in variable phenotypes along a spectrum ranging from non-classic CF, characterized by pancreatic sufficiency, lower sweat chloride levels, later age of diagnosis and longer life expectancy, to CFTR-related disorders such as congenital
absence of the vas deferens (CAVD), to subclinical manifestations (Tsui, 1992; Zielenski & Tsui, 1995).

Depending in part on the mutations found, carrier couples are at risk of having a child anywhere along the phenotypic spectrum. However, the functional classifications provide somewhat limited insight into the genotype-phenotype correlation for CF. There is significant clinical variability in all mutation classes, and the phenotype of any individual with CF is affected by a combination of factors, including genotype, clinical management, and environmental influences (Castellani et al., 2008; McKone, Goss, & Aitken, 2006).

The cloning of the CFTR gene in 1989 made possible the identification of carrier individuals, and by extension, couples at risk of having a child with cystic fibrosis. In 2001 the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics (ACMG) released the first set of Clinical and Laboratory Guidelines for CF carrier screening. The guidelines recommended the use of a 25 mutation pan-ethnic panel made up of “all CF-causing mutations known to have an allele frequency of greater than 0.1% (1 in 1,000) among North American patients with CF” (ACOG, ACMG, & NIH, 2001, p. 9). ACMG revised this mutation panel in 2004 to create the currently recommended 23 mutation panel (Watson et al., 2004).

In essence, the guidelines for CF carrier screening aim to establish a testing scheme that identifies couples at risk of having a child with classic CF while avoiding ambiguous test results and unnecessary risky fetal diagnostic procedures. To this end, professional organizations have remained consistent in their recommendations over the past decade that the mutations included on a screening panel should be the more common mutations that put couples at a 25% risk of having a child with classic cystic fibrosis (ACOG, 2005, 2011;
Mennuti, Thomson, & Press, 1999; Watson et al., 2004). However, surveys of laboratory directors, physicians and genetic counselors suggest that CF carrier screening practices vary in comparison to these guidelines through the use of full gene sequencing and expanded mutation panels that include mild mutations, complex alleles and poorly studied sequence changes (Kaufman et al., 2008; Morgan, Driscoll, Mennuti, & Schulkin, 2004; Langfelder-Schwind et al., 2011).

Use of the ACMG 23 mutation panel does not guarantee avoidance of prognostic ambiguities; the 2004 guidelines recognize that inclusion of the R117H mutation complicates the stated goals of screening since it may be associated with a mild or severe phenotype depending on chromosomal background (Watson et al., 2004). However, the use of expanded panels and sequencing may further increase the complexities involved with counseling about CF carrier screening. The study described here evaluated specific counseling challenges that can arise from the use of expanded panels and sequencing for CF carrier screening, and the responses of genetic counselors to these challenges. Establishing this baseline description of challenges and management strategies is one of the first steps toward helping genetic counselors to provide accurate, consistent and clinically useful CF counseling as part of quality preconception and prenatal patient care.
METHODS

Study Design

The first part of the study consisted of a survey that queried genetic counselors about their current CF carrier screening practices, the challenges they have encountered, strategies used to manage challenging cases, and their opinions on the current state of CF carrier screening.

In the second part of the study, a subset of genetic counselors were interviewed about a challenging case they had encountered, management strategies used, patient response to the counseling, and general questions about the use of expanded panels and sequencing for CF carrier screening.

Sample and Recruitment

The study protocol was approved by the Brandeis University Committee for Protection of Human Subjects. Genetic counselors routinely involved in any aspect of preconception and/or prenatal CF carrier screening as part of their clinical practice within the two years prior to recruitment (December 2009–December 2011) were eligible to complete the survey. Counselors who reported managing a challenging CF carrier screening case were eligible to participate in the interviews.

The survey recruitment notice (see Appendix A) was posted to three National Society of Genetic Counselors (NSGC) discussion forums in late December 2011 and early January 2012: the NSGC General Discussion forum, and both the Cystic Fibrosis and
Prenatal Special Interest Group (SIG) forums. The recruitment notice was also sent electronically to all NSGC members twice in January 2012. At the end of the survey, participants were given the opportunity to volunteer for the interview portion of the study; invitations to participate in an interview were issued to eligible counselors in late January 2012.

Data Collection and Analysis

Quantitative data was collected using an anonymous, web-based survey designed and administered through Qualtrics®. The survey was available from December 27, 2011 through January 31, 2012 and consisted of 35 questions that were primarily multiple-choice items, with some write-in responses (see Appendix B).

Interview volunteers were asked to complete an interview prescreen, which requested background information and an indication of the type of case they wished to discuss (see Appendix C). Informed consent was obtained from interview participants (see Appendix D), and additional background information was collected prior to the interview (see Appendix E). Interview participants were given an ID number to protect confidentiality. Telephone interviews took place between January 20, 2012 and February 21, 2012. Interviews followed a semi-structured interview guide (see Appendix F), and were digitally recorded and transcribed for coding; the average interview time was 30 minutes.

Survey data was analyzed using SPSS 19.0.0 to calculate descriptive and standard bivariate statistics. Atlas.ti 6 was used to code themes in interview data.
RESULTS

Sample Characteristics

There were 158 survey respondents, of whom 129 were eligible and initiated the survey. Eleven survey participants volunteered for the interview portion of the study. Two were ineligible because they had not encountered any challenging cases; of the nine counselors invited to participate, six completed interviews. Demographic characteristics of the participants are shown in Table 1.

Almost all survey participants (93.0%) indicated being involved in prenatal counseling, and about a quarter (27.8%) practiced pre-implantation genetic diagnosis (PGD)/preconception counseling. The majority of survey participants were female counselors (99.1%) working full-time (80.0%), with greater than 50% of their work time spent in clinical counseling (89.5%), and seeing fewer than 20 patients per week for preconception or prenatal counseling (87.7%). Most participants saw more prenatal than preconception patients (89.5%), and counseled about CF carrier testing once a day or more (56.1%).

Interview participants reported specializing in four counseling areas: prenatal (66.7%), PGD/preconception (50.0%), infertility (33.3%), and CF specialty clinic (16.7%). All were female. Half of the interviewees saw fewer than 10 patients per week for preconception or prenatal counseling; the other half saw more than 10 patients per week. The majority saw more prenatal cases than preconception cases (66.7%), and half
counseled about CF carrier testing once a day or more, while the other half counseled on this topic less frequently.

Table 1. Demographic characteristics of study participants

<table>
<thead>
<tr>
<th>Specialty/Type of Practice</th>
<th>Survey Participants</th>
<th>Interview Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Prenatal</td>
<td>93.0</td>
<td>107</td>
</tr>
<tr>
<td>PGD/Preconception</td>
<td>27.8</td>
<td>32</td>
</tr>
<tr>
<td>Infertility, ART/IVF</td>
<td>9.6</td>
<td>11</td>
</tr>
<tr>
<td>CF Specialty Clinic</td>
<td>8.7</td>
<td>10</td>
</tr>
<tr>
<td>Public Health/Newborn Screening</td>
<td>3.5</td>
<td>4</td>
</tr>
<tr>
<td>Adult</td>
<td>12.2</td>
<td>14</td>
</tr>
<tr>
<td>Pediatric</td>
<td>19.1</td>
<td>22</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.7</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>1.7</td>
<td>2</td>
</tr>
<tr>
<td>Primary Work Setting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>University Medical Center</td>
<td>40.8</td>
<td>47</td>
</tr>
<tr>
<td>Private Hospital</td>
<td>23.5</td>
<td>27</td>
</tr>
<tr>
<td>Public Hospital</td>
<td>11.3</td>
<td>13</td>
</tr>
<tr>
<td>Physician's Private Practice</td>
<td>12.2</td>
<td>14</td>
</tr>
<tr>
<td>Health Maintenance Organization</td>
<td>6.1</td>
<td>7</td>
</tr>
<tr>
<td>Commercial Diagnostic Laboratory</td>
<td>0.9</td>
<td>1</td>
</tr>
<tr>
<td>University/Non-Medical Center</td>
<td>2.6</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>2.6</td>
<td>3</td>
</tr>
<tr>
<td>Years Experience as a Genetic Counselor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-10 years</td>
<td>65.8</td>
<td>75</td>
</tr>
<tr>
<td>11-20 years</td>
<td>26.3</td>
<td>30</td>
</tr>
<tr>
<td>&gt; 20 years</td>
<td>7.9</td>
<td>9</td>
</tr>
<tr>
<td>Job Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Time</td>
<td>80.0</td>
<td>92</td>
</tr>
<tr>
<td>Part Time</td>
<td>20.0</td>
<td>23</td>
</tr>
<tr>
<td>Time Spent in Clinical Counseling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50% of time</td>
<td>10.5</td>
<td>12</td>
</tr>
<tr>
<td>&gt; 50% of time</td>
<td>89.5</td>
<td>102</td>
</tr>
<tr>
<td>NSGC Region&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8.8</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>27.2</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>10.5</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>22.8</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>8.8</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>21.9</td>
<td>25</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>99.1</td>
<td>114</td>
</tr>
<tr>
<td>Male</td>
<td>0.9</td>
<td>1</td>
</tr>
<tr>
<td>Patients Per Week for Preconception or Prenatal Counseling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-9</td>
<td>41.2</td>
<td>47</td>
</tr>
<tr>
<td>10-19</td>
<td>46.5</td>
<td>53</td>
</tr>
<tr>
<td>≥ 20</td>
<td>12.3</td>
<td>14</td>
</tr>
<tr>
<td>Patients Seen for Prenatal (Versus Preconception) Counseling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50% prenatal</td>
<td>10.5</td>
<td>12</td>
</tr>
<tr>
<td>&gt; 50% prenatal</td>
<td>89.5</td>
<td>102</td>
</tr>
<tr>
<td>Frequency of Counseling about CF Carrier Testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than once a week</td>
<td>20.2</td>
<td>23</td>
</tr>
<tr>
<td>1-3 times a week</td>
<td>23.7</td>
<td>27</td>
</tr>
<tr>
<td>Once a day or more</td>
<td>56.1</td>
<td>64</td>
</tr>
</tbody>
</table>

<sup>1</sup>Participants were asked to indicate all practice specialties as they relate to CF carrier screening, therefore percentages add to greater than 100 and frequencies to greater than 115 for the survey and greater than 6 for the interviews.

<sup>2</sup>Region 1: CT, MA, ME, NH, RI, VT, CN Maritime Provinces; Region 2: DC, DE, MD, NJ, NY, PA, VA, WV, PR, VI, Quebec; Region 3: AL, FL, GA, KY, LA, MS, NC, SC, TN; Region 4: AR, IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, OK, SD, WI, Ontario; Region 5: AZ, CO, MT, NM, TX, UT, WY, Alberta, Manitoba, Saskatchewan; Region 6: AK, CA, HI, ID, NV, OR, WA, British Columbia
Current Practices

Survey participants were asked to indicate the type of test they most commonly offer to couples with no known family history of CF: the ACMG recommended 23 mutation panel, an expanded panel (and if so, number of mutations), CFTR sequencing, a mutation panel with reflex CFTR sequencing, or another type of test. Mutation panel sizes were coded into the ranges shown in Figure 1. There were 15 responses that could not be coded into a range because counselors indicated that the panel they used varied based on certain variables, including patient ethnicity, patient choice, testing indication and insurance coverage. Subsequent analyses include only those responses contained in one of the ranges shown.

The majority of participants (86.0%) regularly used expanded mutation panels. Only 13.2% used the ACMG 23 mutation panel, and only one participant routinely used sequencing as a carrier test. No participants routinely offered a mutation panel with reflex sequencing. Expanded panels varied in the number of mutations included, with the most common panel sizes being 97 (n = 38), 32 (n = 13), 40 (n = 11) and 100 or more (n = 10).
Other panel sizes were less common, but tended to cluster around these numbers. Only 5.4% of participants reported that the CF test they offer most often is part of a multiplex assay that includes other recessive disorders.

Figure 2 shows situations in which counselors ordered sequencing rather than a mutation panel for carrier testing when there is no known family history of CF.

Sequencing was ordered by two-thirds of counselors when testing the partner of a CF carrier, and by one-third of counselors when the patient asked for sequencing. Common indications for ordering sequencing that were volunteered by participants as write-in responses included detection of fetal echogenic bowel on ultrasound and as a follow-up to a negative result with a mutation panel. Almost 20% of counselors never ordered sequencing, and one-third of counselors ordered sequencing for more than one indication.

**Counseling Challenges**

Based on a literature review and discussions amongst the investigators, seven scenarios were presented in the survey that can arise as a result of using expanded panels
and sequencing and are potentially challenging for genetic counselors. Survey participants were asked how often they encounter each scenario and how challenging they find each to be. Table 2 describes the scenarios encountered and shows the frequency with which they are encountered.

### Table 2. Scenarios encountered with CF carrier screening (N = 125)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Counselors Encountering¹</th>
<th>How Often Scenario is Seen²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counseling about genotype-phenotype correlation when mutations associated with <strong>non-classic CF</strong> (pancreatic sufficiency, lower sweat chloride levels, later diagnosis) are detected [GP correlation non-classic CF]</td>
<td>84.8 106</td>
<td>1.58</td>
</tr>
<tr>
<td>Counseling about genotype-phenotype correlation when mutations associated with a <strong>CFTR-related disorder</strong> (such as isolated CBAVD, sino-pulmonary disease, or chronic pancreatitis) are detected [GP correlation CFTR-related disorder]</td>
<td>84.8 106</td>
<td>1.53</td>
</tr>
<tr>
<td>Offering prenatal diagnosis or counseling about prenatal diagnostic results when the father of the baby is unavailable for carrier testing [PND FOB unavailable]</td>
<td>80.8 101</td>
<td>2.00</td>
</tr>
<tr>
<td>Offering prenatal diagnosis when a fetus is at risk for non-classic CF or an adult-onset CFTR-related disorder based on parental carrier test results [PND non-classic or CFTR-related disorder]</td>
<td>72.8 91</td>
<td>1.44</td>
</tr>
<tr>
<td>Counseling about genotype-phenotype correlation when <strong>complex alleles</strong> are detected [GP correlation complex alleles]</td>
<td>67.2 84</td>
<td>1.29</td>
</tr>
<tr>
<td>Counseling about variants of uncertain significance [VUS]</td>
<td>52.8 66</td>
<td>1.35</td>
</tr>
<tr>
<td>Detection through carrier testing of mildly affected individuals with two <strong>CFTR</strong> mutations in trans [Mildly affected]</td>
<td>40.0 50</td>
<td>1.24</td>
</tr>
<tr>
<td>Other</td>
<td>7.2 9</td>
<td>-</td>
</tr>
<tr>
<td>None of the above</td>
<td>4.0 5</td>
<td>-</td>
</tr>
</tbody>
</table>

¹Participants were asked to indicate all scenarios encountered, therefore percentages add to greater than 100 and frequencies to greater than 125.
²Amongst counselors encountering.
³Scale: 1 - Rarely; 2 - Sometimes; 3 - Quite Often; 4 - Very Often

Of the seven scenarios presented in Table 2, six had been encountered by more than half of respondents; three of these had been encountered by greater than 80% of respondents. However, the frequency with which each scenario was encountered by individual counselors was low, ranging from rarely to sometimes. When asked how challenging they find these scenarios to be, counselors ranked the challenges between 3.94 and 5.04 on a scale from 1 (“Not challenging at all”) to 7 (“Extremely challenging”). All
seven scenarios were ranked as more challenging than counseling about classic CF, which had an average challenge score of 2.81 on the same scale (see Figure 3).

![Figure 3. Mean challenge level compared to classic CF]

In order to learn more about the challenges encountered during CF carrier screening, survey participants reporting experience with a case they perceived as challenging were invited to participate in semi-structured interviews. Interview participants were asked to describe the case and highlight specific aspects that made it challenging. Table 3 shows the background of each case, the testing panel that was used for each partner involved, and the test results.
<table>
<thead>
<tr>
<th>Participant/Case</th>
<th>Background/Reason for Referral</th>
<th>Testing Panel Used</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>(F) tested through OB; GC offering carrier testing to (M); then discussing PND in context of two mild mutations.</td>
<td>(F)&amp;(M): 97 panel</td>
<td>(F): mild mutation; (M): mild mutation</td>
</tr>
<tr>
<td>1b</td>
<td>(F) tested by OB and told she was a carrier; (F) affected status discovered by GC after referral made; GC offering testing to (M).</td>
<td>(F): 23 or 30 panel; (M): sequencing</td>
<td>(F): ΔF508/mild mutation; (M): negative</td>
</tr>
<tr>
<td>2</td>
<td>(F)&amp;(M) tested through referring provider; GC discussing PND in context of previously undescribed variant and poorly characterized mutation.</td>
<td>(F)&amp;(M): sequencing</td>
<td>(F): c.2988+19C&gt;T intron 16 (variant); (M): c.2620-26A&gt;G intron 14a (mutation)</td>
</tr>
<tr>
<td>3</td>
<td>(F)&amp;(M) tested after previous child's NBS; GC discussing PND in context of R117H and 5T.</td>
<td>(F)&amp;(M): targeted based on NBS follow-up testing</td>
<td>Partner 1: R117H-7T (cis); Partner 2: 5T carrier</td>
</tr>
<tr>
<td>4</td>
<td>GC discussing testing options and results/implications in context of IVF due to (M) with CAVD²</td>
<td>Most couples choose sequencing, either starting with (M) or concurrently</td>
<td>N/A</td>
</tr>
<tr>
<td>5</td>
<td>(F)&amp;(M) tested through referring provider; GC discussing sequencing and reproductive options in context of CAVD and partner with 5T/7T.</td>
<td>(F)&amp;(M): 70 panel</td>
<td>(F): 5T/7T; (M): classic mutation, 5T (phase unknown)</td>
</tr>
<tr>
<td>6</td>
<td>(F)&amp;(M) tested through referring provider; GC discussing PND in context of poly(T) variant and R117H.</td>
<td>(F)&amp;(M): 35 panel</td>
<td>(F): R117H; (M): poly(T) variant</td>
</tr>
</tbody>
</table>

¹This table reflects the primary cases discussed in the interviews, however, comments provided by the participants were sometimes in reference to these cases and sometimes in reference to carrier screening in general. (F) = Female partner; (M) = Male partner; GC = Genetic Counselor study participant; OB = Obstetrician; PND = Prenatal Diagnosis; NBS = Newborn Screening; IVF = In Vitro Fertilization; CAVD = Congenital Absence of the Vas Deferens
²This participant described a general referral scenario rather than a specific case.

Numerous factors were identified by the interview participants as contributing to the challenging nature of these and other CF carrier screening cases. The most commonly cited factors are shown in Table 4 and can be separated into three major themes: external factors, ambiguity, and case management. External factors include the practices of non-genetic counselor providers or laboratories, and cost considerations that go into testing. Ambiguity involves the difficulty in conveying variability of clinical symptoms and an uncertain prognosis, and the limited genotype-phenotype information available in the literature for counselors to draw upon during their case preparation. Regarding case management, case preparation was perceived as challenging due to the need for additional
research to investigate the significance of particular mutations, coordinating testing to establish *cis* or *trans* orientation, and determining the most appropriate testing for a partner. Additionally, clinical counseling challenges were attributed to the need for involved counseling sessions during which a great deal of complex information must to be conveyed to the patient in a manner that is understandable and facilitates decision-making.
<table>
<thead>
<tr>
<th>Factor (n)</th>
<th>Sample Quotation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>External Factors</strong></td>
<td></td>
</tr>
<tr>
<td>Correcting information given to patient by previous providers or on lab report (6)</td>
<td>They were first told by their OB that they were both carriers and that they were at risk to have a child with cystic fibrosis, so they were put on kind of the highest alert. And then when they came to see me I said, &quot;Well, this isn't classic. [There] is going to be some variability. This is going to be possibly more mild.&quot; And then they were both encouraged by that, and confused. (Participant 6)</td>
</tr>
<tr>
<td>Incorporating insurance/cost considerations into testing decisions (5)</td>
<td>Mutation panels make my life incredibly difficult, because you have to spend an inordinate amount of time counseling patients about, &quot;Well your insurance wants you to use this lab, which only does 32 mutations, but I know your partner is a carrier, so I really want you to do this panel that does 107 mutations and will give you a further risk reduction, but you're going to have to pay out of pocket for that.&quot; Then you have to talk risks versus benefits of panels, and detection rates and statistics. And really, the patient couldn’t care less. They just want your recommendation on where to go get their blood drawn. But because one is insurance covered and one is out of pocket you have to try to educate them on the subtleties of CF panels. (Participant 5)</td>
</tr>
<tr>
<td><strong>Ambiguity</strong></td>
<td></td>
</tr>
<tr>
<td>Conveying variability of clinical symptoms and uncertain prognosis (5)</td>
<td>Trying to relate information about the variability [...] of the possible symptoms related to that genetic combination is challenging. And then especially kind of how it could present differently in a future pregnancy. If it's a male child, could [he] possibly have CBAVD? Maybe. Could [a child] maybe be symptomatic, yes. So just the kind of ambiguity around the prognosis that we were able to give the family [...], I found that the most challenging. (Participant 3)</td>
</tr>
<tr>
<td>Limited information in literature on genotype-phenotype correlation for mutations present (4)</td>
<td>It's very hard when you talk about the unknown. It's very, very hard for anyone to be comfortable with it. (Participant 6)</td>
</tr>
<tr>
<td><strong>Case Management</strong></td>
<td></td>
</tr>
<tr>
<td>Further investigating mutation characteristics (4)</td>
<td>I had to do a lot of legwork to make sure I knew what these variants meant. I had to break it down into, at the end of the day what does this mean? [...] I think that was the hardest part: it was my job to research these, make sure that what we're saying is correct. And then once I got into the session I felt pretty good, but it still leaves a little pit in your stomach with these variants because they haven’t been seen that often, but we’re making a call for this family. So I felt like that was still a little scary truthfully, because you can do all the research in the world and someone will come out with a new paper and then maybe change their mind. [...] I had to really shelve any of my lingering, nagging feelings of unease. But I think that’s what variants do to us; they put us in a really difficult situation. (Participant 2)</td>
</tr>
<tr>
<td>Having involved counseling sessions and conveying complex information (4)</td>
<td>I think people are more familiar with thinking of [CF] as a mutation, pretty simple, pretty straightforward, kind of black and white. But now we’re introducing some of the complexities of not only looking for mutations and polymorphisms, whether that be TG repeats or poly(T) tracts and how that plays into the phenotype that they’re faced with, but then also the possibility of, okay, we could find very clear-cut mutations that are well-defined, well-documented, we have a real good sense of what they mean. We could find rare mutations where we don’t have as good a sense of what they mean. We may find variants of unknown significance where we may be guessing at what impact it has based on how it’s predicted to affect gene product, and we may have absolutely no clue. So just trying to get them to understand all those complexities and what it means for them and their particular diagnosis, and then [...] also considering [...] a common mutation [panel] versus sequencing for [the partner] and then putting those two results together to give them a residual risk for offspring. [...] A lot of questions usually come from all of that. (Participant 4)</td>
</tr>
</tbody>
</table>
Role of Expanded Panels and Sequencing

Two-thirds of survey participants (68.1%) felt that the practice of offering expanded panels and sequencing for CF carrier screening increases genetic counseling challenges, as compared to use of the ACMG 23 mutation panel. About one quarter (23.5%) felt that this practice does not increase the counseling challenges, and 8.4% were unsure. Although expanded panels and sequencing may increase the number of challenging scenarios that counselors face, counselors felt that there are also potential advantages to these tests. Table 5 shows some of the advantages and disadvantages of expanded panels and sequencing described by interview participants.

Among survey participants, there was a moderate positive correlation between the number of circumstances for which sequencing was ordered and the overall mean of how often challenges were seen (Pearson Correlation = 0.284; p < 0.01; N = 114). In contrast, no correlation was observed between the size of the mutation panels and the overall mean of how often challenges were seen (Spearman’s rho Correlation = -0.022; p = 0.827; N = 98).
Table 5. Advantages and disadvantages of expanded panels and sequencing identified in interviews (N = 6)

<table>
<thead>
<tr>
<th>Advantages (n)</th>
<th>Sample Quotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Useful for particular indications, such as:</td>
<td>Yeah, I mean definitely there’s advantages. If I’m just doing general population screening I have no problem doing a small panel, because for the most part that’s going to be your biggest bang for the buck, and it's easy and it's concise, and it addresses your major risk factors. But if I know that somebody's partner is a carrier or somebody has CBAVD or somebody has a family history, I'm going to do the biggest panel I can get my hands on, just because it gives you a better statistic. [...] So sure, I use expanded panels, even though I think it's not the first place to go; [...] I recognize that on a population level you can only offer so much to everyone, and the smaller panels are fine for someone who is coming in with general risk factors, who’s Caucasian. (Participant 5)</td>
</tr>
<tr>
<td>Partners of individuals with CF or CF carriers (4)</td>
<td></td>
</tr>
<tr>
<td>Non-Caucasians (3)</td>
<td>Yeah, I mean definitely there’s advantages. If I’m just doing general population screening I have no problem doing a small panel, because for the most part that’s going to be your biggest bang for the buck, and it's easy and it's concise, and it addresses your major risk factors. But if I know that somebody's partner is a carrier or somebody has CBAVD or somebody has a family history, I'm going to do the biggest panel I can get my hands on, just because it gives you a better statistic. [...] So sure, I use expanded panels, even though I think it's not the first place to go; [...] I recognize that on a population level you can only offer so much to everyone, and the smaller panels are fine for someone who is coming in with general risk factors, who’s Caucasian. (Participant 5)</td>
</tr>
<tr>
<td>Fetal echogenic bowel (1)</td>
<td></td>
</tr>
<tr>
<td>Useful for maximizing information provided to patients (3)</td>
<td>Certainly an advantage I think is [a panel with more mutations] is going to detect a lot more carriers. And I think it’s incredibly useful information for patients to have whether it’s a mild mutation or not. [...] I think it's really helpful for other health concerns. I think men being born with CBAVD might like to know why, and not just get the big surprise suddenly when they can’t have children. (Participant 1)</td>
</tr>
<tr>
<td>Cost-effective (2)</td>
<td>I think the option of expanded panels offer very good tests for the money, when you kind of look at the cost effectiveness of things. (Participant 3)</td>
</tr>
<tr>
<td>Highest detection rate from sequencing (2)</td>
<td>The clear advantage is [sequencing] offers the highest detection rate that we can get with a carrier test. (Participant 4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disadvantages (n)</th>
<th>Sample Quotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases chance of finding complex alleles, mild alleles, VUS (5)</td>
<td>It’s always difficult to get some sort of novel mutation or variant of uncertain significance and counsel on that. In the prenatal world one of the hardest things to counsel on is that uncertain significant piece. (Participant 6)</td>
</tr>
<tr>
<td>Too many options</td>
<td></td>
</tr>
<tr>
<td>Patient understanding about testing options and meanings (3)</td>
<td>And I think [...] because there are so many different tests out there patients don't always know what they had, or what testing might mean. (Participant 3)</td>
</tr>
<tr>
<td>Difficult to be consistent with offerings (2)</td>
<td>I think it is challenging to figure out, or to be as consistent with the patient population that you're seeing, with so many different choices. And I think sometimes you're limited by the facility you work at or contacts or vice versa, so you're not always able to pick the test you want. (Participant 3)</td>
</tr>
<tr>
<td>Test choice influenced by non-medical factors (1)</td>
<td>And also it’s not just the decision making about doing testing at all, [but] if they’re doing testing, do they want to do full sequencing with deletion analysis or do they want to do common mutation testing; sometimes insurance plays into their decision making process. (Participant 4)</td>
</tr>
<tr>
<td>Creates frustration for patient and counselor and more work for counselors (3)</td>
<td>And then there are labs that think that to put a bigger number on their paper and say that their panel has more things in it they should throw in some variants. And then you get somebody that's positive for one of those, and they say, ’Oh your person [has] a positive CF test. The change that we found is most likely a variant of unknown significance.' And you're like, 'Then why is it on your panel?' So things like that drive me crazy. (Participant 5)</td>
</tr>
<tr>
<td>Difficulties in interpretation by non-genetics providers (2)</td>
<td>I’d say probably the biggest downside is if it’s not a geneticist, you know, genetic counselor, MD genetics professional, ordering the test and discussing it with the patient or reviewing the results, the potential for misinterpretation is pretty extreme. (Participant 4)</td>
</tr>
</tbody>
</table>

| 16 |
Management Strategies

Survey participants identified several strategies they use to manage challenging CF carrier screening cases. Colleague consultation was the most common strategy reported; all 113 participants responding to this item consulted at least one colleague as a strategy to manage challenging cases. The most common consults were with a genetic counselor colleague (90.3%), a lab colleague (70.8%), and/or a physician colleague (60.2%). Less common consultations included CF clinics or specialists (2.7%), nurses (1.8%), and other professionals such as pulmonologists and sonographers (1.8%). Other common strategies used were individual research (90.3%), and obtaining information from the testing laboratory (80.5%). Three participants noted using the resources of a professional organization, including the NSGC Discussion Forum, NSGC CF SIG and the National CF Foundation annual meeting. Table 6 provides a more detailed description of the management strategies used for challenging cases obtained from interview participants.

Table 6. Management strategies used by interview participants (N = 6)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Preparation</td>
<td></td>
</tr>
<tr>
<td>Consult with colleagues outside of testing laboratory</td>
<td>4</td>
</tr>
<tr>
<td>Use testing laboratory resources</td>
<td>4</td>
</tr>
<tr>
<td>Use published literature and databases</td>
<td>4</td>
</tr>
<tr>
<td>Case Management</td>
<td></td>
</tr>
<tr>
<td>Document session for patient and referring provider</td>
<td>5</td>
</tr>
<tr>
<td>Meet or speak with patient multiple times through testing or decision-making process</td>
<td>4</td>
</tr>
<tr>
<td>Spend a great deal of time with patient explaining information (including pre-test session)</td>
<td>3</td>
</tr>
<tr>
<td>Information Giving</td>
<td></td>
</tr>
<tr>
<td>Explain process of evaluating mutations and risks</td>
<td>3</td>
</tr>
<tr>
<td>Explain scientific concepts</td>
<td>3</td>
</tr>
<tr>
<td>Use visuals and provide patient education materials</td>
<td>3</td>
</tr>
<tr>
<td>Layer complex information, explaining in stages</td>
<td>2</td>
</tr>
<tr>
<td>Explain information multiple times</td>
<td>2</td>
</tr>
<tr>
<td>Share case examples to illustrate variability of clinical outcome</td>
<td>1</td>
</tr>
<tr>
<td>Psychosocial Counseling</td>
<td></td>
</tr>
<tr>
<td>Prioritize obtaining and explaining information most relevant to patient decision-making</td>
<td>5</td>
</tr>
<tr>
<td>Check-in throughout session for patient understanding and questions</td>
<td>2</td>
</tr>
<tr>
<td>Validate patient feelings</td>
<td>2</td>
</tr>
</tbody>
</table>
Proposed Changes and Additional Resources

The majority of survey participants reported that they would not change anything about their institution’s practices or their own genetic counseling practices with regards to CF carrier screening (65.4% and 85.0%, respectively; N = 127). Of those who would change some of the practices surrounding CF carrier screening, proposed changes fell into three categories: testing practices, type of testing, and management resources. Interview participants proposed similar changes (see Table 7).

<table>
<thead>
<tr>
<th>Table 7. Proposed changes to CF carrier screening practices</th>
<th>Survey (n)</th>
<th>Interviews (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Testing Practices</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More education for and change in practices of non-genetics providers</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>More standardization of testing by indication across all providers</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Changes in who is offered screening (offer to all, offer based on ethnicity, offer sequencing when partner is a carrier)</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>Changes to cost and insurance coverage (less expensive testing, more transparency with pricing, better insurance coverage)</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Consistent pre-test counseling by genetic counselor or more time for pre-test session</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td><strong>Type of Testing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of larger panel more generally</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>Use of larger panel for non-Caucasians</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Offer CF testing as part of multiplex test</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Remove non-disease causing mutations from panels</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td><strong>Management Resources</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuing education</td>
<td>88</td>
<td>1</td>
</tr>
<tr>
<td>Better patient education materials</td>
<td>73</td>
<td>2</td>
</tr>
<tr>
<td>More exposure during graduate training</td>
<td>22</td>
<td>-</td>
</tr>
<tr>
<td>More genotype-phenotype correlation research and resources</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>On the job training/CF clinic observation</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>
DISCUSSION

Expanded Panels, Sequencing and Counseling Challenges

This study investigated the genetic counseling challenges that can arise from the use of expanded panels and sequencing for CF carrier testing in the preconception and prenatal settings. The data presented here reveals that large expanded mutation panels (greater than 60, but less than 100 mutations) are the carrier tests used most often when there is no known family history of CF, and that sequencing is ordered under certain clinical circumstances. Despite professional practice recommendations, fewer than 20% of counselors routinely use the ACMG 23 mutation panel. Counselors indicated that expanded panels and sequencing are useful for partners of individuals with CF or known CF carriers, for non-Caucasians, and when there is a fetal indication such as echogenic bowel on ultrasound. In addition, counselors felt that there is value to the patient in providing the most information available from testing, despite the risk of ambiguity in the information.

While counselors recognized certain benefits to these tests, the majority of study participants felt that, in general, the use of expanded panels and sequencing increases the genetic counseling challenges associated with CF carrier testing, as compared with use of the ACMG 23 mutation panel. Data from this study clearly suggests that sequencing increases the counseling challenges associated with CF carrier screening. The relationship between the use of expanded panels and counseling challenges is likely much more complicated. There is variability in the make-up of expanded panels, and challenges can arise from the inclusion of mild, complex or variant alleles on any size panel; in other
words, mutation panel content is more important than size when it comes to counseling complexities.

Furthermore, use of the ACMG 23 mutation panel does not guarantee avoidance of prognostic ambiguities, particularly with the inclusion of the R117H mutation, whose expression is modified by CFTR intron 8 poly(T) and TG variants. Three of the seven cases described in the interviews in this study involved counseling about R117H and/or 5T alleles. It is possible that these challenges would also have been seen with use of the ACMG 23 mutation panel, although patients in these cases were not necessarily tested for 5T status according to published guidelines (i.e. as a reflex test after identification of an R117H mutation).

Several of the challenging scenarios presented in the survey had been experienced by a majority of participants, although individual participants reported that these scenarios are seen relatively infrequently in clinical practice. The scenarios were consistently ranked as more challenging than counseling about classic CF due to factors such as ambiguous results, misinterpretation of results by non-genetics providers, and the number of available testing options.

Qualitative data from the interviews reveals that ambiguity due to the identification of mild mutations, complex alleles, and variants of uncertain significance is one of the most significant factors contributing to the challenging nature of these cases. As counselors prepared for these types of cases, they discovered that there was limited information available in the literature detailing the clinical significance of the mutations present, making it “really hard to discuss with the patient exactly how their child was going to be affected” (Participant 1). Counselors felt that discussing an uncertain prognosis can be
frustrating for patients, and for the counselors themselves, when patients feel the need for answers to unanswerable questions in order to make testing or reproductive decisions.

Counselors indicated that they would like to see more research and resources related to the genotype-phenotype correlation of non-classic CF mutations. Such resources could include an updated mutation database and research on how genotype-phenotype correlation information influences reproductive decision-making of patients. A common theme among interview participants was the desire for resources specifically from NSGC to ensure consistent quality. Suggestions for NSGC materials included patient education resources, provider education materials, genotype-phenotype correlation information, and communication tools for discussing challenging cases and making referrals.

While additional research and resources may reduce some of the challenges associated with CF counseling, it is also worth reflecting on the ultimate goal of this counseling. For example, some participants pointed out that prognostic ambiguity is not unique to cystic fibrosis counseling; as one survey participant noted, “CF is not that different from any other condition; there are unknowns, and complexity abound[s] in genetics. […] It is our job to discuss test results and reproductive options based on a patient's situation and help them make decisions, not offer diagnosis. We can't predict severity of Down syndrome, only give an idea of range, so this is what we should be doing for CF as well.”

Even as more is discovered about specific CFTR sequence changes, it is likely that counseling on this topic will always involve discussing a range of clinical severity and the importance of appropriate clinical management for improving outcomes. Finding a balance between learning as much as science will allow about genotype-phenotype generalizations and increasing comfort with counseling about the unknown may be a more realistic goal than searching for exact prognoses based on specific genotypes.
An additional challenge identified by genetic counselors was the frequent need to correct information for patients following inadequate pre-test counseling or misinterpretation of complicated test results by an outside provider. Overall, counselors felt that many improvements could be made in the practices of referring providers, particularly in the areas of indications for carrier testing, timing in pregnancy (ideally pre-conception or first trimester), extent of pre-test counseling, and quality of referral records.

Counselors also reported that the number of testing options creates challenges; the availability of numerous different panels means there is no consistency in test offerings across patients and indications, there is a greater possibility that test choice will be influenced by non-medical factors like insurance coverage, and it can be difficult for patients to understand their options and the meaning of test results with regards to factors such as residual risk.

To avoid some of these challenges, counselors would like to see more consistent practices amongst all providers. However, there was not widespread support in this sample of counselors for use of the ACMG 23 mutation panel. Of all the survey participants who would like to see a change in the type of testing offered, only one mentioned reducing the number of mutations on the panels currently used. Others suggested that a larger panel be used more generally or for non-Caucasians, or that CF testing be offered as part of a multiplex test.

One interview participant summarized the utility and drawbacks of the current testing methodologies:

“So [current practices make] more work truthfully, but […] I know of people who have cystic fibrosis and I know that this is important information for our patients so […] I personally like the idea of an expanded panel for non-Caucasians, a panel that is targeted for ancestry for Caucasians and then sequencing, I still think we kind of have to do it for
[the partner of] a ΔF508 carrier. But then […] we end up hitting these variants. I still think it’s worth it, but I do see why people don’t go right directly to sequencing; it’s really not a good screening methodology because of all these things that come up. We don’t want this coming up all the time. We really don’t. But I guess I am sort of on board with the current way we do it. I feel like there’s utility in it even if it makes our lives more difficult at times” (Participant 2).

It appears that counselors support keeping the current tests that are available, but they would like to see more consistency in the way testing is offered, including the type of testing offered by indication, guidelines on when and to whom particular tests/panels are offered, and consistent coverage by insurance companies so that test choices are made based on medical criteria rather than financial considerations.

Management Strategies for Challenging Cases

Genetic counselors employ a variety of strategies to manage the challenging CF carrier screening cases they encounter. These include consulting with colleagues, reviewing the literature, communicating with the testing laboratory, and utilizing the resources of professional organizations to obtain as much information as possible about the clinical significance of test results. Many of the management strategies described by interview participants are similar to those that are used for any genetic counseling session, such as contracting, explaining information multiple times, validating patient feelings, and documenting the session for the patient and referring provider. However, counselors also described strategies that seem particularly useful for challenging CF cases. Several interview participants mentioned that they explain to the patient the process of evaluating the mutations and risks, which can help patients to better understand and cope with the ambiguity in test results. Many counselors also reported that they prioritize obtaining and explaining the information most relevant to the patient’s decision-making.
In addition, counselors often spend a great deal of time with patients during the testing process. One counselor described extensive pre-test counseling as particularly helpful in managing complex test results because patients “can pull from their prior knowledge from the [pre-test session] in trying to understand [the results],” rather than learning scientific information at the same time that they are dealing with the “emotional and psychological impact” of results (Participant 4). Many counselors who do not see patients for pre-test sessions, or do not have adequate time for pre-test counseling, indicated that this is a change they would like to see in the field.

Study Limitations

The number of study participants was relatively small for both the survey (N = 129) and interviews (N = 6). Given that both survey and interview respondents were self-selected, individuals with either particularly positive or negative experiences with these types of case may have been more motivated to participate. In addition, each interview participant described a different counseling experience; therefore, comparisons could not be made between different types of cases.

Study recruitment was conducted through NSGC, so only those counselors who are dues-paying members of the organization were reached for recruitment. Because this study focused on CF carrier testing in the preconception and prenatal settings, the distribution of practice specialties among study participants was significantly different from that of the NSGC general membership (NSGC, 2010). Current testing practices, counseling challenges and management strategies may be different for other types of CF testing, such

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1 Over-represented in study sample: Prenatal: $\chi^2 = 141.2, p < 0.001$; PGD/Preconception: $\chi^2 = 934.8, p < 0.001$; Infertility, ART/IVF: $\chi^2 = 111.3, p < 0.001$; Public Health/Newborn Screening: $\chi^2 = 10.4, p = 0.001$; Adult: $\chi^2 = 145.0, p < 0.001$; Under-represented in study sample: Cancer: $\chi^2 = 37.2, p < 0.001$
as newborn screening. The study sample was otherwise representative of the NSGC membership with regards to primary work setting, job status, and gender (NSGC, 2010)\(^2\).

The anonymous web-based survey created the possibility of different interpretations of questions without the opportunity to clarify with the researchers. In addition, the survey tool labeled the counseling scenarios as “challenges,” which may have biased participants towards ranking these scenarios as more challenging. It is also not known from this data if counselors find other types of cases that have challenging characteristics to be comparable to challenging CF cases.

\(^2\) Primary work setting: \(\chi^2 = 16.2, p = 0.023\); Job status: \(\chi^2 = 0.2, p = 0.651\); Gender: \(\chi^2 = 4.1, p = 0.042\)
CONCLUSIONS

The purpose of this study was to investigate the counseling challenges that can arise from the use of expanded panels and sequencing for CF carrier screening, and the responses of genetic counselors to these challenges.

There is great variability in the type of testing used for CF carrier screening, with the majority of genetic counselors offering an expanded mutation panel for routine carrier testing, and sequencing for select indications. Counselors find the major benefit of these tests to be their usefulness in maximizing detection rates, their cost-effectiveness, and the provision of the most information available to patients. At the same time, the use of these tests is associated with counseling scenarios that are considered to be more challenging than counseling about classic CF. Reported challenging factors include the availability of many testing options, practices of referring providers, complex case management, and ambiguity related to the identification of mild mutations, complex alleles and variants of uncertain significance. Counselors use several strategies related to case preparation, case management, information giving and psychosocial counseling to manage challenging CF carrier screening cases.

Overall, counselors support the use of expanded panels and sequencing in this field, but would like to see guidelines to create more consistency in test offerings, more education for non-genetics professionals, professional resources for continuing genetic counselor education, and additional research on genotype-phenotype correlation to reduce the challenges encountered with CF counseling.
This study is the first to quantitatively and qualitatively describe some of the genetic counseling challenges associated with cystic fibrosis carrier screening. However, this study has considered only the perspective of genetic counselors counseling about CF carrier testing in the preconception and prenatal settings. It will be useful for future studies to consider the viewpoints of other professionals in the field, including laboratory directors and genetic counselors, primary care physicians, OB/GYNs, and genetic counselors involved with CF testing in other clinical settings.

Important strides continue to be made in the cystic fibrosis field through the identification of CFTR mutations, development of more sophisticated molecular tests to detect them, and attempts to understand their clinical significance. As we continue to make these advances, it is critical that we also explore best testing practices, strategies for counseling about prognostic uncertainty, and how to most effectively meet the informational and psychosocial needs of our patients.
REFERENCES


Cystic Fibrosis Mutation Database. (2012). Available from Cystic Fibrosis Centre at the Hospital for Sick Children in Toronto http://www.genet.sickkids.on.ca/app


APPENDICES

Appendix A. Recruitment Notice

Subject: Student Research Project - Cystic Fibrosis Carrier Screening Challenges

Do you counsel patients about cystic fibrosis carrier test results?

If so, I invite you to participate in a research study investigating genetic counseling challenges associated with cystic fibrosis (CF) carrier screening.

The purpose of this study is to compare genetic counselors’ current CF carrier screening practices to published professional guidelines, and to explore the counseling challenges that can arise from the use of expanded mutation panels and full gene sequencing for CF carrier testing.

Participation in this research study is open to all clinical genetic counselors who have been routinely involved in any aspect of preconception and/or prenatal cystic fibrosis carrier screening as part of their clinical practice within the past two years. This includes counselors who routinely offer screening as well as those who see patients referred for post-test counseling.

If you have been involved in cystic fibrosis carrier screening as part of your clinical practice within the past two years, I invite you to participate in an anonymous online survey as part of this research study. The survey should take approximately 20 minutes to complete.

Participation in this study is completely confidential and voluntary. You may discontinue participation at any time for any reason.

If you are interested in sharing your experiences and thoughts about CF carrier screening, please follow the link below to access the online survey:

https://brandeis.qualtrics.com/SE/?SID=SV_b3eZOSp4mqqaOzi

If you have any questions or comments, please feel free to contact me by email at ewelling@brandeis.edu, or the Brandeis University faculty sponsor, Kate Kramer, at kraka11@brandeis.edu. Thank you in advance for your participation.

Sincerely,
Erica Wellington
Brandeis University Genetic Counseling Program, Class of 2012
Appendix B. Survey

Cystic Fibrosis Carrier Screening: Current Practices and Challenges in Genetic Counseling

Q0.0 Thank you for accepting the invitation to participate in this research study. The purpose of this study is to compare genetic counselors’ current cystic fibrosis (CF) carrier screening practices to published professional guidelines, and to explore the counseling challenges that can arise from the use of expanded mutation panels and full gene sequencing for CF carrier testing. The survey should take approximately 20 minutes to complete. Please answer all of the questions to the best of your ability and knowledge.

This research study has been approved by the Brandeis University Committee for Protection of Human Subjects (IRB). Your participation is completely anonymous and voluntary. By completing the survey, you are consenting to participate in this research study. You may discontinue participation at any time for any reason.

Upon completion of the survey, you will have the opportunity to be entered into a drawing for one of two $50 Amazon.com gift certificates.

Please feel free to contact me with any questions or if you need assistance accessing the survey. I greatly appreciate your participation.

Erica Wellington
Brandeis University Genetic Counseling Program, Class of 2012
ewelling@brandeis.edu

Q1.1 Have you worked as a genetic counselor in a clinical setting at any time during the past two (2) years?

- Yes
- No

If NO:

Q5.1 Thank you for offering to participate in this research study. This study is specifically interested in the responses of clinical genetic counselors who have been involved with CF carrier screening within the past two years. Please feel free to contact me with any further questions regarding your participation in this study.

Erica Wellington
Brandeis University Genetic Counseling Program, Class of 2012
ewelling@brandeis.edu
Q1.2 During the past two (2) years, have you routinely counseled about *preconception and/or prenatal cystic fibrosis carrier screening* as part of your clinical practice?

- Yes
- No

If NO:

Q5.1 Thank you for offering to participate in this research study. This study is specifically interested in the responses of clinical genetic counselors who have been involved with CF carrier screening within the past two years. Please feel free to contact me with any further questions regarding your participation in this study.

Erica Wellington
Brandeis University Genetic Counseling Program, Class of 2012
ewelling@brandeis.edu

Q2.1 Listed below are some counseling topics related to CF carrier testing. Please indicate which of these topics you include in your counseling for CF carrier testing by clicking the appropriate box.

In Column A, please indicate those topics you typically include during **pre-test** sessions.

In Column B, please indicate those topics you typically include during **post-test** sessions when there is an increased risk for a child to have CF (i.e. both parents are known carriers or one parent is a known carrier and the other is untested).

<table>
<thead>
<tr>
<th></th>
<th>A Pre-test sessions</th>
<th>B Post-test sessions when there is an increased risk for a child to have CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF Clinical Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung disease</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Pancreatic symptoms</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Male infertility</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>CF Genetics and Inheritance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meaning of carrier versus non-carrier</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Autosomal recessive inheritance</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>a priori risk based on ethnicity or family history</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Genotype-Phenotype Correlation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

32
| Variability of clinical symptoms | ☐ | ☐ |
| Mutations associated with non-classic CF | ☐ | ☐ |
| **Testing Parameters** | | |
| Detection rate and residual risk | ☐ | ☐ |
| Variants of uncertain significance (VUS) | ☐ | ☐ |
| **Reproductive Options** | | |
| Pre-implantation genetic diagnosis (PGD) | ☐ | ☐ |
| Prenatal diagnosis | ☐ | ☐ |
| Continuation or termination of pregnancy | ☐ | ☐ |
| Adoption | ☐ | ☐ |
| **Newborn Screening** | | |
| **Clinical Management** | | |
| Other Please specify: | ☐ | ☐ |

Q2.2 After counseling, how well do you feel your patients understand CF carrier testing?

- ☐ 1 Not at all
- ☐ 2
- ☐ 3 Somewhat
- ☐ 4
- ☐ 5 Completely

Q2.3 Who determines the CF mutation panel that you use most often for CF carrier testing?

- ☐ I determine the panel
- ☐ My institution
- ☐ The patient's insurance plan
- ☐ The patient
- ☐ Other Please specify: ____________________
Q2.4 What is the most common type of CF carrier testing you offer to couples with no known family history of CF?

- A CF mutation panel with only the 23 mutations recommended by ACMG/ACOG
- An expanded CF mutation panel with >23 mutations Number of mutations: ______
- CFTR sequencing
- A mutation panel with reflex CFTR sequencing
- Other Please specify: ________________

Q2.5 Is the CF mutation panel that you offer most often part of a multiplex assay that includes other recessive disorders?

- Yes
- No

Q2.6 Under what circumstances do you order full gene sequencing as a CF carrier test rather than a panel of characterized CF mutations when there is no known family history of CF? (Choose all that apply)

- This is the standard CF carrier test ordered in my practice
- I only offer testing for a core panel of CF mutations
- For the partner of a patient who is a known CF carrier
- If the patient asks for it
- If the patient is not Caucasian
- Other Please specify: ________________

Q2.7 How satisfied are you with the current practices of your institution regarding CF carrier testing?

- Very Dissatisfied
- Dissatisfied
- Somewhat Dissatisfied
- Somewhat Satisfied
- Satisfied
- Very Satisfied
Q2.8 How satisfied are you with the current genetic counseling practices for CF carrier testing in your **practice** (i.e. amongst you and the other genetic counselors at your institution)?

- Very Dissatisfied
- Dissatisfied
- Somewhat Dissatisfied
- Somewhat Satisfied
- Satisfied
- Very Satisfied

Q2.9 Is there anything you would change about the current practices of your **institution** regarding CF carrier testing?

- No
- Yes  Please explain what you would change about the current practices of your institution regarding CF carrier testing: ____________________

Q2.10 Is there anything you would change about the current genetic counseling practices for CF carrier testing in your **practice**?

- No
- Yes  Please explain what you would change about the current genetic counseling practices for CF carrier testing in your practice: ____________________

Q2.11 If the choice were yours, which of the following would you offer for CF carrier testing to couples with **no known family history of CF**?

- A CF mutation panel with only the 23 mutations recommended by ACMG/ACOG
- An expanded CF mutation panel with >23 mutations  Number of mutations: ______
- CFTR sequencing
- A mutation panel with reflex CFTR sequencing
- Other  Please specify: ____________________
Q2.12 For each of the publications on CF carrier screening guidelines listed below, please choose the statement from the dropdown list that best reflects your familiarity with the publication.

<table>
<thead>
<tr>
<th>Publication</th>
<th>I am not familiar with it</th>
<th>I am familiar with it, but have not read it</th>
<th>I have read it</th>
<th>I have read it and incorporate it into my practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preconception and Prenatal Carrier Screening for Cystic Fibrosis: Clinical and Laboratory Guidelines ACOG, ACMG &amp; NIH (2001)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Cystic Fibrosis Prenatal Screening in Genetic Counseling Practice: Recommendations of the National Society of Genetic Counselors NSGC (2005)</td>
<td>☐</td>
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<td>☐</td>
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<tr>
<td>Committee Opinion Number 325: Update on Carrier Screening for Cystic Fibrosis ACOG (2005)</td>
<td>☐</td>
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<tr>
<td>Committee Opinion No. 486: Update on Carrier Screening for Cystic Fibrosis ACOG (2011)</td>
<td>☐</td>
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<td>☐</td>
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</table>

Q2.13 What do you perceive is the main goal of CF carrier screening?

☐ To identify those couples at risk of having a child with classic CF
☐ To identify those couples at risk of having a child with classic CF or a CF-related disorder
☐ Other Please specify: ____________________
Q2.14 In comparison to other topics you discuss with preconception/prenatal patients, how challenging do you find counseling about **classic CF** to be?

- 1 Not challenging at all
- 2
- 3
- 4
- 5
- 6
- 7 Extremely challenging

Q2.15 Please indicate which of the following challenges you have encountered when counseling about the results of preconception/prenatal CF carrier testing. (Choose all that apply)

- Counseling about genotype-phenotype correlation when mutations associated with **non-classic CF** (pancreatic sufficiency, lower sweat chloride levels, later diagnosis) are detected
- Counseling about genotype-phenotype correlation when mutations associated with a **CFTR-related disorder** (such as isolated CBAVD, sino-pulmonary disease, or chronic pancreatitis) are detected
- Counseling about genotype-phenotype correlation when **complex alleles** are detected
- Counseling about variants of uncertain significance
- Detection through carrier testing of mildly affected individuals with two CFTR mutations in trans
- Offering prenatal diagnosis when a fetus is at risk for non-classic CF or an adult-onset CFTR-related disorder based on parental carrier test results
- Offering prenatal diagnosis or counseling about prenatal diagnostic results when the father of the baby is unavailable for carrier testing
- Other Please specify: ____________________
- None of the above

If None of the above Is Selected, Then Skip To Q2.18
Q2.16 Please indicate how often you encounter each of the following challenges in your clinical practice.

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Quite Often</th>
<th>Very Often</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counseling about genotype-phenotype correlation when mutations associated with <strong>non-classic CF</strong> (pancreatic sufficiency, lower sweat chloride levels, later diagnosis) are detected</td>
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[Other from Q2.15]
Q2.17 Please indicate how challenging you find the counseling to be in each of the following scenarios.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Not challenging at all</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>Extremely challenging</th>
<th>NA</th>
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<td>[Other from Q2.15]</td>
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</table>
Q2.18 Do you think that the practice of offering expanded mutation panels and full gene sequencing, in comparison to the ACMG/ACOG core 23 mutation panel, increases the genetic counseling challenges associated with CF carrier screening?

☐ Yes
☐ No
☐ Unsure

Answer If Q2.15 None of the above Is Not Selected

Q2.19 What strategies do you use to manage challenging CF carrier testing cases? (Choose all that apply)

☐ Individual research
☐ Consult with genetic counselor colleagues
☐ Consult with physician colleagues
☐ Consult with nurse colleagues
☐ Consult with laboratory colleagues
☐ Consult with other colleagues Please specify: ____________________
☐ Utilize information provided by the testing laboratory
☐ Obtain new patient education materials
☐ Other Please specify: ____________________
Q2.20 Please indicate how prepared to counsel you generally feel in each of the following scenarios.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Extremely unprepared</th>
<th>Somewhat unprepared</th>
<th>Don’t know/Unsure</th>
<th>Somewhat prepared</th>
<th>Extremely prepared</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counseling about genotype-phenotype correlation when mutations associated with <strong>non-classic CF</strong> (pancreatic sufficiency, lower sweat chloride levels, later diagnosis) are detected</td>
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<tr>
<td>[Other from Q2.15]</td>
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</tbody>
</table>
**Answer If Q2.15 None of the above Is Not Selected**

Q2.21 After counseling in each of the following scenarios, how well do you feel your patients understand the information presented to them?

<table>
<thead>
<tr>
<th>Counseling about genotype-phenotype correlation when mutations associated with <strong>non-classic CF</strong> (pancreatic sufficiency, lower sweat chloride levels, later diagnosis) are detected</th>
<th>Not at all 1</th>
<th>Somewhat 2</th>
<th>Completely 4</th>
<th>NA 5</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>●</td>
<td>●</td>
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<td>●</td>
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</table>

<table>
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<tr>
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</table>

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<table>
<thead>
<tr>
<th>Counseling about variants of uncertain significance</th>
<th>Not at all 1</th>
<th>Somewhat 2</th>
<th>Completely 4</th>
<th>NA 5</th>
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<th>Detection through carrier testing of mildly affected individuals with two CFTR mutations in trans</th>
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<th>Somewhat 2</th>
<th>Completely 4</th>
<th>NA 5</th>
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<tr>
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<tbody>
<tr>
<td>[Other from Q2.15]</td>
<td>●</td>
<td>●</td>
<td>●</td>
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</tr>
</tbody>
</table>
Q2.22 What resources do you feel would be useful to genetic counselors to better address the counseling challenges associated with CF carrier testing? (Choose all that apply)

- More exposure during graduate training
- Continuing education
- Better patient education materials
- Change in screening practices
- Other Please specify: ____________________

Q2.23 Please provide any additional thoughts or comments you have regarding CF carrier screening that were not covered in this survey.

Q3.1 Please indicate your specialty/type of practice as it relates to counseling about CF carrier testing. (Choose all that apply)

- Prenatal
- PGD/Preconception
- Infertility, ART/IVF
- Cystic Fibrosis Specialty Clinic
- Public Health/Newborn Screening
- Adult
- Pediatric
- Other Please specify: ____________________

Q3.2 Please indicate your primary work setting as it relates to counseling about CF carrier testing.

- University Medical Center
- Private Hospital
- Public Hospital
- Physician's Private Practice
- Health Maintenance Organization
- Commercial Diagnostic Laboratory
- University/Non-Medical Center
- Government Organization or Agency
- Other Please specify: ____________________

Q3.3 Please indicate how many years experience you have as a genetic counselor.
Q3.4 Please indicate if you are a full time or part time genetic counselor.

☐ Full time
☐ Part time

Q3.5 Please indicate what percentage of your job is spend in clinical counseling.

☐ 10%
☐ 20%
☐ 30%
☐ 40%
☐ 50%
☐ 60%
☐ 70%
☐ 80%
☐ 90%
☐ 100%

Q3.6 Please indicate which NSGC region you currently practice in.

☐ Region 1 (CT, MA, ME, NH, RI, VT, CN Maritime Provinces)
☐ Region 2 (DC, DE, MD, NJ, NY, PA, VA, WV, PR, VI, Quebec)
☐ Region 3 (AL, FL, GA, KY, LA, MS, NC, SC, TN)
☐ Region 4 (AR, IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, OK, SD, WI, Ontario)
☐ Region 5 (AZ, CO, MT, NM, TX, UT, WY, Alberta, Manitoba, Saskatchewan)
☐ Region 6 (AK, CA, HI, ID, NV, OR, WA, British Columbia)

Q3.7 Please indicate your gender.

☐ Female
☐ Male

Q3.8 How many patients do you currently see for preconception and/or prenatal genetic counseling in an average week?

☐ 1 - 4
☐ 5 - 9
☐ 10 - 14
☐ 15 - 19
☐ 20 - 25
☐ More than 25 patients
Q3.9 Approximately what percentage of your patients are seen for prenatal versus preconception genetic counseling as it relates to CF carrier testing?

- 0% Prenatal
- 10% Prenatal
- 20% Prenatal
- 30% Prenatal
- 40% Prenatal
- 50% Prenatal
- 60% Prenatal
- 70% Prenatal
- 80% Prenatal
- 90% Prenatal
- 100% Prenatal

Q3.10 How often do you offer CF carrier testing or counsel about CF carrier test results?

- Less than once a month
- Once a month
- 2-3 times a month
- Once a week
- 2-3 times a week
- Once a day
- Multiple times a day

Q4.1 I hope to carry out a number of telephone interviews to learn more about genetic counselors’ experiences with CF carrier screening. Specifically, the interviews will focus on counseling challenges that can arise from the use of expanded mutation panels and full gene sequencing for CF carrier testing. Interviews will last approximately 30 minutes.

If you are willing to participate in the interview portion of this study, please select “Interview Prescreen” below and then click “Next.” You will be asked to provide your contact information and answer a brief questionnaire to assess eligibility. Your contact information will only be used for communication related to the interview. It will not be linked to your survey responses, and your survey responses will remain anonymous.

If you do not wish to volunteer for the interview portion of the study, please select “No Thank You” and then click “Next.”

- Interview Prescreen
- No Thank You

If INTERVIEW PRESCREEN:

(Link to Survey Prescreen)
If NO THANK YOU:

Q6.1  Thank you for taking the time to participate in this research study. The answers and insight you shared will be very helpful. Please feel free to contact me with any questions.

If you wish to be entered into a drawing for one of two $50 Amazon.com gift certificates, please send an email that includes your name and email address to CFSSurveyRaffle@gmail.com. Your email address will only be used for communication related to the gift certificate. It will not be linked to your survey responses, and your survey responses will remain anonymous.

Erica Wellington
Brandeis University Genetic Counseling Program, Class of 2012
 ewelling@brandeis.edu
Appendix C. Interview Prescreen

Q0 Thank you for your interest in the interview portion of this research study. You will be asked a brief set of questions to assess your eligibility for the interview. Some of these questions you saw in the previous survey, but please answer them again to the best of your ability. If you are selected for the interview portion, the student researcher will contact you within 2-3 weeks to review the informed consent and schedule the interview.

Q1 Of the following, please select the one scenario you have encountered and found to be the most challenging when counseling about the results of preconception/prenatal CF carrier testing.

- Counseling about genotype-phenotype correlation when mutations associated with non-classic CF (pancreatic sufficiency, lower sweat chloride levels, later diagnosis) are detected
- Counseling about genotype-phenotype correlation when mutations associated with a CFTR-related disorder (such as isolated CBAVD, sino-pulmonary disease, or chronic pancreatitis) are detected
- Counseling about genotype-phenotype correlation when complex alleles are detected
- Counseling about variants of uncertain significance (VUS)
- Detection through carrier testing of mildly affected individuals with two CFTR mutations in trans
- Offering prenatal diagnosis when a fetus is at risk for non-classic CF or an adult-onset CFTR-related disorder based on parental carrier test results
- Offering prenatal diagnosis or counseling about prenatal diagnostic results when the father of the baby is unavailable for carrier testing
- Other Please specify: ____________________
- I have not encountered any of the above scenarios

Q2 What is the most common type of CF carrier testing you offer to couples with no known family history of CF?

- A CF mutation panel with only the 23 mutations recommended by ACMG/ACOG
- An expanded CF mutation panel with >23 mutations Number of mutations: ______
- CFTR sequencing
- A mutation panel with reflex CFTR sequencing
- Other Please specify: ____________________
Q3 Is the CF mutation panel that you offer most often part of a multiplex assay that includes other recessive disorders?

☐ Yes
☐ No

Q4 Please indicate how many years experience you have as a genetic counselor.

Q5 Please indicate your specialty/type of practice as it relates to counseling about CF carrier testing. (Choose all that apply)

☐ Prenatal
☐ PGD/Preconception
☐ Infertility, ART/IVF
☐ Cystic Fibrosis Specialty Clinic
☐ Public Health/Newborn Screening
☐ Adult
☐ Pediatric
☐ Other Please specify: ____________________

Q6 Please enter your contact information below and then click "Next".

Name:
Email:
Confirm Email:

Q7 Thank you for taking the time to participate in this research study. The answers and insight you shared will be very helpful. Please feel free to contact me with any questions.

If you wish to be entered into a drawing for one of two $50 Amazon.com gift certificates, please send an email that includes your name and email address to CFSurveyRaffle@gmail.com. Your email address will only be used for communication related to the gift certificate. It will not be linked to your survey responses, and your survey responses will remain anonymous.

Erica Wellington
Brandeis University Genetic Counseling Program, Class of 2012
ewelling@brandeis.edu
Appendix D. Interview Informed Consent

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GENETIC COUNSELING GRADUATE PROGRAM

Informed Consent to Participate in Research

Cystic Fibrosis Carrier Screening:
Current Practices and Challenges in Genetic Counseling

Student Researcher: Erica Wellington
Principal Investigator: Kate Kramer, MS, PhD

INTRODUCTION
Erica Wellington is a graduate student in the Genetic Counseling Program at Brandeis University. She is conducting a research study to learn more about the genetic counseling challenges associated with cystic fibrosis (CF) carrier screening. Kate Kramer is a Lecturer in the Brandeis University Genetic Counseling Program.

You are being invited to participate in this study because you are a genetic counselor who has counseled about CF carrier screening as part of your clinical practice within the past two years, and you indicated on the survey portion of this study that you have experience with one or more challenging CF carrier screening cases.

Taking part in this research study is completely voluntary. You can decide to stop your participation at any time for any reason.

Please read all of the following information carefully and ask any questions that you have about this research study. Do not sign this consent form unless you understand the information in it and have had your questions answered to your satisfaction.

If you decide to take part in this research study, you will be asked to sign this form. You will be given a copy of the signed form. You should keep your copy for your records. It has information, including important names and telephone numbers, to which you may wish to refer in the future.

PURPOSE OF STUDY
The purpose of this study is to explore the genetic counseling challenges that can arise from the use of expanded mutation panels and full gene sequencing for CF carrier testing. Your responses to the interview questions will be used to describe the challenges associated with current CF carrier screening practices and the management strategies used by genetic counselors in response to these challenges. Analysis of the study data may be used to
develop ideas for future research projects and recommendations for clinical genetics practices.

PROCEDURES TO BE FOLLOWED
You will be asked to participate in a telephone interview at a time that is convenient for you. During this interview you will be asked questions regarding your experience managing a challenging CF carrier screening case. The interview will last approximately 30 minutes and will be audiotaped.

RISKS
Participation in this study presents no more than minimal risk, which is not greater than risks encountered in everyday life.

BENEFITS
There will be no direct benefit to you for your participation in this study. We hope that in the future information obtained from this study will help us gain a better understanding of the counseling challenges associated with CF carrier screening and the strategies employed by genetic counselors to manage these challenges.

ALTERNATIVES
An alternative is to not participate in this research study.

PRIVACY AND CONFIDENTIALITY
All interview tapes, transcripts and records containing identifying information, such as names, email addresses, telephone or fax numbers, and home or work addresses will be kept strictly confidential during the study and destroyed after completion of the study. All study related documents and materials (including contact information, informed consent forms, interview transcripts, interview notes, and audiotapes) will be kept in a secure location accessible only to the student researcher, and any databases containing survey responses or identifiers will be password protected using a password known only to the student researcher. Transcripts, interview notes, and audiotapes will be labeled with a coded ID number, which will be assigned to you upon enrollment in the study. If you are quoted or referred to in any written or oral reports of this study, you will be given an alternate name and no other identifying information will be used.

PAYMENT
You will receive a $25 gift certificate to Amazon.com for participation in the research study as a gesture of appreciation for your time and expertise.
COST
There will be no cost to you to participate in the study, other than the time it takes to complete the interview.

WHOM TO CONTACT
If you encounter any problems related to study participation or have questions about the study, you may contact the student researcher, Erica Wellington, at ewelling@brandeis.edu or 339-225-0430.

You may also contact the Brandeis University faculty sponsor for this project, Kate Kramer, at kraka11@brandeis.edu.

If you have questions about your rights as a research study subject, contact the Brandeis Committee for Protection of Human Subjects by email at irb@brandeis.edu, or by phone at 781-736-8133.
PARTICIPANT’S STATEMENT

I have read this consent form and have discussed with Erica Wellington the procedures described above. I have been given the opportunity to ask questions, which have been answered to my satisfaction. I understand that any further questions that I might have will be answered verbally or, if I prefer, with a written statement.

I understand that my participation is voluntary. I understand that I may refuse to participate in this study. I also understand that if, for any reason, I wish to discontinue participation in this study at any time, I will be free to do so.

If I have any questions concerning my rights as a research subject in this study, I may contact the Brandeis Committee for Protection of Human Subjects by email at irb@brandeis.edu, or by phone at 781-736-8133.

I have been fully informed of the above-described study with its risks and benefits, and I hereby consent to the procedures set forth above.

I understand that as a participant in this study my identity and data relating to this research study will be kept confidential.

Please indicate your willingness to be audiotaped by initialing here: _______

_________________________________________          Date
Participant Signature

_________________________________________          Date
Student Researcher Signature
Appendix E. Interview Demographics Questionnaire

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DEPARTMENT OF BIOLOGY
GENETIC COUNSELING GRADUATE PROGRAM

Interview Demographics Questionnaire

Cystic Fibrosis Carrier Screening:
Current Practices and Challenges in Genetic Counseling

Student Researcher: Erica Wellington
Principal Investigator: Kate Kramer, MS, PhD

1. Please indicate your primary work setting as it relates to offering CF carrier testing.
   - University Medical Center
   - Private Hospital
   - Public Hospital
   - Physician’s Private Practice
   - Health Maintenance Organization
   - Commercial Diagnostic Laboratory
   - University/Non-Medical Center
   - Government Organization or Agency
   - Other ________________

2. How many patients do you currently see for preconception and/or prenatal genetic counseling in an average week?
   - 1 - 4
   - 5 - 9
   - 10 - 14
   - 15 - 19
   - 20 - 25
   - More than 25 patients

3. Approximately what percentage of your patients are seen for prenatal versus preconception genetic counseling as it relates to CF carrier testing?
   - 0% prenatal
   - 10% prenatal
   - 20% prenatal
   - 30% prenatal
   - 40% prenatal
   - 50% prenatal
   - 60% prenatal
   - 70% prenatal
   - 80% prenatal
   - 90% prenatal
   - 100% prenatal
4. How often do you offer CF carrier testing or counsel about CF carrier test results?
   ☐ Less than once a month
   ☐ Once a month
   ☐ 2-3 times a month
   ☐ Once a week
   ☐ 2-3 times a week
   ☐ Once a day
   ☐ Multiple times a day

5. Please indicate your gender.
   ☐ Female
   ☐ Male
Appendix F. Interview Guide

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Interview Guide and Notes

Cystic Fibrosis Carrier Screening:
Current Practices and Challenges in Genetic Counseling

Student Researcher/Interviewer: Erica Wellington

Introduction
Thank you for accepting the invitation to participate in the interview portion of this research study. Through this interview, I hope to learn more about your experiences managing a challenging cystic fibrosis carrier screening case, which may contribute to the development of ideas for future research projects and recommendations for clinical genetics practices. As a reminder, this interview is being recorded. Your participation is voluntary and you may choose to stop participating at any time for any reason. I am going to ask you a series of questions, but it is my hope that we can have a conversation about your experiences. Do you have any questions before we begin?

[Build rapport by confirming answers given on interview prescreen and demographics questionnaire.]

You indicated on your prescreen for this interview that you have experience counseling about [Insert Scenario From Prescreen Form]. I’m interested in hearing more about this case.

Questions
1. Can you please give a brief description of the case?
   [Prompts:
   a. Prenatal vs. preconception
   b. Reason for referral
   c. Indication for screening (known family history, ethnicity, etc.)
   d. Patient/counselor interaction during pre-test session
   e. Testing performed
   f. Results (specific mutations)
   g. Follow-up testing
   h. Patient/counselor interaction during post-test session
   i. Patient decision/case outcome]

2. In what ways was this case challenging for you?
   [Prompt:
   a. How did this case differ from other cases?]
3. What factors do you think contributed to the challenging nature of this case?
   [Prompts:
   a. Scientific unknowns (ex. VUS, genotype-phenotype correlation)
   b. Delivery of complex information (ex. variable phenotype, complex alleles, identification of mildly affected parent)
   c. Ethical considerations (ex. testing fetus for mild or adult-onset condition)
   d. Psychosocial situation (ex. FOB unavailable for testing, identification of mildly affected parent)
   e. Educating other providers about complexity of case
   f. Lack of guidance from professional guidelines or institution
   g. Lack of resources to educate self and patient]

4. What strategies did you use to manage the case?
   [Prompts:
   a. Individual research
   b. Consult with colleagues (GC, physician, nurse, laboratory liaison)
   c. Use lab-provided information
   d. Obtain new patient education materials]

5. How did the patient respond to your counseling?

6. Do you feel that the patient was satisfied with the counseling encounter and/or testing process?

7. How satisfied were you with how the challenge was handled?
   [Prompts:
   a. What do you feel went well?
   b. What would you do differently next time?]

8. What do you think are some other current challenges in offering preconception/prenatal CF carrier testing?

9. What other strategies do you think may be helpful for managing challenging CF carrier testing cases?
   a. [Follow-up]: Which of these have you used?

10. What resources do you feel would help genetic counselors to provide better counseling about CF carrier testing and results?
    [Prompts:
    a. More exposure during graduate training
    b. Continuing education
    c. Better patient education materials
    d. Change in screening practices]

11. What changes would you like to see in the field of CF carrier screening, if any?
12. What testing panel was used in this case? [If not answered above]
   [Prompts:
   a. A CF mutation panel with only the 23 mutations recommended by ACMG/ACOG
   b. An expanded CF mutation panel with > 23 mutations (Text Box: Number of mutations)
   c. CFTR sequencing
   d. A mutation panel with reflex CFTR sequencing
   e. Other]

13. What do you think are the advantages and disadvantages of using expanded panels and sequencing as part of CF carrier testing?

Thank You
Thank you for taking the time to participate in the interview portion of this research study. As a gesture of appreciation for your time and expertise, you will receive a $25 gift certificate to Amazon.com via email. It is unlikely that I will need to contact you again, but if I do have any follow-up questions to our discussion today, may I be in touch?

☐ Yes
☐ No

[Confirm email and preferred follow-up contact.]