The Current Landscape of Prenatal Aneuploidy Screening: Perspectives of Genetic Counselors in the United States

Master’s Thesis

Presented to

The Faculty of the Graduate School of Arts and Sciences
Brandeis University
Genetic Counseling Program
Barbara Lerner, PhD, CGC; Advisor

In Partial Fulfillment
of the Requirements for the Degree

Master of Science

by
Jamie L. Silver

August 2012
ACKNOWLEDGEMENTS

To my committee members - Barbara Lerner, PhD, CGC; Lauren Briere, MS, CGC; Jennifer Hume, MS, CGC – for your invaluable help and guidance throughout this process.

To the faculty of the Brandeis Genetic Counseling department – Beth Rosen-Sheidley, Gretchen Schneider, Judith Tsipis, Janet Rosenfield, David Rintell, and Missy Goldberg – for all of your support, advice, candy, and tissues.

To my classmates in the GC class of 2012 - for all the laughing, crying, ranting, raving, processing, loving, supporting, studying, and ice cream and gummy bear eating.

To my friends – for keeping me happy and (relatively) sane, and for always being there when I need a hug, a laugh, a supportive word, or just a shoulder to cry on.

To my family – who have always loved and supported me unconditionally, and have never hesitated to show it.

To Lucy – my emotional support beagle, my pride and joy.

To Mathew – my doggy daddy, my nerd in shining armor, and the love of my life.
ABSTRACT

The Current Landscape of Prenatal Aneuploidy Screening: Perspectives of Genetic Counselors in the United States

A thesis presented to the Genetic Counseling Program

Graduate School of Arts and Sciences
Brandeis University
Waltham, Massachusetts

By Jamie Silver

Currently, there are at least eight different methodologies available to expectant parents who wish to screen prenatally for Down syndrome and other aneuploidies. These techniques, which can incorporate serum, ultrasound and most recently free fetal DNA (fDNA) technologies, have yielded an evolving menu of options with considerable variability in both sensitivity and specificity. The aim of our study was to assess how genetic counselors are utilizing these various methodologies and to solicit their opinions and recommendations regarding fetal aneuploidy screening programs. We recruited currently practicing prenatal counselors via the NSGC listserv to participate in an anonymous online survey. We received 207 eligible responses to our survey, which consisted of questions regarding specific screening methodologies offered at their
institutions, experiences and challenges in counseling patients, and required elements for optimal screening programs.

Our results indicate that there is considerable variability in the prenatal screening methods used. First trimester screening is the most widely used methodology, offered regularly by 82% of respondents. However, 52% of respondents reported that they regularly offer sequential screening, and 57% offer ffDNA screening either routinely or on a limited case-by-case basis. Many counselors expressed concern about the quality of informed consent when undertaken by non-genetics providers. Of note, almost two-thirds (59%) of respondents indicated that they sometimes, often, or always saw patients for discussion of screening results who did not recall consenting to screening. Factors positively correlated with optimal screening programs were the ability to offer CVS, first trimester screening, ffDNA screening, and pre-screening appointments. The landscape of prenatal aneuploidy screening is likely to change drastically in the coming years, and it is imperative that genetic counselors be involved in the development and implementation of screening programs that effectively integrate both current and future methods while optimizing patient comprehension and autonomy.

Key words: genetic counseling, maternal serum screening, non-invasive prenatal diagnosis, aneuploidy screening
# Table of Contents

Acknowledgements........................................................................................................... ii

Abstract.............................................................................................................................. iii

Table of Contents.................................................................................................................. v

List of Tables and Figures.................................................................................................... vi

Introduction........................................................................................................................... 1

Materials and Methods........................................................................................................ 9

Results................................................................................................................................. 11

Discussion............................................................................................................................ 27

Conclusion............................................................................................................................ 32

Appendices........................................................................................................................... 33
  
  *Appendix A: Recruitment email* .................................................................................... 33
  *Appendix B: Survey* ........................................................................................................ 34

Bibliography.......................................................................................................................... 44
List of Tables/Figures

Table 1: Respondent demographics ...........................................................................................................12
Table 2: Practice/institution characteristics ............................................................................................13
Figure 1: Screening options offered ........................................................................................................14
Table 3: Important considerations when deciding which screening options to offer .......................14
Figure 2. Additional Ultrasound findings offered in first trimester risk assessment .......................15
Figure 3. Which statement best represents ffDNA plans? .................................................................15
Figure 4. How many of the patients with whom you discuss screening results
have you already met with prior to their screening test being performed? ...........................16
Figure 5. How often do you see patients to discuss results of screening
who do not recall consenting to the screening? ..............................................................................17
Figure 6. Level of agreement: I offer the most cost-effective screening method(s) ......................18
Figure 7. Level of agreement: I offer the most accurate screening method(s) ................................18
Figure 8. Level of agreement: I offer the most accurate screening method(s) ................................19
Figure 9. Optimal screening correlation with meeting patients prior to results session .............20
Figure 10. Optimal screening correlation with seeing patients who don’t recall consent to screening .............................................................20
Figure 11. Optimal screening correlation with offering CVS ..........................................................22
Figure 12. Optimal screening correlation with offering 1st trimester screening ..........................22
Figure 13. Optimal screening correlation with offering ffDNA methods .......................................23
Figure 14. Optimal screening correlation with working with OB/GYN ..........................................23
Figure 15. Cost-effectiveness of screening in California vs. all other states .................................24
Figure 16: Institution type correlation with seeing patients who don’t recall consenting to screening ....................................................................................................................25
Figure 17: Percentage of respondents offering fetal nasal bone assessment on ultrasound .................................................................................................................................26
Figure 18: Perceived screening accuracy by institution type ..........................................................26
Introduction

History of Prenatal Screening

The first screening test for aneuploidy in pregnant women - and indeed the only such test available for several decades - was maternal age. In 1933, Penrose found a positive correlation between increasing maternal age and the risk for Down syndrome (Penrose, 1933). The first prenatal diagnosis of Down syndrome was made in 1968, utilizing the newly discovered diagnostic technique of amniocentesis (Valenti, Schutta, & Kehaty, 1968). It soon became common practice to offer this new invasive diagnostic testing to all women over the age of 35.

A few years later an elevated concentration of the analyte α-fetoprotein (AFP) circulating in maternal blood was linked to the occurrence of open neural tube defects such as spina bifida and anencephaly in fetuses (Brock & Sutcliffe, 1972). AFP measurement became a routine prenatal screening test for open neural tube defects. The case of a woman who gave birth to a baby with trisomy 18 after having an undetectable AFP level during pregnancy spurred a large retrospective investigation which uncovered a significant association between low maternal serum levels of AFP and chromosomal abnormalities including Down syndrome, trisomy 18, and trisomy 13 (Merkatz, Nitowsky, Macri, & Johnson, 1984). In 1987, Cuckle et al published a method for calculating an individual pregnant woman’s risk of her fetus being affected with Down syndrome based on both her AFP level and her age (Cuckle, Wald, & Thompson, 1987). Gaussian distributions of AFP levels in both affected and unaffected pregnancies were
plotted on a scale of multiples of the median (MoMs). The height of the affected curve at a particular point divided by the height of the unaffected curve generated an odds risk ratio, which could then be multiplied by the underlying age-related risk to calculate individual odds for an affected pregnancy. This method of applying distribution-based odds ratios to baseline risk has become the standard for all serum screening. In the late 1980s, two more analytes were found to correlate with Down syndrome – high levels of human chorionic gonadotropin or hCG (Bogart, Pandian, & Jones, 1987) and low levels of unconjugated estriol or uE3 (Canick et al., 1988).

Wald’s group proposed the “triple test” in 1988, which combined maternal age risk with measurements of the three aforementioned analytes in maternal serum during the second trimester of pregnancy to calculate individual risk for a Down syndrome affected pregnancy (Wald et al., 1988). They estimated that using this new method would reduce the number of children born with Down syndrome each year in the United Kingdom from 900 to about 350.

In 1992, inhibin was yet another analyte discovered to have associations with Down syndrome risk in the second trimester (Van Lith, Pratt, Beekhuis, & Mantingh, 1992). With the addition of inhibin, the “quadruple test” became the gold standard for second trimester Down syndrome screening, with a detection rate of 70% at a false positive rate of 5% (Nicolaides, 2011). Women are given a risk of 1 in X for their pregnancy being affected, and empirical validation of 100,000 cases showed that the prevalence of Down syndrome among women who are given particular risk estimates is concordant with the stated risk (Wald, Kennard, Hackshaw, & Huttly, 1996).
Nicolaides et al found a strong association between chromosomal abnormalities and the thickness of the fetal nuchal translucency (NT) as measured on a first trimester ultrasound (Nicolaides, Azar, Byrne, Mansur, & Marks, 1992). They performed a prospective study of 827 fetuses that underwent first trimester karyotyping. For fetuses with an NT greater than 3 mm in thickness, the incidence of chromosomal abnormalities was 35%. Only 1% of the fetuses with an NT measurement less than 3 mm had chromosomal abnormalities. The first trimester nuchal translucency was found to be a much better indicator of chromosomal abnormalities than the analogous measurement in the 2nd trimester, the nuchal fold. Maternal serum concentrations of pregnancy-associated plasma protein A (PAPP-A) and free beta subunits of hCG were also found to be reliable first trimester markers of Down syndrome and trisomy 18 (Ozturk et al., 1990; Spencer, 1991; Wald et al., 1992). The combination of maternal age, the two serum markers and the NT in the first trimester was found to be an even more efficacious screening tool than the second semester quadruple screen, for both Down syndrome (Wald & Hackshaw, 1997) and trisomy 18 (Wapner, 2003).

Development of screening paradigms

In 1999, Wald et al proposed an integrated testing strategy - combining the first and second trimester screenings (Wald & Hackshaw, 1997). They found that by using a screen-positive cutoff of 1 in 120, the integrated test detected 85% of cases of Down syndrome with a false positive rate of less than 1%.

Gilbert et al did an analysis of available screening strategies to determine efficacy, safety, and cost effectiveness (Gilbert et al., 2001). According to their model,
the integrated screening is the safest and most effective. It has the highest detection rate at 95% with a 5% false positive rate. They estimate that by using this integrated screening method, there are 0.14 miscarriages due to invasive testing per birth of every affected child prevented - a measure they call the “safety cost”. By contrast, the safety cost of first trimester combined screening, isolated NT measurement, and the second trimester quadruple test are 0.22, 0.34, and 0.42 miscarriages, respectively. In terms of cost effectiveness, the study concludes that switching from the current standard of care in the UK (a second trimester measurement of AFP and hCG) to the integrated test would result in 2.3 fewer affected babies per 10,000 births, at a cost of £13,000 (more than 20,000 US$) per additional affected baby prevented.

The First and Second Trimester Evaluation of Risk (FASTER) trial was conducted to compare detection rates for Down syndrome, mathematically evaluating first trimester screening, second trimester screening, and the combination of the two (Malone et al., 2005). This was a prospective study with a sample size of more than 38,000 women, creating a robust data set upon which many subsequent studies have been based. In this trial, integrated screening was found to be most effective, with a 95% detection rate. The authors suggested implementing a sequential method of screening in order to provide earlier diagnoses for some women while still allowing for the calculation of an integrated result in others.

Benn et al proposed another strategy for maternal serum screening, called “contingent screening” (P Benn, Wright, & Cuckle, 2005). Women underwent first trimester serum screening and NT measurement, and were classified as high risk, borderline risk, or low risk. The women who were low risk after first trimester
assessment did not receive any further testing. Those women who were high risk after the first trimester screen were offered invasive diagnostic fetal testing. The women who were borderline risk went on to receive second trimester serum screening and were re-categorized into high or low risk at that point. They estimated that over 60% of affected pregnancies would be detected in the first trimester and that less than 20% of women would require a second trimester screening assessment. The authors claimed this strategy would identify 89% of cases with only a 3.1% false positive rate, and would significantly reduce anxiety for many women by giving them an early answer.

Two years later, Benn et al proposed yet another approach for screening for Down syndrome and trisomy 18, which they called stepwise sequential screening (P. Benn, Campbell, Zelop, & Ingardia, 2007). This strategy is similar to integrated screening in that it incorporates both first and second trimester screening, but all women are told their preliminary risk for an affected pregnancy after their first trimester test, rather than only receiving the final risk after two trimesters of testing. Women may choose to go on to invasive diagnostic testing after high risk first trimester results, or they can wait and re-evaluate their desire to pursue diagnostic testing after their second trimester results are integrated into the risk calculation. Women who were not considered high risk after first trimester screening could still go on to have the second trimester test to improve the accuracy of their result. The authors suggest that stepwise sequential screening provides an optimal balance of maximizing detection rate and minimizing invasive testing.
Current practices

In 2007, ACOG recommended that all women, regardless of age, should be offered maternal serum screening for aneuploidy (ACOG Practice Bulletin No. 77: screening for fetal chromosomal abnormalities, 2007). They went on to mention the different types of screening available, including first trimester, second trimester quad screen, integrated, sequential, and contingent screening. They did not endorse any particular screening method, leaving that to the discretion of providers. In 2009, 95% of obstetrician-gynecologists (OB/GYN) and maternal fetal medicine (MFM) specialists said that they offered screening for Down syndrome to all pregnant patients (Driscoll, Morgan, & Schulkin, 2009). The type of screening and the uptake of the testing varied based on region. For instance, in the Northeast, physicians reported that 72% of women under age 35 and 82% of women above age 35 accepted screening, while those numbers were 48% and 58%, respectively, in the Midwest. One concerning finding was that 17% of obstetricians offered to perform the first-trimester screen and quad screen as mathematically independent tests on the same woman, despite the specific denouncement of this method in the 2007 ACOG statement. Additionally, California has its own state screening program wherein every pregnant woman presenting in the first trimester is offered one state-wide option – namely, sequential screening (The California Prenatal Screening Program Provider Handbook, 2009).

Non-invasive prenatal diagnosis

In 1997, Y.M. Lo’s research group first reported the existence of fetal DNA circulating in maternal blood plasma (Lo et al., 1997). Since then, researchers have been
attempting to harness this free fetal DNA (ffDNA) technology for the prenatal detection of aneuploidies as well as Rh blood type testing and fetal sex determination. In October 2011, ffDNA testing methods for trisomy 21 became commercially available in the United States to women considered “high risk” due to age, serum screening results, ultrasound anomalies, and/or family history. This testing is considered non-invasive to the fetus, as it involves only a maternal venous blood draw. The sensitivity and specificity were both quoted as >99% in the high risk population (Palomaki et al., 2011). In 2012, the clinically available ffDNA methods were expanded to include testing for trisomies 13 and 18 (Palomaki et al., 2012). Although sometimes referred to as “non-invasive prenatal diagnosis”, this testing is not considered to be diagnostic and does not eliminate the need for CVS or amniocentesis.

Study aims

The US does not currently have a national screening program for prenatal detection of aneuploidies, there is little guidance provided by the experts, and there is still an ongoing debate to identify the optimal screening method(s) (Tapon, 2010). Some studies claim that contingent screening is the strategy with the best performance (Gekas, Gagne, Bujold, Douillard, & Forest, 2009) and highest cost-effectiveness (Ball et al., 2007). However, the Ball et al study also showed that sequential screening actually had better performance than contingent screening. Yet another prominent study claims that integrated screening is superior to the other methods in both performance and cost-effectiveness (Wald, 2010). It is up to individual institutions and practitioners to design and implement a prenatal screening program that will keep their patient population
satisfied and health care costs reasonable while constantly adapting to incorporate the newest prenatal screening technologies.

One group of healthcare specialists often responsible for educating and interpreting the results of these screening tests has not yet weighed in on the debate. As frontline providers of prenatal testing, prenatal genetic counselors have extensive experience in the application of these different methods and can add a different perspective to the discussion. The aim of this study was to assess how genetic counselors in the prenatal setting utilize these various methodologies – including how they decide between screening paradigms and how they are implemented. We sought to characterize the degree and nature of the variation in the care that women receive across the United States. Specifically, do practices differ significantly based on location, type of institution, or any other demographic factors? Additionally, what is counselors’ level of satisfaction with their institution’s testing protocol for testing at their individual institutions? Finally, recommendations to improve the quality of delivering prenatal screening were sought from the counselors.
Materials and Methods

This project was a cross-sectional quantitative study of currently practicing prenatal genetic counselors in the United States, administered via an anonymous online survey. This study was exempt from review by the Brandeis Institutional Review Board.

Sample and Recruitment

An email was sent from the National Society of Genetic Counselors to all current members on March 28th, 2012 inviting them to participate in the study (see Appendix A). A reminder email was sent on April 11th, 2012. The study was closed to participants on April 18th, 2012. After completing the survey, the respondents were directed to another, unlinked survey where they could enter their contact information to be included in a drawing for one of two $50 gift cards to Amazon.com.

Inclusion criteria required that a participant was a practicing genetic counselor, was board eligible or board certified by the American Board of Genetic Counseling, and spent at least 25% of his/her work hours providing care to prenatal patients.

Data Collection

The survey (see Appendix B) was hosted on Qualtrics (www.qualtrics.com), an online survey tool. Data was collected between March 28th, 2012 and April 18th, 2012, and stored on the secure Qualtrics servers. The survey included a total of 20 questions.
incorporating multiple choice, Likert scales, and open response formats. The first question helped determine eligibility by asking how much time the counselors spent on prenatal counseling. If they answered “less than 25%”, they were automatically directed to the end of the survey.

Data Analysis

The data was analyzed using Statistical Package for the Social Sciences (SPSS) version 19 and Microsoft Excel 2011. Univariate analysis was performed on each question to determine the frequency of responses; we obtained the mean and standard deviation of responses when applicable. Bivariate analyses were done using independent sample t-tests, chi-square tests, and cross-tabulations.
Results

There were 234 responses to the survey. Of those, 23 were excluded (10%) who indicated they spent less than 25% of counseling time providing prenatal care and 2 respondents (<1%) who only partially completed the survey. The analysis was based on the 207 remaining respondents. It is not possible to calculate a response rate, as the total number of eligible counselors who received the email is unknown.

Demographics

We asked several multiple-choice questions to determine the demographics of respondents. Table 1 shows the breakdown of these responses. The participants were asked which state they practice in, and those states were grouped into the four regions defined by the US Census Bureau. The four regions were represented relatively evenly – 22% from the Midwest, 27% Northeast, 25% South and 25% West. There was a wide range of the total years in prenatal practice of the respondents, with 37% practicing for 1-4 years and 25% practicing 5-9 years. The majority of respondents (67%) classified the area around their institution as urban, while 30% said suburban and only 3% said rural. The most frequently identified practice setting was university/academic hospitals, with 44% of respondents. Community hospitals represented 29% and private clinics represented 16%. Eleven percent of the respondents practiced in other settings.
Table 1: Respondent demographics

<table>
<thead>
<tr>
<th>Regions</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midwest</td>
<td>46</td>
<td>23%</td>
</tr>
<tr>
<td>Northeast</td>
<td>55</td>
<td>27%</td>
</tr>
<tr>
<td>South</td>
<td>51</td>
<td>25%</td>
</tr>
<tr>
<td>West</td>
<td>52</td>
<td>25%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urban</td>
<td>139</td>
<td>67%</td>
</tr>
<tr>
<td>Suburban</td>
<td>61</td>
<td>30%</td>
</tr>
<tr>
<td>Rural</td>
<td>7</td>
<td>3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Years in practice</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4 years</td>
<td>74</td>
<td>37%</td>
</tr>
<tr>
<td>5-9 years</td>
<td>49</td>
<td>25%</td>
</tr>
<tr>
<td>10-14 years</td>
<td>23</td>
<td>12%</td>
</tr>
<tr>
<td>15-19 years</td>
<td>23</td>
<td>12%</td>
</tr>
<tr>
<td>20-24 years</td>
<td>13</td>
<td>7%</td>
</tr>
<tr>
<td>25+</td>
<td>16</td>
<td>8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Setting</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community hospital</td>
<td>61</td>
<td>29%</td>
</tr>
<tr>
<td>University/academic hospital</td>
<td>91</td>
<td>44%</td>
</tr>
<tr>
<td>Private clinic</td>
<td>33</td>
<td>16%</td>
</tr>
<tr>
<td>HMO</td>
<td>7</td>
<td>3%</td>
</tr>
<tr>
<td>Pharma/Biotech company</td>
<td>6</td>
<td>3%</td>
</tr>
<tr>
<td>Other</td>
<td>15</td>
<td>4%</td>
</tr>
</tbody>
</table>
Respondent practice partners and prenatal diagnostic procedures are summarized in Table 2. The vast majority of respondents (91%) worked with a Maternal Fetal Medicine physician (MFM), while 44% said they worked with a physician specializing in OB/GYN. More than three-quarters (79%) of respondents said that their institution offered chorionic villus sampling (CVS), while nearly all (99%) offered amniocentesis.

Table 2: Practice/institution characteristics

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you work with an OB/GYN?</td>
<td>44%</td>
<td>56%</td>
<td>207</td>
</tr>
<tr>
<td>Do you work with an MFM?</td>
<td>91%</td>
<td>9%</td>
<td>207</td>
</tr>
<tr>
<td>Do you work with a genetecist?</td>
<td>55%</td>
<td>45%</td>
<td>207</td>
</tr>
<tr>
<td>Do you offer CVS at your institution?</td>
<td>79%</td>
<td>21%</td>
<td>207</td>
</tr>
<tr>
<td>Do you offer amnio at your institution?</td>
<td>99%</td>
<td>1%</td>
<td>207</td>
</tr>
</tbody>
</table>

We asked respondents to select from a list of screening options all of the methods they routinely offer to a pregnant woman who presents in her first trimester. Figure 1 shows the distribution of options respondents routinely offer. The most frequently offered option was 1st trimester screening, (82%), followed by sequential screening (53%), and 2nd trimester quad screen (47%). More than a third of respondents offer fflDNA methods (38%). It is notable that 3% of respondents say that they offer the 2nd trimester triple screen as a stand-alone option.
Respondents were asked to rate how important certain considerations were in determining which screening options to offer to patients. Based on a 5-point Likert scale, with 1 being “Not at all important” and 5 being “Extremely important”, Table 3 shows the average importance rating for each factor. Institutional policies were perceived to be the most important factor with a mean importance of 3.48 (SD 1.25), and counselor preference was the least important with a mean of 2.3 (SD 1.17).

Table 3: Important considerations when deciding which screening options to offer.

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Mean importance</th>
<th>StdDev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institutional policies</td>
<td>3.48</td>
<td>1.24</td>
</tr>
<tr>
<td>Lab capabilities</td>
<td>3.34</td>
<td>1.33</td>
</tr>
<tr>
<td>Insurance coverage</td>
<td>3.20</td>
<td>1.29</td>
</tr>
<tr>
<td>Expected patient compliance</td>
<td>2.88</td>
<td>1.22</td>
</tr>
<tr>
<td>Physician preference</td>
<td>2.77</td>
<td>1.25</td>
</tr>
<tr>
<td>Convenience</td>
<td>2.70</td>
<td>1.12</td>
</tr>
<tr>
<td>Counselor preference</td>
<td>2.30</td>
<td>1.17</td>
</tr>
</tbody>
</table>
Respondents were asked which, if any, 1<sup>st</sup> trimester ultrasound markers (aside from NT) they offer at their clinic. The results are seen in Figure 2. A substantial number of respondents offer the fetal nasal bone assessment (43%), but all of the other markers discussed were offered by less than 10% of respondents.

**Figure 2. Additional Ultrasound findings offered in first trimester risk assessment**

Which additional ultrasound findings do you incorporate into your first trimester screening?

We asked respondents to pick which statement best represented their clinic’s plans regarding ffDNA testing. These results are seen in Figure 3. A plurality of respondents (32%) indicated that they had begun to implement ffDNA on a limited case-by-case basis, while 26% said they had been offering ffDNA as routine practice. Another 27% of respondents said that they plan to begin implementation of ffDNA methods in the near future. However, 16% of respondents said that either they had not discussed ffDNA at their institution or that they had decided not to begin offering it.
We asked respondents about the workflow of counseling patients and returning results at the respondents’ institutions. Figure 4 and Figure 5 show the results of two of these questions, respectively. A total of 28% of responding counselors said that they meet with none (5%) or very few (23%) of their patients before their screening tests are performed. Additionally, a total of 57% of responding counselors said that they sometimes (38%), often (19%), or always (2%) meet with patients to give results who do not recall consenting to the screening.
The counselors responded to questions designed to assess their opinions about the maternal serum screening program policies at their institutions. We asked them to rate how strongly they agreed that they offered a cost-effective, an accurate, or an optimal screening program. The results are shown in Figure 6, Figure 7, and Figure 8, respectively. Overall, a total of 54% of respondents agreed or strongly agreed they offered the most cost-effective screening, while 64% agreed or strongly agreed they
offered the most accurate, and 79% agreed or strongly agreed that they have an optimal maternal serum screening program.

Figure 6. Level of agreement: I offer the most cost-effective screening method(s)

![Cost-Effective Screening Method Chart]

Figure 7. Level of agreement: I offer the most accurate screening method(s)

![Accurate Screening Method Chart]
Figure 8. Level of agreement: I offer the most accurate screening method(s)

We noted a positive correlation between respondent’s opinions that their institutions offered an optimal screening and agreeing that the screening was accurate ($r = 0.629$, $p < 0.000$), as well as a positive correlation to agreement that the screening was cost-effective ($r = 0.288$, $p < 0.000$).

Two other factors that correlated with the counselor’s level of agreement that they offer optimal screening were how many of the patients they had met prior to giving results, as well as how often they saw patients who did not recall consenting to the screening. (Figure 9 and Figure 10). The more patients that counselors are able to meet with prior to giving results, the more likely they are to agree that their screening program is optimal ($R = 0.207$, $p = 0.033$). The more patients they see who do not recall being consented prior to screening, the less likely the counselors are to agree that their screening program is optimal ($R = -0.246$, $p = 0.015$).
Figure 9. Optimal screening correlation with meeting patients prior to results session.

How many of the patients with whom you discuss screening results have you already met with prior to their screening test being performed?

Figure 10. Optimal screening correlation with seeing patients who don’t recall consenting to screening.

How often do you give results to patients who do not recall consenting to screening?
We found several components of a screening program that were significantly associated with a counselor’s opinion that their center offered an optimal program, including: 1) offering CVS (Figure 1), 2) offering 1st trimester screening (Figure 12), 3) offering ffDNA methods (Figure 13), and 4) working with an OB/GYN (Figure 14). Among counselors who offered CVS at their institution, the mean agreement that they offered optimal screening was 4.08, compared to 3.57 for counselors who did not offer CVS (p = .002). Counselors who offered 1st trimester screening were more likely to agree that they offered optimal screening than those who did not (means: 4.03 vs 3.57, p = .001). Counselors who offered ffDNA were also more likely to agree that they offered optimal screening than those who did not (means: 4.22 vs 3.81, p = .002). Counselors who worked with an OB/GYN were less likely to agree that they offered an optimal screening program than those who did not, regardless of which other doctors they worked with (means: 3.75 vs 4.06, p = .009).
Figure 11. Optimal screening correlation with offering CVS.

Do you offer CVS at your institution?

<table>
<thead>
<tr>
<th>Offer CVS at Your Institution</th>
<th>Offer Optimal Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Mean: 4.08</td>
</tr>
<tr>
<td>No</td>
<td>Mean: 3.57</td>
</tr>
</tbody>
</table>

p = .002

Figure 12. Optimal screening correlation with offering 1\textsuperscript{st} trimester screening.

Do you offer 1\textsuperscript{st} trimester screening?

<table>
<thead>
<tr>
<th>Offer 1\textsuperscript{st} Trimester Screening</th>
<th>Offer Optimal Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Mean: 4.03</td>
</tr>
<tr>
<td>No</td>
<td>Mean: 3.48</td>
</tr>
</tbody>
</table>

p = .001
Figure 13. Optimal screening correlation with offering ffDNA methods.

Figure 14. Optimal screening correlation with working with OB/GYN.
We investigated how respondents in California viewed their screening programs (Figure 15). Those in California were more likely to agree that they offered the most cost-effective screening than those who were outside of California (means 4.01 vs 3.49, p = 0.004). However, there was no significant difference in the means or the distribution of responses regarding accuracy and offering an optimal program.

Figure 15. Cost-effectiveness of screening in California vs. all other states.

Of the several different regional and organizational characteristics distinguishing the respondents, only one – the type of institution - was found to find to be significantly associated with screening practices and methods. Academic hospitals are more likely to encounter the situation of giving results to patients who do not recall consenting (Figure 16) than were the other setting types (p = 0.025). Private clinics were much more likely to offer an ultrasound examination of the fetal nasal bone (Figure 17) than the other types of institutions (p = 0.013). Community hospitals were significantly less likely to agree that they offered the most accurate methods (Figure 18), compared to the other
types of settings (p = 0.029). Community hospitals showed a trend toward being less likely to agree that they offered optimal screening, but it did not achieve statistical significance. There was no association between institution type and agreement that they offered the most cost-effective screening. Practices did not differ significantly between regions when California and New York (where ffDNA is not approved by the state board of health) were excluded from their respective regions.

Figure 16: Institution type correlation with seeing patients who don’t recall consenting to screening

How often do you see patients who don't recall consenting to screening?
Figure 17: Percentage of respondents offering fetal nasal bone assessment on ultrasound

![Chart showing the percentage of respondents offering fetal nasal bone assessment on ultrasound by institution type. The chart indicates that community hospitals have the highest percentage, followed by private clinics and university/academic hospitals.]

Figure 18: Perceived screening accuracy by institution type

![Chart showing perceived screening accuracy by institution type. The chart indicates that community hospitals have the highest perceived accuracy, followed by private clinics and university/academic hospitals. The mean scores are 3.42 for community hospitals, 3.84 for private clinics, and 3.81 for university/academic hospitals.]

I offer the most accurate screening

- Strongly Agree
- Agree
- Neither Agree nor Disagree
- Disagree
- Strongly Disagree
Discussion

This study showed that there is indeed considerable variation in the way that prenatal screening is performed at different institutions across the United States. We were able to identify several practice characteristics that correlated with the respondents’ satisfaction with their prenatal screening programs.

Important practice characteristics

Respondents indicated that the most important factors in determining their screening protocols were extrinsic factors; such as institutional policies, insurance concerns, and lab capabilities. One factor we did not include in our study, but may be captured at least partially under “institutional policies” is state policies – including the California regulated screening program and the New York state board non-approval of ffDNA methods. To that end, genetic counselors and other providers involved in the process may not have the authority and/or flexibility to design truly optimal programs for their patient population.

Access to technology appears to play a large role in predicting a counselor’s satisfaction with their screening program. Three of the factors that correlated with increased belief that a respondent offered an optimal program were offering CVS, offering ffDNA methods, and offering first trimester screening. First trimester screening is included as a technology issue because the limiting factor behind being able to offer
first trimester screening is likely to be a lack of access to machines and trained staff that can accurately measure the nuchal translucency. Additionally, an institution may be less likely to offer first trimester screening if they do not offer CVS for diagnostic confirmation.

One surprising factor that correlated with counselors’ satisfaction with their screening program was whether or not they worked with an OB/GYN. Those who worked with OB/GYNs were, on average, less satisfied with their screening program than those who didn’t. While almost all respondents (91%) worked with a MFM physician, less than half (44%) worked with an OB/GYN. A study of physicians done roughly a year after the latest ACOG screening guidelines came out showed that MFMs were much more likely to have thoroughly read the guidelines than OB/GYNs, and also more likely to report that they used internet searches and journals to keep themselves informed about advances in genetic screening (Driscoll, et al., 2009).

*The role of counseling*

An issue that merits discussion, possibly even more than the methods of screening used, is that of appropriate pre-test counseling and informed consent. An alarming 57% of respondents said that they sometimes, often, or always encounter patients to discuss the results of their screening test who do not recall consenting to the screening. A comment from a respondent illustrates part of the issue:

“[There needs to be] better education of the OB/GYN and STAFF of the testing and HOW to communicate results to patients. It is still the biggest reason for misunderstanding by patients regarding the testing and the results. In fact some had declined testing but it was still drawn.”
It is appalling to imagine that prenatal testing would be conducted even after a patient had declined testing. While many counselors opined in their comments that the consent process was best performed by a genetic counselor, some also acknowledged that the sheer volume of pregnant women compared to the number of prenatal counselors would make it impossible for every woman to see a genetic counselor before receiving prenatal screening. Some respondents had suggestions for overcoming this difficulty, including running group sessions with a genetic counselor and/or distributing thorough and accurate literature to introduce women to the prenatal screening options. I also believe that a thorough documentation of consent should be obtained in order to prevent discrepancies.

Incorporating new technologies

The use of ffDNA technologies was somewhat controversial, which is suggested by the wide distribution of responses to the question about respondents’ plans to incorporate ffDNA testing into their practice (see Figure 3), and further confirmed by the free-response comments. Some respondents hailed ffDNA as the “wave of the future” and believe it will all but replace serum screening. However, there are serious concerns about the pre-test counseling and consent process. With both sensitivity and specificity around 99%, the implications and ramifications of a positive screen with ffDNA are very different than a positive screen with serum screening, which has far lower accuracy. The International Society for Prenatal Screening released a statement shortly after ffDNA methods became commercially available in the United States cautioning that these methods should not become part of the “standard” pregnancy blood tests and should only
be performed after a patient has received genetic counseling by a qualified individual (P. Benn et al., 2012).

One respondent provided a shocking example of the misuse of ffDNA methods among non-GC providers.

“It is clear that general providers don't understand [ffDNA screening] because they are still ordering quads after [performing ffDNA screening] ...”

However, offering ffDNA methods was a factor that was significantly associated with respondents believing they offered an optimal screening program. This would suggest that many more programs will be incorporating this technology in the future. As this technology becomes more available, it is imperative that genetic counselors be involved in the design and implementation of new screening protocols. One respondent expressed:

“ffDNA is the direction of the future. GCs need to be involved in the development of these protocols for offering testing. Without that involvement we will encounter patients who are unhappy this testing was done which significantly impacts their pregnancy. There are still many women who do not want to know the genetic status of their fetus and yet they are encouraged to do testing. [With ffDNA testing,] (t)his would be much more severe and change the context of our conversations with these patients completely.”

Limitations

A major limitation with this study is selection bias. There is no way to be sure that the views of this self-selecting sample are representative of the genetic counseling community as a whole. Because of the anonymous nature of the survey, it was impossible to account for multiple respondents at the same institution or even within the same practice. In addition, we were not able to calculate a response rate as the
recruitment email was sent to an undisclosed list via the NSGC. An oversight in the survey was that the option of proceeding directly to invasive diagnostic testing was not included among the screening methods. Many counselors used the “other” field to represent this option.
Conclusion

Currently, there are at least eight different methodologies available to expectant parents who wish to screen prenatally for Down syndrome and other aneuploidies. These techniques, which can incorporate serum, ultrasound and most recently free fetal DNA (ffDNA) technologies, have yielded an evolving menu of options with considerable variability in both sensitivity and specificity. The aim of our study was to assess how genetic counselors are utilizing these various methodologies and to solicit their opinions and recommendations regarding fetal aneuploidy screening programs.

Our results indicate that there is considerable variability in the prenatal screening methods used. First trimester screening is the most widely used methodology, followed by sequential screening. Factors positively correlated with optimal screening programs were the ability to offer CVS, first trimester screening, ffDNA screening, and pre-screening appointments. Many counselors expressed concern about the quality of informed consent when undertaken by non-genetics providers, which is particularly important in the wake of the new ffDNA technologies. The landscape of prenatal aneuploidy screening is likely to change drastically in the coming years. It is imperative that genetic counselors be involved in the development and implementation of screening programs in order to effectively integrate both current and future methods while optimizing patient comprehension and autonomy as well as cost-effectiveness.
Appendix A: Recruitment email

Seeking prenatal genetic counselors to participate in a research study!

The Current Landscape of Prenatal Aneuploidy Screening: Perspectives of Genetic Counselors in the United States

The primary goal of my project is to get a scope of the current practices among genetic counselors who provide screening for fetal chromosomal abnormalities to pregnant women. My aim is to determine the degree and nature of the variation in the care that women receive across the United States.

I am a graduate student in Genetic Counseling at Brandeis University seeking volunteers to complete an online survey.

The survey will take approximately 15 minutes of your time. Your responses will be anonymous. All participants who complete the survey will have the opportunity to enter a drawing for one of two $50 gift certificates to Amazon.com.

If you are a prenatal genetic counselor, currently practicing in the United States, and are interested in participating, please follow this link to access the survey:

https://brandeis.qualtrics.com/SE/?SID=SV_eb1gybr55k5eG0I

I thank you in advance for your participation. If you have any questions, concerns, or comments, please contact Jamie Silver at gcjamie@brandeis.edu or the Brandeis faculty sponsor, Barbara Lerner, MS, PhD at lerner@brandeis.edu.

Sincerely,

Jamie Silver
Brandeis University
Genetic Counseling Masters Program
Class of 2012
Appendix B: Survey

Thank you for participating in this study. This study is entitled: ‘The Current Landscape of Prenatal Aneuploidy Screening: Perspectives of Genetic Counselors in the United States’ In this survey you will be asked questions about your practices and opinions with regard to prenatal aneuploidy screening. All information will remain anonymous. At the end of the survey, you will be asked for your email address to be entered to win one of two gift certificates. Your email address will NOT be linked to your survey responses and will be kept completely confidential. Please note that participation is voluntary and you may exit the survey at any time. By clicking next you acknowledge that you are over 18 years of age you have read the above information and that you wish to participate in the survey. This study has been reviewed and approved by the Institutional Review Board of Brandeis University. If you have any questions about your rights as a research subject, please contact the Brandeis Institutional Review Board at irb@brandeis.edu or (781) 736-8133. If you have any questions about this study, please contact:

Jamie Silver  
Brandeis University  
Genetic Counseling Masters Program  
Class of 2012  
Email: gcjamie@brandeis.edu

Barbara Lerner, MS, PhD  
Faculty Sponsor  
Email: lerner@brandeis.edu
1 What percentage of your counseling time is spent with prenatal patients?
- Less than 25% (1)
- 26-50% (2)
- 51-75% (3)
- 76-100% (4)

If Less than 25% Is Selected, Then Skip To End of Survey

2 Which of the following best describes the setting where you primarily practice?
- Community hospital (1)
- University/academic hospital (2)
- Private clinic (3)
- Public health department (4)
- Military/veterans hospital (5)
- Pharmaceutical/Biotech company (6)
- Other (7) ____________________
3 In which state do you practice?
- Alabama (1)
- Alaska (2)
- Arizona (3)
- Arkansas (4)
- California (5)
- Colorado (6)
- Connecticut (7)
- Delaware (8)
- District of Columbia (9)
- Florida (10)
- Georgia (11)
- Hawaii (12)
- Idaho (13)
- Illinois (14)
- Indiana (15)
- Iowa (16)
- Kansas (17)
- Kentucky (18)
- Louisiana (19)
- Maine (20)
- Maryland (21)
- Massachusetts (22)
- Michigan (23)
- Minnesota (24)
- Mississippi (25)
- Missouri (26)
- Montana (27)
- Nebraska (28)
- Nevada (29)
- New Hampshire (30)
- New Jersey (31)
- New Mexico (32)
- New York (33)
- North Carolina (34)
- North Dakota (35)
- Ohio (36)
- Oklahoma (37)
- Oregon (38)
- Pennsylvania (39)
- Rhode Island (40)
- South Carolina (41)
- South Dakota (42)
- Tennessee (43)
4 Which of the following best describes the location of the institution where you primarily practice?
- Urban (1)
- Suburban (2)
- Rural (3)

5 How many years in total have you been practicing as a prenatal counselor?
- Less than 2 years (1)
- 2-5 years (2)
- 6-10 years (3)
- 11-15 years (4)
- 16-20 years (5)
- More than 20 years (6)

6 How many prenatal genetic counselors (including yourself) work at your institution?
- 1 (1)
- 2-4 (2)
- 5-7 (3)
- 8-10 (4)
- 11 or more (5)
7 Approximately how many new patients do you see per week?

- 1 (1)
- 2 (2)
- 3 (3)
- 4 (4)
- 5 (5)
- 6 (6)
- 7 (7)
- 8 (8)
- 9 (9)
- 10 (10)
- 11 (11)
- 12 (12)
- 13 (13)
- 14 (14)
- 15 (15)
- 16 (16)
- 17 (17)
- 18 (18)
- 19 (19)
- 20 (20)
- 21 (21)
- 22 (22)
- 23 (23)
- 24 (24)
- 25 (25)
- 26 (26)
- 27 (27)
- 28 (28)
- 29 (29)
- 30 (30)
- 31 (31)
- 32 (32)
- 33 (33)
- 34 (34)
- 35 (35)
- 36 (36)
- 37 (37)
- 38 (38)
- 39 (39)
- 40 (40)
8 Which of the following physicians do you work with? (Mark all that apply)
- OB/GYN (1)
- Geneticist (2)
- Maternal Fetal Medicine specialist (3)
- Other (4)________________________
- None of the above (5)

9 Do you offer chorionic villus sampling (CVS) at your institution?
- Yes (1)
- No (2)

9a Do you refer patients for CVS to an affiliated institution within 30 miles of your institution?
- Yes (1)
- No (2)

10 Do you offer amniocentesis at your institution?
- Yes (1)
- No (2)

10a Do you refer patients for amniocentesis to an affiliated institution within 30 miles of your institution?
- Yes (1)
- No (2)
11 When a pregnant woman comes to you in her first trimester to discuss prenatal aneuploidy screening, which of the following options do you explicitly offer to her? (Mark all that apply)

- First trimester serum screen + NT measurement +/- other ultrasound markers (1)
- Second trimester triple screen (2)
- Second trimester quadruple screen (3)
- First and second trimester integrated screen (No results until after second trimester blood draw) (4)
- First and second trimester contingent screening (Only patients with elevated risk move on to second trimester testing) (5)
- First and second trimester sequential screening (Results after first and second trimester screens) (6)
- Free fetal DNA screening methods (i.e. Maternati21) (7)
- Other (8) __________________

12 Of the women who you see in their first trimester to discuss screening options, please approximate the percentage who elect for each option. (Drag the bars or type numbers into boxes. Answers must total to 100%.)

- No screening (1) ______

13 How important are the following factors when determining which prenatal screening options you offer to patients?

<table>
<thead>
<tr>
<th>Factor</th>
<th>Not at all Important (1)</th>
<th>A little important (2)</th>
<th>Somewhat important (3)</th>
<th>Very Important (4)</th>
<th>Extremely Important (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institutional policies (1)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Lab capabilities (2)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Counselor preference (3)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Physician preference (4)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Insurance coverage (5)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Convenience (6)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Expected patient compliance (7)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
14 When communicating screening results to a patient, which of the following do you usually discuss (mark all that apply)?
- Her numeric probability of having an affected pregnancy (i.e. 1 in 100) (1)
- Her percentage risk of having an affected pregnancy (i.e. 1%) (2)
- Her numeric risk result of having an unaffected pregnancy (i.e. 99 in 100, or 99%) (3)
- Her percentage risk of having an unaffected pregnancy (i.e. 99%) (4)
- Her designation as "screen positive" or "screen negative" (5)
- Her baseline risk for an affected pregnancy based on her age (6)
- None of the above (7)

15 How many of the patients with whom you discuss screening results have you already met with prior to their screening test being performed?
- None (1)
- Very few (2)
- Some (3)
- Most (4)
- All (5)

16 How often do you see patients to discuss results of screening who do not recall consenting to the screening?
- Never (1)
- Very rarely (2)
- Sometimes (3)
- Often (4)
- Always (5)

17 Which of the following ultrasound markers (besides NT) do you incorporate into your routine first trimester aneuploidy risk assessment? (Mark all that apply)
- Presence/absence of fetal nasal bone (1)
- Facial angle measurement (2)
- Ductus venosis flow (3)
- Tricuspid valve flow (4)
- Other (5) ____________________
- None of the above (6)
18 Which of the following statements best represents your plans regarding free fetal DNA screening (e.g. Maternati21)?

- I have already begun to incorporate ffDNA screening as routine practice (1)
- I have already begun to incorporate ffDNA screening on a limited case-by-case basis (2)
- I have plans to begin implementation of ffDNA screening as routine practice within the next 1 or 2 years. (3)
- I have plans to begin implementation of ffDNA screening on a limited case-by-case basis within the next 1 or 2 years. (4)
- I have discussed ffDNA screening with colleagues or superiors and will most likely begin implementation in the future, however I have no specific plans at the moment. (5)
- I have discussed ffDNA screening with colleagues or superiors but do not intend to begin integrating it into my prenatal care in the foreseeable future. (6)
- There has been very little or no discussion of ffDNA screening at my institution. (7)

19 Please indicate your level of agreement with the following statements regarding the prenatal aneuploidy screening that you offer.

<table>
<thead>
<tr>
<th></th>
<th>Strongly Disagree (1)</th>
<th>Disagree (2)</th>
<th>Neither Agree nor Disagree (3)</th>
<th>Agree (4)</th>
<th>Strongly Agree (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I believe that the prenatal screening method(s) that I use is/are the most accurate. (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I believe that the prenatal screening method(s) that I use is/are the most cost-effective. (2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel that I offer an optimal maternal serum screening program. (3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I think that most patients do/would benefit from having their choice of several</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
screening paradigms. (4)
I think that most patients are/would be confused by being offered a choice of several prenatal screening paradigms. (5)

20 If you were part of a committee writing a national guideline for the clinical use of maternal serum screening, what recommendations would you make? - Which screening paradigm(s) would you endorse? - How would you suggest providers ensure that women are making an informed decision before undergoing screening? - What is the best way to present the risk results to patients? - What other input can you offer based on your knowledge or field experience?


