Genetic counseling perspectives on prenatal array CGH testing

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By
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ABSTRACT

Array-based comparative genomic hybridization (aCGH) has become an increasingly frequent genomic screen in clinical practice. Challenges posed by aCGH testing include the possibility of results of uncertain significance and limited predictive clinical information. These challenges are particularly significant in the prenatal setting where aCGH results may affect pregnancy management, including decisions regarding termination. Previous studies have proposed approaches to result interpretation and thorough pre-test counseling from the perspective of genetic counselors affiliated with aCGH testing labs. The purpose of this study was to explore aCGH practices in detail, with particular emphasis on the experiences and views of genetic counselors regarding the use of this technology in a prenatal setting. We interviewed nine prenatal and pediatric genetic counselors who practice in the United States and who work for academic hospitals, private clinics and aCGH testing labs. The semi-structured interviews consisted of 22 open-ended questions focused on the current practices and opinions of counselors experienced in offering aCGH. The interview transcripts were coded using ATLAS.ti software. Results showed a lack of uniformity in practice and diverse opinions regarding appropriate indications for offering aCGH to patients. Counselors raised many concerns based on their experiences with offering aCGH in pediatrics, including the frequency of results of uncertain significance and situations in which testing resulted in unanticipated and/or pre-symptomatic diagnosis. Counselors’ responses revealed no clear consensus regarding whether or not aCGH testing should be offered routinely in prenatal settings, but study participants were in agreement that there is a need for standardized implementation and practice guidelines. The results of our qualitative pilot
study highlight the challenges of reaching a consensus about appropriate prenatal aCGH practices and suggest a need for additional studies to assess genetic counselors’ experiences and comfort levels with prenatal aCGH testing.
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INTRODUCTION

Array-based comparative genomic hybridization (aCGH) is a relatively new and increasingly applied test (Shinawi and Cheung, 2008). Array CGH can simultaneously test multiple regions in the genome for deletions and duplications of DNA (Slavotinek, 2008). Traditional cytogenetic techniques, including high-resolution karyotyping and fluorescence in situ hybridization (FISH) studies are the standard for detecting chromosomal imbalances (Shaffer et al., 2007). However, aCGH is more sensitive (i.e. can detect smaller imbalances) than karyotyping and can examine multiple genomic regions in a more cost-effective manner compared to FISH (Bejjani & Shaffer, 2006). Clinical uptake of aCGH is steadily increasing (Slavotinek, 2008).

Previous studies have reviewed the benefits and limitations of aCGH. A main benefit is that aCGH combines increased sensitivity, simultaneous testing of multiple genomic regions, cost-effectiveness and a relatively fast turnaround time (Shaffer et al., 2007). A primary limitation of aCGH testing is incomplete knowledge regarding the clinical significance of deletions and duplications that are not associated with a previously described genetic syndrome (Gouas et al., 2008). Such findings are termed results of uncertain clinical significance, which means that the aCGH testing laboratory cannot determine whether the genetic change is a benign polymorphism or causative of the patient’s features (Darilek et al., 2008). In addition, aCGH tests can only detect gains and losses of genetic material and cannot detect balanced chromosome rearrangements (Shinawi and Cheung, 2008).

Earlier research has outlined the risks and challenges aCGH testing poses to patients and healthcare providers. Reported risks to the patient include possible diagnosis
of a condition unrelated to the original indication for testing, potentially before symptoms of the condition have developed, or the possibility of receiving a result of uncertain clinical significance (Darilek et al., 2008, Gouas et al., 2008). Reported challenges for healthcare providers include becoming adept at test result interpretation and familiar with the complex range of test platforms, test detection rates and symptoms of possible conditions (de Ravel et al., 2007).

Currently, no practice guidelines for offering aCGH testing exist. Although, physician colleges have developed practice guidelines for other genetic tests, such as fetal karyotyping, to help ensure that healthcare providers offer testing in a way that is beneficial to patients (ACOG, 2007). The absence of practice guidelines leaves healthcare providers to independently balance the benefits and drawbacks of a test and may increase the chance that testing is not offered in an optimally beneficial way (Veermesch et al., 2007). Healthcare providers’ current practices regarding aCGH testing are not well established.

Offering aCGH testing in the prenatal setting poses specific challenges. One potential challenge is interpreting results of uncertain significance in the context of relatively limited fetal phenotypes. Another potential challenge is the limited time available for result interpretation and follow-up. Ambiguous results, specifically results of uncertain clinical significance, and limited follow up time can be of particular consequence given that they may influence decision regarding pregnancy management, including termination (Darilek et al., 2008).

Other challenges those offering aCGH testing face is selecting the type of array platform to use. Currently, array platforms used for aCGH testing consist of either
Overall, oligonucleotide platforms can detect smaller gains and losses of genetic material than BAC platforms, and are more likely to detect a genetic change of uncertain clinical significance (Bejjani & Shaffer, 2006). In addition, testing labs have designed prenatal-specific arrays that primarily test for recognized genetic syndromes and have a relatively low chance of detecting a genetic change of uncertain clinical significance (Bi et al., 2008). Array CGH testing labs have applied both BAC and oligonucleotide platforms in prenatal-specific arrays (Bi et al., 2008; Cain et al., 2008).

Previous studies have proposed approaches to counseling for aCGH testing. For example, Darilek et al., (2008) emphasized the importance of extensive pretest education, informed consent, and parental testing to determine if a patient’s genomic imbalance is familial or new. Approaches to test result interpretation and the benefits of current databases of chromosomal imbalances have also been published (de Ravel et al., 2007). However, a qualitative study in which genetic counselors are interviewed and asked to detail their experiences with and opinions regarding aCGH testing has yet to be reported. A study of this nature could reveal previously unreported clinical practices among genetic counselors, clinical aCGH testing practices that genetic counselors view as appropriate, genetic counselors’ comfort levels with offering aCGH testing, and genetic counselors’ suggestions for clinical aCGH testing practice guidelines. We aimed to carry out the first such study to provide genetic counselors and other healthcare providers with a detailed examination of experiences and views regarding aCGH testing. Given the potential challenges of prenatal aCGH testing, we chose to focus on practices and opinions regarding aCGH testing in the prenatal setting. We hoped to highlight challenges that the
genetics field can focus on overcoming as well as ideas that the field can build on. The findings are based on a collection of interviews with prenatal and pediatric genetic counselors practicing in the United States and may suggest future studies of counseling practices, comfort levels and approaches to guideline development for aCGH testing.

METHODS

SAMPLING/RECRUITMENT

We conducted semi-structured, qualitative telephone interviews with genetic counselors to examine their experiences with and thoughts on array CGH testing, particularly prenatal array CGH testing. We recruited genetic counselors by emailing a recruitment notice (please refer to Appendix B) to the National Society of Genetic Counselors (NSGC) listserv. We posted the recruitment notice for two weeks. Nine counselors responded to our recruitment notice. A short eligibility-screening tool (see Appendix C) administered by telephone confirmed that all nine respondents were eligible for study participation. Eligible participants were genetic counselors who currently see prenatal and/or pediatric patients, currently offer array CGH testing to patients, have offered array CGH testing to patients for at least one year and have worked for 5 or more years as a genetic counselor in a clinical prenatal or clinical pediatric setting (i.e. setting where at least 50% of time at work is spent seeing prenatal or pediatric patients). We offered study participants a gift certificate to a bookstore as a gesture of our appreciation for their time and effort.

DESIGN OF INTERVIEW QUESTIONS
We designed a semi-structured interview guide with open- and closed-ended interview questions (please see Appendix E) to capture the scope of study participants’ views and experiences regarding aCGH testing, with a focus on prenatal aCGH testing. Questions were designed to ascertain counselors’ opinions about aCGH, challenges encountered while offering aCGH testing, ideas for improving how aCGH is offered, the existence and nature of institutional policies and genetic counselors’ current practices, such as indications for which aCGH testing is offered, and information about aCGH typically disclosed to patients. With regard to prenatal aCGH testing, questions were designed to discern whether counselors offered aCGH in this setting, indications viewed as appropriate, and perceived benefits and limitations. Question design stemmed from the authors’ clinical experiences and knowledge of literature related to aCGH testing.

DATA COLLECTION

Before proceeding with interviews, we obtained informed consent from participants (please see Appendix D). We interviewed study participants for approximately 30 to 60 minutes each. We audiotaped each telephone interview. To protect participant confidentiality we did not mention participant names during interviews and labeled audiotapes, interview notes and study files with identification numbers rather than participant names. We conducted semi-structured interviews comprised largely of open-ended questions with a few closed-ended questions. A semi-structured approach allowed the interviewee to respond freely and without interruption. We kept our responses and the order of questions flexible, which allowed interviewee and interviewer to explore ideas and themes as they arose. We adapted questions to account for original thoughts expressed by the interviewee, although the overall interview content remained consistent.
DATA ANALYSIS

A transcriptionist put the audio taped interviews into writing. We imported transcripts as rich text files into the qualitative analysis software, Atlas.ti (version 5.0), for thematic analysis. We used codes (referred to as elements in Results) to identify and group sections of text that represent a similar view, practice or experience that we viewed as significant. Coding our interviews allowed us to identify groups of codes, where each group represents a theme. Themes are broad topics that study participants frequently spoke of or emphasized. After completing transcript analyses, we selected themes and codes that were representative of study participants’ most prominent and significant views and experiences.

RESULTS

DEMOGRAPHICS

We recruited nine genetic counselors as study participants, hereafter referred to as counselors. The nine eligible counselors all practiced genetic counseling in the United States and represented four time zones. At the time of the interviews, two study participants saw only prenatal patients, three saw both pediatric and prenatal patients, and four saw only pediatric patients. Table 1 shows each counselors’ current type of employer and work setting, years of clinical prenatal and pediatric work experience, and years of genetic counseling experience. Currently, counselors 1 and 2 see only prenatal patients. Counselor 3 primarily sees pediatric patients, but also sees prenatal patients. Counselors 4 and 5 did not specify whether they see primarily pediatric or prenatal patients. Currently,
counselors 6, 7, 8 and 9 see pediatric patients and do not see prenatal patients. Table 2 summarizes the group of counselors’ genetic counseling experience.

<table>
<thead>
<tr>
<th>Counselor</th>
<th>Current employer</th>
<th>Current area of specialty</th>
<th>Years of clinical pediatric experience</th>
<th>Years offering aCGH in pediatric setting</th>
<th>Years of clinical prenatal experience</th>
<th>Years offering aCGH in prenatal setting</th>
<th>Total years genetic counseling experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>aCGH testing lab</td>
<td>Clinical prenatal</td>
<td>0</td>
<td>N/A</td>
<td>5-9</td>
<td>5-9</td>
<td>5-9</td>
</tr>
<tr>
<td>2</td>
<td>Private hospital</td>
<td>Clinical prenatal</td>
<td>1-4</td>
<td>0</td>
<td>5-9</td>
<td>1-4</td>
<td>5-9</td>
</tr>
<tr>
<td>3</td>
<td>Academic hospital</td>
<td>Clinical pediatric and prenatal</td>
<td>10+</td>
<td>1-4</td>
<td>10+</td>
<td>1-4</td>
<td>10+</td>
</tr>
<tr>
<td>4</td>
<td>Private hospital</td>
<td>Clinical pediatric and prenatal</td>
<td>10+</td>
<td>5-9</td>
<td>10+</td>
<td>0</td>
<td>10+</td>
</tr>
<tr>
<td>5</td>
<td>Academic hospital</td>
<td>Clinical pediatric and prenatal</td>
<td>5-9</td>
<td>1-4</td>
<td>5-9</td>
<td>0</td>
<td>5-9</td>
</tr>
<tr>
<td>6</td>
<td>aCGH testing lab</td>
<td>Clinical pediatric</td>
<td>5-9</td>
<td>5-9</td>
<td>10+</td>
<td>0</td>
<td>10+</td>
</tr>
<tr>
<td>7</td>
<td>Academic hospital</td>
<td>Clinical pediatric</td>
<td>1-4</td>
<td>1-4</td>
<td>1-4</td>
<td>0</td>
<td>10+</td>
</tr>
<tr>
<td>8</td>
<td>Academic hospital</td>
<td>Clinical pediatric</td>
<td>10+</td>
<td>1-4</td>
<td>&lt;1</td>
<td>0</td>
<td>10+</td>
</tr>
<tr>
<td>9</td>
<td>Academic hospital</td>
<td>Clinical pediatric</td>
<td>1-4</td>
<td>1</td>
<td>5-9</td>
<td>0</td>
<td>5-9</td>
</tr>
</tbody>
</table>

Table 1. The current type of employer and area of specialty, years of clinical prenatal and pediatric work experience, years offering aCGH testing in a clinical prenatal or pediatric setting, and total years of genetic counseling experience, for each counselor interviewed.
<table>
<thead>
<tr>
<th>Genetic counseling work experience</th>
<th>Number of study participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current type of employer</strong></td>
<td></td>
</tr>
<tr>
<td>Academic hospital</td>
<td>5</td>
</tr>
<tr>
<td>Private hospital</td>
<td>2</td>
</tr>
<tr>
<td>aCGH testing lab</td>
<td>2</td>
</tr>
<tr>
<td><strong>Area of specialty</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical prenatal</td>
<td>9</td>
</tr>
<tr>
<td>Clinical pediatric</td>
<td>8</td>
</tr>
<tr>
<td><strong>Experience offering aCGH testing</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical prenatal setting</td>
<td>3</td>
</tr>
<tr>
<td>Clinical pediatric setting</td>
<td>7</td>
</tr>
<tr>
<td><strong>Median total years of genetic counseling experience</strong></td>
<td>11 years</td>
</tr>
</tbody>
</table>

Table 2. Summary of study participant demographics showing the number of participants working in each area of specialty, the number of counselors with clinical prenatal or pediatric experience, the number of counselors with experience offering aCGH testing in the clinical prenatal or pediatric setting, and the median total years of genetic counseling experience.

**THEMES**

We analyzed nine interview transcripts and distinguished four themes that exemplify challenges that counselors currently encounter when counseling patients for aCGH testing. The themes are:

1. Variations in prenatal aCGH implementation

2. Counseling for unanticipated results
3. Inconsistency regarding support for prenatal aCGH testing

4. Need for improved/standardized implementation of aCGH testing

Each theme is comprised of specific elements (referred to as codes in Methods), where each element represents a specific challenge or idea disclosed by counselors, which the corresponding theme encompasses. In addition, we sorted particularly broad themes into sub-themes. Tables 3 and 4 display each theme with corresponding sub-themes and elements. Then, for each theme and sub-theme, we summarize counselors’ comments and, for each element, we use tables to present illustrative quotes from counselors’ responses.
<table>
<thead>
<tr>
<th>Theme</th>
<th>Sub-theme</th>
<th>Element</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.1 Disparity regarding whether prenatal aCGH offered</td>
<td>Counselor had offered aCGH testing to prenatal patients&lt;br&gt;Counselor had not offered aCGH testing to prenatal patients</td>
</tr>
<tr>
<td></td>
<td>1.2 Differences in types of professionals who decide whether prenatal aCGH offered</td>
<td>Employer decides whether prenatal patients offered aCGH testing&lt;br&gt;Genetic counselor leads decision on whether to offer prenatal aCGH testing&lt;br&gt;Physician counselor leads decision on whether to offer prenatal aCGH testing&lt;br&gt;Physician and genetic counselor collaborate on whether to offer prenatal aCGH testing</td>
</tr>
<tr>
<td></td>
<td>1.3 Variation among indications for which prenatal aCGH offered</td>
<td>Indication: Patient highly interested in having aCGH testing&lt;br&gt;Indication: Abnormal fetal ultrasound finding&lt;br&gt;Indication: Family history of a genetic condition or an undiagnosed condition involving multiple abnormalities&lt;br&gt;Indication: Family history of chromosomal rearrangement&lt;br&gt;Indication: Family history of recurrent miscarriage&lt;br&gt;Indication: Abnormal fetal karyotype&lt;br&gt;Indication: Patient specifically requests prenatal aCGH testing</td>
</tr>
<tr>
<td></td>
<td>1.4 Disparity in information about limitations of aCGH routinely discussed with prenatal patients</td>
<td>Limitation: Results of uncertain significance&lt;br&gt;Limitation: Conditions covered&lt;br&gt;Limitation: Detection rates</td>
</tr>
<tr>
<td></td>
<td>1.5 Differences in aCGH platforms used in the prenatal setting</td>
<td>Counselor offers whole genome platform&lt;br&gt;Counselor offer prenatal platform</td>
</tr>
</tbody>
</table>

Table 3. The sub-themes and elements classified under the theme: Variations in prenatal aCGH implementation.
<table>
<thead>
<tr>
<th>Theme</th>
<th>Sub-theme</th>
<th>Element</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Counseling for unanticipated results</td>
<td></td>
<td>Unanticipated aCGH finding: Duplication of region associated with deletion syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unanticipated aCGH finding: Genetic condition indicated by result inconsistent with patient phenotype</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unanticipated aCGH finding: Presymptomatic diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unanticipated aCGH finding: Diagnosis of condition with severe prognosis</td>
</tr>
<tr>
<td>3. Inconsistency regarding support for prenatal aCGH testing</td>
<td></td>
<td>Overall high support</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benefit: Information</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benefit: Satisfy patient interest in testing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benefit: Similar to other genetic tests</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benefit: Reassurance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benefit: Potential compliance with ACOG guidelines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall less supportive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drawback: Ambiguity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drawback: Limited time for result interpretation</td>
</tr>
<tr>
<td>4. Need for improved/standardized implementation of aCGH testing</td>
<td></td>
<td>Guideline development lead by genetic counselors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Guideline development lead by physicians</td>
</tr>
<tr>
<td>4.1 Approaches to guideline development</td>
<td></td>
<td>Counseling tool: Visual aids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Counseling tool: Reading materials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Counseling tool: Genetic counselor</td>
</tr>
<tr>
<td>4.2 Counseling tools</td>
<td></td>
<td>Research tool: Databases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Research tool: Literature</td>
</tr>
<tr>
<td>4.3 Research tools</td>
<td></td>
<td>Genetic counselor education</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physician education</td>
</tr>
<tr>
<td>4.4 Healthcare provider education</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. The corresponding sub-themes and elements categorized under the themes:

Counseling for unanticipated results, Inconsistency regarding support for prenatal aCGH testing, and Need for improved/standardized implementation of aCGH testing.
THEME 1. Variations in prenatal aCGH implementation

Throughout the interviews, counselors differed in how they currently approach aCGH testing, including whether prenatal aCGH testing is offered, types of professionals who decide whether a center offers prenatal aCGH testing, indications for which aCGH has been or would be offered, information disclosed about limitations of aCGH, and platforms used. Each sub-theme and element helps characterize diverse approaches to prenatal aCGH testing that have formed in the absence of practice guidelines.

SUB-THEME 1.1 Disparity regarding whether prenatal aCGH offered

Five of the nine counselors interviewed currently see prenatal patients. Among these five, three had offered aCGH testing to prenatal patients and two had not (Table 5).

Counselors 1, 2 and 3 reported offering aCGH testing to prenatal patients. Counselors 4 and 5 noted that they had not yet offered aCGH testing to prenatal patients.

<table>
<thead>
<tr>
<th>Sub-theme</th>
<th>Element</th>
<th>Counselors</th>
<th>Counselors' quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Disparity regarding whether prenatal aCGH offered</td>
<td>Counselor had offered aCGH testing to prenatal patients</td>
<td>1, 2, 3</td>
<td>“I would say I have…been ordering it for probably a year.” (Counselor 2)</td>
</tr>
<tr>
<td></td>
<td>Counselor had not offered aCGH testing to prenatal patients</td>
<td>4, 5</td>
<td>“…right now we don't.” (Counselor 4)</td>
</tr>
</tbody>
</table>

Table 5. Variation regarding whether or not counselors had offered aCGH testing to prenatal patients, displaying the counselors whose responses agreed with a particular element and illustrative quotes from counselors’ statements.
SUB-THEME 1.2 Differences in types of professionals who decide whether prenatal aCGH offered

Among counselors who currently see prenatal patients, the decision makers regarding whether or not aCGH testing is offered to prenatal patients differed amongst counselors’ work settings (Table 6). Different decision makers included the counselor’s employer, as well as genetic counselors and physicians either independently or cooperatively. Of note, counselors who collaborated with physicians on the decision chose not to offer prenatal aCGH testing. Counselor 1 works for an aCGH testing lab and reported offering the most current platform that her employer offers and considers appropriate for prenatal patients. Counselor 2 noted taking a lead role in introducing aCGH testing to her prenatal clinic. In counselor 3’s academic hospital work setting, a physician took the lead in starting aCGH testing. Counselors 4 and 5 worked with physicians on the decision of whether or not to offer aCGH testing.
<table>
<thead>
<tr>
<th>Sub-theme</th>
<th>Element</th>
<th>Counselor(s)</th>
<th>Counselors' quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2 Differences in types of professionals who decide whether prenatal aCGH offered</td>
<td>Employer decides whether prenatal patients offered aCGH testing</td>
<td>1</td>
<td>“Basically, we have evolved with the evolving [lab] platform.” (Counselor 1)</td>
</tr>
<tr>
<td></td>
<td>Physician counselor leads decision on whether to offer prenatal aCGH testing</td>
<td>2</td>
<td>“…in my experience, it's really the counselors that drive all of this. So it's really been me that's been the one in our practice to set up this as a protocol. And I've done the education and everything.” (Counselor 2)</td>
</tr>
<tr>
<td></td>
<td>Physician counselor leads decision on whether to offer prenatal aCGH testing</td>
<td>3</td>
<td>“The doctor I work with is one who loves to be at the forefront of everything that’s new and hot, and so as the arrays have gotten better, she's wanted to make sure that we're offering the biggest and the best…” (Counselor 3)</td>
</tr>
<tr>
<td></td>
<td>Physician and genetic counselor collaborate on whether to offer prenatal aCGH testing</td>
<td>4, 5</td>
<td>“…the perinatalogist I work with talked to me about it, and he was like, “What do you think? It seems like this is just opening up a can of worms that we can't handle.” And I said I agree.” (Counselor 4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>“I'm the only counselor that works with the maternal fetal medicine doctor here, and we've talked about it a little bit… trying to counsel patients about that prenatally is just not something we've been up to doing yet.” (Counselor 5)</td>
</tr>
</tbody>
</table>

Table 6. Variations regarding the type of professionals who decided whether or not prenatal aCGH testing is offered, showing the counselor(s) whose responses agreed with a particular element and illustrative quotes from counselors’ comments.
SUB-THEME 1.3 Variation among indications for which prenatal aCGH offered

The five counselors who see prenatal patients all disclosed that they have offered or would offer prenatal aCGH testing for specific types of indications (Tables 7a and 7b). However, perceived appropriate indications varied and included abnormal ultrasound findings, a family history of a genetic condition, chromosome rearrangement or recurrent miscarriage, abnormal fetal karyotype, and a patient’s interest in testing or specific request for aCGH testing. Counselors 1, 2, and 4 stated that they would offer aCGH if a parent or couple showed a lot of interest in having aCGH testing. Counselors 1 and 2 noted offering aCGH for abnormal fetal ultrasound finding. Additional indications viewed as appropriate by counselors 1 and 2 include a family history of a genetic condition or an undiagnosed condition involving multiple anomalies, a family history of a chromosome rearrangement, and a family history of recurrent miscarriage. Counselors 2 and 3 reported that they offered aCGH to help interpret abnormal fetal chromosome analysis findings. Counselor 5 stated that they would offer aCGH testing upon a patient’s specific request.
<table>
<thead>
<tr>
<th>Sub-theme</th>
<th>Element</th>
<th>Counselors</th>
<th>Counselors' statements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication:</strong> Patient highly interested in having aCGH testing</td>
<td></td>
<td>1, 2, 4</td>
<td>“…for those patients who really are asking for more information.” (Counselor 1)</td>
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<td></td>
<td></td>
<td></td>
<td>“…because she said that she needed to know, was sure that she needed to know what was going on…” (Counselor 2)</td>
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<td></td>
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<td></td>
<td>“…if there is somebody who really wanted to do all the testing that is available, and really, that was really important to them…” (Counselor 4)</td>
</tr>
<tr>
<td><strong>Indication:</strong> Abnormal fetal ultrasound finding</td>
<td></td>
<td>1, 2</td>
<td>“…cases where on ultrasound we've had abnormalities that seem…like a skeletal dysplasia…There could be a small deletion in a region that happens to house a gene that causes skeletal dysplasia…” (Counselor 1)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>“…most of the time they are abnormal ultrasound findings with a normal karyotype.” (Counselor 2)</td>
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<td></td>
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<td>“…something…like ventriculomegaly or hydrocephalus or absent corpus colosum…” (Counselor 2)</td>
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<td></td>
<td></td>
<td></td>
<td>“…we had one with lissencephaly…and…I had one that was suspected holoprosencephaly.” (Counselor 2)</td>
</tr>
<tr>
<td><strong>Indication:</strong> Family history of a genetic condition or an undiagnosed condition involving multiple abnormalities</td>
<td></td>
<td>1, 2</td>
<td>her first child had CHARGE, and was found to have a mutation…for her second pregnancy…in addition to doing the CHARGE testing, she was also offered the array…” (Counselor 1)</td>
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<td></td>
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<td>“I had one case where it was a couple who had had a pregnancy with Wolf-Hirschhorn syndrome, previous, and just for peace of mind we ended up doing a limited prenatal array.” (Counselor 2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>“…a family history of an unknown multiple abnormality syndrome of some kind that wasn't known…” (Counselor 2)</td>
</tr>
</tbody>
</table>

Table 7a. A selection of the indications for which different counselors have offered or would offer prenatal aCGH testing, showing the counselors whose responses agreed with a particular element and illustrative quotes from counselors’ comments.
Table 7b. A selection of indications for which different counselors have offered or would offer prenatal aCGH testing, showing the counsel(s) whose statements agreed with a particular element and illustrative quotes from counselors’ responses.

SUB-THEME 1.4 Disparity in information about limitations of aCGH routinely discussed with prenatal patients

Among the counselors interviewed, counselors 1, 2 and 3 have offered aCGH testing in the prenatal setting. These counselors reported discussing the limitations of aCGH testing with prenatal patients to different levels of detail (Table 8). Counselors 1 and 3 noted...
consistently discussing the possibility of results of uncertain significance and counselor 2 recalled reviewing the possibility of unclear results with about 50% of patients considering prenatal aCGH testing. In addition, counselors 1 and 3 noted talking to patients about the possibility of testing parents to help interpret unclear results. Counselors 1 and 3 also noted discussing the limited number of conditions that aCGH tests for with patients. As well, counselor 1 recalled talking to patients about the range of detection rates for different conditions with regards to aCGH testing.
<table>
<thead>
<tr>
<th>Sub-theme</th>
<th>Element</th>
<th>Counselor(s)</th>
<th>Counselors' statements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Limitation: Results of uncertain significance</td>
<td>1, 2, 3</td>
<td>“…the possibility for results of uncertain significance. And also how we try to resolve those results of uncertain significance. So discussing why we ask for parental bloods…” (Counselor 1)</td>
</tr>
<tr>
<td>1.4 Disparity in information about limitations of aCGH routinely discussed with prenatal patients</td>
<td>Limitation: Conditions covered</td>
<td>1, 3</td>
<td>“I try to be very up front about the idea that we may get information that we don't know what to do with…I do try to make sure to talk to the parents up front and say that “There's a reasonable chance that we will be coming back to you and asking you for your blood.”” (Counselor 3)</td>
</tr>
<tr>
<td></td>
<td>Limitation: Detection rates</td>
<td>1</td>
<td>“…making sure that they understand that it doesn't cover every single genetic disease that is out there... And there are certain genetic disorders that an array just is not the test to do.” (Counselor 1)</td>
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<td></td>
<td></td>
<td></td>
<td>“We can't realistically test anybody for all...known genes. It's just not scientifically possible and it would cost you millions and millions of dollars. So we don't do that. What we do is a targeted suggestion based on what seems reasonable based on what your clinical situation is.” (Counselor 3)</td>
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<td></td>
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<td></td>
<td>“I always discuss detection… They have to understand that there might be a condition that's on there where maybe 10% of cases are due to a deletion, so just because we've gotten a normal result doesn't necessarily mean we've ruled out every possibility for that particular condition.” (Counselor 1)</td>
</tr>
</tbody>
</table>

Table 8. Differences among counselors regarding the limitations of aCGH routinely discussed with prenatal patients, displaying the counselor(s) whose responses agreed with a particular element and illustrative quotes from counselors’ comments.
SUB-THEME 1.5 Differences in aCGH platforms used in the prenatal setting

Among the interviewees who offer prenatal aCGH testing (counselors 1, 2 and 3), different aCGH platforms were offered to prenatal patients (Table 9). The type of platform counselor 2 recalled offering partly depended on the patient’s awareness of the limitations of aCGH, whereas counselor 1 recalled offering a whole genome platform and counselor 3 noted offering a prenatal-specific platform. Counselor 1 offered patients the most current whole genome platform available from the aCGH testing lab for which they work. Counselor 2 offered a whole genome array to a patient who had a relatively good grasp of the limitations of aCGH testing. In another case, counselor 2 offered a prenatal array to a patient who showed relatively little understanding of the limitations of aCGH testing. Counselor 3 offered a prenatal platform because it provided the least chance for ambiguous results.
Table 9. Variability regarding the aCGH platforms used in the prenatal setting, showing the counselors whose responses agreed with a particular element and illustrative quotes from counselors’ statements.

<table>
<thead>
<tr>
<th>Sub-theme</th>
<th>Element</th>
<th>Counselors</th>
<th>Counselors’ statements</th>
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</thead>
<tbody>
<tr>
<td>1.5 Differences in aCGH platforms used in the prenatal setting</td>
<td>Counselor offers whole genome platform</td>
<td>1, 2</td>
<td>“we have evolved with the evolving [lab] platform...we...take off regions that are highly polymorphic that don't have any clinical significance. And so you are left with the regions that really do give you information and have a low probability of giving you ambiguity in those results...sometimes that means using a slightly smaller platform until the larger one is more tested” (Counselor 1)</td>
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<tr>
<td></td>
<td>Counselor offers prenatal platform</td>
<td>2, 3</td>
<td>“I ordered...the whole genome, because for her that was an appropriate, she would have understood, and I did go into with her the possibility of a result we wouldn't be able to explain” (Counselor 2)</td>
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<td></td>
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<td></td>
<td>“…what I did with her was the prenatal test. Because the level of understanding of what it was we were looking for and the suspicion of even finding anything was lower…” (Counselor 2)</td>
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<td></td>
<td></td>
<td></td>
<td>“...you wouldn't put anything on the array that didn't already have a name or some kind of defined pattern of characteristics to it.” (Counselor 3)</td>
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THEME 2. Counseling for unanticipated results

Both prenatal and pediatric counselors reported counseling for unanticipated aCGH testing results (Tables 10a, 10b and 10c). In all instances, results were unanticipated by the interviewed counselors and their patients. Unanticipated results included duplications of regions associated with deletion syndromes, results indicating genetic conditions that did not correspond to the patient’s phenotype, a pre-symptomatic diagnosis and a
diagnosis of a condition with an unexpectedly severe prognosis. Counselor noted pediatric cases, except for counselor 1 who spoke of a prenatal case. Counselors recalled challenges with regards to result interpretation, clarifying to families how a patient’s result is similar and distinct from a known condition, and supporting families while they receive bad news. Regarding families who pursued aCGH testing, counselors 1, 3 and 7 reported counseling for duplications of regions associated with deletion syndromes. Regarding these cases, counselor 1 noted struggling with result interpretation. Counselor 3 recalled the challenge of distinguishing to a parent how a duplication differs from the reciprocal deletion and clarifying the currently scant knowledge regarding the patient’s duplication. Counselor 7 did not report encountering great challenges when interpreting and counseling for a duplication of a region associated with a deletion syndrome, however, in this instance, the patient’s phenotype indicated the corresponding deletion syndrome. Counselors 4 and 8 recalled counseling for aCGH findings that indicated conditions that did not correspond well to the patient’s phenotype. Counselor 4 noted challenges in deciding how to disclose to a parent the limited explanation that the aCGH finding provided. Counselor 8 recalled a frustrating case where the indicated condition involved features that the patient did not have. In addition, counselor 4 recalled counseling for a deletion detected by aCGH where the deletion explained the pediatric patient’s features, but also indicated an additional condition pre-symptomatically. Counselor 4 noted the difficulty of delivering this unexpected bad news to the family. Furthermore, counselor 8 spoke of a case in which aCGH testing detected a condition with an unexpectedly severe prognosis. Counselor 8 noted that disclosing this finding to
the family was difficult, however, the counselor also felt that having an explanation for
the patient’s symptoms was empowering to the patient’s mother.

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<tr>
<th>Element</th>
<th>Counselors</th>
<th>Counselors' statements</th>
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<tbody>
<tr>
<td>Unanticipated aCGH finding: Duplication of region associated with deletion syndrome</td>
<td>1 (prenatal setting), 3, 7</td>
<td>“I think the hardest thing is when you get, and a lot of times it happens where it's the reciprocal of something that's documented. So there's a disease out there that's caused by a deletion, but nobody's ever documented what the reciprocal duplication does. What does that mean? Those are the toughest.” (Counselor 1)</td>
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<td>“…there was the duplication of the Williams region, the deletion, Mom had already gone online and looked up Williams, so it was kind of a re-education process to say “No, it's not that. And here's why.” So it's, the other counseling challenge would be the information seeking parents because our information about these results is so limited, and it's hard to tell them, “We know something, but we don't know everything.” So you're dangling the carrot out in front of their face.” (Counselor 3)</td>
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<td></td>
<td></td>
<td>“I had this kid who we saw in clinic, and we were like, “He totally has Noonan syndrome.” So we sequenced PTPN11, and didn't find a mutation…he ended up having a duplication of PTPN11. So he has three copies of PTPN11 in the surrounding stuff. So we were like, &quot;Well, I guess he has Noonan Syndrome.&quot; And again, just really helpful to the family. They were like, “You know what, we are taking our Noonan Syndrome diagnosis and going home.” Like in a good way. They were very happy to be firmly in a category.” (Counselor 7)</td>
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Table 10a. Unanticipated aCGH findings involving duplications of regions associated with deletion syndromes, showing the counselors whose responses agreed with a particular element and illustrative quotes from counselors’ comments.
<table>
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<tr>
<th>Element</th>
<th>Counselors</th>
<th>Counselors' statements</th>
</tr>
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<tbody>
<tr>
<td>Unanticipated aCGH finding: Genetic condition indicated by result inconsistent with patient phenotype</td>
<td>4, 8</td>
<td>“…it came back they had Klinefelter...He came in with a lot of other issues. When the Klinefelter came back, there were parts of it that fit. Pubertal immaturity, and some other things that honestly when I got it back, I called the lab and I said, “Can you tell how many X's he had?” Because he had so many other behavioral issues, autistic spectrum disorder, that I'm like, “this is not classic Klinefelter, and I don't know what to tell the Mom. This is not the answer”…we ended up having to do that additional testing to confirm there's only two X's and to say there's more going on with this kid, but we don't know what.” (Counselor 4)</td>
</tr>
<tr>
<td>Unanticipated aCGH finding: Genetic condition indicated by result inconsistent with patient phenotype</td>
<td>4, 8</td>
<td>“The one that’s coming to mind is a patient with a 16p dup that has been reported in patients maybe with autism, and our patient had autistic features, but he didn't fit anything else that had been described with the syndrome, he didn't fit any of the behavioral phenotype other than the autism. He didn't have the dysmorphic features, he didn't have the minor physical anomalies. And so when we were counseling Mom, and giving her information, and showing pictures, and talking about it, she says, “You know, this really doesn't fit.” And we kind of had to agree with her.” (Counselor 8)</td>
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Table 10b. Unanticipated aCGH findings involving associated phenotypes that are inconsistent with the patient’s phenotype, including the counselors whose responses agreed with a particular element and illustrative quotes from counselors’ statements.


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<tr>
<th>Element</th>
<th>Counselor</th>
<th>Counselors’ statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unanticipated aCGH finding: Pre-symptomatic diagnosis</td>
<td>4</td>
<td>“…one where we found that there was a deletion in the NF2 gene, and that he'd probably develop NF2…he had other issues that the family had dealt with, and the CGH found a deletion and it encompassed NF2 gene…it looked like a deletion of the entire gene, and he'd develop it at some point, but he was like six, so a pre-symptomatic diagnosis with NF2 from...That was probably the worst one ever…to tell this family of the six year old boy who had had multiple medical issues…” (Counselor 4)</td>
</tr>
<tr>
<td>Unanticipated aCGH finding: Diagnosis of condition with severe prognosis</td>
<td>8</td>
<td>“Mom…came to me and she said, “I just want an answer. I just want an answer. Do anything.” And we did CGH and we got an answer, and it ended up being horrible. It's this Pitt-Hopkins syndrome where very kind of Rett- and Angelman-like where only half the kids learn to walk, most of them have no speech, or only a few words, and this is an 8 month old. So I think that kind of knowledge has real pros and cons. She was wanting the information…And she got it, and I think she's doing well…Positively or negatively, but families feel like they have more information than before, and I think that's empowering.” (Counselor 8)</td>
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</tbody>
</table>

Table 10c. Unanticipated aCGH findings involving a pre-symptomatic diagnosis and a diagnosis of a condition with a severe prognosis, showing the counselor whose comments agreed with a particular element and illustrative quotes from counselors’ statements.

THEME 3. Inconsistency regarding support for prenatal aCGH testing

All counselors interviewed noted benefits and limitations of prenatal aCGH testing. In general, counselors shared concerns about the possibility of unclear results and valued the information and reassurance aCGH testing has the potential to offer. However, overall support for prenatal aCGH varied. Some counselors showed relatively high support for prenatal aCGH testing, whereas other counselors showed relatively low support, leading us to present relatively high or relatively low support as sub-themes. In addition,
counselors gave specific reasons for their levels of support, which we identified as elements of either sub-theme.

**SUB-THEME 3.1 Relatively high support for prenatal aCGH testing**

Counselors 1, 2, 6, 7 and 9 were relatively supportive of aCGH testing. Each counselor shared their general opinion of prenatal aCGH testing and highlighted specific benefits of prenatal aCGH testing (Tables 11a and 11b). Counselors 1, 2, 6, 7 and 9 shared general views that were relatively supportive of aCGH testing in the prenatal setting, and spoke of the additional information aCGH testing offers, beyond chromosome analysis. In addition, counselors 1, 2, 6 and 7 noted that offering aCGH testing can meet a patient’s interest in having testing. Counselors 1, 6 and 7 remarked on how aCGH testing is similar to other genetic tests with regards to potentially yielding ambiguous results, and all three counselor compared aCGH results of uncertain significance to marker chromosomes.

These counselors also compared unclear aCGH results to abnormal fetal ultrasound findings, chromosomal mosaicism and unclear molecular genetic test results. Counselor 1 and 2 noted the added reassurance that negative aCGH results have given patients, beyond a normal karyotype, in pregnancies with no detected ultrasound abnormalities. Counselors 1 and 6 referred to the American College of Obstetricians and Gynecologists guidelines, which state that diagnostic prenatal testing should be offered to every pregnant woman, and they questioned whether counselors have to offer prenatal aCGH testing in order to comply with these guidelines.
<table>
<thead>
<tr>
<th>Element</th>
<th>Counselors</th>
<th>Counselor's statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall high support</td>
<td>1, 2, 6, 7, 9</td>
<td>&quot;...I really do think it's a good option to have out there, and it's definitely something that can be very beneficial in some situations…” (Counselor 1)</td>
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<td></td>
<td></td>
<td>&quot;I certainly think it should be available.” (Counselor 6)</td>
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<td>&quot;I think it's a useful tool.” (Counselor 7)</td>
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<td></td>
<td></td>
<td>&quot;I think it holds a lot of value prenatally.” (Counselor 9)</td>
</tr>
<tr>
<td>Benefit: Information</td>
<td>1, 2, 6, 7, 9</td>
<td>“Definitely with the power of the array to not only get you the information that chromosome analysis can get you, but other information as well…” (Counselor 1)</td>
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<td></td>
<td></td>
<td>“My personal opinion is that information is important, and if you can, even if you're going to terminate the pregnancy, to have an answer about something may be important to you down the road.” (Counselor 2)</td>
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<td></td>
<td></td>
<td>“…if a family is willing to do an invasive test to find out about Down syndrome, they should be made aware that there are many other conditions that some people would think are a whole lot worse than Down syndrome that they would probably want to know about, or that they might want to know about.” (Counselor 6)</td>
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<td></td>
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<td>“I think that in the prenatal arena it has huge advantages that it can pinpoint a chromosomal abnormality, a very small one, within the prenatal period.” (Counselor 9)</td>
</tr>
<tr>
<td>Benefit: Satisfy patient interest in testing</td>
<td>1, 2, 6, 7</td>
<td>“…depending on how much information they are looking for.” (Counselor 1)</td>
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<tr>
<td></td>
<td></td>
<td>“…if someone is having invasive testing because they want, if someone is telling you they want to know if their child has a problem, I think they should be offered this test.” (Counselor 6)</td>
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<tr>
<td></td>
<td></td>
<td>“I just think that they are a great tool for, you have families that come in...People have money here. And they want to spend that money to have healthy children. So when people, people come in and say “I want every test. There is no test that I don't want.” (Counselor 7)</td>
</tr>
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</table>

Table 11a. A selection of elements classified under the sub-theme: Relatively high support for prenatal aCGH testing and the theme: Variations in prenatal aCGH implementation, displaying the counselors whose comments agreed with a particular element and illustrative quotes from counselors’ statements.
<table>
<thead>
<tr>
<th>Element</th>
<th>Counselors</th>
<th>Counselor's statement</th>
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<tbody>
<tr>
<td>Benefit: Similar to other genetic tests</td>
<td>1, 6, 7</td>
<td>“…we do a lot of counseling about uncertainty. You have an ultrasound finding of hydrocephalus. Goodness knows there's a whole spectrum that can happen there. The same thing applies to this. In the same way when counselors years ago were first explaining marker chromosomes and things like that, we're doing that now, just on a more detailed level.” (Counselor 1)</td>
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<tr>
<td>Benefit: Reassurance</td>
<td>1, 2</td>
<td>“Because you could get a mosaicism or a marker or something that you didn't know what it was going to mean. So I don't really think it's any different.” (Counselor 6)</td>
</tr>
<tr>
<td>“…the variants of uncertain clinical consequence...It's the same issues of things like markers on prenatal testing, though. Or variants of uncertain etiology and sequencing results. A subset of these results is simply going to be beyond our frame of knowledge.” (Counselor 7)</td>
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<tr>
<td>Benefit: Potential compliance with ACOG guidelines</td>
<td>1, 6</td>
<td>“…there are definitely situations where it'll give patients reassurance.” (Counselor 1)</td>
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<td>&quot;The thing I've appreciated so far having normal results is that I can kind of provide a further degree of reassurance to people who are in a situation where they are already worried about their pregnancy…” (Counselor 2)</td>
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<td>“…with ACOG coming out and saying everybody should be offered the option of doing prenatal testing, I think that opens insurance up to considering what does that really mean? What kind of prenatal testing does that mean?” (Counselor 1)</td>
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<td>“…you have, depending on how you interpret the ACOG guidelines, if you are offering invasive testing to everyone…whoever decides they want invasive testing, regardless of their indication, I think they should be made aware that this is available.” (Counselor 6)</td>
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Table 11b. A selection of elements classified under the sub-theme: Relatively high support for prenatal aCGH testing and the theme: Variations in prenatal aCGH implementation, showing the counselors whose responses agreed with a particular element and illustrative quotes from counselors’ statements.
SUB-THEME 3.2 Relatively low support for prenatal aCGH testing

Counselors 3, 4, 5 and 8 varied in their level of support for prenatal aCGH testing, however, overall they were less supportive than other interviewed counselors. Counselors disclosed their overall views of prenatal aCGH testing in addition to specific drawbacks of aCGH testing in the prenatal setting (Table 12). Counselor 3 agreed with offering aCGH testing to prenatal patients as a way to help interpret abnormal cytogenetic findings, but not abnormal fetal ultrasound findings. Counselor 8 agreed with offering prenatal aCGH testing for abnormal cytogenetic or abnormal fetal ultrasound findings. Counselors 4 and 5 agreed with offering prenatal aCGH testing for patients who were highly interested in testing (refer to sub-theme 1.3). Counselor 4 also noted that their approach to aCGH testing is shaped by the preferences of their patient population. All nine counselors interviewed shared concerns about the potential for aCGH results of uncertain significance in the prenatal setting, and the possibility of ambiguous results was a primary concern of interviewed counselors. In addition, counselors 3, 5 and 8 noted the limited time window for result interpretation available in the prenatal setting and compared it to the typically more open-ended time window for available for follow-up in the pediatric setting.
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<tr>
<th>Element</th>
<th>Counselors</th>
<th>Counselor’s statement</th>
</tr>
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<tbody>
<tr>
<td>Overall less supportive</td>
<td>3, 4, 5, 8</td>
<td>“I still have hesitation doing it unless there's a really obvious indication for it…” (Counselor 3)</td>
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<td></td>
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<td>“I think there's a lot of limitations to what you can realistically predict prenatally, and I think sometimes that gets lost when you're just trying to find a diagnosis for the family” (Counselor 4)</td>
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<td>“We have a lot less interest in invasive testing, so I think a lot of my approach is also born of the fact that this is a conservative community.” (Counselor 4)</td>
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<td>“I am really hesitant about it.” (Counselor 5)</td>
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<td>“I think aCGH would be great as an adjunct for figuring out abnormal results.” (Counselor 8)</td>
</tr>
<tr>
<td>Drawback: Ambiguity</td>
<td>1, 2, 3, 4, 5, 6, 7, 8, 9</td>
<td>“I've seen how much ambiguity there is in the pediatric setting. I worry about putting that level of ambiguity into the prenatal setting.” (Counselor 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“…you wouldn't put anything on the array that didn't already have a name or some kind of defined pattern of characteristics to it.” (Counselor 3)</td>
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<td></td>
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<td>“…we find this deletion of uncertain significance, what does that mean? And prenatally is that helpful for that family? I don't think a lot of times necessarily it is.” (Counselor 4)</td>
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<td></td>
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<td>“…the possibility of finding something that is novel or little is known about it and trying to counsel patients about that prenatally is just not something we've been up to doing yet.” (Counselor 5)</td>
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<td></td>
<td>&quot;I think that as a first-line test it is an awful, horrible, no-good, very bad idea, simply because this is a time during pregnancy…when a yes or no answer is very important.” (Counselor 8)</td>
</tr>
<tr>
<td>Drawback: Limited time for result interpretation</td>
<td>3, 5, 8</td>
<td>“in pediatrics…you've got plenty of time, and you've got availability for follow-up, and that kind of stuff. In the prenatal setting, your time and your follow-up are much more limited.” (Counselor 3)</td>
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<td></td>
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<td>“…the timing, by the fact that by the time we do a level 2 ultrasound, get an amnio, get that result back, and then turn around try and do another test…if they're thinking about…possibly terminating…we're really pushing the limits on that timing in the pregnancy.” (Counselor 5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“…a “maybe” result that requires parental samples and takes a while to do is simply not a good idea…” (Counselor 8)</td>
</tr>
</tbody>
</table>

Table 12. Elements with corresponding quotes classified under the sub-theme: Relatively low support for prenatal aCGH testing and the theme: Variations in prenatal aCGH implementation.
THEME 4. Need for improved/standardized implementation of aCGH testing

Most of the counselors interviewed shared ideas about how the implementation of aCGH testing can be improved. Counselors’ ideas applied to prenatal and pediatric settings and encompassed guideline development and healthcare provider education (Table 13a) as well as counseling and research tools (Table 13b). Regarding approaches to guideline development, counselors 1 and 2 remarked on how genetic counselors can take a lead role in helping to establish practice guidelines for aCGH testing. As well, counselors 1 and 2 noted that physicians could put forth practice guidelines. Concerning improvements to healthcare provider education, counselors suggested a number of ways that genetic counselors and physicians can become versed in aCGH testing and learn how to bring aCGH testing into their clinic. For instance, counselor 1 suggests that peers could learn from more experienced genetic counselors, organize and attend symposia, and include aCGH testing in genetic counseling training program curricula. Counselor 9 noted that physicians could improve their awareness of aCGH testing through medical training programs and continuing education. Regarding counseling tools counselors had ideas for aids that would help explain aCGH testing to patients. Specifically, counselors 2 and 8 spoke of a need for simple visual counseling aids. Counselor 2 disclosed a need for improved reading materials, such as simple fact sheets for patients. Counselor 9 underlined genetic counselors as important counseling resources and highlighted the benefits of involving genetic counselors when offering aCGH testing. With regards to research tools that aid result interpretation, counselors spoke of ways to more efficiently share information about aCGH findings. Counselors specifically supported establishing centralized databases that catalogue aCGH findings and increasing case publications. For
example, counselors 3 and 7 noted a need for a database that catalogues aCGH findings.

In addition, counselors 4 and 9 reported a need for more case reports.

<table>
<thead>
<tr>
<th>Element</th>
<th>Counselors</th>
<th>Counselor's statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guideline development lead by genetic counselors</td>
<td>1, 2</td>
<td>“...a good article in the Journal of Genetic Counseling, or in a prospectus, a general approach to prenatal aCGH or how a department can try to incorporate that testing, and what aspects you need to think of from offering it to patients to having the support that you need on the follow-up end of things with results.” (Counselor 1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“…as a group we really need, we need to have some kind of standards as a group of counselors.” (Counselor 2)</td>
</tr>
<tr>
<td>Guideline development lead by physicians</td>
<td>1, 2</td>
<td>“...what I would really like to see developed and I think this is something that's coming are recommendations…maybe something that ACOG and ACMG come out with” (Counselor 1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&quot;I think ACOG could definitely put out guidelines as well.” (Counselor 2)</td>
</tr>
<tr>
<td>Genetic counselor education</td>
<td>1</td>
<td>“I definitely think that one place to start is again, talking to the counselors at the lab, so that, getting a tutorial on what type of an array do you offer, what is the coverage like, in your particular experience what are the chances of getting a variant of uncertain significance versus a diagnosis.” (Counselor 1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“I definitely think we are getting to the point where it probably would be a great educational breakout session, or a pre-conference symposia over at NSGC to have as a workshop on prenatal aCGH and things like that.” (Counselor 1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“…it's going to be a responsibility of the genetic counseling programs to make sure that this technology is something that's covered in the curriculum…” (Counselor 1)</td>
</tr>
<tr>
<td>Physician education</td>
<td>9</td>
<td>“I think it involves educating people at the training level, whether it be medical school or residents…And I think it involves continuing education on the part of medical professionals” (Counselor 9)</td>
</tr>
</tbody>
</table>

Table 13a. A selection of elements classified under the theme: Need for improved/standardized implementation of aCGH testing, showing counselors whose statements agreed with specific elements and illustrative quotes.
<table>
<thead>
<tr>
<th>Element</th>
<th>Counselors</th>
<th>Counselor's statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counseling tool: Visual aids</td>
<td>2, 8</td>
<td>“I think some simple diagrams to help families understand what this test is and how it's different from testing that's been done before…these are the things that CGH can detect and chromosomes can't. And this is what CGH is going to miss that chromosomes will pick up.” (Counselor 8)</td>
</tr>
<tr>
<td>Counseling tool: Reading materials</td>
<td>2</td>
<td>“...one of the things that's really, really lacking is patient friendly information that's in a fact sheet format.” (Counselor 2)</td>
</tr>
<tr>
<td>Counseling tool: Genetic counselor</td>
<td>9</td>
<td>&quot;I always feel that clinics really benefit from having a genetic counselor involved, because I think genetic counseling is such a broad knowledge base, and such an acute understanding of how to work with patients in a useful way that a lot of other professionals don’t.&quot; (Counselor 9)</td>
</tr>
<tr>
<td>Research tool: Databases</td>
<td>3, 7</td>
<td>“I would love to see a gene test like catalog for the more common duplication deletion things. And that's going to take time, because we're still gathering these cases and trying to figure out what they mean.” (Counselor 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“In an ideal world, there would be a centralized database, a national database where we could just toss all of our abnormal random micro-arrays in, and people could meet up with each other.” (Counselor 7)</td>
</tr>
<tr>
<td>Research tool: Literature</td>
<td>4, 9</td>
<td>“…what we need to start doing is publishing more of these cases…” (Counselor 4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“…each one of them is a publishable case, and it's always so useful to say “In the literature, we have seen two other cases of children like this, and this is what their outcomes were,” or what have you.” (Counselor 9)</td>
</tr>
</tbody>
</table>

Table 13b. A selection of elements classified under the theme: Need for improved/standardized implementation of aCGH testing, exhibiting counselors whose statements agreed with specific elements and illustrative responses.
DISCUSSION

LACK OF UNIFORM APPROACH

Practice guidelines for aCGH testing, including prenatal aCGH testing, have yet to be developed by genetic counselors or physicians. Our study revealed a lack of uniformity regarding the implementation of prenatal aCGH testing among interviewed counselors. Specifically, we noted differences regarding whether counselors offered prenatal aCGH testing, types of professionals who decided whether a center offered prenatal aCGH testing, indications for which aCGH testing had been offered, limitations of aCGH testing disclosed to patients, and aCGH platforms used. These diverse practices suggest dissimilar views among genetic counselors, lab directors and physicians concerning the current appropriateness of prenatal aCGH testing and situations for which it should be offered. In addition, differences in approaches are evidence of the current lack of guidelines regarding the practice of aCGH testing in either pediatric or prenatal settings.

LESSON LEARNED FROM PEDIATRICS

Reported pediatric cases involving unanticipated aCGH findings offer important lessons for aCGH testing in the prenatal setting. Specifically, cases involving unexpected aCGH results experienced by counselors highlight the implications of such results in the prenatal setting, the importance of pre-test counseling and the limits of predictive knowledge. With regard to reciprocal duplications of deletion syndromes discovered prenatally, counselor 1 stated, “What does that mean? Those are the toughest,” pointing out the current limits of predictive knowledge in the prenatal setting. Of note, healthcare providers have published a number of studies involving reciprocal duplications. A study
by Hannes et al. (2009) showed that reciprocal microdeletions and microduplications of 1q21.1 represent a spectrum of developmental delay and other anomalies. Brunneti-Pierri et al., (2008) demonstrated that 16p13.11 deletions likely cause mental retardation, microcephaly and epilepsy whereas the reciprocal duplications are of uncertain clinical significance. Furthermore, other researchers have reported cases involving reciprocal duplications of regions associated with 22q11.2 deletion syndrome, Williams syndrome and Smith-Magenis syndrome (Ou et al., 2008; Ensenauer et al., 2003; Torniero et al., 2008; Potocki et al., 2007). However, many more such studies are required before the implications of reciprocal duplications can be confidently predicted.

Also, counselor 4 recalled a case involving a patient whose presentation was suggestive of Noonan syndrome and who, through aCGH testing, was found to have a duplication of PTPN11, the primary gene associated with Noonan syndrome. This case points out how much patient phenotype can aid result interpretation and leads us to consider the limitations of phenotypic information available in the prenatal setting. Accurate predictive information is especially important in the prenatal setting where phenotypic information is limited and predictions may influence how patients’ manage pregnancies (Darilek et al., 2008).

As well, reported cases involving aCGH results that were inconsistent with pediatric patient phenotype underline the importance of caution when informing patients of the implications of aCGH findings. For example, the additional, reportedly unrelated features of counselor 4’s patient with Klinefelter syndrome suggests that those offering aCGH testing should consider disclosing to families the possibility of a finding that only explains some of the patient’s features. Although, because researchers have shown an
association between Klinefelter syndrome and autism spectrum disorder, we cannot
dismiss the possibility that the patient’s autistic features may due to his molecular
diagnosis of Klinefelter syndrome (Bruining et al., 2009). Also, given counselor 8’s
patient with a 16p duplication who did not display any of the predicted dysmorphic
features, such as long philtrum and upslanting palpebral fissures, or physical anomalies,
such as syndactyly of the fingers, perhaps those offering aCGH testing should disclose to
patients the possibility of a result with associated anomalies that are more severe than the
patient’s presentation (Behjati et al., 2008). Significantly, these cases also point out the
broad spectrum of severity associated with many genetic conditions, including several
detected by aCGH. Examples include the wide spectrum of cognitive deficits associated
22q11.2 deletion syndrome, and the inconsistent occurrence of congenital heart disease in
individuals with trisomy 21 (Campbell et al., 2006; Keckler et al., 2008). Overall, these
cases indicate a need for health providers offering aCGH testing to consider how to
disclose to patients the possibility of aCGH results that offer an incomplete explanation
or an imprecise predicted phenotype.

Importantly, aCGH testing contributes to phenotypic information about
microdeletions and microduplications. In particular, because aCGH testing can detect
genetic conditions not known to be associated with the patient’s phenotype, it is a
genotype-first approach. In contrast, a phenotype-first approach involves recommending
a specific genetic test based on a patient’s features. The objective nature of aCGH testing
can result in the detection of deletions and duplications of known syndromic regions in
patients without the full predicted phenotype. As these patients are discovered, the
phenotypic spectrum of microdeletions and microduplications broadens. Altogether, an
important aspect of aCGH testing is its potential to provide genetic diagnoses for individuals who exhibit subtle and/or atypical phenotypes.

In addition, the cases involving pre-symptomatic and unexpectedly severe results discussed by counselors 4 and 8, respectively, further emphasize the importance of pre-test counseling. As Darilek et al., (2008) outlined, those offering prenatal aCGH testing should disclose to families the possibility of genetic information that the family feels, on reflection, is regrettable. Such diagnoses include conditions not associated with apparent birth defects, for instance, neurofibromatosis 2, which aCGH testing uncovered in counselor 4’s patient. With regard to the prenatal implications of counselor 8’s patient with Pitt-Hopkins syndrome, such severe findings highlights the importance of a pre-test discussion about the range of severity among detected syndromes, as recommended by Darilek et al., (2008). Further, this case leads us to consider the indications for which prenatal aCGH testing should be offered. Pitt-Hopkins is associated with facial dysmorphism, clubbed fingertips and hypoplastic corpus callosum (Peippo et al., 2006), which could potentially be detected prenatally via fetal ultrasound, although, no reports of prenatal diagnosis for this condition exist. Given the diverse indications for which counselors report offering prenatal aCGH testing and that many conditions detected by aCGH may not present prenatally, pre-test counseling should address the possibility of detecting conditions with later onset and severe anomalies.

Another point to consider is the incidence of positive (i.e. abnormal) aCGH results in the prenatal setting. Numerous reports have shown that the frequency of positive abnormal aCGH test results is much lower in the prenatal patient population than in either neonatal or pediatric patient populations (Lu et al., 2008; Shaffer et al., 2008;
Stankiewicz and Beaudet, 2007). Those who offer prenatal aCGH testing have to weigh the benefits of information and potential reassurance with the possibility of unclear findings.

**COMFORT LEVEL WITH PREGNATAL aCGH**

Counselors’ different levels of support for prenatal aCGH testing suggests that a significant number of counselors may not currently feel comfortable offering this test to prenatal patients. Interviewed counselors showed diverse views regarding the current appropriateness of prenatal aCGH testing, and emphasized different benefits and drawbacks of this type of testing. Counselors all acknowledged the value of genetic information offered by aCGH. However, counselors’ predominant concerns regarding the possibility of ambiguous findings, as well as counselors’ concerns about the limited time available for result interpretation in the prenatal period, suggest that currently many counselors are not entirely comfortable with counseling for prenatal aCGH testing. Alternatively, the range in support for prenatal aCGH may suggest differences among counselors regarding their awareness of aCGH testing, which would indicate a need for genetic counselors considering offering prenatal aCGH testing to closely examine this type of testing. As well, different levels of support may reflect dissimilar experiences regarding aCGH testing. For example, counselor 2 showed relatively high support for prenatal aCGH testing and noted that, “The thing I appreciate so far is having normal results,” which may indicate that support is influenced by clinical experience.

Counselors’ comments also indicated an overall regard for patient interest in and request for testing. For instance, counselor 1 noted offering prenatal aCGH testing, “depending on how much information they are looking for.” In addition, counselor 4 stated, “We
have a lot less interest in invasive testing, so I think a lot of my approach is also born of the fact that this is a conservative community.” Therefore, a patient populations’ interest in a genetic test may influence the corresponding counselor’s level of support for the test. In general, counselors’ predominant concern about the potential for ambiguous aCGH findings and hesitancy about offering prenatal aCGH testing, indicates that some counselors are currently not comfortable with offering this test prenatally.

NEED FOR aCGH PRACTICE GUIDELINES

The observed differences in current approaches to prenatal aCGH testing prompts consideration of the development of practice guidelines. In particular, diverse counselor opinions underline a need for practice guidelines to promote a collective, close examination of the benefits and drawbacks of prenatal aCGH testing that would help ensure the most advantageous patient care. However, counselors’ perspectives allude to the complicated task of thoroughly considering all the pros and cons of prenatal aCGH testing, in addition to reaching a consensus among guideline developers. For example, those who develop guidelines will have to weigh the benefits of potential information and reassurance and meeting a patient’s interest in testing, with the drawbacks of unclear or unexpected results. Of note, counselors showed support for guideline development by either genetic counselors or physicians. Overall, the diverse ways in which counselors appear to currently offer prenatal aCGH testing signals a need for practice guidelines to help ensure optimal patient care.

STUDY LIMITATIONS

Study limitations include the detail and scope of interview questions and the number of study participants. More interview questions aimed at the details of
counselors’ experiences may have illuminated more concerns and challenges related to counseling for aCGH testing. For example, asking counselor 1 about specific cases involving reciprocal duplications may have revealed counseling challenges that such findings pose in the prenatal setting. More detailed questions such as asking counselors why they think particular indications or platforms are appropriate or inappropriate may have further illustrated counselors’ views and areas in which testing could be improved. Also, questions regarding hypothetical prenatal situations may have helped detail counselors’ opinions and comfort levels regarding aCGH testing. Additional questions that prompted counselors’ ideas about aCGH practice guidelines could have revealed possible avenues for guideline development. Another study limitation is the small number of counselors interviewed, which limits our ability to discern whether study participants’ responses accurately represent the practices, experiences and concerns of the majority of pediatric and prenatal counselors. Possible reasons for low recruitment include that relatively few counselors have experience with prenatal aCGH testing. As well, perhaps counselors who are relatively more experienced or opinionated about aCGH testing tended to respond to our recruitment notice. Overall, we view this research as a pilot study that may help inform thinking about gathering data from a larger number of respondents.

CONCLUSION

Interviews with genetic counselors regarding prenatal aCGH testing indicate diverse perspectives and practices. Some counselors emphasized the potential genetic information and reassurance prenatal testing offers and supported prenatal aCGH testing.
Other counselors focused on limits of current clinical knowledge and the possibility for unclear results, and voiced lower support for prenatal aCGH testing. Counselors looked forward to growth in current clinical knowledge about aCGH findings and noted the years needed to collect and interpret a wide range of possible findings. Also, counselors showed a dedication to and awareness of patient interests and concerns, and voiced support for guideline development. Counselors also showed interest in making improvements to current counseling and research tools. Variations in current practices regarding prenatal aCGH testing highlight a need for practice guidelines. Of note for potential guideline developers, some counselors’ relatively low support for prenatal aCGH testing, in particular due to concerns about possible ambiguous results, suggests that a significant number of genetic counselors are not comfortable with currently offering prenatal aCGH testing. Future studies could survey a larger study population and examine possible approaches to guideline development and changes needed in order for more counselors to feel comfortable with offering prenatal aCGH testing.
REFERENCES


Genetic counseling perspectives on prenatal array CGH testing

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Salt Lake City, UT

IRB Submission Date: 4 December 2008
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Genetic counseling perspectives on prenatal array CGH testing

The purpose of this study is to explore genetic counselors’ experiences with and opinions regarding array-based comparative genomic hybridization (array CGH) testing, particularly in the prenatal setting. Array CGH is a relatively new test that can detect microscopic (detectable through the light microscope) chromosomal imbalances as well as submicroscopic genomic losses and gains, also called deletions and duplications. Currently, array CGH is the most thorough test that surveys the genome for deletions and duplications, and offers patients a workable cost and turnaround time. Also, the clinical use of array CGH is steadily growing. Previous research has outlined the benefits, limitations and counseling challenges of array CGH testing. However, detailed accounts of individual genetic counselors’ experiences with and thoughts on this topic have yet to be reported. Specifically, a qualitative study in which genetic counselors are interviewed and asked to detail their perspectives on array CGH testing has not yet been published. My goal is to produce the first such study, with a focus on testing in the prenatal setting. In particular, I hope to expose common challenges and concerns that may prompt further research. In addition, I hope this study will serve as a resource that the clinical genetics field can build on.

The Brandeis University Genetic Counseling Program

Sansan Lee is a graduate student in the Brandeis Genetic Counseling Master’s Program and is conducting this study as a requirement for fulfillment of her Master’s degree.

Until recently, high-resolution karyotyping and fluorescence in situ hybridization (FISH) studies were viewed as the gold standard for detecting chromosomal imbalances (Shaffer et al., 2007). However, array CGH is currently challenging the status of these strategies. Array CGH can simultaneously test multiple regions in the genome for deletions and duplications of DNA (Slavotinek, 2008). Array CGH is much more sensitive (i.e. can detect much smaller imbalances) than karyotyping and can examine multiple genomic regions in a much more cost-effective manner compared to FISH (Bejjani & Shaffer, 2006). Clinical uptake of array CGH is steadily increasing (Slavotinek, 2008).

Previous studies have reviewed the benefits and limitations of array CGH. A main benefit is that array CGH combines increased sensitivity, simultaneous testing of multiple genomic regions, cost-effectiveness and a relatively fast turnaround time (Shaffer et al., 2007). A primary limitation of array CGH testing is incomplete knowledge regarding the clinical significance of deletions and duplications that are not associated with a previously described genetic syndrome (Gouas et al., 2008).
Earlier research has outlined the risks and challenges array CGH testing poses to patients and healthcare providers. Reported risks to the patient include possible diagnosis of a condition unrelated to the original indication for testing, potentially before symptoms of the condition have developed (Darilek et al., 2008). Another risk, especially difficult in the prenatal setting, is the possibility of receiving a result of uncertain significance, which means the prognosis is unclear (Gouas et al., 2008). Reported challenges for healthcare providers include becoming adept at test result interpretation and familiar with the complex range of test platforms, test detection rates and symptoms of possible conditions (de Ravel et al., 2007).

Previous studies have proposed approaches to counseling for array CGH testing. For example, Darilek et al (2008) emphasized the importance of extensive pretest education, informed consent and parental testing to determine if a patient’s genomic imbalance is familial or new. Approaches to test result interpretation and the value of current databases of chromosomal imbalances have also been published (de Ravel et al., 2007). However, a qualitative study in which genetic counselors are interviewed and asked to detail their experiences with and opinions regarding array CGH testing has yet to be reported. Such a study could reveal previously unreported challenges that genetic counselors face and approaches to counseling for array CGH testing that genetic counselors use. I propose carrying out the first such study to provide clinical genetic counselors and other healthcare providers with an analysis of in-depth experiences in offering array CGH testing. This study may highlight challenges that the genetics field can focus on overcoming and ideas that the field can build on.

SUBJECT CHARACTERISTICS
The research subjects are genetic counselors who currently see prenatal and/or pediatric patients and currently offer array CGH testing to patients.

SUBJECT INCLUSION/EXCLUSION CRITERIA
Eligible participants are genetic counselors who:
1) Currently see prenatal and/or pediatric patients  
2) Currently offer array CGH testing to patients  
3) Have offered array CGH testing to patients for at least one year  
4) Have worked for 5 or more years as a genetic counselor in a clinical prenatal or clinical pediatric setting (i.e. setting where at least 50% of time at work is spent seeing prenatal or pediatric patients)

JUSTIFICATION FOR USE OF ANY SPECIAL/VULNERABLE SUBJECT POPULATIONS
This study does not specifically recruit any subjects belonging to a special or vulnerable population.

STUDY DESIGN
I plan to conduct semi-structured, qualitative telephone interviews with genetic counselors to examine their experiences with and thoughts on array CGH testing, particularly prenatal array CGH testing. I will recruit genetic counselors as participants. I
will interview each of 8-10 participants for approximately 30 minutes. I will audiotape the interviews, have the interviews transcribed, and I will perform qualitative analysis on the interviews using ATLAS software.

STUDY PROCEDURES

Recruitment
I plan to recruit genetic counselors by emailing a recruitment notice (Appendix A: Recruitment notice) to the National Society of Genetic Counselors (NSGC) listserv through my primary committee member and Brandeis University professor, Beth Rosen Sheidley. My contact information will be included in the notice and interested genetic counselors may contact me via email. If at least 8-10 eligible counselors have not been recruited within 2 weeks, the recruitment notice will be sent up to two more times.

Before enrolling participants in my study, I will determine her/his eligibility using a brief screening tool (Appendix B: Eligibility Screening Tool). I will administer the screening tool via telephone.

Following the recruitment period, if more than 10 genetic counselors satisfy eligibility criteria, I will randomly select 8-10 genetic counselors to participate in my study. If responses to screening questions show distinct groups of respondents, e.g. groups who work in prenatal or pediatric settings, or groups who oppose or support prenatal array CGH testing, than participants will be randomly selected from each group to promote studying a diverse pool of participants.

Eligible individuals who are not selected, as well as ineligible individuals, will be notified and thanked for their responses and time.

Data Collection
I plan to interview 8-10 genetic counselors for approximately 30 minutes each. I will audiotape each telephone interview as it takes place. I will conduct semi-structured interviews comprised largely of open-ended questions with a few closed-ended questions. I will base my questions on my interview guide (Appendix D: Interview Guide). A semi-structured approach will allow the interviewee to respond freely and without interruption. I will keep my responses and the order of questions flexible, allowing the interviewee and I to explore ideas and themes as they arise. I may also adapt questions to account for original thoughts expressed by the interviewee, although, the overall interview content will remain consistent.

Data Analysis
I will perform descriptive analysis using ATLAS software to identify themes revealed during the interviews. Interview analysis may reveal themes, such as prevalent views of and approaches to array CGH testing. Data analysis will hopefully highlight approaches and ideas that genetic counselors and other healthcare providers can build on, and prompt questions that future research can explore.
INFORMED CONSENT
Before proceeding with the interviews, I will obtain informed consent from participants. Once I have selected 8-10 eligible genetic counselors, I will mail them an informed consent form (ICF, Appendix C: Informed Consent Form) and schedule a telephone conversation to review the ICF together. Once I have received a signed ICF, I will proceed with scheduling and conducting the interview. In addition, upon receiving an ICF, I will sign on as Principal Investigator and mail a copy to the participant. I will not interview any participants without informed consent.

ADVERSE EVENTS
I do not anticipate any physical or psychological risks to participants.

COMPENSATION
I will compensate each participant with a $25 gift certificate for amazon.com.

PRIVACY/CONFIDENTIALITY
To protect study participants I will assign each a coded ID number. The only link between the participant’s name and ID number will be a password-protected spreadsheet. I will store participant names, contact information and demographic information only in this spreadsheet. Only I will know the password to the spreadsheet. During the interviews, I will address participants using their ID number rather than their name. Audiotapes, interview notes and study files will be labeled with the ID number rather than participant names or other identifiers. At the end of the study, I will delete the spreadsheet and study files and destroy the audiotapes and interview notes. In addition, I will delete contact information for and email responses from ineligible individuals and destroy any notes taken during screening interviews after completion of the study.

COSTS
There will be no costs to study participants. All telephone charges will be covered by the study.

REFERENCES


APPENDIX B: RECRUITMENT NOTICE

Do you have experience with array CGH testing?

I am a graduate student in the Genetic Counseling Program at Brandeis University. I am seeking volunteers to take part in a research project, the goal of which is to explore genetic counselors’ experiences with and opinions regarding prenatal array comparative genomic hybridization (CGH) testing.

- You are eligible if you:
  - Currently see prenatal and/or pediatric patients
  - Currently offer array CGH testing to patients
  - Have offered array CGH testing to patients for at least one year
  - Have worked for 5 or more years as a genetic counselor in clinical prenatal or clinical pediatric settings (i.e. settings where your primary role is seeing prenatal or pediatric patients)

- The study involves a telephone interview lasting approximately 30 minutes
- Participation will take a total of about 45 minutes of your time
- Participation is confidential and voluntary
- Each participant will receive a $25 gift certificate to Amazon.com

If you are interested, please contact me at: sansan@brandeis.edu. Thank you for your consideration!

Sincerely,
Sansan Lee
Brandeis University Genetic Counseling Student
APPENDIX C: ELIGIBILITY SCREENING TOOL

Date:
Interviewee name:
Interviewee contact information:

Eligibility screening tool questions:

1) Please describe your current position.
2) Do you currently offer array CGH testing to patients?
3) How long ago did you start offering array CGH testing to patients?
4) How many years have you worked as a genetic counselor in a clinical prenatal setting (i.e. setting where at least 50% of time is spent seeing prenatal patients)?
5) How many years have you worked as a genetic counselor in a clinical pediatric setting (i.e. setting where at least 50% of time is spent seeing pediatric patients)?
6) Overall, what is your opinion of prenatal array CGH testing?

Eligible participants are genetic counselors who:

5) Currently see prenatal and/or pediatric patients
6) Currently offer array CGH testing to patients
7) Have offered array CGH testing to patients for at least one year
8) Have worked for 5 or more years as a genetic counselor in a clinical prenatal or clinical pediatric setting (i.e. setting where see prenatal or pediatric patients at least 50% of time at work)

Following the recruitment period, if more than 10 genetic counselors satisfy eligibility criteria, I will randomly select 8-10 genetic counselors to participate in my study. If responses to screening questions show distinct groups of respondents, e.g. groups who work in prenatal or pediatric settings, or groups who oppose or support prenatal array CGH testing, then participants will be randomly selected from each group to promote studying a pool of participants with diverse expertise and opinions.
Eligible individuals who are not selected, as well as ineligible individuals, will be notified and thanked for their responses and time.
APPENDIX D: INFORMED CONSENT FORM

Informed consent to participate in research study

Brandeis University Genetic Counseling Program

Please take a moment to read the following consent agreement:

I understand that this is a research study exploring genetic counselors’ experiences and opinions regarding array-based comparative genomic hybridization (array CGH) testing in the prenatal setting. I am aware that my responses to the interview questions will be used to assess counselors’ approaches to and thoughts on array CGH testing, including counselors’ perceptions of patient beliefs and understanding. Analysis of my responses may be used to develop ideas for future research projects and clinical genetics practices.

I understand that I will be contacted for a telephone interview at a time that is convenient for me. The interview will last approximately 30 minutes and will be audiotaped. All records containing my identifying information, such as name, email address, telephone number, home address and work address, will be kept strictly confidential during the study and destroyed after completion of the study. I understand that if I am quoted or referred to in any written or oral reports of the study, I will be given a false name.

I understand that I will receive a $25 gift certificate to Amazon.com for participation in the research study as a gesture of appreciation for my time and expertise.

I understand that participation is voluntary, and I may refuse to participate or choose to stop participating at any time without consequence. If I have any questions regarding this research, I may contact Sansan Lee, the Principal Investigator, at 781-373-2042 or sansan@brandeis.edu.

If I have any questions regarding my rights as a study participant, I may contact Lorrie Clark, Administrator of the Brandeis Committee for Protection of Human Subjects, at mclark@brandeis.edu.

Please sign to indicate your willingness to participate in this study under these conditions.

______________________________________________    ________________________
Participant’s Signature                  Date

______________________________________________    ________________________
Investigator’s Signature                  Date
APPENDIX E: INTERVIEW GUIDE

Introduction
Thank you for participating in this interview. Your feedback will help inform the field about current genetic counseling perspectives on array CGH testing. We’ll start by talking about your career in genetic counseling. Then, I’ll ask you about your experiences with and opinions regarding array CGH testing.

Your participation is completely voluntary and anonymous. To protect your privacy I’ll address you using a study ID number in place of your name. I’d like to audiotape this interview, which will allow me to focus on our discussion rather than note taking. If there is a question that you would rather not answer, please tell me.

Opening questions
Let’s start by talking about your career in genetic counseling.
1) Can you share a brief overview of where have you worked?
2) How many years have you been in the clinical genetics field?
3) In what specialty areas have you worked? (setting, proportion of time spent seeing patients, years spent in specialty)
4) Where do you work now? (setting, proportion of time spent seeing patients, years in current position)

Experience with array CGH
5) Can you describe some of your initial cases that involved array CGH testing? (prenatal or pediatric setting, why was array CGH offered, what was the outcome)
6) Can you tell me about cases involving array CGH testing that have stuck with you? (prenatal or pediatric setting, why was array CGH offered, what was the outcome)

Probing questions (when talking about a specific case during questions 5 and 6)
a. Tell me about what was most rewarding/challenging to you about this case.

b. What are your thoughts on using array CGH testing in this situation? (benefits, limitations, concerns)

c. Tell me about things you did during the case to describe the benefits/limitations of array CGH. Do you feel the patient understood your discussion? How did you know?

d. Describe what the patient viewed as advantages/disadvantages of having array CGH testing?

e. Tell me about what was the most helpful/confusing/unhelpful part of array CGH testing to the patient. Did the patient tell you or did you infer this? If inferred, what gave you this impression?

f. Tell me about resources that helped you counsel about array CGH.

g. Tell me about resources that you feel would help you counsel about array CGH.

7) What are your thoughts on array CGH testing in the prenatal setting? (benefits, limitations, concerns, compared to opinions for pediatric setting)

8) What are your thoughts on counseling for the different possible test results? (de novo/familial variants of uncertain significance, pre-symptomatic diagnoses)

9) Tell me about your comfort (i.e. familiarity, knowledge) level regarding the various available array CGH platforms.

**Institutional policy**

10) Regarding your current position, do you know when your medical center first began offering array CGH?

11) Does your medical center have a policy regarding whom to offer array CGH to? Can you tell me more about it? Can have a copy?

12) (If pediatric setting) Does your institution offer prenatal array CGH testing? (Ask questions 13-15 time permitting)

13) Can you tell me about how your institutional policy addresses the cost of array CGH testing?
14) Can you tell me about how your institution decided which array CGH platform to use?
15) Can you tell me about how your institution decided which array CGH lab to use?

Consent process
16) Can you tell me about the consent process you use when offering array CGH? (is specific consent form required)
17) What do you include in the discussion? (test limitations including variants of uncertain significance, copy number variants, degree of genomic coverage, cost and options to cover cost)
18) How does this consent process compare to the consent processes for other genetic tests (e.g. karyotype, FISH, molecular and biochemical tests)?
(Ask question 19 time permitting)
19) What types of questions have patients asked?

Closing
Thank you so much for sharing your experiences in counseling about array CGH. Overall, I gather that (summary). Is there anything you would like to add?