NON-GENETIC SPECIALISTS' EXPERIENCES ORDERING CHROMOSOMAL MICROARRAYS

by

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ABSTRACT

Chromosomal microarray (CMA) is a first-tier clinical diagnostic test for individuals with developmental delay or intellectual disability, autism spectrum disorder, or multiple congenital anomalies. Due to the limited number of genetics professionals in the United States, non-genetic specialists often find themselves in situations where a CMA is indicated for their patient, but an evaluation by a clinical geneticist is not required. Many studies have identified barriers that non-genetic specialists experience when ordering genetic testing such as poor knowledge of genetics, cost of testing, uncertainty of genetic testing issues, and fear of discrimination. There are currently no studies investigating barriers that non-genetic specialists' encounter when ordering CMA. A survey was distributed to neurologists, developmental pediatricians, cardiologists, and endocrinologists at the Children's Hospital of Pittsburgh of UPMC. The results of this survey were analyzed using descriptive statistics. Results showed that 43.8% of participants were ordering CMAs less often than they believe would be beneficial for their patients. The majority of participants (93.8%) indicated that the most significant barrier to ordering CMA was lack of insurance coverage. Participants indicated that on average, 48.1% of insurance pre-authorization requests get approved, regardless of insurance policy. Approximately 50-70% of participants

indicated that they order CMA for the patient indications outlined in the 2010 American College of Medical Genetics consensus guidelines. Most respondents (88.9%) reported being comfortable ordering a CMA. Respondents indicated that they were comfortable providing pre-test counseling (83.3%) and routinely discuss some, but not all issues relevant to CMA. Although not every study participant reported working with a genetic counselor, almost all respondents agreed that genetic counselors would be valuable or very valuable throughout all aspects of ordering a CMA. The public health significance of this study is that CMA plays an important role in the diagnostic evaluation of a significant number of patients. Given the limited supply of genetic professionals, non-genetic specialists may increasingly be expected to order CMA, and may experience barriers that prevent the effective use of this test in relevant clinical situations. Therefore, it is important to understand potential barriers to allow for appropriate implementation of CMA.

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PREFACE

I would like to take this opportunity to thank the many individuals who have supported me throughout graduate school. To my family and friends, thank you for all of your love, help, and encouragement. I am grateful for the many Skype conversations and audio messages that were shared over the past two years, and for the care packages that always arrived at the perfect time. To Kim, Allison, Linda, Charlotte, and Priyana, thank you for taking the time to teach me about the genetic counseling profession, and for giving me the tools to succeed during my training. I look forward to working with you as a colleague!

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1.0 INTRODUCTION

Providing patients with a genetic diagnosis can be essential to developing the best management plan for their care. A genetic diagnosis can inform treatment options, patient prognosis, and disease recurrence risk within a family. A chromosomal microarray (CMA) is a genetic test that looks at gains and losses of DNA regions that are too small to be detected by traditional karyotype analysis, and can be a vital tool when making a genetic diagnosis. In 2010, the American College of Medical Genetics published a consensus statement indicating that CMA is a first-tier clinical diagnostic test for individuals with developmental delay or intellectual disability, autism spectrum disorder, or multiple congenital anomalies (Miller et al, 2010), thereby underscoring the clinical importance of this test for certain indications. There is currently a limited number of genetics professionals in the United States (American Board of Medical Genetics and Genomics, 2016; Mary Henderson at American Board of Genetic Counseling, personal communication, February 22, 2016); therefore, it can be expected that many non-genetic specialists will find themselves in situations where their patients will benefit from a CMA, but may not need an evaluation by a clinical geneticist. Numerous studies have identified poor knowledge of genetics, cost of testing, uncertainty of genetic testing issues, and fear of discrimination as barriers that non-geneticists experience when ordering genetic testing (Klitzman et al., 2013; Duncan et al., 2007; Salm et al., 2014; Watson et al., 1999; Nippert et al., 2011; Rosas-Blum et al., 2007; Reiff et al., 2013). This presents significant challenges when

there are many patients who could benefit from genetic testing, such as a CMA, and a limited number of genetics professionals to facilitate this testing. Additionally, some insurance companies are now requiring that pre- and post-test genetic counseling be provided to patients when a CMA is ordered (Cigna Medical Coverage Policy, effective 7/15/2016). The aim of this study was to evaluate the current experiences that non-genetic specialists have in a tertiary care academic hospital setting when ordering CMAs, in order to help identify barriers that need to be addressed to improve patient access to this valuable test.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 OVERVIEW

2.1.1 Chromosomal Microarray

A chromosomal microarray (CMA) is a genetic test that is used to identify submicroscopic chromosome rearrangements across the entire genome that cannot be detected using traditional karyotype analysis (Battaglia et al., 2013; Miller et al., 2010). Current CMA technology relies on oligonucleotide platforms and can detect deletions and duplications in DNA regions that are less than 1 Megabase pair (Mb) in size. Therefore, this test can have a resolution up to 1000 times higher than conventional karyotype analysis (Trakadis and Shevell, 2011; Coulter et al., 2011). CMAs are widely used across a variety of clinical settings including prenatal and pediatric specialty clinics to investigate whether or not there is a genetic etiology that explains a particular medical condition. A genetic diagnosis can be essential to best manage patient care by informing treatment options, patient prognosis, and disease recurrence risk within a family.

2.1.2 Consensus Guidelines for the Use of Chromosome Microarray

In 2010, the American College of Medical Genetics (ACMG) published a consensus statement indicating that CMA is a first-tier clinical diagnostic test for individuals with non-syndromic developmental delay or intellectual disability (DD/ID), autism spectrum disorders (ASDs), or multiple congenital anomalies (MCA) not associated with a well-delineated genetic syndrome (Manning and Hudgins, 2010). Consensus guidelines were also released upon the culmination of two international workshops from the International Standard Cytogenomic Array (ISCA) Consortium (Miller et al., 2010). This consensus statement and the consensus guidelines underscore the clinical importance of CMA for these disorders, which are relatively common in the population. DD is clinically characterized as significant impairment in cognitive and adaptive functioning diagnosed before the age of 18 years, and ID is defined as an impairment with adaptive functioning which can range from borderline (an IQ of 75-85) to profound (IQ <20-25) (Battaglia et al., 2013; Miller et al., 2010). The incidence of DD/ID is approximately 3% in the population (Battaglia et al., 2013; Miller et al., 2010). ASDs encompass a group of disorders that are characterized by impairments in social and cognitive functioning, and can co-occur with intellectual disability and/or other co-morbid features, such as epilepsy (Battaglia et al., 2013; Stobbe et al., 2014). Approximately 1 in 88 children have been diagnosed with some form of ASD, and the diagnosis rate has continued to increase over recent years (Stobbe et al., 2014). Understanding the etiology of these conditions is often elusive, and a clinical diagnosis is typically based on patient symptoms alone.

2.1.3 Benefits of CMA

Various studies have examined the clinical detection rate of CMA for DD/ID, ASDs, and/or MCA, which ranges from 5-35% (Battaglia et al., 2013; Stobbe et al., 2014; Roberts et al., 2014; Lay-Son et al., 2015; Coulter et al., 2011, Shin et al., 2015). Importantly, studies have shown that CMA results, both known pathogenic variants and variants of possible clinical significance, can influence medical management for patients (Coulter et al., 2011; Riggs et al., 2014; Gannon et al., 2011). Variants of possible significance (VPS) have been defined as variants that include deletions or duplications that overlap with reported pathogenic deletions/duplications, deletions or duplications containing genes that are suspected in disease pathogenesis, or changes that involve a gene for which loss of one copy through deletion would imply that the person is a carrier for a recessive trait (Coulter et al., 2011). VPS are commonly referred to as a variants of unknown significance (VUS) in many clinical settings. Retrospective analyses that investigated CMAs ordered for all clinical indications revealed that for patients with abnormal pathogenic variants, results impacted clinical management over 50% of the time (Coulter et al., 2011). Changes in patient management also occurred over 30% of the time for individuals who were found to have a VPS (Coulter et al., 2011). Clinical action that was undertaken in these cases included specialist referral, imaging studies, additional diagnostic testing, and medication prescription (Coulter et al., 2011).

Additionally, studies have hypothesized that ordering CMAs as a first-line genetic test can result in significant cost savings by avoiding additional testing required to make a genetic diagnosis (Coulter et al., 2011; Regier et al., 2010). Coulter et al. (2011) reported that over 88% of patients who had a CMA that identified a positive result (pathogenic variant or VPS) previously had other genetic, metabolic, and/or neurologic testing. Tests included karyotype,

Fragile X, Prader-Willi methylation studies, plasma amino acids, urine organic acids, various single gene tests, and a variety of other biochemical tests. These tests identified a patient diagnosis in approximately 13% of cases, suggesting that ordering a CMA initially would be a cost-effective approach to finding a diagnosis for these patients (Coulter et al., 2011). Another study used decision analytic modeling to evaluate the cost-effectiveness of ordering CMAs as a first-line test for patients with intellectual disability (Regier et al., 2010). This analysis showed that based on cost and clinical detection rate, CMAs provide better value for the cost of testing compared to conventional karyotype analysis (Regier et al., 2010). Value was determined based on the trade-off between cost and clinical effectiveness, and cost of testing used in the modeling was determined by the fee schedule from the British Columbia Ministry of Health Services. In this scenario, CMAs cost $217 more than conventional karyotype analysis, however, CMAs yielded 8.2 diagnoses more per 100 patients tested. If decision makers were willing to pay $4,550 for an additional diagnosis, ordering a CMA as a first line test to diagnose individuals with ID would be more cost effective than ordering a conventional karyotype followed by additional testing required to make a diagnosis. (Regier et al., 2010).

2.2 PHYSICIANS EXPERIENCES ORDERING GENETIC TESTING

2.2.1 Limited Number of Clinical Genetics Professionals

A 2003 survey of the American Board of Medical Genetics certified geneticists was conducted to evaluate the state of the medical geneticist workforce (Cooksey et al., 2005). At the

time, there were approximately 3.5 MD clinical geneticists per one million people in the United States, and new entrants into the medical genetics profession were declining (Cooksey et al., 2005). Today, there are approximately 1,594 MD clinical geneticists who are certified by the American Board of Medical Genetics and Genomics, and 3,623 genetic counselors who are certified by the American Board of Genetic Counseling. This totals approximately 5.0 MD clinical geneticists, and 11.3 genetic counselors per one million people in the United States (American Board of Medical Genetics and Genomics, 2016; Mary Henderson at American Board of Genetic Counseling, personal communication, February 22, 2016). To contrast this with another specialty, there are as many as 110 neurologists per one million people in urban areas in the United States (Avitzur, 2010). The limited number of clinical genetics professionals in the United States presents a problem as the knowledge and clinical applications in the field of genetics continues to expand.

Many health-care providers who do not have specialized training in genetics may find themselves in situations where their patients could benefit from genetic testing, and might not need an evaluation by a clinical geneticist. Due to the complexity of interpreting genetic testing results, as well as the evolving landscape of genetic testing technologies, non-genetic specialists have not routinely ordered genetic testing. However, the benefits of genetic testing for certain patient indications challenges the idea that clinical geneticists should be the only physicians who order this testing, particularly due to the limited size of the genetics professional workforce. In particular, physicians in specialties such as neurology, cardiology, and endocrinology often consider genetic testing in the evaluation of their patients.

2.2.2 Non-Genetic Specialists' Experiences Ordering Genetic Testing

Despite increasing accessibility of genetic testing, studies suggest that primary care clinicians and other types of health-care providers generally lack sufficient training and/or knowledge in genetics to explain the complexities of genetic testing and technology to patients (Collier, 2012). For example, a survey administered by Powell and colleagues revealed that only 15% of physician participants felt prepared to answer questions related to direct-to-consumer genetic testing (Powell et al., 2012; Collier, 2012). Studies have identified poor knowledge of genetics, cost of testing, lack of time to provide genetic counseling, low comfort level with genetic counseling, and fear of discrimination, as barriers that non-geneticists experience when ordering genetic testing (Klitzman et al., 2013; Duncan et al., 2007; Salm et al., 2014; Watson et al., 1999; Nippert et al., 2011; Rosas-Blum et al., 2007; Reiff et al., 2013).

In 2013, Klitzman et al. surveyed 220 internists from two academic medical centers regarding their utilization of genetic testing. Approximately 74% of individuals rated their knowledge of genetics as very/somewhat poor, and 87% of individuals rated their knowledge of genetic testing guidelines as very/somewhat poor. Approximately 80% of study participants indicated that more training should be required for physicians in a variety of areas including when to order genetic testing, how to counsel patients, and genetic test result interpretation (Klitzman et al., 2013). Interestingly, the study showed that physicians were more likely to order genetic testing if they had a geneticist or genetic counselor to whom to refer patients. Physicians' perceived needs for training was not significantly associated with ordering a genetic test. This suggests that physicians with varying levels of knowledge about genetic testing are currently ordering genetic testing for their patients.

A survey of pediatric otolaryngologists investigated how often these non-genetic specialists' order genetic testing for their patients with sensorineural hearing loss, and how comfortable they are providing genetic counseling and disclosing patient results (Duncan et al., 2007). 71% of study participants reported explaining the limitations and benefits of genetic testing to families, while 24% of individuals preferred to refer patients with sensorineural hearing loss directly to genetics professionals. With regards to results disclosures, 59% of pediatric otolaryngologists reported disclosing positive genetic test results, whereas 66% reported disclosing negative genetic test results. Nearly a third of participants stated that they schedule extra time to disclose both positive and negative results, whereas 15% of participants indicated that they only schedule extra time to disclose positive test results. For disclosing a positive result, 28% of physicians said that they refer patients to genetics professionals whereas 18% of physicians refer patients to a genetics clinic for disclosing both positive and negative results. For those individuals who did not order genetic testing themselves, 74% said they preferred to have a genetics expert order and explain the testing. Other reasons for not ordering genetic testing included insufficient time to obtain consent, and limited knowledge regarding testing that did not allow physicians to properly obtain informed consent or explain the results to families.

A study that surveyed neurologists and psychiatrists to ascertain their knowledge, attitudes, and behaviors involving genetic testing for neurodevelopmental and neurodegenerative disorders revealed that only 33% of respondents felt confident about how to order genetic testing and where to send genetic tests (Salm et al., 2014). Of the individuals who had previously ordered genetic testing, 74% reported that they could use more training in how to interpret test results. The majority of respondents (68% of those who had ordered tests and 55% of those who

had not) indicated that genetic testing should be performed more often in their specialty. This suggests that barriers exist that affect how often non-genetic specialists order genetic testing for their patients. Evidently, confidence in how to order and where to send tests significantly impacted ordering behaviors. Providers also indicated that they had concerns about genetic testing potentially causing psychological harm for their patients, and that lack of privacy of genetic data could possibly lead to patient discrimination.

These studies propose that non-genetic specialists recognize the benefits of certain genetic tests, but can have insufficient knowledge about genetic testing and interpretation of test results, which can make pre-test counseling and consenting a patient within their specialty difficult. Additionally, many physicians lack the time required to thoroughly review information about genetic testing with patients, and address their possible questions. These issues present significant challenges when there are many patients who could benefit from genetic testing, such as a CMA, and a limited number of trained genetics professionals to facilitate this testing.

2.2.3 Additional Barriers When Ordering CMA

Although ACMG published the 2010 consensus statement that recommended CMA as a first-tier clinical diagnostic test for individuals with non-syndromic DD/ID, ASDs, or MCA, physicians have encountered difficulties when trying to obtain insurance pre-authorization for this test (Hughes, 2010; Riggs et al., 2014). In 2011, Riggs et al. surveyed members of the National Society of Genetic Counselors (NSGC) and the ACMG regarding their experiences ordering CMAs for their patients (Riggs et al., 2014). Only 18% of these genetics professionals reported ordering CMA testing every time it was indicated. The most common reason for not ordering this test for certain patients was lack of insurance coverage. Over 70% of study

participants indicated that they had received denial from insurance companies when ordering this test. The main reason was that insurance companies considered this test to be "experimental." An additional reason included that testing was considered to not be medically necessary due to a lack of impact on the patient's clinical management.

If a substantial number of genetics professionals are receiving denials from insurance companies for CMA, it is important to consider how the insurance pre-authorization process affects non-genetic specialists when they want to order CMAs for their patients. Typically, this process involves writing a letter of medical necessity to the insurance company describing why a CMA is medically necessary for a patient, followed by possible appeal letters if the letter of medical necessity is declined. It is unclear for which indications CMA was being ordered in the Riggs et al. (2014) study, however, the participants (genetics professionals) commented that CMAs were indicated for these patients. Moreover, some insurance companies are now requiring that pre-test and post-test genetic counseling be provided to patients when a CMA is being ordered (Cigna Medical Coverage Policy, effective 7/15/2016). This requirement is particularly relevant for non-genetic specialists who may feel less comfortable or lack sufficient time to provide genetic counseling to their patients.

The purpose of this study was to better understand the current experiences of non-genetic specialists who order CMA in a tertiary hospital setting. Previous studies have revealed many barriers that non-genetic specialists can encounter when ordering genetic testing; therefore, it is important to understand barriers that might exist for physicians in this context. Study results will allow for appropriate interventions to address potential barriers in order to improve access to CMA for those patients who would truly benefit from this genetic test.

3.0 MATERIALS AND METHODS

3.1 SPECIFIC AIMS

Aim 1: Assess non-genetic specialists' perceived knowledge of CMAs to determine if lack of information can affect when CMAs are ordered for patients.

Aim 2: Explore non-genetic specialists' comfort level providing genetic counseling to patients, and how this affects the CMA result disclosure process.

Aim 3: Ascertain non-genetic specialists' experiences with insurance pre-authorization when ordering CMAs.

Aim 4: Evaluate genetic counselor involvement with non-genetic specialists when ordering CMAs, in terms of education, results disclosure, and the insurance pre-authorization process.

3.2 SURVEY DESIGN

The study and survey were approved as an expedited study by the Institutional Review Board of the University of Pittsburgh (PRO#15090294) (see **Appendix B** for the IRB approval form). The survey design was based upon a questionnaire used in a previous study that evaluated internists' experiences ordering genetic testing (Klitzman et al., 2013). Dr. Klitzman and his research team gave this study permission to use their survey for the purposes of survey design. The survey was built using Qualtrics survey software. Questions assessed physicians' comfort level ordering different types of genetic testing and providing genetic counseling when ordering CMA. Questions examined the process with which different types of CMA results are disclosed, when CMAs are ordered, how often CMAs are ordered, and factors that may limit how often CMAs are ordered. The survey also assessed how genetic counselors have been involved in cases when a CMA has been ordered by a non-genetic specialist, and asked questions regarding the insurance pre-authorization process for CMAs. The survey also included questions regarding demographic information. Survey responses were initially linked to each participant's email to allow for possible follow-up studies, however, responses were assigned a code to anonymize the data prior to analysis. The questionnaire was reviewed by several non-genetic specialists at the Children's Hospital of Pittsburgh of UPMC who provided feedback regarding survey content, including readability and relevance of each question. A copy of the survey can be found in **Appendix A**.

3.3 SURVEY DISTRIBUTION

The link to the Qualtrics survey was emailed to all neurologists, developmental pediatricians, cardiologists, and endocrinologists at the Children's Hospital of Pittsburgh of UPMC using emails from the UPMC email directory. Physicians were surveyed from these specialties as they were most likely to have ordered CMA regularly for their patients. Therefore, the survey was sent to 67 non-genetic physicians in the specialties listed above. A recruitment letter was provided in the body of the email (**Appendix A**), and the survey was emailed a total of five times from December 2015 until February 2016. Department chairs were asked to remind physicians about the survey at their department meeting in February 2016. Survey data was collected and stored using Qualtrics. Survey data was initially linked to email identifiers, which were removed and stored in a separate document linking responses to email addresses, prior to data analysis. De-identified data was downloaded from Qualtrics and stored on a secure server at the Children's Hospital of Pittsburgh with password protection. The document containing email identifiers was also stored on this secure server with password protection, and accessible to only PI and research staff.

3.4 ANALYSIS OF RESULTS

Descriptive analysis was performed for all survey questions. Of the 67 non-genetic specialists who received an email about the study, 67 (100%) of them opened the email. 21 of these individuals (31.3%) clicked on the survey link, and of those physicians who opened the survey, 16 (76.2%) responded to every question in the survey. Three of the individuals who

clicked on the survey link (14.3%) did not continue the survey after reading the consent information. Two additional individuals answered some of the survey questions, but did not complete the entire survey. One of these participants indicated that they do not order CMAs for their patients.

Non-responders were not included in the analysis of each question. Therefore, analyses for the majority of questions were based on responses from the 16 participants who completed the entire survey. Some questions were analyzed based on responses from 17 or 18 individuals, which is indicated in the tables and figures for each question.

4.0 RESULTS

4.1 DEMOGRAPHICS

Of the 67 non-genetics specialists employed at Children's Hospital of Pittsburgh of UPMC who were sent the survey, 16 (23.9%) completed the questionnaire. Of the 16 respondents, 37.5% were neurologists (n=6), 18.8% were developmental pediatricians (n=3), 12.5% were cardiologists (n=2), and 31.3% were endocrinologists (n=5). The majority of participants were female (75%), between the ages of 40-59 years (68.7%), and had completed their medical training prior to the year 2000 (68.7%). The survey response rate varied by specialty: 30% for neurology (6/20), 60% for developmental pediatrics (3/5), 6.7% for cardiology (2/30), and 41.7% for endocrinology (5/12). The average time to complete the survey (n=16) was 9 minutes and 12 seconds (range = 4 minutes and 49 seconds – 16 minutes and 38 seconds). **Table 1** shown below describes the demographic information of the 16 participants in the study who completed the entire survey.

Table 1. Demographic summary of participants.

	Total (n=16)	
	n	%
Provider Specialty		
Neurology	6	37.5
Developmental Pediatrics	3	18.8
Cardiology	2	12.5
Endocrinology	5	31.3
Genetics Training		
Conference and Lecture	8	50
Lecture only	4	25
Certificate	0	0
N/A	4	25
Sex		
Male	4	25
Female	12	75
Age		
20-29	0	0
30-39	2	12.5
40-49	6	37.5
50-59	5	31.2
60+	3	18.8
Completed Medical Training Decade		
1960-1969	0	0
1970-1979	1	6.3
1980-1989	5	31.2
1990-1999	5	31.2
2000-2009	4	25
2010-2019	1	6.3
Still in training	0	0

Almost half of the study participants (43.75%) indicated that they order CMAs less often than they believe would be beneficial for their patients. This statistic was calculated by comparing survey responses for how often providers have a patient that they think would benefit from a CMA each month, and how often each provider orders CMAs each month. Nine providers indicated that they order CMAs as often as they think would be beneficial for patients, and seven providers indicated that they order CMAs less often than they think would be beneficial for patients. None of the respondents indicated that they order CMAs more often than they think would be beneficial for patients. **Figure 1** illustrates how many times study participants typically order CMAs each month, by provider type.

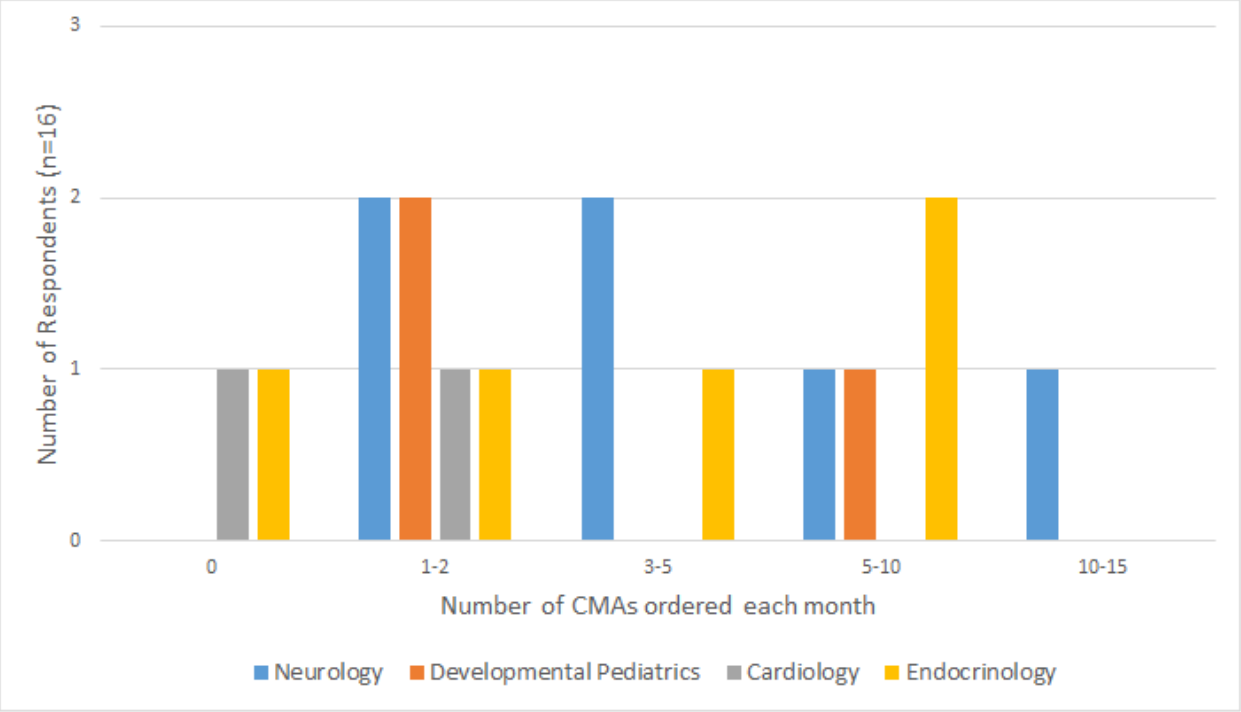

Figure 1. Number of CMAs ordered each month by participant and provider specialty (n=16).

4.2 BARRIERS TO ORDERING CMA

Respondents were queried about potential barriers that prevent them from ordering CMAs for their patients. Survey responses that indicated “strongly agree” or “agree” were combined to represent those respondents who agreed with each question. Survey responses that indicated “strongly disagree” or “disagree” were combined to represent those respondents who disagreed with each quesiton. Most respondents (93.8%) agreed that a lack of insurance coverage for genetic testing limited the number of CMAs ordered by non-genetic specialists. Participants also agreed that the patient’s concerns about costs (75%) and the provider’s concerns about costs (66.7%) prevented non-genetic specialists from ordering CMAs for their patients.

In terms of knowledge regarding CMA, 50% of respondents disagreed that insufficient knowledge/experience about genetic testing limited the number of CMAs they ordered, and 62.5% of individuals disagreed that a lack of knowledge regarding how to order and where to send CMAs limited the number of CMAs they order in their practice. These results are shown in **Table 2**. Non-reponses from participants were not included in the analysis of each question, and the number of responses for each question is listed in the table.

Table 2. Factors limiting the number of CMAs ordered by non-genetic specialists.

	Number of Respondents	Agree	Neutral	Disagree
Patient's concerns about insurance discrimination	16	6 (37.5%)	3 (18.8%)	7 (43.8%)
My concerns about insurance discrimination	15	7 (46.7%)	4 (26.7%)	4 (26.7%)
Patient's concerns about costs	16	12 (75%)	1 (6.3%)	3 (18.7%)
My concerns about costs	15	10 (66.7%)	1 (6.7%)	4 (2.7%)
Lack of insurance coverage of genetic testing	16	15 (93.8%)	0 (0.0%)	1 (6.3%)
My insufficient knowledge/experience about genetic testing	16	4 (25%)	4 (25%)	8 (50%)
My lack of knowledge of how to order/where to send tests	16	3 (18.8%)	3 (18.8%)	10 (62.5%)
Lack of detailed family history available	16	1 (6.3%)	6 (37.5%)	9 (56.3%)
Language barrier	16	2 (12.5%)	3 (18.8%)	11 (68.8%)
Patient's level of education	16	2 (12.5%)	3 (18.8%)	11 (68.8%)
Lack of clinical guidelines	16	3 (18.8%)	3 (18.8%)	10 (62.5%)
My lack of access to geneticists/genetic counselors	16	3 (18.8%)	3 (18.8%)	10 (62.5%)
Other (please indicate)	0			

4.2.1 Knowledge

Most respondents (88.9%) specified that they were somewhat or very comfortable ordering CMA, and 81.3% of participants agreed that they were confident about the process for ordering a CMA. One study participant commented "I would appreciate having a resource person come lecture to new hires, residents, fellows, staff". **Figure 2** describes how comfortable respondents are ordering different types of genetic testing. Those participants who indicated that

they did not order next generation sequencing panels or whole-exome sequencing were not included in the analysis.

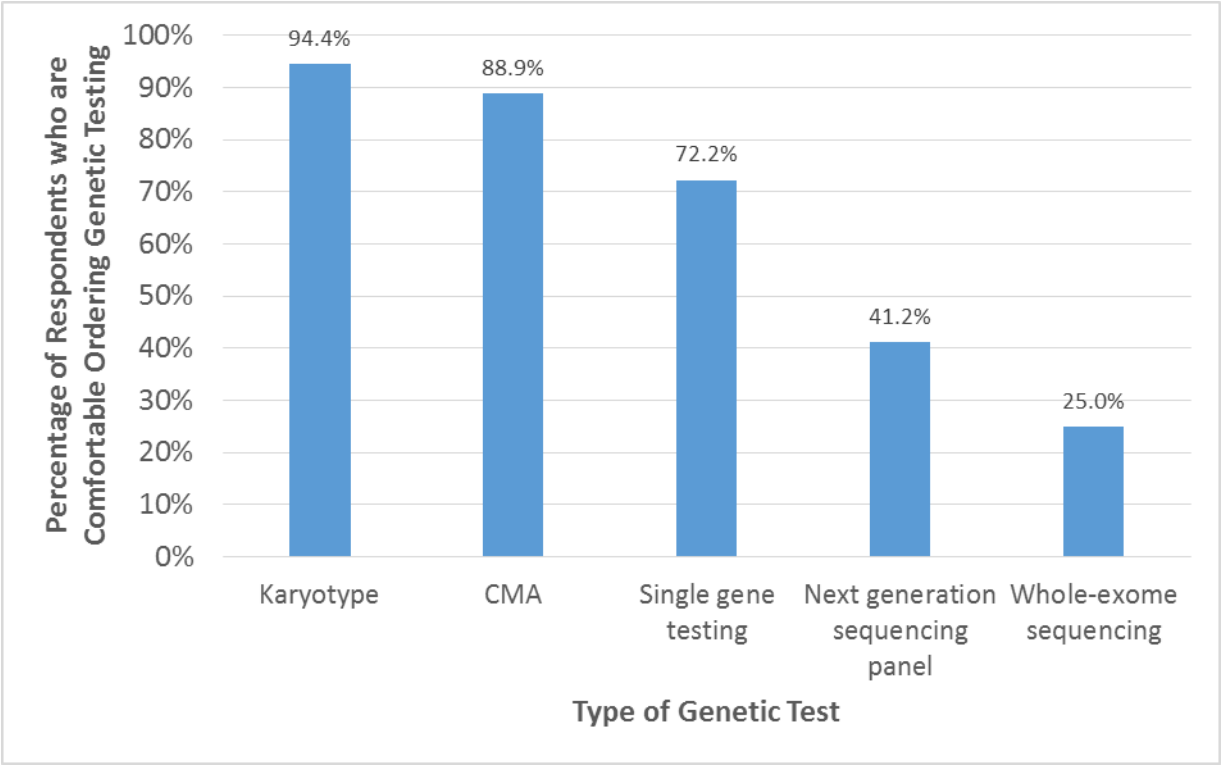

Figure 2. The percentage of respondents who feel somewhat or very comfortable ordering different types of genetic testing: karytoype (n=18), CMA (n=18), single gene testing (n=18), next generation sequencing panel (n=17), whole-exome sequencing (n=16).

The most common patient indications for which participants ordered CMA were global developmental delay (68.8%), developmental delay and multiple congenital anomalies (68.8%), multiple congenital anomalies only (62.5%), developmental delay and seizures and multiple congenital anomalies (56.3%), Autism spectrum disorder (50%), developmental delay and seizures (50%), and seizures and multiple congenital anomalies (50%). **Figure 3** demonstrates

the different patient indications for which repondents order a CMA. Due to issues with the Qualtrics software, participants were unable to specify a response for "other".

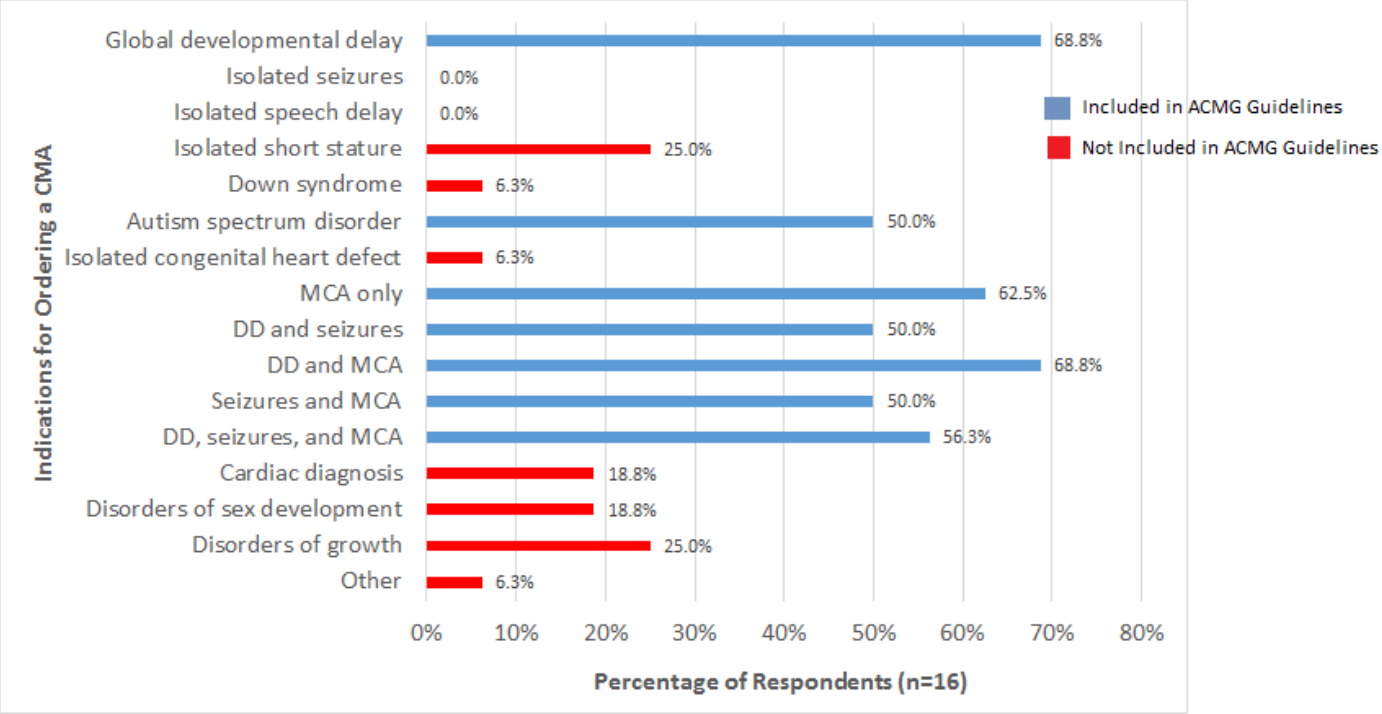

Figure 3. The percentage of respondents who order CMA for different patient indications (n=16).

4.2.2 Collaboration with Genetics Professionals

Most respondents (n=16) indicated that they referred patients for a genetics consult either once per month (43.8%) or once per week (43.8%). Respondents had fewer informal conversations with genetics professionals about their patients, typically once per month (60%), with some participants specifying that they do not have informal patient conversations with a genetics professional (13.3%).

When comparing survey responses regarding how often non-genetic specialists referred a patient to genetics vs. the number of CMA ordered each month, it appears that study participants referred their patients to genetics more frequently when they ordered CMA more often. Due to

the low response rate in this study, there is limited statistical power to analyze this relationship, and investigate whether different types of non-genetic specialists refer their patients to a genetics professional more often. **Table 3** summarizes how often respondents referred their patients to a genetics professionals and how often they ordered CMAs each month.

Table 3. The number of genetics referrals made by non-genetic specialists compared with the number of CMA ordered each month (n=16).

Number of CMA ordered each month	**Number of Genetics Referrals**		
	>1 per week	**1 per week**	**1 per month**
0	0 (0.0%)	1 (6.3%)	1 (6.3%)
1-2	1 (6.3%)	2 (12.5%)	2 (12.5%)
3-5	0 (0.0%)	4 (25.0%)	2 (12.5%)
5-10	1 (6.3%)	0 (0.0%)	1 (6.3%)
10-15	0 (0.0%)	0 (0.0%)	1 (6.3%)

4.2.3 CMA Result Disclosure

The majority of respondents (81.3%) indicated that they have disclosed a CMA result in the last 6 months (n=16). Out of all the study participants (n=17), most expressed that normal results are disclosed over the phone, either by the physician themselves (70.6%) or a physician extender (65%). An abnormal CMA result is most often disclosed by the physician themselves, either in person (76.5%) or over the phone (52.9%). An uncertain CMA result is also most often disclosed by the physician themselves, either in person (70.6%) or over the phone (65%). With regards to referring a patient to review their CMA result with a genetics professional, this

happens most often with an uncertain CMA result (58.8%) or an abnormal CMA result (52.9%). Participants also refer their patients with a normal CMA result to genetics (35.3%). In some instances, respondents indicated that they send a CMA result letter to their patient and/or primary care provider in addition to providing a genetics referral or disclosing the result over the phone. **Table 4** summarizes the different ways that respondents disclose CMA results.

Table 4. Disclosure method for different types of CMA results (n=17)

Type of Result	Result Disclosure Method					
	In Person		Over the Phone		Referral to Genetics	Other: Letter[1]
	Physician	Physician extender[2]	Physician	Physician extender[2]		
Normal	8 (47.1%)	4 (23.5%)	12 (70.6%)	11 (65%)	6 (35.3%)	2 (11.8%)
Abnormal	13 (76.5%)	2 (11.8%)	9 (52.9%)	1 (5.9%)	9 (52.9%)	1 (5.9%)
Uncertain	12 (70.6%)	1 (5.9%)	11 (65%)	3 (17.6%)	10 (58.8%)	1 (5.9%)

[1]To the patient and/or primary care provider
[2]Nurse, medical assistant

4.2.4 Genetic Counseling

The majority of study participants expressed being either somewhat or very comfortable providing pre-test counseling (83.3%) or post-test counseling for a normal CMA result (88.9%). Fewer respondents expressed either being somewhat or very comfortable providing post-test counseling for an abnormal CMA result (55.6%) or a variant of uncertain significance (61.1%). **Figure 4** demonstrates how comfortable respondents are providing different types of genetic counseling for CMA.

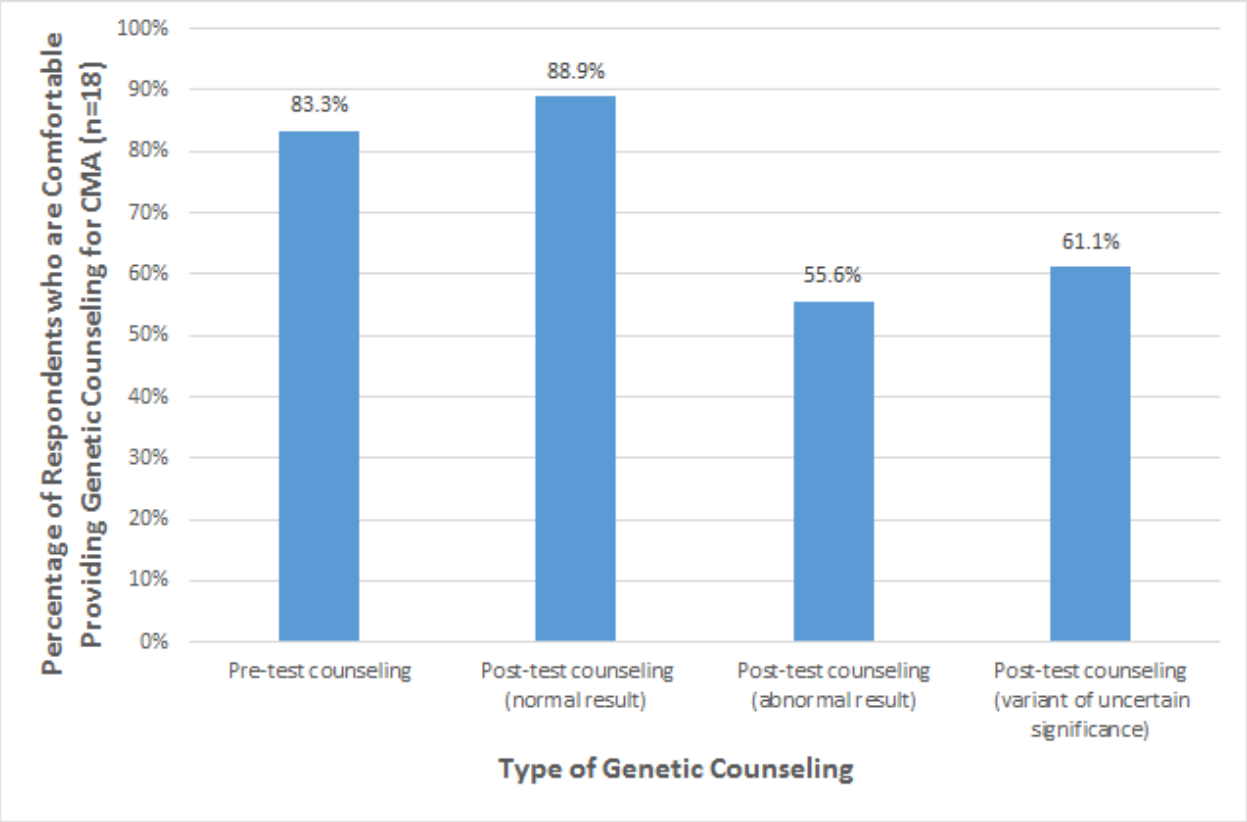

Figure 4. Percentage of respondents who are comfortable providing different types of genetic counseling when ordering a CMA (n=18).

Issues discussed most often during pre-test counseling (n=16) include different result outcomes (positive, normal, or uncertain result) (93.8%), test turn-around time (93.8%), and limitations of testing (87.5%). The issues that were discussed least often with patients included the possibility of disclosing family relationships such as non-paternity (6.3%), and test sensitivity (12.5%). **Figure 5** describes how often study participants discuss different issues related to CMA testing with their patients when providing pre-test counseling for CMA. Due to issues with the Qualtrics software, participants were unable to specify a response for "other".

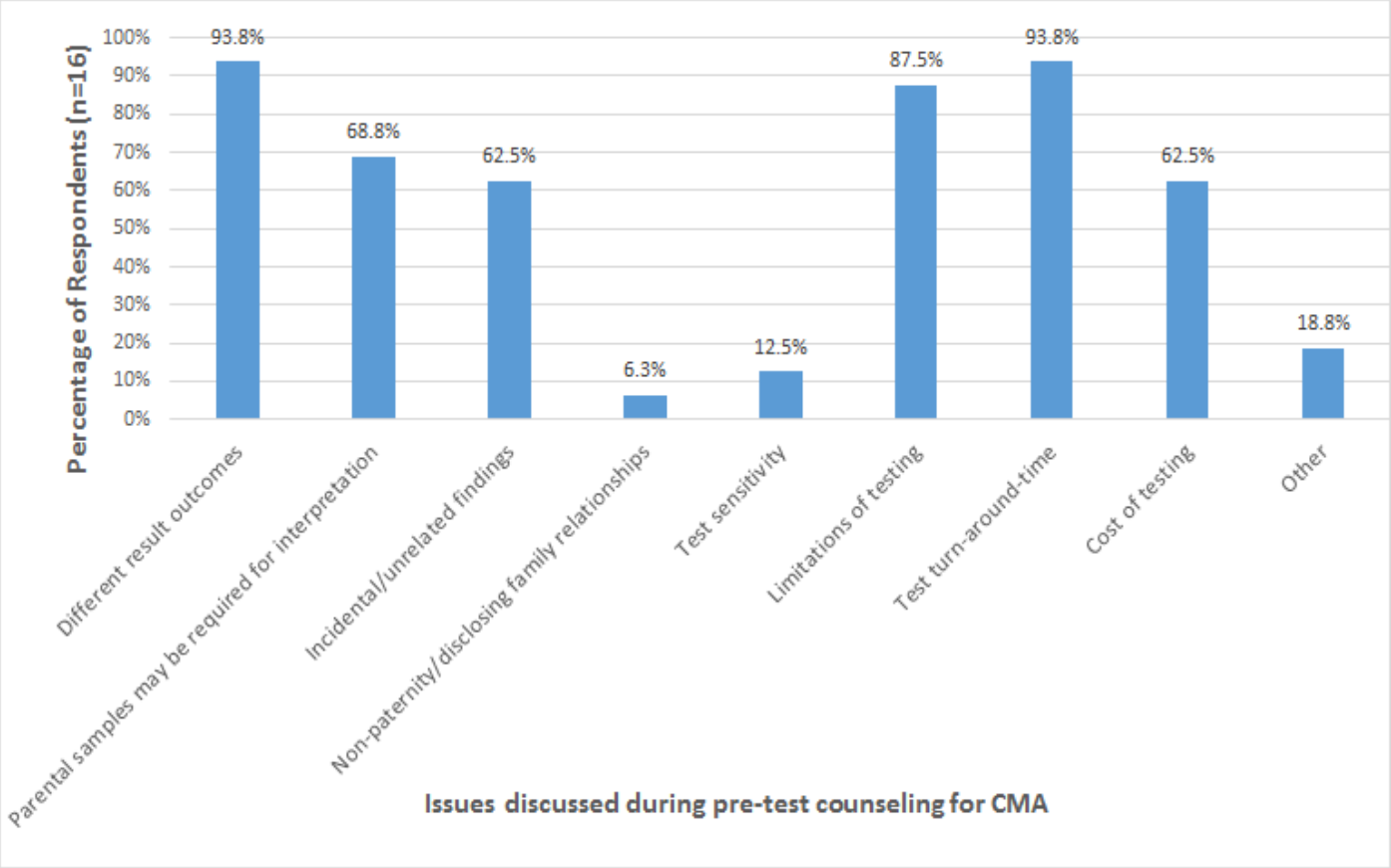

Figure 5. The percentage of respondents who discuss various issues during pre-test counseling for CMA (n=16).

Study participants indicated that genetic counselors are most often involved in patient care when providing post-test counseling for CMA (75.0%). Genetic counselors are also often involved in the insurance pre-authorization process (37.5%) and CMA result disclosure (37.5%). 18.8% of respondents stated that genetic counselors are not involved in patient care when a CMA is ordered (n=16). **Figure 6** describes how a genetic counselor has been involved in the care of patients seen by non-genetic specialists when a CMA has been ordered.

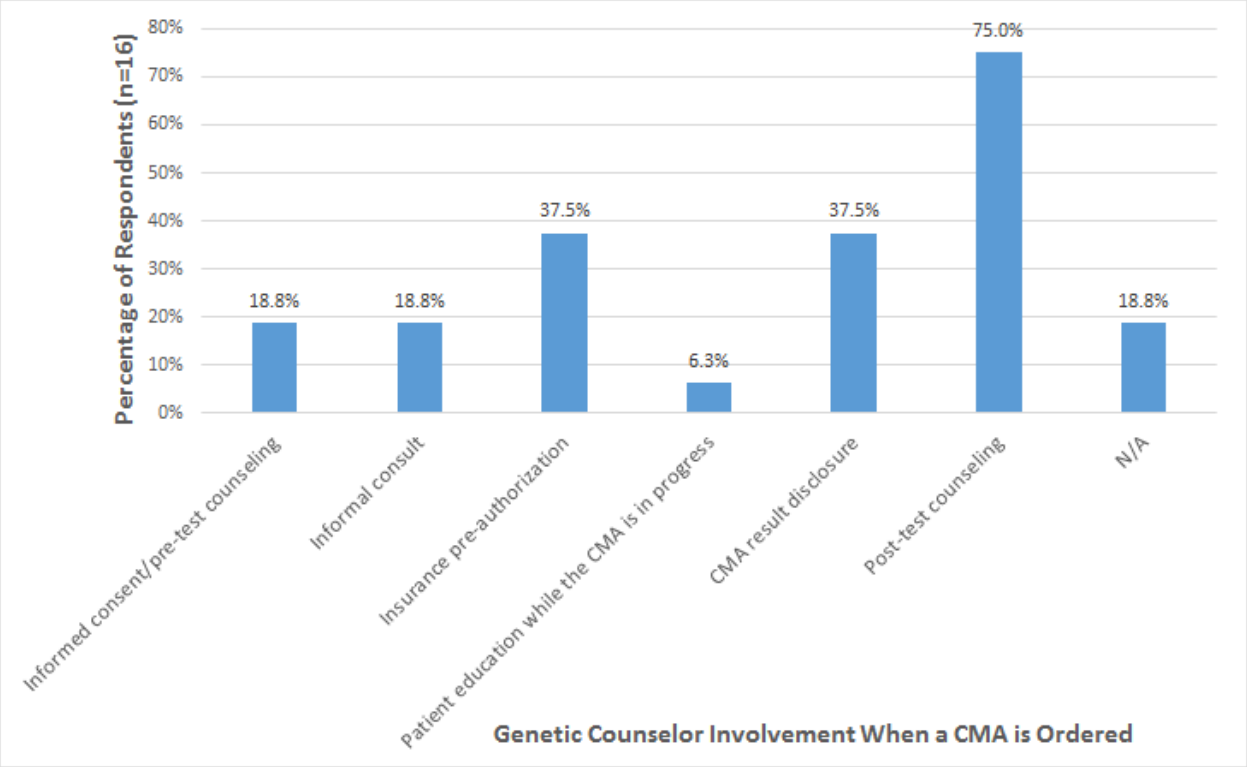

Figure 6. Genetic counselor involvement with non-genetic specialists when a CMA is ordered (n=16).

All respondents agreed that genetic counselors would be valuable or very valuable when reviewing genetic testing options based on patient indication(s), pre-test counseling for CMA, and post-test counseling for CMA. The large majority of participants (93.8%) stated that genetic counselors would be valuable or very valuable in regards to the insurance pre-authorization process for CMA, and with CMA result interpretation.

4.2.5 Insurance Pre-Authorization Process

The majority of participants (87.5%) agreed that the insurance pre-authorization process is a barrier for patient care when ordering CMA (n=16). Respondents indicated that on average,

48.1% (range = 5-90%) of insurance pre-authorization requests get approved, regardless of insurance policy (n=15). All of the participants agreed that there is a significant difference in time spent on CMA insurance pre-authorization based on the patient's insurance policy (n=15).

Most respondents (77.0%) indicated that letters of medical necessity (LMN) for a CMA took 30 minutes or more for each patient (n=13), and 37.5% of respondents indicated that an MD is involved in writing the LMN (n=16). Many participants (87.0%) specified that administrative staff and/or nurses also write LMNs (n=16). The neurologists in this study specified that LMNs could take anywhere from 10 minutes to more than 30 minutes, whereas all of the developmental pediatricians, cardiologists, and endocrinologists responded that an LMN for CMA requires at least 30 minutes of their time.

For those insurance pre-authorization requests that were declined, most participants (78.6%) indicated that appeals took more than 30 minutes for each patient (n=14). 50% of respondents indicated that an MD is involved in writing the appeal (n=16), and 31.3% of participants indicated that only the MD is involved in the appeal process (n=16).

Table 5 displays how much time participants spent on CMA letters of medical necessity and appeals during the insurance pre-authorization process for each patient. Those participants who indicated "N/A" or did not respond to the related survey questions were not included in the analysis. One neurologist specified that he/she does not write LMN for CMA, but is involved in the appeal process. This participant was only included in the analysis for time spent on appeals.

Table 5. Average time spent on a CMA letter of medical necessity and CMA appeal per patient by provider specialty (n=14).

Provider specialty	**Number of Respondents**	**Time spent**				
		<10 minutes	10 minutes	20 minutes	30 minutes	>30 minutes
Neurology	**6**	**Letter of medical necessity (n=5)**				
		0 (0.0%)	1 (20.0%)	2 (40.0%)	1 (20.0%)	1 (20.0%)
		Appeal (n=6)				
		1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	4 (66.7%)
Developmental Pediatrics	**2**	**Letter of medical necessity**				
		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100.0%)
		Appeal				
		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100.0%)
Cardiology	**1**	**Letter of medical necessity**				
		0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
		Appeal				
		0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
Endocrinology	**5**	**Letter of medical necessity**				
		0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (40.0%)	3 (60.0%)
		Appeal				
		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (100.0%)
All specialties	**14**	**Letter of medical necessity (n=13)**				
		0 (0.0%)	1 (7.8%)	2 (15.4%)	4 (30.8%)	6 (46.2%)
		Appeal (n=14)				
		1 (7.1%)	0 (0.0%)	0 (0.0%)	2 (14.3%)	11 (78.6%)

5.0 DISCUSSION

5.1 SURVEY ANALYSIS

5.1.1 Demographics

The group of physicians who were surveyed in this study represent a specific subset of non-genetic specialists as they work at the Children's Hospital of Pittsburgh of UPMC, which is a tertiary care academic hospital with a well-established clinical genetics division. However, it is important to better understand experiences of non-genetic specialists in this setting, because barriers that prevent these physicians from ordering CMA for their patients likely affect non-genetic specialists in other hospital settings. The data from this survey showed that a sizeable number of study participants (43.75%) were ordering CMAs less often than they believe would be beneficial for their patients. This supports previous findings in the literature which suggest that barriers exist which prevent non-genetic specialists from ordering this genetic test, such as poor knowledge of genetics, cost of testing, lack of time to provide genetic counseling, low comfort level with genetic counseling, and fear of discrimination (Klitzman et al., 2013; Duncan et al., 2007; Salm et al., 2014; Watson et al., 1999; Nippert et al., 2011; Rosas-Blum et al., 2007; Reiff et al., 2013).

5.1.2 Knowledge

Study participants reported having a good understanding of genetic testing which differs from previous findings in the literature (Klitzman et al., 2013; Salm et al., 2014; Powell et al., 2012; Collier, 2012; Nippert et al., 2011). While these studies have shown that the large majority of non-genetics specialists rate their knowledge of genetics and genetic testing guidelines as poor (Klitzman et al., 2013; Salm et al., 2014), participants in this study reported having a good understanding of genetics and genetic testing, and indicated that they were comfortable ordering certain types of genetic testing. In the Klitzman et al. (2013) study, findings showed that physicians were more likely to order genetic testing if they had a geneticist or genetic counselor to whom to refer patients. It is possible that the physicians who participated in this study feel more comfortable ordering genetic testing because there are genetics professionals within their hospital where they can refer their patients.

Most participants stated that they were comfortable ordering a karyotype (94.4%), CMA (88.9%), and single gene testing (72.2%), with fewer participants stating that they were comfortable ordering next generation sequencing panels (41.2%) and whole-exome sequencing (25.0%). While there is limited information in the literature regarding physician's perceptions about different types of genetic testing, participants in this study may feel less comfortable ordering next generation sequencing panels and whole-exome sequencing due to the increased complexity of the technology and potential results. For example, the clinical utility of whole-exome sequencing can vary by patient, and there are unclear guidelines regarding when this test should be ordered (Volk et al., 2015). Non-genetic specialists may also feel unequipped to provide adequate informed consent for whole-exome sequencing due to the complexity of the testing (Pinxten and Howard, 2014).

Half of respondents did not believe that insufficient knowledge/experience about genetic testing limited the number of CMAs that they order, and most participants (81.3%) agreed that they were confident about the process for ordering a CMA. One study participant commented "I would appreciate having a resource person come lecture to new hires, residents, fellows, staff" which is congruent with findings in the literature where non-genetic specialists indicate that more training in genetics should be required for physicians (Klitzman et al., 2013; Salm et al., 2014). While studies have shown that non-genetic specialists report having an insufficient understanding of genetic testing guidelines (Klitzman et al., 2013; Salm et al., 2014), most participants (62.5%) disagreed that lack of clinical guidelines is a barrier when ordering genetic testing. This may be due to the availability of the ACMG guidelines for CMA, or the accessibility of genetics professionals within the same center who can clarify when CMA is indicated for a patient.

Study participants reported ordering CMA for indiciations outlined in the 2010 ACMG consensus statement and the 2010 ISCA Consortium consensus guidelines. These indications include global DD (68.8%), DD and MCA (68.8%), MCA only (62.5%), DD and seizures and MCA (56.3%), ASD (50%), DD and seizures (50%), and seizures and MCA (50%). While some physicians ordered CMA for individuals with seizures, this was always when other indications were present such as DD and/or MCA. CMA was never ordered for patients with seizures only. Therefore, most respondents reported ordering CMA for the appropriate indiciations outlined in the ACMG guidelines. As expected, the cardiologists and endocrinologists who participated in this study were less likely to see individuals with the above indications compared to respondents who were neurologists or developmental pediatricians. These physicians indicated that they ordered CMA for patients with isolated short stature (25%), disorders of growth (25%), disorders

of sexual development (18.8%), a cardiac diagnosis (18.8%), or an isolated heart defect (6.3%). These indications have not been included in the ACMG guidelines for CMA suggesting that some studey participants may be less aware of the recommended patient indications for CMA. It is not clear based on the data if physicians ordering CMA for these indications encounter more insurance issues than the physicians who order CMA for the recommended indications. It is also uncertain whether or not the cardiologists and endocrinologists who did not participate in the study also order CMA for these indications, or if they chose not to participate because they do not see patients with DD/ID, ASD or MCA, and therefore do not regularly order CMA. It would be beneficial to administer the survey to more physicians in the future to better understand how often non-genetic specialists are ordering CMA for indications that are not listed on the consensus guidelines for CMA.

5.1.3 Genetic Counseling

Previous studies have demonstrated that non-genetic specialists feel uncomfortable providing genetic counseling, or lack sufficient time to provide adequate counseling (Rosas-Blum et al., 2007; Watson et al., 1999). A study conducted by Duncan et al. (2007) revealed that 71% of otolaryngologists who were surveyed provided genetic counseling to their patients, and discussed the benefits and limitations of genetic testing for sensorineural hearing loss. However, 45% of study participants answered questions regarding recurrence risks incorrectly, or indicated that they did not know the answer to certain questions. Unlike these research findings, the majority of participants in this study reported being either somewhat or very comfortable providing genetic counseling for CMA.

The majority of respondents felt comfortable providing pre-test counseling for CMA (83.3%). In “A Guide to Genetic Counseling”, Uhlmann et al. (2009) describe the importance of discussing the following issues during pre-test counseling for genetic testing: how genetic testing will affect healthcare and life decisions, insurance implications of genetic testing, sensitivity and other test parameters, cost of testing, uses and limitations of test results, how testing will affect other family members at risk, and supportive resources. All of this information is important to help a patient and/or family determine whether they are interested in genetic testing, and how genetic testing could affect their child and other family members in the future. Results from this study showed that respondents routinely discuss a variety of issues during pre-test counseling including different result outcomes (positive, normal, or uncertain result) (93.8%), limitations of testing (87.5%), the cost of testing (62.5%), and the possibility of revealing incidental or unrelated findings (62.5%). Issues that were discussed less often include the possibility of disclosing family relationships such as non-paternity (6.3%), and test sensitivity (12.5%). While many of the issues included in recommended pre-test counseling guidelines (Uhlmann et al., 2009) were often discussed, the possibility of disclosing family relationships was rarely discussed with patients. This type of conversation can be difficult to have with families, but it is essential to provide them with this information in case there is a risk that genetic testing would reveal information that would affect family relationships in a negative way. Other issues like the possibility of revealing incidental or unrelated findings were discussed by most participants, but almost 40% of participants did not discuss this issue during pre-test counseling for CMA. This suggests that additional training may be warranted to ensure that physicians understand potential result outcomes from CMA, and are comfortable communicating this information with their patients to ensure that patients are prepared for this type of information. It is uncertain whether

physicians prioritize issues to be discussed during pre-test counseling due to insufficient time to review all relevant issues. This data was not ascertained from the study.

Most respondents also expressed feeling somewhat or very comfortable providing post-test counseling for a normal CMA result (88.9%). Fewer respondents expressed either being somewhat or very comfortable providing post-test counseling for an abnormal CMA result (55.6%) or a variant of uncertain significance (61.1%). Study participants reported referring patients to a genetics professional for all CMA result types, most often for an uncertain CMA result (58.8%) or an abnormal CMA result (52.9%), and less often for a normal CMA result (35.3%). Most respondents indicated that they referred patients for a genetics consult either once per month (43.8%) or one per week (43.8%). These findings are consistent with results from previous research where non-genetic specialists reported disclosing a normal genetic test result more often than an abnormal genetic test result (Duncan et al., 2007). Non-genetic specialists have also indicated that they refer their patients to a genetics professional more often for an abnormal or uncertain result compared to a normal result (Duncan et al., 2007).

With regards to working with a genetic counselor when ordering a CMA, 81.2% of respondents indicated that a genetic counselor is typically involved in the CMA ordering process, most often to provide post-test counseling (75.0%), as well as with the insurance pre-authorization process (37.5%) and CMA result disclosure (37.5%). Although not every study participant reported working with a genetic counselor, all respondents agreed that genetic counselors would be valuable or very valuable when reviewing genetic testing options based on patient indication(s), providing pre-test counseling for CMA, and providing post-test counseling for CMA. Most participants (93.8%) also stated that genetic counselors would be valuable or very valuable in regards to the insurance pre-authorization process for CMA and with CMA

result interpretation. While these non-genetic specialists indicated that they value genetic counselors, it appears that they may not have the opportunity to work with them directly. This is likely due to the limited number of genetic counselors who are available to work with non-genetic specialists at this medical center, as most of the genetic counselors see patients with clinical geneticists.

5.1.4 Insurance Pre-Authorization Process

While lack of knowledge about genetics and genetic testing guidelines, low comfort level providing genetic counseling, and lack of access to a genetics professional do not appear to be barriers for ordering CMA in this physician cohort, most respondents (93.8%) agreed that lack of insurance coverage for genetic testing can limit the number of CMAs ordered by non-genetic specialists. This finding is consistent with previous findings in the literature that suggest a large proportion of insurance pre-authorization requests for CMA are denied due to a lack of evidence that CMA will change medical management for the patient (Hughes, 2010; Riggs et al., 2014). Most participants (87.5%) agreed that the insurance pre-authorization process is a barrier for patient care when ordering CMA, and indicated that on average, 48.1% of insurance pre-authorization requests get approved, regardless of insurance policy. This approval rate for CMA is low despite approximately 50-70% of respondents indicating that they order CMA for the appropriate patient indications outlined in the ACMG guidelines.

All participants agreed that there is a significant difference in time spent on CMA insurance pre-authorization based on the patient's insurance policy. Most respondents (77.0%) indicated that letters of medical necessity for a CMA took 30 minutes or more for each patient. For those insurance pre-authorization requests that were declined, most participants (78.6%)

indicated that appeals took more than 30 minutes for each patient. It does not appear that other studies have investigated how much time is required by physicians to write letters of medical necessity or appeals for genetic testing. Based on the results from this study, the insurance pre-authorization process for CMA can take well over an hour per patient which is significant when these physicians have busy clinics and see many patients who could benefit from CMA. This could potentially lead to physicians ordering fewer CMAs, or lacking sufficient time to write an appeal within the potential time constraints required by insurance companies. Genetic counselors could help improve access to CMA by using their expertise to write both LMNs and appeals, thereby, saving valuable clinic time for these physicians.

Importantly, some insurance companies are now requiring pre-test and post-test genetic counseling for patients when a CMA is ordered (Cigna Medical Coverage Policy, effective 7/15/2016). If these patients have DD/ID, ASD, and/or MCA, CMA will be covered by certain insurance companies when genetic counseling is provided, and insurance pre-authorization would not be required. For some insurance policies, genetic counseling can be provided by a certified medical geneticist, a certified genetic counselor, or a credentialed genetic nurse (Cigna Medical Coverage Policy, effective 7/15/2016). Respondents from this study reported being amenable to working with genetic counselors as they believe genetic counselors are valuable when ordering a CMA. Genetic counselors would be an asset for non-genetic specialists to provide genetic counseling when a CMA is ordered. Not only would working with a genetic counselor save physicians' time, but genetic counselors also have the expertise to discuss difficult issues during pre-test counseling. In particular, only 6.3% of respondents indicated that they discuss the possibility of disclosing family relationships such as non-paternity during pre-test counseling. Genetic counselors have experience conducting these challenging conversations

with families, and would be able to provide comprehensive pre-test counseling for these patients, which would increase access to CMA by following insurance company policies.

5.2 PUBLIC HEALTH SIGNIFICANCE

In recent years, precision medicine has become a national initiative with the ultimate goal of personalizing patient care in order to improve health outcomes. Genetic testing can contribute to personalized medicine by allowing healthcare providers to better understand how an individual's genetic information can impact their health. As genetic testing continues to expand and become relevant to many individuals, non-genetic specialists will increasingly be found in situations where they are expected to order genetic testing. It is essential to evaluate barriers that non-genetic specialists experience when ordering genetic testing, including barriers to accessing testing like the insurance pre-authorization process, as well as ethical barriers that affect individuals who are having genetic testing. For example, if comprehensive pre-test and post-test genetic counseling are not available to individuals, this raises ethical concerns that prevent patients from having a full understanding of genetic testing, and how it may impact their life.

Genetic testing guidelines and policies are critical to ensure that individuals have access to genetic testing and are provided with appropriate genetic counseling. Genetic counselors have the expertise to provide pre-test and post-test genetic counseling, in addition to providing recommendations to insurance companies regarding insurance policies. Through collaboration with insurance companies, genetic counselors can provide the necessary expertise concerning different types of genetic testing to ensure equal access to testing for all individuals, in a way that is cost effective for insurers.

Additionally, it is essential that genetics professionals invest time in educating non-genetic specialists about genetic testing policies, and elements to be included in pre-test and post-test genetic counseling. This will help non-genetic specialists navigate through the genetic testing process in situations when there are a limited number of genetics professionals to order testing and provide genetic counseling for patients.

5.3 LIMITATIONS OF THE STUDY AND FUTURE DIRECTIONS

There were several limitations to this study. The overall response rate of the questionnaire was relatively low at 23.9% (16/67). Study recruitment using predominantly email did not appear to be an effective way to recruit physicians for study participation. Previous studies have shown that physician response rate for online surveys is typically lower than the response rate for other types of research participants at 35-44% (Cunningham et al., 2015; Martins et al., 2007). It is unclear whether or not low response rate was due to insufficient time to complete the survey, or if physicians felt that their responses would be less relevant if they do not order CMA often. One respondent had filled in part of the survey, and then specified that he/she does not order CMAs. Due to the low response rate, it was not possible to compare data between different types of non-genetic specialists.

Non-genetic specialists who were surveyed work in a tertiary care academic hospital, and have access to genetics professionals. Most respondents were neurologists or developmental pediatricians (56.3%), female (75%) and between the ages of 40-59 years (68.7%). Therefore, these results are not generalizable to all non-genetic specialists in the United States. Fellows and

residents were not included in the study, and it would be interesting to better understand their experiences ordering CMA.

In the future, it would be important to improve the recruitment strategy and increase the response rate. This could be accomplished by allocating 10-15 minutes in departmental meetings to complete a paper copy of the survey for those physicians who are interested. A study by Martins et al. (2007) demonstrated that follow-up telephone calls with physician study participants who had been sent an electronic survey increased the response rate from 44% to 71%. Follow-up telephone calls could also be attempted in future studies to see if this improves the response rate.

The wording of certain questions could be improved to better capture the data. For example, some survey questions asked how often participants refer their patients to genetics, while additional questions asked how different types of CMA results are disclosed, which included disclosure by a genetics professional. Sometimes it was reported that a genetics professional disclosed a CMA result when the patient was not referred to genetics. Exploring this discrepancy could provide valuable data. For the purposes of the data analysis, information about the number of genetics referrals was based on whether or not a respondent indicated that they made a genetics referral for different types of CMA results. These questions would need to be edited to better understand how genetics professionals are involved when CMA results are disclosed. Due to technical problems with the Qualtrics software, certain questions did not allow participants to specify an answer when they selected "other" as a response. This issue would need to be resolved in a future study.

It would be interesting to include more knowledge-based questions in a future study. Most of the questions assessing physician knowledge in this study were based on self-reporting,

and it is unclear if this is an accurate way to measure physician knowledge regarding CMA. Most participants indicated being comfortable providing pre-test counseling for CMA, however, some did not discuss important issues that are recommended to be reviewed with patients during the pre-test counseling process. Therefore, although physicians reported being comfortable ordering CMAs, it would be important to ask additional questions that are not based on self-reporting to evaluate physician knowledge. This would provide a better understanding of whether knowledge of CMA affects when a CMA is ordered, and determines the type of information discussed with patients during the pre-test and post-test counseling process.

Finally, it would be interesting to survey non-genetic specialists who do not work in a tertiary care academic hospital to see what their experiences have been when ordering CMA. Knowledge about genetic testing and comfort level providing genetic counseling could be assessed for those physicians who do not work closely with genetics professionals, or are unable to easily refer their patients to a genetics clinic within their center. This additional information would enhance the understanding of non-genetic specialists' experiences ordering CMA to inform insurance policies and improve access to this test.

6.0 CONCLUSION

Non-genetic specialists who work in a tertiary care academic hospital were surveyed to better understand their experiences ordering CMA. Survey answers were analyzed using descriptive statistics. The majority of study participants reported being knowledgeable about genetics and genetic testing guidelines, and most participants felt comfortable ordering genetic testing, and providing genetic counseling when a CMA is ordered. The majority of respondents agreed that the insurance pre-authorization process is the greatest barrier when ordering CMA. Most respondents have worked with genetic counselors when a CMA was ordered, and agree that a genetic counselor would be valuable or very valuable throughout the entire CMA ordering process.

These results will be useful to insurance companies who are developing policies to streamline the pre-authorization process for CMA requests. Most non-genetic specialists in this clinical setting are aware of the clinical indications for CMA, and feel comfortable working with a genetic counselor or providing pre-test and post-test genetic counseling themselves when this test is ordered.

APPENDIX A: STUDY SURVEY

A.1 RECRUITMENT LETTER

Study Title: Non-Genetic Specialists' Experiences Ordering Chromosomal Microarrays

To Whom It May Concern:

You are being asked to participate in a research study to learn more about non-genetic specialists' experiences ordering chromosomal microarrays (CMAs). You have been contacted because you are a neurologist, developmental pediatrician, cardiologist, or endocrinologist employed by the Children's Hospital of Pittsburgh.

You will be asked to complete an online survey inquiring about your experiences when ordering CMAs, including counseling patients, result disclosure, and the insurance pre-authorization process. Completing this survey will take approximately 10 minutes of your time. Should you choose to participate in this study, your UPMC email address will be documented. Survey responses will be linked to your email address to allow for a possible follow-up survey in the future. Your responses will be stored in a password protected database, and will only be accessible to the principal investigator and research team. You may be contacted in the future regarding participation in follow-up studies. More information about any follow-up studies

would be provided at the time of study recruitment, and you would have the choice whether or not to participate.

Please see the following survey link for this study (Survey Link specific to each participant here). For more information, please contact Jodie Vento, study PI and genetic counselor at the Children's Hospital of Pittsburgh (412-692-8641, Jodie.Vento@chp.edu) or Amy Davis, study co-investigator and genetic counseling Master's student at the University of Pittsburgh (aed50@pitt.edu). Thank you for your time.

Sincerely,

Amy Davis

A.2 INFORMED CONSENT SCRIPT

You are being asked to participate in a research study to learn more about non-genetic specialists' experiences with ordering chromosomal microarrays. A chromosomal microarray (CMA) is a genetic test that analyzes deletions and duplications of DNA regions that are too small to be detected by traditional karyotype analysis. This survey is being administered to non-genetic specialists at the Children's Hospital of Pittsburgh.

If you are willing to complete the following survey, which will take approximately 10 minutes of your time, you will be asked about your experiences when ordering CMAs, including counseling patients, CMA result disclosure, and the insurance pre-authorization process. Demographic information will be collected, and your email address will automatically be documented along with the survey data. Your answers will be saved as you complete the survey, and you can stop and return to the survey at any time. This survey cannot be completed on a mobile device.

Your participation is entirely voluntary, and you can withdraw from this study at any time. Whether or not you decide to participate will have no impact on your employment status at the Children's Hospital of Pittsburgh. There is no possible risk of breach of confidentiality associated with this project, nor are there any direct benefits to you. Your email address will be collected, and we may contact you in the future regarding participation in follow-up studies. You are not required to participate in any follow-up studies. All survey responses are confidential, and will be stored in a password protected database. Only the study PI, co-investigator, and their

study team will have access to identifiable data. Authorized representatives from the University of Pittsburgh Research Conduct and Compliance Office may review your data for the purpose of monitoring the conduct of this study. This study is being conducted by the University of Pittsburgh and the Children's Hospital of Pittsburgh. This study has been approved by the University of Pittsburgh Institutional Review Board. For more information on this study, please contact Jodie Vento, study PI and genetic counselor at the Children's Hospital of Pittsburgh (412-692-8641, Jodie.Vento@chp.edu) or Amy Davis, study co-investigator and genetic counseling Master's student at the University of Pittsburgh (aed50@pitt.edu).

If you wish to withdraw from the study in the future, please contact Jodie Vento, study PI, and all responses that were collected will be destroyed.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions.

Do you agree to participate?

☐ Yes

☐ No

A.3 SURVEY

1) How comfortable are you ordering the following types of genetic testing?

	Very uncomfortable	Somewhat uncomfortable	Neither comfortable nor uncomfortable	Somewhat comfortable	Very comfortable	N/A
Karyotype	☐	☐	☐	☐	☐	☐
Chromosomal microarray (CMA)	☐	☐	☐	☐	☐	☐
Single gene testing	☐	☐	☐	☐	☐	☐
Next generation sequencing panel	☐	☐	☐	☐	☐	☐
Whole-exome sequencing	☐	☐	☐	☐	☐	☐

2) How comfortable are you in the following situations providing:

	Very uncomfortable	Somewhat uncomfortable	Neither comfortable nor uncomfortable	Somewhat comfortable	Very comfortable	N/A
Pre-test counseling for a CMA	☐	☐	☐	☐	☐	☐
Post-test counseling for a normal CMA	☐	☐	☐	☐	☐	☐

result

Post-test counseling for an abnormal CMA result	☐	☐	☐	☐	☐	☐
Post-test counseling for an unclear CMA result (“variant of unknown significance”)	☐	☐	☐	☐	☐	☐

3) With regards to disclosing CMA results, please indicate how the following types of results are disclosed (check all that apply):

Normal result

- ☐ Disclose in person
- ☐ Disclose over the phone
- ☐ Refer patient to genetics
- ☐ N/A
- ☐ Other (please specify) _____

If checked “normal result - disclose in person”:

Who discloses results (check all that apply):

- ☐ I do
- ☐ Physician extender (nurse, medical assistant)
- ☐ Genetics professional
- ☐ Other (please specify) _____

If checked “normal result - disclose over the phone”:

Who discloses results (check all that apply):

- ☐ I do
- ☐ Physician extender (nurse, medical assistant)
- ☐ Genetics professional
- ☐ Other (please specify) _____

4) With regards to disclosing CMA results, please indicate how the following types of results are disclosed (check all that apply):

Abnormal result

- ☐ Disclose in person
- ☐ Disclose over the phone
- ☐ Refer patient to genetics
- ☐ N/A
- ☐ Other (please specify) _____

If checked “abnormal result - disclose in person”:

Who discloses results (check all that apply):

- ☐ I do
- ☐ Physician extender (nurse, medical assistant)
- ☐ Genetics professional
- ☐ Other (please specify) _____

If checked “abnormal result - disclose over the phone”:

Who discloses results (check all that apply):

- ☐ I do
- ☐ Physician extender (nurse, medical assistant)
- ☐ Genetics professional
- ☐ Other (please specify) _____

5) With regards to disclosing CMA results, please indicate how the following types of results are disclosed (check all that apply):

Uncertain result

- ☐ Disclose in person
- ☐ Disclose over the phone
- ☐ Refer patient to genetics
- ☐ N/A
- ☐ Other (please specify) _____

If checked “uncertain result - disclose in person”:

Who discloses results (check all that apply):

- ☐ I do
- ☐ Physician extender (nurse, medical assistant)
- ☐ Genetics professional
- ☐ Other (please specify) _____

If checked “uncertain result - disclose over the phone”:

Who discloses results (check all that apply):

- ☐ I do
- ☐ Physician extender (nurse, medical assistant)
- ☐ Genetics professional
- ☐ Other (please specify) _____

6) Which of the following issues do you routinely discuss with patients/families when ordering a CMA (check all that apply):
   - ☐ Different result outcomes (positive, normal, uncertain result)
   - ☐ Uncertain result may require parental samples for further interpretation
   - ☐ Incidental/unrelated findings
   - ☐ Non-paternity/disclosing family relationships
   - ☐ Test sensitivity
   - ☐ Limitations of testing
   - ☐ Test turn-around-time
   - ☐ Cost of testing
   - ☐ I do not provide pre-test counseling
   - ☐ I do not order CMAs
   - ☐ Other (please specify): _____

7) Have you disclosed CMA results in the last 6 months?
   - ☐ Yes
   - ☐ No

8) How often do you have a patient who you think would benefit from a CMA?
   - ☐ 0 patients per month
   - ☐ 1-2 patients per month
   - ☐ 3-5 patients per month
   - ☐ 5-10 patients per month
   - ☐ 10-15 patients per month

9) How often do you order CMAs for your patients?
   - ☐ 0 times per month
   - ☐ 1-2 times per month
   - ☐ 3-5 times per month
   - ☐ 5-10 times per month
   - ☐ 10-15 times per month

10) To what extent do you agree or disagree with the following statement: The following factors limit how many genetic tests, such as CMAs, I order in my practice:

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	N/A
Patient's concerns about insurance discrimination	☐	☐	☐	☐	☐	☐
My concerns about insurance discrimination	☐	☐	☐	☐	☐	☐
Patient's concerns about costs	☐	☐	☐	☐	☐	☐
My concerns about costs	☐	☐	☐	☐	☐	☐
Lack of insurance coverage of genetic testing	☐	☐	☐	☐	☐	☐
My insufficient knowledge/experience about genetic testing	☐	☐	☐	☐	☐	☐
My lack of knowledge of how to order/where to send tests	☐	☐	☐	☐	☐	☐
Lack of detailed family history available	☐	☐	☐	☐	☐	☐
Language barrier	☐	☐	☐	☐	☐	☐
Patient's level of education	☐	☐	☐	☐	☐	☐

Lack of clinical guidelines	☐	☐	☐	☐	☐	☐
My lack of access to geneticists/genetic counselors	☐	☐	☐	☐	☐	☐
Other (please indicate) _____	☐	☐	☐	☐	☐	☐

11) For what patient indication(s) do you order a CMA (check all that apply):
- ☐ Global developmental delay
- ☐ Isolated seizures
- ☐ Isolated speech delay
- ☐ Isolated short stature
- ☐ Down syndrome
- ☐ Autism spectrum disorder
- ☐ Isolated congenital heart defect
- ☐ Multiple congenital anomalies only
- ☐ Developmental delay and seizures
- ☐ Developmental delay and multiple congenital anomalies
- ☐ Seizures and multiple congenital anomalies
- ☐ Developmental delay, seizures, and multiple congenital anomalies
- ☐ Cardiac diagnosis (Long QT, Sudden death, DCM, HCM, VT)
- ☐ Disorders of sex development
- ☐ Disorders of growth
- ☐ I do not order CMAs
- ☐ Other (please indicate): _____

12) To what extent do you agree or disagree with the following statement: I am confident about the process for ordering a CMA:

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	N/A
☐	☐	☐	☐	☐	☐

➔ If answered ‘strongly disagree’, please explain:

13) How often do you refer a patient for a formal genetics consultation?
- ☐ Almost every day
- ☐ More than once a week
- ☐ Once a week
- ☐ Once a month
- ☐ Never

14) How often do you have an informal conversation with a genetics professional regarding one of your patients?
- ☐ Almost every day
- ☐ More than once a week
- ☐ Once a week
- ☐ Once a month
- ☐ Never

15) Please indicate how a genetic counselor has been involved in the care of your patient when a CMA has been ordered (check all that apply):
- ☐ Informed consent and pre-test counseling prior to ordering the CMA
- ☐ Informal consult
- ☐ Insurance preauthorization
- ☐ Patient education while the CMA is in process
- ☐ CMA result disclosure
- ☐ Post-test counseling
- ☐ N/A

16) How valuable do you think a genetic counselor would be in the following areas when ordering a CMA for a patient:

	Not valuable	Somewhat valuable	Neutral	Valuable	Very valuable
Review of genetic testing options based on patient indication(s)	☐	☐	☐	☐	☐
Pre-test counseling	☐	☐	☐	☐	☐
Insurance pre-authorization	☐	☐	☐	☐	☐
CMA result interpretation	☐	☐	☐	☐	☐

Post-testing counseling	☐	☐	☐	☐	☐

17) Approximately how much time is spent on CMA insurance pre-authorization per patient for the following tasks:

	Less than 10 minutes	10 minutes	20 minutes	30 minutes	Greater than 30 minutes	N/A
Letter of medical necessity	☐	☐	☐	☐	☐	☐
If insurance pre-authorization is denied, time spent on appeals	☐	☐	☐	☐	☐	☐

18) Please indicate which member on your staff normally writes a letter of medical necessity for CMA (check all that apply):
- ☐ Administrative staff
- ☐ Nurse
- ☐ I handle letters of medical necessity
- ☐ Other (please specify) _____
- ☐ N/A

19) Please indicate which member on your staff normally writes an appeal for CMA (check all that apply):
- ☐ Administrative staff
- ☐ Nurse
- ☐ I handle insurance appeals
- ☐ Other (please specify) _____
- ☐ N/A

20) To what extent do you agree or disagree with the following statement: There is a significant difference in time spent on CMA insurance pre-authorization based on the patient's insurance policy:

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	N/A
☐	☐	☐	☐	☐	☐

21) Regardless of insurance policy, on a scale of 0-100%, what percentage of CMA insurance pre-authorization requests do you estimate usually get approved: _____% □ N/A

22) To what extent do you agree or disagree with the following statement: The insurance pre-authorization process is a barrier for patient care when ordering CMAs:

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	N/A
☐	☐	☐	☐	☐	☐

Physician demographics:

23) Provider specialty
- ☐ Neurology
- ☐ Developmental pediatrics
- ☐ Cardiology
- ☐ Endocrinology
- ☐ Other (please specify) _____

24) Please indicate any genetics training you have received (check all that apply):
- ☐ Conference
- ☐ Certificate
- ☐ Lecture
- ☐ Other (please specific): _____
- ☐ N/A

25) Gender
- ☐ Male
- ☐ Female

26) Age
- ☐ 20-29
- ☐ 30-39

- □ 40-49
- □ 50-59
- □ 60+

27) Completed medical training decade:
- □ 1960-1969
- □ 1970-1979
- □ 1980-1989
- □ 1990-1999
- □ 2000-2009
- □ 2010-2019
- □ Still in training

28) Thank you for taking the time to fill out our survey. We would appreciate if you could provide feedback on our survey and any suggestions for improvement:

APPENDIX B: IRB APPROVAL FORM

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Jodie Vento , MS

From: IRB Office

Date: 11/17/2015

IRB#: PRO15090294

Subject: Non-Genetic Specialists' Experiences Ordering Chromosomal Microarrays

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The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110. Your research study was approved under:

45 CFR 46.110.(7)

The IRB has approved the waiver for the requirement to obtain a written informed consent.

The risk level designation is Minimal Risk.

Approval Date: 11/17/2015

Expiration Date: 11/16/2016

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

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