I, Lauren E Grote, hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled:
Variability in Laboratory Reporting and Genetic Counseling for Regions of Homozygosity Associated With Parental Consanguinity/Incest

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Variability in Laboratory Reporting and Genetic Counseling for Regions of Homozygosity Associated With Parental Consanguinity/Incest

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ABSTRACT

Purpose: SNP microarrays, used as a first tier test for individuals with unexplained developmental disabilities and/or congenital anomalies, are capable of detecting regions of homozygosity (ROH) which can suggest parental consanguinity or incest. This study was designed to describe the variable reporting practices of clinical laboratories in the United States regarding ROH found on SNP microarrays and the follow up practices of laboratory personnel when ROH indicate consanguinity or incest. The study also describes pre-test and post-test counseling practices of genetics professionals regarding ROH and explores the comfort level of genetics professionals in the follow-up of such results. Finally, the survey highlights legal and ethical dilemmas faced by incidental findings that suggest a parental blood relationship. Methods: A 20 question survey was administered to 18 laboratories offering clinical SNP microarrays. A 35 question survey was administered to 240 genetic counselors and geneticists who had ordered/counseled for a SNP microarray. The results are presented using descriptive statistics. Results: Laboratories were found to include variable information about ROH and the interpretation of ROH on SNP microarray reports. Most laboratories report the number, size, and locations of ROH as well as their recommendations based on the findings, while only 55.5% of the laboratories report percent homozygosity. 13.3% or 2/15 reported that they speculate the degree of relationship based on the ROH found. All laboratories agreed they have a duty to inform the ordering physician of results suggesting consanguinity or incest, but the follow through practices varied. 55.6% reported taking additional steps when consanguinity is found. These steps include contacting the ordering healthcare provider. 77.8% reported taking additional steps when incest is found. These steps include contacting the ordering healthcare provider. 14.3% contacted an ethics board and 7.1% contacted social work. No laboratories had contacted the authorities for either consanguinity or incest. Similarly, there was variation in the pre-test and post-test counseling practices of genetic counselors and geneticists regarding SNP microarrays. 8% reported pre-test counseling patients that SNP microarray detects ROH, 7.5% reported pre-test counseling that ROH can indicate a parental blood relationship, and 18% reported pre-test counseling about both. Additionally, there was a wide range of comfort and knowledge of related laws on consanguinity, incest, and cousin relationships. Around 40% of respondents felt familiar with state laws regarding cousin relationships. 20% were familiar with their duty to report incest. 57% felt comfortable receiving results of consanguinity and 17% felt comfortable receiving results of incest. Providers who pre-test counseled patients about ROH were more comfortable discussing incidental results with patients. Conclusion: This study discovered variability in reporting practices and follow-up procedures for microarray results consistent with parental consanguinity or incest. It highlights the discrepancies in pre-test and post-test counseling surrounding ROH and SNP microarrays for genetics professionals, in respondents feelings and knowledge surrounding counseling on these results, and legal, moral, and ethical dilemmas that have arisen due to these findings. This study identifies a need for professional organizations to offer guidance to genetics professionals about how to handle results suggesting consanguinity or incest.

KEY WORDS: Regions of homozygosity, microarray, consanguinity, incest, heterozygosity, genetic counseling
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INTRODUCTION

Single nucleotide polymorphism (SNP) microarray is a genetic test that is frequently performed in the diagnostic evaluation of individuals with idiopathic developmental disabilities, undiagnosed syndrome, and/or congenital anomalies. Microarrays are small chips made of glass, silicon or nylon membranes that are spotted with DNA in a specific pattern. A DNA sample from the patient is allowed to hybridize to the chip, attaching to DNA probes. These microarrays identify small and large duplications and deletions as well as regions of homozygosity (ROH) throughout the genome. Constitutional ROH is consistent with uniparental isodisomy (UPD), ancestral relatedness, or a parental blood relationship. A single ROH or multiple ROH on the same chromosome may represent UPD, which can be confirmed with methylation analysis. The inheritance of small identical chromosomal segments can occur without immediate parental relatedness; moderately sized ROH (>4 MB) have been found frequently across all populations and are termed ancestral ROH. In contrast, long, uninterrupted ROH, on multiple chromosomes are present in individuals who are the product of a consanguineous relationship.

In clinical genetics, consanguinity is defined as the union of individuals related as second cousins or closer. Worldwide, couples who are second cousins or closer and their children encompass 10.4% of the population. Rates of consanguinity are influenced by ethnicity, religion, and cultural beliefs on parental relatedness. Consanguinity is more common in the Middle East, North Africa, and West Asia, where it is thought to comprise 20-50% of all marriages. In the United States, consanguinity is significantly less common and thought to occur in <5% of marriages, with certain parts of the US having higher rates than others. The difference is believed to be due to Western attitudes towards consanguinity and laws discouraging relationships between individuals related as first cousins (third degree relatives) or closer. In the United States, marriages between first cousins or closer is illegal or a criminal offense in 31 of 50 states. In all 50 states, incest is classified as sexual relations between first
degree relatives, such as between a parent and child or between two biological siblings. In some states, incest also includes sexual relations between second degree relatives, for example a relationship between half-siblings, an aunt and a nephew, an uncle and a niece, or a grandparent and a grandchild. Incest may also be defined as involving non-blood relatives such as step-parents and step-children.

Genetic counseling of consanguineous couples is different than counseling for non-related couples because offspring of both consanguineous and incestuous unions are at an increased risk for autosomal recessive disorders. Empirical studies show progeny of first cousin relationships have an increased risk for stillbirths and infant mortality; additionally, the risk for birth defects is 2-3% over the generation population risk. Precocious mortality and morbidity for offspring of an incestuous relationship has been found to occur in 31.6% of those studied. Additional research has shown that when mental handicap is added in addition to precocious mortality and morbidity, the risk increases to 37%. A thorough family history to determine the presence of medical or genetic disorders, ethnicity, and degree of relationship of parents and patients is essential for competent genetic counseling. According to Bennett et al. (2002), the estimated risk for the offspring of a consanguineous couple must be determined by considering the combination of the background population risk, degree of consanguinity, and relevant family history. In addition, psychosocial concerns in families with consangunity may vary. Some families may be trying to keep the relationship hidden due to fear of legal prosecution, discrimination, or ridicule. In the United States where consanguineous marriages are mostly disapproved of and in some states illegal, families may be experiencing feelings of shame and loneliness.

SNP microarray testing is ordered by physicians from multiple medical specialties, often with little or no consent process. Informed consent should occur prior to genetic testing and consists of information, comprehension, and voluntariness. During a genetic counseling session, the informed
consent process often occurs during pre-test counseling. Specifically, patients should be provided with information about the testing, the condition they are being tested for, possible outcomes of the testing, and future steps once the test is completed. It is the healthcare provider’s job to ensure that the patient understands the procedure, it’s benefits and limitations, and is voluntarily undergoing the test. When counseling patients prior to ordering a SNP microarray, genetic counselors and clinical geneticists may use guidelines from their institution or their personal discretion as to the details provided in the consent process. This consent or pre-test counseling process may not include the possibility of discovering a parental relationship whether it is given by genetics professionals or other specialties.

While there are published guidelines for pre-test and post-test counseling on CGH microarray, there have been no publications to discuss pre-test and post-test counseling for SNP microarray. Discovery of a possible parental consanguineous or incestuous relationship by SNP microarray may be an unexpected finding for the laboratory, the ordering physician, and even the family. There are currently no standards for reporting results of clinical SNP microarrays that show multiple ROH suggestive of consanguinity or incest. In the absence of standards, it is unknown what, if any, information laboratories are including about ROH and the implications of ROH on microarray reports. It is also unclear if results suggesting consanguinity or incest are being communicated to the ordering physician or family of the patient. Due to the lack of pre-test and post-test counseling guidelines for SNP microarrays, it is unknown if patients are receiving information about the potential of microarray to suggest parental relatedness. It is possible that patients are getting incomplete pre-test counseling.

Laboratories, genetic counselors, and geneticists work closely to coordinate SNP microarray testing for patients; consequently, the actions of one affect the other. Laboratories performing SNP microarrays do not have an established standard format for reporting test results related to ROH. Similarly, genetic professionals lack standard of care procedures for pre-test and post-test counseling a
patient regarding discovery of ROH on a SNP microarray. A lack of direction can lead to legal and ethical dilemmas surrounding informed consent, reporting, result disclosure and relationships.

In this study, laboratories that perform clinical SNP microarrays were surveyed to determine how they report ROH. Description of laboratory reporting practices will be useful in the development of standards for responsible reporting of ROH. Genetic counselors and geneticists were also surveyed to determine their pre-test and post-test counseling practices for SNP microarray, to describe their feelings surrounding receipt and counseling for results that suggest consanguinity or incest, and to help outline the legal and ethical dilemmas surrounding patient consent, results reporting and disclosure when microarray results suggest consanguinity or incest.

This study will be presented in two parts. Part 1 is titled “Variable reporting practices for ROH indicating parental relatedness identified by SNP Microarray.” This part will include methods, results and discussion of the laboratory survey. This section is followed by Part 2 entitled, “Variability in Genetic Counseling Practices for Regions of Homozygosity Associated with Parental Consanguinity or Incest.” Part 2 will also include a methods, results and discussion in regards to the second survey. The conclusion discusses the main findings from both sections.
Part 1:
Variable laboratory reporting practices for regions of homozygosity indicating parental relatedness identified by SNP microarray
MATERIALS AND METHODS

Participants and Procedures

Clinical laboratories throughout the United States that offer SNP microarray on peripheral blood samples met inclusion criteria for this study. Laboratories that did not offer SNP microarrays or offered SNP microarrays solely for oncology analysis were excluded. Eligible laboratories were identified by attendance of representatives from various laboratories at cytogenetics conferences, identification of additional laboratories meeting inclusion criteria from other participants, and knowledge of the authors regarding which laboratories currently offer SNP microarray. Laboratory websites were reviewed to confirm that SNP microarray was offered as a diagnostic test. In addition, laboratories were contacted prior to survey invitation to verify that SNP microarray was offered on a clinical basis. Upon verification, microarray experts were contacted to complete the survey. Experts were selected by contacting the main phone number available for the laboratory, and asking for an individual who played a role in creating/editing SNP microarray reports. All respondents confirmed their status as a microarray expert by responding “yes” to the question, “Are you familiar with your laboratory’s process of finding and reporting ROH on a SNP microarray?” This paper includes data from the laboratories’ perspective. A forthcoming paper will address genetic counselors and geneticists’ perspectives on pre-test and post-test counseling for SNP microarrays and the associated legal and ethical dilemmas providers may face. This study was approved by Cincinnati Children’s Hospital Medical Center (CCHMC) and The University of Cincinnati Institutional Review Boards (Study # 2011-1248).

Survey Development

A twenty item survey was developed to assess the variability in reporting practices of clinical laboratories throughout the United States regarding ROH identified by SNP microarrays. This survey contained fifteen close-ended questions and five open-ended questions (See Supplemental data). It was developed based on the authors’ experiences with SNP microarray reports and definitions of
terminology in the field. The survey was reviewed and edited by the authors and was piloted for face validity by four colleagues.

Survey Measures

This survey consisted of five sections. Part one queried respondents about demographic information including their gender, job title, length of employment in a laboratory setting, length of time the laboratory has offered a SNP microarray, and the name of the SNP microarray currently run at the laboratory. Part two inquired about information listed on each laboratory’s SNP microarray report including specifics about ROH and the laboratory’s interpretations of ROH. The survey then asked participants to select their laboratory’s definition of incest based on percent homozygosity and indicate the number of times the laboratory has reported an array that indicated the possibility of incest. Part four asked questions regarding the laboratories’ duty to report findings of consanguinity or incest and any standard follow up practices they completed. The follow up practices were separated into steps taken when finding consanguinity and steps taken when finding incest. Part five included four open ended questions to determine the laboratories’ cut off for reporting ROH, method of calculation for percent homozygosity, methods for differentiation between ROH and UPD, and definition of ancestral ROH.

Each representative was contacted by phone or email and was offered the opportunity to complete the survey by phone. Upon agreement, a time and date were set to conduct the survey. Phone surveys were subsequently recorded and open-ended questions were transcribed. In addition, potential responders were given the option of completing an online format of the survey using SurveyMonkey®, which is a website designed for the creation, distribution, and analysis of surveys through collection of responses using the internet. Those electing not to complete the survey by phone were emailed the website link. Nonresponders received a follow up email two and four weeks after the
initial contact. Lastly, laboratory representatives were contacted by phone as a final reminder of the survey opportunity.

Data Analysis

The survey was conducted between September 2011 and December 2011. Telephone survey responses were entered into SurveyMonkey® for consistency in data analysis. The data was sorted and prepared for analysis by the SurveyMonkey® software. Incomplete answers were excluded and removed from the final analysis. Frequencies were determined for each close-ended question. Open-ended questions were post-coded according to common themes and frequencies for each theme were determined.

RESULTS

Respondent Characteristics

In total, 32 laboratories were invited to participate in the survey. Before completing the survey, six laboratories were excluded: five did not offer SNP microarrays and one offered a SNP microarray for oncology samples only. Of the remaining 26 laboratories, seven declined to participate, one laboratory primarily responded to demographic questions and was subsequently excluded, and 18 laboratories completed the survey (5 by telephone and 13 online) for an overall response rate of 72%. Fourteen (77.8%) laboratories reported using an Affymetrix platform and four (22.2%) used an Illumina platform. Six (33.3%) respondents were genetic counselors, 11 (61.1%) were laboratory directors, and 1 (5.6%) was a clinical cytogeneticist/clinical geneticist. The respondents were employed in a laboratory setting for the following time spans: 4 (22.2%) for 0-2 years; 2 (11.1%) for 3-5 years; 4 (22.2%) for 6-8 years; 1 (5.6%) for 9-11 years; 1 (5.6%) for 12-14 years; and 6 (33.3%) for 15 or more years.

Calculation of Percent Homozygosity (Froh)

Laboratories were asked to describe their methods for calculation of percent homozgyosity (Froh) from SNP microarray results. Among the fifteen laboratories answering this question, 6 (40%) reported they complete the calculation by adding the total Mb of ROH identified and dividing by the
total Mb of DNA found in the entire genome; 8 (53.3%) laboratories divided the total megabases (Mb) of ROH by the total Mb of DNA found in the autosomes only; and 1 (6.7%) laboratory did not calculate the percent of homozygosity. Three laboratories stated that they list their methods for calculation of Froh on their SNP microarray report.

**Definitions**

Laboratories were asked to define ancestral ROH. Nine laboratories provided different definitions including ancestral ROH is: the “presence of ROH on a few chromosomes,” a “large number of (usually >50) of independent stretches of homozygosity,” “1Mb blocks and higher” of ROH, >3Mb blocks of ROH, ROH “ranging in size from 0.5Mb to 10Mb but the majority range from 0.5 to 5-6Mb,” “a very low percentage of the genome being homozygous,” based on “size and number of ROH” found, “large blocks of homozygosity over multiple chromosomes,” and many individuals have “at least one ROH ≥5Mb.” Seven of the remaining nine laboratories, 38.9%, stated that they do not define or report ancestral ROH and 2 (11%) were not sure how to define ancestral ROH.

When asked to distinguish between ROH resulting from uniparental disomy versus consanguinity, 13 (72.2%) laboratories stated that one large ROH on one chromosome is due to UPD whereas multiple ROH on multiple chromosomes are due to consanguinity, 2 (11%) laboratories indicated they complete additional testing to determine the cause of the ROH, 1 (5.6%) laboratory requests a family history and possible parental studies, and 2 (11%) laboratories did not know or did not define a difference.

Laboratories were asked how they define incest using percent homozygosity. Eleven (61.1%) laboratories use a threshold of >20% as indicative of incest while 5 (27.8%) use a threshold of >12.5%. Two (11.1%) do not report incest in any situation. Fifteen of 18 (83.3%) laboratories surveyed have identified a SNP microarray suggestive of parental incest. Table 1 lists the number of times each
laboratory reported observing results suggesting parental incest and the length of time they have offered a SNP microarray clinically.

**Variability of SNP Microarray Reports**

Table 2 contains the information participants reported including on SNP microarray reports. Of note, 100% of laboratories include any microdeletions/microduplications found, syndrome(s) associated with the microduplications/microdeletions, the microarray karyotype, the limitations of the testing, regions of homozygosity on their SNP microarray reports, and interpretation of findings. As shown in Table 3, variability increases when laboratories are reporting specific information about ROH. Most laboratories report the number, size, and locations of ROH as well as their recommendations based on the findings, while only 10/18 (55.5%) of the laboratories report percent homozygosity. Two of eighteen laboratories report the size, number, and locations of ROH but only for cases of suspected UPD and not for consanguinity or incest. Of those laboratories that report percent homozygosity, one laboratory states the percent is only calculated and reported for suspected cases of incest, and another only completes calculations for cases of consanguinity or incest but not for UPD. Three laboratories reported that they include a general statement about the risks associated should the ROH overlap with a recessive disorder known to map to a specific region of ROH.

Table 4 summarizes the information laboratories included on their report regarding interpretation of findings of ROH. All of the laboratories report suspected UPD, around half report when the parents are related by blood and findings of ancestral ROH, and very few report cases of incest or the specific degree of relationship. Two of fifteen (13.3%) laboratories reported that they state the suspected degree of relationship based on the ROH found; one laboratory only speculates if the case is suspicious for incest while the other speculates for both parental consanguinity and parental incest.

Laboratories decide upon a certain size threshold for reporting ROH. Seven (41.1%) laboratories require $\geq 10$Mb of ROH present before they are reported. Two (11.8%) laboratories use a threshold of
≥5Mb and another (5.9%) uses ≥8Mb. Three (17.6%) laboratories use a total percentage of the genome with a threshold of either 2% or 3%; the size of ROH used in these calculations was not specified. Two (11.8%) additional laboratories require a single segment ≥10Mb or a total percentage of the genome ≥2% or ≥3% calculated by using only ROH ≥3Mb. One laboratory (5.9%) requires the presence of 1 ROH >10Mb or two or more ROH >5Mb. Lastly, one (5.9%) laboratory requires a total of 3-5% of the genome to be homozygous using only ROH >3Mb; once this percentage is met, smaller regions >1Mb are included and added to the final calculation of percent homozygosity. One laboratory did not answer this question.

**Laboratory Duty to Report**

All eighteen laboratories surveyed felt that it was their duty to notify the ordering physician of results suggestive of consanguinity or incest. The option to elaborate was offered and thirteen of eighteen laboratories went on to explain their reasoning. Three laboratories (23%) stated that their duty only applied to cases of incest, not consanguinity. Feelings of duty to report for three (23.0%) laboratories arose from the “legal and ethical issues”, such as duty to report child abuse. Two (15.4%) laboratories stated their duty to report arose from medical necessity, as the test result may influence a diagnosis or future family planning. Two (15.4%) additional laboratories reported that they notify the ordering physician of every abnormal result, whether it shows a deletion or multiple ROH. Finally, three (23.0%) laboratories stated that they typically are made aware of parental relationship information ahead of time, but felt it was their duty to inform the ordering physician if it is new information.

Ten laboratories (55.6%) reported taking different action when a test result revealed consanguinity then when it did not reveal consanguinity. Specifically, all ten laboratories contacted the ordering healthcare provider. Four (40%) laboratories recommended that the ordering physician take additional steps such as performing clinical testing for a recessive disorder that fit with the phenotype observed and the ROH found. None of these laboratories directly contacted the authorities, social work
teams, or an ethics board. Fourteen (77.8%) laboratories reported taking different steps when a result suggested an incestuous relationship versus when a result did not suggest an incestuous relationship. All 14 laboratories reported contacting the ordering healthcare provider. Three (21.4%) recommended that the ordering physician take additional steps, two (14.3%) contacted an ethics board and one (7.1%) laboratory had contacted social work. No laboratories report contacting the authorities.

DISCUSSION

SNP microarrays detect regions of homozygosity (ROH) that can imply uniparental disomy (UPD) or parental consanguinity or incest. ROH can be used to calculate percent homozygosity, which can then be compared to known inbreeding coefficients to estimate the degree of parental relatedness. Based on findings from this study, current reporting and follow-up practices for SNP microarray ROH are variable.

Variation in SNP microarray reporting may be due to a lack of established guidelines and/or differing professional opinions regarding reportable results (See Tables 2-4). Current technology can suggest parental consanguinity or incest based on SNP microarray results. However, 8 out of 18 laboratories (44.4%) do not report the possibility of parental consanguinity and 16 (88.9%) out of 18 did not include the possibility of parental incest on their reports. There are no guidelines to suggest whether such incidental findings should be included in a laboratory report. There are multiple reasons why laboratories may choose not to report parental relationships. Some possibilities include concern that percent homozygosity may be an overestimate that is complicated by multiple generations of inbreeding or ancestral ROH. There may also be concerns about methods for calculation of percent ROH and classification of the degree of relationship, and/or inaccurate family histories. Laboratories may also think that findings of consanguinity or incest are incidental, as it was not the purpose of the SNP microarray.
Although all laboratories in this survey felt that it was their duty to notify the ordering physician when results are suggestive of consanguinity or incest, they were unclear about the proper steps to take. Some laboratories reported the decision to report ROH is based on the need for follow up medical management or testing if a recessive condition is identified; others reported the inclination to report was related to “legal and ethical issues” presented by both consanguinity and incest. For the above reasons, many laboratories report contacting the ordering physician directly to discuss results even if they do not include information in the report. Neither results of consanguinity nor results indicating incest garnered steps taken by the laboratory to contact legal authorities. In addition, only one laboratory contacted social work when incest was suspected. A reluctance to contact social work or legal authorities could be due to the lack of accessibility of a social work team, uncertainty regarding family history, uncertainty regarding additional demographic/clinical information, a lack of precedence regarding the use of SNP microarrays as proof in a legal setting, or the belief that it is the ordering physicians’ responsibility to intervene.

Microarray results suggesting homozygosity may also lead to legal dilemmas for laboratories and ordering physicians that could impact clinical practice. In the clinic, physicians must balance their duty to report abuse with the privileged physician-patient relationship that is protected by HIPAA. For example, Ohio Revised Code 2151.421 states that any individual who is a physician or health care professional is required to report to the appropriate county child services agency or police authority “in the county in which the child resides or in which the abuse or neglect is occurring or has occurred” any "facts that would cause a reasonable person in a similar position to suspect, that a child under eighteen years of age or a mentally retarded, developmentally disabled, or physically impaired child under twenty-one years of age has suffered or faces a threat of suffering any physical or mental wound, injury, disability, or condition of a nature that reasonably indicates abuse or neglect of the child . . . "

Ohio Revised Code 5123.61 extends this same requirement for individuals who are of any age with mental
retardation or developmental disability. However, these laws do not require reporting when there is evidence of an adult son or daughter with full mental capacity engaging in an incestuous relationship with his mother or father; in fact, such a report would be a violation of HIPAA.

Ohio laws require any health care professional, including laboratory personnel, to report suspicions of child abuse. However, in most circumstances, laboratory personnel do not have access to all of the information (family history information, patient mental status, age of a parent at pregnancy conception and/or psychosocial status) which might lead one to suspect child abuse. Rather they have only one piece of the puzzle, the microarray results. A more tenable approach is that either the physician alone or a physician/laboratory team assemble all of the relevant information and make a decision about whether to contact authorities.

There are several limitations to this study. Respondents identified themselves as familiar with the SNP microarray at their laboratory, reported a range of experience levels and recalled past results as well as hypothetical situations, all of which were unable to be validated by the researchers. In addition, the number of laboratories performing SNP microarrays was small.

As the number of laboratories offering SNP microarray increases, it becomes even more important to develop guidelines for reporting such incidental findings. This study demonstrates variability in the reporting practices of clinical laboratories with respect to ROH identified by SNP microarray. It also highlights differences in reporting practices and actions taken for follow-up of such results. This study supports the need for laboratory guidelines as first suggested by Schaaf et al. (2011) following incidental detection of ROH in order to help laboratories address legal and ethical dilemmas that may arise. Such guidelines will ensure consistency in reporting and follow-up and enable laboratories to take the recommended steps when genetic testing suggests parental consanguinity or incest. The concerns identified in this study will be amplified as the capability to detect parental consanguinity or incest extends to other genetic tests, such as whole exome/whole genome
sequencing\textsuperscript{22,23}. It is imperative that the genetics community develop guidelines to address these concerns both in the laboratory and in the clinic.
Part II:

Variability in Genetic Counseling Practices for Regions of Homozygosity Associated With Parental Consanguinity or Incest
MATERIALS AND METHODS

Participants and Procedures

The study population included genetic counselors who are members of The National Society of Genetic Counselors (NSGC) and clinical geneticists with email addresses listed on genetics websites of major centers throughout the United States. The survey was made available to 2064 genetic counselors who were members of NSGC and 305 clinical geneticists. NSGC members were contacted by direct email three times over a 6 week period. NSGC members were also alerted about the study by a NSGC List serv and discussion forum post. Clinical geneticists were first contacted directly by email with the initial request for participation, a second time two weeks later as a reminder, and a third time one month later as a final reminder.

An eligibility question asked if the respondent had ever “ordered or counseled for a SNP microarray or any array platform that includes a SNP backbone for a patient at any point in his/her career.” Respondents who selected “no” were excluded from this study while respondents who selected “yes” met the inclusion criteria for the survey. This study was approved by Cincinnati Children’s Hospital Medical Center and The University of Cincinnati Institutional Review Boards (Study # 2011-1248).

Survey Development

A thirty-five item survey was developed using SurveyMonkey® to 1) assess the pre-test and post-test counseling practices of genetic counselors and geneticists relating to regions of homozygosity (ROH) on SNP microarrays, 2) elicit the comfort level and feelings of genetic counselors and geneticists surrounding receiving and counseling for SNP microarray results suggesting consanguinity or incest, and 3) assess genetic counselors and geneticists familiarity with the laws regarding health care professionals’ duty to report incest, child abuse, and statutory rape and familiarity with laws regarding degrees of relationships in their state of practice. The survey included five open-ended questions and thirty close-
ended questions (See Appendix C). The survey was developed by the project team using knowledge gained from discussions with colleagues regarding pre-test and post-test counseling techniques, comfort level surrounding results suggesting consanguinity and incest, and uncertainty about laws regarding such findings in a clinical setting. Respondents were sent a link to the online survey on SurveyMonkey.com through their email, the NSGC listserv, or the NSGC discussion forum.

Survey Measures

Demographic and professional characteristics

Demographic information collected included the respondent’s gender, ethnicity, occupation, and age. Professional characteristics included years of experience seeing patients in a clinical setting, current region of practice, the percentage of SNP microarrays ordered in each clinical setting, and if the respondent had ever ordered or counseled for a SNP microarray or any array platform that included a SNP backbone for a patient.

Pre-test and Post-test counseling for SNP microarray

The pre-test counseling procedures of genetic counselors and clinical geneticists were assessed with two questions. The first question asked respondents to select the items on which they typically provided pre-test counseling for a SNP microarray. The options included test methodology, test objective, type of sample required, possible outcomes, price, providing a consent form to be signed, none of the above, and an “other” section for open-ended responses.

The second question further assessed pre-test counseling about specific possible outcomes of the SNP microarray. Respondents were asked to select which items they typically discussed with patients from the following: the test may not find any clinically significant abnormalities, the test may find clinically significant abnormalities which are known to be associated with a genetic condition, the test may find a result of uncertain significance, the findings from the test may need to be followed up by parental testing, and the test is capable of finding microdeletions/microduplications, chromosome
imbbalances, regions of homozygosity, parental blood relationship based on regions of homozygosity, uniparental disomy, adult-onset disorders, and x-linked disorders which may impact reproductive risk.

To assess what information respondents have to post-test counsel about, they were asked to recall the information typically included in SNP microarray reports they receive from a laboratory. In addition, they were asked to select the type of information that was included in the SNP microarray report specifically related to ROH and possible explanations for the presence of ROH. Respondents also reported their ability to calculate percent homozygosity or described their access to help with this calculation.

Post-test counseling practices and follow-up methods were assessed by eight questions. The first included information typically discussed with the patient after receiving a SNP microarray report. Respondents were then asked their first and subsequent steps taken when SNP microarray results suggested an incestuous relationship, and the first and subsequent steps taken by the respondent when SNP microarray results suggested a consanguineous relationship. Respondents were also asked what ethical concerns arose when a report suggested an incestuous or a consanguineous relationship. Professionals who had not previously experienced results of consanguinity or incest were asked to answer in a hypothetical manner. In addition, respondents were asked to “briefly describe a session where you informed a patients or family about SNP microarray results that suggested consanguinity incest.”

Comfort Level and Feelings after Receiving Results Suggesting Consanguinity or Incest

Respondents were asked to report their level of comfort when they received SNP microarray results that suggested consanguinity or incest. Further questions were asked to elucidate the reason for comfort/discomfort in each scenario. In addition, to target ideas that would help increase comfort level, respondents were asked to suggest additional information that would be helpful in interpreting ROH and reporting its presence to patients and families. Respondents also were asked if they would like to
see a statement given from their professional organization regarding a SNP microarray report that has ROH indicative of consanguinity or incest. Finally, respondents were asked an open-ended question so that they could “describe any personal moral concerns that have arisen when a report suggested that a patient was the product of a consanguineous relationship.”

**Familiarity with Laws Regarding Duty to Report and Degrees of Relationships**

The definition of an incestuous relationship was selected by respondents. Those who knew how to calculate percent homozygosity were asked to define an incestuous relationship by a percentage. The individuals who had not personally calculated percent homozygosity were asked to define an incestuous relationship by selecting statements including examples of degrees of relatedness. The survey then assessed their familiarity with the laws in their state regarding the health care professional’s duty to report incest, child abuse, and statutory rape. They were also asked to report their familiarity with the laws in their state regarding first cousin, second cousin, and third or more distant cousin relationships. Lastly, individuals were asked to report how many times they had received a SNP microarray result suggesting consanguinity and the amount of times they had received a result suggesting incest.

**Data Analysis**

This survey was conducted between September and December, 2011. The data was sorted and prepared for analysis by the SurveyMonkey® software. Incomplete answers were excluded and removed from the final analysis. Frequencies were reported for close-ended questions. The responses to open-ended questions were post-coded and reported according to common themes. As both genetic counselors and geneticists responded to the survey, a comparison between specialties was considered. However, with only 40 geneticists participating, the sample size made the groups too small to compare. Additionally, since some institutions may have policies regarding counseling for ROH, counseling
practices may be more likely to vary by institution, rather than specialty, particularly since genetic counselors and geneticists often work together to counsel their patients.

RESULTS

Demographic and Professional Characteristics

The inclusion question “Have you ordered or counseled for a SNP microarray or any array platform that includes a SNP backbone for a patient at any point in your career?” was answered by 394 respondents. Only 240/394 (60.9%) responded with “yes,” which qualified them to continue on answering the survey. Of the 240 respondents, 171 reported their occupation. One hundred and nineteen (69.6%) were clinical genetic counselors, 40 (23.3%) were clinical geneticists, 6 (3.5%) were clinical and laboratory genetic counselors, 2 (1.2%) were genetics residents, 2 (1.2%) were laboratory genetic counselors, 1 (0.6%) was a laboratory director and 1 (0.6%) was a clinical and research genetic counselor. Of 171 respondents, 146 (85.4%) were female and 25 (14.6%) were male. Respondents were asked to select the amount of time they had spent seeing patients in a clinical setting over the duration of their career. Of 171 respondents, 28 (16.4%) said 0-2 years, 32 (18.7%) said 3-5 years, 25 (14.6%) said 6-8 years, 17 (9.9%) said 9-11 years, 8 (4.7%) said 12-14 years, and 61 (35.7%) said greater than 15 years.

The surveyed individuals reported most commonly ordering SNP microarrays for patients in the pediatric and prenatal settings.

Pre-test and Post-test Counseling for SNP Microarray

Pre-test Counseling for SNP Microarray

Respondents were asked to select the information they typically pre-test counseled their patients about. 98.1%, 94.3%, and 88.0% of respondents pre-test counseled about the objective of the test, the possible outcomes of the test, and the type of sample required, respectively (Table 5).

Respondents were required to select examples of possible outcomes typically stated during a pre-test counseling visit. Seventeen (8.1%) respondents reported only pre-test counseling patients that SNP
microarray detects ROH, 16 (7.7%) reported only pre-test counseling that ROH can indicate a parental blood relationship, and 37 (17.7%) reported pre-test counseling about both (Table 6).

Post-test Counseling for SNP Microarray

To better assess what the respondents were post-test counseling about, they were asked to describe the typical SNP microarray report they receive from the laboratory. One hundred and twenty-four (66.7%) reported that ROH was included. Specifically, 110 (59.1%) stated the results report included the size of the ROH found, 106 (57.0%) stated the report included the locations of the ROH, 98 (52.7%) stated the report included the number of ROH, 61 (32.8%) stated the report included percent homozygosity and 57 (30.6%) stated the report included the implications of ROH. Respondents also reported possible explanations given by laboratories to explain the presence of ROH. According to respondents, 86 (46.2%) individuals had seen consanguinity listed as a possible outcome, 82 (44.1%) had seen uniparental disomy, 48 (25.8%) had seen ancestral ROH described, 33 (17.7%) had seen the phrase “parents are related by blood,” and 29 (15.6%) had seen an incestuous relationship listed as a possible explanation.

Individuals were also asked if they had ever calculated percent homozygosity (Froh) to define a parental relationship for a clinical patient. Of 209 respondents, 30 (14.4%) had personally calculated Froh, 60 (28.7%) had not personally calculated Froh but have had it calculated for them on a report, and 119 (56.9%) had never seen or calculated percent homozygosity.

Respondents were asked to select the information they discussed with patients once a result report was received (Table 7). The respondents who had previously received a result suggesting consanguinity were asked what their first step upon receiving this result was. Fifty one (48.1%) respondents reported their first step taken was to compare the results to the reported pedigree (Table 8). After the initial step taken, respondents selected additional steps that were completed. Seventy eight (73.6%) respondents’ reported their additional steps included discussing the result with the
patient and/or parents/guardian. Eight (7.5%) reported researching the literature for guidelines on the appropriate steps of action and 14 (13.2%) reported researching the literature for similar cases (Table 9). Lastly, respondents were asked what ethical concerns they felt could arise when a report suggested that the patient was a product of a consanguineous relationship. Fifty six (45.3%) did not feel any ethical concerns arose and 42 (39.6%) felt that an ethical concern arose when disclosing the relationship to the parents (Table 10).

The respondents who had never received a result suggesting consanguinity were asked the same three questions in a hypothetical manner. Twenty nine (39.2%) respondents selected that they would first compare the results to the reported pedigree and 19 (25.7%) reported they would discuss the results with a colleague first (Table 8). Forty nine (66.2%) reported they would then discuss the results with a colleague and 38 (51.4%) reported they would then discuss the results with the patient and/or parents/guardian. In contrast to those who had previously received a result suggesting consanguinity many more researched the literature when they did not have any previous experience to use as a starting point. Specifically, 26 (35.1%) respondents reported researching the literature for guidelines on the appropriate steps of action and 17 (23.0%) respondents reported researching the literature for similar cases (Table 9). Respondents were asked what potential ethical concerns could arise when receiving a result suggesting consanguinity. Forty nine (66.2%) respondents stated that disclosure of the relationship to the parents is a potential ethical concern for them. In addition, 48 (64.9%) individuals reported disclosure of the parental relationship to the patient is a potential ethical concern (Table 10).

Respondents were also asked if they had received a result suggesting an incestuous relationship. The 66 respondents who had previously received a result suggesting incest were asked about the first step they took upon receiving such a result. Twenty three (34.8%) respondents reported their first step was to compare the results to the reported pedigree, 14 (21.2%) reported that they gathered more
information from the laboratory and 13 (19.7%) reported that they discussed the results with a colleague (Table 11). Subsequent steps that were taken were also reported. Forty five (69.2%) respondents stated that they then discussed the results with the patient and/or parents/guardian and 32 (49.2%) stated they then discussed the results with a colleague (Table 12). Only 10 (15.4%) researched the literature for guidelines on the appropriate steps of action and 12 (18.5%) researched the literature for similar cases. Respondents selected which ethical concerns might arise if they received a result suggesting an incestuous relationship. The most common ethical concern that arose when respondents received a result suggesting incest was disclosure of the relationship to the parents as reported by 44 (68.8%) respondents. The second most common issue was reported by 34.3% as having legal concerns regarding the potential for an illegal relationship. Additional concerns were reported surrounding disclosure of the relationship to the authorities (32.8%) and healthcare providers giving incomplete consent prior to testing (23.4%) (Table 13). Twenty respondents (31.3%) had the opposite response and stated that they did not feel any ethical concerns arose when a SNP microarray report suggested incest.

The same three questions were asked in a hypothetical manner of individuals who had never received a results report suggesting an incestuous relationship. Thirty nine (33.3%) respondents stated that they would first compare the results to the reported pedigree, 35 (29.9%) respondents stated they would discuss the results with a colleague, and 30 (24.8%) respondents stated they would gather more information from the laboratory (Table 11). Subsequent steps that would be taken include: 58 (50.9%) respondents stated they would also discuss the results with the patient and/or parents/guardian, 55 (48.2%) stated they would then discuss the results with a colleague, and 54 (47.4%) stated they would then consult an ethics team (Table 12). Similarly to those who had never received a result suggesting consanguinity, those who had never received a result suggesting incest searched the literature more often than those who had previous experienced with a result suggesting incest. Specifically, 56 (49.1%)
stated they would then research the literature for guidelines on the appropriate steps of action and 27 (23.7%) researched the literature for similar cases (Table 12). Some ethical concerns that respondents felt could arise surrounded disclosure of the relationship to the patient (82.9%) and disclosure of the relationship to the parents (80.3%). Eighty nine (76%) felt that an ethical concern would arise due to the potential of an illegal relationship and 75 (64.1%) felt that an ethical concern would arise around disclosing the relationship to the authorities (Table 13). Zero respondents stated that there were no ethical concerns that could arise if incest was suggested on a SNP microarray report.

Respondents were asked how many times they had received a results report suggesting an incestuous relationship. Of 186 responses, 119 (64%) said zero, 59 (31.7%) said 1-3, 7 (3.8%) said 4-6, zero said 7-9, 1 (0.54%) said 10-12, and zero had seen more than 12. Respondents were also asked how many times they received results suggesting a consanguineous relationship. Of 185 responses, 77 (41.6%) said zero, 57 (30.8%) said 1-3, 32 (17.3%) said 4-6, 4 (2.2%) said 7-9, 5 (2.7%) said 10-12, 1 (0.54%) said 13-15, and 9 (4.9%) said greater than 15 times.

Open-ended responses provided additional insight into genetic counselors’ and geneticists’ personal experiences receiving and counseling results suggesting consanguinity or incest. When describing scenarios that occurred in a counseling session, the following scenarios emerged: parental acknowledgement of relationship occurred prior to running the SNP microarray, parental denial of relationship when results were received, parental acknowledgement of relationship when results were received, providers request for legal or ethical team’s advice, the relationship was truly previously unknown to parents, revelation of results to a guardian who is not the biological parent, and using cultural explanations to explain the suspected relationship when results are received. Respondents also gave examples for how they counsel a result suggesting consanguinity or incest (Table 16).
Comfort Level and Feelings When Receiving Results Suggesting Consanguinity or Incest

Genetic counselors and geneticists were asked to describe their comfort level when receiving and discussing results suggesting both consanguinity and incest. Ninety nine (57.3%) reported feeling very comfortable or comfortable and 19 (11.0%) reported feeling uncomfortable or very uncomfortable when receiving results suggesting consanguinity. The remaining 55 (31.7%) individuals reported feeling neutral. Twenty nine (17.0%) reported feeling very comfortable or comfortable and 110 (64.3%) reported feeling uncomfortable or very uncomfortable when receiving results suggesting incest. The remaining 32 (18.5%) individuals reported feeling neutral.

When asked to select their reasons for comfort or discomfort when receiving a SNP microarray result suggesting consanguinity or incest, 46 (26.6%) report being comfortable overall. Sixty seven (38.7%) respondents reported feeling uncomfortable because of uncertainty regarding the accuracy of the microarray to predict the reported relationship, 56 (32.4%) respondents reported feeling uncomfortable because of a lack of institutional guidelines regarding how to act upon such results, 54 (31.2%) respondents reported feeling uncomfortable because of a lack of professional guidelines regarding how to act upon such results and 6 (3.5%) respondents reported feeling uncomfortable because they were not aware SNP microarrays could detect such information.

Respondents were asked to describe their feelings surrounding counseling a patient about the results of a SNP microarray that suggest consanguinity or incest. Fifty two (30.1%) reported generally feeling comfortable when counseling results suggest consanguinity or incest because they provided pre-test counseling their patients that a parental relationship could be detected by the technology, 37 (21.4%) respondents reported feeling uncomfortable when counseling about these results because they felt unprepared to deal with issues surrounding discovery of a parental relationship, and 28 (16.2%) respondents felt uncomfortable when counseling these results because they did not know how to accurately interpret the data. Additionally, 5 (2.9%) individuals reported feeling uncomfortable because
they either elected not to or were instructed not to discuss the information about a parental relationship.

Respondents were asked to describe what additional information would be helpful in interpreting results detailing regions of homozygosity. Of all responses, the most common included: 14 respondents (23%) would like more information on the regions affected, genes in the regions, and association of those genes with recessive conditions, 5 (8.1%) would like to know the degree of relationship suspected, 5 (8.1%) would like to know the accuracy of the degree of a relationship when it is provided, and 4 (6.6%) would like to be know their professional organization guidelines. In addition, of 173 respondents, 149 (86.1%) stated that they would like to see a statement from their professional organization regarding regions of homozygosity and consanguinity.

Respondents were then asked to describe their moral concerns when a result suggested the patient was the product of a consanguineous relationship. From the 22 individuals who responded, the following concerns arose: the results could be damaging to the family dynamics, the results may not be fully accurate/there is an alternative explanation, the family may have already denied such a relationship or given a different relationship than the one found, and the mother may be in a potentially dangerous situation. Others stated that they did not have any moral concerns regarding consanguinity as a result because the consanguinity was mostly found in cultures where it was accepted or encouraged.

**Familiarity with Laws Regarding Duty to Report and Degrees of Relationships**

The definition of incest as provided by respondents varied. Using percent homozygosity, 33 (37.9%) defined incest as Froh >25%, 8 (9.2%) defined incest as Froh > 20%, and 16 (18.4%) defined incest as Froh >12.5%. Thirty (34.5%) respondents selected “Other.” Ten respondents who selected “Other” stated that they were unsure of their definition, 10 stated they do not define incest using Froh, 4 stated they do not use the term incest, 4 stated they do not believe Froh can give an accurate
estimated of relationship, and 2 stated they rely on the laboratory to define Froh. Using vocabulary to describe an incestuous relationship, 28 (23.7%) defined incest as a sexual relationship between first degree relatives including a parent and child or between siblings. Eighty five (72.0%) respondents defined incest as a sexual relationship between first degree relatives including a parent and child or between siblings or between second degree relatives including an aunt/uncle and niece/nephew, between half siblings, or between a grandparent/grandchild. Five additional responses (4.2%) of people selected “Other.” One respondent suggested use of their state of practice laws, another respondent stated a relationship between relatives, one stated cultural preferences define incest, and two stated that this did not apply.

This survey assessed respondents’ familiarity with the laws in their state regarding the health care professionals’ duty to report incest, the health care professionals’ duty to report child abuse, and the health care professionals’ duty to report statutory rape. The majority of respondents (78.6%) reported themselves to be extremely or moderately familiar with their duty to report child abuse. This number decreased to 47.7% for respondents who reported they were extremely or moderately familiar with their duty to report statutory rape. Only one-fifth or 20.2% of the respondents reported that they are extremely or moderately familiar with their duty to report incest (Table 14).

Respondents also stated their familiarity with the laws in their state regarding first, second, and third or more distant cousin relationships. The responses to this question were more evenly split between respondents who reported that they felt extremely or moderately familiar with those that reported that they were slightly or not at all familiar. Seventy-two respondents (41.6%) felt extremely or moderately familiar with laws regarding first cousin relationships while 75 (43.3%) reported feeling slightly or not at all familiar. Sixty-nine respondents (39.9%) felt extremely or moderately familiar with laws regarding second cousin relationships while 80 (46.2%) reported feeling slightly or not at all familiar. Seventy-four respondents (42.8%) felt extremely or moderately familiar with laws regarding
third or more distant cousin relationships while 77 (44.5%) reported feeling slightly or not at all familiar (Table 15).

**DISCUSSION**

SNP microarrays can detect ROH associated with both consanguinity and incest. It was previously unknown how clinical providers responded to results suggesting consanguinity or incest. The current study found that pre-test and post-test counseling techniques of genetic counselors and geneticists for ROH detected by SNP microarrays are variable. In addition, provider’s comfort level and feelings receiving results suggesting consanguinity or incest also vary. These variations could be based on experience, degree of relationship, and/or concerns about accuracy. Lastly, respondents’ knowledge of laws surrounding cousin relationships and duty to report incest, child abuse, and statutory rape differ.

**Pre-test and Post-test counseling for SNP Microarray**

*Pre-test Counseling for SNP Microarray*

Less than one-fifth of respondents reported that they pre-test counseled their patients about the possibility of finding regions of homozygosity and that they pre-test counseled that ROH can provide information about parental blood relationships. These findings suggest that a majority of families are not being informed about the capability of SNP microarray to detect a parental blood relationship. As information about ROH and parental relatedness is often left out, proper informed consent is not being obtained. Slightly over a third of those responding stated that they provide a consent form to the patient or family, although the form may not include the possibility of finding regions of homozygosity and the implications. Providers not pre-test counseling about the possibility of parental relatedness encounter difficulties when the results come back and they must perform post-test counseling about an incidental finding that the family is not expecting or prepared to discuss. Families who are uninformed of the possibility of discovering a parental blood relationship may feel surprise, shock, and even shame at discovering their relationship has been revealed through SNP microarray testing.
Post-test Counseling for SNP Microarray

Respondents were asked to discuss the first step and additional steps taken when a test result suggests consanguinity or incest. Regardless of experience, respondents felt that their first step in the case of either result would be to compare the results to the reported pedigree. Additional steps varied between respondents, but there were several themes that arose. Individuals who never experienced a result suggesting consanguinity or incest selected that they would be likely to contact the laboratory for more information, search the literature for guidelines or case reports detailing previous instances of results suggesting parental relatedness, and even discuss the result with colleagues to gain perspective. Those who had actually received a result suggesting consanguinity or incest selected the same responses, but much less often. Those who have dealt with the situation before may have already worked through the potential ethical, legal, and moral issues that could arise and therefore would need less assistance with such matters. In addition, experienced providers may already be aware of the lack of guidance the literature has to offer about how to handle test results suggesting consanguinity or incest and decide to forgo putting time into research in those areas. Lastly, decisions about steps to take could vary due to potential differences in a hypothetical question versus being faced with a real life situation of incest or consanguinity.

Information provided about first and additional steps taken provided insight into what genetic counselors and geneticists are doing to inform families about findings of ROH and the fact that findings of ROH can suggest parental relatedness. Slightly less than half of the respondents reported post-test counseling on parental relatedness suggested by SNP microarray results which means that only around half of respondents are revealing results to their patients in the clinical genetics setting. This trend could be also true for other specialties who may feel less equipped to handle this type of result. Additionally, only slightly more than half of people counsel on the clinical implications of ROH such as its usefulness in finding areas that may harbor an autosomal recessive condition. One explanation for a lack of post-test
counseling on parental relatedness could be that providers do not see the benefit in sharing such results with their patients. They also may feel that the revelation of this relationship could cause harm to the family dynamics, put the provider in an uncomfortable situation, or even damage the relationship between the provider and the patient or family. In the eyes of the provider, the potential downfalls just stated could outweigh any benefits.

When respondents are broken into groups of those with experience receiving results of consanguinity and incest, the responses differ. Those who have experienced either consanguinity or incest results reported informing the parents about the results of consanguinity or incest around 70% of the time. Respondents who have not experienced results of consanguinity or incest stated that they would inform the family of results of consanguinity or incest around 50% of the time. Additionally, respondents were more likely to contact authorities and/or an ethics team for incest than consanguinity, although both instances were rare. Not all providers are contacting the authorities based on SNP microarray results that suggest a parental relationship. It is unclear when it is obligatory for the healthcare provider to report findings of consanguinity or incest, and this may vary by state. It would be helpful for providers to know when they have the duty to report a suspected relationship and what type of information is necessary for them to report an incestuous or consanguineous relationship in a legal setting.

Those who requested involvement of an ethical team or legal authorities were in the minority; however, from an ethical standpoint, there are many factors to consider when determining if parental relatedness should be discussed with families or the authorities including beneficence, nonmaleficence, confidentiality, and autonomy of the patient.\textsuperscript{24} When promoting beneficence, or the well-being of others, providers must balance the benefits against the harms while at the same time balance nonmaleficence (to not inflict harm).\textsuperscript{24,25} Perhaps providers wished to protect the well-being of patients and families and were reluctant to hurt family relationships by providing this information. It is also
possible that providers felt the confidentiality and respect for autonomy outweighed the need to involve an ethics team or the authorities.\textsuperscript{24,25} It is important to consider that there are true benefits to finding ROH as this can give providers an idea of where in the genome to start looking for autosomal recessive conditions.

This survey highlighted many challenges of post-test counseling patients and their families about results that suggest consanguinity or incest. Several respondents stated that they wished they had pre-test counseled about the potential for a result suggesting parental relatedness so that the family was aware of this potential outcome. In addition, respondents mentioned that when physicians from other medical specialties order SNP microarrays, the genetics provider may not be aware of what information, if any, has been given to the patient in the pre-test counseling session. This uncertainty resulted in discomfort when discussing results with the patient. Therefore, we suggest that genetic counselors and geneticists as well as all health care providers begin to develop procedures for pre-test counseling to prepare patients for all possible outcomes so that patients are truly providing informed consent when they agree to testing. Information on the potential for finding parental relatedness could also be included in a consent form from the institution or laboratory running the SNP microarray or in their verbal discussion of the testing which could combat the time taken away from other counseling needed in the session.

**Comfort Level and Feelings Surrounding Receiving Results Suggesting Consanguinity and Incest**

Providers were asked to describe their comfort level receiving results suggesting consanguinity. The majority of respondents felt comfortable or neutral when receiving a result suggesting consanguinity which may reflect awareness of cultural norms. Consanguineous marriage is often preferred in certain cultures due to religious, social, and political factors that play a role in selecting a spouse.\textsuperscript{11} Consanguineous marriages account for 20-30% of all marriages in some populations.\textsuperscript{11} The sizeable presence of consanguineous marriages means that health care providers will likely encounter
parents who are related in their practice. However, in this study, only slightly over half of the respondents had previously experienced a result suggesting consanguinity. This could be due to laboratories not reporting ROH or not offering an explanation for ROH that included the possibility of consanguinity. Contrary to results suggesting consanguinity, respondents were mostly uncomfortable receiving results suggesting incest. This difference could be due to the fact that a result suggesting incest has not been experienced as frequently by the majority of providers, incest involves a closer degree of relationship between relatives and is more likely to have ethical/legal implications, or that providers did not pre-test counsel that a parental relationship could be found.

It is likely that discrepancies in family histories that do not report consanguinity or incest may cast doubt on the accuracy of molecular findings and result in discomfort for providers. A previous study found that in some scenarios, discrepancies in consanguinity as reported by family history vs. molecular testing can be explained by the fact that the family is from an isolated population or are distant relatives and are unaware of their relationship, the relationship is known but the family has chosen not to disclose this information, or that certain patient ethnicities have multiple generations of consanguinity which would result in more ROH than expected. In addition, it is common for families have to incomplete or inaccurate information about their family history.26,27

To begin to address the discomfort respondents felt due to inexperience or moral/ethical concerns, the survey asked what information would be useful in interpreting results of ROH and describing these to their patients. Respondents stated that they needed more information on the regions affected, genes in those regions, the association of those regions with recessive disease as well, and assistance in understanding percent homozygosity. They also requested more information on the degree of the parental relationships suspected and the accuracy of this suspicion. This information could be useful during the creation of consistent guidelines for both laboratories providing results reports and genetics professionals counseling for ROH. The majority of respondents would like to see a
statement from their professional organization regarding how to properly handle situations where test results suggest consanguinity or incest to help combat their discomfort.

**Familiarity with Laws Regarding Duty to Report and Degrees of Relationships**

This survey has shown that providers are very familiar with their duty to report child abuse. Their familiarity could be due to training given to all healthcare providers by their employers or training during educational programs when studying to become a genetics professional. Respondents’ understanding of a duty to report incest, however, is much less well known. Findings of incest were not readily available by genetic testing until the use of genome wide SNP microarray tests. With the rise of next-generation sequencing and continued use of SNP microarrays, the availability of results suggesting incest will only increase. Therefore, it is important that genetics professionals familiarize themselves with the laws in their state regarding incest.

Respondents were split evenly regarding their familiarity or lack of familiarity with laws regarding first, second, and third or most distant cousin relationships. Similar to results suggesting incest, some of this lack of knowledge could be due to the recent introduction of genetic testing capable of finding ROH that implies cousin relationships. However, the fact that an almost equal portion of respondents stated familiarity with these laws shows that consanguinity is being seen in patients receiving care in the United States. This may be due to the influx and increased acceptance of various cultures in the United States or even due to a decline in social stigma surrounding these relationships.

**Limitations**

There are several limitations to this study. Respondents were a motivated population who were willing to take the time to complete a survey online so there is a possibility of selection bias, the survey population of geneticists was limited and may not be representative of all geneticists, and respondents differed in experience levels with ROH and SNP microarray results. Recall bias, the ability of
hypothetical responses to predict actual behavior, and generalizability of results are all possible limitations of this study.
CONCLUSION

As the number of laboratories offering SNP microarray increases, and new genetic testing become available, it becomes even more important to develop guidelines for reporting of incidental findings such as ROH that suggests parental consanguinity or incest. This study demonstrates variability in the reporting practices of clinical laboratories with respect to ROH identified by SNP microarray. It also highlights differences in follow up practices by the laboratories surveyed. There are legal and ethical dilemmas surrounding the detection of a suspected illegal consanguineous or incestuous relationship that laboratories are currently unequipped to deal with as a whole. Collaboration between professional organizations and laboratories is necessary to make decisions on how to proceed with such findings in terms of notification of providers, patients, and proper authorities.

Similarly, as the number of providers ordering SNP microarrays increases, it is necessary to develop guidelines for pre-test and post-test counseling regarding incidental detection of ROH. This study has demonstrated the variability in pre- and post-test counseling comfort level with receipt of such results, and action taken upon discovery of consanguineous or incestuous relationships. Without proper pre-test counseling by health care providers, patients, their families, and their providers will continue to be surprised by results suggesting parental relatedness and health care providers will be looking for guidance on how to properly handle these situations. Comfort level of health care providers, found to be variable in this study, can be increased by giving providers knowledge on steps to take, consent information to provide, and counseling techniques to use when they find themselves in a situation with a patient or family where parental relatedness is found. Additionally, education of providers about the laws in their state regarding cousin relationships and their duty to report incest can help to increase their comfort level with receipt of results suggesting consanguinity or incest.

This study supports the need for both laboratory and provider guidelines following incidental detection of ROH in order to help laboratories address legal and ethical dilemmas that may arise. The
concerns identified in this study will be amplified as the capability to detect parental consanguinity or incest using regions of homozygosity extends to other genetic tests, such as whole exome/whole genome sequencing. It is imperative that the genetics community develop guidelines to address these concerns both in the laboratory and in the clinic.
REFERENCES


### Table 1: Number of Incest Cases and Years of running a SNP microarray

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<tr>
<td>13</td>
<td>1-3</td>
<td>1-2 years</td>
</tr>
<tr>
<td>14</td>
<td>4-6</td>
<td>2-3 years</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>No response</td>
</tr>
<tr>
<td>16</td>
<td>10-12</td>
<td>2-3 years</td>
</tr>
<tr>
<td>17</td>
<td>&gt;15</td>
<td>1-2 years</td>
</tr>
<tr>
<td>18</td>
<td>7-9</td>
<td>2 years</td>
</tr>
<tr>
<td>Variable</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Interpretation of findings</td>
<td>18</td>
<td>100</td>
</tr>
<tr>
<td>Microdeletions/microduplications found</td>
<td>18</td>
<td>100</td>
</tr>
<tr>
<td>Syndrome(s) associated with microdeletions/microduplications found</td>
<td>18</td>
<td>100</td>
</tr>
<tr>
<td>Microarray karyotype</td>
<td>18</td>
<td>100</td>
</tr>
<tr>
<td>ROH</td>
<td>18</td>
<td>100</td>
</tr>
<tr>
<td>Limitations of testing</td>
<td>18</td>
<td>100</td>
</tr>
<tr>
<td>Other appropriate testing</td>
<td>17</td>
<td>94.4</td>
</tr>
<tr>
<td>Recommendation for referral for genetic counseling</td>
<td>17</td>
<td>94.4</td>
</tr>
<tr>
<td>Clinical Implications</td>
<td>16</td>
<td>88.9</td>
</tr>
<tr>
<td>Suggestions for management techniques of an identified disorder</td>
<td>3</td>
<td>16.6</td>
</tr>
<tr>
<td>References</td>
<td>17</td>
<td>94.4</td>
</tr>
<tr>
<td>Methodology</td>
<td>17</td>
<td>94.4</td>
</tr>
<tr>
<td>Variable</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>----</td>
<td>-----</td>
</tr>
<tr>
<td>Number of these regions</td>
<td>15</td>
<td>83.3</td>
</tr>
<tr>
<td>Size of these regions</td>
<td>17</td>
<td>94.4</td>
</tr>
<tr>
<td>Locations of these regions</td>
<td>16</td>
<td>88.9</td>
</tr>
<tr>
<td>Percent of the genome the regions encompass</td>
<td>10</td>
<td>55.5</td>
</tr>
<tr>
<td>Recommendations for findings</td>
<td>16</td>
<td>88.9</td>
</tr>
<tr>
<td>Variable</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----</td>
<td>-----</td>
</tr>
<tr>
<td>Uniparental Disomy</td>
<td>18</td>
<td>100</td>
</tr>
<tr>
<td>Ancestral ROH</td>
<td>8</td>
<td>44.4</td>
</tr>
<tr>
<td>Incest</td>
<td>1</td>
<td>5.6</td>
</tr>
<tr>
<td>Parents related by blood</td>
<td>10</td>
<td>55.6</td>
</tr>
<tr>
<td>Degree of relationship suspected*</td>
<td>2</td>
<td>13.3</td>
</tr>
</tbody>
</table>

*Data only available from 15 laboratories
Table 5: What items do you typically discuss when pre-counseling a patient before ordering a SNP microarray?

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective of the test</td>
<td>205</td>
<td>98.1</td>
</tr>
<tr>
<td>Possible outcomes</td>
<td>197</td>
<td>94.3</td>
</tr>
<tr>
<td>Type of sample required</td>
<td>184</td>
<td>88</td>
</tr>
<tr>
<td>Prices</td>
<td>129</td>
<td>61.7</td>
</tr>
<tr>
<td>Test methodology</td>
<td>129</td>
<td>61.7</td>
</tr>
<tr>
<td>Provide a consent form</td>
<td>77</td>
<td>36.8</td>
</tr>
<tr>
<td>None of the Above</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 6: Which of the following possible outcomes of a SNP microarray do you typically discuss with a patient during the pre-counseling process?

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>The test may not find any clinically significant abnormalities</td>
<td>203</td>
<td>97.1</td>
</tr>
<tr>
<td>The test may find clinically significant abnormalities that are known to be associated with a genetic condition</td>
<td>202</td>
<td>96.7</td>
</tr>
<tr>
<td>The test may find a variant of uncertain significance</td>
<td>200</td>
<td>95.7</td>
</tr>
<tr>
<td>The findings from this test may result in a need to test one or both parents to assess significance</td>
<td>196</td>
<td>93.8</td>
</tr>
<tr>
<td>The test is capable of detecting chromosome imbalances - loss or gain of regions</td>
<td>177</td>
<td>84.7</td>
</tr>
<tr>
<td>The test is capable of detecting hundreds of microdeletions/microduplications associated with genetic syndromes</td>
<td>140</td>
<td>67</td>
</tr>
<tr>
<td>The test is capable of detecting regions of homozygosity</td>
<td>17</td>
<td>8.1</td>
</tr>
<tr>
<td>The test is capable of detecting a parental blood relationship based on regions of homozygosity</td>
<td>16</td>
<td>7.7</td>
</tr>
<tr>
<td>The test is capable of detecting regions of homozygosity and detecting a parental blood relationship based on regions of homozygosity</td>
<td>37</td>
<td>17.7</td>
</tr>
<tr>
<td>The test is capable of detecting adult onset disorders</td>
<td>39</td>
<td>18.7</td>
</tr>
<tr>
<td>The test is capable of detecting uniparental disomy</td>
<td>36</td>
<td>17.2</td>
</tr>
<tr>
<td>The test is capable of identifying X-linked disorders which may impact future reproductive risks</td>
<td>20</td>
<td>9.6</td>
</tr>
<tr>
<td>I don't discuss possible outcomes</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>None of the above</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 7: After you obtain a SNP microarray report, which of the following do you typically discuss with your patients? (Choose all that apply)

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microdeletions/Microduplications</td>
<td>177</td>
<td>95.2</td>
</tr>
<tr>
<td>Syndromes associated with microdeletions/microduplications found</td>
<td>178</td>
<td>95.7</td>
</tr>
<tr>
<td>Other appropriate testing (ex. Parents, siblings)</td>
<td>155</td>
<td>83.3</td>
</tr>
<tr>
<td>Suggestions for management techniques of an identified disorder</td>
<td>122</td>
<td>65.6</td>
</tr>
<tr>
<td>Clinical implications of ROH</td>
<td>116</td>
<td>62.4</td>
</tr>
<tr>
<td>Implications for parental relatedness</td>
<td>90</td>
<td>48.4</td>
</tr>
<tr>
<td>Uniparental disomy</td>
<td>85</td>
<td>45.7</td>
</tr>
<tr>
<td>Recommendations for referral for genetic counseling</td>
<td>77</td>
<td>41.4</td>
</tr>
<tr>
<td>Presence of ROH</td>
<td>75</td>
<td>40.1</td>
</tr>
<tr>
<td>Number of ROH</td>
<td>44</td>
<td>23.7</td>
</tr>
<tr>
<td>Size of ROH</td>
<td>38</td>
<td>20.4</td>
</tr>
<tr>
<td>Locations of ROH</td>
<td>36</td>
<td>19.4</td>
</tr>
<tr>
<td>Percent of genome</td>
<td>30</td>
<td>16.1</td>
</tr>
</tbody>
</table>
Table 8: First step taken when a SNP microarray result suggests consanguinity

<table>
<thead>
<tr>
<th>Have you ever had a result suggesting consanguinity?</th>
<th>Yes</th>
<th></th>
<th>No</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compared the results to the reported pedigree</td>
<td>51</td>
<td>48.1%</td>
<td>29</td>
<td>39.2%</td>
</tr>
<tr>
<td>Discussed the results with the patient and/or parents/guardian</td>
<td>8</td>
<td>7.5%</td>
<td>5</td>
<td>6.8%</td>
</tr>
<tr>
<td>Discussed the results with a colleague</td>
<td>14</td>
<td>13.2%</td>
<td>19</td>
<td>25.7%</td>
</tr>
<tr>
<td>Gathered more information from the laboratory</td>
<td>12</td>
<td>11.3%</td>
<td>12</td>
<td>16.2%</td>
</tr>
<tr>
<td>Consulted an ethics team</td>
<td>2</td>
<td>1.9%</td>
<td>1</td>
<td>1.4%</td>
</tr>
<tr>
<td>Alerted the proper authorities</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Researched the literature for similar cases</td>
<td>3</td>
<td>2.8%</td>
<td>1</td>
<td>1.4%</td>
</tr>
<tr>
<td>Researched the literature for guidelines on the appropriate steps of action</td>
<td>2</td>
<td>1.9%</td>
<td>5</td>
<td>6.8%</td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
<td>13.3%</td>
<td>2</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

Totals: n = 106 100% n = 74 100%
Table 9: Additional steps taken when a SNP microarray result suggests consanguinity

<table>
<thead>
<tr>
<th>Have you ever had a result suggesting consanguinity?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alerted the proper authorities</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Compared the results to the reported pedigree</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>Consulted an ethics team</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Discussed the results with a colleague</td>
<td>42</td>
<td>49</td>
</tr>
<tr>
<td>Discussed the results with the patient and/or parents/guardian</td>
<td>78</td>
<td>38</td>
</tr>
<tr>
<td>Gathered more information from the laboratory</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>Researched the literature for guidelines on the appropriate steps of action</td>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>Researched the literature for similar cases</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Nothing</td>
<td>14</td>
<td>3</td>
</tr>
</tbody>
</table>

n = 106 n = 74
Table 10: Ethical Concerns when a SNP microarray result suggests consanguinity

<table>
<thead>
<tr>
<th>Have you ever had a result suggesting consanguinity?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disclosure of the relationship to the authorities</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Disclosure of the relationship to the parents</td>
<td>42</td>
<td>49</td>
</tr>
<tr>
<td>Disclosure of the relationship to the patient</td>
<td>21</td>
<td>48</td>
</tr>
<tr>
<td>Incomplete consent prior to testing</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>Legal concerns regarding the potential of an illegal relationship</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>No ethical concerns arose</td>
<td>56</td>
<td>8</td>
</tr>
<tr>
<td><strong>n = 106</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>n = 74</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you ever had a result suggesting incest?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Discussed the results with the patient and/or parents/guardian</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>(%)</td>
<td>4.6%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Discussed the results with a colleague</td>
<td>13</td>
<td>35</td>
</tr>
<tr>
<td>(%)</td>
<td>19.7%</td>
<td>29.9%</td>
</tr>
<tr>
<td>Gathered more information from the laboratory</td>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>(%)</td>
<td>21.2%</td>
<td>24.8%</td>
</tr>
<tr>
<td>Compared the results to the reported pedigree</td>
<td>23</td>
<td>39</td>
</tr>
<tr>
<td>(%)</td>
<td>34.8%</td>
<td>33.3%</td>
</tr>
<tr>
<td>Consulted an ethics team</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(%)</td>
<td>1.5%</td>
<td>0.85%</td>
</tr>
<tr>
<td>Alerted the proper authorities</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(%)</td>
<td>1.5%</td>
<td>0.85%</td>
</tr>
<tr>
<td>Researched the literature for similar cases</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(%)</td>
<td>1.5%</td>
<td>0.85%</td>
</tr>
<tr>
<td>Researched the literature for guidelines on the appropriate steps of action</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>(%)</td>
<td>0.0%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>(%)</td>
<td>15.2%</td>
<td>5.1%</td>
</tr>
<tr>
<td><strong>Totals: n = 66</strong></td>
<td>100%</td>
<td>118</td>
</tr>
<tr>
<td>Have you ever had a result suggesting incest?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------</td>
<td>-----</td>
</tr>
<tr>
<td>Alerted the proper authorities</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Compared the results to the reported pedigree</td>
<td>17</td>
<td>45</td>
</tr>
<tr>
<td>Consulted an ethics team</td>
<td>10</td>
<td>54</td>
</tr>
<tr>
<td>Discussed the results with a colleague</td>
<td>32</td>
<td>55</td>
</tr>
<tr>
<td>Discussed the results with the patient and/or parents/guardian</td>
<td>45</td>
<td>58</td>
</tr>
<tr>
<td>Gathered more information from the laboratory</td>
<td>20</td>
<td>45</td>
</tr>
<tr>
<td>Researched the literature for guidelines on the appropriate steps of action</td>
<td>10</td>
<td>56</td>
</tr>
<tr>
<td>Researched the literature for similar cases</td>
<td>12</td>
<td>27</td>
</tr>
<tr>
<td>Nothing</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

n = 65  
n = 114
Table 13: Ethical Concerns when a SNP microarray result suggests incest

<table>
<thead>
<tr>
<th>Have you ever had a result suggesting incest?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disclosure of the relationship to the authorities</td>
<td>21</td>
<td>75</td>
</tr>
<tr>
<td>Disclosure of the relationship to the parents</td>
<td>44</td>
<td>94</td>
</tr>
<tr>
<td>Disclosure of the relationship to the patient</td>
<td>11</td>
<td>97</td>
</tr>
<tr>
<td>Incomplete consent prior to testing</td>
<td>15</td>
<td>57</td>
</tr>
<tr>
<td>Legal concerns regarding the potential of an illegal relationship</td>
<td>22</td>
<td>89</td>
</tr>
<tr>
<td>No ethical concerns arose</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

n = 64 n = 117
Table 14: How familiar are you with the laws in your state regarding:

<table>
<thead>
<tr>
<th></th>
<th>n = 173</th>
<th>Extremely/Moderately Familiar</th>
<th>Somewhat Familiar</th>
<th>Slightly Familiar</th>
</tr>
</thead>
<tbody>
<tr>
<td>The health care professionals’ duty to report incest</td>
<td>35</td>
<td>20.2%</td>
<td>27</td>
<td>15.6%</td>
</tr>
<tr>
<td>The health care professionals’ duty to report child abuse</td>
<td>136</td>
<td>78.6%</td>
<td>27</td>
<td>15.6%</td>
</tr>
<tr>
<td>The health care professionals’ duty to report statutory rape</td>
<td>82</td>
<td>47.7%</td>
<td>40</td>
<td>23.3%</td>
</tr>
</tbody>
</table>
Table 15: How familiar are you with the laws in your state regarding:

<table>
<thead>
<tr>
<th></th>
<th>Extremely/Moderately Familiar</th>
<th>Somewhat Familiar</th>
<th>Slightly/Not at all Familiar</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 173</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First cousin relationships</td>
<td>72</td>
<td>41.6%</td>
<td>26</td>
</tr>
<tr>
<td>Second cousin relationships</td>
<td>69</td>
<td>39.9%</td>
<td>24</td>
</tr>
<tr>
<td>Third cousin or more distant relationships</td>
<td>74</td>
<td>42.8%</td>
<td>22</td>
</tr>
</tbody>
</table>
Table 16 – Interviewee responses to the question “Please briefly explain a session where you informed a patient or family about SNP microarray results that suggested consanguinity/incest. Desired information includes how you determined that the results suggested consanguinity/incest, how you feel about receiving/sharing these results, what you said to the patient and/or family, and how the family reacted to the news.”

* Some responses were edited for grammar, punctuation, and overall clarity.

<table>
<thead>
<tr>
<th>Parental Denial of Relationship When Results Were Received</th>
</tr>
</thead>
<tbody>
<tr>
<td>The mother of the child denied that a relative was the father of her child (&quot;unless my father had another son I didn't know about and we were brother/sister&quot;) but then also stated that some of her relatives had accused her father of molesting her &quot;but it wasn't true&quot;. (Participant 13)</td>
</tr>
<tr>
<td>I met with the family once results were received. The mother and patient were present, and I had not met them previously. Mother had previously denied consanguinity when reviewing family history and continued to decline during appointment. (Participant 382)</td>
</tr>
<tr>
<td>A close relationship (2nd degree) suspected on report for young child. I was uncomfortable delivering news because mom reported she has no memory of conception (rape). Family matter of-fact in receiving news. Mom denied fear or danger in her current living situation. No action was taken regarding authorities. (Participant 220)</td>
</tr>
<tr>
<td>Mother denied that there was a possibility of a close family relationship with any of the potential fathers of her child. I suggested that there might have been a time when she was not fully aware - such as after a party or when she might have been under the influence of a drug, which was part of her lifestyle at the time. This conception had occurred years before and I could tell that it came as a shock. It left her feeling uneasy because she was not sure which male relative, perhaps her brother who was mentally retarded, was the culprit. I offered to test the mentally retarded brother but she has not tried to arrange this. (Participant 329)</td>
</tr>
<tr>
<td>We had a child with a very complex set of malformations; we suspected consanguinity but it had been denied multiple times. The SNP microarray had very high levels of homozygosity indicating a close relationship (father/daughter incest in this case). We struggled to have that opportunity to talk individually to the mother of our patient about the issue. She responded that she understood but did not wish to address the issue further. The family has returned for additional care one time since then without additional discussion of this topic. No direct action was taken other than to let the family know we were aware. (Participant 330)</td>
</tr>
</tbody>
</table>

Legal/Ethical Team Involvement

One was particularly difficult for me as the mother of the child was bipolar and a little slow (but not MR) - she still lived with her parents (and we suspected her father was the father of her child). She was now in her mid-20s, but the child was born when she was 16 or 17, and she still lived in the home where incest may still be occurring. We were counseled by our legal department that since she was over 18 we could not report it, even though she was under 18 when the child was born. At the child's next visit we talked to the mother alone, with a social worker available. However, in the meantime her father had actually passed away... so, that changed the situation that she was no longer in the environment where incest was occurring. (Participant 13)
In all cases (we have seen three here in the past year) of AOH for ~25% of the genome, the test results reported to the mother and explained to her. In all cases, she denied any possibility of consanguinity. CPS was contacted in all three cases, with little to no action taken on their part. (Participant 322)

I have informed both the county attorney and the district attorney that, in cases of consensual relationships between 2nd and 3rd degree relatives, I will NOT report the relationship to the authorities, even though the relationship is technically illegal. (Participant 322)

A 7 year old was being taken care of by a great aunt because the mother had died from an unrelated cause. He has autism and the array showed around 28% homozygosity, suggesting father-daughter or brother-sister consanguinity. I felt the father of the child was likely the mother’s father. I contacted the legal department at my institution to determine the route of action. Since the mother had died and the father lived in another state, they did not feel there was any legal recourse and that I did not need to contact the police. I then called the great aunt and told her, and she was surprised but did recall that the father did seem somewhat inappropriate with his daughter. (Participant 375)

We had a case in which the child was the product of consanguinity and the maternal grandmother was the guardian - based on the pedigree and degree of relationship it was felt that the mother and father were likely brother and sister. In this case the mother “never would report who the father was”. We were told by our legal dept we could not discuss the results with the mother in confidence (since she was not the guardian) and we elected not to discuss them with the grandmother. (Participant 13)

In our incest case we made the decision not to discuss it with the patient as it did not pertain to the issue at hand, nor did she need to be protected as her biological father was deceased. We had an impromptu ethics consult about this. Consanguinity is a piece of cake in comparison! (Participant 120)

The was a first degree case that we did not disclose since we were informed by our legal dept we could not disclose to the mother (since her mother was the legal guardian) and we did not feel comfortable disclosing to the grandmother of the child. (Participant 13)

**Examples of How Respondents Counsel Regarding Findings of ROH**

Families usually calm, sometimes amused, not usually upset. I present this as very positive and helping to understand the child. I explain that many people do not know they are related and discuss how this can occur in isolated ranchos in Mexico (usual situation for us) or in ethnic minorities. (Participant 390)

The typical situation would involve some degree of LOH around 3-4%. I would describe the finding of LOH to the parents and explain that this could suggest some type of blood relationship between the parents, but that we cannot make any definite conclusion. (Participant 380)

It was determined from the lab report - it stated the percent of the autosomal region that was homozygous (indicated consanguinity not incest). I feel pretty comfortable relaying this information - I put the emphasis on what was found and what it can mean. I mention that there are a few reasons why a person can have such regions, and these include UPD if it is just one chromosome or a common ancestor between the parents if there is more than one. (Participant 178)

Most families act surprised and even laugh stating there is no way that they are related. I always ask about consanguinity and discuss this possibility beforehand. When a relationship is unknown, we typically just counsel about recessive inheritance and that the regions of LOH could increase the risk for a recessive condition although we cannot say which particular recessive condition. (Participant 19)
The microarray report did not identify the degree of relationship between the parents. Our discussion explained that the microarray identified that the parents were related in some way, and because they had passed down the same information to their child, it was possible that the child's condition is a rare recessive condition. (Participant 104)

These cases are very difficult and we treat them on a case by case basis - but they have certainly changed the way I pretest counsel patients (I did not used to talk about consanguinity as an incidental finding and now I always do - and we have actually had a parent change their mind about having their child test with microarray after that was mentioned (although I cannot be sure that was why). (Participant 13)

In general, I pre-counsel that the SNP microarray can find LOH and that this can be because parents are related, are of the same ethnicity, or because there are two copies of one parent and none of the other parent (UPD). I don't go into any more detail than that, but at least parents are aware that this is a possible finding. (Participant 261)

**Parental Admission of Relationship When Results Were Received**

I had one case where there were multiple regions of homozygosity. In looking through the patient's records, there were conflicting reports about the degree of relationship. I spoke directly to the family and explained how these results could happen (i.e., could be due to chance or could be because they were related). The mother did disclose that they were second cousins, which I was aware was not illegal so I did not feel compelled to act further. (Participant 7)

The number and amount of ROH were noted on the report to be suggestive of consanguinity. I was apprehensive about sharing the results with the family, and began by describing that while we didn't see anything missing or extra on the chromosomes we found several areas that, instead of looking different, looked the same. When I began explaining the different reasons behind this, including being from the same small geographic area or having relatives in common, the parents offered that they were third cousins which had not been clarified in the original pedigree, and so after determining that, it was no longer an issue. (Participant 31)

Pediatric patient followed for dysmorphic features and developmental delay. Patient is in custody of maternal grandparents. Mom never told them who father was. We disclosed results and grandparents said they always suspected. Mom eventually disclosed father was her first cousin. (Participant 22)

I got SNP array results from a POC (pt had not been seen for genetic counseling prior) suggesting parents were first cousins. I asked the patient if they were related, she said yes, they were first cousins once removed. I attributed the difference in reported relationship to the fact this couple is from an inbred group and they may be more distantly related in other ways they are not aware of. I was not surprised because I know it is more prevalent in their culture. We discussed implications. (Participant 127)

The couple had denied it, but when I presented them with the results, they admitted, and said that they felt uncomfortable telling Western doctors because they felt looked down upon, as though it were unacceptable. (Participant 119)
We had a case in which incest was suspected. Unfortunately, this parent was not pre-counseled about the potential for this discovery. The FOB was incarcerated and his mother often attended the child's appts, including this one where we were going to disclose results. We asked the "mother-in-law" to please stay in the waiting room so we could speak to the mother alone. We shared the finding and asked if it was possible that the child's father was a relative. The mother initially did not want to fess up that she had relations with her 1/2 brother but eventually did. We asked if it was consensual and she alluded that it was not but that she was not interested in pursuing legal action. (Participant 245)

<table>
<thead>
<tr>
<th>Cultural/Location Explanation Determined When Results Were Received</th>
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<tbody>
<tr>
<td>I had a phone conversation with the family after discussing the result with the lab. We reviewed the relevant family and social history and confirmed that the parents were not knowingly related within 3 or 4 generations, but that the extended families did come from the same relatively close geographic area. There were no consequences from this conversation or from the subsequent in-person counseling session. (Participant 328)</td>
</tr>
<tr>
<td>In cases I have counseled, the family said that they understand why their child has the regions (they come from a culture where they marry relatives). Their focus was on how they could help their daughter and what next steps were involved and whether they needed to test their son. I think they were in early stages of accepting this risk and how it fit in with their daughter's clinical problems. They were actually hoping that a more firm genetic result would help acquire services in the school setting. (Participant 178)</td>
</tr>
<tr>
<td>The array stated 30% ROH. The couple had been together for 15 years with 3 children, one with FTT/DD. They are from the same small town in Puerto Rico with very limited information about who mom's biological parents were. They were not surprised that they were related but didn't realize how close it could be. I spoke to mom privately, and she denied non-paternity or known incest. How closely related they are was not going to change their committed relationship. (Participant 251)</td>
</tr>
<tr>
<td>Consanguineous (cousin) relationship on report for older child of couple of nationality where relationship was not a surprise. Uncomfortable only in that unable to give specific info re: medical implications for family. (Participant 220)</td>
</tr>
<tr>
<td>There was one family where incest was suspected from microarray. We met with the mother separately to review results. The mother was not surprised but requested we not relay this to her husband. She was from another country and the incestuous relationship presumably took place in that country. We tried to word discussion with her husband and in the letter carefully so as not to disclose incest, but at the same time to convey that results suggested that recessive inheritance was likely. (Participant 36)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>ROH Result Expected Ahead of Time</th>
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<tbody>
<tr>
<td>Mother had said that the baby's father could be her own father so was no surprise; also CPS went ahead and did paternity testing with similar results. (Participant 349)</td>
</tr>
<tr>
<td>All of the SNP arrays that have indicated a consanguineous relationship were already known to the family prior to testing. Discussed during pedigree collection and again when reviewing the consent process and possible test outcomes. (Participant 209)</td>
</tr>
<tr>
<td>Pedigree taken beforehand noted the consanguinity and the SNP array confirmed it. This has been the case several times in my practice. (Participant 344)</td>
</tr>
</tbody>
</table>
The majority of cases I have dealt with involving incest or consanguinity was known prior to the test being ordered. In all but one of the cases of incest I have come across, the patient was already adopted out of the biological family. I am comfortable sharing this information with families and find that it can be helpful to narrow the list of possible causative genes. I am not comfortable dealing with the cases of incest in which the child is older, and the percentage of homozygosity comes out between 1st and 2nd degree relatives. The families I have shared this information with have either known already, and one family that did not know was not too concerned since the patient was adopted. (Participant 191)

I had a case where the parents were half siblings and the child had microcephaly and failure to thrive. The child was seen in the genetics clinic and the family was open about the relationship between the parents (rape occurred and had been reported). I was able to pre-counsel the likely result of homozygosity, which helped the family to understand the results when we did receive them. Thankfully, they already knew so I wasn’t breaking the news to them. (Participant 174)

I see families from a certain ethnic group that tends to stay within their ethnic group and therefore have more stretches of homozygosity than would typically be expected. Those families are not overly concerned about the results but I do explain them. (Participant 174)

The incest was between mentally retarded persons (brother/sister). Relationship was already suspected. (Participant 321)

The first case was confirming a case of child abuse that resulted in the patient. There had been two possible fathers, a boyfriend and her father. Since the child abuse was part of the reason for the testing and disclosed prior to the testing, the session was very straight forward when the results came back with first-degree consanguinity. (Participant 224)

I had a family that admitted to 4th or 5th cousin status when we took the pedigree, and the SNP array revealed 2nd cousin status as described in the report; when brought it up they brushed by the information, acting as if it didn't matter, and it likely didn't. (Participant 316)

My experience with ROH suggesting consanguinity and incest has been limited to patients where the parent’s relationship was known and the child is now in foster care. In these cases the results are expected so nobody is really surprised or upset. (Participant 261)

The patient suspected consanguinity of his parents and was somewhat disappointed that the identified areas of homozygosity did not contribute to a diagnosis for him. (Participant 334)

The parents had expressed that they were from a small town and believed they may be distantly related at the time of the pedigree. When I gave them the results, I explained there were areas of homozygosity and this could be explained by consanguinity. I then explained the possible clinical implications of this finding-ie the possibility of recessive conditions etc. The family received the news fairly well. It was similar to the way a family reacts to a variant of unknown significance-this finding could mean something clinically but may not and it seemed like they were aware they were probably related somehow, although they couldn’t give information as to how closely related. (Participant 131)

We had a family from India where parents reported to us that they were first cousins beforehand, so SNP array results were not a surprise. (Participant 36)
The only situation that comes to mind was a family where consanguinity (1st cousins) was reported and they had two children severely affected. The family and ourselves were already aware of the consanguinity and we were using SNP to determine which regions the two children had in common to narrow down AR conditions. (Participant 143)

<table>
<thead>
<tr>
<th>Relationship Previously Unknown to Parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child had minimal findings. Multiple areas of LOH determined. Not a high level of them--incest not suspected. Father of baby not in picture. Mother of baby was surprised and embarrassed by result. She knew who the father was, but did not know of any familial relationship between them. (Participant 319)</td>
</tr>
<tr>
<td>I let a family know that the data suggested that they were first cousins - they were surprised and unaware of the level of consanguinity. (Participant 296)</td>
</tr>
<tr>
<td>The patient’s mother did not know the father of the child since the child was the product of a drunken night for which the mother has no memory. The patient was found to have ROH suggesting 1st degree consanguinity. The patient’s mother required counseling after disclosure of results. (Participant 37)</td>
</tr>
<tr>
<td>We had a mother who unknowingly married her father. She had never known him growing up, met him as an adult, fell in love, and married. There had been small town rumors that he had known her mother. Their second child was admitted for failure to thrive. The state assumed custody of the child. In a way, these results vindicated the mother. She was more worried about being accused of being a bad mom than she was about the consanguinity. The father was incarcerated for other reasons. She admitted that there was a good chance that he was her father, but she hadn’t wanted to face it. She was reassured to learn there was a medical reason for her daughter’s FTT. In the end the parents divorced and the mother gave up custody of both of her children. It was really sad. Socioeconomically, educationally...this woman never had much of a chance. (Participant 184)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The Patient is in the Care of Someone Other Than Biological Parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>My most recent encounter with a SNP microarray revealing LOH involved a girl who was adopted from overseas and very little was known about her biological parents. I felt comfortable discussing the SNP microarray results that suggested consanguinity of the patient’s birth parents. In other situations that involved the parents as the patient’s caregivers, the situations are much more difficult. (Participant 340)</td>
</tr>
<tr>
<td>The array showed 25% homozygosity in an adult with MR adopted as a baby - they now have a reason for the MR. I don't think parents relayed this to their adopted adult (still living with them). (Participant 315)</td>
</tr>
<tr>
<td>The second case I have been involved in was a child that had been adopted by a non-biological great aunt (married into the family). The father of that child had been unknown prior to the testing. There were two possible first-degree male relatives who could be the father. The adopted mother was shocked upon the revelation of incest, but quickly recovered. She was mainly concerned with the health of the child. (Participant 224)</td>
</tr>
<tr>
<td>We evaluated a child who was adopted for whom an incestuous relationship was suspected but never confirmed (over a decade ago), and I reported to the adopted family that this testing confirmed the prior suspicions. (Participant 31)</td>
</tr>
</tbody>
</table>
Appendix B: Interview Guide for Laboratory Personnel

1. What is your gender?
   a. Female
   b. Male

2. What is your current occupation?
   a. Genetic Counselor
   b. Clinical Geneticist
   c. Cytogeneticist (Non director)
   d. Laboratory Director
   e. Laboratory Supervisor
   f. Medical Director
   g. Other (please specify)__________________________________

3. Which of the following ranges describes how many years have you been employed in a laboratory setting?
   a. 0-2
   b. 3-5
   c. 6-8
   d. 9-11
   e. 12-14
   f. Greater than 15

4. What is the name(s) of the SNP microarray(s) that your lab currently runs on a clinical basis?
   _______________________________________________________________________

5. Have you reviewed or generated a SNP microarray report run by the laboratory?
   a. Yes
   b. No
6. What information does your laboratory typically include in SNP microarray reports? After each option please respond “Yes” or “No”.
a. Interpretation of findings
b. Microdeletions/microduplications found
c. Syndrome(s) associated with microdeletions/microduplications found
d. Microarray karyotype
e. Regions of homozygosity
f. Limitations of testing
  i. Clinical implications
  j. Suggestions for management techniques of an identified disorder
  k. References
l. Methodology
m. Other (Please specify) ___________________________________________

7. What does your laboratory typically include in SNP microarray reports about regions of homozygosity? After each option please respond “Yes” or “No”. (If nothing (g), skip logic to number 9).
a. Number of these regions
b. Size of these regions
c. Locations of these regions
d. Percent of genome
e. Recommendations for findings (genetic counseling, ethics consult, implications of multiple ROH, etc.)
f. Other (Please specify) ___________________________________________
  g. Regions of homozygosity are not reported on SNP microarray test results.

8. Which of the following interpretations of the findings of regions of homozygosity (ROH) does your laboratory report typically include? After each option please respond “Yes” or “No”.
a. Uniparental disomy
b. Consanguinity
c. Ancestral ROH
d. Incest
e. Parents related by blood (percent homozygosity not given)
f. Other (please specify) ___________________________________________
  g. Regions of homozygosity are not reported on SNP microarray test results.
9. What cutoff does your laboratory use for reporting ROH?

10. Which of the following answers describes how your laboratory defines an incestuous relationship by percent homozygosity? (Ask following questions based on response, 12.5% or 20% or 25%)
   a. Froh >25%
   b. Froh >20%
   c. Froh >12.5%

11. Which of the following ranges describes how many times has your laboratory reported an array that indicated the possibility of parental incest (over 20% of the genome is found to be homozygous/ 12.5%/25%)?
   a. 0
   b. 1-3
   c. 4-6
   d. 7-9
   e. 10-12
   f. 13-15
   g. Greater than 15

12. How does your laboratory calculate the percent of homozygosity from microarray results?

13. How does your laboratory determine whether a region of homozygosity is due to uniparental isodisomy versus consanguinity?

14. How does your laboratory define ancestral ROH?

15. Please respond with “Yes” or “No.” Does your laboratory feel that it is its duty to notify the ordering physician of results suggesting parental consanguinity or incest?
   a. Yes
   b. No
   Why or why not?
16. Please respond with “Yes” or “No.” Does your laboratory do anything differently when reporting test results that reveal *consanguinity* (greater than 1% homozygosity) versus when reporting a result that does not? (If no, skip to number 18).
   a. Yes
   b. No

17. If yes, which of the following steps does your laboratory take? After each option please respond “Yes” or “No”.
   a. Contact the ordering healthcare provider
   b. Contact the appropriate authorities
   c. Contact social work at the patient’s hospital
   d. Contact an ethics board
   e. Recommend that the ordering physician takes additional steps
   f. Other (please specify)_____________________________________________

18. Please respond with “Yes” or “No.” Does your laboratory do anything differently when reporting test results that reveal an *incestuos* relationship (greater than 12.5% OR 20%) versus reporting a result that does not? (If no, skip to number 20)
   a. Yes
   b. No

19. If yes, which of the following steps does your laboratory take? After each option please respond “Yes” or “No”.
   a. Contact the ordering healthcare provider
   b. Contact the appropriate authorities
   c. Contact social work at the patient’s hospital
   d. Contact an ethics board
   e. Recommend that the ordering physician takes additional steps
   f. Other (please specify)_____________________________________________

20. Are you willing to provide a de-identified microarray report? Or a sample report? (If they include ROH, send a sample of a patient with ROH. If not, just send any)
   a. Yes
   b. No
   If yes, please fax to:
Appendix C: Questionnaire for Genetic Counselors and Geneticists

1. What is your gender?
   a. Female
   b. Male

2. What is your occupation?
   a. Clinical Genetic Counselor
   b. Laboratory Genetic Counselor
   c. Clinical/Laboratory Genetic counselor
   d. Clinical Geneticist
   e. Genetics Resident
   f. Other (please specify)__________________________

3. During your professional career, how many years have you seen patients in a clinical setting?
   a. 0-2
   b. 3-5
   c. 6-8
   d. 9-11
   e. 12-14
   f. Greater than 15

4. During the last five years of your professional career, have you actively worked with patients in a clinical setting?
   a. Yes
   b. No

5. In what region do you practice? (Choose all that apply):
   a. Region 1 (CT, ME, MA, NH, RI, VT)
   b. Region 2 (DE, DC, MD, NJ, NY, PA, VA, WV)
   c. Region 3 (AL, FL, GA, KY, LA, MS, NC, SC, TN)
   d. Region 4 (AR, IL, IN, IA, KS, MI, MN, MO, NE, ND, OH, OK, SD, WI)
   e. Region 5 (AZ, CO, MT, NM, TX, UT, WY)
   f. Region 6 (AK, CA, HI, ID, NV, OR, WA)
   g. Outside of the United States

6. What is your age? ________________
7. Which best describes your ethnicity?
   a. American Indian
   b. Asian
   c. Black or African American
   d. Hispanic
   e. Latino
   f. Native Hawaiian or Other Pacific Islander
   g. White

8. Have you ordered a SNP Microarray (Excludes: CGH array and oligonucleotide arrays without SNPs) or any array platform that includes a SNP backbone for a patient at any point in your career? (If no, will use skip logic and end survey)
   a. Yes
   b. No

9. Please describe what percentage of the total SNP microarrays you order are for each clinical setting below. The total must add up to 100%.

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal</td>
<td></td>
</tr>
<tr>
<td>Pediatric (non cancer related)</td>
<td></td>
</tr>
<tr>
<td>Adult (non cancer related)</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
</tr>
<tr>
<td>Total (must equal 100%)</td>
<td></td>
</tr>
</tbody>
</table>

10. What items do you typically discuss when pre-counseling a patient before ordering a SNP microarray? (Choose all that apply)
    a. Test methodology
    b. Objective of the test
    c. Type of sample required
    d. Possible outcomes
    e. Prices
    f. Provide a consent form to be signed
    g. Other (Please specify)___________________________________________
    h. None of the above
11. Which of the following possible outcomes of a SNP microarray do you typically discuss with a patient during the pre-counseling process? (Choose all that apply)
   a. I don’t discuss possible outcomes.
   b. The test may not find any clinically significant abnormalities.
   c. The test may find clinically significant abnormalities that are known to be associated with a genetic condition.
   d. The test may find a variant of uncertain significance.
   e. The findings from this test may result in a need to test one or both parents to assess significance.
   f. The test is capable of detecting hundreds of microdeletions/microduplications associated with genetic syndromes.
   g. The test is capable of detecting chromosome imbalances – loss or gain of regions.
   h. The test is capable of detecting regions of homozygosity.
   i. The test is capable of detecting a parental blood relationship based on regions of homozygosity.
   j. The test is capable of detecting uniparental disomy.
   k. The test is capable of detecting adult onset disorders.
   l. The test is capable of identifying X-linked disorders which may impact future reproductive risks.
   m. Other (Please specify)__________________________________________________________
   n. None of the above

12. From what laboratory did you most recently order a SNP microarray?
    _____________________________________________

13. Have you ever calculated percent homozygosity (Froh) to define a parental relationship for a clinical patient? (If b skip to 15, if a or c, continue to 14)
   a. Yes, I have calculated percent homozygosity.
   b. No, I have never calculated percent homozygosity.
   c. No, I have never calculated percent homozygosity, but I have had it calculated for me on a patient report.

14. Based on percent homozygosity, how do you define an incestuous relationship? (Skip 15)
   d. Froh >25%
   e. Froh >20%
   f. Froh >12.5%
   g. Other (please specify)_________________________________________________________
15. How do you define an incestuous relationship? (Skip logic to questions including first degree relatives versus those including first and second degree relatives versus those who choose ‘other’)
   a. A sexual relationship between first degree relatives including a parent and child or between siblings.
   b. A sexual relationship between first degree relatives including a parent and child or between siblings or between second degree relatives including an aunt/uncle and niece/nephew, between half siblings, or between a grandparent and grandchild.
   c. Other

16. Which of the following do you typically find in the SNP microarray report that you receive from the laboratory? (Choose all that apply)
   a. Interpretation of findings
   b. Microdeletions/microduplications found
   c. Syndrome(s) associated with microdeletions/microduplications found
   d. Microarray karyotype
   e. Regions of homozygosity
   f. Limitations of testing
      a. Other appropriate testing (ex. Testing the parents or siblings for the same results)
   g. Recommendation for referral for genetic counseling
   h. Clinical implications
   i. Suggestions for management techniques of an identified disorder
   j. References
   k. Methodology
   l. Other (Please specify)__________________________

17. Which of the following regarding regions of homozygosity do you typically find in the SNP microarray report that you receive from the laboratory? (Choose all that apply)
   a. Number of the regions of homozygosity
   b. Size of the regions of homozygosity
   c. Locations of the regions of homozygosity
   d. Implications of the regions of homozygosity
   e. Percent of genome that is homozygous
   f. Suggestions for follow up of parental homozygosity
   g. Other (Please specify)__________________________
   h. Regions of homozygosity are not reported
18. If regions of homozygosity are listed on the SNP microarray report, please indicate if the following possible explanations are also listed: (Choose all that apply)
   a. Uniparental disomy
   b. Consanguinity
   c. Ancestral regions of homozygosity
   d. Incestuous relationship
   e. Parents are related by blood (percent homozygosity is not given)
   f. Other (Please specify)___________________________________________
   g. N/A

19. After you obtain a SNP microarray report, which of the following do you typically discuss with your patients?
   a. Microdeletions/microduplications found
   b. Syndrome(s) associated with microdeletions/microduplications found
   c. Number of regions of homozygosity
   d. Size of regions of homozygosity
   e. Locations of regions of homozygosity
   f. Clinical implications of regions of homozygosity
   g. Percent of genome that is homozygous
   h. Presence of regions of homozygosity
   i. Implications for parental relatedness
   j. Uniparental disomy
   k. Other appropriate testing (ex. testing the parents or siblings for the same results)
   l. Recommendation for referral for genetic counseling
   m. Suggestions for management techniques of an identified disorder
   n. Other (Please specify)___________________________________________

20. How many times in your career have you received a SNP microarray result where you have suspected parental incest? (If zero, will go on to answer the hypothetical questions 21-23; If any other answer, questions 21-23 will ask what their steps were in that experience)
   a. 0
   b. 1-3
   c. 4-6
   d. 7-9
   e. 10-12
   f. 13-15
   g. Greater than 15
21. If the SNP microarray results suggest an incestuous relationship, what would be your first step?
   a. Discuss the results with the patient and/or parents/guardian
   b. Discuss the results with a colleague
   c. Gather more information from the laboratory
   d. Compare the results to the reported pedigree
   e. Consult an ethics team
   f. Alert the proper authorities
   g. Research the literature for similar cases
   h. Research the literature for guidelines on the appropriate steps of action
   i. Other (Please specify)___________________________________________

22. After completing the chosen step from question number 21, what are the subsequent steps you would take? (Choose all that apply)
   a. Discuss the results with the patient and/or parents/guardian
   b. Discuss the results with a colleague
   c. Gather more information from the laboratory
   d. Compare the results to the reported pedigree
   e. Consult an ethics team
   f. Alert the proper authorities
   g. Research the literature for similar cases
   h. Research the literature for guidelines on the appropriate steps of action
   i. Other (Please specify)___________________________________________
   j. Nothing

23. Which of the following, if any, ethical concerns arose when a report suggested that a patient was the product of an incestuous relationship?
   a. Incomplete consent prior to testing
   b. Legal concerns regarding the potential of an illegal relationship
   c. Disclosure of the relationship to parents
   d. Disclosure of the relationship to the patient
   e. Disclosure of the relationship to the authorities
   f. Other (Please specify)___________________________________________
   g. No ethical concerns arose
24. How many times in your career have you received a SNP microarray result where you have suspected that the parents are related by blood or parental consanguinity? (If zero, will go on to answer the hypothetical questions 25-27; If any other answer, questions 25-27 will ask what their steps were in that experience)
   a. 0
   b. 1-3
   c. 4-6
   d. 7-9
   e. 10-12
   f. 13-15
   g. Greater than 15

25. If the SNP microarray results suggest that the parents are related by blood or parental consanguinity, what would be your first step?
   a. Discuss the results with the patient and/or parents/guardian
   b. Discuss the results with a colleague
   c. Gather more information from the laboratory
   d. Compare the results to the reported pedigree
   e. Consult an ethics team
   f. Alert the proper authorities
   g. Research the literature for similar cases
   h. Research the literature for guidelines on the appropriate steps of action
   i. Other (Please specify)___________________________________________
   j. None of the above

26. After completing the chosen step from question number 25 what are the subsequent steps you would take? (Choose all that apply)
   a. Discuss the results with the patient and/or parents/guardian
   b. Discuss the results with a colleague
   c. Gather more information from the laboratory
   d. Compare the results to the reported pedigree
   e. Consult an ethics team
   f. Alert the proper authorities
   g. Research the literature for similar cases
   h. Research the literature for guidelines on the appropriate steps of action
   i. Other (Please specify)___________________________________________
   j. Nothing
   k. None of the above
27. Which of the following, if any, ethical concerns arose when a SNP microarray result suggested that a patient was the product of a consanguineous relationship? (Choose all that apply)
   a. Incomplete consent prior to testing
   b. Legal concerns regarding the potential of an illegal relationship
   c. Disclosure of the relationship to parents
   d. Disclosure of the relationship to the patient
   e. Disclosure of the relationship to the authorities
   f. Other (Please specify) ____________________________
   g. None of the above

28. Please describe your comfort level when you receive the following SNP microarray result.

<table>
<thead>
<tr>
<th></th>
<th>Very Comfortable</th>
<th>Comfortable</th>
<th>Neutral</th>
<th>Uncomfortable</th>
<th>Very Uncomfortable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consanguinity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

29. Please select all that apply regarding your feelings surrounding receiving SNP microarray results that suggest consanguinity/incest. (Choose all that apply):

   a. I am comfortable when receiving this type of result.
   b. I feel uncomfortable when the results suggest consanguinity/incest because I am unsure if the relationship suspected is accurate.
   c. I feel uncomfortable when the results suggest consanguinity/incest because there are no guidelines released by my institution on how to act upon such results.
   d. I feel uncomfortable when the results suggest consanguinity/incest because there are no guidelines released by my certifying body on how to act upon such results.
   e. I feel uncomfortable because I didn’t know that SNP microarrays could detect such information.
   f. None of the above
   g. Other (Please specify) ____________________________
30. Please *select all that apply* regarding your feelings surrounding counseling a patient about the results of a SNP microarray that suggest consanguinity/incest.

a. I generally feel comfortable when I counsel about results of consanguinity/incest, because I pre-counsel my patients that these relationships can be detected on microarray.
b. I feel uncomfortable when I provide patients/families information from a report that suggests a parental relationship because I feel unprepared to deal with these issues.
c. I feel uncomfortable when I provide patients/families with information from a report that suggests a parental relationship because I do not know how to accurately interpret the data.
d. I feel uncomfortable when I provide patients/families information from a report that suggests a parental relationship because I choose to leave out information that suggests a parental relationship.
e. I feel uncomfortable when I provide patients/families information from a report that suggests a parental relationship because I *am instructed* to leave out information that suggests a parental relationship.
f. None of the above
g. Other (please specify)_______________________________

31. Please describe any personal moral concerns that have arisen when a report suggests that a patient was the product of a consanguineous relationship.

_____________________________________________________________________________________

32. How familiar are you with the laws in your state regarding:

<table>
<thead>
<tr>
<th>The health care professionals’ duty to report incest</th>
<th>Extremely Familiar</th>
<th>Moderately Familiar</th>
<th>Somewhat Familiar</th>
<th>Slightly Familiar</th>
<th>Not at all familiar</th>
</tr>
</thead>
<tbody>
<tr>
<td>The health care professionals’ duty to report child abuse</td>
<td></td>
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<tr>
<td>The health care professionals’ duty to report statutory rape</td>
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</tr>
</tbody>
</table>

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33. How familiar are you with the laws in your state regarding:

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Extremely Familiar</th>
<th>Moderately Familiar</th>
<th>Somewhat Familiar</th>
<th>Slightly Familiar</th>
<th>Not at all familiar</th>
</tr>
</thead>
<tbody>
<tr>
<td>First cousin relationships</td>
<td></td>
<td></td>
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<tr>
<td>Second cousin relationships</td>
<td></td>
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<tr>
<td>Third cousin or more distant relationships</td>
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</table>

34. Please briefly describe a session where you informed a patient or family about a SNP microarray results that suggest consanguinity or incest. Desired information includes how you determined that the results suggested consanguinity/incest, how you felt about receiving/sharing these results, what you said to the patient and/or family, and how the family reacted to the news.

__________________________________________________________________________________
__________________________________________________________________________________
__________________________________________________________________________________

35. What additional information would be useful to help you interpret results of ROH and report these results to your patients?

__________________________________________________________________________________
__________________________________________________________________________________
__________________________________________________________________________________

36. Would you like to see a statement from your certifying body regarding regions of homozygosity and consanguinity?

a. Yes
b. No