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Physicians' Perspectives on the Uncertainties and Implications of Chromosomal Microarray Testing of Children and Families

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Abstract

Chromosomal microarray analysis (CMA) has improved the diagnostic rate of genomic disorders in pediatric populations, but can produce uncertain and unexpected findings. This paper explores clinicians' perspectives and identifies challenges in effectively interpreting results and communicating with families about CMA. Responses to an online survey were obtained from 40 clinicians who had ordered CMA. Content included practice characteristics and perceptions, and queries about a hypothetical case involving uncertain and incidental findings. Data were analyzed using non-parametric statistical tests. Clinicians' comfort levels differed significantly for explaining uncertain, abnormal, and normal CMA results, with lowest levels for uncertain results. Despite clinical guidelines recommending informed consent, many clinicians did not consider it pertinent to discuss the potential for CMA to reveal information concerning biological parentage or predisposition to late-onset disease, in a hypothetical case. Many non-genetics professionals ordering CMA did not feel equipped to interpret the results for patients, and articulated needs for education and access to genetics professionals. This exploratory study highlights key challenges in the practice of genomic medicine, and identifies needs for education, disseminated practice guidelines, and access to genetics professionals, especially when dealing with uncertain or unexpected findings.

Keywords

Cytogenomics; incidental findings; uncertainty; health communication; pediatrics; genomic medicine; genetic counseling

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INTRODUCTION

Chromosomal microarray analysis (CMA) is a clinical diagnostic tool used to evaluate conditions including developmental delay, autism spectrum disorders, and multiple anomalies.[1,2] The increased sensitivity of CMA compared to traditional cytogenetics has improved the rate of detection of genomic variations and the diagnosis of specific syndromes. However, concerns have been raised regarding variants of uncertain significance (VUS), incidental findings (IFs), and the implications of CMA results for relatives.[2–6]

Clinicians ordering cytogenomic testing have an important role in preparing families for testing and communicating results. Guidelines specific to CMA emphasize the importance of pre-test counseling and informed consent to ensure that families are prepared for the information, and make an informed decision about how much information to receive.[1,2,4,7–9] Initial guidelines suggest informing patients of the potential for unexpected findings, which should be reported with consideration of clinical relevance as well as social, ethical and legal issues. For a VUS, some guidelines recommend genetic consultation, genetic counseling, or both, and monitoring of the medical literature by the physician with an ongoing patient relationship.[8] The American Academy of Pediatrics (AAP) recommendations for genetic testing predate the clinical use of CMA, but are still relevant. They recommend informed consent for genetic tests, provision of information to parents about potential treatment of disorders detected in their child, discussion of potential harms in gaining genetic information, and collaboration among pediatricians and genetics professionals.[10,11]

We believe that it is important to understand the perspectives of physicians using CMA in their clinical practice, to identify practices that may correspond with or deviate from current guidelines, to understand reasons for diverging practices, and to identify specific challenges in ordering, interpreting and conveying CMA results. Our study explores current practices and considerations pertaining to CMA testing among a group of physicians who have ordered CMA testing for pediatric patients. This paper focuses on physicians' responses to uncertain and incidental findings of CMA, and their views on reporting and communicating these findings. The ethical and psychosocial concerns raised by CMA technology reflect issues that will apply on a larger scale to whole genome sequencing and other clinical applications of genomics.[12]

MATERIALS AND METHODS

The results described here represent one component of an exploratory study of the impact of CMA testing on families and health providers of pediatric outpatients. The study included interviews, observations and a survey involving families and providers. A previous paper reported findings pertaining to parents' understandings of CMA results.[13]

Sample

Physicians who ordered CMA testing at least once through the Cytogenomics Laboratory at the Children's Hospital of Philadelphia (CHOP) between May 2008 and March 2011 were sent emails inviting their participation in an anonymous online survey, for which a link was provided. Surveys were completed between March and May 2011.

Emails were sent to 324 physicians, and 51 (16%) responded, of whom 40 were included in the analysis for this paper. Response rates were 21% for pediatricians, 26% for geneticists, and 11% for specialists. Since we were interested only in physicians with patient contact in the pediatric setting we excluded 3 pathologists and one obstetrician/gynecologist. We also excluded 7 respondents who failed to provide responses for most items analyzed in this

paper. Some items had missing responses, and sample sizes for these are noted in the tables (n=37 is the lowest).

The study was approved by the Institutional Review Board at the Children's Hospital of Philadelphia.

Instrument—The survey was informed by preliminary qualitative analysis of interviews and clinical observations involving health professionals and families of children undergoing CMA testing.[13] Items about genetics training and knowledge were based on a national survey of physicians' utilization of genetic testing.[14] The online survey comprised 50 items, divided into 7 sections: 1) demographics; 2) medical practice characteristics and training in genetics; 3) education and general experience with CMA testing; 4) an evolving hypothetical scenario (see Table 2 for specific items); 5) level of comfort interpreting and explaining CMA results; 6) impact of CMA testing on clinical practice; and 7) personality characteristics.

This paper focuses on physicians' experience and perceptions regarding CMA, and their responses to the evolving scenario. Responses were measured for some items by 6-point Likert scales, and for others by selection of pre-determined responses. Several questions included open-text options for additional responses and clarification.

Data analysis

Statistical analyses were performed using SPSS and SAS software. Wilcoxon signed rank tests were used for paired comparisons between responses to varying hypothetical situations in the scenario (e.g., likelihood of disclosing a genetic predisposition to Alzheimer disease as compared to colon cancer). Friedman's tests were similarly used for the repeated measures on comfort levels when explaining the 3 different types of results (VUS, normal, and abnormal). For all the three-way comparisons among the independent medical specialties, Kruskal-Wallis tests were used for the Likert scales, and Fisher's exact tests for dichotomous outcomes.

Open-text responses were categorized according to themes by 2 independent coders (MR and KR). Discrepancies were resolved by discussion, and the frequency of respondents reporting each theme was calculated.

RESULTS

Sample characteristics and experience with CMA testing

Respondents included physicians from 3 medical specialty groups: general pediatrics (27.5%), medical genetics (12.5%), and pediatric subspecialties (60%; including 7 neonatologists, 5 neurologists, 4 pediatric endocrinologists, 3 developmental pediatricians, 1 hematologist, 1 gastroenterologist, 1 oncologist, 1 ophthalmologist, and 1 critical care specialist). Sample characteristics are presented in Table 1.

Comfort levels differed for explaining the three types of results (normal, abnormal, and VUS), with lowest comfort levels for VUS results (see Table 1).

Responses to evolving hypothetical scenario (see Table 2)

Most physicians were likely to offer the CMA test for a hypothetical patient (mean 4.14±1.66 on a 6-point scale). Upon receiving a VUS result, most respondents (70%) indicated that they would disclose to parents "the location and approximate size of the deletion, and that the findings were inconclusive". Several non-geneticists added (in open

text) that they would explain the meaning of the finding and refer for a medical genetics consultation if the parents had further questions.

Pre-test preparation for parental testing—Prior to parental testing, 59% of physicians considered it pertinent to discuss the potential for an unexpected finding of a predisposition to certain diseases. Thirty percent of respondents thought it pertinent to discuss the potential for findings regarding biological parentage, and 10% were unsure what to discuss.

Implications of a VUS result for relatives—Opinions were divided regarding the likelihood of recommending testing for a relative following a VUS finding. Open-text responses (provided by 21 respondents) revealed that some physicians thought that an inconclusive result was not meaningful, and therefore there was no reason to test the patient's relative, while others thought that testing could help to inform reproductive decisions, or to facilitate finding a diagnosis. Respondents articulated that their decision would be guided by the specific nature of the findings, family preferences, and ethical considerations: some suggested that contingencies (such as variable penetrance, an X-linked condition, the genes in the deleted region) were relevant to their decision, and several stated that it was the family's decision.

Response to an incidental finding—Physicians were asked about their preferences for reporting an IF in the maternal array test associated with a predisposition to develop Alzheimer disease. While about 60% of respondents preferred full disclosure of IFs in the laboratory report, the remaining 40% chose other options: to be informed verbally; not to be informed at all; to leave it to the laboratory's discretion; or were unsure. One respondent noted that laboratories appear to differ in what they report.

Physicians rated colon cancer as more actionable than Alzheimer disease ($p<.0001$), and were more likely to disclose a genetic predisposition to colon cancer versus Alzhiemer disease ($p< .0001$). Thirty percent of respondents were likely (scored ≥4) to suggest that a parent inform her sibs of a predisposition to Alzheimer disease.

Comparison among medical specialties

All the medical geneticists reported ordering more than 30 cytogenomic arrays, compared with 37.5% of the pediatric sub-specialists, and none of the general pediatricians. Perceived need for more education about interpreting and explaining results was highest for pediatricians, followed by pediatric sub-specialists and medical geneticists, and the differences among the 3 means were significant (respective means were 5.0±1.3, 4.0±1.6, and 2.0±1.2; $p=.006$). Ratings of parents' understanding differed among the 3 specialty groups; means were 4.0±1.4 for geneticists, 2.2±1.1 for pediatricians and 2.3±0.8 for subspecialists ($p=.027$). Most non-geneticists (82% of pediatricians and 62% of pediatric sub-specialists) reported that they would discuss a VUS finding with a genetic specialist.

All of the general pediatricians considered it pertinent to discuss the potential for an IF prior to testing a parent, while only 39% of the pediatric sub-specialists and 60% of medical geneticists agreed ($p<.001$).

Pediatricians also tended to prefer full disclosure of a predisposition to Alzheimer disease (70% of pediatricians, 59% of specialists, and 40% of geneticists), and to be more likely to recommend informing relatives of an IF (46% of pediatricians, 25% of specialists and 20% of geneticists scored ≥4 on a 6-point scale), although these differences were not considered statistically significant.

DISCUSSION

The results of this exploratory study provide insight into the ways physicians are managing genomic medicine and elucidate some key challenges regarding uncertain and incidental findings, with implications for pre- and post-test counseling and provider education.

Pre-test counseling

An important finding of this study was the variety of opinions regarding appropriate information to convey before parental testing. Forty-one percent of respondents did not consider it pertinent to discuss the potential for IFs. If parents are told only that the test will determine whether the child's deletion/duplication is also present in a parent, they may not be aware of the full scope of potential results. While there are no formal requirements for informed consent for CMA, clinical guidelines recommend that patients and families should be informed of the potential for IFs[2,4,7,8] Our study suggests some discrepancies between clinical practice (as reported regarding a hypothetical situation) and recommended practice with respect to pre-test counseling about IFs.

Physicians may not be inclined to discuss the potential for IFs for several reasons: in the context of CMA, IFs are rare, seen in only 1% of the population tested;[15] and discussion of such findings may be anxiety-provoking and time-consuming. Given the vast number of possibilities, it is not feasible to discuss options for reporting each potential finding,[16,17] but it is also inappropriate to present the choice of whether or not to be informed only after detecting a deleterious variant.[3] A "generic consent" option[18] could provide information about general categories rather than specific outcomes, and some suggest that pre-test discussions review possible IFs in terms of age of onset, severity, treatability and prevention, and consider interests of children, parents and other relatives.[17]

Post-test counseling

Disclosing incidental findings—The differing opinions articulated by respondents regarding disclosure of IFs echo recognized controversies. While clinicians have a responsibility to inform patients of clinically meaningful IFs, such results in a healthy individual may lead to unnecessary and expensive interventions.[19,20] Additionally, genetic testing has been found to benefit patients and their relatives[21] and facilitate preventative interventions, but adverse psychological responses have been reported in some individuals and concerns about privacy and confidentiality often intervene.[11,21,22] We cannot assume that everyone would want to be informed of an IF, even if medically actionable, as demonstrated by findings that many people from families with adult-onset genetic disorders (e.g., Huntington disease, hereditary breast cancer, HNPCC-colon cancer, hereditary hemorrhagic telangiectasia, Alzheimer disease) choose not to have genetic testing.[11,23–25] An added complication of CMA is that parental testing increases the complexity and quantity of genetic data generated, and the findings may be beyond the expertise of the ordering physician.

Our finding that physicians were more likely to disclose a genetic propensity for a medically actionable disease (colon cancer) compared with one that is currently less actionable (Alzheimer disease) is consistent with the approach in genetic research, where treatability and clinical utility guide disclosure decisions.[26–28] Berg and colleagues suggest that clinically actionable IFs should always be reported, while reporting of clinically valid but not directly actionable variants (e.g., alleles associated with Alzheimer disease) should be based on patient preference.[16] Confounding these issues is the current indecision among genetics professionals as to which IFs to report.[29] If patients' wishes are unclear, or laboratorians feel uncomfortable not reporting IFs, decisions about reporting and counseling

should be made in collaboration with clinicians familiar with the clinical and social situation of the family, weighing harms and benefits of the information.

Uncertain findings—Our finding that physicians' levels of comfort explaining results to families were lowest for VUS results was consistent with other reports,[3,4,30] and possibly attributable to health physicians' general discomfort with uncertain results of genetic tests.[31,32]

With whole-genome sequencing, VUS results will increase dramatically.[12] Berg and colleagues suggest that variants of no known clinical significance (i.e., not linked to a phenotype, clinical outcome or intervention) not be included in the primary clinical record or discussed with patients.[16] While this approach may be helpful in managing the quantity of VUS results, the issue will continue to be challenging since it is customary to disclose findings of genetic testing according to preferences of the family, and families may wish to know about all VUS results.[3] In addition, some VUS results will later be classified as deleterious, and awareness of the result and its reinterpretation in theory would permit a clinician to update a patient. However, this 'duty to re-contact' is fraught with logistic, economic and legal considerations.[33] We recommend counseling the patient or parents that much remains to be learned and that, if interested, they should re-contact their physician in the future to learn if new information is available.

Implications for relatives—The diversity of opinion in our study regarding testing relatives reflects ethical dilemmas concerning the duty to inform relatives and the patient's right to privacy.[21,34–39] The physicians in our sample tended to assess the specific genetic findings, medical risk, and implications for reproductive decisions in the context of the personal preferences and family relationships of the individuals tested, suggesting a complex decision-making process that appears consistent with a shared decision model.[40]

CMA and non-genetics providers

Our findings that pediatricians and pediatric specialists reported a need for more education about CMA are consistent with reports that non-genetics medical professionals lack the confidence, knowledge and communication skills required for effective genetic counseling.[41–43] Lower ratings of parents' understanding by non-geneticists than by geneticists concurs with findings that parents' understanding can be impeded by receiving results from providers lacking genetics expertise, and improved by consultations with genetics professionals.[13] Our finding that, on receiving a VUS result, non-genetics clinicians are likely to consult with and/or refer to a geneticist, highlights the recognized need for patients and providers to have timely access to genetics professional, especially as genetic information becomes increasingly available.[12] However, the current medical genetics workforce is not sufficient to manage the demand for their services.[7,44] Non-geneticist clinicians are playing an increasing role in genomic medicine, and they require additional genetics training.[11,41,43–47] Our data support the view that educational resources need to be developed for non-genetics providers to facilitate their interpretation of CMA results and counseling of families.[2]

Limitations

While our study provides valuable insights into some key issues faced by physicians ordering CMA, there are several limitations: like many other surveys of physicians, our response rate was low,[47] and those who participated are likely to have greater interest in the topic; respondents were associated with a laboratory at a university-affiliated hospital, therefore findings are not generalizable to physicians in community-based practices;

hypothetical scenarios may not mirror how physicians might respond to actual patients; and sample size is insufficient to control statistically for demographic and interaction effects.

Despite the limitations, our findings contribute to our understanding of how health professionals incorporate new genetic technologies. This is the first study we know of to describe the ways in which providers are likely to act with respect to ordering CMA and discussing results with patients and families. Even in this relatively small sample of physicians there is little consensus about important issues regarding managing IFs. Our findings are helpful in identifying needs of providers for educational interventions addressing pre- and post-test counseling regarding uncertain and unexpected results.

Recommendations for future research and practice

A larger survey is needed to assess the opinions of a wider range of clinicians and to gain deeper insights into their perspectives. Future studies need to explore ethical and psychosocial issues raised by CMA, the best ways to address IFs in clinical practice, and the reasons underlying providers' divergent opinions about communicating the potential for IFs. The evaluation of new genomic tests should be accompanied by research on informed consent procedures and on the implicatons of incidental and uncertain findings for patients and relatives. Interventions need to be developed to train providers in interpreting and conveying CMA results, and it is important to elicit perspectives of patients and families as well as providers regarding informed consent and communication of results. Guidelines need to be updated and disseminated to non-geneticists ordering CMA.

Collaboration between geneticists, clinical laboratories, and other health care specialists needs to be facilitated in order to support providers and families, including assistance with interpretation of results and monitoring research for new information about VUS results. Clearly considerations about IFs (which IFs are medically actionable, at what age to report, should all be included in the medical record, etc.) will evolve over time as a variety of research consortia grapple with these issues.

Conclusions

CMA is a new technology presenting challenges to providers with respect to uncertain and incidental findings. Our study explored perspectives of providers using the test, and can be used to gauge likely early reactions and needs with respect to whole genome sequencing. While recommendations and guidelines for genetic testing suggest providing pre-test information to prepare families for IFs, a sizable proportion of clinicians did not consider it pertinent to explain the potential for IFs. We identified needs for education and access to guidelines, especially in the presence of uncertain or unexpected findings.

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Table 1

Participant characteristics and experience with CMA (N=40)

	Mean (SD)	% (N)
Gender		
Female		52.5% (21)
Male		47.5 (19)
Race/ethnicity		
White		72.5(29)
Black		7.5 (3)
Asian		10.0 (4)
Hispanic		5.0 (2)
Age in years	41.02 (9.02)	
Years since graduating medical school	15.10 (10.09)	
Type of practice		
University-affiliated hospital		92.5 (37)
Single specialty group practice		7.5 (3)
Training in genetics (select all that apply)		
Medical school curriculum		82.5(33)
Assigned reading/self study		52.5 (21)
Clinical rotation during med school		37.5 (15)
CME		37.5 (15)
Fellowships		30.0 (12)
Web-based training		10.0 (4)
None		5.0 (2)
Other (residency or fellowship rotation/electives/ research)		27.5 (11)
Medical specialty		
General pediatrician		27.5 (11)
Pediatric sub-specialty		60.0 (24)
Medical genetics		12.5 (5)
Ordered >30 CMA tests		35.0 (14)
Comfort level explaining results of CMA [a b c]		
Normal result	4.84 (1.67)	
Abnormal result	3.86 (1.69)	
Variant of uncertain significance (VUS) result	3.46 (1.69)	
Assessment of most parents' level of understanding of CMA results [a b]	2.49 (1.19)	

[a] Using a 6-point Likert scale: (1 =very low to 6=very high)

[b] Responses not present for all cases; N=37

[c] Comparison of comfort levels among 3 means (Normal, Abnormal, VUS) P<.0001

Table 2

Responses to evolving hypothetical scenario

Survey Item	Mean (SD)	% (N)
The patient (John) is a 2 year old male with the following characteristics: Multiple minor anomalies; Slight developmental delay (walking and speech); Height and weight 20th percentile for age; Physical exam does not point toward a specific diagnosis; No family history of similar anomalies.		
1. How likely would you be to offer the microarray test for this patient? [a]	4.14 (1.66)	
The results show a 2Mb deletion containing 8 genes. The clinical significance of the deletion is unknown at this time, according to the laboratory.		
2. What would you do? (More than one option may be selected)		
Do nothing – no other genetic testing is necessary		2.5 (1)
Resend the microarray on the patient		0
Offer parental testing		50 (20)
Refer the patient to a geneticist		52.5 (21)
Discuss the finding with a genetics professional		62.5 (25)
Review the result with the testing laboratory		27.5 (11)
Evaluate the genes involved for potential clinical significance		47.5 (18)
Unsure		5.0 (3)
Assuming the result is a variant of unknown significance		
3. What would you tell the parents? (More than one option may be selected)		
In-depth explanation of results including exact size and location of deletion		12.5% (5)
There is a small deletion on one of the chromosomes (but not exact size and location)		17.5% (7)
The findings were normal		0
The findings were inconclusive (not disclose specific result)		15.0% (6)
Location and approximate size and that findings were inconclusive		70.0% (28)
Nothing and refer to genetics professional		10.0% (4)
Unsure		5.0% (2)
Assuming that you offered the microarray test to John's parents in order to obtain more information about the result from John's microarray test.		
4. Which of the following would you consider pertinent to discuss with John's parents before they have the microarray test performed? (More than one option may be selected)		
Testing can determine if John's deletion is also present in a parent		92.3% (36)
Testing might show that a parent carries a genetic predisposition to certain diseases [d]		59.0% (23)
Testing might show that John is not the biologic child of both parents		30.8% (12)
Unsure		10.3% (4)
Suppose that John's parents decide to have the microarray test performed on themselves. The test results show that one parent (John's mother) carries the same deletion as John. The mother does not have features similar to John's. The mother reports that her sister's child (her nephew) has some similar features to John.		
5. Would you suggest that the nephew get tested for the same deletion? [b] [c]	3.98 (1.42)	
John's mother's test results additionally showed an incidental finding of a duplication that is associated with a high risk for developing Alzheimer disease.		
6. What would be your preference for return of this type of result from the laboratory to you regarding the incidental finding? [b] (Select one option)		
Not to be informed of the incidental finding either in the laboratory report or verbally		8.1% (3)
Be informed verbally by the laboratory, but not to include incidental findings in the laboratory report		5.4% (2)

Survey Item	Mean (SD)	% (N)
Full disclosure of the incidental finding in the result report		59.5% (22)
Leave it to the discretion of the laboratory whether or not to include the incidental finding in the laboratory report		8.1% (3)
Unsure/Don't know		18.9% (7)
7. How medically actionable (meaning there is a treatment or prevention strategy) do you consider Alzheimer's disease to be? [d]	2.86 (1.31) [e]	
8. How medically actionable (meaning there is a treatment or prevention strategy) do you consider colon cancer to be? [d]	5.32 (0.97) [e]	
9. If you were informed that an incidental finding were discovered in John's mother, please rate how likely you would be to disclose this information to her for the following results: [a]		
A genetic predisposition indicating a moderate risk of Alzheimer's disease	4.24 (1.42) [f]	
A genetic predisposition indicating a moderate risk of colon cancer	5.40 (0.86) [f]	
10. How likely would you be to suggest that John's mother inform her siblings of the result indicating risk for Alzheimer's disease? [b a g]	2.92 (1.30)	

[a] Using a 6-point Likert scale: 1 (very unlikely) to 6 (very likely)

[b] Not present for all cases, total N values are 40 for items 1–3; 39 for item 4–5; and 37 for items 6–10

[c] Using a 6-point Likert scale: 1 (definitely no) to 6 (definitely yes)

[d] Using a 6-point Likert scale: 1 (not at all) to 6 (extremely)

[e] p<.0001

[f] p<.0001

[g] 30% scored ≥ 4 (i.e. were likely to suggest informing relatives)