Healthcare providers' perspectives on the impact of genome-wide testing on pediatric clinical practice: Implications for informed consent and result disclosure

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INTRODUCTION

Genome-wide testing in pediatrics:
Genome-wide tests are increasingly utilized in pediatric clinical practice. *Chromosomal microarray (CMA)* is recommended as a first-tier diagnostic test to evaluate developmental delay, autism spectrum disorders (ASDs) and multiple congenital anomalies, with significant public health implications. CMA has improved diagnostic rates, and clinical utility has been demonstrated. However, genomic testing can generate information that may be uncertain and unanticipated, presenting ethical and practical challenges regarding informed consent and results disclosure, particularly in pediatric populations. Uncertain and incidental findings will increase with the introduction of *whole genome and whole exome sequencing* into clinical practice, thereby increasing the challenges for providers using genomic medicine.

In our mixed-method studies, we seek to understand the perspectives of healthcare providers and family members regarding the impact of genomic testing of children. This presentation focuses on how providers deal with CMA in their practice, and their views on incidental findings and informed consent.

Potential chromosomal microarray (CMA) results:
1. *Negative* (approx 82% of tested individuals)
   - No potentially pathogenic copy number variants
2. *Pathogenic* (11%)
   - Variant known to result in a genetic condition
3. *Variant of unknown significance (VUS) (7%)*
   - Deletion or duplication not previously described
   - Not seen in controls
   - Incomplete data on the genes in the region

Parental testing:
- Determines whether a variant is *de novo* or inherited
- Variants inherited from a phenotypically normal parent are likely to be benign, but a parent may have a mild or unexpressed form of the child's condition

Incidental findings (IFs):

- Unanticipated clinically significant findings unrelated to the reason for referral
- Testing of a parent or child may yield IFs

Guidelines (ACMG):

- Provide pre-test information to prepare families for IFs (Kearney et al., 2011)
- Laboratories conducting clinical sequencing seek and report mutations for selected genes and conditions (Green et al., 2013)

OBJECTIVES

- Elicit providers' perspectives regarding the impact of CMA on clinical practice
- Identify challenges raised by VUSs and IFs
- Understand reasons for divergent practices surrounding IFs and informed consent
- Formulate potential policies to address challenges

QUALITATIVE STUDY

Data Collection and Analysis

- Semi-structured, open-ended interviews
- Content analysis using Nvivo software

Sample (N=15)

- Providers who ordered CMA through a hospital laboratory

Medical geneticists (MG)	27% (4)
Genetic counselors (GC)	47% (7)
Non-genetics providers (NGP) pediatrician, pediatric neurologist, developmental pediatrician, nurse practitioner	27% (4)

Results

Themes and illustrative statements	
Incidental findings	
Benefits of IFs	*It's a good thing that you're getting the information before it's a problem. … For the cancer genes you could institute screening protocols …(PR07;MG)*
Psychological stress of IFs	*I don't think it's great for the families that they're identified young because that's so much emotional distress on a family that would not have had to deal with that emotional distress for years. (PR08;NGP-NP)*

Duty to convey information	*I feel like it's my duty. ….It's their information so they should know everything… (PR09;GC)*
Informed consent process	
Formal consent not obtained for IFs	*It's just not possible to go through a hundred percent consent process.… I've never said "We could find also that there is a cancer predisposition." I don't say that ahead of time. (PR04;GC)*
Pre-counseling for IFs can arouse anxiety	*I think that would increase the anxiety while they're waiting for test results. … for the 99% of patients that that's not going to be the case for, but making it easier for the handful of people that that is going to be the case for. (PR12;GC)*
Patients should have information & options	*..you could see them not wanting to know… you would probably give them the option as to how much information they wanted rather than just forcing that on them or just choosing not to mention it at all. (PR12;GC)*
How to address needs of providers & families	*…the limitations of being in clinic and trying to get everything done… it's hard to go into sufficient detail with everyone and then open a whole can of worms. …Literature provided beforehand would be a good way to put it out there (PR12;GC)*

QUANTITATIVE STUDY

Data Collection and Analysis

- Online survey
- Statistical analysis using SPSS and SAS software

Sample (N=40)

- Providers who ordered CMA through a hospital laboratory

Medical geneticists	13% (5)
General pediatricians	27% (11)
Pediatric sub-specialists 7 neonatologists, 5 neurologists, 4 endocrinologists, 3 dev. pediatricians, hematologist, gastroenterologist, oncologist, ophthalmologist, critical care specialist	60% (24)

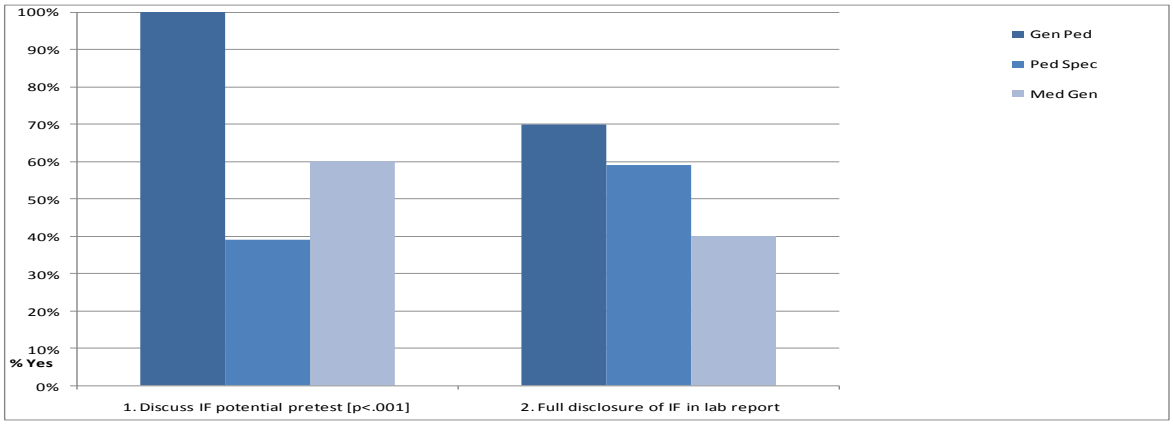
Results

Selected items from an evolving scenario:

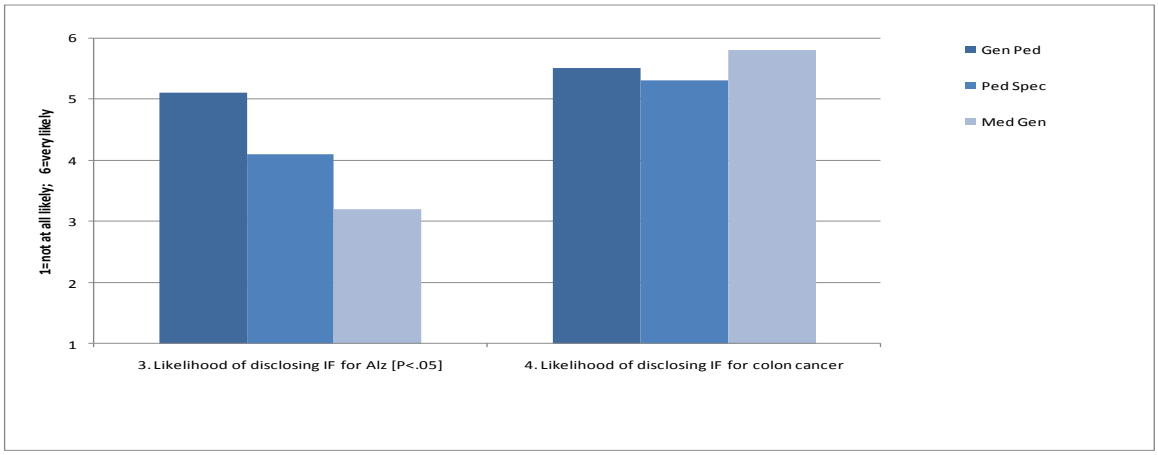
A child has CMA and receives a variant of unknown significance (VUS) result…

Parental testing is recommended….

Survey item	General Ped	Ped Specialist	Med Geneticist	P value
1. Before the parents have CMA performed, do you consider it pertinent to discuss the potential for IFs? [% agree; Freq]	100% (11)	39% (9)	60% (3)	<.001
2. An IF associated with high risk for Alzheimer disease is detected in a parent. Would you want full disclosure in the lab's report to you?	70% (7)	59% (13)	40% (2)	ns



Survey item [scale 1-6; not at all likely to very likely]	**General Ped**	**Ped Specialist**	**Med Geneticist**	**P value**
3. How likely would you be to disclose an IF associated with a moderate risk for Alzheimer disease to the affected parent? [mean; SD]	5.1 (1.10)	4.1 (1.34)	3.2 (1.64)	<.05
4. How likely would you be to disclose an IF associated with a moderate risk for colon cancer disease to the affected parent? [mean; SD]	5.5 (0.71)	5.3 (0.98)	5.8 (0.45)	ns



CONCLUSIONS

- Overall, disclosing IFs leading to early detection of an *actionable* condition (e.g., colon cancer) was considered beneficial
- Opinions varied about benefits and harms of disclosing IFs for *late-onset and non-actionable* conditions (e.g., Alzheimer disease)
- Concerns were expressed about *psychosocial harms* of disclosing pre-symptomatic incidental findings
- *Time pressures* can impede pre-test counseling and informed consent process
- Perspectives differed by *medical specialty*: Generalists tended to endorse more pre-test discussion and disclosure of IFs
- Results are consistent with *parent reports* that potential for IFs tends not to be discussed in pre-test counseling for CMA testing of children (preliminary results from an ongoing study; PI, Reiff, R21-HG-006560)

PRACTICE & POLICY: PUBLIC HEALTH APPROACHES

Decision-making models

- *Shared decision-making (SDM)* is a public health priority. The delivery of patient-centered care, the focus of SDM, is a priority area for improvement in healthcare for the 21st century (Institute of Medicine, 2009).
    - With SDM, families and clinicians participate in medical decisions, exchange information, express preferences, and jointly determine a treatment plan (Charles et al., 1999).
- *Models to delineate and reduce uncertainty* can promote clarity and address informational needs regarding genomic testing (Han et al., 2011; Reiff et al., 2012).

Provider and family level interventions

- Use *decision aids* to facilitate shared decision making -- weighing benefits, harms and scientific uncertainty in context of personal values (Stacey et al., 2011).
- Provide *written and online resources* for families and clinicians, pre- and post-test.
- *Parents* who have been through the experience could be a resource for new families (e.g., peer-to-peer counseling).
- *Options* about IF disclosure should be provided to families.

System level interventions

- *Guidelines and resources* for non-geneticists should be provided via specialty organizations and CME.
- Encourage *collaboration* among clinicians and laboratories.
- Improve access to *genetics professionals*.
- Improve *genetic literacy* in order to enable informed medical decisions

LIMITATIONS

- Small sample size
- Affiliation of most participants with a single medical institution

RECOMMENDATIONS FOR FUTURE RESEARCH

- Include a larger and more diverse sample, with more medical sub-specialties
- Compare provider and family perspectives regarding informed consent and IFs
- Evaluate potential interventions to facilitate shared and informed decision-making (e.g., decision aids, informational materials)

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