

# Key Informants' Perspectives of Implementing Chromosomal Microarrays Into Clinical Practice in Australia

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High-resolution genomic tests have the potential to revolutionize healthcare by vastly improving mutation detection. The use of chromosomal microarray (CMA) represents one of the earliest examples of these new genomic tests being introduced and disseminated in the clinic. While CMA has clear advantages over traditional karyotyping in terms of mutation detection, little research has investigated the process by which CMA was implemented in clinical settings. Fifteen key informants, six clinicians, and nine laboratory scientists from four Australian states were interviewed about their experiences during and in the time since CMA was adopted for clinical use. Participants discussed challenges such as result interpretation and communication. Strengths were also highlighted, including the collaborative approaches of some centers. Clinical experiences and opinions can inform larger studies with a range of stakeholders, including patients. The historical perspectives from this retrospective study can be helpful in guiding the implementation of future genomic technologies such as whole exome/genome sequencing.

■ **Keywords:** chromosomal microarray, clinical genomic medicine, whole genome testing, qualitative research

Rapid advances in genomic testing capabilities are driving the growth of genomic medicine, and high-resolution genomic testing has entered clinical practice. An early move toward clinical genomic diagnostics came with chromosomal microarray (CMA) testing, recommended in 2010 as a first tier test for patients with unexplained developmental delay/intellectual disability and/or congenital malformations (Gijsbers et al., 2009; Miller et al., 2010). The next logical advance in genomic diagnostics involves the widespread adoption of massively parallel sequencing technologies and reports of research to build this capability are becoming more frequent (Feero et al., 2012; Need et al., 2012; Topper et al., 2011).

Advantages of genomic testing include the ability to interrogate regions of the genome outside known disease-causing genes and to detect changes simultaneously in multiple regions. These particularly benefit patients in whom traditional targeted testing has not led to a diagnosis. However, concerns exist about the difficulty of data interpretation and the increased frequency of unexpected findings (Ali-Khan et al., 2009; Biesecker, 2012; Health Council of the Netherlands, 2010). The challenges related to genomic test-

ing have been acknowledged in the literature, with limited guidance in counseling and patient management available early on (Berg et al., 2011; Darilek et al., 2008).

Most initial publications were based on anecdotes or case studies (Berg et al., 2011; Bruno et al., 2011; Lu et al., 2007; Shaffer et al., 2007). There has been limited published research investigating the clinical application, including the test ordering process, test interpretation, and result communication to patients. One example investigated the opinions of genetic specialists from the United States, focusing on the disclosure of unexpected or incidental findings (Green et al., 2012; variants detected but unrelated to the original reason for testing). For approximately 65% of a range of

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incidental findings, specialists were in agreement about result disclosure; however, conflicting opinions were reported about the return of the remaining 35% (Green et al., 2012).

Results of uncertain or unknown clinical significance also require careful attention. 'Uncertain clinical significance' refers to results that have variable penetrance and are those for which there is conflicting evidence in databases and literature about the variant's contribution to disease. Distinct from uncertain results are those classified as having unknown significance and relate to a novel variant that has not previously been described in affected individuals or healthy controls. There is some research on patients' understanding of these types of results (Reiff et al., 2012); however, as yet there is little on the most effective approaches to manage uncertain results in the clinical setting.

In Australia, prior to 2010, CMA testing was piloted by a number of genetic diagnostic laboratories, although these pilot studies did not incorporate investigation into the wider clinical implications of CMA. Following this pilot stage, CMA testing for the investigation of pediatric patients presenting with developmental delay/intellectual disability and/or congenital malformations (Palmer et al., 2012) became available on the federal Medical Benefits Schedule (a funding mechanism for many pathology tests, although currently for only a very small number of genetic tests; Australian Government Department of Health and Ageing, 2012). This testing can now be requested by non-specialists.

Our study aims to understand how CMA was implemented clinically in Australia by exploring key informants' perspectives.

## Methods

### Study Design

A qualitative approach was chosen to allow for in-depth discussion of the integration of genomic technologies into clinical practice.

### Ethics

The project was approved by the Royal Children's Hospital Human Research Ethics Committee (Melbourne) in 2011 (HREC ref. number 31136).

### Sampling and Recruitment of Participants

Key informants were selected because they were health professionals with extensive experience working in clinical genomic medicine, including individuals from both clinical and laboratory genetics services. Potential participants who worked in clinical genetics services or private pathology laboratories were initially sampled purposively (Patton, 1990) through professional networks of the researchers. Snowball sampling (Corbin & Strauss, 1990) was also used when participants were asked to recommend other clinicians or scientists who might be appropriate and interested in participating. Invitations were sent by email and participants

who did not respond were sent a follow-up email approximately two weeks after the initial invitation, asking them to respond even if they were not interested in being involved.

### Data Collection and Analysis

Interviews were conducted by ET between August 2011 and February 2012 either face to face or via the telephone and were digitally recorded; interviews ranged from 25 to 35 minutes. Audio-recorded interviews were transcribed verbatim and de-identified. Transcripts were analyzed using thematic analysis (Corbin & Strauss, 1990), where data collection and analysis occurred in parallel. Interviews followed a semi-structured question guide, where questions covered topics such as the test ordering processes, the interviewee's opinions about and experiences of the integration of chromosomal microarray into clinic, the process of result interpretation, and future genome technologies. The interview guide was modified throughout the data collection/analysis stage in an inductive manner to incorporate and explore emerging concepts. Analysis used the constant comparison approach, whereby concepts emerging from current analysis were compared with concepts from earlier analysis. Interviews were independently co-coded by SM. Interviews continued until no new themes emerged from the data, a process known as data saturation (Corbin & Strauss, 1990). Data were managed using NVivo9.0 (QSR International, Australia).

## Results

A total of 18 individuals were invited to take part in an interview. Of these, all responded to either the initial invitation email or the follow-up email, and 15 individuals agreed to participate, including six genetic clinicians and nine genetic diagnostic laboratory scientists. Those who declined to participate gave the reason of being too busy.

Table 1 summarizes the main characteristics of participants.

Those individuals who were interviewed had considerable experience with CMA, with representation from the top four laboratories/clinical services performing over 66% of CMA tests reported nationally at the time (personal communication, Mark Pertile, Senior Medical Scientist, Cytogenetics at the VCGS).

There were three major themes that emerged from the data: (1) having high expectations of the technology leading to early implementation and diffusion, (2) facing interpretation difficulties due to the use of genomic technologies with increased resolution, and (3) challenges arising when a genomic test is available for non-specialists to request.

### Having High Expectations of the Technology Leading to Early Implementation and Diffusion

When describing how CMA was implemented in their jurisdiction, many spoke of 'reactive' and 'proactive'

**TABLE 1**  
Participant Characteristics

		Number of participants (total = 15)
Participant category	Scientist — cytogenetics	6
	Scientist — molecular genetics	3
	Clinician — pediatric/adult	4
	Clinician — prenatal	2
Years of experience in job (qualified)	<10 years	4
	10–20 years	3
	21+ years	8
	Range: 2–27 years	
Private/public healthcare setting	Public	13
	Private	1
	Public and private	1
Place of practice	Victoria	9 (three laboratories/clinical services)
	New South Wales	4 (two laboratories/clinical services)
	South Australia	1
	Western Australia	1

approaches. Reactive approaches represent the wider implementation of a test before its impact and implications are fully understood. Proactive approaches included assessing the implications of the new test in the clinic before it was introduced, through appropriate research and clinical trials.

The majority of participants described a reactive approach to CMA introduction in Australia, feeling that introduction was possibly premature, with staff needing to react to, and deal with, the challenges and potential harms as they arose.

One of the difficulties is knowing, should we approach these technologies reactively or proactively? . . . at the moment we are tending to react to this [the use of CMA in the clinic]. (Clinician 3)

I think they [scientists implementing microarrays] didn't quite expect to find out all the things [uncertain results and incidental findings] that they have been finding out, because they didn't put things in place to deal with it beforehand. (Scientist 4)

Despite many believing CMA was introduced prematurely into the clinic, on reflection participants were comfortable with how the process occurred.

I think it [the introduction of CMA to the clinic] has worked reasonably well, there are things that I would very much like to do differently, but we don't have the freedom to do that . . . so I'm comfortable with what we achieved, recognizing that it was less than perfect. (Clinician 3)

Participants discussed the multiple stakeholders driving the use of a new technology into the clinic.

So one of the drives I think that makes it [new technology] maybe introduced quite quickly, is the drive from the doctors because we know there's something new and exciting that will help our patients, the drive from some families who are aware that there's a new test available, and certainly the drive from the lab to want to be commercially the first lab to have this new

test, and so all those things push it at a certain pace. (Clinician 1)

Contrasting views on the impact of CMA on genetic practice were expressed: some individuals did not think it had changed or significantly impacted on practice, others felt introduction of these genomic technologies is the start of a change in genetic practice and the roles of genetic health professionals. These individuals predicted an excessive amount of data being produced, impacting heavily on their workload.

. . . it's going to massively change our job I think, when we get to the point . . . where we're not selecting which patients and which genes to look at, they'll [the patient] have had it all done [tests ordered by pediatricians] and my job will be to sort out the mess at the end. (Clinician 1)

Participants stated that results generated by CMA may need to be followed up in future when new research produces information that needs to be incorporated. When discussing these changes to follow-up protocols, participants mentioned being anxious about the need for more resources and funding to facilitate the changes.

It's the resources that are a problem, it's finding the time to do all of this and whose job is it and who pays for it? (Clinician 5)

Maybe you can look at what you need to know now [results related to the patient's condition] and store the DNA [to analyze later when more scientific knowledge is available] . . . but, who says the patient is coming back to you? . . . and at the end of the day, who's going to pay for all of that? Are . . . patients going to now pay for storage of their information, because they may want it down the track? (Scientist 4)

#### Facing Interpretation Difficulties due to the Use of Genomic Technologies With Increased Resolution

Participants explained the process of interpreting results, particularly those of uncertain or unknown clinical

significance. When these results were encountered, participants felt they relied heavily upon tools used to help with interpretation, in particular databases (internal and public such as DECIPHER (<http://decipher.sanger.ac.uk/>) and dbSNP (<http://www.ncbi.nlm.nih.gov/snp/>)) and the literature. When limited information is available about a variant, participants explained that there is greater need for interaction between the laboratory staff and the clinical team to interpret results, compared with a variant which is clearly pathogenic or benign.

For a while we had . . . a sort of working group [made up of scientists and clinicians] where we would look at all the abnormal results [variants of uncertain and unknown significance] and talk about them. Which I think is a real strength of the system here [at this clinical service], that is not present everywhere. (Clinician 1)

If there's something [a microarray result] there that we're not really sure about . . . I would consult with clinicians . . . and other very experienced scientists who have . . . analyzed thousands of microarrays and get a, sort of a collective opinion about the benefits of reporting and not reporting. (Scientist 2)

Testing parental samples of the child under investigation was considered an important step in the process of result interpretation. Participants explained that this will often have to be performed in the case of a result of uncertain significance, to ascertain if the variant is *de novo* or inherited.

Just because there's a bit of a long waiting time for clinics, we get the parental samples done in the meantime while we're waiting for the appointment and so that when they do come to see us, we've got parentals plus child, so it's much easier to interpret. (Clinician 6)

While information from parental testing will sometimes help with interpretation, it may also make the process more complicated.

It's [parental testing] helpful for large copy number changes where there are many genes and the majority of those will turn out to be *de novo* [CNV]. There are, nonetheless, a small minority that turn out to be inherited from a parent and so they're particularly challenging because they break the . . . dogma I suppose that [only] *de novo* copy number change is pathogenic. (Scientist 1)

Individuals described anxieties relating to interpreting whether an uncertain/unknown variant is contributing to the patient's clinical phenotype. In these cases, hypotheses regarding the variant's function will be made when little evidence is available. They mentioned concerns that a variant which is reported as possibly pathogenic could in future be confirmed as benign and vice versa.

In terms of considerations surrounding disclosure of results, it was apparent from discussions that practices differ in terms of whether or not incidental findings are reported. Some laboratories have protocols that stipulate this infor-

mation will not be reported, whereas other laboratories will decide this on a case-by-case basis.

So in terms of maybe a young child being referred for developmental delay or autism, it's [a deletion on the Y chromosome] an incidental finding, it's not related to their reason for referral, but as that child gets older, they may experience infertility later down the track so there's a bit of a dilemma as to whether we report that or whether we don't because the child is obviously not able to consent to whether they want that information known or not. So currently we don't report them, but that's continually being reviewed as people change their way of thinking. (Scientist 9)

Participants discussed negative aspects of the test in terms of anxieties they had about the detection of incidental findings and the communication of this information to patients. On the other hand, participants also outlined positive aspects of the test, which, due to an increased diagnostic rate, has been very helpful for many families. It became apparent that participants experienced a tension between the advantages of the test and negative aspects or concerns about the test.

### Challenges Arising When a Genomic Test Is Available for Non-Specialists to Request

Individuals believed that it is crucial for the clinicians both ordering and explaining the results to have a good understanding and knowledge about the technology. Now that CMA testing is available through the Medical Benefits Scheme (MBS) in Australia, participants discussed that clinicians who are not genetic specialists are requesting CMA. Participants felt that these non-genetic clinicians may lack the appropriate knowledge and understanding about CMA required to provide their patients with pre-test counseling and consent.

Since the microarray test has now come on the Medicare schedule, anyone can order it which does have implications . . . at the moment, the issue of consent, because of Medicare, doctors just send it in, you know, it's a bit of a dog's breakfast [i.e., a mess]. (Scientist 9)

Participants warned that if the information is being misinterpreted, this can have harmful implications for patients.

Often . . . the GP or the specialist might say 'this is the cause of your problems', and so the patient actually thinks that there's a one-on-one direct cause for this variation to the phenotype or the problem, and that's often not the case, it's often much more complicated than that. (Clinician 5)

Participants talked about the importance of education surrounding the use of a new test in the clinic. They reflected on their involvement with educating others about CMA. Both scientists and clinicians explained they had given seminars about new technologies to medical and postgraduate students and other health professionals. However, participants also expressed concerns about the effectiveness of these

education initiatives, and more broadly about the level of genomic knowledge of health professionals.

Often times the people who are using the test don't come to your talk [seminar explaining the technology]... I think expert users [genetic specialists] know how to use it [CMA] and most other people are confused by it. (Clinician 5)

The clinician's level of knowledge was considered to influence the process of ordering the test: those with limited knowledge may contact the laboratory to ask for their opinion, or the lab may have to contact the referring clinicians if an inappropriate request is made. The test being available on the MBS has further influenced this process.

... certainly a lot of the pediatric neurologists who might be requesting tests, I know them well enough now that they will accept when I say 'We need more information' or 'This is not an appropriate test'. (Scientist 7)

Participants explained that when scientists write the report, they make a decision about which information should be on the report and which should be withheld. The laboratory team will often independently make decisions about reporting a result that is clearly pathogenic or clearly benign though, as outlined above, liaison between the clinical team and laboratory staff occurs in some centers when an uncertain/unknown variant or incidental finding is detected. The majority of participants in our study explained that it is the laboratory scientist who writes the report and the authorizing senior scientist will make the final decision about whether a variant is reported:

We don't always agree, ultimately the lab people write the report. (Clinician 1)

## Discussion

Through these qualitative interviews, we retrospectively explored genetic specialists' views and experiences of using a new genomic technology in a clinical setting. The results provide a descriptive account and an indication of practice in Australia at the time of implementing CMA in clinical settings. We found that at the time of interviewing, many of these key informants had anxieties and concerns about current genomic testing. In addition, we found that inconsistencies existed across Australian genetics centers with regard to protocols and disclosure of results to patients.

Genomic diagnostics is a fast-moving area. In the short time since these interviews were conducted, changes have already occurred and some of the issues identified in these interviews have been or are currently being resolved in the context of whole exome/genome sequencing (see Table 2).

In March this year, the American College of Medical Genetics and Genomics (ACMG) released guidelines specifying which incidental findings should be reported to patients undergoing whole exome/genome sequencing (Table 2). In-

**TABLE 2**  
Issues Identified and Progress Made

Issue	Progress in 2013
Detection of results of uncertain and unknown clinical significance	Frequency of detecting these types of results is expected to decrease as the volume of CMA tests increases and knowledge about individual variants increases. The Royal College of Pathologists of Australasia (RCPA) has drafted guidelines for the use of exome/genome sequencing (RCPA, 2013). The guidelines refer to the detection of uncertain results and may be of value to the clinical use of CMA also. Research surrounding the management of these types of results has expanded (Reiff et al., 2012, 2013).
Education of non-specialists	Guidelines for the use of exome/genome sequencing released by the RCPA may be of educational benefit to non-specialists using genomic tests. The importance of genomics education is mentioned in these guidelines with the suggestion that laboratories should consider organizing in-house training programs (RCPA, 2013).
Detection of incidental findings	American College of Medical Genetics and Genomics have released guidelines with suggestions surrounding the disclosure of these results (Green et al., 2013). These guidelines are to be used in the case of genome/exome sequencing; however, the recommendations may be used to make judgments relating to disclosure of incidental findings detected using CMA. It should be noted, however, that these guidelines may not be relevant to an Australian setting. Additionally, in recent months, research around the disclosure of incidental findings in a clinical setting has expanded (Downing et al., 2013; Green et al., 2012; Lemke et al., 2012; Townsend et al., 2012).

cidental findings have been a longstanding part of clinical medicine, particularly in medical imaging, though incidental findings were previously rare in genetic testing due to the fact that most genetic testing has been targeted to a specific gene and/or mutation(s). While recommendations such as these can provide valuable guidance to clinicians, it is important to note that some suggestions put forward by the ACMG are contrary to longstanding ethical standards, such as the right of a patient 'not to know' and recommendations regarding the return of genetic information in children.

A recent study from Canada using focus groups with genetics healthcare professionals, the general public and parents whose children had undergone genetic testing discussed the importance of pre-test counseling and consent (Townsend et al., 2012). They highlighted that this is complicated by the involvement of clinicians who are not genetic specialists. This was a concern raised by participants in our study also, who had some experience in educating colleagues without specialist genetics training about new

technologies. To them, it appeared that, due to the rapid introduction of CMA into a clinical setting, these initiatives were arranged retrospectively rather than as an integrated step of the process. An example of an education program occurring in parallel to a change in practice (in a different clinical context) is one that relates to a revised newborn screening consent process in Victoria. This has included a state-funded position for a person to educate staff in every hospital in Victoria about the new consent process and act as a contact for any staff or parent enquiries (personal communication, Sally Morrissy, Newborn Screening Nurse).

Previous research shows limited knowledge of fundamental genetic/genomic principles by health professionals who do not have specialist genetics training (Baars et al., 2005; Harvey et al., 2007; Houwink et al., 2012; Metcalfe et al., 2002), stressing the importance of education when introducing new genomic technologies into clinical practice. When assessing applications for tests to be listed on the MBS, the guidelines state considerations may include the 'skills required for ordering, performing and interpreting the test' (Medical Services Advisory Committee, 2005). The results from our study highlight the importance of these guidelines in the context of genomic testing. They will become even more significant for the use of CMA in prenatal testing, and for implementation of next-generation sequencing technologies in diagnostics.

While data from our interviews focused on the challenges encountered when introducing CMA, participants also discussed an aspect of CMA implementation they felt had worked well in some centers; that is, strong collaboration between the laboratory team and the clinical team. Liaison is crucial when uncertain results arise as the two teams have differing expertise. The clinician is able to interpret the result in the context of the patient and take into consideration their family history and phenotype, whereas the laboratory team has expertise in bioinformatics gained from interpreting large volumes of results. It is potentially questionable whether this situation would occur when genomic testing is performed by private pathology laboratories which may not have such relationships, and is especially concerning for direct-to-consumer testing (Borry et al., 2011).

Our findings provide some novel and valuable commentary on how CMA was put into clinical practice, although we acknowledge that there are limitations to the study. The results do not include perspectives of other health professionals who may have ordered CMA or of parents of children on whom CMA testing was performed; however, it was our intention to focus on stakeholders actually involved in implementation. Also, the findings relate only to an Australian context and some aspects of the data may not be generalizable beyond Australia; for example, in New Zealand, interpretation of their Code of Rights (Health and Disability Commission, 2009) would imply that information cannot be withheld from pa-

tients, that is, all analyzed laboratory results must be reported.

In conclusion, this study offers a snapshot of health professionals' experiences during the implementation phase of CMA into clinical practice in Australia. The challenges and strengths presented can inform those planning to adopt high resolution genomic technologies for diagnostic use and may be included in a framework for developing policy, planning education strategies, and counseling.

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