CLINICAL GUIDELINES

Practice guideline: joint CCMG-SOGC recommendations for the use of chromosomal microarray analysis for prenatal diagnosis and assessment of fetal loss in Canada

Christine M Armour,1 Shelley Danielle Dougan,2 Jo-Ann Brock,3,4 Radha Chari,5 Bernie N Chodirker,6,7 Isabelle DeBie,8 Jane A Evans,7 William T Gibson,9,10 Elena Kolomietz,11 Tanya N Nelson,9,12,13 Frédérique Thy,14 Mary Ann Thomas,15,16 Dimitri J Stavropoulos,17 On-Behalf-Of The Canadian College of Medical Geneticists

ABSTRACT

Background The aim of this guideline is to provide updated recommendations for Canadian genetic counsellors, medical geneticists, maternal fetal medicine specialists, clinical laboratory geneticists and other practitioners regarding the use of chromosomal microarray analysis (CMA) for prenatal diagnosis. This guideline replaces the 2011 Society of Obstetricians and Gynaecologists of Canada (SOGC)-Canadian College of Medical Geneticists (CCMG) Joint Technical Update. Methods A multidisciplinary group consisting of medical geneticists, genetic counsellors, maternal fetal medicine specialists and clinical laboratory geneticists was assembled to review existing literature and guidelines for use of CMA in prenatal care and to make recommendations relevant to the Canadian context. The statement was circulated for comment to the CCMG membership-at-large for feedback and, following incorporation of feedback, was approved by the CCMG Board of Directors on 5 June 2017 and the SOGC Board of Directors on 19 June 2017. Results and conclusions Recommendations include but are not limited to: (1) CMA should be offered following a normal rapid aneuploidy screen when multiple fetal malformations are detected (II-1A) or for nuchal translucency (NT) ≥3.5 mm (II-2B) (recommendation 1); (2) a professional with expertise in prenatal chromosomal microarray analysis should provide genetic counselling to obtain informed consent, discuss the limitations of the methodology, obtain the parental decisions for return of incidental findings (II-2A) (recommendation 4) and provide post-test counselling for reporting of test results (III-A) (recommendation 9); (3) the resolution of chromosomal microarray analysis should be similar to postnatal microarray platforms to ensure small pathogenic variants are detected. To minimise the reporting of uncertain findings, it is recommended that variants of unknown significance (VUS) smaller than 500 Kb deletion or 1 Mb duplication not be routinely reported in the prenatal context. Additionally, VUS above these cut-offs should only be reported if there is significant supporting evidence that deletion or duplication of the region may be pathogenic (III-B) (recommendation 5); (4) secondary findings associated with a medically actionable disorder with childhood onset should be reported, whereas variants associated with adult-onset conditions should not be reported unless requested by the parents or disclosure can prevent serious harm to family members (III-A) (recommendation 8). The working group recognises that there is variability across Canada in delivery of prenatal testing, and these recommendations were developed to promote consistency and provide a minimum standard for all provinces and territories across the country (recommendation 9).

BACKGROUND

Introduction Invasive prenatal diagnosis (PND) has been available since the 1970s and, since that time, has largely involved conventional karyotyping. Historically, PND was offered for primary investigation of possible fetal aneuploidy, with other structural chromosomal anomalies being detected simultaneously. Technological advances have increased the PND options to include quantitative fluorescence PCR (QF-PCR), which has now wholly replaced conventional cytogenetic analysis in some centres, for cases where the sole indication is increased risk of fetal aneuploidy of chromosomes 13, 18, 21, X or Y.1 Whereas karyotyping is used in other specific higher-risk situations, this type of analysis has limitations, including limited genomic resolution and necessity of using cultured cells for analysis.

In addition to its ability to identify cases of aneuploidy, chromosomal microarray analysis (CMA) is a high-resolution technology capable of detecting microdeletions and microduplications throughout the genome. Depending on the methodology used, microarray analysis can detect additional concerns, including varying levels of mosaicism, cases of uniparental disomy (UPD) and possible consanguinity. For some time now, CMA has been used in the evaluation of children with unexplained developmental delay, autism spectrum disorder or congenital anomalies and has been shown to increase the diagnostic yield in such populations by up to 15% over conventional karyotyping.2,3 The improved resolution provided through CMA yields...
an increased rate of diagnosis of chromosome anomalies, as well as an increase in the rate of uncertain findings, unrelated findings or adult-onset disease indicators.

**Canadian context**
The delivery of healthcare services in Canada is largely regulated by the Canada Health Act that governs universal coverage for medically necessary healthcare services. However, which services are medically necessary is not defined in the Act; rather, it is up to each provincial and territorial government to determine the services that they will cover. Variation in provincial and territorial health programmes and policies results in significant inter-regional disparity among prenatal genetic screening and diagnostic programmes, despite established and emerging national guidelines. Further discrepancy is noted when evaluating service availability in rural versus urban contexts. In addition, individual physicians must balance the needs of their patients with the responsible use of finite resources within the system.

Given that access to prenatal testing is variable across Canada, this document is meant to provide some consistency and a minimum standard that should be available across the country. It is recognised that jurisdictions may choose to augment the minimum recommendations according to their own resource availability with due consideration of the implications of expanded testing. Therefore, it is strongly recommended that provincial/territorial standards be developed to ensure equal access across each region. Additionally, while access to services varies both among and within provinces, the recommendations that follow assume access to high quality ultrasound as a basic or fundamental minimum.

**Methods**
A multidisciplinary group consisting of medical geneticists, genetic counsellors, maternal fetal medicine specialists and clinical laboratory geneticists was assembled to review existing literature and guidelines for use of CMA in prenatal care and to make recommendations relevant to the Canadian context. The quality of evidence in this document was rated using modified criteria described in the Report of the Canadian Task Force on Preventive Healthcare, as used in the previous Society of Obstetricians and Gynaecologists of Canada (SOGC) guidelines. The statement was circulated for comment to the Canadian College of Medical Geneticists (CCMG) membership-at-large for feedback and, following incorporation of feedback, was approved by the CCMG Board of Directors (5 June 2017) and the SOGC Board of Directors (19 June 2017). The CCMG is a Canadian organisation responsible for certifying medical geneticists and clinical laboratory geneticists and for establishing professional and ethical standards for clinical genetics services in Canada. The SOGC is a Canadian organisation which produces national clinical guidelines for both public and medical, education and clinical practice, on important women’s health issues. This guideline replaces the 2011 SOGC-CCMG Joint Technical Update.

**CLINICAL INDICATIONS**
Given the complexity of interpretation and counselling, clinical prenatal chromosomal microarray analysis should only be ordered by a clinical geneticist or other physician with sufficient expertise in the use of the technology and the clinical interpretation of the results. In all instances, it is recommended that rapid aneuploidy detection (RAD) techniques be performed prior to chromosomal microarray analysis.

**For samples obtained via invasive prenatal testing**
In most jurisdictions, prenatal CMA is being employed in cases where multiple fetal anomalies have been detected by obstetric ultrasound. A 2011 joint SOGC-CCMG technical update concluded that prenatal CMA is advantageous in these situations.

In instances with certain isolated fetal anomalies, prenatal CMA has been shown to provide additional diagnostic yield over that of conventional karyotyping and has also been recommended in such situations. Meta-analyses of CMA results in cases with isolated defects indicate a rate of pathogenic variants of ~5%, however, determining which individual malformations are most strongly associated with abnormal CMA results is challenging, as many papers report aggregate data by system, while others provide details of defects only in CMA positive cases. The systems with the highest yields of positive results in isolated cases are central nervous system (~6%), gastrointestinal (~7%), musculoskeletal (~8%) and cardiac (~7%). Higher detection rates for pathogenic variants (8%) have been observed with individual malformations including holoprosencephaly, cerebellar hypoplasia, hypoplastic left heart, cleft lip and/or palate and omphalocele. In contrast, abnormal CMA results on fetuses with certain other isolated anomalies (eg, ventriculoseptal defect, gastrochisis, renal agenesis and lower urinary tract obstruction) do not appear to have been reported to date.

However, when a single structural defect is seen in association with other non-structural ultrasound findings, the frequency of pathogenic CMA results is higher, especially with intrauterine growth retardation or overgrowth (13.6%) or abnormal amniotic fluid volume (9.1%).

Increased nuchal translucency (NT) ≥3.5 mm, or >99 percentile, is associated with increased risk of fetal aneuploidy as well as increased risk of certain syndromes and other structural defects. A recent meta-analysis of the use of CMA in fetuses with increased NT and normal karyotype demonstrated incremental yields in diagnosis between 4% (in cases with isolated NT) and 7% (in cases with other malformations), with aberrations including those involving 22q11.2.

In cases where an invasive procedure is undertaken for other reasons (eg, familial genetic conditions, positive prenatal screen, maternal age or anxiety), CMA is more frequently becoming an option after normal RAD results are available. This approach could be viewed as a form of opportunistic rather than diagnostic testing. As such, it may identify unrelated findings. A prospective study found that approximately 1.7% of pregnancies with late maternal age or a positive prenatal screen have a pathogenic or likely pathogenic copy number change. In any screening approach, the net benefit should be evident, healthcare providers with sufficient expertise should be available for appropriate follow-up and potential harms mitigated.

**Recommendation 1**
A. Offer of chromosomal microarray analysis (in addition to any other relevant diagnostic testing) is recommended in cases with multiple fetal anomalies identified by a comprehensive obstetric ultrasound (II-1A). Other diagnostic testing may include specific single gene, multigene panels or other genetic tests if the pattern of anomalies suggests a specific genetic condition not identified by array (II-2 A).

B. Single structural defects in association with other abnormal ultrasound findings (eg, intrauterine growth restriction
(IUGR), oligohydramnios) should not be considered isolated, and thus array should be offered if RAD is normal (III- B).

C. In cases with a single fetal anomaly, prenatal CMA should be considered for those malformations associated with a high frequency of abnormal results. Its use in cases where the diagnostic yield is lower may be considered, if resources are available (III- B).

D. In fetuses with an NT ≥3.5 mm, prenatal CMA should be offered (II-2 B).

The working group recognises that, in some instances, local resources allow for prenatal chromosomal microarray analysis to be available for all invasive prenatal specimens, outside of the above indications. While an approximate 1.7% risk of abnormal findings has been documented,14-15 there is also the impact of incidental findings and variants of unknown significance (VOUS) in a broad population (the so-called ‘toxic knowledge’) to be considered.16 At present, there is a paucity of evidence regarding the overall clinical utility and impact on outcomes associated with the broad use of CMA in routine prenatal diagnosis.17 Therefore, local decision-makers must use caution and weigh the options and resources available prior to including CMA in the routine PND menu. In such situations, it is advised that this only be undertaken when there are concomitant clinical resources available to facilitate thorough pretest counselling and follow-up care.

For analysis of fetal loss prior to 20 weeks gestation

The majority of chromosome anomalies identified in early pregnancy loss are aneuploidies, detectable with conventional karyotyping.18 The 2010 CCMG guidelines recommended cytogentic analysis of early pregnancy losses with evidence of growth retardation or congenital anomalies.19 Conventional cytogenetic analysis can be complicated by technical challenges that can result in low diagnostic yield from these non-viable pregnancies. Conversely, microarray can be performed directly on DNA from fetal samples, obviating the need for live, dividing cells and can provide a higher resolution analysis.20-22

Recommendation 2

In cases of congenital anomalies and/or IUGR, in any fetal loss prior to 20 weeks gestation, if QF-PCR methodologies and/or other directed diagnostic inquiries do not provide a diagnosis and further cytogentic analysis is intended, it is recommended that karyotype be replaced with chromosomal microarray analysis (III-B).

In the previous CCMG 2010 recommendation, parental karyotyping was recommended for couples after their third pregnancy loss.21 The working group noted that some jurisdictions may have the capacity to undertake CMA investigations for products of conception in these situations. Although there is little evidence to suggest that it has advantages over conventional cytogentic analysis of the parents, CMA does have the potential to detect unbalanced translocations in the fetus that may not be detectable by G-banding. Therefore the potential exists for higher diagnostic yield by using CMA to investigate the products of conception/fetus and should be considered further.

For samples from stillbirths, that is, fetal deaths at ≥20 weeks gestation

Evidence on the clinical utility of CMA in stillbirths is limited and is based on studies with wide-ranging criteria, methods and analysis. One area of clear advantage is with respect to failure rate associated with testing; unlike conventional karyotyping, CMA does not require live cells, which allows for analysis of samples that would otherwise not be amenable to karyotype analysis.24-25 Some limitations of CMA include the inability to detect balanced translocations or polyploidy, and maternal contamination can still be a concern if extraembryonic tissue is analysed.26 Interpretation of the significance of potentially pathogenic copy number variants (CNVs) can be problematic, especially if parental samples are not available.27 When parental samples are available, few VOUS are found to be de novo events.28

In stillbirths, aneuploidy is a more common finding (6%–7%) than pathogenic CNVs (~3%).27-28 Both are more frequent in stillbirths with structural malformations than in those without and in antepartum versus intrapartum fetal deaths.23 Exact figures vary depending on whether array was done on all cases versus being done only if karyotyping failed or was normal. VOUS frequency is variable across subgroups; studies have reported ranges between 0.6%–2.1%29 and 5%–6%30 of samples.

Recommendation 3

A. Aneuploidy is the most common abnormal chromosomal finding in stillbirths. If RAD and/or other directed diagnostic inquiries are uninformative, it is recommended that in cases complicated by congenital anomalies and/or IUGR, karyotype be replaced with CMA when further cytogenetic analysis is desired (II-2B).

B. In stillbirths without structural fetal anomalies, CMA may be considered in the context of local resource availability and site-based postmortem protocol (whether complete, limited or external only) (II-2B).

Pretest counselling

The various types and potential ambiguity of results available through prenatal CMA necessitates clear and thorough pretest counselling and consent. A professional with expertise and understanding of the complexity of CMA and the potential results, and who has the ability and time to provide unbiased information, should facilitate this counselling. For a list of specialty genetics centres across Canada, please refer to the Canadian Association of Genetic Counsellors website at www.cagc-acgc.ca.

Discussion around approaches to incidental findings follows later in this document, but centres that choose to report such findings should ensure that patients receive counselling by qualified health professionals, focusing on both the risks and benefits of learning about this type of result. Counselling must include recognition of and discussion of possible adverse outcomes, including parents’ learning about secondary findings that they did not wish to know, such as identification of an adult onset disorder.

Recommendation 4

Given the varied contexts in which prenatal chromosomal microarray analysis may be offered, it is essential that pretest counselling be undertaken by a professional with expertise in the utilisation of CMA in the prenatal setting. The counselling content should be documented in the medical record. This pretest counselling should include:

A. Formal informed consent for chromosomal microarray analysis, including the parental decisions regarding the receipt of secondary findings (subject to the limitations described in Recommendation 8), should be communicated clearly to the laboratory via the requisition to ensure that the
Position statement

report reflects only that information that was agreed to by the parents.
B. Information regarding the limitations of the test methodology used,
C. Occurrence of variants of uncertain significance and the possibility of secondary findings.
D. Discussion of possible outcomes, including what will and what will not be reported, such as:
   I. variants of uncertain significance;
   II. CNVs associated with variable expressivity or penetrance;
   III. secondary findings not related to the reason for testing;
   IV. carrier identification, both for autosomal recessive and X-linked disorders.
E. Potential issues related to insurance and discrimination.
F. Potential need for parental samples and additional testing, accompanied by a discussion of what may be reported from parental samples.
G. Educational material that can be provided to supplement the clinical discussion to enable reflection beyond the clinic encounter.
H. If the family is concerned about the risk of a specific adult-onset condition, they should also be counselled regarding the pattern of inheritance and the appropriate testing options available to family members (III A).

CONSIDERATIONS FOR TECHNICAL ASPECTS AND REPORTING

CMA encompasses all types of array-based genomic copy number analyses, including array-based comparative genomic hybridisation and single nucleotide polymorphism (SNP) arrays. Both platforms can detect large scale and submicroscopic chromosomal imbalances (gains and losses) and mosaicism as low as approximately 10%-20%. The advantages of SNP arrays include the detection of copy neutral absence of heterozygosity (AOH), which may suggest UPD, identity by descent, parental consanguinity or loss of heterozygosity, as well as the detection of triploidy. Neither platform can identify balanced rearrangements.

In terms of testing methodology, direct testing on uncultured cells should be performed wherever possible. When performing analysis of chorionic villi, DNA should be isolated from the mesenchymal core cell fraction of uncultured chorionic villi. In ongoing pregnancies, protocols should be established (eg, establish reserve cell culture) to avoid the need to recollect a sample should initial DNA extraction fail to meet established quality standards, or should additional testing be required (eg, G-banding to resolve structural chromosome abnormalities). Maternal cell contamination should be investigated as per CCMG guideline: ‘Recommendations for the Indications, Analysis and Reporting of Prenatal Specimens’ (2010) (pending revision).

Copy number analysis

The working group agreed with the classification of CNVs recommended by the American College of Medical Genetics (ACMG):
- pathogenic;
- uncertain clinical significance: likely pathogenic;
- uncertain clinical significance;
- uncertain clinical significance: likely benign;
- benign.4

Prenatal CMA should be capable of detecting CNVs with the same resolution as for postnatal CMA to ensure small ‘pathogenic’ variants, or ‘uncertain clinical significance: likely pathogenic’ variants will be detected and reported. It is recommended that larger minimum threshold sizes for reporting variants of ‘uncertain clinical significance’ should be applied for prenatal testing to decrease the reporting of such findings to parents, which can lead to significant parental anxiety.39 35 A 2014 Canadian microarray symposium reached consensus that for prenatal array, thresholds should be set at 500 kb for deletions and 1 Mb for duplications; CNVs of ‘uncertain clinical significance’ that are smaller than these size limits should not be reported.36 It was also agreed that variants of ‘uncertain clinical significance’ exceeding these size thresholds should not be reported automatically; rather, such variants should only be reported if there is some published, but not necessarily conclusive, evidence that they may be pathogenic.

Recommendation 5

A. CNVs should be interpreted by the laboratory after review of available literature and appropriate databases of benign and pathogenic variants (eg, ClinGen, ClinVar, Database of Genomic Variants, DECIPHER), including databases of missense, nonsense and in-del variants in the genes affected by the abnormality detected by CMA. This review should include consideration of the potential mechanism of morbidity of the impacted gene(s) (eg, loss or gain of function). Care should be taken in interpreting results where a parent originates from a population that is poorly represented in publicly available databases. Therefore, the lab should request parental ethnicity on the requisition.

B. The resolution of analysis should be similar to that obtained from postnatal chromosomal microarray analysis2 to ensure small variants that are classified as:
   a. ‘pathogenic’, or
   b. ‘uncertain clinical significance: likely pathogenic’ can be detected and reported (III-B).

C. To minimise the reporting of uncertain findings, it is recommended that variants of ‘uncertain clinical significance’ smaller than 500 Kb deletion or 1 Mb duplication not be routinely reported in the prenatal context. Additionally, such variants above these cut-offs should only be reported if there is some, but not necessarily conclusive, evidence that they may be pathogenic (III-B).

D. Variants characterised as:
   a. ‘uncertain clinical significance: likely benign’ or;
   b. ‘benign’ should not be reported.

E. When possible, parental CMA analysis or fluorescent in situ hybridisation/qPCR studies should also be performed to aid clinical interpretation, considering the possibility of reduced penetrance and variable expressivity.

Variable penetrance and expressivity

Many CNVs are associated with phenotypes that have reduced penetrance and/or variable expressivity, including autism spectrum disorder, psychiatric conditions and cognitive developmental disability.37 Given that the predictive value is uncertain for the vast majority of such CNVs, other jurisdictions have narrowed the recommended reportable list of these susceptibility variants to those where the risk of neurodevelopmental disorders is established and where the CNV is associated with structural malformations that warrant additional ultrasound follow-up.9 38

Recommendation 6

A. The laboratory should report only those CNVs characterised by reduced penetrance/variable expressivity that have
multiple lines of evidence supporting a high risk of the deletion/duplication for neurodevelopmental abnormalities or congenital malformations. Examples of CNVs that fit these criteria have been published previously; however, the laboratory should apply the same principles as new CNVs meeting these criteria are identified.

B. In the case of a female fetus found to be a carrier of a CNV on the X-chromosome, the report should indicate potential for phenotypic heterogeneity and the need for clinical interpretation.

Absence of heterozygosity
SNP arrays have the advantage of detecting long continuous stretches of homozygosity, which may reveal instances of UPD, identity by descent or loss of heterozygosity. The threshold for reporting AOH has been suggested to be greater than 10 to 13.5 MB. The absence of heterozygosity

Recommendation 7
A. In cases with no identified consanguinity: (III-A)
   I. If a segment with AOH larger than 10 Mb is detected in one chromosome, and in the absence of genome-wide AOH (eg, total autosomal AOH <6%), then the possibility of UPD should be reported for chromosomes associated with an imprinting disorder (ie, 6, 7, 11, 14, 15).
   II. If AOH is detected in a chromosome associated with a known UPD syndrome, definitive UPD testing is necessary.
   III. As detection of AOH can be observed in the absence of UPD, and SNP arrays cannot detect all instances of UPD, it is recommended that the report include a disclaimer that SNP array is not a diagnostic assay for UPD.
B. In cases with known consanguinity:
   I. AOH should not be reported unless specifically requested. However, in such instances, it is suggested that the report indicate that ‘regions of AOH are available on request’.
   II. As detection of AOH results in the CMA report.

Approach to secondary findings
Prenatal chromosomal microarray analysis is employed specifically to correlate clinical indications with potential underlying chromosomal abnormalities, with the intent to inform immediate management of the pregnancy. The committee agrees prenatal chromosomal microarray analysis should not specifically search for CNVs unrelated to the primary reason for referral. Similarly, the CCMG guideline for genome-wide sequencing recommends a cautious approach to reporting secondary findings, which includes the avoidance of analysing genes unrelated to the primary diagnosis. However, the nature of chromosomal microarray analysis is such that CNVs often include many genes and may include those related to secondary or incidental findings associated with adult-onset conditions or carrier status.

Other jurisdictions have reached differing conclusions regarding reporting of secondary findings. In the UK, unsolicited pathogenic findings are recommended to be reported only when the identified variant may inform present or future management of the pregnancy or family; non-actionable findings are not to be reported. When considering incidental findings in clinical exome and whole genome sequencing, the ACMG has allowed patients to opt out of such results, requiring discussion at the time of patient consent, prior to sample submission.

The working group recognises that there is limited evidence available with regard to the benefits, risks and costs of disclosing secondary findings arising from prenatal CMA and that the reporting of secondary findings is a controversial issue. For secondary findings that have been identified during the course of prenatal chromosomal microarray analysis, the working group used a similar rationale to the CCMG guideline for genome-wide sequencing. Since all scenarios identified by the working group for prenatal CMA were not addressed in the CCMG guideline for genome-wide sequencing, the recommendations were based on the available evidence and group consensus.

Recommendation 8: (III-B)
A. Secondary findings that reveal risk for a highly penetrant condition that is medically actionable during childhood should be reported.
B. It is recommended that laboratories not report fetal risk for adult-onset conditions unless
   I. the parents specifically request this information, or
   II. disclosure of the information could prevent serious harm to the health of other family members (eg, pathogenic mutation in a gene with high risk of cancer susceptibility).
C. It is recommended that laboratories report non-actionable secondary findings (eg, related to early onset Alzheimer’s disease).
D. The laboratory does not have the obligation to later re-contact patients to advise of potential adult-onset conditions if they were not included in the prenatal array report.
E. It is not recommended that the analysis seek to identify CNVs associated with carrier status for autosomal recessive disorders. However, if in the course of analysis such information is identified, carrier status of autosomal recessive disease with a high carrier frequency in the population being tested (eg, ≥1/50 as has been suggested by other jurisdictions or as per local policy) should be reported.
F. It is not recommended that the analysis seek to identify CNVs associated with X-linked recessive carrier status. However, if in the course of analysis such information is identified, the laboratory should report female carriers of X-linked recessive mutations associated with childhood-onset disorders, since there may be significant risk to the family for conceiving affected males.

It is important for each centre to have a clear policy for each consideration above to facilitate transparent practices and patient counselling.

POST-TEST COUNSELLING
As with pretest counselling, prenatal CMA results should be provided to parents by a professional with thorough understanding of and experience with microarray analysis. Even in the context of well-described conditions, there can remain
ambiguity due to phenotype variability that cannot be clarified in the prenatal setting.19

All CMA results should be interpreted in the particular clinical context in which the analysis was undertaken. The professional communicating results should discuss that a negative result does not guarantee a normal postnatal outcome, reviewing testing limitations as was done in the pretest counselling. Regardless of the potential severity of the returned results, involvement of a specialist genetics service in the interpretation, counselling and follow-up of prenatal CMA is recommended.

Recommendation 9: (III-A)

A. As with conventional karyotyping or other targeted diagnostic testing, the possibility of other genetic anomalies that are not detectable by CMA should be discussed.

B. Any CNVs reported to parents should be in the context of appropriate genetic counselling, incorporating parental results and any additional information available.

C. Irreversible obstetrical decisions due to CMA findings should not be made without referring to a genetics specialty service,19 41 unless the decisions are based on the presence of malformations or other pregnancy concerns. The resources and expertise for multidisciplinary discussion and counselling, including ethics consultation, may be required in some cases.

D. Special precautions should be taken in counselling families who have educational, linguistic and/or cultural barriers to a full understanding of the counselling and who may have different prior assumptions about the predictive value of genetic testing results (sometimes referred to as ‘genetic determinism’).

CONCLUSION

This practice guideline serves to inform Canadian providers with direction regarding the use of chromosomal microarray analysis in the prenatal setting across Canada. It was developed based on current evidence and will evolve as further evidence arises.

Author affiliations
Department of Genetics, Children’s Hospital of Eastern and Children’s Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada
BORN Ontario, Children’s Hospital of Eastern Ontario, Ottawa, Ontario, Canada
Departments of Obstetrics and Gynecology, Dalhousie University Medical School, Halifax, Nova Scotia, Canada
Department of Laboratory Medicine, Dalhousie University Medical School, Halifax, Nova Scotia, Canada
Department of Obstetrics and Gynecology, University of Alberta, Edmonton, Alberta, Canada
Department of Pediatrics and Child Health, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
Department of Biochemistry and Medical Genetics, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
Department of Medical Genetics and Core Molecular Diagnostic Laboratory, McGill University Health Centre, McGill University, Montreal, Quebec, Canada
Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada
Division of Medical Genetics, BC Children’s Hospital Research Institute, University of British Columbia, Vancouver, British Columbia, Canada
Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada
Department of Pathology and Laboratory Medicine, BC Children’s and BC Women’s Hospitals, Vancouver, British Columbia, Canada
Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada
Service de Génétique Médicale, CHU Sainte-Justine, Université de Montréal, Montreal, Quebec, Canada
Department of Medical Genetics, University of Calgary, Calgary, Alberta, Canada
Alberta Children’s Hospital Research Institute for Child and Maternal Health, University of Calgary, Calgary, Alberta, Canada

Genome Diagnostics, Department of Pediatric Laboratory Medicine, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

Acknowledgements
The authors would like to acknowledge the SOGC Genetic Committee (Francois Audibert, MD, Montreal, Quebec, Canada; J-AB, MD, Halifax, Nova Scotia, Canada; Richard N Brown, MD, Beaconsfield, Quebec, Canada; Carla Campagnolo, MSc, London, Ontario, Canada; June C Carroll, MD, Toronto, Ontario, Canada; IDB, MD, PhD, Montreal, Quebec, Canada; Jo-Ann Johnson, MD, Calgary, Alberta, Canada; Nanette Okun (chair), MD, Toronto, Ontario, Canada; Melanie Pastuck, RN, Cochrane, Alberta, Canada; Karine Vallee-Pouliot, RM, Montreal, Quebec, Canada; R Douglas Wilson, MD, Calgary, Alberta, Canada; Rhonda Zwingerman, MD, Toronto, Ontario, Canada) for review of the document.

Contributors
CMA, SDD, JAB, RC, BNC, IDB, JAE, WFG, EF, FT, MAT, TNN, and DIS conceived and developed the content. CMA, SDD, RC, IDB, JAE, WFG, EF, FT, MAT, TNN and DIS drafted the initial version. All authors critically reviewed the article and approved the final version.

Funding
The authors also acknowledge funding from The Hospital for Sick Children Centre for Genetic Medicine and the University of Toronto McLaughlin Centre.

Competing interests
None declared.

Provenance and peer review
Not commissioned; externally peer reviewed.

Open Access
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES
10 de Wit MC, Srebnik M, Govaerts LC, Van Opstal D, Gailjaard RJ, Go AT. Additional value of prenatal genomic array testing in fetuses with isolated structural ultrasound
Position statement

abnormalities and a normal karyotype: a systematic review of the literature. 
17 Harris R. Overview of screening: where are we and where we may be headed. Epidemiol Rev 2011;33:1–6.