Prenatal genomic microarray and sequencing in Canadian medical practice: towards consensus

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Canadian medical genetics professionals and international guest advisors gathered in Toronto on October 2, 2014, at the invitation of the University of Toronto's McLaughlin Centre. The Centre's mandate is to advance genomic medicine through education and research, and the purpose of the symposium was to consider the challenges in applying new genome-wide technologies to prenatal testing in Canadian genetics centres, and to set the stage for practice guidelines with the hope of national consensus. The gathering included 59 clinical or laboratory geneticists, genetic counsellors, and maternal fetal medicine specialists, representing 17 genetics centres from 8 provinces. Other contributing speakers were Toronto ethicist Dr. Kerry Bowman, and geneticists Dr. Bettina Blaumeiser and Dr. Bronwyn Kerr from Belgium and the United Kingdom (UK), respectively. Expository presentations were followed by break-out discussion groups to address four topics.

The Canadian context

Canadian health care is under provincial jurisdiction, with policy and choices about services controlled by the various provincial and territorial Ministries of Health. There is considerable inter-provincial discrepancy in resources for genetics and related services, and access may be further stratified by geographical issues, such as proximity to major centres. Nationally, Health Canada's mandate includes a supporting role in resource planning and adoption of new technologies. The Canadian College of Medical Geneticists (CCMG) and Canadian Association of Genetic Counsellors (CAGC) are the professional certifying bodies, both national in scope, and they, as well as the Society of Obstetricians and Gynaecologists of Canada (SOGC), contribute to standards of practice in genetic medicine through policy and practice guidelines, for consideration by individual provinces and centres. These practicing professionals recognize the benefits of early guidance as a means to minimize regional disparities, although local influences and new technology development usually move much more quickly than policy development. This one-day conference was offered as a means to bring practitioners together from across the country to consider how to anticipate what is poised to be a dramatically different paradigm for prenatal testing.

Transition

Eventually, prenatal testing will be through relatively non-invasive means, will be relatively standardized, and will involve the collection of comprehensive fetal whole genome sequence data for various interpretations. In the meantime, a big transition phase is taking

place, with many available options and complex driving forces. To what extent will new genomic technologies be able to replace the current prenatal practices, as applied for screening or diagnosis of abnormalities?

Genomic ("chromosomal") microarrays have become the standard of care in the work-up for various *post*natal diagnostic issues, revealing variations and abnormalities in copy number of chromosomes or smaller genomic segments[1, 2]. With greatly enhanced resolution, these arrays have now replaced traditional G-banded karyotype analysis for neurodevelopmental disorders, congenital anomalies and autism, though they would miss certain alterations such as balanced rearrangements. They are also not suitable for ascertaining single base or small sequence changes in DNA, but other strategies such as whole-exome or whole-genome sequencing can do so. Experience in the postnatal realm is valuable as we consider application of these approaches to prenatal testing, but the challenges and stakes will be greater. These genomic analyses can reveal changes of unknown significance, and this creates a burden of uncertainty at a time when critical decisions about a pregnancy are urgent. Not only will the postnatal experience inform prenatal applications, but the experience with microarrays will guide approaches using whole-genome sequencing, which will inevitably follow in time.

Prenatal testing in context

Information about the genetic well-being of a pregnancy begins with knowledge of family history. Specific risks may be addressed with specific assays; for example, a molecular test for a particular disease-associated genetic mutation, or karyotype analysis for risk of an unbalanced chromosome rearrangement due to a parental balanced translocation. The next level of information for essentially all pregnancies comes from routine ultrasound, which, in addition to confirming and dating the pregnancy, can reveal various structural signs of abnormalities to warrant further investigation. A maternal blood sample can provide additional sources of information: serum contains biochemical markers associated with risk of chromosome abnormalities (i.e., specific aneuploidies) or structural defects (open neural tube defects (NTD) or abdominal wall defects (AWD)), and (more recently) cell-free fetal DNA can be used for genetic analysis. Chorionic villus sampling (CVS) or amniocentesis provide access to fetal tissue for genetic testing, and amniocentesis can also be a source of biochemical markers to detect open NTDs or AWDs. Due to the small but concerning risk of pregnancy loss, these "invasive" tests are not undertaken routinely, but may be offered in situations of elevated risk, and are the means of definitive diagnosis.

These various analyses provide different kinds of information, with a spectrum of associated certainty and risk. The focus of the symposium was on prenatal genomic assays (microarrays and sequencing), which could be applied to fetal DNA from amniotic fluid, CVS or (perhaps eventually) maternal circulation. For several reasons, however, this needs to be considered in the context of the other sources of information. What are the questions and concerns about the pregnancy that are to be addressed? What combination of tests can most effectively and efficiently address those questions? Given other information, when is a genomic assay indicated? Will these assays eventually usurp other approaches to monitoring pregnancies?

David Chitayat outlined approaches to prenatal diagnosis from an historical context leading up to current practices, and emphasized its role in primary prevention of congenital disorders. Recognition that the risk of Down syndrome increases with advanced maternal age was an early driver for screening tests, and prompted the development of biomarkers that inform about risk for certain aneuploidies as well as structural anomalies (NTDs or AWDs). He suggested that early second trimester ultrasound is a better strategy for detection of NTD/AWD and, in Ontario, should replace the current maternal serum alpha-fetoprotein (AFP) determination.

Maternal serum screening progressed from “triple screening” (AFP, human chorionic gonadotropin (hCG), and estriol (uE3)) to “quad screening” (includes inhibin A), undertaken in the second trimester. An integrated prenatal screen (IPS) that combines maternal age data, ultrasound measurement of nuchal translucency at 11-14 weeks gestation and maternal serum biomarkers provides a more accurate risk assessment, with increased detection and lower false positive rate for trisomy 21. However, this analysis requires blood tests in the first and second trimester, which can impede compliance, and provides risk estimates later in the pregnancy. Dr. Chitayat proposed a first trimester screen that includes ultrasound measurement of nuchal translucency along with first trimester biomarkers as an appropriate compromise toward screening accuracy, earlier risk estimates (typically within the first trimester), and increased compliance. It was also noted that there are significant challenges to providing equal access to prenatal screening. For example, the expertise to provide accurate nuchal translucency measurements is typically only available in urban centres with ultrasound labs, and the screening regimen offered to expectant parents can vary among health care practitioners in each province, and certainly across Canada. There is a need to establish a minimum standard (or better, a target standard) across the country, and certainly equal access to a standard screening protocol provincially.

A more direct screening strategy has been commercially available since 2011, called non-invasive prenatal testing (NIPT), by which cell-free fetal DNA in maternal circulation is assayed for evidence of aneuploidy. This approach is seen as a positive new strategy because it has a high detection rate (99% for trisomy 21) and low false positive rate (<0.1%), can be done early in pregnancy and reported quickly, and does not depend on nuchal translucency measurement. Specific tests originally included the common trisomies (21,18 and 13) but repertoires are gradually being expanded to included sex chromosome aneuploidies and certain microdeletion syndromes, though these have higher associated false positive rates and lower positive predictive value. At present, NIPT is a screening test and not a diagnostic test, and any abnormal finding needs to be followed with a diagnostic test through one of the “invasive” routes [3]. As the benefits (including cost) of NIPT over previous screening methods become realized, each province must establish criteria for access to testing in a public health system.

Experience of others

Bronwyn Kerr shared the experience of the UK, where they began a process of examining the utility of prenatal arrays about a year earlier. She provided pre-publication results of a 3-year study called Evaluation of Array Comparative genomic Hybridisation in prenatal diagnosis of foetal anomalies (“EACH”) [4]. The strong message communicated was that uncertainty during pregnancy is toxic [5, 6]. As in Canada, the UK’s healthcare is publicly funded (through the National Health Service (NHS)) but with regional variation in policies and priorities; there is also a smaller private healthcare sector. Genetics services are concentrated into 8-10 centres, and roles that would be handled by genetic counsellors in Canada are managed by midwives. The multi-centred EACH study compared outcomes of array comparative genome hybridization (aCGH) to those from traditional G-band analysis, in pregnancies with ultrasound abnormalities. Arrays indeed detected 50% more findings. In order to avoid detection of CNVs that would be problematic (i.e., unrelated to the reason for testing, or variants of unknown significance (VOUS)), one participating centre developed a strategy of high-resolution aCGH testing with low-resolution and targeted detection through custom-designed software [7]. Filters avoided the recognition of variants smaller than a pre-set threshold (3 megabases), other than those with an established pathogenic association. The approach is highly adaptable to individual circumstances and evolving information, since the *in silico* filters – not the microarray platform – would be adjusted to accommodate each clinical situation. Other centres made use of an expert panel to consider whether to report various unclear findings.

A UK Joint Committee on Genomics in Medicine sponsored a prenatal array workshop in February 2014, agreeing that aCGH should replace karyotype in the context of specific ultrasound findings (increased nuchal translucency or structural abnormality), and considered issues that would eventually apply to NIPT and fetal whole-exome or whole-genome sequencing. Five working groups were established to prepare guidance on the issues. Dr. Kerr discussed many of their recommendations, and guidelines on these subjects will be published shortly[4]. On the basis of the research findings, they are advocating for funding for this service through the NHS.

Working groups for UK Joint Committee on Genomics in Medicine

- National information sheet and consent
- Care pathway
- Obstetrics workforce and genetic counselling education
- Variant determination and reporting
- Expert advisory panel

Another European perspective was presented by Bettina Blaumeiser of Belgium. Eight genetics centres - all associated with medical schools - have relatively few geneticists (royally appointed) who meet regularly, work closely together, and are entitled to charge genetic microarray analyses (but not NIPT) to the refund health insurance system. They came to consensus about procedures for prenatal microarray that are overseen by an *ad hoc* committee [8]. A national database for prenatal microarray results is in progress. She noted that counselling is required (physician geneticists or midwives), and the consent process does not offer any opt-out choices for the family (i.e. regarding VOUS or secondary findings). Consensus includes reporting policies, but problematic issues (about 20-25% of cases) are referred to the *ad hoc* committee.

Since most of the prenatal cytogenetic microarrays for Ontario have, to date, been carried out in American commercial laboratories, Marsha Speevak undertook to summarize the United States (US) approach, where analysis by chromosomal microarray has become the standard of care for invasive prenatal testing. Primary influences have included the American Congress of Obstetricians and Gynecologists (ACOG) [9], a study by Wapner et al. [10] and the American College of Medical Genetics and Genomics (ACMG) statement on NIPT [11]. The Wapner et al. study [10] compared chromosomal microarray to karyotype for routine prenatal diagnosis in >4000 samples, concluding that microarrays identified additional clinically relevant cytogenetic information, missing only balanced rearrangements and triploidies. On that basis, ACOG revised their original guidelines [9] in 2013 [12] to recommend microarray for prenatal analysis for women of any age with abnormal ultrasound findings, and for analysis of fetal demise or stillbirth, emphasizing the need for pre- and post-test counselling and documentation of informed consent, particularly with respect to findings of uncertain significance. The ACMG statement [11] addresses screening for trisomies 13, 18 and 21 using NIPT, but predicts that this is a first step toward eventual whole fetal genome sequencing. They comment that it should not replace more comprehensive testing by amniocentesis or CVS when fetal abnormalities are detected, and that all positive screen results must be confirmed by CVS or amniocentesis. It is most suited to pregnancies with elevated risk of specific trisomies based on serum markers; one study found that availability of NIPT increased the uptake of follow-up testing and replaced invasive testing for some women [13].

Secondary influences on prenatal use of microarrays include the ongoing improvements in public databases for CNVs, array platforms and analysis tools, and knowledge bases from laboratories doing post-natal microarrays, including private databases. The health insurance

industry is a significant driver in the US, and providers are revising policies in light of the findings described. In Canada, provincial health ministries are similarly following suit.

Canadian Experience

Prenatal diagnosis (as opposed to screening) is poised to take advantage of the enhanced detection, resolution and efficiency associated with microarrays, but this comes with the dilemma of how to interpret the vast majority of information revealed, and the associated uncertainty.

Frédérique Tihy described five years of laboratory experience at Montreal's Hôpital Ste. Justine with the first 1000 prenatal genomic microarrays, most in response to abnormal ultrasound findings. About 10% yielded pathogenic results, including some that were undetectable by G-banded karyotype. She detailed the few outcomes of uncertain significance. Relative to postnatal applications of array data, the prenatal context has little phenotype information, and decisions may be of a life-or-death nature, with great urgency. Tihy's group developed a reporting protocol for various scenarios, generally being more conservative in the reporting of VOUS prenatally than for postnatal diagnostics. This is reflected in a consent form which describes what will and will not be reported, and offers a single choice (which concerns findings with adult-onset implications). She advocated strong guidelines for reporting, including the issue of where the responsibility lies for withholding certain findings – i.e. with the laboratory or the referring physician.

What to report? Ste Justine consensus

- predisposing genes (<100% penetrance) – report
- adult onset – choice on consent
- recessive gene deletion – don't report (if common, discuss with physician)

To help predict the challenges of prenatal microarray analysis, Abdul Noor brought the experience at SickKids Hospital with processing of about 4,000 postnatal diagnostic cases per year. Using thresholds of 500 kb for duplications and 200 kb for deletions, they (and the lab at Credit Valley Hospital) found that 15% of patients referred postnatally due to developmental delay or multiple congenital anomalies had VOUS. He classified instructive cases as those with challenges in interpretation and those with technical issues. Loci associated with neuropsychiatric disorders may have a clear risk association, but variable penetrance and expression make the phenotype unpredictable. This is a relatively young science, and published data for a given new variant may only emerge over time. Size of a variant is considered, but is not an entirely reliable predictor of effect. X-linked variants in females can have unpredictable effects due to X inactivation. Technical issues include missing smaller CNVs that can nonetheless be pathogenic, questions about involvement of exons near the CNV breakpoint, confirmation of suspected mosaicism, and suspected unbalanced structural abnormalities that must be resolved in a timely manner using additional genetic tests. Discussion followed about whether criteria should be different for predicting pathogenicity and reporting in the prenatal scenario.

Hana Sroka contributed the counselling perspective, and experience at Toronto's Mount Sinai Hospital as a broker for new prenatal technologies. She emphasized the balancing act between benefits and harms associated with microarrays: autonomy and choice vs. harmful information and uncertainty, resting on a fulcrum of informed consent and shared decision-making. Not every pregnant couple needs or wants the information that could be revealed, and research is needed to better understand the target audience. Despite concerns over VOUS, uncertainty is far from a new dilemma in prenatal genetics, and counsellors need to draw on experience to

manage new situations. Penetrance may be a less useful genetic concept than variable expressivity. With enhanced knowledge, VOUS are moving towards known classifications (pathogenic or benign), and along with decreased risks associated with invasive procedures, these developments will encourage more frequent use of prenatal microarray. Counterbalancing this, however, is the uptake of NIPT for specific aneuploidies, which is likely to increase as service providers add the option of microdeletion screening to the assay panels. Some of these services are publicly funded in some provinces, or can be purchased privately, but as screening tools, they will create a certain need for follow-up (i.e. by aCGH) by the public healthcare system. Issues raised now will eventually apply with greater intensity to fetal genome sequencing. Whether we should offer any of these tests widely depends on the ability to offer necessary supports, and the counselling role will be ever greater.

Challenges of Consent

The question of what kind of predictive information pregnant women are seeking, and the purpose of expanded prenatal testing was picked up by Kerry Bowman, who considered what the drivers are. Acknowledging the market forces in technology, he also advised a focus on how the widening test options may expand reproductive choice, rather than on improving population health. Tests need to be aligned to the questions being asked, with balance between diagnostic advantages and ambiguity. By their explorative nature, the broader approaches are blurring distinctions of diagnosis and screening, intended and incidental findings, and the research threshold. Presenting relatively unfiltered uncertain information may impair a woman's autonomous choice.

Consent to testing is necessary, with absolute clarity as to whether it involves a research component. What does consent need to look like in the prenatal context? It is intimately connected to counselling, involving a collaborative process for information retrieval in accordance with the patient's values and wishes. Counselling capacity must be in place before testing is expanded. We need better knowledge of the wishes of patients, and research into the means for more nuanced forms of consent, being prepared to adapt models as needs arise. Subsequent discussion included consideration of how social cultural issues can be accounted for, given population migration that is so relevant to the Canadian context.

Pre-conference survey

Hana Sroka surveyed conference registrants in advance of the meeting, under the title "Working towards a consensus", with questions around testing availability and access, VOUS, choice and consent. She could report relative agreement among these Canadian practitioners that: 1) they would benefit from national guidelines, 2) a consent form is needed, 3) women should be offered some choice with respect to the nature of information to be delivered or withheld, and 4) NOT all women should be offered invasive prenatal testing. She also saw evidence of a shift in thinking towards expanding the use of microarray. *(Post-conference note: In 2015, at least three centres in Ontario - Mt. Sinai, Credit Valley, North York General Hospitals - have begun to offer microarray testing for all "invasive" prenatal procedures; despite earlier opinions, they do not offer choice about the disclosure of results)*. Respondents included roughly similar numbers of laboratory geneticists, clinical genetics and genetic counsellors, with a few additional specialists.

Discussion Group: Testing availability and access

This discussion was wide-ranging with astute questions raised and few answered. The group acknowledged that prenatal screening is already disparate across provinces, including access to first trimester ultrasound or measuring nuchal translucency, and entry points for considering tests such as microarrays or NIPT will be similarly non-uniform. The first question (which remained unanswered) is what criteria justify an invasive diagnostic test, but then for those who will undergo the procedure, should they all be assayed by genomic microarray? Or, does rapid aneuploidy detection (RAD) with results limited to specific aneuploidies suffice in some situations? Discussion revisited the matter raised by Dr. Bowman that testing needs to match the question(s) at hand and be tailored to needs of the patient, as well as acknowledging the possible harmful effects of unanticipated information. On the other hand, there is a long-standing precedent of a karyotype for every prenatal diagnostic test, regardless of the primary reason for testing, and this too is a genome-wide screen, albeit at lower resolution than microarray, but also with the possibility of ambiguous findings. The difference is one of degree, but perhaps the original premises and model need reconsideration at this time, given the significantly higher frequency of VOUS currently associated with high resolution genomic analyses. One commented that we cannot focus overly on rare issues, but should begin with common sense. Until whole genome sequencing becomes the norm, many possible genetic disorders will be undetected by microarrays. Eventually there was consensus that microarray should be offered in response to specific abnormal ultrasound findings or increased nuchal translucency, but not on whether all invasive tests for other indications should include such analysis. When offered, it should be a publicly-funded service, including pre- and post-test counselling, so as to avoid two-tiered inequities. New questions emerged: Who should be allowed to order the test? Only a geneticist? How would that contribute to equitable access?

Discussion groups

Availability and Access to Testing

- *How do we ensure access to testing is medically appropriate and equitable in a public healthcare system?*
- *How should screening and detection algorithms change as NIPT and microarray become available?*
- *What is the role of G-banding?*

Counselling and Education

- *How do we overcome the challenges associated with education and consenting?*
- *What are the key elements of the consenting process?*
- *Should a signed consent be mandatory for invasive genomic testing?*
- *Should parents have a choice for return of results?*

Genomic Technologies and Reporting of Results

- *Microarray resolution – same as for postnatal or lower resolution?*
- *Under what circumstances do we report VOUS from prenatal arrays?*
- *Considerations for susceptibility loci associated with neuropsychiatric disorders.*
- *How do we deal with medically actionable incidental findings, carrier status, and X-linked mutations identified in a female fetus?*

Considerations for the future

- *How will advances in genomic diagnostics impact screening and invasive diagnostics in 3 to 5 years?*

Around matters of reporting, a possible dichotomy was noted between laboratory and clinical geneticists, with clinicians somewhat more conservative, inclined to limit reporting to questions at hand, while laboratory scientists were reluctant to filter results. Analogy was noted from the realm of radiology.

Clearest consensus was on the remaining role of the G-banded karyotype, with agreement that it is needed for follow-up to determine mechanism of imbalance, to confirm trisomy or other aneuploidy, when a microarray fails, or for family history suggestive of a chromosome rearrangement.

Discussion Group: Counselling and education

The group proposed that tools developed as aids to counselling and consenting could be shared among centres, and that there could be a national initiative to do so. The program Genetics Education Canada – Knowledge Organization (GECKO) was suggested as a mediator. In particular, pre-counselling tools such as videos could save counselling time, but might also help to address issues around the need for pacing of information and decision-making, which are particularly problematic for patients unable to attend multiple clinic visits. Language and cultural barriers require special attention.

Consent is a process, the key elements of which are the elicitation of the patient's own values and issues, and dialogue about what tests are appropriate for the family's needs (as opposed to monologue about what is available). Until recently, consent has pertained to the invasive procedure, but not to what results would or would not be delivered. Arguably, there has never been consent for a karyotype, so why should microarray be different? If the answer is that it is a useful learning tool for service providers and ensures that issues have been covered (especially when choices are offered), then, is a signed information sheet enough, or documented verbal consent? Whether it should be mandatory was not resolved, but responsibility of non-genetics professionals was considered relevant.

The group recommended that there be few choices at most within the consent, so as not to complicate the process. Research is needed, not about the efficacy of microarrays but about its impact on clinical care. Decisions about what to report should be largely in the hands of clinicians, not patients.

Discussion Group: Genomic technologies and reporting of results

This group agreed that a prenatal array should be with the same platform (i.e. resolution) as used for postnatal analyses – leaving open the possibility of reassessment later – and a reporting threshold of 500kb for deletions, and 1Mb for duplications. CNVs would be classified as benign, pathogenic, unknown or incidental. They agreed that medically-actionable findings should be reported, and recessive carrier status when carrier frequency is >1/50 and other testing available. There was no consensus on reporting of findings related to late-onset conditions and whether or not to use current ACMG guidelines for reporting of secondary findings. To deal with this, and with reporting of VOUS and of CNVs associated with neuropsychiatric disorders of variable expressivity, they would recommend establishment of an *ad hoc* committee for further guidance, which would be a short list of responders ready for rapid turnaround; labs would be responsible for copying final reports to them. Discussion reflected that practitioners from across the country would benefit from sharing experience, and that an *ad hoc* committee should be voluntary with representation from clinical, lab and counsellors – perhaps through the CCMG and CAGC. Decisions about reporting should be agnostic of platform, but based on lists that are agreed as pathogenic in the prenatal context. A suggestion

was made to collect prenatal data along with decisions made, analogous to the database of genomic variants (DGV) [14], perhaps as an arm of that.

Discussion Group: Considerations for the future

This group foresaw that, within 5 to 10 years, biochemical screening will be replaced by the option of 1st trimester NIPT for all pregnant women. The recommended and anticipated protocol would include

- 1st trimester ultrasound for dating, chorionicity, and number of fetuses
- nuchal translucency measurement
- 1st trimester NIPT for all, with microdeletion/microduplication tests added as technology and cost allows
- 2nd trimester detailed "genetic" ultrasound to detect fetal structural abnormalities

Those with increased nuchal translucency, abnormal NIPT or fetal structural abnormalities would be offered invasive testing for confirmation and follow-up. The group was divided on the question of whether every invasive test specimen should have microarray testing – the no camp saying that screening should not be opportunistic for 1-2% CNVs. They anticipated transition through a combination of microarray with whole exome sequencing (since these pick up different kinds of variants) but eventually, fetal whole genome sequencing. There was a consensus concept of a Canadian model with one or a few reference centres doing all whole-genome sequencing but delivering to local centres for interpretation, though later discussion raised the possibility of centralized interpretation and decentralized sequencing.

Concluding Remarks

Steve Scherer thanked participants for a productive day addressing true translational medicine, with important data for the professional bodies to use in drafting guidelines for the Canadian landscape. He heard the message that many solutions will require more counsellors, particularly to ease some tension between laboratory and clinical services with respect to responsibilities, and he expects that counsellors will be able to play a greater role in the research realm. He was struck that, despite offering more and more information to families, it is not enough without solutions to the problems, and we need to continue to couple this research to development of treatments. Finally, though this was a very Canada-centric forum, many technologies with the biggest impact are coming from China, and we need to stay cognizant of such developments.

End-of-the-day consensus

- Provincial jurisdiction notwithstanding, Canada would be best served by common policies concerning prenatal genomic testing (microarrays and sequencing), and equitable access to related services.
- Resources could be shared, including technology platforms, policy development, experience and expertise, and communication tools.
- National professional bodies such as the CCMG, SOGC and CAGC should recommend practice guidelines.
- For prenatal testing, microarray resolution should be the same as for postnatal analyses, but reporting thresholds more conservative.
- The process of informed consent is important and warrants special consideration.
- Genomic microarray should be offered to women with structural fetal abnormalities or NT > 3.5mm detected on ultrasound (and others, but this was the consensus threshold).
- When offered, testing - including counseling - should be a publicly-funded service.
- A multi-disciplinary *ad hoc* committee should be established to provide further guidance and sharing of experience among Canadian jurisdictions, perhaps coordinated by CCMG and CAGC.
- Research is needed into the impact of these new prenatal tests on clinical care.

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