Chromosomal microarray as first-tier approach in low-risk pregnancies: detection rate should not be the only criterion for its application

We read with interest the paper by Hillman *et al.*[1] concerning the use of chromosomal microarray (CMA) in prenatal diagnosis. Presented datasets included: a prospective cohort of pregnant women with ultrasound abnormalities and a systematic review and meta-analysis of studies on prenatal cases referred for any indication, fetal ultrasound abnormalities included.

The authors corroborated the usefulness of CMA in pregnancies with ultrasound abnormalities, and reported an additional detection rate of abnormalities by CMA compared with karyotyping of 4.1% in their cohort and of 10% in the whole meta-analysis. These different figures were likely due to the different analytical sensitivity of the CMA platforms used (i.e. bacterial artificial chromosome (BAC) *vs* oligoarray). A BAC platform comparable to that utilized in the Hillman study has been tested by other groups[2,3], who claimed higher detection rates, by also incorporating into their results large imbalances detectable by means of good-quality chromosomal preparations. Accordingly, Hillman *et al.* emphasize the relevance of high-quality laboratory practices to compare CMA and karyotyping results in order to avoid a significant bias in any conclusion. Furthermore, copy number variations (CNVs) such as the *PMP22* deletion, classified as a 'positive' result, should be regarded as incidental findings[1,2] and should not be considered in the detection rate estimation of CMA when comparing with karyotyping; moreover, such results are unlikely to address the particular concerns the couple may have when seeking prenatal diagnosis for abnormal ultrasound findings. However, the results reported by Hillman *et al.* agree with published guidelines and statements indicating that pregnancies with ultrasound abnormalities would benefit from CMA.

Subanalysis of the pregnancies referred for 'any indication' disclosed highly heterogeneous results, with the additional detection rate of abnormalities by CMA compared with karyotyping ranging from 0.4 to 50%, while the detection rate of VOUS (variants of unknown significance) was 1.4%. Therefore, given the heterogeneity and increasing resolution over the years of CMA platforms and the merging of low- and high-risk populations, it is difficult to draw any final conclusion, particularly regarding CMA use in low-risk pregnancies. A recent report has indeed shown that when advanced maternal age or anxiety were the only or main indications for referral, the detection gain by CMA ranged from 1.0% and 0.6%, respectively[4]. These figures are evidently low compared with the VOUS detection rate.

In our opinion, the higher diagnostic capacity of CMA should not be the only criterion for updating health policy committee statements; such decisions should be planned only after careful assessment of the large-scale application of CMA to unselected populations. In this perspective, several crucial issues await resolution, including the appropriate array design, assessment of the clinical relevance of a CNV with variable penetrance and expressivity, consensus on reporting VOUS and the related emotional burden of such findings.

In order to assess comprehensively the large-scale application of CMA in low-risk pregnancies, we reiterate the advocacy for a model such as ACCE[5], which is formulated based on the main criteria for evaluation of a genetic test (analytical validity, clinical validity and clinical utility) but which also consciously considers ethical, legal and social implications. The latter considerations are of particular importance when proposing

genetic testing in a prenatal setting. We think that to better balance the costs and benefits of CMA application in prenatal diagnosis without specific indications, teamwork between geneticists, obstetricians and public health methodologists should be established, with partnership of the non-scientific stakeholders (i.e. pregnant couples/family and patient support organizations).

A. Baroncini†, L. Sinibaldi*‡, L. Bernardini‡, P. Cavalli§, F. Faravelli¶, M. Gentile**, M. Lituania††, P. Volpe‡‡, L. Camurri§§, A. Novelli‡, and B. Dallapiccola¶¶

*†ASL di Imola, Italy, UOC di Genetica Medica, Dip. Materno-Infantile, Imola, Italy; ‡IRCCS Fondazione Casa Sollievo della Sofferenza, Laboratorio Mendel, San Giovanni Rotondo, Italy; §Azienda Istituti Ospitalieri di Cremona, Servizio di Genetica, Cremona, Italy; ¶IRCCS Ospedali Galliera, SSD Genetica Medica Genova, Genova, Italy; **Ospedale di Venere, ASL di Bari, UOC Genetica Medica, Bari, Italy; ††IRCCS Ospedali Galliera, SSD Fisiopatologia Preconcezionale e Prenatale, Genova, Italy; ‡‡Ospedale di Venere, ASL di Bari, UOC Medicina Fetale, Bari, Italy; §§RDI Rete Diagnostica Italiana, Genetica Medica, Padova, Italy; ¶¶IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italy*

**Correspondence.*

(e-mail: l.sinibaldi@css-mendel.it)

DOI: 10.1002/uog.13261

References

1. Hillman SC, McMullan DJ, Hall G, Togneri FS, James N, Maher EJ, Mellers CH, Williams D, Wapner RJ, Maher ER, Kilby MD. Use of prenatal chromosomal microarray: prospective cohort study and systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2013; **41**: 610–620.
2. Fiorentino F, Napoletano S, Caiazzo F, Sessa M, Bono S, Spizzichino L, Bono S, Sessa M, Nuccitelli A, Biricik A, Gordon A, Rizzo G, Baldi M. Chromosomal microarray analysis as a first-line test in pregnancies with a priori low risk for the detection of submicroscopic chromosomal abnormalities. *Eur J Hum Genet* 2013; **21**: 725–730.
3. Lee CN, Lin SY, Lin CH, Shih JC, Lin TH, Su YN. Clinical utility of array comparative genomic hybridisation for prenatal diagnosis: a cohort study of 3171 pregnancies. *BJOG* 2012; **119**: 614–625.
4. Shaffer LG, Rosenfeld JA. Microarray-based prenatal diagnosis for the identification of fetal chromosome abnormalities. *Expert Rev Mol Diagn* 2013; **13**: 601–611.
5. CDC: Public Health Genomics, Genomic testing. http://www.cdc.gov/genomics/gtesting/ACCE/index.htm [Accessed 24 September 2013].