

Editorial

Genetic training for obstetricians and gynaecologists

One of the major breakthroughs in obstetrics and gynaecology practice in the last decade is clinical application of advanced genomic technology. The advancement is multi-dimensional: from traditional cytogenetics to high-resolution molecular karyotyping using chromosomal microarray (CMA)¹ and whole exome sequencing (WES)²; from invasive prenatal diagnostic approach to non-invasive prenatal testing using circulating fetal cell-free DNA³; from prenatal genetic testing to pre-implantation genetic testing⁴; the scope of carrier screening is also expanded from a few individual hereditary diseases to a more comprehensive panel of multiple diseases using WES⁵. Advances in genetics and genomics have affected not only the practice of fetal medicine, but also reproductive medicine and gynaecology.

Genetic technology enables a more precise genetic diagnosis, a safer clinical approach, and a faster reporting time. However, this also brings medical, legal, and ethical concerns that should be carefully handled. Very often there are no straightforward or uncontroversial answers to these concerns. What practice is acceptable to society depends not only on the accuracy of the tests but also the cost and contemporary medical knowledge, which all change rapidly with time.

1. How far should we investigate on a genetic diagnosis for a suspected fetal abnormality?

When a fetal malformation is identified, we used to perform amniocentesis and karyotyping to look for any chromosomal abnormalities. Many fetal malformations are associated with a number of microdeletion syndromes that would be missed by karyotyping⁶, so we often offer CMA for fetal diagnosis. The Hospital Authority is considering replacing karyotyping with CMA as the primary prenatal diagnostic test in 2019. If CMA results are normal, should we counsel the parents about the small chance of monogenic disorders, and advise further investigation? Sometimes the presence of specific ultrasonic phenotypes may guide us to do specific genetic tests (eg Noonan panel), but very often the prenatal phenotypes are unspecific⁷. A more comprehensive survey by WES may be useful. The positive yield of WES in abnormal fetal cases but normal karyotyping and CMA can be as high as 24%⁸. As prenatal

WES is relatively more affordable and the reporting time is faster than before, parents have the right to know and make the choice, especially if they want to keep their fetus. However, such prenatal counselling to patients could be time consuming, anxiety-causing, and disheartening when the test is neither affordable nor covered by the public health care.

2. How much genetic information should we report to our clients?

Although CMA allows detection of fetal microdeletion syndromes⁶, the resolution of CMA is so good that it can incidentally reveal copy number variants of unknown clinical significance, or those associated with largely variable and unpredictable phenotypes. Reporting these uncertain findings to the parents, could result in unnecessary anxiety, making prenatal counselling difficult and consequently leading to an innocent pregnancy termination. Nonetheless, if these uncertainties remain unreported and the fetus is born with birth defects or developmental disorders, clinicians may have to bear the medicolegal responsibility of the missed diagnosis, or deprive the parent of the right to know and a chance to consider termination of pregnancy. Vastly different from the postnatal setting, more but uncertain information could be troublesome in prenatal diagnosis and counselling⁹.

3. To what extent should we screen for the parental carrier status of hereditary diseases?

In both public and private sectors, screening of parental thalassemia status is routinely offered in prenatal setting, because thalassemia trait is relatively prevalent in Chinese (5%-10%), and screening by taking peripheral blood for mean corpuscular volume of the parental red cells is simple, accurate, and inexpensive. The intervention option available to affected parents is termination of an abnormal pregnancy. However, carrier screening for other rarer hereditary diseases (autosomal recessive) may not be cost-effective in the public setting, unless there is a strong family history or other risk factors such as consanguineous marriage. Nonetheless, expanded carrier screening is readily available at an affordable price¹⁰. Multiple hereditary diseases can be screened by a single blood

sampling and sequencing test during antenatal check-up, before conception, or even before assisted reproductive treatment. Should married couples also be informed of the potential benefits of such test, and allow them to decide if it is worth to pay for the test¹¹? Although the carrier rates of individual genetic diseases are usually lower than that of thalassemia (eg, spinal muscular atrophy: 1/50; fragile X disease: 1/1000 women)¹², preliminary data have shown that the chance of detecting at least one genetic disease in Hong Kong Chinese women using a commercially available panel could be as high as 40%, even after exclusion of thalassemia¹³.

Practitioners should update their knowledge and skills on genetic and genomic technology to provide the best advice and management. Professional organisations should provide structured training to maintain the quality of care. The Hong Kong College of Paediatricians has established the subspecialty of genetics and genomics in 2017 (http://www.paediatrician.org.hk/index.php?option=com_content&view=article&id=277&Itemid=125), and accredited first five fellows of this subspecialty. A 3-year subspecialty training program has also been started. The Hong Kong College of Obstetricians and Gynaecologists has not set up a similar subspecialty or training program, although genetics is a component of the curriculum of maternal fetal medicine. As knowledge in genetics involving obstetrics and gynaecology has expanded quickly, it is time for our College to review the current curriculum to enhance the genetic training and to accredit relevant genetic qualification, in order to improve the quality of professional care and meet the needs of our society. In addition, our College may also draft clinical guidelines regarding the practice of genetic counselling and investigation. These are challenging tasks, as they require a lot of work by experts in the genetic field, which are in short supply in Hong Kong. Hence our College must work closely with the

Hospital Authority and both universities in Hong Kong to complete the missions.

Unlike skill-based surgical training, clinical genetics requires a strong foundation of knowledge in a variety of rare diseases. The Hong Kong College of Paediatricians values the knowledge-based education in the 3-year genetic and genomic subspecialty training program. If a subspecialty trainee has completed a relevant Master of Science course in genetics, 6 months of clinical training can be exempted. Our College may also take this as a reference when we construct our training program. Of course, practical components such as clinical attachments and logbooks are mandatory. Both universities have Master of Science or diploma courses on clinical genetics, and a number of maternal fetal medicine subspecialists have completed the Master of Science in Medical Genetics at the Chinese University of Hong Kong, which is a quotable qualification approved by the Hong Kong Medical Council. However, our College has no consensus on how to position genetics in the training structure. Possible options include a separate subspecialty in genetics, or a combination of fetal medicine and genetics, or 'genetic counselling' as a special skill training and accreditation (similar to laparoscopy and colposcopy training). The last option has advantages that it is not confined to fetal medicine subspecialists, and the training program can be constructed independently from subspecialties.

Tak Yeung LEUNG

Chairman, Department of Obstetrics and Gynaecology, Faculty of Medicine, The Chinese University of Hong Kong

President, Hong Kong College of Obstetricians and Gynaecologists

Correspondence to: Prof TY LEUNG

Email: tyleung@cuhk.edu.hk

References

1. Wapner RJ, Martin CL, Levy B, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. *N Engl J Med* 2012;367:2175-84. [Crossref](#)
2. Yang Y, Muzny DM, Xia F, et al. Molecular findings among patients referred for clinical whole-exome sequencing. *JAMA* 2014;312:1870-9. [Crossref](#)
3. Chiu RW, Akolekar R, Zheng YW, et al. Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study. *BMJ* 2011;342:c7401. [Crossref](#)
4. Vermeesch JR, Voet T, Devriendt K. Prenatal and pre-implantation genetic diagnosis. *Nat Rev Genet* 2016;17:643-56. [Crossref](#)
5. Haque IS, Lazarin GA, Kang HP, Evans EA, Goldberg JD, Wapner RJ. Modeled fetal risk of genetic diseases identified by expanded carrier screening. *JAMA* 2016;316:734-42. [Crossref](#)
6. Wang H, Chau MHK, Cao Y, Kwok KY, Choy KW. Chromosome copy number variants in fetuses with syndromic

- malformations. *Birth Defects Res* 2017;109:725-33. [Crossref](#)
7. Best S, Wou K, Vora N, Van der Veyver IB, Wapner R, Chitty LS. Promises, pitfalls and practicalities of prenatal whole exome sequencing. *Prenat Diagn* 2018;38:10-9. [Crossref](#)
 8. Fu F, Li R, Li Y, et al. Whole exome sequencing as a diagnostic adjunct to clinical testing in fetuses with structural abnormalities. *Ultrasound Obstet Gynecol* 2018;51:493-502. [Crossref](#)
 9. Coughlin CR 2nd, Scharer GH, Shaikh TH. Clinical impact of copy number variation analysis using high-resolution microarray technologies: advantages, limitations and concerns. *Genome Med* 2012;4:80. [Crossref](#)
 10. Lazarin GA, Haque IS. Expanded carrier screening: a review of early implementation and literature. *Semin Perinatol* 2016;40:29-34. [Crossref](#)
 11. Lau TK. Obstetricians should get ready for expanded carrier screening. *BJOG* 2016;123(Suppl 3):36-8. [Crossref](#)
 12. Cheng YK, Lin CS, Kwok YK, et al. Identification of fragile X pre-mutation carriers in the Chinese obstetric population using a robust FMR1 polymerase chain reaction assay: implications for screening and prenatal diagnosis. *Hong Kong Med J* 2017;23:110-6. [Crossref](#)
 13. Choy KW. Evaluation of carrier frequencies and variants for Mendelian disorders in the Chinese population identified by expanded carrier screening with NGS. (unpublished data from the Chinese University of Hong Kong).