European Journal of Obstetrics and Gynecology 299 (2024) 336–341

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology

Full length article

Current status and future of genomics in fetal and maternal medicine: A scientific review commissioned by European Board and College of Obstetrics and Gynaecology (EBCOG)

M. O'Brien [a], S. Doyle [a,b], F.M. McAuliffe [a,*], Frank Leuven [c], Tahir Mahmood [d]

[a] UCD Perinatal Research Centre, University College Dublin, National Maternity Hospital, Dublin, Ireland
[b] Clinical Genetics, National Maternity Hospital, Dublin, Ireland
[c] Division of Obstetrics and Prenatal Medicine, Department of Gynaecology and Obstetrics, Universitätsklinikum Frankfurt Goethe-Universität, Germany
[d] Spire Murrayfield Hospital, Edinburgh, Scotland

ARTICLE INFO

Keywords:
Maternal medicine
Foetal medicine
Pregnancy
Prenatal testing
Invasive genetic testing
Non invasive testing
Genomic testing
National regulations
Education
Training
Ethics
Patient involvement
Public interest
Standards of care
Economics

ABSTRACT

This EBCOG guidance reviews the current and future status of genomics within fetal and maternal medicine. This document addresses the clinical uses of genetic testing in both screening and diagnostic testing prenatally. The role of genomics within fetal and maternal medicine is described. The research and future implications of genetic testing as well as the educational, ethical and economic implications of genomics are discussed.

Background

The role of genetics in fetal and maternal medicine is changing. In recent years, genetic testing capabilities have evolved at an unprecedented rate. Technologies are outpacing the ability of organisations to adjust, legislate and provide clinical guidance. This outline provides a framework to provide much-needed clarity on the clinical uses of genetic testing as it pertains to the mother and the developing fetus. Education is a vital element for both patients who consent to testing, and staff who provide the testing. The ethics and economic implications will also be discussed.

Genetic testing of the developing fetus can influence care given antenatally and postnatally and can be used to plan for future pregnancies. The potential of genetic testing was first illuminated in 1966 when Steele and Breg reported on chromosomal analysis of amniocytes [1]. For the first time, parents and clinicians were given an insight into the genetics of the developing fetus. Later, the development techniques such as qf-PCR and microarray (array CGH) made rapid diagnosis of fetal aneuploidies possible and could provide more information than conventional karyotyping. Despite the advances in technology, this form of genetic testing still required invasive sampling of the amniotic fluid or placental tissue – a procedure which confers a 0.5–1 % procedure-related risk of miscarriage [2].

It is non-invasive prenatal diagnosis that has recently changed the landscape of fetal medicine and what is achievable in terms of prenatal diagnosis. Since the presence of cell free fetal was first reported in by Lo et al. in 1997, non-invasive prenatal screening has very rapidly evolved [3]. Using different techniques non-invasive prenatal diagnosis can give information about chromosomal aneuploidies, copy number variants, paternal and de novo mutations. Detectable from four weeks gestation,

* Corresponding author.
E-mail address: fionnuala.mcauliffe@ucd.ie (F.M. McAuliffe).

https://doi.org/10.1016/j.ejogrb.2024.05.019

Available online 21 May 2024

fetal DNA increases with gestation and can represent 10–12 % of the fraction of all DNA in the maternal circulation by 10–12 weeks' gestation [4].

Whole exome sequencing have filled a diagnostic gap in cases where aneuploidies and large copy number variants have failed to provide a unifying diagnosis in a fetus with multiple structural abnormalities [5,6]. This gap continues to close with high throughput next-generation sequencing and continued improvement in interpretation of variants detected and genes that present with a prenatal phenotype. Whole genome sequencing is possible and may be introduced into clinical care in the future. Whole exome sequencing with the application of virtual panels allow for timely analysis of data and reporting required [7].

Understanding and interpreting these complex findings requires significant multidisciplinary involvement with clinicians and laboratory scientists working collaboratively, whether using whole genome or whole exome sequencing or virtual panels.

Although there is some crossover, the role of genetics in maternal medicine is somewhat different. There are two streams of patients which may come to the attention of the genetic services – patients with a pre-existing genetic diagnosis and patients with a new or suspected genetic diagnosis in pregnancy. Patients in the latter group may require targeted gene sequencing in pregnancy to achieve a diagnosis.

While technology continues to evolve at pace, it is important to acknowledge that at the centre of a robust fetal and maternal medicine service are well-trained professionals who are experienced in pre- and post-test counselling who are supported by an accredited laboratory which is subject to regular quality assessments. Only then can informed consent be achieved with pre-test education and counselling and where the patient understands the complexities of obtaining a prenatal diagnosis and the potential implications of genetic testing for themselves and their family.

Clinical

The clinical application of genetic testing in fetal medicine is to achieve a molecular diagnosis for the parents which may inform decisions surrounding termination, the care of the developing fetus and infant at birth, and management in future pregnancies. Methods for genetic testing have evolved from direct sampling of the amnion or placental tissue to non-invasive testing of maternal blood testing in select circumstances. As non-invasive testing and whole exome sequencing become widely available the clinical utility of screening for abnormalities in an unselected population needs to be understood by both the clinicians and the patients. It is important here to note that screening tests are not diagnostic and each test is limited by its sensitivity and specificity and these test metrics must be considered before embarking on any genetic test.

Screening

Screening refers to prenatal screening using non-invasive prenatal testing (NIPT) alone or NIPT sequential to a positive nuchal translucency screen to diagnose three main chromosomal abnormalities Down, Patau or Edwards syndrome.

– First trimester screening in general populations

Single-step testing utilizing NIPT alone was first adopted as a government-supported screening programme in 2017 for trisomies 13, 18 and 21 in Netherlands. TRIDENT-2 was a large-scale screening programme in an unselected population yielded a conclusive test in 99.7 %. With this approach it was noted that additional findings which were not trisomies 13, 18 and 21 resulted in requests for further invasive testing [8].

– Clinically-indicated testing

Two-step clinically indicated testing is an approach used in the United Kingdom (UK) as the basis of the NHS fetal anomaly screening programme (FASP) where a combined test is used as a screening tool. Patients with a "screen-positive combined test", i.e. increased nuchal translucency on ultrasound and/or high-risk bloods PAPP-A, and free beta hCG are then offered NIPT or referred to a confirmatory invasive test such as amniocentesis.

Concerns regarding the risk of false positives and unnecessary interventions have been cited as the basis for retaining the combined test as a screening approach to select at-risk individuals in UK [9]. Using NIPT as a second-tier test in patients at high risk for fetal trisomies based on positive combined test or medical history was the basis of TRIDENT-1. This study showed that with this approach invasive testing such as CVS or amniocentesis was reduced by up to 65 % [10].

Recommendation: Prenatal screening – whether clinically-indicated testing or testing in unselected populations – using non-invasive prenatal testing (NIPT) should be made available to patients in pregnancy. In countries where screening is not available with government funding, patients should be made aware of the availability of these tests should they wish to avail of them privately.

Diagnosis

– Non-invasive cell free DNA analysis

The implementation of cell-free fetal DNA as a diagnostic tool has resulted in safer and earlier diagnosis of some genetic disorders. Targeted testing with Rhesus factor D antigen (RhD) determination and achondroplasia or thanatophoric dysplasia have proven utility. A clinical challenge remains, however, in the diagnosis of autosomal recessive, maternally inherited X-linked conditions or dominant conditions where the mother is also affected due to the presence of high volumes of maternal mutant allele in the plasma [11,12]. While some non-invasive testing can be performed for anomalies seen on scan, for other clinical indications such as a predisposing family history, targeted preconception work-up is required which can take up to three months.

– Invasive testing

Previously the mainstay of testing for genetic diagnosis, invasive testing with chorionic villous sampling (CVS) and amniocentesis stands to become less and less common as non-invasive testing becomes more intelligent and reliable [10]. The small but real 0.5–1 % procedure related risk of miscarriage with invasive testing is no comparison to the absolute safety of non-invasive testing.

At present, however, whole genome or whole exome sequencing is only clinically possible on amniocytes or trophoblastic cells. Increased diagnostic yield with the use of virtual panels or fetal anomaly panels is meaningful for patients carrying pregnancies with multiple abnormalities without a unifying diagnosis.

Genomic testing and whole exome sequencing

With evolving technologies and next generation sequencing, whole exome sequencing is now increasingly available. The high resolution of whole exome sequencing down to a single base-pair allows for the identification of monogenic disorders. Research into the clinical utility of exome sequencing has reported very widely varying diagnostic rates of between 6.2 % and 80 % [13]. This extreme variance underlines the importance of selection of appropriate cases for testing based on the fetal phenotype and whether or not a clinical geneticist feels the fetus is likely to have a monogenic condition.

Role of the multidisciplinary team

Organisational structuring of an effective fetal medicine department

includes the presence of a core group of clinicians (fetal medicine, radiology, neonatology, genetics, pathology), genetic counsellors, sonographers, midwives and laboratory scientists engaging as part of a multidisciplinary team. This ensures the provision of holistic, patient-centred care.

Recommendation: Fetal medicine services performing both non-invasive and invasive genetic testing should involve a multidisciplinary team (MDT) to include a clinical geneticist, to ensure quality and standards are maintained in testing and decision making.

Maternal medicine

The clinical care of patients with a pre-existing or yet unknown genetic diagnosis requires the obstetrician to first identify the patient with a personal or family history of a genetic condition. Practical skills in history taking and family pedigrees may reveal the first clues to a genetic diagnosis. If a genetic diagnosis is suspected a consultation with a geneticist – who may then carry out genetic investigation – can be initiated. Before a patient embarks on genetic testing in pregnancy, the patient must understand the potential implications for the fetus of a genetic diagnosis and how this may trigger the need for more invasive testing.

Where a pre-existing diagnosis already exists, the focus shifts to the safe care of these patients and their infants during pregnancy. Pre-conceptual counselling is at the cornerstone of safe and informed care of patients with a pre-existing genetic diagnosis [14]. This allows for pre-implantation genetic testing for monogenic conditions (PGT-M) where appropriate formation of a pregnancy management plan and optimisation of the patient's own genetic condition in advance of pregnancy, e.g. Phe-restricted diet in the case of phenylketonuria (PKU) [15]. Involvement of the multidisciplinary team – including the patient's primary medical team – allows for careful planning around the potential pregnancy-related complications specific to the genetic disease. The heritability of the genetic condition must be a consideration and genetic testing of the fetus may be indicated.

Recommendation: Pregnant patients undergoing genetic testing in pregnancy should receive both pre- and post-test counselling by a qualified practitioner.

A genetic predisposition to obstetric disease processes such as pre-eclampsia [16], gestational diabetes [17] and obstetric cholestasis [18] has been demonstrated in multiple studies and may have some clinical utility in the development of prediction models or tools. Screening for these genes in pregnancy is not yet onstream and the significance of a genetic predisposition to an obstetric complication remains to be elucidated further.

Research and future of genomics

Cell-free whole exome sequencing

Cell-free fetal DNA has demonstrated its worth in the prenatal screening of aneuploidy and some monogenic conditions, e.g. cystic fibrosis [12]. Whole exome and whole genome sequencing of cell-free fetal DNA is possible [19]. While not yet cost-effective or achievable in a timely manner, whole exome sequencing of cell-free fetal DNA will likely become more streamlined as technologies advance.

In-utero treatments

Clinical trials exploring the clinical utility of in-utero therapies are ongoing. The use of enzyme replacement therapies (ERT) in lysosomal storage disorders diagnosed antenatally shows promise. The unique fetal physiology and early stage at intervention may have better outcomes for baby [20]. While still in its infancy, in-utero gene therapies appear to be a feasible treatment option for morbid and lethal genetic disorders using gene editing technology [21].

Recommendation: Future availability of cell-free whole exome sequencing and in-utero treatments should be anticipated and organisations should consider the clinical implications of these technologies, and work to develop and deliver training and education ahead of time.

Changing role of the fetal medicine specialist

As non-invasive prenatal diagnosis demonstrates increasing reliability, the need for invasive testing will diminish. Thus, a more integrated approach to care may lie ahead with phenotyping clinics where the fetal medicine specialist and geneticist work together.

Changing role of the pathologist in fetal medicine

As the diagnostic yield of whole exome/genome sequencing continues to expand, parents will increasingly receive a genetic diagnosis antenatally avoiding the need for a later post-mortem. In cases where an antenatal diagnosis was not possible, the pathologist should work closely with the geneticist in deep phenotyping to achieve a molecular diagnosis at post-mortem.

Education

As the field of genomics expands so too does the need for clinicians to become fluent in their understanding of genomic techniques and applications. The increasing availability of low-cost genomic sequencing presents a significant challenge to the care provider who may be faced with results of both pathogenic or of uncertain significance. The ability to navigate these results, to communicate them to the patients and to activate the appropriate management pathways requires the clinician to have literacy in and knowledge of this area.

Clinicians

Education of doctors across specialties and midwives is urgently needed as genetic testing becomes mainstream. Training bodies across Europe must work to incorporate genetics into the training curriculum in the form of mandatory courses and attendance at dedicated genetics clinics.

With some grounding in genetics, the clinician may then be able to obtain valid informed consent for genetic testing and identify patients who would benefit from genetic testing. Knowledge of the specific genetic test required, the implications of unexpected results and the interpretation of genetic results is of key importance if genetic information is to be clearly communicated to the patient.

Recommendation: Integration of training in genetics as part of fetal and maternal medicine curricula should be developed by training bodies across Europe.

Multidisciplinary team training

Involvement of the multidisciplinary team is essential not only to case discussions but in the care of patients who receive genetic diagnoses. Here, the provision and access to educational tools should be cross-sectional and involve midwives, social workers, sonographers.

Patients and public

Working on the development of patient education materials (audio-visual and written) is of utmost priority. Across Europe, organisations must work to involve relevant stakeholders to develop culturally appropriate material in the spoken language of the communities which

they serve. Charity groups such as Antenatal Results and Choices [www.arc-uk.org] and Support Organisation for Trisomy 13 and Trisomy 18 [www.soft.org.uk] in the UK provide information for patients to help them understand diagnosis, support them through decision making and to help plan for future pregnancies. Here too, when giving a diagnosis of a rare or complex condition either antenatally or postnatally, sign posting patients to relevant and evidence-based resources such as Eurodis (https://www.eurordis.org) is very helpful.

Recommendation: Parents receiving a genetic diagnosis should be directed to relevant support groups and online resources where available.

Resources

Colleges and training bodies throughout Europe should look to integrate genetic education in the Obstetrics and Gynaecology training scheme. Ancillary genetics educational content is currently being offered by training bodies throughout Europe including EBCOG-PACT (Progress Towards Achieving Consensus in Training) curriculum and others i.e. Royal College of Obstetricians and Gynaecologists (RCOG), Institute of Obstetricians and Gynaecologists at Royal College of Physicians of Ireland (RCPI), and Nordic Federation of Societies of Obstetrics and Gynaecology. To date this mainly consists of online or in-person courses, webinars and conferences on genetics, but formalised clinical training in this area for obstetrics and gynaecology trainees is scarce. Harmonising the standard of genetic training is important and EBCOG-PACT has developed a training curriculum to ensure that there is a minimum standard across Europe.

Organisations

European organisations offer training courses in fetal medicine diagnostics, annual meetings. ERN-ITHACA (European Reference Network on congenital malformations and rare intellectual disability), the Fetal Medicine Foundation UK, European Society of Human Genetics (ESHG) all provide courses and training materials for diagnostics including invasive testing and non-invasive testing. Internationally, the International Society of Prenatal Diagnosis (ISPD) is involved in ongoing publication of peer-reviewed research and organising an annual international conference.

Ethics and inequalities

Much has been written about the ethical considerations of prenatal testing. Issues of confidentiality, uncertainty, time constraints and the legal status of the fetus may be encountered [22].

Patient voice

Patient, family and carer voices are central to planning and development of genetics services. The patient experience and priorities can inform policy and guidelines.

Whole exome sequencing

As technology evolves and processes become cheaper, the widespread availability of genetic testing poses an ethical challenge with the unexpected findings that may occur. There may be significant consequences with the potential discovery of non-paternity, incidental findings which may have significant and far-reaching consequences for the patients and their wider families, and challenges in variant interpretation [23]. The autonomy of the developing fetus must also be considered. Genetic investigations inherently deny the child their autonomy to receive a genetic diagnosis and predictive genetic testing in pregnancy should only be performed after appropriate genetic counselling.

Pre-implantation testing

Lack of equity in access is problematic in the setting of pre-implantation genetic testing where this is testing unfertilised ova in polar body testing or blastocyst biopsy in preimplantation genetic screening. With certain European countries providing some funding for patients who would benefit from a pre-implantation genetic test in the case of known genetic disorders this is not the case for all.

Legal/legislative

Access to fertility treatment and termination varies throughout Europe. This has influenced the development of genetic testing particularly in countries where access to termination remains restricted.

Lack of diversity

Sequencing predominantly occurs in Caucasian populations [24]. A significant proportion of the population in Europe is non-Caucasian and efforts should be focused on diversity and representation in genomic studies.

Access

The socioeconomic divide in Europe and the aforementioned legislative dissonance between states has resulted in vastly differing access to genetic services.

Recommendation: Clinical practice across Europe varies from jurisdiction to jurisdiction. Individual organisations should work to deliver guidelines relevant to their country.

Standards

Laboratory standards

Work done by EU-funded Eurogentest has helped to improve the structure of external quality assessment (EQA) schemes, developed guidelines and an accreditation scheme for genetic laboratories. Laboratories are subject to an annual assessment which is both a technical assessment and assessment of the management system.

Recommendation: Genetic testing should be carried out in an accredited laboratory which is subject to ongoing quality controls and assessment.

Economic implications

Non-invasive prenatal diagnosis (NIPD)

The use of NIPD as a first screening test has been shown to reduce the number of invasive procedures and ultimately the cost of prenatal screening [25]. Conflicting data reported on the use of clinically indicated non-invasive prenatal testing means that the cost effectiveness of this strategy is uncertain. Using non-invasive prenatal screening in an unselected population, while more effective than traditional screening at detecting abnormalities, may not be cost effective in every country [26].

Whole exome sequencing

There is a significant work-load involved in the processing and packaging of information gathered by whole exome sequencing to achieve a diagnosis. Variant interpretation is labour-intensive and requires significant input from genetics services and laboratory scientists. Identification of incidental findings, follow-up and further testing is an

additional cost.

Pre-implantation genetic testing

Pre-implantation genetic testing includes pre-implantation genetic screening for aneuploidy and testing for monogenic conditions and structural rearrangements.

The economic value of pre-implantation genetic screening for aneuploidy has yet to be proven. One American study reported the cost to prevent one miscarriage using PGS was up to US$50,000.[27] Interpretation of genetic testing on day 5 blastocysts is complicated and some abnormal embryos may go onto be healthy unaffected children.[28].

Recommendation: Countries should consider the health economic implications of introducing non-invasive prenatal testing, whole exome sequencing and pre-implantation genetic testing across their populations.

Conclusion

Fetal and maternal medicine are both directly affected by the burgeoning science of genetic medicine. Clinical practice and what is achievable has changed remarkably in the last number of years and will continue to evolve as genetic testing becomes more intelligent, faster and more cost-effective. Guidance and standards which are dynamic in the face of this rapidly changing topography must be delivered to meet the clinical need.

Key messages

- Prenatal screening – whether clinically-indicated testing or testing in unselected populations – using non-invasive prenatal testing (NIPT) should be made available to patients in pregnancy. In countries where screening is not available with government funding, patients should be made aware of the availability of these tests should they wish to avail of them privately.
- Fetal medicine services performing both non-invasive and invasive genetic testing should involve a multidisciplinary team (MDT) to include a clinical geneticist, to ensure quality and standards are maintained in testing and decision making.
- Pregnant patients undergoing genetic testing in pregnancy should receive both pre- and post-test counselling by a qualified practitioner.
- Future availability of cell-free whole exome sequencing and in-utero treatments should be anticipated and organisations should consider the clinical implications of these technologies, and work to develop and deliver training and education ahead of time.
- Integration of training in genetics as part of fetal and maternal medicine curricula should be developed by training bodies across Europe.
- Parents receiving a genetic diagnosis should be directed to relevant support groups and online resources where available.
- Clinical practice across Europe varies from jurisdiction to jurisdiction. Individual organisations should work to deliver guidelines relevant to their country.
- Genetic testing should be carried out in an accredited laboratory which is subject to ongoing quality controls and assessment.
- Countries should consider the health economic implications of introducing non-invasive prenatal testing, whole exome sequencing and pre-implantation genetic testing across their populations.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: 'The authors have no conflict of interest to declare. This paper has been endorsed by the European Association of Perinatal Medicine. This paper was approved by the council of European Board and College of Obstetrics and Gynaecology at its meeting in May 2024.'.

References

[1] Steele MW, Breg Jr WR. Chromosome analysis of human amniotic-fluid cells. Lancet 1966;1(7434):383–5.
[2] Navaratnam K, Alfirevic Z, Royal College of Obstetricians and Gynaecologists. Amniocentesis and chorionic villus sampling: Green-top Guideline No. 8 July 2021: Green-top Guideline No. 8. BJOG 2022;129(1):e1–15.
[3] Lo YM, Corbetta N, Chamberlain PF, et al. Presence of fetal DNA in maternal plasma and serum. Lancet 1997;350(9076):485–7.
[4] Norton ME, Brar H, Weiss J, et al. Non-Invasive Chromosomal Evaluation (NICE) Study: results of a multicenter prospective cohort study for detection of fetal trisomy 21 and trisomy 18. Am J Obstet Gynecol 2012;207(2).
[5] Lord J, McMullan DJ, Eberhardt RY, et al. Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study. Lancet 2019;393(10173):747–57.
[6] Petrovski S, Aggarwal V, Giordano JL, et al. Whole-exome sequencing in the evaluation of fetal structural anomalies: a prospective cohort study. Lancet 2019;393(10173):758–67.
[7] Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405–24.
[8] van der Meij KRM, Sistermans EA, Macville MVE, et al. TRIDENT-2: National implementation of genome-wide non-invasive prenatal testing as a first-tier screening test in the Netherlands. Am J Hum Genet 2019;105(6):1091–101.
[9] Taylor-Phillips S, Freeman K, Geppert J, Madan J, Uhlman O, Agbebiyi A, et al. Systematic review and cost-consequence assessment of cell-free fetal DNA testing for T21, T18 and T13 in the UK. Final Report. UK National Screening Committee; 2016.
[10] Oepkes D, Page-Christiaens GCL, Bax CJ, et al. Trial by Dutch laboratories for evaluation of non-invasive prenatal testing. Part I-clinical impact. Prenat Diagn 2016;36(12):1083–90.
[11] Hanson B, Paternoster B, Povarnitsyn N, Scotchman E, Chitty L, Chandler N. Non-invasive prenatal diagnosis (NIPD): current and emerging technologies. Extracell Vesicles Circ Nucleic Acids 2023;4(1):3–26.
[12] Drury S, Mason S, McKay F, et al. Implementing non-invasive prenatal diagnosis (NIPD) in a National Health Service Laboratory; From dominant to recessive disorders. Adv Exp Med Biol 2016;924:71–5.
[13] 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(1):10–9.
[14] van Eerde AM, Krediet CTP, Rookmaaker MB, van Reekum FE, Knoers NVAM, Lely AT. Pre-pregnancy advice in chronic kidney disease: do not forget genetic counseling. Kidney Int 2016;90(4):905–6.
[15] van Wegberg AMJ, MacDonald A, Ahring K, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis 2017;12(1):162.
[16] Rasmussen M, Reddy M, Nolan R, et al. RNA profiles reveal signatures of future health and disease in pregnancy. Nature 2022;601(7893):422–7.
[17] Lowe Jr WL, Scholtens DM, Sandler V, Hayes MG. Genetics of Gestational Diabetes Mellitus and Maternal Metabolism. Curr Diab Rep 2016;16(2):15.
[18] Liu X, Lai H, Zeng X, et al. Whole-exome sequencing reveals ANO8 as a genetic risk factor for intrahepatic cholestasis of pregnancy. BMC Pregnancy Childbirth 2020;20(1):544.
[19] Fan HC, Gu W, Wang J, Blumenfeld YJ, El-Sayed YY, Quake SR. Non-invasive prenatal measurement of the fetal genome. Nature 2012;487(7407):320–4.
[20] Herzeg A, Borges B, Lianoglou BR, et al. Intrauterine enzyme replacement therapies for lysosomal storage disorders: Current developments and promising future prospects. Prenat Diagn 2013. https://doi.org/10.1002/pd.6460. Published online November 13, 2023.
[21] Lederer CW, Koniali L, Buerki-Thurnherr T, et al. Catching them early: Framework parameters and progress for prenatal and childhood application of advanced therapies. Pharmaceutics 2022;14(4). https://doi.org/10.3390/pharmaceutics14040793.
[22] Royal College of Physicians, Royal College of Pathologists and British Society for Genetic Medicine. Ethical issues in prenatal genetic diagnosis. guidance for clinical practice. Report of the Joint Committee on Genomics in Medicine. London: RCP, RCPath and BSGM; 2022.
[23] Chandler NJ, Scotchman E, Mellis R, Ramachandran V, Roberts R, Chitty LS. Lessons learnt from prenatal exome sequencing. Prenat Diagn 2022;42(7):831–44.
[24] Sirugo G, Williams SM, Tishkoff SA. The missing diversity in human genetic studies. Cell 2019;177(1):26–31.
[25] Xie X, Wang M, Goh ESY, et al. Noninvasive prenatal testing for trisomies 21, 18, and 13, sex chromosome aneuploidies, and microdeletions in average-risk pregnancies: A cost-effectiveness analysis. J Obstet Gynaecol Can 2020;42(6):740–749.e12.

[26] García-Pérez L, Linertová R, Álvarez-de-la-Rosa M, et al. Cost-effectiveness of cell-free DNA in maternal blood testing for prenatal detection of trisomy 21, 18 and 13: a systematic review. Eur J Health Econ 2018;19(7):979–91.
[27] Neumann K, Sermon K, Bossuyt P, et al. An economic analysis of preimplantation genetic testing for aneuploidy by polar body biopsy in advanced maternal age. BJOG 2020;127(6):710–8.
[28] Popovic M, Dhaenens L, Boel A, Menten B, Heindryckx B. Chromosomal mosaicism in human blastocysts: the ultimate diagnostic dilemma. Hum Reprod Update 2020; 26(3):313–34.