Right or wrong? Looking through the retrospectoscope to analyse predictions made a decade ago in prenatal diagnosis and fetal surgery

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1 INTRODUCTION

Usually, around mid-October, the Associate Editors of Prenatal Diagnosis meet to make plans for the year to come and reflect on the year just gone. At this meeting we discuss the key progress made in the specialties of prenatal diagnosis and fetal therapy and begin to put together our traditional end of year publication “In Case You Missed It” to keep you up to date with developments in our field.1-7 We take turns to host the editors’ meeting and have met in Washington, Leuven, Boston, London and Hertfordshire. This year, however, was different in more ways than one! COVID-19 meant we could not travel and so, instead of meeting in person in North America, we met by Zoom for two, 3-h sessions over a weekend – at 07.00 in the USA and Toronto, 22.00 in Melbourne, 13.00 in Belgium and midday in the UK (Figure 1). Not nearly so much fun, but none-the-less productive. The other difference is that this is Prenatal Diagnosis’ 40th anniversary, and we chose to reflect on the predictions made 10 years ago in our 30th Anniversary issue,8-12 as COVID-related issues have eclipsed many advances made this year and are discussed elsewhere in this issue.

Rick Klausner, M.D., former Director of the US National Cancer Institute, once said “There are far many more historians than prophets”. A corollary to this statement is that it is much easier to critique what has happened in the past decade than it is to predict was will happen over the next 10 years. We hope you enjoy these reflections and look forward to a more “normal” times in 2021.

2 A DECADE OF FETAL ULTRASOUND

Most of the educated guesses on the future of ultrasound (US) screening and diagnosis made by Robson 10 years ago have come to fruition.8 As expected, most of the inroads have been accomplished
not by further refinements in US screening and diagnosis at centres of excellence in high risk groups, but rather via a concerted effort by national and international organisations who have produced evidenced based guidelines in order to standardise the performance, content and quality of US screening and diagnostic tests among low risk women, and to facilitate and encourage their adoption by practitioners worldwide through accreditations and certifications.

As predicted, the first trimester combined screen has become the standard 1st trimester screening test for common aneuploidies worldwide, and includes the nuchal translucency (NT) measurement where available. However, over recent years this is being combined with or has even been replaced by, the offer of cell-free (cf) DNA testing because of its superior accuracy in screening for trisomy 21. First trimester US offers the possibility of detection of nearly half of major abnormalities in low-risk or unselected populations and thus continues to have a place in the era of cfDNA. However, as predicted by Robson, such detection rates are significantly impacted by lack of utilisation of standardised anatomical protocols for use in first trimester US screening.

The 10-year predictions by Robson were also on target as they pertained to prenatal US detection of structural fetal anomalies. Cardiac anomalies are the most frequent congenital anomalies, hence the impetus by leading organisations to standardise and improve the diagnosis of congenital heart defects (CHD). In 2013, the American Institute of Ultrasound in Medicine (AIUM) and the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines recommended that cardiac outflow tract assessment should be incorporated routinely into obstetric US screening. Nationwide implementation of such recommendations has led to a significant increase in prenatal detection of transposition of great arteries, from 14% to 77%. A 3-vessel view is now recommended in addition to visualisation of cardiac chambers and outflow tracts. Nationally screening programmes incorporating such recommendations have seen a significant improvement in the detection rates of CHD, with highest detection rates (>93%) for hypoplastic left heart syndrome, other univentricular defects and complex defects. Dramatic increases have also been noted for prenatal detection of conotruncal anomalies, including transposition of great arteries (from 44% to 82%) and tetralogy of Fallot (from 44% to 68%) compared with the detections rates antedating the introduction of the 3-vessel view. The introduction of
standardised screening programmes has also improved the prenatal detection of renal anomalies.\textsuperscript{20} As for 3-dimensional (3D) US, several studies and meta-analyses have confirmed that 3D US can improve the diagnostic accuracy of 2D US in the evaluation of facial clefts, craniosynostoses, neural tube defects, cardiac, brain and skeletal anomalies.\textsuperscript{21} However, as predicted by Robson, 3D imaging volume reconstruction is highly dependent on operator skill and experience; this limitation, together with need for dedicated 3D transducers, lack of uniformity in industry standards regarding storage format for volume datasets generated by US, lack of cross-compatibility among US manufacturers (leading to vendor-specific workstations and programmes) have led to underutilisation of 3D US by practitioners outside of specialist centres.\textsuperscript{22}

What does the future hold for ultrasound? One of the most common reasons for missed prenatal diagnoses is the inability to obtain adequate images.\textsuperscript{23} Evidence points to the importance of experience (volume of ultrasound screens performed) in determining the skills of the sonographer.\textsuperscript{24} Artificial intelligence in the near future may overcome this inherent limitation of prenatal ultrasonography.\textsuperscript{25,26} Furthermore the detection of fetal anomalies may move even earlier with advances in transvaginal imaging and operator experience\textsuperscript{27} especially as novel imaging technologies are facilitating excellent post-mortem examination even in very small fetuses.\textsuperscript{28} One might have expected that the place of fetal ultrasound in prenatal diagnosis will be diminished with the rapid advances being made with molecular genetic prenatal diagnosis.\textsuperscript{29,30} Instead we are increasingly becoming aware of the role of accurate fetal imaging to define the fetal phenotype to improve the efficiency of molecular testing,\textsuperscript{21} aid interpretation of complex sequencing results as we recognise that fetal phenotypes may differ from post-natal ones\textsuperscript{32,33} and improve our understanding of fetal development.

3 | A DECADE OF FETAL THERAPY

Ten years ago, when Choolani et al. were asked to gaze into the future of fetal therapy,\textsuperscript{7} they predicted slow, incremental increases in knowledge and technology for the near future but also speculated about nanobots, microsurgery, natural orifice surgery and fetal gene and stem cell therapy. So, what did they get right, what was over-optimistic and what did they not see coming?

In the past decade, the international fetal surgery community has, as predicted, gained incremental knowledge by completion of multiple large, multicentre, randomised controlled trials (RCTs). The Management of Myelomeningocele (MOMS) trial,\textsuperscript{34} which demonstrated superiority of open fetal surgery over postnatal care for spina bifida, has been a game changer in many respects and is a showcase for the fetal therapy community. First, it caused a paradigm shift by adding the first non-lethal anomaly to fetal surgery, second, it put “open” fetal surgery back on the agenda.\textsuperscript{35} and third, it boosted the unanticipated set up of new fetal surgery programmes worldwide.\textsuperscript{36} The “Solomon” trial,\textsuperscript{37} which demonstrated the added value of superficially dividing the placenta along the vascular equator in the prevention of twin anaemia polycythaemia sequence, as well as the Tracheal Occlusion To Accelerate Lung growth (TOTAL) trial’s examining the effect of fetal TOTAL in congenital diaphragmatic hernia (http://www.TOTALtrial.org) are other examples of successfully completed trials of fetal therapy. The results of the latter trial are still awaited, but are expected to confirm findings of earlier smaller studies\textsuperscript{38-41} and impact significantly on the state-of-the-art care for fetuses with diaphragmatic hernias. In contrast to the Solomon trial, which recruited 274 participants in only 4 years, both the MOMs and the TOTAL trials took almost a decade to be completed, due to slow patient recruitment and, for CDH, a gradual divide in the fetal medicine community around the concept of “equipoise”.\textsuperscript{42-44} The latter also ended up being fatal to the Percutaneous vesicoamniotic shunting in Lower Urinary Tract Obstruction (PLUTO) trial on the treatment of fetal urinary tract obstruction with vesico-amniotic shunting,\textsuperscript{45,46} which was terminated with only 31 of the planned 150 patients recruited over a 4-year timespan. This demonstrates the difficulty of running trials in fetal medicine. Going forward, the fetal surgery community will need to develop alternative trial designs to solve outstanding research questions, including the best approach for fetal spina bifida closure (open vs. fetoscopic)\textsuperscript{47} and the benefit of fetal cardiac interventions.\textsuperscript{48}

Choolani et al. also accurately predicted that we would work towards less invasive therapies including better instrument design, and cell and gene therapies. Indeed, in an attempt at minimising the invasiveness of fetal surgery, engineers are now working on thinner instruments, robotic solutions,\textsuperscript{49-51} and improved intra-operative image processing and image guided surgical planning.\textsuperscript{52,53} We are, however, still far from futuristic nanobots and natural orifice surgery.

A giant, unpredicted, technical step forward that may also enable new fetal therapies, and certainly has the potential of improving outcomes for the extremely preterm neonate, was the development of the “artificial placenta”.\textsuperscript{54,55} Using the umbilical cord vessels, this system connects a pumpless extracorporeal membrane oxygenator to the fetus, who is kept in a closed bag filled with fluid, thereby reproducing the intra-uterine environment of the womb. Lambs connected to this device maintain a stable fetal circulation and normal oxygenation parameters for up to 4 weeks, and this device is now being prepared for its first clinical trials in humans.\textsuperscript{54,55}

As with invasive fetal therapies, work in the field of fetal stem cell and gene therapies has progressed steadily, and gathered the necessary critical mass of investigators to initiate the creation of the International Fetal Transplantation and Immunology Society (IFeTIS).\textsuperscript{56} Members of this group are now assessing the feasibility and effectiveness of fetal stem cell therapy in human phase I/II studies, including in vitro transplantation with maternal haematopoietic stem cells for alpha thalassaemia major (NCT02986698) and mesenchymal stem cells for osteogenesis imperfecta (BOOST4, NCT03706482). First in human experiments with other minimally invasive or transplacental therapies, addressing directly the molecular basis of rare fetal disorders, have also been successfully applied in the past decade, including intra-amniotic injection of the recombinant receptor-binding domain of ectodysplasin A for X-linked hypohydrotic ectodermal dysplasia or maternal administration of rapamycin, which inhibits the upregulated m-Tor pathway in cardiac rhabdomyomas in fetal
tuberous sclerosis.\textsuperscript{58,59} Additionally, transplacental indomethacin has been used to restrict the fetal ductus arteriosus and decrease the risk of hydrops and death caused by the circular shunting physiology in Ebstein’s anomaly.\textsuperscript{60}

Over the past decade, enthusiasm for fetal therapy has continued growing and the list of indications for fetal intervention is rapidly expanding. Promising in vitro and animal studies are published on a near weekly basis. One of the main challenges for the fetal medicine community in the next decade will be to translate these procedures to the bedside, making these exceptional treatments for rare conditions available to those who need it, while ensuring safety and expertise,\textsuperscript{61} as well as access to care.

4 | A DECADE OF CYTOGENETICS

Ten years ago, Charles Lee was charged with forecasting how cytogenetics would evolve over the forthcoming decade.\textsuperscript{10} At that time, chromosomal microarray analysis (CMA) was the “new” thing and Lee forecast that once laboratories gained the appropriate expertise in differentiating pathogenic genomic imbalances from the numerous clinically insignificant copy number variants (CNVs), then widespread adoption of prenatal CMA would occur. To a large extent, his prediction proved correct but it took large, national multi-centre prenatal CMA studies\textsuperscript{62,63} to catalyse the adoption of CMA as the first-tier test in the diagnostic evaluation of fetal structural anomalies and for national bodies to issue supportive guidance.\textsuperscript{64,65} This in turn spurred an increased utilisation of microarrays in the prenatal setting. Lee insisted that CMA analysis should be interpreted in the context of chromosome structure. That prediction too appeared to be a forshadowing of the logic for eliminating individual molecular genetics and clinical cytogenetics training programs. Across the globe we now see these disciplines combined into a single Laboratory Genetics and Genomics programme to train the clinical scientists of the future.

Lee was optimistic that we would have a good grasp on the various epistatic factors that influence the phenotypic heterogeneity of certain CNVs. While an increased number of CNVs with reduced penetrance and phenotypic heterogeneity have subsequently been identified (e.g. deletions and duplications involving 1q21.1, 2q13, 15q11.2, [BP1-BP2 including NIPA], 16p11.2, 16p13.11 and 22q11.2 [distal region]), we are no closer to elucidating the specific factors that attenuate the phenotype in individual cases.

In 2010, next generation sequencing (NGS) technology was rapidly entering the clinical diagnostic field and Lee reasoned that it “will undoubtedly be increasingly used in clinical genetic diagnostics and will eventually supersed e use of even SNP-detecting platforms”.\textsuperscript{10} Indeed, the biggest change in the field of prenatal diagnosis has been observed in the area of cytogenomics where microarray and NGS technologies have become the preferred genomic tool for the assessment of preimplantation embryos and fetuses. The introduction of these newer genomic technologies has had a major effect on the success rates of in vitro fertilisation (IVF), as demonstrated in recent prospective randomised clinical trials. Low-pass genome sequencing is now threatening to replace SNP-based microarray in routine prenatal diagnosis,\textsuperscript{66-68} but larger scale prospective studies remain forthcoming. The ultimate goal is to have a single technology that would simultaneously detect CNVs, single nucleotide variants as well define the structure of balanced and unbalanced rearrangements. Whole genome sequencing is currently the best prospective option for achieving this. However, it will require a significant reduction in sequencing costs (reagents and equipment), highly developed and validated algorithms for uncovering the various genomic abnormalities and considerably advanced knowledge-databases concerning the pathogenicity of discovered variants. Indeed, this will take quite some time to accomplish.

In the meantime, we rely on trained experts with considerable experience to interpret the wealth of data stemming from these new technologies.

“Cytogenetics is dying” is a common phrase heard by cytogeneticists. In fact, this phrase has been propagated for over five decades, primarily after new technologies were introduced. In the words of the late Dorothy Warburton: “I have been told by my department chairman and other advisers that cytogenetics is dying at least three times: in 1968 (just before banding), in 1984 (just before fluorescent in-situ hybridisation - FISH) and in 2001 (just before microarrays)”. Dorothy’s response was simply to say that “Cytogenetics is defined by the questions it asks not by the techniques it uses” and “We continue to look at chromosomes, just in different ways”. These words of wisdom continue to resonate just as loudly today. Cytogenetics and molecular genetics have melded into the field of cytogenomics that considers both large chromosome aberrations as well as gene-level changes. Since large scale chromosome abnormalities have a considerable impact on viability and morbidity, and, as we gain deeper knowledge of the effects of single base-pair changes on fetal development, cytogenomics will dominate prenatal diagnosis. We may just continue to change the flavour of the technique that performs the best in this category.

5 | A DECADE OF CELL-FREE DNA TESTING

Ten years ago, Dennis Lo made some bold predictions regarding “Noninvasive Prenatal Diagnosis in 2020”.\textsuperscript{11} Although many of the things that Lo envisioned have come true, there are sections that probably would be different had the paper been written today. For starters, the use of the term “diagnostic” in the title and elsewhere in the paper is problematic. In 2010 there was a widely held expectation that non-invasive prenatal testing (NIPT) for aneuploidy would perform so well as to be (almost) diagnostic. This was overly optimistic. We now know that the source of the circulating cell-free DNA (cfDNA) in maternal plasma is mainly maternal with a variable fraction originating from the placenta.\textsuperscript{69} Therefore, abnormal NIPT results could be due to confined placental mosaicism (CPM) or a maternal health issue.\textsuperscript{70} Industry also promoted the concept that NIPT would replace prenatal diagnostic procedures. This led to further confusion, and although the rate of invasive testing has decreased,\textsuperscript{71} it is still required for confirmation of abnormal NIPT results. NIPT results that
are discordant with the fetal karyotype could reflect maternal mosaic sex chromosome or autosomal aneuploidies, maternal autoimmune or haematologic disorders, a maternal disorder of sex differentiation, a prior solid organ transplant from a male donor, or a maternal malignancy.\textsuperscript{70,72–74}

After a decade we know that NIPT is the most accurate screening test for the major fetal chromosomal aneuploidies (trisomies 13, 18, 21) with positive predictive values that are 10–20 fold higher than combined biochemical screening with NT measurement.\textsuperscript{70} The extremely high negative predictive value has resulted in many high-risk women choosing not to have a diagnostic procedure. For this reason, NIPT has been adopted globally as a second-tier test for women at high risk of having an aneuploid fetus due to advanced maternal age or a positive maternal screen result for aneuploidy. As of 2020, only two countries (the Netherlands and Belgium) universally offer NIPT as a first-tier screen for aneuploidy,\textsuperscript{75} though self-funded first-tier NIPT is thought to be widespread in high income settings.\textsuperscript{75} A positive NIPT result, however, needs to be confirmed with a fetal or neonatal diagnostic test.

Lo was probably correct in predicting that “DNA sequencing would become the dominant technology used for the [NIPT] of fetal chromosomal aneuploidies from maternal plasma” but he hedged his bets by saying “workers in the field will have many alternative sequencing platforms to choose from, including those that are based on ‘old technologies’...”. Indeed there are several platforms in widespread use across the globe. The majority of them are based on massively parallel sequencing (MPS), and others employ more targeted approaches using array technology or single nucleotide polymorphisms (SNPs).\textsuperscript{76}

Lo also predicted that “single molecule analysis methods, especially MPS, will become the dominant technology for the NIPT of monogenic diseases” and that “by 2020 many groups would routinely be using MPS technology for the NIPT of multiple monogenic diseases from maternal plasma”. Whilst NIPT is the appropriate terminology for cfDNA analysis for single gene disorders since, as currently used in high risk situations, it is truly diagnostic and does not require confirmation by invasive testing. Unfortunately, however, NIPT is not yet the dominant technology for monogenic prenatal diagnosis. With the exception of England, where it forms part of the accredited public health genomic service,\textsuperscript{77} NIPT for monogenic disorders is largely only offered on a research basis elsewhere in the world. In England NIPT is offered routinely to families with a relevant history of a genetic disorder\textsuperscript{78} or when ultrasound examination suggests specific conditions\textsuperscript{79} A recent review of the NIPT public health service since 2013 showed that NIPT has been delivered to nearly 2000 families for more than 190 different monogenic conditions, including rare conditions developed on a bespoke family basis,\textsuperscript{78} panel-based testing for FGFR2 and 3 mutations\textsuperscript{78,80} and, as predicted by Lo, relative haplotype dosage (RHDO) for recessive conditions such as cystic fibrosis,\textsuperscript{81} Duchenne Muscular dystrophy\textsuperscript{82} and spinal muscular atrophy.\textsuperscript{83}

Finally, as predicted, the whole fetal genome has been sequenced using cfDNA,\textsuperscript{84,85} but this has proven to be challenging and expensive. Some commercial organisations are now using larger gene panels to analyse cfDNA in maternal plasma for up to 150 monogenic disorders,\textsuperscript{86–88} but there are scant published data and validation, and details of gene coverage are largely absent. There remain many technical challenges to be overcome before this approach to screening the all-risk population can be applied safely, and for now the focus for public health services is on NIPT for monogenic conditions in pregnancies known to be at increased risk.

Lo correctly foresaw that NIPT/NIPD results would generate multiple ethical issues. The potential to use prenatal testing for fetal sex selection\textsuperscript{89} or termination of fetuses with chromosomal abnormalities has been a concern related to all forms of prenatal testing for many years, even prior to the development of genome sequencing. To date, there has been no evidence that NIPT has led to a decrease in the live birth rate of infants with Down syndrome.\textsuperscript{90} What is notable, however, are the post-NIPT “gender reveal” parties that have become spectacles, sometimes with deadly consequences due to explosive devices designed to generate pink or blue smoke. Newspaper reports document enormous wildfires (resulting in the death of at least one firefighter) and in a separate incident, a bystander’s death due to flying debris.\textsuperscript{91} Lastly, due to the potential of detection of maternal CNVs in the maternal plasma, an entire family was shown to have duplication of APP on chromosome 21.\textsuperscript{92} Initially detected as a false positive fetal screen for Down syndrome, the end result was that multiple family members were identified as being at early risk of developing Alzheimer disease.

The unprecedented commercial drive to implement NIPT for aneuploidy over the past decade has meant that we have learnt a lot about cell-free fetal DNA. It has clearly changed the face of prenatal diagnosis and no doubt will continue to pose ethical challenges\textsuperscript{93} as our understanding improves and its potential scope broadens. We must hope that the high standards of validation that are required in public sector laboratories can be applied to the commercial sector, which has been key in driving progress, and that we can hasten slowly and with care to avoid harm as new tests are developed.

### 6 A DECADE OF INVASIVE PROCEDURES

In 2010, Ron Wapner contemplated the predictions of a decline in invasive testing due to noninvasive prenatal testing (NIPT) and other imminent improvements in Down syndrome screening.\textsuperscript{12} He opined that “this was unlikely and in actuality the number of patients sampled will increase”.

However, there was indeed a global decline in invasive prenatal diagnostic testing in the years following the widespread uptake of NIPT after 2011.\textsuperscript{71,94,95} Importantly, this decline in invasive procedures has not been associated with a decline in the detection of major chromosome abnormalities. Population-based data showed that the diagnostic yield of amniocentesis and chorionic villus sampling actually increased during this period.\textsuperscript{96} However, at least in Australia, the rate of invasive procedures appears to have plateaued in recent years, reaching a steady state of approximately 2% of births.\textsuperscript{97}

In 2010, NIPT was being conceptualised primarily as a screening test for trisomy 21. Wapner considered that this limited scope would
prompt continued utilisation or even increased uptake of invasive testing to maximise the number of conditions detected via prenatal testing. What we have seen however, is the rapid expansion of conditions detectable by cfDNA, such that NIPT is now offered for the detection of sex chromosome conditions, fetal sex, rare autosomal trisomies, microdeletion syndromes, triploidy, segmental aneuploidy, and twin zygosity assessment.98-103 However, the accumulating number of conditions per NIPT assay will also result in increasing screen positive rates. In fact, if sex chromosome conditions and “no call" results are included, the screen positive rate of NIPT approaches that of combined first trimester screening.104 If this trend to expanding the scope of NIPT continues, this is likely to lead to an increase in invasive procedures in the coming years due to an increase in screen positive results.

In 2010, the emerging molecular technology of chromosomal microarray (CMA) was also predicted by Wapner to present a new rationale for offering invasive testing to all women. Since then CMA has become the standard of care for women undergoing invasive testing for fetal abnormalities,63,64 and more recently, CMA has rapidly expanded to become the standard method of prenatal chromosome analysis for all indications in high income settings.97,105 The diagnostic yield of CMA in structurally-normal fetuses has since confirmed to be 1 in 270, which is around the threshold for which diagnostic testing has been traditionally offered to women.106 In 2020, the Society for Maternal Fetal Medicine in the United States recommended that all women be offered the option of primary diagnostic testing without prior screening.11 At least in the United States, this has borne out Wapner’s prediction that the increasing yield of invasive testing among the general population would make it “difficult to refute the argument that screening should be abandoned and all patients should be offered invasive testing”. The debate around the best approach continues and invasive testing is not being widely adopted, as there are both economic and ethical consequences of offering universal diagnostic testing and abandoning the presumption of a normal infant in otherwise uncomplicated pregnancies.96

Wapner correctly predicted that genetic counselling would consequently become more complex. “Throughout this coming decade, the human genome will continue to be interrogated and will yield increasing information about the developing fetus. This will lead to discussions of patient autonomy, social responsibility, resource utilization, and ethics”. This could not be more true in the CMA era,109 and with the advent of fetal exome sequencing, which is now being incorporated into clinical care in the UK and USA, increasing the complexity of prenatal counselling.107

7 | CONCLUSIONS

Many of the predictions made by our experts in 2010 have come to fruition, but many are yet to be realised. What is clear is that the next 10 years will certainly see the continuation of these challenges for our field as we navigate the era of genomic medicine. The increasing use of personalised medicine with exome and genome sequencing, technical advances that will enhance fetal therapy and the potential for gene editing,108,109 will all bring particular challenges. These will be both technical and ethical, but possibly it is the ethical ones that may become most challenging of all.

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