**Title:** Maternity healthcare professionals' views and experiences of fetal genomic uncertainty: a review

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**ABSTRACT**

The field of prenatal screening and diagnosis for fetal anomalies has been marked by a rapid succession of technological advances, including most notably, chromosomal microarray analysis and next generation sequencing. Despite the diagnostic advantages of these technologies, their incorporation into prenatal testing has created additional challenges of revealing genomic variants of unknown or uncertain significance, and secondary findings. While detailed post-test counselling about uncertain variants is best performed by medical geneticists, many of the screening and diagnostic tests that lead to this information are actually ordered by general maternity health care professionals (HCPs), such as obstetricians, midwives and family physicians. Maternity HCPs support pregnant women through to the conclusion of their pregnancy and the postpartum period, and thus are close observers of the psychosocial impart of fetal genomic uncertainty on women and their families. Whilst there have been many studies exploring the handling of genomic uncertainty by

genetics HCPs there has been relatively less attention paid to maternity HCPs without speciality training in genetics. This review explores the current literature surrounding non-genetic maternity HCPs' views and experiences of genomic uncertainty and returning uncertain results in the prenatal setting.

**Bullet points**

What is known about this topic

- Genomic testing can produce several types of uncertainty, including the detection of variants of uncertain significance, variants with variable penetrance/expressivity and secondary findings unrelated to the indication for testing.
- Genomic uncertainty can have a profound psychosocial impact on patients in the prenatal setting
- Genetics health care professionals have specialist knowledge and training to counsel patients in situations of genomic uncertainty
- The perspectives of non-genetics health care professionals on fetal genomic uncertainty are important due to their crucial role in maternity care

**What this article adds**

- There is a lack of information on the views of obstetricians, midwives and family physicians with regard to fetal genomic diagnostic uncertainty created by prenatal chromosome microarrays and fetal exome sequencing.
- Further research on the perspectives of these stakeholders is critical to informing the successful implementation of genomics in the prenatal setting.

**Keywords**: prenatal diagnosis, genomics, variants of uncertain significance, obstetricians, midwives, family physicians

**Word length:** 3330 words

Running title: Maternity health care professionals views of fetal genomic uncertainty

**INTRODUCTION**

The field of prenatal screening and diagnosis for fetal anomalies has been marked by a rapid succession of technological advances, including most notably, chromosomal microarray analysis (CMA) and next generation sequencing (NGS).[1,2] CMAs are now widely adopted as the current standard of care for fetuses with structural abnormalities, providing improved yield of clinically relevant copy number variants (CNVs).[2] NGS has revolutionized noninvasive prenatal testing for chromosomal and genetic conditions using maternal plasma cell-free DNA, as well as facilitating fetal exome sequencing of invasively obtained DNA.[3,4] Despite the diagnostic advantages of CMA and NGS, their incorporation into prenatal testing has created additional challenges by revealing genomic variants of unknown or uncertain significance. Whilst uncertainty is not a new concept to prenatal testing, the additional challenges of disclosing uncertain genomic results has exacerbated clinical and ethical dilemmas for maternity health care professionals (HCPs).[5-6] In contrast to traditional prenatal testing methods, modern molecular technologies produce genetic information about the fetus on an unprecedented scale, threatening to overwhelm our current services with an increasing number of 'uncertain' results.[7,8]

Genomic testing can produce several types of diagnostic uncertainty, including variants of uncertain significance (VOUS), which are genomic copy number variants CNVs that cannot be classified as benign nor clinically significant.[9] These may include recurrent CNVs of 'uncertain' significance that have incomplete penetrance or variable expressivity. An example of a VOUS is 16p11.2 deletion, which is associated with autism and developmental delay, but is also compatible with completely normal outcomes. VOUS also include CNVs for which no information is available and their pathogenicity and relationship to the fetal phenotype is unknown (CNVs of 'unknown' significance).

Prenatal genomic testing may also generate uncertainty by detecting secondary findings that are unrelated to the indication for testing. These may cause dilemmas about whether or not it is appropriate to disclose results to the pregnant woman or not.[10] Secondary findings include the

prenatal detection of adult-onset conditions (e.g. Lynch syndrome or Huntington's disease) and carrier-status for autosomal recessive and X-linked diseases. The American College of Medical Genetics guidance for the disclosure of these types of results in paediatric and adult medicine are explicitly not applicable to the prenatal setting.[11] Parental testing may be required to assist in interpretation of fetal results, which may raise additional ethical and clinical concerns. It is even possible, via single nucleotide polymorphisms (SNP) microarrays, to identify consanguinity, and very rarely, incestuous relationships, hence introducing further ethical complexity.[12,13]

While detailed post-test counselling regarding genomic uncertainty is best performed by specialist genetics services, many of the screening and diagnostic tests that lead to this information are actually ordered by maternity HCPs (obstetricians, midwives and family physicians). In many countries, pregnant women are under the primary care of a maternity 'HCP' throughout their pregnancy, and generally only access genetics HCPs (medical geneticists, and genetic counsellors) after they are identified as 'high risk' by their primary maternity HCP. Maternity HCPs perform the majority of pre-test counselling for aneuploidy screening and routine fetal morphology ultrasounds, and return these test results to patients. Maternity HCPs thus have the primary responsibility of addressing initial concerns about increased genetic risk and referring the patient to genetic counsellors and clinical geneticists. They also support pregnant women through to the conclusion of their pregnancy, and thus have numerous opportunities to observe the psychosocial impact of fetal genomic uncertainty on women and their families.

Whilst there have been many studies exploring the handling of genomic uncertainty by genetics HCPs[14-15] there has been relatively less attention paid to non-genetic maternity HCPs such as obstetricians, midwives and family physicians (FPs). It is unknown how maternity HCPs perceive uncertain results arising from genomic testing, such as VOUS. This review aims to synthesize the current literature surrounding maternity HCPs' views and experiences of genomic uncertainty in the

prenatal setting.

## METHODS

Medline Ovid and PubMed databases were searched on 19/07/2019 using a combination of the domains search terms presented in Table 1. English-language studies published from 2006 to 2019 were selected, based on their relevance to the topic, and reference lists manually searched for additional relevant studies. Only original studies that included non-genetic HCPs that specifically addressed fetal genomic diagnostic uncertainty in whole exome sequencing (WES) and CMA were included. Studies primarily investigating aneuploidy or carrier screening were not included. Professional society consensus statements and reviews and commentaries of high relevance to the topic were collected during our literature search.

## RESULTS AND DISCUSSION

The results of the literature search are presented in Figure 1 and Table 2. A total of 34 full text papers were examined. Duplicate results and studies that did not include specific information on fetal genomic uncertainty were excluded. The final five studies all investigated the views of obstetricians (2 obstetricians only studies, 3 multidisciplinary studies). There were no eligible studies of midwives or PFs. Due to the small number of studies, noninterventional nature, and heterogenous designs (qualitative/quantitative/mixed methods), data extraction and quality assessment for a systematic review according to established protocols[16]was not possible. Instead, a narrative synthesis of the published literature is provided, summarizing the current state of knowledge.

### Obstetricians

The five included papers on obstetrician's experiences of genomic diagnostic uncertainty covered a range of tests, including CMA[17,18,19] whole genome sequencing,[20] and exome sequencing.[21] (Table 2).

Cheng et al. administered a questionnaire on prenatal CMAs to 73 Hong Kong obstetricians to identify the needs and gaps prior to planned transition from karyotype to CMA.[18] In Hong Kong, genetic counselling is most commonly carried out by obstetricians specializing in prenatal diagnosis, and the number of clinical geneticists is limited. They found that 25% of doctors would not offer CMA to a patient undergoing an invasive prenatal diagnostic procedure. The detection of VOUS was one of the major justifications for not offering CMA, including "the test may detect findings of unclear clinical significance" or "unwanted information that is not related to the pregnancy may be found". None of the doctors refusing CMA were concerned about detection of clinically significant genetic conditions. Only 24% of the doctors who would offer CMA were willing to offer pre and post testing counselling. The proportion willing to offer CMA increased to 62% among maternal fetal medicine specialists, highlighting the variation in expertise and confidence among obstetricians in HK.

Shkedi et al used both qualitative and quantitative analysis (Q-methodology) to understand the views of genetics health professionals, fetal medicine consultants, obstetricians and fetal medicine midwives on prenatal CMA testing.[16] Four main viewpoints were identified: (i) in favour of only disclosing findings for proximate medical benefits to the child, (ii) in favour of disclosing a wide range of findings including VOUS;, (iii) giving parents an active role in deciding what information to receive; and (iv) in favour of a panel of experts and national guidelines to determine which findings are disclosed. In this study, the authors observed that the genetics HCPs recognised the difficulties in preparing parents for the possible outcomes from prenatal CMA, yet were more likely than other HCPs to believe that parents should take an active role in deciding what information to receive. Unfortunately, it was not otherwise possible to separate out the views of participants based on their profession (genetic vs non-genetic HCPs).

In a UK multidisciplinary study on prenatal whole exome sequencing, uncertain findings were also identified as potentially negative aspects of testing, but participants did not view this as a reason to

withhold testing altogether.[21] In the focus groups conducted, a multidisciplinary group of clinicians including fetal medicine specialists and geneticists reported that genomic uncertainty could cause distress and anxiety to patients, but they believed that uncertain results should still be disclosed in order to respect patient autonomy. There were differing opinions among these clinicians as to whether secondary findings should be reported, with some considering this to be "screening by subterfuge". There was ambivalence about nondisclosure of prenatal secondary findings, however, as it was acknowledged that subsequent postnatal diagnosis could damage the therapeutic relationship if the parents felt that the information had been deliberately withheld during pregnancy. This was in keeping with Shkedi et al, in which HCPs felt that information should be disclosed during pregnancy, or not at all.[16]

Bayefsky and colleagues found similar concerns in their national survey of members of the American Congress of Obstetricians and Gynecologists (ACOG).[20] Among the 1114 respondents who were asked about their attitudes to whole genome sequencing (WGS), obstetricians were most concerned with increasing parental anxiety with complex genomic information, subsequent overtreatment and higher costs of care. More than half of respondents (52.3%) thought that *all* medical information should be disclosed to patients. Obstetricians were most concerned about ordering tests that may reveal nonmedical information or a learning disability. Lower levels of concern about prenatal WGS was associated with practitioners being older, and having higher genetic literacy. The large majority did not believe they had sufficient resources to interpret and communicate WGS results, with one respondent reflecting: "It's like opening Pandora's box". The obstetricians also stated that they would feel more comfortable counselling patients receiving 'uncertain' results and that their perceived burden of disclosure would lighten if they were able to refer to clinical guidelines.

In a study designed to answer the question "what should be detected in prenatal diagnosis?", a national multidisciplinary expert group comprised of 24 prenatal specialists (8 clinical cytogeneticists, 8 clinical geneticists, 8 obstetricians) was assembled in The Netherlands in 2008.[19]

The convenors systematically elicited the views of the panel on which specific chromosome abnormalities should be reported as a result of prenatal diagnosis. There was agreement on 12 out of 15 pre-selected chromosome abnormalities, mainly those with severe consequences. However, obstetricians differed to the geneticists in their attitudes to disclosing results with variable expressivity or penetrance. Consensus could not be reached for the abnormalities with uncertain or mild consequences, including triple X syndrome, normal variants, and mosaic trisomy 20. These opinions differed markedly despite agreement on the range of phenotype variation and clinical consequences for these conditions. Obstetricians voted more frequently *against* detection, compared with the other experts. Obstetricians also changed their opinions more than the other expert groups. Overall, there was agreement that the reporting of abnormalities without clinical consequences should be avoided. The authors observed that the failure of their expert group to reach agreement on all 15 conditions was not due to knowledge gaps, but more due to differing weighting of the competing principles of the patient's "right to be informed" vs clinical utility of reporting the finding. They therefore concluded that a uniform nationwide policy was unlikely to be achieved, given the lack of consensus among the group of experienced stakeholders.

**Midwives and**

There were no studies specifically examining the perspectives of midwives or with regard to fetal genomic diagnostic uncertainty. The fetal medicine midwives included in a multidisciplinary study discussed above did not have their results reported as a separate group.[16]

**Consensus statements and guidelines**

Six professional society statements or publications outlining recommendations for reporting and management of genomic uncertainty were identified. These are summarized in Table 3.

**Discussion**

This literature review on maternity HCPs' perspectives of uncertainty in prenatal genomics has demonstrated a paucity of studies in this area, despite the central role of obstetricians FPs, midwives in providing pregnancy care. This is a concern given that maternity HCPs may increasingly be tasked with counselling patients about genomic tests that may result in uncertain findings. They are also likely to provide ongoing care of patients who have been given a prenatal result of genomic uncertainty. While we identified several studies that included obstetricians and fetal medicine specialists, there was a notable absence of studies exploring midwives and FPs views, most likely due to the perception of their peripheral role in prenatal diagnosis. However, there is increasing recognition that FPs and midwives must engage with the growing impact of genomics in health care.[22,23] Coupled with the preliminary evidence from this review that diagnostic uncertainty is viewed as one of the major negative consequences of prenatal testing, further research is needed to inform the implementation of fetal genomics into maternity care.

One of the major themes common across all maternity HCPs was that fetal diagnostic uncertainty raises ethical and clinical dilemmas, and creates parental anxiety, often with little perceived clinical benefit. Obstetricians were less likely to agree to prenatal testing that might result in uncertain results than geneticists, as they appeared to place more weight on the negative aspects of diagnostic uncertainty. A possible explanation is that in some settings, the obstetrician will continue to provide the routine prenatal care for all the other non-genetic aspects of pregnancy care and birth. These prenatal visits may provide more frequent opportunities for obstetricians to observe any negative impacts of VOUS compared with clinical geneticists who have a more limited involvement in the woman's care. In addition, genetic healthcare specialists are likely to have more experience in counselling patients about uncertainty (e.g. genetic conditions that have variable penetrance or expressivity) and may therefore feel more comfortable offering such tests.

It was revealing that the national consensus group in the Netherlands could not agree on what chromosome conditions should be reported to patients where there was an element of uncertainty

regarding the severity of the phenotype.[19] This dispute was not about the facts of each medical condition, but rather arose from varying priorities placed on the principles of patient autonomy and clinical utility/medical actionability. Disagreements amongst professional and clinical stakeholders around what uncertain results should be given to patients (not in the prenatal setting) has been reported elsewhere. This suggests that an international consensus on the reporting of uncertain variants would be even less likely, and that practice will continue to be driven by local context, specific cultures and individual laboratory practices.

The World Health Organisation has estimated that globally, midwives provide 87% of the care to women and their newborns,[24] and midwives may become increasingly instrumental in providing patients with prenatal testing (at least in high income countries). Although there is an emerging appreciation of the importance of genomics in nursing and midwifery education, the current literature on midwives and genomics appears limited to assessing educational needs and genetic knowledge, rather than any specific exploration of midwifery perspectives on genomic VOUS.[21] This suggests that midwives are at an earlier phase of engaging with genomics and have not yet accumulated a collective experience of genetic VOUS.

However, studies that explore midwifery perspectives on ultrasound "soft markers", may provide some indication of how fetal diagnostic uncertainty in general are viewed by midwives. In a Swedish qualitative study of 25 midwives, the theme of "acknowledging ultrasound as optimizing care but also creating worry and ethical dilemmas" could be analogous to the issues in prenatal genomics.[25] In an Australian study of 37 midwives' views on prenatal ultrasound, clear "pros and cons" were similarly identified. The positive aspects included optimising pregnancy outcomes and providing choice, reassurance and bonding. The negative aspects included the increased medicalization of pregnancy, creating of complex and sometimes "uncertain decision making" dilemmas, and contributing to parental anxiety.[26] There is an inherent conflict between the perspective of pregnant women who see prenatal screening as a method of providing reassurance, and that of HCPs who

view testing as a means to obtain a diagnosis. The nature of the pretest counselling is key in preparing women for the results of any prenatal screening.

Another important theme from this Australian study included the normalization of ultrasound and the erosion of informed consent. The midwives also reported that some women focussed on ultrasound as a method to find out the sex of the fetus, and were shocked when an abnormality was found. Ultrasound technology was seen to lead to increased "personification" of the fetus, potentially displacing the woman from her central role in the pregnancy.[26] It is very plausible that midwives hold similar perspectives with regard to fetal genomic uncertainty. It is important to acknowledge that midwives approach pregnancy from a wellness perspective and that they may view advances in genomics as promoting the medicalization of healthy pregnancies, routinisation of prenatal genetic testing (with associated erosion of informed consent), and personification of the fetus, all of which have the potential to detract from a pre-existing paradigm of woman-centred care.

In contrast, FPs are already engaged in personalized genomics in health care in the adult and paediatric settings, although our literature review reveals that they have not been specifically studied with respect to prenatal genomics. In a single qualitative focus group study of Australian FPs' experiences of prenatal screening, communicating complex information about screening was identified as highly important.[27] The FP acted variously as an "interpreter" of medical information, and a "gatekeeper" of prenatal tests, as well as a "time-keeper" for the consultation. FPs also saw screening tests as "quite a downer" when they had to discuss them when women are feeling excited about being pregnant. FPs clearly saw it as their role to explain the possibilities and limitations of prenatal screening, including providing information on uncertainty in testing: "We should be explaining the greyness… there's almost nothing we can offer and almost nothing we can do (that) will have an absolutely definite black or white answer".[27] They also saw themselves as an intermediary and advocate for the women, trying to empower them to make an informed choice

and avoid being coerced into testing by obstetricians who may present testing as “routine” or “compulsory”.

Outside of the prenatal setting, FPs believe that communicating genomic risk is a responsibility of primary care and recommended a shared decision-making approach to guide the testing.[23] FPs believe it is important to ensure that patients understand genomic risk and do not experience long-term adverse psychological responses. FPs desire clinical practice guidelines that specify recommendations for genomic risk assessment and patient management, point-of-care resources, and risk prediction tools that include genomic and traditional risk factors. All these findings may be highly relevant to FP attitudes to uncertainty in prenatal genomics.

Even the very limited results of this literature review suggest that maternity HCPs may have very different perspectives on prenatal testing to genetics and fetal medicine specialists. The willingness to engage in a discussion about genomic uncertainty appears to be directly related to genetic knowledge and familiarity with genetic testing and can be understood in terms of the context of each HCPs expertise and relationship with the pregnant woman.

The consensus statements identified during this literature review provide some guidance on the introduction of CMA and WES into clinical practice and how to handle uncertain results. In the area of CMA, where there is now substantial clinical experience, several national societies have published recommendations on the use of prenatal CMAs.[28,29,30] The recommended indications for prenatal CMA do vary between national guidelines, with the UK supporting the use of CMA for fetal abnormality or increased nuchal translucency ($\geq$ 3.5mm)[29] while the Belgium guideline supports the use of CMA for all indications for invasive prenatal testing.[30] The Belgian and UK guidelines provide specific advice for reporting and non-reporting of VOUS in the prenatal settings, in order to provide consistency in variant reporting and to provide clinical guidance on actionable and non-actionable

secondary findings. For example, the UK and Belgium guidelines both recommend against reporting deletions or duplications of the susceptibility loci 15q11.2 BP1-BP2.

Other societies, such as The Australasian Society of Diagnostic Genomics and the Human genetics society of Australasia do not make recommendations on the reporting and nonreporting of specific CNVs and susceptibility loci for prenatal CMAs, but rather state: "Laboratories should have their own policy on the reporting of low penetrant CNVs, adult-onset disorders cancer predisposition, and carrier status for autosomal recessive conditions for prenatal and postnatal diagnosis." [31]

The American College of Obstetricians and Gynecologists and the Society for Maternal Fetal Medicine detail the clinical indications for prenatal CMA, and pre-test and post-test counselling issues, acknowledging that abnormal results, including variants of uncertain significance, can have "profound psychosocial effects on patients and their families".[32,33]

The Joint Position Statement from the International Society for Prenatal Diagnosis and the Society for Maternal Fetal Medicine (USA) acknowledge that practices will vary by region with regard to returning variants of uncertain significance, or conditions with adult onset, and advise that these issues be addressed during pre-test counselling: "Such counselling requires communicating detailed and often complex genetic information in a manner that balances explaining possible knowledge gaps with the reality of variable genetic literacy and time constraints."[34]

**The importance of consensus and HCP education in the genomic era**

Despite the challenges of working in a field with rapidly emerging knowledge and regional variations in practice, there are key messages that are raised consistently in the published consensus documents and guidelines. More than ever, pre-test counselling of pregnant women and their partners is acknowledged as central to the ethical and clinically-robust delivery of care. Successfully communicating the purpose of testing, and the potential for uncertainty or unexpected findings, is

key to minimising the potential harms of genomic testing. In Belgium, where prenatal testing is usually integrated into a routine prenatal consultation without prior counselling by a geneticist or genetic counsellor, a thorough examination of the ethical implications[35] and provision of written patient information leaflets on CMA have been published by a national consortium to help support clinical practice.[36] Similarly, the UK has developed written resources to improve the quality and consistency of pretest counselling with a national sample consent form and information sheet for prenatal CMA.[30] Other notable measures to address the challenges of genomic uncertainty include the formation of national databases[29] and committees to discuss ambiguous cases and provide reporting recommendations,[36] and decision aids to augment clinical consultations.[37]

The other key message from the consensus statements is that improving the genetic education of HCPs involved in maternity care is an essential component of responsibly advancing the field of prenatal diagnosis. Targeted, flexible and scalable methods of delivering continuing medical education to maternity HCPs will be the key to ensuring that pregnant women have access to best practice in prenatal diagnosis.

**CONCLUSION AND FUTURE DIRECTIONS**

There is a paucity of research on maternity HCP's views of prenatal diagnostic uncertainty, although the available literature suggests there may be unique perspectives according to the way in which each HCP engages with women during pregnancy. Obstetricians, who are the maternity HCPs in closest proximity to prenatal diagnostic procedures, appear to be very aware of the negative consequences of prenatal VOUS and were found to place less emphasis on the patient's "right to know", than genetics specialists. Midwives, who focus on pregnancy and birth as normal processes, have not been specifically studied in regard to their views of uncertain result in fetal genomic testing. FPs have engaged with prenatal screening for several decades, but their views on advanced prenatal diagnostic testing with CMA and WES are unknown. Given their central role of these

stakeholders, further research on the perspectives of maternity HCPs is critical to informing the successful implementation of genomics in the prenatal setting.

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37. Halliday JL, Muller C, Charles T, et al. Offering pregnant women different levels of genetic information from prenatal chromosome microarray: a prospective study. Eur J Hum Genet. 2018;26: 485-494.

**Figure legends**

Figure 1. Flowchart of literature search and included studies.

HCP, health care professionals

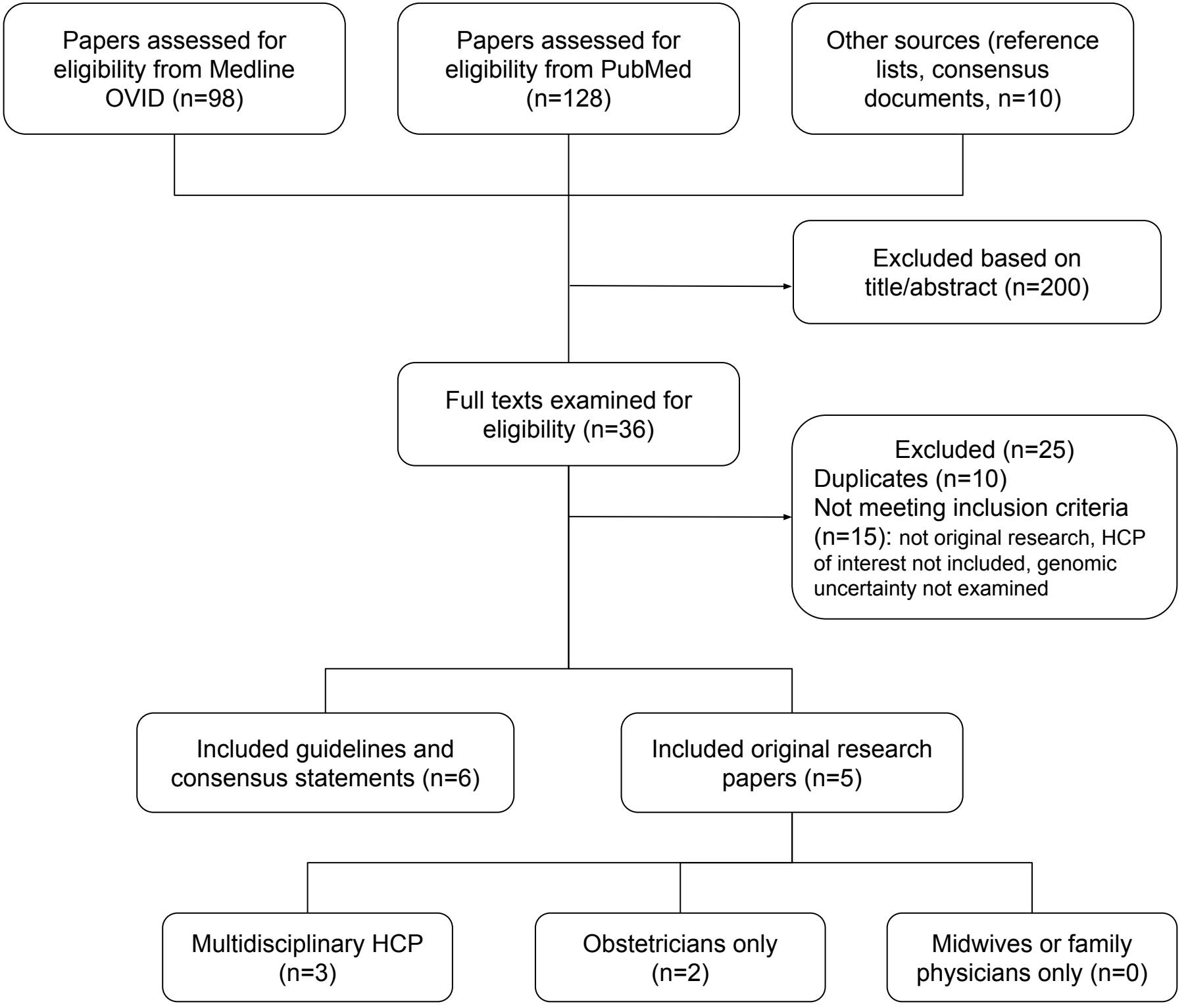
Papers assessed for eligibility from Medline OVID (n=98)
Papers assessed for eligibility from PubMed (n=128)
Other sources (reference lists, consensus documents, n=10)
Excluded based on title/abstract (n=200)
Full texts examined for eligibility (n=36)
Excluded (n=25)
Duplicates (n=10)
Not meeting inclusion criteria (n=15): not original research, HCP of interest not included, genomic uncertainty not examined
Included guidelines and consensus statements (n=6)
Included original research papers (n=5)
Multidisciplinary HCP (n=3)
Obstetricians only (n=2)
Midwives or family physicians only (n=0)

Table 1 Literature search terms (Medline Ovid 2006-2019)

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 |
|---|---|---|---|---|
| Health professional* | Experienc* | Uncertain* | Prenatal | Genomics |
| Obstetrician* | Communicat* | Result* | Perinatal | Microarray |
| General practi* | Disclos* | Finding* | Prenatal Diagnosis, Prenatal Care, Perinatal Care | Whole exome sequencing, Exome |
| Midwi* | View* | Diagnos* | Fetal | |
| Physician* | Discuss* | | Pregnancy | |
| Clinician* | | | Prenatal screening | |
| Nurse* | | | | |
| Primary care | | | | |
| Primary healthcare* | | | | |
| Counsel* | | | | |

| Ref | First author | Year | Title | Country | Study Design | Healthcare professionals | No. of participants |
|---|---|---|---|---|---|---|---|

Table 2. Summary of included original research studies

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Mixed HCPs** | | | | | | | |
| 17 | Shkedi-Rafid | 2016 | What results to disclose, when, and who decides? Healthcare professionals' views on prenatal chromosomal microarray analysis | United Kingdom | Q-methodology (quantitative and qualitative) | Medical geneticists (n=7), genetic counsellors (n=9), genetics registrar (n=3), fetal medicine specialists (n=2), fetal medicine midwives (n=6) obstetricians (n=1), lab-scientists (n=12) | 40 |
| 21 | Quinlan-Jones | 2016 | Prenatal whole exome sequencing: the views of clinicians, scientists, genetic counsellors and patient representatives | United Kingdom | Qualitative (focus group interviews) | Focus group 1: patients and charities (n=5)<br>Focus group 2: fetal medicine specialists (n=2), genetic counsellors (n=2), consultant clinical geneticists (n=2) and clinical scientists (n=2) | 13 |
| 19 | Boormans | 2010 | Aiming at multidisciplinary consensus: what should be detected in | The Netherlands | Expert Panel Consensus | Clinical geneticists n = 8<br>Clinical | 24 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | prenatal diagnosis? | | | cytogeneticists n = 8<br>Obstetricians n = 8 | |
| **Obstetricians** | | | | | | | |
| 18 | Cheng | 2017 | Bridging the gap from prenatal karyotyping to whole-genome array comparative genomic hybridization in Hong Kong: survey on knowledge and acceptance of health-care providers and pregnant women | Hong Kong | Quantitative (Cross-sectional survey) | Obstetricians | 73 |
| 20 | Bayefsky | 2016 | Views of American OB/GYNs on the ethics of prenatal whole-genome sequencing | United States of America | Quantitative (survey) | Obstetricians (members of ACOG) | 1114 |

Table 3. Consensus statements and guidelines addressing prenatal genomic diagnostic uncertainty

| **Reference** | **Authors** | **Year** | **Title** | **Country** | **Article type** | **Healthcare professionals involved** |
|---|---|---|---|---|---|---|
| 28 | Armour | 2018 | Practice guideline: joint CCMG-SOGC recommendations for the use of | Canada | Professional society practice guideline | Medical geneticists, genetic counsellors, maternal fetal |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | chromosomal microarray analysis for prenatal diagnosis and assessment of fetal loss in Canada | | | medicine specialists and clinical laboratory geneticists |
| 29 | Muys | 2018 | The Belgian MicroArray Prenatal (BEMAPRE) database: A systematic nationwide repository of fetal genomic aberrations | Belgium | National prenatal CMA consortium including reporting consensus | Clinical and laboratory geneticists from every genetic centre in Belgium |
| 30 | Gardiner | 2015 | Recommendations for the use of chromosome microarray in pregnancy | United Kingdom | Joint society recommendations (RCOG, RCP, BSGM) | Clinical geneticists, maternal fetal medicine specialists, clinical laboratory geneticists |
| 32 | ACOG/SMFM | 2017 | Counselling about genetic testing and communication of genetic test results | United States of America | ACOG Committee opinion | Obstetricians |
| 33 | ACOG/SMFM | 2016 | Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology | United States of America | Society for Maternal Fetal Medicine | Maternal fetal medicine specialists |

| | | | | | | |
|---|---|---|---|---|---|---|
| 34 | ISPD | 2018 | Joint Position Statement from the International Society for Prenatal Diagnosis, the Society for Maternal Fetal Medicine, and the Perinatal Quality Foundation on the use of genome-wide sequencing for fetal diagnosis | International | Society consensus statement | Multidisciplinary |

ACOG, American College of Obstetricians and Gynecologists; BSGM, British Society for Genetic Medicine; CCMGS-SOGS, Canadian College of Medical Geneticists-Society of Obstetricians and Gynaecologists of Canada; ISPD, International Society for Prenatal Diagnosis; RCOG, Royal College of Obstetricians and Gynecologists; RCP, Royal College of Pathologists; SMFM, Society for Maternal Fetal Medicine