Prenatal Diagnosis

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Use of Prenatal Exome Sequencing: Opinion Statement of the French Federation of Human Genetics Working Group

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ABSTRACT

Objective: Prenatal whole exome sequencing (pES) is increasingly prescribed for fetuses with ultrasound anomalies. Starting from the local French prenatal medicine practice, healthcare system and legal landscape, we aimed to address the broad medical and ethical issues raised by the use of pES for women and couples as well as for prenatal care providers.

Method: The French Federation of Human Genetics established a working group composed of clinicians and biologists from all over France to discuss pES challenges. A literature review was also performed.

Results: We emphasize the importance of non-directive information that helps couples make a decision that is consistent with their personal values and ideas. We address the difficulty of obtaining informed consent that respects the couple's autonomy, despite the complexity of the information and regardless of their level of education and cultural background. We address whether variants of uncertain significance and unsolicited results should be reported. We emphasize the need for national harmonization of access to pES and the need for multidisciplinary meetings in complex situations. We point out that the specific French context of healthcare financing and the French law have a major influence on medical care organization and support for couples. The outcome of the working group is the development of 12 proposals.

Conclusion: This opinion statement, dedicated to prenatal care providers worldwide although linked to the French context, will provide food for thought and assist them in understanding the complexity and implications of pES.

Summary

- What's already known about this topic?
  - Prenatal whole exome sequencing raises complex medical and ethical questions.
- What does this study add?
  - A French working group has drawn up a set of proposals for the use of exome sequencing in prenatal medicine, and compared its findings with those of genetic societies in other countries.

1 | Introduction

Approximately 2%–4% of pregnancies feature isolated or multiple congenital anomalies [1]. Ultrasonography (US) during pregnancy is the key examination used to identify those anomalies. Many etiologies (placental, infectious, toxic elements) may explain fetal structural anomalies. However, the anomalies are mainly due to genetic disorders [2]. For years, the genetic examinations available in prenatal medicine were limited, essentially based on karyotype, fluorescent in situ hybridization and Sanger sequencing, allowing for targeted gene sequencing. More recently, chromosomal microarray (CMA), focusing on copy number variations allowed for an increase in diagnostic yield [3]. Despite targeted analyses and CMA, for about 70% of fetuses with multiple congenital anomalies, the molecular diagnosis remains to be identified [4, 5]. In this context of limited diagnostic yield, exome sequencing (ES), which had already proven its interest postnatally, was introduced into fetal medicine.

Prenatal ES (pES) aims at identifying the genetic origin of one or several anomalies seen in a fetus. The women's and couples' expectations regarding this analysis vary: decreasing uncertainty and helping to decide on pregnancy continuation or termination of pregnancy (ToP). The identification of a pathogenic or likely pathogenic variant (P/LP) can remove the uncertainty that the fetal structural abnormalities cast on the diagnosis and/or prognosis.

However, pES raises ethical issues for women and couples as well as for clinicians at each stage of the process: pre-test information, reporting (which variants to report) and post-test visit. The first challenge, during the pre-test visit, is to obtain an informed consent which respects the couple's autonomy despite the complexity of the information and regardless of their educational and cultural background. Second, pES raises questions about which variants to report: only those that are responsible for the fetal anomalies that motivated pES? Or should we also report the variants of uncertain significance (VUS) as biologists usually do in postnatal exome sequencing? Indeed, the consequences are different because the time frame of the pregnancy might not be sufficient to reclassify a VUS as P/LP or benign. What about unsolicited findings? Of course, the answers to these questions condition the information during the pre-test visit. All these genetic findings are discussed during a multidisciplinary meeting. Third, the quality of the post-test counseling is decisive for the couple's choice. If genetic and prenatal expertise is naturally required to properly ensure meaningful results, the support of women and couples in the difficult choices they face also requires a know-how and interpersonal skills. Finally, fetal anomaly findings during pregnancy generate a psychological distress for the women or couples over the course of the process [6]. Therefore, addressing beforehand the inherent ethical issues of pES is paramount to avoid unnecessary anxiety for the women or couples.

The French Federation of Human Genetics established a working group on ethics composed of clinicians and biologists from all over France to discuss pES challenges. The group aimed to address the broad medical and ethical issues raised by pES, which are distinct from those raised by postnatal exome sequencing (Table 1). The outcome is an opinion statement that, while taking into account the local French healthcare system and law, can be used as an educational resource for all healthcare providers worldwide in prenatal medicine. It aims to help them understand the complexity and implications of pES.

2 | Methods

2.1 | Working Group

This opinion statement was developed by a working group of both clinicians and biologists from all over France and representing a wide diversity of prenatal specialties (clinical genetics, cytogenetics, molecular genetics, genetic counseling, fetopathology and obstetrics). The working group met remotely and regularly between February 2022 and September 2023. We started this work by the identification of pES medical and ethical issues from two sources: first, we gathered the collective insights from our medical background and experience as specialists in prenatal medicine and/or genetics who have been dealing with pES for years. We then interviewed three geneticists with extensive experience in pES clinics. Once we selected the ethical issues rooted in our French medical practice, we reviewed three fields of the literature: ethics related to pES (e.g., women and couples' experiences of pES result report for unsolicited findings and variants of uncertain significance), clinical practice of pES (e.g., diagnostic yield of various fetus' abnormalities) and other national and international societies' opinions (e.g., American society of medical genetics (ACMG), international society for prenatal diagnosis (ISPD) etc.). From both collective discussions and extended literature review, we established a document intended for prenatal healthcare providers. No vote took place, and all members largely agreed on the main document, which was finally accepted in a plenary session on September 25, 2023.

2.2 | The French Context

The French healthcare system is guided by an annual funding law that provides universal coverage for all healthcare users, based on a solidarity principle [7, 8]. Thus, for the patients, prenatal care is fully funded by the French healthcare system. The equity of access to all medical examinations for all French citizens is a law-protected standard of care [9].

TABLE 1 | Specificities of prenatal and postnatal whole exome sequencing (ES).

Categories	Prenatal ES	Postnatal ES	Comments
Clinical utility of pES	+++	++	Help in decision-making
Rapidity of result report required	+++	+	Request a specific organization for prenatal ES
Emotional burden of the process	+++	++	Termination of pregnancy issues (only for prenatal ES)
Territorial accessibility	+	++	General resolutions are required for prenatal ES to be accessible to every pregnant woman in France
Homogeneity of accessible indications throughout the territory	+	++	Indications accepted in some genetics departments and refused in others: Need for a global viewpoint to homogenize the territory indications
Full phenotype accessibility	−	++	Access to the full fetal phenotype is usually limited, thus exposing to a risk of wrong variant classification or missing a causal variant
Need to analyze the data in one's expertise domain	++	+	If the analysis is performed locally, the biologist is more susceptible to interpret data out of their expertise domain: A thought to maintain analysis quality of pES is required
Risk of false positive and mosaicism	+++	−	Bioinformatics pipeline needs to be carefully calibrated because of contamination risk by maternal cells, twins' pregnancy, placental mosaicism, real fetal mosaicism or chimerism
Ethical issues of report of variants of uncertain significance (VUS)	+++	−	Risk of an interruption of pregnancy demand, even prenatal or preimplantation diagnosis for future pregnancies
Possibility to reclassify VUS	−	++	The short turnaround time limits the possibility to perform complementary analyses.
Possibility to consent to secondary and incidental findings by the concerned individual	Not possible	+ (related to the age)	Need to think of the information, the consent and the report of secondary and incidental data. Risk for the patient to become an "incoming-patient" from birth.
Risk of interference of incidental and secondary findings on the management decision by the women or couples	+++	−	Need to think of the information, the consent and the report of secondary and incidental findings

In France, US is systematically offered at each pregnancy semester (3 in total), usually at 12 to 22 and 32 gestational weeks (GW). If an anomaly is identified by standard US, additional and/or specialized US (e.g., cardiographic US) can be performed to precisely characterize the anomaly and further guide the diagnostic examinations to be performed. If considered as severe, the clinical situation will mandatorily be discussed at a multidisciplinary meeting, in a fetal medicine center, which must include at least one obstetrician, an ultrasonographist, a medical geneticist and one pediatrician/neonatologist, and optionally a biologist, a psychologist, or a psychiatrist [10]. The staff can deliberate whether a genetic test to further investigate the anomaly might be relevant. If asked by the women or couples, those meetings can also include a discussion and further acceptance of a medical ToP. Unlike voluntary ToP, which is legally possible until 16 GW, medical ToP is allowed in France until the end of the pregnancy in case of a severe disease without current available treatment after a mandatory multidisciplinary meeting. In contrast to France, medical ToP is only authorized until 24 GW in some countries [11–13]. About 1% of all pregnancies end by medical ToP in France [14].

The legal framework for the performance of prenatal genetic testing has been clarified following the revision of the new Bioethics Law in August 2021 [15]. Concerning incidental findings, compared to the previous legislation, Article 16.10 of the

Civil Code now clearly establishes the obligation of health professionals, where applicable, to inform individuals, at the time of proposing a genetic test revealing constitutional information, of "the possibility that the test may incidentally reveal genetic characteristics unrelated to its original indication, but knowledge of which would enable the person or members of his or her family to benefit from preventive measures, including genetic counseling, or care" [16]. Specific provisions for the implementation of these rules in the context of prenatal genetic testing have also been adopted in the 2021 law [15], which specify the time and modalities for providing the pregnant woman, and her partner, with adequate information and obtaining her informed consent [17]. Information and consent in the field of fetal medicine is carried out through a step by step approach in which all the pregnant women are first informed (most often by the gynecologist) of the possibility of having access to medical examinations (biological and imaging). Secondly, if a risk suggestive of a genetic cause is identified, the pregnant women and couples will be referred to a medical geneticist for additional biological tests (including genetic tests) who will discuss the potential results expected and the possibility of obtaining incidental information. All the information, including any incidental findings, is summarized in a jointly signed certificate (the pregnant woman and the doctor), and if the woman decides to have a genetic test performed, she will be asked to give her written informed consent [18].

Professional guidelines in France are established by the French Agence de la Biomédecine, a public institution created by the 2004 Bioethics law. Therefore, this statement does not serve as professional guidelines but aims to highlight ethical and medical issues for consideration in pES use.

3 | Points to Consider

3.1 | Pre-Test Considerations

3.1.1 | Challenges in the Clinical Indications of pES

The main idea of the pre-test visit is to provide information to women and couples regarding the potential benefit to expect from pES, the process and the time required to the result report, and the possible findings and types of result reports. All this information aims to help couples make a decision that is consistent with their personal values and ideas.

For many women or couples, the main expectation of pES is to help them decide whether to continue or terminate the pregnancy, although we list other motivations below [13, 19]. When pES is inconclusive, the women or couples should rely on fetus anomalies to decide on ToP. Also, women or couples should be informed that an inconclusive pES result does not mean no genetic cause for the phenotype exists. Using "inconclusive" instead of "negative" might contribute to their understanding.

Outside this clear pES utility, we mention a set of difficulties:

- Some women or couples state that they want to pursue the pregnancy despite severe fetal abnormalities giving a poor prognosis. In this situation, most do not ask for pES. However, some do to prepare themselves for future disabilities and make plans for postnatal management. In this situation, there is no clinical utility of pES regarding the current pregnancy management. Because we know from experience that women's or couples' decisions can evolve during pregnancy and that the result might affect newborn postnatal care, with for instance invasive procedures, we recommend that clinicians not adopt a strict medical opposition to pES in this situation. Instead, we encourage them to provide clear information on the possible issues.
- Sometimes, US fetal anomalies are so severe that they are sufficient to provide a poor prognosis. Although diagnostic yield is high in this situation [20], we consider that the US prognosis is sufficiently severe for decision making. In addition, the emergency of the situation and the limited human resources (clinicians, biologists, technicians, genetic counselors etc.) during the whole process of pES would generate a heavy burden to the whole organization in a context in which the clinical utility is limited. Thus, pES should only be performed exceptionally in this situation. Furthermore, performing a pES in this situation could be harmful, suspending the medical ToP decision [13]. pES, or alternatively genome sequencing, more relevant for diagnostic approach, should be performed after birth or termination, ideally after a fetal autopsy in the latter case.

3.1.2 | Challenges in the Application of pES During Pregnancy

3.1.2.1 | Should We Set a Gestational Week Time Limit for pES? pES results should be delivered as quickly as possible to limit the women's or couples' anxiety [1, 21]. The process is considered relatively urgent. A recent French study showed that the median turnaround time from sample reception to molecular report is 28 days [22]. Worldwide, some genetic departments set a limit of pES at 32 GW because of the risk of birth occurring before pES report, and others do not set any limit [12, 20, 23].

Late pregnancy pES may exacerbate an already stressful and time-sensitive situation. In general, about half of would-be parents describe significant anxiety and stress after a fetal anomaly diagnosis, often feeling overwhelmed by an unexpected diagnosis [24]. The turnaround time of a pES is an additional matter of concern for women or couples [21]. We consider that, if there is clear information that birth can occur before the pES report is delivered, no pES limit should be imposed during pregnancy.

We also argue that the absence of a strict limit of pES respects equity between women or couples for whom fetal congenital anomalies were identified at 22 versus 32 GW because the latter is related to late identifiable fetal anomalies or suboptimal care providing and counseling.

3.1.2.2 | Who Should Prescribe the pES and How? In France, all medical physicians, even general practitioners, can legally prescribe genetic testing as long as an individual is symptomatic. Thus, they can theoretically prescribe a pES for a

fetus with US anomalies. However, some challenges specific to prenatal medicine need to be addressed. First, the physician's ability to understand and anticipate the different results is essential for the women and couples to grasp the consequences of their choices. This ability helps to avoid added complexity and uncertainty due to misunderstandings of potential molecular problems. Second, the healthcare provider must find a fine-tuned equilibrium between two extremes: directive information that would impose its views on the situation, and a totally non-directive information that would leave the women or couple alone to make the decision. According to the position of Dondorp et al., we believe that the clinician should allow himself/herself to explore with the couple their values, which will ultimately help them to make not only an informed but also a meaningful decision [25]. Expertise in prenatal medicine is also necesseray to appropriately apply this model. Only a handful of specialists have this expertise and in practice, a multidisciplinary team discusses pES indications for every case. In line with the International Society for Prenatal Diagnosis (ISPD) [26], we thus think that expertise in both the field of genetics and fetal medicine is required for the care provider who will inform women or couples and ultimately prescribe pES. Indeed, it has been proven that the standard of care and management of genetic conditions is most often better when given by a geneticist professional than another physician [27], which is particularly true regarding genetic testing results with uncertainty [28]. A medical visit specifically dedicated to genetic testing implications should be the standard of care.

3.1.2.3 | pES Timing in the Genetic Test Landscape of Prenatal Medicine. During pregnancy, when US anomalies are discovered in a fetus, the genetic analyses usually performed are mainly CMA and pES. In France, some laboratories perform these analyses in parallel (CMA and pES), whereas others wait for the results of the CMA to begin the pES. The second sequential strategy has the advantage of being more rational from an economical and organizational perspective. However, women or couples must successively experience two periods of negative emotions lasting a few weeks. In addition, as compared with the parallel strategy, the sequential strategy delays the final genetic result, and the approach to the end of the pregnancy increases the stress and is more emotionally difficult of the would-be parents. In line with the Prenatal UK Society (NHS) [29], considering the highest interests of the women and couples to the economical and organizational considerations in this situation, our group believes that genetic departments should prioritize performing these prenatal analyses in parallel.

3.1.3 | Territory Access

At the time of writing, only a few genetic departments in France gave access to pES, with a discrepancy between indications. Hence, the principle of solidarity, which ensures that every French citizen has access to the same medical coverage, is not guaranteed. Therefore, we ask for a nationwide debate to harmonize pES indications and care provided. Because the health system architecture of France is specific and the principle of solidarity is not central in other healthcare systems [1, 30], this opinion might not apply to other countries.

3.2 | Reporting Results

3.2.1 | Concerns About Analysis Quality

3.2.1.1 | Biological Interpretation. Adequate and accurate phenotyping is a significant challenge in pES because phenotype features might be invisible on US or only observed at a certain gestational age and because the prenatal description of Mendelian disorders is poor [22, 31]. However, deep phenotyping is required to ensure the best possible performance of pES interpretation.

pES can be locally developed in a specific genetic department. This approach preserves the interaction between clinicians and biologists because new phenotype elements may arise during pregnancy. The quality of information sharing between the clinician and the biologist is crucial for accurate interpretation. However, the local development force biologists to analyze all indications, some of them outside their expertise. For instance, a biologist who usually analyzes ES and genome sequencing results for intellectual disability can have difficulty analyzing pES data for a fetus with cardiac malformations. As a result, a non-expert biologist might miss a genetic diagnosis, which ultimately can have dramatic consequences for the decision-making regarding the current pregnancy (whether to continue or not) and the future pregnancies (whether to undergo prenatal/preimplantation diagnosis or not). Therefore, ideally, a biologist should not interpret any genetic test outside their expertise. To guarantee the quality of the pES analysis and avoid harmful situations, a double interpretation by two biologists is strongly recommended.

Furthermore, for terminated pregnancies, fetal autopsy should be systematically proposed because it provides supplementary information in 25% of cases [32]. Half of the time, this information is helpful to establish the final diagnosis [33].

3.2.1.2 | Variants of Uncertain Significance. pES reveals about 10% of VUS [22]. By definition, these variants can neither confirm a diagnosis with certainty nor lead to genetic counseling resulting in a request for prenatal diagnosis or preimplantation diagnosis. Postnatally, several strategies can lead to the reclassification of the identified variants upwards (likely pathogenic or pathogenic variant) or downwards (likely benign or benign variant): clinical re-evaluation, segregation analyses, or functional tests. However, during pregnancy, time is limited, and additional analyses are sometimes difficult to carry out, with most VUS remaining after thorough investigations. In their study, Tran Mau-Them and colleagues showed that additional analyses aiming at reclassifying VUS were not contributive for most fetuses (12/17, 71%) [22]. The ethical tension results from the willingness for transparency with the women or couples to respect their autonomy of decision and the willingness to protect them from data that

are themselves sources of additional uncertainty and distress [6, 24].

Wou et al. studied the experience of 29 women and partners who underwent pES during the pregnancy and obtained the results on average 3 months after the end of the pregnancy [24]. Of note, no VUS was reported. Overall, 86% of them would wish the result of a variant with some degree of uncertainty, which highlights the strong desire to obtain as much information as possible to make a decision. However, other studies report that after being confronted with the reality of a VUS, women or couples usually express "surprise", "frustration", and "the toxicity" of a VUS report and ultimately regret their initial decision [34, 35]. Most women and couples are aware that if a VUS was reported, their anxiety would increase [13, 36]. In situations in which no additional investigation is carried out to reclassify the variant or in situations in which additional investigations do not allow for reclassifying the variant, knowledge of the variant is not useful for decision-making and often leads to confusion [30]. However, misunderstanding of a VUS must be prevented for two reasons: (1) to avoid a request for termination of the pregnancy based on the existence of this variant or (2) to avoid a request for prenatal or pre-implantation diagnosis for a future pregnancy. In conclusion, VUS seems to be a harmful element with often harmful consequences on women or couples. Therefore, our group suggests that a VUS should not be reported to would-be parents during the pregnancy.

Of note, the difficulty of interpretation can sometimes be resolved in advance through a discussion with both clinicians and biologists, including the healthcare provider managing the pregnancy or even an expert in the pathology linked to the gene altered by the identified variant. This consultation seems more efficient than familial segregation attempts [37]. Hence, we recommend a systematic collective discussion including the ordering clinician, notably for a careful and directed postnatal follow-up.

3.2.1.3 | Misattributed Parentage. Because pES is mainly performed in trios, misattributed parentage (MP) can occur, such as in the case of a wrong paternity or a gamete donation [30]. The frequency of MP is 1%–2% in Western populations [38, 39]. A survey of a lay adult public revealed significant differences in opinions on whether and how to report MP [40]. In France, from a legal framework, there is no duty to disclose a MP. Internationally, only a few professional guidelines exist, which leads to a wide variety of disclosure practices [41]. This diversity reflects the complex and often embarrassing situation for care providers, with the risk of disrupting family relationships and contributing to psychological and emotional trauma [41]. The identification of a MP is intimate information from a fortuitous discovery but has consequences on the pES analysis: the trio analysis can no longer be carried out, and pES is performed in a duo analysis with a reduction in the diagnostic yield. In addition, the report will mention the duo strategy of analysis. According to the American College of Medical Genetics and Genomics (ACMG) guidelines [42], we consider that laboratories can orally communicate the identification of an MP to the ordering clinician. Most importantly, would-be parents must be aware of this risk when they sign the consent.

3.2.2 | Secondary and Incidental Findings

Secondary and incidental findings are genetic variants not involved in the observed phenotype but have a possible impact on health. Secondary findings (SFs) are pathogenic variants not related to the initial genetic test indication and are actively sought by the biologist from a list of "actionable" genes, which are accessible to primary or secondary prevention [43]. Incidental findings (IFs) are also unrelated to the fetus phenotype but are not actively sought and therefore are a fortuitous discovery. Searching for SFs is not allowed by French law. The IFs are now authorized to appear on laboratory reports to patients. However, as legislation evolves, the working group strongly highlights potential issues in this case.

In general, women or couples are keen to obtain SFs and IFs, with consent to the analysis ranging from 74% to 96% depending on the type of SFs and IFs sought [6, 21]. These positive attitudes toward learning about SFs and IFs are linked to the perception that advantages outweigh the associated risks [44, 45]. Indeed, the additional information could lead to disease prevention and changes in lifestyle behaviors and reproductive choice, not only for the individual involved but also potentially for other family members [46–48].

However, the high desire during the pre-test visit contrasts with women's or couples' general negative experience with IFs or SFs reports, especially in prenatal medicine [6]. Indeed, after the IFs or SFs report, women or couples experience psychological distress, have difficulty adapting, feel overwhelmed and perceive the information as useless [6, 13]. This discrepancy raises questions about the ability to accurately anticipate the consequences of reporting additional findings [6]. The first question is the larger spectrum of the lifetime appearance of the disease (childhood- or adult-onset), phenotype/organ involved (cardiovascular, cancer, neurological etc.) and disease severity (life-threatening, debilitating etc.) [47]. Second, poor public understanding and knowledge of both genetic conditions and disability hamper the ability to accurately represent the possible future lives of individuals affected by genetic diseases [49, 50]. Instead, we know that women or couples usually feel a duty to avoid any disease in their future children [51, 52]. In this complex situation, they might essentially rely on the latter for their decision. This mindset would explain why they first desire to obtain SFs and IFs (duty approach) and finally express regrets after SFs and IFs reports (medical reality).

Below, we describe different situations for guiding clinicians and biologists in their thoughts and practice regarding IFs and SFs.

3.2.2.1 | Incidental Findings

3.2.2.1.1 | ... of Childhood-Onset Diseases. Usually, when a structural anomaly is identified in the fetus, the altered prognosis pertains to a disease of childhood onset. Therefore, IFs responsible for childhood-onset disease with severe symptoms and untreatable at the time of diagnosis are in the same timeline category. For this reason, from the medical and the would-be parent perspective, we consider that their reporting is appropriate and legitimate. However, these cases should be collectively discussed, as mentioned above.

3.2.2.1.2 | ... of Adult-Onset Diseases. Legally, in France, women and couples have the possibility to give their written informed consent to the report of all IFs revealed by pES, whether of childhood or adult-onset. However, the ethical issues of adult-onset diseases are more complex for three main reasons [48].

First, the impact of such reports is more difficult to perceive than the report of childhood-onset diseases. Although most women or couples express a willingness to know adult-onset diseases from pES data, whether treatable (76%) or non-treatable (74.3%) [21], we emphasize that IFs can interfere with women or couples' decision about a medical ToP in the context of the identification of US anomalies. Indeed, pre-test explanations concerning IFs related to adult-onset diseases are complex, and a truly informed consent is impossible to obtain. In addition, there is a high risk that women or couples do not fully grasp the implications of such a result in a short period of time during the pre-test visit. For instance, in a family in which a pathogenic *BRCA1/2* variant is known to segregate, one can assume that intense discussions occurred before pregnancy on the relevance of knowing this information in the antenatal period. In contrast, IFs such as a *BRCA1/2* pathogenic variant during pregnancy force one to make a quick decision without anticipation. The limited time for reflection spawns a high emotional burden, increasing the likelihood of making mistakes in their choice. To tackle this issue and avoid emotional overwhelming, the Canadian College of Medical Genetics (CCMG) suggests giving these results after pregnancy [30]. This suggestion raises other concerns that are outside the scope of this article.

Second, the potential benefit of the report of a risk to an adult-onset disease to the future person that the fetus will be raises concerns about its future possibility to exert its autonomy, hindering its future right of “not to know” [25]. According to the “deliberative” model proposed by Emanuel and Emanuel, which is defined by a physician's role in providing explanations on why certain health-related values are more valid and should be pursued, we suggest that physicians invite would-be parents to consider responsibilities toward their future child, including respect for the child's future autonomy [53].

Finally, an IF of adult-onset disease from the fetal DNA can be inherited by an as-yet unaffected would-be parent who could therefore directly benefit from prevention measures [54]. This situation would somewhat fall in the area of a pre-symptomatic test (cause it reveals to an asymptomatic individual a risk to develop a disease), which is framed by the law in France [55, 56]. However, it would not respect the provisions governing pre-symptomatic tests in France. Indeed, this framework has several steps that, by definition, cannot be respected in the context of prenatal IFs: a medical follow-up can only be carried out in an accredited “multidisciplinary team” for pre-symptomatic test, a minimum delay of 1 week between the first visit with a medical doctor having an “expertise in asymptomatic patients” and the blood withdrawal, a required visit with a psychologist [56]. The philosophy underlying this framework is to make sure that the at-risk individual sufficiently weighs the pros and cons of its situation to make a personal decision. Therefore, although the possibility to identify and report IFs from pES is mandatory to discuss and does not legally fall into the pre-symptomatic area, we see that their report in the prenatal context to would-be parents is in opposition with the philosophy of the law behind pre-symptomatic tests.

In conclusion, there is an ethical dilemma between the two positions. On the one hand, reporting late-onset IFs is due to the parents' interest in knowing them (particularly for preventive measures) and, on the other hand, not reporting them to protect the future person's right not to know about them. We estimate that the potential harm of reporting of late onset diseases IFs during the pregnancy is sufficient to ethically question the recent Bioethics law, published in 2021 in France, which obligates healthcare professionals to inform individuals of the possibility of identifying IFs. This statement is in line with the NHS statement but in opposition to the ACMG statement [1, 29]. It highlights how a nation's context influence medical practice and guide further potential laws and practice evolutions and how newly medically adopted law may contradict the already existing legal landscape.

3.2.2.2 | Secondary Findings. The search for secondary findings during the analysis is legally not allowed in France. In the literature, according to women's or couples' perspectives, two informed consent possibilities exist for SFs: opt-in (whereby a couple must actively accept the search for SFs) and opt-out (whereby secondary data analysis is part of the analysis and women or couples must oppose this research) [1]. The latter is the current practice in countries such as the United States and Denmark. Participation rates are high: 86.2% and 100%, respectively [49, 50]. SFs are allowed in Canada; however, the CCMG estimates that they are not beneficial [30]. SFs are not actively searched in the United Kingdom [29]. Therefore, there is no international consensus. The aforementioned elements about adult-onset IF diseases stand true for SFs. For all these reasons, the working group considers that the French law is appropriate and that SFs should remain not actively sought, at least during the pregnancy.

3.2.2.3 | Identification of a Heterozygous P/LP Variant in an Autosomal Recessive Disorder. Heterozygous P/LP variants can be found in autosomal recessive genes during pES analysis, in the fetus but also in the parents when analysis is performed in duo or trio. These individuals are then considered “carriers”, which can also affect other family members. This complex question is outside the scope of the working group. Nevertheless, we consider that the ACMG guidelines to not report heterozygous variants for autosomal recessive disorders are appropriate in the context of pES [1].

3.3 | Post-Test Considerations

Fetal anomaly findings are sources of increased anxiety among women or couples, for various reasons: the fear of disabilities, waiting for results, and difficult decisions about continuing or not the pregnancy [51, 57]. Thus, several studies and surveys exploring parental experiences show negative psychological outcomes, with distress and difficulty to adapt [6, 13, 21]. As such, psychological follow-up should systematically be proposed

to women or couples during the pregnancy, regardless of pregnancy termination [19, 58]. Micke et al. even suggested a systematic follow-up at 3–6 months after pregnancy [58].

In addition, inconclusive pES data can be reanalyzed after pregnancy termination or birth, precisely when new symptoms arise after birth or when complementary investigations, familial segregation or functional analysis results are available, especially for VUS. On reanalyzing more than 300 intellectual disabilities and/or multiple congenital anomalies 12 months after an initial inconclusive ES, Ewans et al. demonstrated that reanalysis increased the diagnostic yield by 11% [59]. Bruel et al. obtained similar results by reviewing 313 inconclusive ES reports [60].

4 | Conclusions

The recent application of ES in prenatal medicine has raised ethical questions regarding pre-test counseling, the reporting of results, and post-test communication and follow-up. To address these issues, several societies such as ACMG, CCMG, or the ISPD have established statements and recommendations for the clinical application of pES. However, medical practices and country laws vary, which affect the overall application of other recommendations. Therefore, the French Federation of Human Genetics established a working group of clinicians and biologists from across France to address the medical and ethical challenges of pES. Based on their experience as well as statements from foreign societies and a review of the literature, the working group synthesized 12 proposals to improve prenatal care in France (Figure 1). Since no vote was taken on each of these proposals, we cannot quantify the approval of each of them. However, the group agreed on the overall position stated and no opposition was expressed. Our views align with those of other societies regarding the need for the ordering clinician to provide adequate phenotyping to generate an accurate interpretation (ACMG, CCMG), the genetics and prenatal medicine expertise required (ACMG, ISPD), and the need for a delivery time (ACMG, CCMG), among others. However, they differ regarding VUS, SF and IF reports (ACMG, ISPD, CCMG), for example. Finally, probably linked to the specific French context of healthcare financing and other specificities, we addressed subjects that were little or not addressed by other organizations,

1. The autonomy of the women's or couples' decision should be respected even if they do not want prenatal exome sequencing (pES) or if they decide to continue the pregnancy regardless of the pES results.
2. pES accessibility and indications should be harmonized in the French territory.
3. Parallel genetic tests (mainly chromosomal microarray and pES) should be prioritized, as should their common delivery.
4. Although every medical doctor can order a pES in France, the healthcare professional's expertise in fetal medicine and genetics is required to providing quality information and obtaining a truly informed consent.
5. Incidental findings can be reported for childhood-onset severe and untreatable diseases.
6. Incidental findings for adult-onset severe and untreatable diseases should not be reported.
7. Secondary findings should not be actively sought.
8. Variants of uncertain significance should not be reported in a prenatal context.
9. Heterozygous pathogenic/likely pathogenic variants in autosomal recessive disorders should not be reported.
10. Collective discussions for all uncertain finding should be standard of care.
11. Fetal autopsy should be systematically suggested to couples when applicable, whether pES identified a cause or not.
12. A psychological visit should systematically be suggested regardless of how the pregnancy ended.

FIGURE 1 | Main opinion statements of the French Federation of Human Genetics working group.

such as the need for national harmonization of access to territory and the need for collective multidisciplinary reflection on complex situations. These suggestions have been developed according to the current legal landscape, medical practices, culture and society. Thus, they are likely to evolve in the future. We believe that this opinion statement can serve as an educational resource to improve healthcare professionals' reflections and practices worldwide and ultimately provide better care and support for women and couples.

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Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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