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Prenatal exome sequencing

Optimised diagnosis for fetal malformations

Congenital malformations affect 2-5% of pregnancies, with widely variable potential postnatal outcomes. Providing accurate information to women and couples about the prognosis of these malformations and pregnancy management options is thus a main prenatal clinical concern.

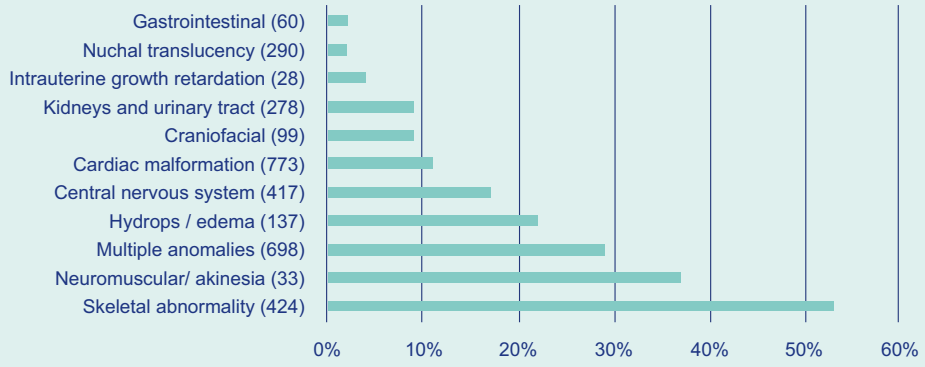
Prognosis depends on the severity of the anomaly observed via ultrasound examination and also on its isolated or syndromic context. If a genetic disease is identified, a more accurate prognosis can be given (even though some genetic diagnoses are associated with highly variable expressivity). A genetic counselling could then be provided for the couple and their families, and in some cases, a medical termination of pregnancy could be considered.

When a congenital malformation is discovered, and after excluding trisomies 13, 18 and 21 and monosomy X, chromosomal microarray analysis (CMA), with or without karyotype, is suggested to women and couples, but presents a low diagnostic yield, of around 4-5% for isolated congenital malformation and 8% in the case of multiple malformations (Mastromoro et *al*. 2022).

To improve congenital malformations diagnostic yield, exome sequencing is now proposed for fetal anomalies with uncertain prognosis and showing evidence of a monogenic anomaly.

Indeed, **exome sequencing brings in average 20-30% more diagnoses for fetuses with normal cytogenetics results.** This yield is highly varying according to the type and number of malformations (Mellis et *al*., 2022, Tran Mau-Them et *al*., 2023).

Prenatal exome yield by clinical entry *(no. of fetuses studied)*



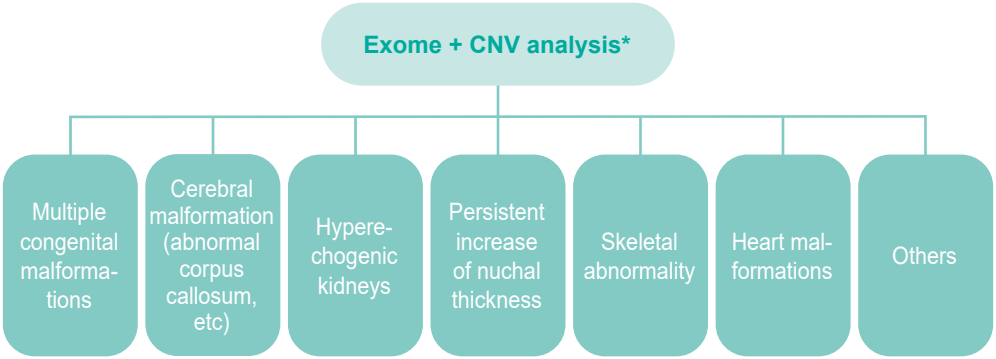
Exome sequencing in the prenatal context

Exome analysis can be used to search **for variations in the coding sequence** of all the genes identified in the human genome, as well as **copy number variations (CNV)** such as deletions or duplications, with a performance comparable to that of CMA.

Analysis in a trio-based strategy (fetus, father, mother) is preferred in an emergency context. Contamination of the fetal sample (amniotic fluid or chorionic villi) with maternal tissue is systematically checked. Identity monitoring of the samples is observed during the whole analytical proess.

Exome data are analysed independently by two competent clinical pathologists including at least one certified by the Agence de la biomédecine (the French agency of biomedecine). The prescribing physician(s) can also interpret the data. A multidisciplinary meeting is systematically performed to sequence the selected variations. According to the French law, variants of uncertain significance are not reported to the patient. Incidental data, unrelated to the fetal phenotype, are reported according to the wishes of the prescribers and if the parent gives their written consent.

Indications



**after excluding trisomies 13, 18 and 21 and monosomy X*

Analysis requests must be validated by both a clinical geneticist and the obstetrician in charge of the pregnancy and even with the multidisciplinary team of fetal medicine. Family history, the state of health of the parents, ultrasound reports and informed consents are required.

Results are available within three weeks.

Clinical benefits

A positive exome result is obtained in approximately 20 to 30% of cases.

- It helps to refine the favourable or unfavourable prognosis of the malformation(s) observed via ultrasound examination.
- It informs on the management of the child at birth.
- It specifies the recurrence risk for future pregnancies and for relatives, if applicable.

Please note:

- Some monogenic diagnoses still have uncertain prognosis.
- A negative result does not rule out a genetic disease as only 2% of the genome are analysed: deep intronic variations, promoter and intergenic regions, balanced abnormalities (inversions, translocations, etc.), amplifications in repeated regions of the genome are not analysed.

Key takeaways

- **Exhaustive analysis** of known genes in human pathology (OMIM) and newly identified genes.
- **Prescriptions must be validated by a geneticist and the obstetrician following the pregnancy** and even after validation by a multidisciplinary center of fetal medicine.
- **Trio exome analysis** in prenatal context allows the fastest and most accurate result.
- **Systematic review of the results** in a multidisciplinary meeting (including clinical pathologist, scientist, clinical geneticist, obstetrician, etc.) before validation of the variant classification. Variants of uncertain significance are not reported to the patients.

Exome sequencing by Eurofins Biomnis

Eurofins Biomnis sequences the genetic material of the patient and relatives and offers:

- Availability of raw data (fastQ, VCF, BAM and quality report) via a secure interface within two weeks,
- Analysis of more than ten thousand variants according to the rules of the ACMG (American College of Medial Genetics and Genomics) and French NGS-Diag consortium,
- Classification of the selected variations in accordance with the prescribing physician,
- Issuing of a detailed results report within an optimised turnaround time of 3 weeks.

Technique and performance

- Sequencing on Illumina Novaseq-type automated system
- Analysis and interpretation of data using the SeqOne bioinformatics solution
- ~ 98 % of bases covered beyond 30X
- > 99 % sensitivity

Why Eurofins Biomnis?

- Specialised medical biology laboratory
- ISO 15189 certified
- Authorisation to carry out constitutional genetic tests
- Certified clinical pathologists by the Agence de la biomédecine
- Expertise in sequencing techniques in diagnostic practice.
- Ongoing biopathological support: test implementation, interpretation, participation in multidisciplinary consultation meeting.

References

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Kalynchuk EJ, Althouse A, Parker LS, Saller DN Jr, Rajkovic A. Prenatal whole-exome sequencing: parental attitudes. Prenat Diagn. 2015;35(10):1030-1036. doi:10.1002/pd.4635

Tran Mau-Them F, Delanne J, Denommé-Pichon AS, *et al*. Prenatal diagnosis by trio exome sequencing in fetuses with ultrasound anomalies: A powerful diagnostic tool. Front Genet. 2023;14:1099995. Published 2023 Mar 23. doi:10.3389/fgene.2023.1099995

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Practical details

Exome sequencing & CNV analysis in prenatal context	
Turnaround time	**3 weeks**
Sample	Fresh or cultivated amniotic fluid, fresh or cultivated chorionic villi, miscarriage product. Nota Bene: Trio exome sequencing assay requires an EDTA whole blood sample for each parent (mother and father)
Required documents	- **B34-INTGB** request form - **D44-INTGB** Information and Consent form Available on **www.eurofins-biomnis.com** > Test guide > Analysis code **EXOPN**
Price	Contact us

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For more information

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