Evaluating Prenatal Exome Sequencing Study

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This study evaluates the impact of the various outcomes of prenatal exome sequencing (definitive diagnosis, probable diagnosis and incidental findings) on clinical decision making and on parental psychological wellbeing, compared between different...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Congenital and hereditary disorders NEC
Study type	Observational non invasive

Summary

ID

NL-OMON54303

Source
ToetsingOnline

Brief title
EPES Study

Condition

- Congenital and hereditary disorders NEC
- Foetal complications

Synonym
Congenital anomalies, ultrasound findings

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Exome sequencing, Parental wellbeing, Prenatal

Outcome measures

Primary outcome

- Percentages of prenatal exome sequencing outcome: definitive diagnoses, probable diagnoses and incidental findings.

Secondary outcome

- Clinical impact of prenatal exome sequencing including medical or surgical in utero intervention, pregnancy termination, location and mode of delivery, decisions on comfort care and neonatal policy;

- Patients perspectives on probable diagnoses and incidental findings including psychological wellbeing as measured by questionnaires;

- Influence of different analysis strategies (whole exome versus genepanel) ion pES outcomes (definitive diagnosis, probable diagnosis and incidental findings);

- Number of identified new disease genes.

Study description

Background summary

Foetal anomalies as detected on prenatal ultrasound are present in 2-3% of pregnancies. The diagnosis of a genetic syndrome as the underlying cause often has significant consequences for the prognosis and therefore also a significant impact on parental reproductive decision making. In addition to chromosomal testing, prenatal exome sequencing (pES) is increasingly being offered. Although prenatal diagnostic rates are promising, no studies report on the actual implementation of pES in routine care and thus several important knowledge gaps remain regarding clinical utility (the balance between potential

harms and benefits) and the preferred analysis strategy (broad versus targeted analysis). A broad analysis has a possible higher diagnostic yield, but it is unknown whether the increased chance of finding a probable diagnosis (class 4 or 5 according to the American College of Medical Genetics but with an unclear or partial correlation to the prenatal phenotype, or class 3 with a multidisciplinary consensus on a strong possibility of clinical relevance) and Incidental Findings outweighs this benefit when it comes to clinical decision making and parental psychological wellbeing.

Study objective

This study evaluates the impact of the various outcomes of prenatal exome sequencing (definitive diagnosis, probable diagnosis and incidental findings) on clinical decision making and on parental psychological wellbeing, compared between different analysis strategies to investigate the clinical utility, defined as the balance between potential harms and benefits.

Study design

This study will be a multicenter cohort study with prospective data collection. Patients will be informed about the study during their first consultation at the Clinical Genetics department. The clinical geneticist or the researcher (PhD candidate) will then provide the patient information letter and will get informed consent. Data will be collected from exome analysis, medical records and for live born children we will request medical information from the Dutch pediatric public healthcare system. Online questionnaires will be sent at (Q1) the time of inclusion, (Q2) 1-2 weeks after pES result and (Q3) 6-8 weeks after delivery or termination of pregnancy.

In a small subset of patients of the LUMC (target n = 15), two additional interviews will be conducted by telephone in parallel to the quantitative questionnaires. These interviews contain similar questions as the questionnaires. After verbal informed consent is received, the researcher will contact the participants in the time period between the initiation of pES and the return of results for the first interview. The second interview will take place approximately 6 months after the results were shared with patients. The coded interview data will be analyzed together with the interview data of a similar research cohort in Australia (called 'PreGen').

Study burden and risks

Since the study subjects are capacitated adults who will be asked to fill in questionnaires and possibly participation in interviews by phone, no risks are present. Potential burdens are;
1. Additional time patients need for filling in the questionnaires (approximately one hour spread out over one year) and the possible interviews

by phone (approximately one and a half hour spread out over six months).
2. Psychological discomfort due to the sensitive questions regarding, amongst others, decisional regret about testing and the choice of pregnancy outcome.
These potential burdens are in proportion to the scientific value of the potential outcomes of this research, especially since the results will be used to reduce psychological discomfort in future patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Pregnant women and their partners with one or more congenital malformation(s) as detected on prenatal ultrasound, who consent to prenatal exome sequencing.

Exclusion criteria

There are no exclusion criteria.

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-04-2022
Enrollment:	850
Type:	Actual

Ethics review

Approved WMO

Date:	09-02-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	29-03-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	28-10-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	12-05-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	23-05-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	25-09-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL77927.058.21