# Research on the validation and acceptance of Non-Invasive Prenatal Diagnosis (NIPD) as a safe and reliable alternative for invasive prenatal testing for monogenic disorders.

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Objective: In this project we, as a collaborative network of Netherlands academic hospitals from Utrecht, Amsterdam, Rotterdam, Leiden and Groningen, propose to further optimize and validate MG-NIPD at early stages (week 8-10) of pregnancy, in order...

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

## Summary

### ID

NL-OMON45858

**Source**
ToetsingOnline

**Brief title**
NIPD for monogenic diseases

### Condition

- Congenital and hereditary disorders NEC

**Synonym**
cystic fibrosis, Duchenne or one of the serious recessive diseases present in a genetically isolated population, hemophilia, sickle cell anemia, Spinal Muscular Dystrophy, thalassemia

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Hubrecht Instituut, KNAW
**Source(s) of monetary or material Support:** Ministerie van OC&W

## Intervention

**Keyword:** monogenic diseases, NIPD, prenatal diagnostics, validation study

## Outcome measures

### Primary outcome

Main study parameters/endpoints: Percentage of concordant results between MG-NIPD performed early in pregnancy and PND (or postnatal cord blood) carried out at a later stage, percentage of tests yielding inheritance predictions with >99% confidence (Part I), and patients* and professionals* perspectives on NIPD (Part II).

Ad. Part I: The statistics behind MG-NIPD were established with Dr. Gerard te Meerman (UMCG) and have been described in detail in our publication (Vermeulen et al., 2017). In this study, MG-NIPD predictions for 100-120 different risk pregnancies will be compared to the PND (or cord blood) measured genotype of the fetus. We will report how often MG-NIPD correctly predicted the actual genotype of the fetus, how often the test was inconclusive and how often the wrong prediction was made (as mentioned, we expect this to not happen). We will also report the confidence levels of our predictions (which we aim to always be >99%). Based on these performance parameters, the to be determined exact costs of the test and the turn-around time of results (MG-NIPD can be completed within one week, possibly faster), clinics should individually decide whether

or not they wish to offer MG-NIPD to risk couples carrying a monogenic disease.

Ad. Part II: We will analyse the interview data according to principles of constant comparison. Along this path of analysis, initial *open coding* (initial codes given to fragments of text) will be replaced by *axial coding* (description and integration of codes). In the final phase of *selective coding*, core concepts will be determined and the relationships between important categories will be tested and interpreted.
For the survey data descriptive analyses will be used. For any comparison, chi-squared test will be used for categorical data and t-tests for continuous data.

**Secondary outcome**

not applicable

# Study description

**Background summary**

Our current health care system offers various prenatal genetic tests to future parents and pregnant women who wish to be informed whether their unborn child is affected with a severe genetic disease. In case of monogenic disorders such as cystic fibrosis, thalassemia, Duchenne muscular dystrophy, etc, pregnant couples at risk currently rely on chorionic villus sampling or amniocentesis; two invasive prenatal diagnostics (PND) procedures that both carry a small procedure-related risk of miscarriage. Their invasive character and associated risk of losing a healthy pregnancy are perceived as highly burdensome by the pregnant women. Couples may also opt for pre-implantation genetic diagnostics (PGD), which offers the possibility to select embryos without the genetic disorder, which are then transferred into the uterus. However, PGD treatment also imposes a burden because of the intensive and long treatment, medication side effects and complications of the ovary stimulation. After PGD, there is a small residual risk of ~2% of misdiagnosis. Because of this residual risk, PND

is offered to these couples for reassurance, but often declined because of the miscarriage risk.
In recent years, a major advance in prenatal testing has been the delivery of a safer, earlier and more accurate non-invasive prenatal test (NIPT) aiming at aneuploidy such as Down syndrome. NIPT has resulted in a significant reduction in invasive testing, but is still a screening test that requires confirmation by invasive testing. Moreover, NIPT can only identify large chromosomal abnormalities, not the subtle genetic variation that typically underlies monogenetic disorders such as cystic fibrosis, thalassemia, etc. For this diverse category of disorders, we recently developed a revolutionary new test called Monogenic Non-Invasive Prenatal Diagnosis (MG-NIPD). As we published, MG-NIPD only requires a simple blood draw from both parents to determine with high confidence, high sensitivity and in a cost-efficient manner the disease/carrier status of the fetus early during pregnancy.

## Study objective

Objective: In this project we, as a collaborative network of Netherlands academic hospitals from Utrecht, Amsterdam, Rotterdam, Leiden and Groningen, propose to further optimize and validate MG-NIPD at early stages (week 8-10) of pregnancy, in order to be able to clinically implement the test (Part I: Validation study). Moreover, we will explore patient and health professional perspectives on MG-NIPD (Part II: Patients and Professional perspectives study).

## Study design

Part I: Prospective parallel study design with 100-120 couples.
Part II: Mixed methods approach using qualitative and quantitative research methods.

## Study burden and risks

The study involves the comparison of two diagnostic prenatal tests; invasive testing (PND) and MG-NIPD (Study Part I). Outcomes of the MG-NIPD are not given to the participants. The study will also be blinded for both the laboratory specialists involved in MG-NIPD/PND and the clinicians involved in the PND. Participating couples (both partners) are asked to donate one blood sample before testing (preferably before pregnancy). Subsequently, women are asked to donate a second blood sample in early pregnancy. Whenever possible, this blood draw will be combined with the regular blood draw in pregnant women. Follow-up and postnatal assessment of the health of the child (presence of the disorder) is already included in the standard care. The participants are asked for permission to use left-over DNA from routine PND (or postnatal genotyping on cord blood) for more detailed genetic analysis of the disease locus of the fetus, necessary for detailed evaluation of MG-NIPD accuracy and performance.

No risks or discomfort, other than drawing blood, is expected for study participants.
To explore couples* perspectives, preferences and needs towards MG-NIPD (Study Part II), couples potentially eligible for MG-NIPD will be asked to participate in one 45-min. semi-structured interview(s) or to complete (a) questionnaire(s).

## Contacts

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

### Inclusion criteria

* Pregnant couples (or couples planning a pregnancy) at increased risk (25%) of carrying a child with one of the following severe monogenic recessive diseases (thalassemia, sickle cell anemia, cystic fibrosis, hemophilia, Spinal Muscular Dystrophy, Duchenne or one of the serious recessive diseases present in a genetically isolated population) AND opting for PND

(or postnatal cord blood).
OR
* Pregnant couples (or couples planning a pregnancy) from a genetically isolated population with one partner carrier of a severe recessive disease (+/-couples).

### Exclusion criteria

* Multiple gestation/vanished twin/empty sac(s) detected at any time before blood sampling during pregnancy
* Maternal age <18 years
* Insufficient knowledge of Dutch or English language or impossibility to understand the study purpose.
* Women carrier of an X-linked recessive disorder and pregnant of a girl.
* Gestational age > 14 weeks

## Study design

### Design

**Study type:** Observational invasive

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| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Diagnostic |

### Recruitment

NL

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| Recruitment status: | Recruiting |
| Start date (anticipated): | 23-04-2019 |
| Enrollment: | 120 |
| Type: | Actual |

## Ethics review

Approved WMO

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| Date: | 19-09-2018 |
| Application type: | First submission |

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| Review commission: | METC NedMec |
| Approved WMO Date: | 27-03-2019 |
| Application type: | Amendment |
| Review commission: | METC NedMec |

# 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 | NL66219.041.18 |