WGS-first approach: One-tests-fits-all to diagnose rare genetic disorders

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We aim to proof that introduction of (rapid) NGS-based sequencing (WES/WGS) as a first tier genetic test in the diagnostic process for critically ill newborns admitted at the NICU and patients with severe neurodevelopmental disorders leads to faster…

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

Summary

ID

NL-OMON42881

Source
ToetsingOnline

Brief title
WGS-first approach

Condition

- Congenital and hereditary disorders NEC

Synonym
genetic changes causing disease; (de novo) genetic disease-causing mutations

Research involving
Human

Sponsors and support

Primary sponsor: Genetica
Source(s) of monetary or material Support: Programma DOELMATIGHEID; projectnummer 843002608 & Programma PERSONALIZED MEDICINE project nummer 80-84600-98-2005

Intervention

Keyword: Impacting clinical decision making, Neonatal intensive care unit, Neurodevelopmental disorders, Next generation sequencing, Rapid genetic testing

Outcome measures

Primary outcome

Primary outcome measure: number of definitive genetic diagnosis

Secondary outcome

Secondary outcome measures: time-to-diagnosis, cost-of-diagnosis,

cost-effectiveness, perspective analysis of joint decision-making process and

the impact on therapeutic interventions.

Study description

Background summary

There are approximately 5,000-8000 rare diseases, affecting 6-8% of the population. Rare diseases are often lifethreatening and can lead to chronic and serious disabilities. As these diseases are rare, detailed knowledge on the disorders is often lacking, making the diagnostic odessey for patients a lengthy one. For 3,879 of these rare diseases, the underlying genetic cause is known. Hence, genetic testing is the ultimate way to diagnose patients with rare disease.

Approximately 75% of rare diseases manifests during childhood and 30% of children dies before the age of 5. Many of rare diseases even manifest during the neonatale fase, and account for a substantial part of neonatal deaths. Clinical symptoms of these rare diseases during this early stage of life are often aspecific, and heterogeneous, thereby not allowing for accurate diagnosis, confirmed by geneticu testing. Treatment of this patient cohort is therefore mostly focussed on clinical symptoms without exact and detailed knowledge of the underying cause and prognosis.

For at least 6-8% of neonates admitted to the NICU, a genetic diagnosis would be a welcome addition to determine the appropriate treatment plan. This can either be surgical intervention for a patient with good prognosis, but could also be withdrawal of interventions in case of terminal illness preventing

needless suffering. The incidence of severe intellecutal disability is 0,5% in the Western World. Many of these patients experience a diagnostic odessey taking years to identify the genetic cause of disease. This quest consists of multiple sequential gene-based tests, and exome sequencing as 'last resource' test.

Genetic diagnostic testing is mostly based on a gene-by-gene basis, leading to a turn-around time that exceeds the window of opportunity to influence medical decision making in the acute fase of a NICU setting. Technological developments, such as next generation sequencing, now allow to determine the genetic blueprint of an individual in a single experiment. Application of these tests has led to increasing diagnostic yields, especially for clinical and genetically heterogeneous disorders. Hence, this technology would have immense value for neonates admitted to the NICU if turn-around-times could be further reduced to ~5-7 days. Recently, the genetic test, referred to as 'exome sequencing' even further improved, making such turn-around times achievable. Hence, the goal of our project is to determine the added value of implementing rapid genetic exome sequencing for neonates admitted to the NICU.
In addition, we wish to proof that the use of NGS-based testing (WES and WGS) are most efficient when used as a 'first tier test' rather than a last resource. We hypothesize that the use of WES/WGS as first tier test will increase the diagnostic yield, using less diagnostic testing, while decreasing costs and being less burdensome to patients.

Study objective

We aim to proof that introduction of (rapid) NGS-based sequencing (WES/WGS) as a first tier genetic test in the diagnostic process for critically ill newborns admitted at the NICU and patients with severe neurodevelopmental disorders leads to faster and more accurate diagnosis, more targeted treatments and interventions and a reduction of health care costs, and being less burdensome to patients.

Study design

Prospective parallel design where patients receive the 'intervention' along side the standard diagnostic work-up.

Intervention

The control arm receives genetic care involving sequential gene-by-gene Sanger sequencing guided by clinical phenotype, and the invention arm receives rapid next generation sequencing (NGS), by whole exome (WES).

Study burden and risks

The study involves the comparison of two genetic diagnostic procedures, e.g. the routine gene-by-gene testing using Sanger sequencing and whole exome sequencing and the procedure where WES/WGS is used as first tier (rapid) test. The patient will not have to undergo additional invasive tests when participating in our study, as venapuncture for genetic testing is withdrawn as standard work-up for patients admitted at the NICU who are suspected of a genetic disorder. We also wish to measure the role of the genetic report in *shared decision making* and the impact of the diagnosis on the medical decision making process. Hereto, parents will be asked to fill out 4-6 questionnaires, taking ~10-20 minutes each.

The risks of participating are minimal as WES is currently used as a routine diagnostic test in (older) patients (and their respective parents), and detailed protocols on the entire procedure, to which we will adhere, are available within the participating centres.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

We focus on critically ill neonates and patients with severe neurodevelopmental disorders of which it is expected that the condition has a genetic defect. ;In the Netherlands, ~4,100 critically ill newborns are annually admitted to the NICU. At least 6% of these patient (285 newborns) will suffer from such rare genetic condition, but due to ascertainment bias given the patient population we are facing, this percentage is likely to be an extreme underestimation.;The newborns with disease of suspected genetic origin may present with various symptoms e.g. encephalopathies, ataxia, growth retardation, seizures and/or MCA. Providing a differential diagnosis in these newborns is difficult as the symptoms are frequently aspecific and newborns are too young to show all recognizable features of disease.;For neurodevelopmental disorders, >3,500 patients are seen in tertiary clinical genetic centres.;Patients are eligable for inclusion if both the consulting clinical geneticist (and neonatologist for NICU [atients) believes that the cause of the symptoms observed in the patient could be of genetic origin, and when the patient has not had any other genetic testing done before.

Exclusion criteria

Patient who are not eligable for inclusion are those who have (lifetreatening) disorder of clear non-genetic origin such as (birth)trauma, or those who have had genetic testing done before.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2016
Enrollment:	145
Type:	Anticipated

Ethics review

Approved WMO Date:	01-12-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-11-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL57511.091.16