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The NeuralNET Cerebral Palsy Pilot Study

Submission date
05/04/2023

Recruitment status
No longer recruiting

Registration date
10/05/2023

Overall study status
Ongoing

Last Edited
26/03/2025

Condition category
Nervous System Diseases

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
The NeuralNET Cerebral Palsy Pilot Study is testing a genetic testing pathway in the NHS for children with cerebral palsy (CP). Other studies suggest that almost one in three peoples' CP is caused by a change in their genes, but more studies are needed to confirm this. A genetic test called whole genome sequencing (WGS) will be used for children who have CP to look for rare changes in genes that cause the condition, and the results of the test will be given to children's doctors within 12 weeks. Knowing that CP has a genetic cause could lead to changes being made to a child's care or treatment that could improve their condition.

The results of this pilot study will tell us if it is feasible for the NHS to use WGS to test children with CP. If so, a larger study testing more children with CP can then be carried out to help decide if this type of WGS-based testing should be made available through the NHS to children with CP whose clinical care might be changed by the result. The genetic findings from this study will also be made available to other researchers and doctors to do more research into CP that might help us better understand and treat the condition.

Who can participate?
The study will test 66 children with CP from 3 hospitals, and also their biological parent(s) if they're available.

What does the study involve?
Following informed consent, we will collect a blood sample from everyone taking part which will be sent for WGS. It is important to understand what families think and feel about the testing. We will ask parents/guardians of the children taking part to fill in two questionnaires, one before and one after WGS. Some parents/guardians will also be interviewed after getting the WGS result, to ask about their experience of the testing. The study will take up to 16 months per family.

What are the possible benefits and risks of participating?
Children who participate in this study may benefit from the identification of a genetic change that either caused or was a risk factor for their diagnosis of CP.
For children who do receive a genetic diagnosis from the study, one potential benefit would be to obtain information about their prognosis and whether there is a possibility of other problems developing which are associated with the genetic diagnosis. A child receiving a genetic diagnosis

may also become eligible to take part in clinical trials or to have their treatment personalised with the addition of existing therapies for that genetic condition. The child and family may also be able to take advantage of support groups or organisations specific to the child's genetic diagnosis. Another potential benefit to both the child and the family from receiving a genetic diagnosis is to obtain information about the likelihood that other family members or future children could either be affected by or pass down the genetic condition, which could inform medical care and/or future reproductive decision-making.

Potential risks to the child and biological parent(s) as part of the study associated with blood sample collection could include pain/discomfort during the test, the chance of subsequent bruising, or the child may become distressed. Children and families have a risk of emotional distress from discussing and/or answering questions about difficult topics such as the family's experience surrounding the CP diagnosis, illness in family members, and/or difficult family relationships. Children and families also risk emotional distress from waiting for and/or receiving the genetic test result, and possibly due to receiving and adjusting to a genetic diagnosis. There is a potential risk that a genetic result could undermine a legal case of medical negligence that a family has in progress or might want to pursue. Children and families also risk discovering genetic relationships via WGS that were not previously known and/or disclosed (e.g., non-paternity, adoption).

Where is the study run from?
Cambridge University Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
September 2022 to January 2026

Who is funding the study?
1. National Institute for Health and Care Research (NIHR) (UK)
2. Rosetrees Trust (UK)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
319781

ClinicalTrials.gov (NCT)
NCT05858268

Protocol serial number
IRAS 319781, CPMS 54900, SA2020\100001

Study information

Scientific Title
The NeuralNET: Research to impact diagnosis, mechanistic understanding and treatment of children's brain and mental health disorders – A pilot study in cerebral palsy

Acronym
NeuralNET

Study objectives
The study hypothesis is that it is feasible to deliver whole-genome sequencing to children with cerebral palsy from specialist NHS clinics by using a WGS pipeline in the NHS to analyse and report data with a turnaround time of fewer than 12 weeks.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 14/02/2023, Wales Research Ethics Committee 5 Bangor (Health and Care Research Wales, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, United Kingdom; +44 (0) 2922 940910; Wales.REC5@wales.nhs.uk), ref: 23/WA/0012

Study design
Observational genetic epidemiology

Primary study design
Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Cerebral palsy

Interventions
Early studies in other countries which have performed genetic testing on people with CP have shown that approximately 1 in 3 people with CP will have a genetic change that either caused or contributed to their diagnosis and that these changes can occur in many different genes associated with a wide range of genetic conditions. Genetic testing based on a diagnosis of CP has not yet been done in the UK, so it is unclear what proportion of people with CP in the UK might have a genetic cause for their diagnosis. Also, since the significant genetic contribution to CP has only recently been discovered and most studies have focused on the genetic findings themselves, little is known about how individuals and their families would react to the offer of genetic testing for CP or about the psychosocial impact of the genetic testing.
As the number of genes that can be associated with CP continues to grow, whole-genome sequencing (WGS) promises to serve as a particularly useful diagnostic tool. WGS can simultaneously screen for changes in the genes already known to be associated with CP, and it may also help to discover new gene associations that have not yet been identified. Although WGS-based tests are increasingly being used by the NHS for the diagnosis of neonatal and paediatric conditions, CP is not currently a diagnosis for which WGS is offered.
Before offering NHS genetic testing for CP, it is important to determine what the rate of uptake would be for genetic testing by families with children affected by CP. Therefore, we propose a

study which offers WGS for CP to children in the UK. To explore the feasibility of doing such a study, a small survey of 18 children with CP and/or their families/carers was first undertaken at the three sites to be involved in the study. This survey found that just over half (56%) of respondents would take up an offer of genetic testing. This increased to 67% if the respondents who were undecided about WGS had their questions and concerns addressed (unpublished PPI data). Therefore, we hypothesize that there will be a good rate of uptake of whole-genome sequencing for CP by families in the UK.

In anticipation of the possibility that whole-genome sequencing for CP might eventually be offered by the NHS in the future, we also want to explore families' attitudes toward and experiences of whole-genome sequencing for CP. The feedback we received from patients and their families on the feasibility survey indicated a need for having questions and concerns addressed to facilitate decision-making. We think that further exploration of their attitudes and experiences will allow us to best understand their questions and concerns about genetic testing and to make recommendations on the support requirements for future WGS testing in this patient group. To this end, we have developed two questionnaires to be completed by the child's parent/guardian, one before testing and one a year after they received their child's result. We have decided on a longitudinal design and have included validated measures of attitude about genomic testing, parental empowerment, and family impact on quality of life to reflect the psychosocial impact of WGS more specifically and accurately. We have also designed a semi-structured optional post-result interview to be offered to the parent/guardian and their family to explore their experience of whole-genome sequencing and any suggestions they might have for improvement of the process.

Since a primary motivation for considering WGS for the diagnosis of genetic conditions associated with CP is the potential to improve children’s clinical care, we will also be gathering information from clinicians and families about what clinical impact the children’s WGS result had on their clinical care. We will ask clinicians to complete a validated questionnaire (14) about the clinical utility of the WGS result. The clinicians will be asked to complete the questionnaire 12 months after they have given the child’s result to the family so that sufficient time will have passed for adjustments to care to be made.

A sample size of 66 trios is planned for this pilot study, where a ‘trio’ is a child with a clinical diagnosis of CP and their biological parent(s) if they are available. This number is based on the number of WGS trios that Illumina has offered to provide for the study. Based on the feedback from the feasibility survey that at least 56% of families would take up an offer of genetic testing, we would anticipate that about 120 families would need to be invited to reach our recruitment goal of 66 children. Furthermore, given that 10-31% of individuals with CP were identified in early studies to have a genetic cause or contribution to their diagnosis, we expect that we would find that 7-20 children in our cohort have a genetic finding associated with their CP diagnosis.

The children will be recruited from 3 different sites, which include Cambridge, Colchester, and Newcastle, from CP clinics at those sites. We aim to recruit 22 trios from each site. Clinicians at each site will review their CP clinic lists to identify children eligible for the study. Other studies of clinically unselected cases of CP have found no significant correlations between pertinent genetic findings and other clinical factors, so the eligibility criteria for this study have been designed to allow participation by children of all ages and gross motor skills levels. The clinician will contact the families of eligible patients to invite them to the study. We had considered using site CP registers to randomly select eligible children for an invitation, however patient consent has not been given for their information in these registers to be used for research purposes. Therefore, clinicians will be asked to review their existing clinic lists 1-2 months ahead of the booked appointments and invite all eligible patients.

When an eligible patient is invited, their parent/guardian will be asked to indicate to the clinician whether they wish to consider taking part in the study and consent to be contacted by the study team. If the parent/guardian indicates that they do not wish to take part in the study, they will

be given the option to respond why they have declined. If the parent/guardian indicates to the clinician that they consent to contact by the study team, they will be asked to complete and return a 'participant form' to the clinician and include their preferred method of contact and contact information. Clinical sites will maintain a record of how many children are invited to the study to allow us to assess the rate of uptake of WGS. Clinical sites will also be asked to record any reasons provided by families who decline. The latter information will be anonymised and submitted in the aggregate to the study team.

The clinician will send the study team the participant forms from families who agree to be contacted. A member of the study team will contact the parent/guardian by their preferred method to briefly explain the study, and to arrange the first study appointment (visit 1) if the family is still interested in participating. Visit 1, which can occur face-to-face to coincide with a scheduled CP clinic appointment or by phone or video call, will include a detailed discussion of the study, and a member of the study team will obtain informed consent if the family agrees for their child to participate. This should take about 20-30 minutes.

If the family consents to participate, then a member of the study team will take a pertinent family medical history and arrangements will be made for blood collection for the child and for the biological parent(s) if available. If visit 1 is face-to-face, the parent/guardian will also be asked to complete the pre-test questionnaire online at the appointment. If visit 1 is by phone or video call, a link for an online version of the questionnaire will be sent by email (or a paper copy sent by post if that is the family's preference) to the parent/guardian for completion and return after the visit. The questionnaire should take 20-30 minutes to complete. Families will be asked at visit 1 if they would like to receive a summary of the study findings and/or a link to the full report/publication at the end of the study. Following visit 1, the child's clinician will be asked to complete and return an online form with the clinical information about the child's CP diagnosis that is required for the interpretation of the WGS result.

The WGS test result should be available within 12 weeks from when the laboratory has received: i) the WGS test request ii) any required clinical information about the child's diagnosis of CP and iii) all blood samples and consent forms from the child and participating biological parent(s). The laboratory will send the result report to the child's clinician. The clinician is responsible for arranging visit 2 with the family, which can be face-to-face or by video or phone call. At visit 2, the clinician will confirm whether the family consents to continue in the study. If the family consents, the clinician will disclose and explain the result of the child's WGS testing to the family, with optional support from a member of the study team. The clinician will then send a secure email to the study team to notify them that the result has been given to the family. If any onward referrals for additional investigations or to specialist medical teams are indicated based on the WGS result, these will be the responsibility of the child's clinician.

Visit 3, which does not actually require an appointment, will be 12 months after the family receives their child's WGS result. One week prior to visit 3, the family will be contacted by the study team to confirm their consent to continue in the study. If the family consents to continue, the same parent/guardian who completed the pre-test questionnaire will be asked to complete and return the post-test questionnaire. A link for an online version of the questionnaire will be sent by email (or a paper copy sent by post if that is the family's preference). The questionnaire should take 20-30 minutes to complete.

When they are contacted by the study team a week prior to visit 3, the family will also be asked if they would like to participate in the optional post-result interview by phone or video call. If a family is willing to be interviewed, visit 4 will be arranged for a date within 13 months of receiving their child's WGS result. The interview at visit 4 will be conducted via a 30–45-minute phone or video call (Zoom), which will be recorded (audio-only) so the study team can later transcribe it. The topic guide for the interview has been developed by the study team based on existing literature. The topic guide will be refined after the first few interviews have taken place with input from an advisory team which includes patient advocates, behavioural scientists, and community paediatricians.

Intervention Type
Genetic

Primary outcome(s)
Feasibility of delivering a whole-genome sequencing study in NHS clinics to children with cerebral palsy measured using the successful recruitment of 66 children with CP from specialist NHS clinics and the use of a WGS pipeline in the NHS to analyse and provide results of WGS testing with a 12-week turnaround time

Key secondary outcome(s))
1. Percentage of uptake of WGS testing by families with a child with CP measured by comparing the number of families invited to the study to the number who proceed with testing at baseline
2. Reasons for declining the offer of WGS provided by families voluntarily to the referring clinician measured using a questionnaire collected anonymously in aggregate at the close of the recruitment
3. Specific genetic contributors to CP in children in the UK measured using the collation of WGS results at the close of the recruitment
4. Clinical and psychosocial impact of undergoing WGS testing on CP patients and families measured using questionnaires at baseline and at 16 months, and by an optional interview at 16 months
5. Clinical utility of WGS testing in children with CP from the Paediatrician's perspective measured using a questionnaire at 16 months
6. Candidate variants for further investigation of pathogenicity via collaborative studies measured using the collation of potentially pathogenic variants of uncertain significance at the close of the recruitment
7. Data to support the refinement of clinical criteria for assessing CP patient suitability for WGS testing measured using the correlation of clinical features with identification of causative variants by WGS
8. Data to support recommendations for meeting the needs of paediatric patients and their families undergoing WGS measured using questionnaires at baseline and 16 months

Completion date
31/01/2026

Eligibility

Key inclusion criteria
Children with cerebral palsy (CP):
1. Has a clinical diagnosis of CP in the medical record
2. Any GMFCS score (GMFCS 1-5)
3. Does not have a known genetic diagnosis that explains the CP phenotype
4. Has a parent/legal guardian available who can consent and is willing to complete study questionnaires

Biological parents of children with CP will also be included in the study if they are:
1. A biological parent of the child
2. Aged 18 years or above
3. Willing and able to give informed consent for participation in the study

Participant type(s)

Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
0 years

Upper age limit
16 years

Sex
All

Key exclusion criteria
Children with cerebral palsy (CP):
1. Children that have a pre-existing genetic diagnosis from whole genome sequencing or whole exome sequencing
2. Children not matching the inclusion criteria

Biological parents of children with CP will be excluded from the study if they do not meet the biological parent inclusion criteria i.e. they ARE NOT:
1. A biological parent of the child
2. Aged 18 years or above
3. Willing and able to give informed consent for participation in the study

Date of first enrolment
14/02/2023

Date of final enrolment
31/01/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Colchester General Hospital
Colchester District General Hosp.
Charter Way
Turner Road

Colchester
United Kingdom
CO4 5JL

Study participating centre
Cambridgeshire Community Services NHS Trust
Unit 7-8
Meadow Park
Meadow Lane
St. Ives
United Kingdom
PE27 4LG

Study participating centre
Freeman Road Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Government

Funder Name
NIHR Cambridge Biomedical Research Centre

Alternative Name(s)
Cambridge Biomedical Research Centre, NIHR Cambridge BRC, National Institute for Health Research Cambridge Biomedical Research Centre

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
United Kingdom

Funder Name
Rosetrees Trust

Alternative Name(s)
Teresa Rosenbaum Golden Charitable Trust, Rosetrees

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publicly available repository. Oversight of data sharing will be by the study coordinators and will be aligned with permissions granted in the informed consent. Where a parent/legal guardian has consented, anonymised variant and phenotype data will be uploaded to the DECIPHER database. The East Genomics Laboratory Hub (the NHS genomics laboratory coordinating the study analysis) routinely deposits pathogenic variants identified from all forms of genetic testing into ClinVar. The East Genomics Laboratory Hub (EGLH) will deposit anonymised pathogenic variants identified in this study into ClinVar, along with the interpretation rationale and some high-level phenotype data e.g. a clinical diagnosis of CP.
Where participants are co-recruited to the NIHR BioResource Rare Diseases study, the EGLH will transfer WGS and phenotype (HPO terms) data to the NIHR BioResource using a secure method. The NIHR BioResource will store the data securely on the Cambridge HPC. Their Data Access Committee will control further access to and use of the data as outlined in their protocol. Anonymised data will be made accessible to bona fide and authorised medical researchers upon request at the discretion of the chief investigator. We may send anonymised data collected as part of the study (e.g. questionnaire responses, genomic findings, interview transcripts, DNA) outside the European Economic Area (EEA). Organisations and researchers can only use the data to conduct research in accordance with the UK Policy Framework for Health and Social Care Research, and the participants' data could be used for research in any aspect of health or care.

IPD sharing plan summary

Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 5.0	16/10/2023	05/04/2024	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes