UCL INSTITUTE OF CHILD HEALTH

Great Ormond Street Hospital for Children NHS Foundation Trust

Joint Research and Development Office
Division of Research and Innovation

Study Title: IMAGINE-2: Stratifying Genomic Causes of Intellectual Disability by Mental Health Outcomes in Childhood and Adolescence

Protocol Number: 18PP38
Protocol Version: *Version 1.4 – Amendment 03.11.21*

Short title or acronym: IMAGINE-2

Note: This study is an extension of IMAGINE-1 which ran from 2014 to 2020 (R&D: 13BS11; UCL REC: 13/LO/1069). The ethics for IMAGINE-1 was managed by PI Prof Lucy Raymond based at the University of Cambridge. Prof Raymond is retiring so the ethics for IMAGINE-2 is now being managed by Prof David Skuse based at University College London.

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There are no potential conflicts of interest with the funder.

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The Chief Investigator, Principal Investigators and Sponsor have discussed this protocol. All have agreed to perform the investigation as written and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

Chief Investigator

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Date: 24/07/20

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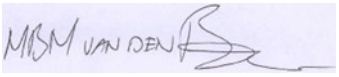

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Signature

Date: 24/07/20

1 Amendment History

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	V1.1	04/01/2021	Dr Jeanne Wolstencroft & Harriet Housby	**9.2 Informed consent** Updated the consent process. Capacity will be assessed by IMAGINE team based on data for ID severity collected in IMAGINE 1 and a phone call given by team member to +16s with a mild intellectual disability. **9.5 Subsequent visits:** *Workstream 2 (subset of cohort face to face)* Made clear a £30 voucher would be given to parents as a thank you for taking part. **11.3 Data Recording and Record Keeping** Made explicit that anonymised data (e.g. questionnaire responses, genetics, interview recording, biological samples) may be sent out of the EEA. **13 Sample Collection, Storage, Transfer and Analysis** **Sample transfer** Made explicit that anonymized data collected as part of the study (e.g. questionnaire responses, genetics, interview recording, biological samples) may be sent outside the European Economic Area (EEA). **Appendix B Demographic Updates** Added Ethnicity question. Change Education question "left school before compulsory education completed" to "left school before exams".

2 Abbreviations

CI	Chief Investigator
CNV	Copy Number Variant
CRF	Case Report Form
GCP	Good Clinical Practice

GOSH	Great Ormond Street Hospital
GP	General Practitioner
ICF	Informed Consent Form
ISF	Investigator Site File
ICH	International Conference of Harmonisation
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SNV	Single Nucleotide Variant
TMF	Trial Master File
UCL	University College London

3 Study Synopsis

Title	IMAGINE-2: Stratifying Genomic Causes of Intellectual Disability by Mental Health Outcomes in Childhood and Adolescence
Sponsor name	**Great Ormond Street UCL Institute of Child Health**
Primary objective	Baseline assessments were made during IMAGINE-1 (2014-2020). During IMAGINE-2: - *Workstream 1* aims to map trajectories of developmental risk (at the biological, psychological and social level) over a 5-year period of follow-up from baseline assessments. - *Workstream 2* aims to deliver a face-to face follow-up study of young people who have been identified as carrying one of the prioritized high-risk CNVs for mental health and who were seen originally during IMAGINE-1. We aim to identify genetic and environmental contributions to the variability in cognitive and psychopathological variation within participants, both cross-sectionally as well as changes over time.

Secondary objective (s)	*Workstream 1:* - To test hypotheses on potential mechanisms that underlie vulnerability and resilience, exemplified by differentiated trajectories and outcomes. - To provide a framework for the development of personalized preventive interventions that are more effective than current treatments, and which are guided by the individual patient, their psychosocial and educational environment, and their genome. *Workstream 2:* - Will study the development of cognition, neurodevelopment and mental health and the impact on these of genetic factors as well as environmental factors such as family function. Workstream 2 will complement Workstream 1 and should enable us identify targets for potential intervention (affecting educational and clinical outcomes).
Study Design	Longitudinal follow-up study of the IMAGINE-1 cohort with two workstreams: - *Workstream 1* will follow up the whole cohort using online questionnaires on an annual basis and link to administrative records (Hospital Episode Statistics, NHS Digital and National Pupil Database, Department for Education). - *Workstream 2* will conduct an intensive face-to-face follow up a subset of the cohort
Study Endpoints	Data on child neurodevelopment and psychopathology and factors that influence this
Sample Size	Workstream 1: n=3,402 Workstream 2: n=520
Summary of eligibility criteria	Recruited for IMAGINE-1: i) Participant has an intellectual disability; ii) Participant has had a diagnostic microarray by an accredited Regional Genetic Centre, or has had next-generation sequencing; iii) Participant has at least one Copy Number Variant or Single Nucleotide Variant reported as pathogenic; iv) There is a legal guardian available to consent and provide detailed medical and behavioural history. Self-referrals for IMAGINE-2: i) Participant has an intellectual disability; ii) Participant has had a diagnostic microarray by an accredited Regional Genetic Centre, or has had next-generation sequencing; iii) Participant has at least one Copy Number Variant or Single Nucleotide Variant reported as

	pathogenic; iv) There is a legal guardian available to consent and provide detailed medical and behavioural history; v) aged 4 to 26 at recruitment.
Procedures: Screening & enrolment	Conducted as part of IMAGINE-1 (NHS REC: 13/LO/1069)
Baseline	Conducted as part of IMAGINE-1: *Workstream 1:* - Development and wellbeing questionnaire - Strengths and Difficulties Questionnaire - Adaptive behaviours assessment Schedule -3 - Everyday Feelings Questionnaire - Comparison of IMAGINE mental health research data (from Workstream 1 questionnaires) with the Mental Health Children and Young People data of the general population (MHCYP, anonymous data from NHS Digital) *Workstream 2:* - Modified Lewis scale - Child and Adolescent Psychiatric Assessment (CAPA) - Autism Diagnostic Interview–Revised (ADI-R) - Structured interview for Prodromal Symptoms (SIPS) - Autism Diagnostic Observation Schedule (ADOS) - Wechsler Abbreviated Scales of Intelligence-2nd Edition (WASI-II) - Developmental Behaviour Checklist (DBC) - Wisconsin Card Sorting Test (WCST) - Cambridge Neuropsychological Test Automated Batter (CANTAB) - Family Environment Scale - Iowa Family Interaction Rating Scales - Life Events Checklist - Physical Health (including seizures and epilepsy) and medication use - Development Coordination Disorder Questionnaire (DCDQ) - Strengths and Difficulties Questionnaire (SDQ – parent and teacher reports) - Social Communication Questionnaire (SCQ) - Social Responsiveness Scale (SRS) - Repetitive Behavior Scale Revised (RBSR) - Pubertal development (Peterson assessment) - Child Eating Behaviour Questionnaire (CEBQ) and the Hyperphagia Questionnaire (HQ) - Epilepsy screening questionnaire (ESQ) - Blood and saliva sample collection
Longitudinal follow up	*Workstream 1:* - Data linkage to Hospital Episode Statistics (HES) - ~~and~~Ccomparison of HES data of the IMAGINE and

	control cohorts (pseudonymised control data from individuals without intellectual disability, NHS Digital) - Data linkage to National Pupil Database (NPD) - Development and Wellbeing questionnaire - **Annual follow-up (for 5 years):** - Strengths and Difficulties Questionnaire - Everyday Feelings Questionnaire - Adaptive behaviours assessment Schedule - Family Life Questionnaire - Wessex Scales - Demographic updates - Impact of COVID-19 on mental health - Study Impact Questionnaire *Workstream 2:* - Modified Lewis scale - Child and Adolescent Psychiatric Assessment (CAPA) - Autism Diagnostic Interview–Revised (ADI-R) - Structured interview for Prodromal Symptoms (SIPS) - Autism Diagnostic Observation Schedule (ADOS) - Wechsler Abbreviated Scales of Intelligence-2nd Edition (WASI-II) - Developmental Behaviour Checklist (DBC) - Wisconsin Card Sorting Test (WCST) - Computerised Neurocognitive Battery (CNB) - Family Environment Scale - Iowa Family Interaction Rating Scales - Life events checklist - Physical Health (including seizures and epilepsy) and medication use - Development Coordination Disorder Questionnaire (DCDQ) - Strengths and Difficulties Questionnaire (SDQ – parent and teacher reports) - Social Communication Questionnaire (SCQ) - Social Responsiveness Scale (SRS) - Repetitive Behavior Scale Revised (RBSR) - Pubertal development (Peterson assessment) - Child Eating Behaviour Questionnaire (CEBQ) - Hyperphagia Questionnaire (HQ) - Epilepsy screening questionnaire (ESQ) - Blood and saliva sample collection - Eating Disorder Examination Adolescent Questionnaire (EDE-A) - Pica, ARFID, and Rumination Disorder Interview (PARDI-AR-Q) - ARFID brief screener (ARFID-BS) - Nine Item ARFID screen (NIAS)

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4 Introduction

4.1 Background and Rationale

In England, there are over a million people with learning disabilities, a quarter of whom are children of school age. Most moderate to severe intellectual disability (ID) has a genetic cause. In order to identify those genetic risks, the NHS is now routinely screening the DNA of children who have significant developmental delays. Being informed that their child's ID is caused by a genetic change is of value to parents. But, at present, we can rarely use that information to advise on best management of behavioural and educational issues, or to reduce the risk of poor mental health outcomes. Our study aims to fill that gap in knowledge.

Our IMAGINE-1 programme of research began in 2014. By 2019 we had recruited 3,402 UK families whose child has ID due to a genetic cause. Using a combination of online interviews, questionnaires, and face-to-face meetings with families, we built up a comprehensive picture of those children's strengths and weaknesses. We discovered there was a far greater risk of severe behavioural and emotional problems than was previously recognised. Whilst children with ID from the general population are about six times as likely to have problems of this nature, the risk is over thirty times greater if the disability has a genetic cause.

We also discovered that children whose genetic risk was inherited had more severe emotional and behavioural problems than those in which the equivalent change occurred by chance. Perhaps parents who carry the genetic anomaly could be mildly affected by it, although they do not share the same degree of disability as their child. They are more likely than other families participating in our research programme to live in disadvantaged circumstances with overcrowding, poor quality housing, and unemployment. Adverse social circumstances would contribute to parenting difficulties and exacerbate their child's problems. We need to learn more about these important points of vulnerability. Families at risk could be identified sooner, and supported more effectively in future, if we understood more about the processes that led to their difficulties. These questions will be addressed by our new research.

We aim to follow up and interview all participants 5 years after our initial assessment. We will be asking: first, have the mental health issues we uncovered in the previous study persisted? Second, if they have persisted, or improved, what are the genetic and environmental factors that have changed since we first met those families?

Most children we saw in the first study were between 6 and 13 years of age. During our follow-up, they will be entering adolescence or early adulthood. That is a time when the risks of some mental health problems become substantially greater. We will be endeavouring to discover whether the young person's behavioural and emotional adjustment, or their risk of emerging mental health disorders, is influenced by the educational, medical or other support their families have received over the past 5 years. We will be looking for clues that pinpoint those children with the best and worst outcomes.

More than one in three children in IMAGINE-1 had an Autism Spectrum Disorder. A quarter had ADHD, and a similar proportion had either severe anxiety or serious challenging behaviour. We aim to answer questions, such as, what was the impact on those children's educational progress? To what extent were those conditions recognised and treated by their local medical and mental health services?

4.2 Objective and purpose

	Outcome Measures/Endpoints
Primary Objective	*Workstream 1:* To map contrasting trajectories of developmental risk over a 5-year period of follow-up from baseline assessments during IMAGINE-2 (using the SDQ) *Workstream 2:* Deliver a face-to face follow-up study of young people who have been identified as carrying one of the prioritized high-risk CNVs for mental health and who were seen originally during IMAGINE-2. We aim to identify genetic and environmental contributions to the variability in cognitive and psychopathological variation within participants, both cross-sectionally as well as changes over time.
Secondary Objectives	*Workstream 1:* - *T*o test hypotheses on potential mechanisms that underlie vulnerability and resilience, exemplified by differentiated trajectories and outcomes. - To provide a framework for the development of personalized preventive interventions that are more effective than current treatments, and which are guided by the individual patient, their psychosocial and educational environment, and their genome. *Workstream 2:* - To study the development of cognition and family function, as well as subtleties of psychopathology in a way that complements the Workstream 1 contribution to IMAGINE-2, should enable us identify targets for potential intervention (affecting educational and clinical outcomes).

4.3 Study Design

We are conducting a 5-year longitudinal study of the cohort with annual online phenotyping of all participants and linking to administrative records (Workstream 1), supplemented by intensive face-to-face assessments of 520 young people with highly pathogenic CNV that were intensively studied in our first phase (Workstream 2). Two research centres are involved: University College London's Great Ormond Street Institute of Child Health and Cardiff University's Neuroscience and Mental Health Research Unit.

Population

Our genotype-first study IMAGINE-1 recruited 3,402 children from UK NHS Regional Genetics Clinics, whose intellectual disability (ID) is associated with either a pathogenic Copy Number Variant (CNV- 75.9%) or Single Nucleotide Variant (SNV- 23.6%) or both (0.5%). 84% of consented families provided standardized assessments of their child's mental health, functional adaptation, medical and educational history, and family/social environment, by completing online questionnaires. We have data on 4,054 genetic variants, logged for 3,398 individuals, representing 3,117 CNVs (1,534 in recognised syndromes, 1,583 unique) and 944 SNVs in 278 different genes. 57% of IMAGINE-1 participants had one or more psychiatric diagnoses: Autism Spectrum Disorders (38%); ADHD (24%); anxiety disorders (12%); challenging behaviour (13%). 31% had a history of seizures, of whom 57% take anticonvulsant medication.

A subset of this group comprised 520 individuals with a specific range of CNVs and their siblings. These comprised children with 16 CNVs across 9 loci. All families in this subset were visited at home for individual face-to-face assessments and agreed to be re-contacted for future studies. We aim to make contact at least 500 participant families. With permission (and with due regard to Covid restrictions) they will be reassessed during a face-to-face visit, with a focus on the affected child as well as the children's unaffected (control) siblings who had been recruited as part of IMAGINE-1.

4.4 Inclusion Criteria

All child participants recruited in IMAGINE-1 will be eligible to take part in IMAGINE-2. Approximately 30% of families taking part in IMAGINE 1 were diagnosed with a familial genetic variant, in which the condition was inherited from a parent. In some of these families, younger siblings have been diagnosed with the same genetic condition since our original investigation. Many families have been in touch to ask if their newly diagnosed child could enrol into IMAGINE-2. In addition, families that were not participants in the original study have been in touch with the study team to express interest in taking part in IMAGINE-2, after reading about our programme online. We would like to recruit eligible siblings as well as families who self-refer to the study, providing they meet the inclusion criteria described below.

IMAGINE-1

Workstream 1 inclusion criteria:

Inclusion criteria for 'proband' (e.g. child with rare genetic disorder):

1. A generalised intellectual disability or developmental delay diagnosis made by a specialist physician
2. Diagnostic microarray analysis of DNA and/or next-generation sequencing
3. At least one CNV or SNV reported as being clinically significant
4. Has a legal guardian available who can consent and can provide detailed medical and behavioural history
5. Aged 4 to 26 years old at recruitment

Workstream 2 inclusion criteria (a subset of IMAGINE-1 Workstream 1):

Inclusion criteria for 'proband' (e.g. child with rare genetic disorder):

1. Diagnosis microarray confirmation of a priority CNV
2. Additional consent to take part in the face-to-face interview and home visit
3. Has a legal guardian available who can consent and can provide detailed medical and behavioural history

Inclusion criteria for control siblings that have taken part in IMAGINE-1 (n=150) are:
1. Full sibling
2. No pathogenic CNV present
3. Closest eligible sibling in age to the child with CNV

Inclusion criteria for parents:
1. Biological parents
2. Additional consent to take part in the face-to-face interview and home visit

4.5 Exclusion Criteria

Those individuals are not matching the above inclusion criteria.

5 Study Procedures

5.1 Recruitment

All participants recruited in IMAGINE-1 will be approached to take part in IMAGINE-2. Participants that self-refer to the study will be permitted to take part in IMAGINE-2 if they meet the study's inclusion criteria.

Further information about how participants will be approached is described below.

5.2 Informed Consent

In IMAGINE-1, some participants consented to be contacted about "other medical research". We will approach participants that agreed to take part in additional research to take part in IMAGINE-2.

Consent procedure
Participants will be contacted using their preferred mode of communication, as indicated in IMAGINE-1. Participants that completed the IMAGINE-1 questionnaires online (over 85% of the cohort) will be sent an invitation to take part in IMAGINE-2 by email. Participants that required telephone assistance to take part in IMAGINE-1 will be sent a paper consent pack in the post.

Participants self-referring to the IMAGINE-2 study will be contacted using their preferred mode of communication, using the procedures described below.

Online consent
The email invitation will include a link to a digital study pack. The digital study pack will include a video which describes the study in layman's language (Transcript of video in Appendix A), the information sheet which will be made available for download, and a digital consent form.

Pen and Paper consent
The paper pack will include an invitation letter, information sheet and consent form. The information sheet will contain a QR code and link to the study website where the layman's information sheet video will be made available. Freepost envelopes will be provided for participants to send their signed consent forms back to the study.

Informed consent
Families will be encouraged to take the time to read the study information sheet and ask questions about the study. No study-related procedures will be carried out before consent has been obtained. All participants will be offered a telephone or video-call with the research team to discuss any

questions they may have about the study. When communicating with the prospective participant the research team will also make themselves available for further questions by phone, text, video-call, email or post depending on the participant's preference. All research team members will have undertaken Good Clinical Practice (GCP), Good Research Practice, and Mental Capacity and Consent training.

Specific consent
There are a number of different ways that families can choose to engage with the IMAGINE-2 study (e.g. online, data-linking, face to face, sample collection). Participants will be permitted to decide which part of the study to take part in; for example, they may opt-in to online questionnaires completion and/or face to face visits and opt out of data-linking, or vice-versa.

Consent archiving and records
Consent forms will be archived in the UCL Data Safe Haven. Families consenting online or using pen and paper forms will be able to request a copy of their signed consent form for their records. This will be returned to them by email or post, depending on their preference.

Optional telephone consent
We will also offer participants the option to consent over the phone or video-call (Microsoft teams or Enterprise Zoom). If they choose to do this an audio recording of the consent process (e.g. reading the consent form statements by the researcher and verbal consent from the participant). The consent process will be recorded on a Dictaphone, Microsoft Teams or Zoom. The recordings will be transferred to password-protected files on University servers shortly afterwards.

Parent, Adult and Consultee consent procedures
We will assess capacity on a case-by-case basis. As part of IMAGINE-1 (2015-2020) we assessed participants' intellectual functioning. Whilst the chronological age of participants has changed, their level of intellectual impairment will normally have remained stable between IMAGINE-1 and IMAGINE-2 (2020-2024). Based on this assessment, we already possess information about participants who have a mild intellectual disability and those who have a moderate-severe intellectual disability.

For families self-referring to IMAGINE-2, a trained study researcher will assess capacity on a case-by-case basis.

To obtain consent for participation in IMAGINE-2, all those above the age of 16 with a mild intellectual disability will be contacted by phone (by a member of the study team who has been appropriately trained), to determine whether they have capacity to consent on their own behalf (N ~ 112). We will discuss issues regarding potential changes in the participant's capacity to give consent since they participated in IMAGINE-1, where that is relevant because of their age at follow-up (2021-2024). Each changed situation will be discussed with the project team, either by the PI Prof David Skuse (Child & Adolescent Psychiatrist) or Co-I Prof William Mandy (Clinical Child & Adolescent Psychologist).

Participants who are above the age of 16, and who have a moderate to severe intellectual disability range (83% of over 16s in IMAGINE-2) may not be able to give consent on their own behalf. Accordingly, we will initially approach the parents or caregivers who participated in IMAGINE-1 to determine the appropriateness of their acting as consultees. We will establish a protocol whereby

any time a member of our research staff initially interacts with a participant, that individual's capacity to give consent will be monitored.

We are keen to include adults (under the age of 27 years) with ID in online research and are committed to developing best practice procedures to ensure they participate in IMAGINE-2. Adults with ID are seriously under-represented in mental health research, a historic situation that has contributed to existing substantial health inequalities.

Parent Consent for Child: For children aged under 16 years old parental consent will be sought (Parent Consent Form). Additional Assent will be sought from the child.

Adult Consent: All participating children who have turned 16+ years old since IMAGINE-1 and have a mild disability, will be offered the opportunity to consent on their own behalf (Adult Consent Form). This may be completed online or via telephone. In this instance the young adult nominates a trusted adult or parent to complete the study questionnaires on their behalf. We do not expect children 16+ categorised with moderate to severe intellectual disability in IMAGINE 1 to have the capacity to consent on their own behalf.

Consultee Consent: For all participating children who have turned 16+ years old since IMAGINE-1 and a moderate/severe disability, their parents/caregivers will be asked to become consultee (Consultee Consent Form). A young person with mild ID may also choose to delegate responsibility for consent to their parent (Consultee Consent Form).

We are keen not to exclude adults (under the age of 27 years) with ID from online research and committed to developing best practice online procedures to ensure they are included in research. All families will be offered the opportunity to consent to taking part in the study over the phone.

Families will be asked to complete initial consent forms for IMAGINE-2 at the first annual follow-up point. At subsequent annual follow-up assessment waves families will be advised that they have the right to withdraw from the study. However, in families whose child turns 16 during the course of the study that young adult will be offered the opportunity to complete an Adult or Consultee consent at the next appropriate assessment follow-up wave.

The digital consent pack will use branching logic to determine which consent form the family are asked to complete. The branching logic will be based on the participant's age and capacity (Figure 1).

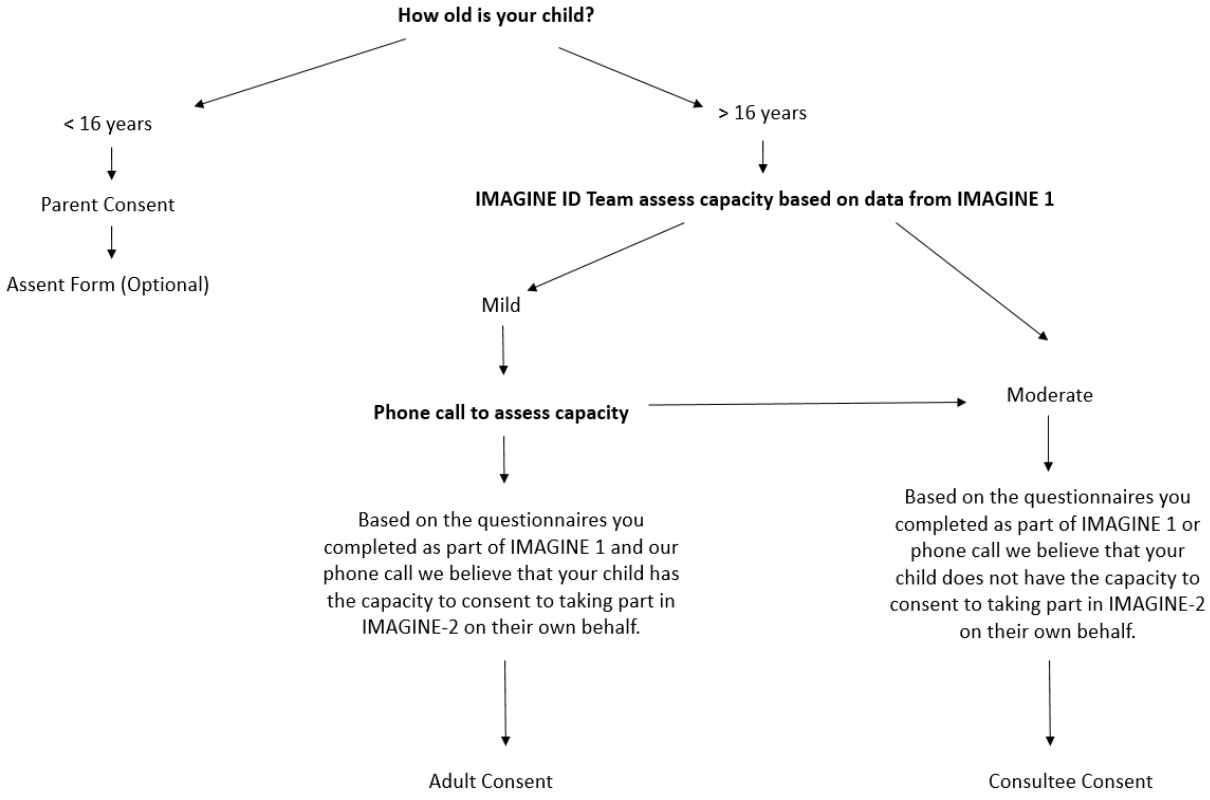

Figure 1: Digital consent pack survey branching logic

Additional consent for face-to-face meetings: As part of the face-to-face visits additional consent will be sought from an additional biological parent (if available; Parent Consent for child), an unaffected sibling (Sibling Consent Form) and the child's teacher (Teacher Consent Form). Additional consent is optional, families will still be able to take part in the face-to-face visits if additional family members and the teacher consent is not obtained.

Withdrawals
Should participants not wish to take part in the follow up study, they will be offered the opportunity to withdraw. However, data collected up until withdrawal (i.e., that gathered in the course of IMAGINE-1) will remain in the study.

5.3 Screening and Eligibility Assessment

Screening and eligibility assessment was carried out during the recruitment phase in IMAGINE-1. All participants recruited in IMAGINE-1 are eligible to take part in IMAGINE-2.

Screening and eligibility of families self-referring to IMAGINE-2 will be established based on the criteria described in section 8.1 by a trained study researcher.

5.4 Baseline Assessments

Baseline assessments conducted during ***IMAGINE-1*** (2014-2019) included:

Workstream 1 (full cohort online):

Completed by: Parents/caregivers of children with a rare genetic disorder and associated intellectual disability.
Completion time: ~3h parents. Questionnaire answers are automatically saved and participants were advised that they did not need to complete the assessments in one sitting. In IMAGINE-1 participants typically completed the baseline questionnaires at their convenience, in smaller chunks of time.
Location: Families can complete the questionnaires online at home. Should families not have access to the internet, the questionnaires will be sent in paper form by post or administered over the phone.

Assessments:

- ***Development and Wellbeing Assessment*** (DAWBA; 2-2.5h)

The DAWBA will be used to collect information on the child's behavioural adjustment and mental health. The DAWBA has been used both in UK national and international surveys (Ford et al., 2003; Green et al., 2004; Heiervang et al., 2008; Emerson et al., 2007).
This methodology has been used successfully to gather data of high quality by parental on-line report. We will use a validated automated diagnostic algorithm system devised for this purpose, compatible with ICD-10/DSM-V. The DAWBA is available in 26 languages (http://www.dawba.com/) and we do not intend to exclude families on the basis of ethnicity or inability to speak/understand English.

- ***Strengths and Difficulties Questionnaire*** (SDQ; 5 min)

The SDQ is a brief behavioural screening questionnaire about 4-18 year olds (Goodman et al., 2011). Many child and adolescent mental health clinics now use the SDQ as part of the initial assessment.

- ***Adaptive Behavior Assessment System, Second Edition*** (ABAS-3; 30 min)

The ABAS-3 is a measure of adaptive function (Harrison and Oakland, 2003). It covers three broad domains (conceptual, social and practical). Within these domains, it assesses 10 skill areas. Items focus on practical, everyday activities required to function, meet environmental demands, provide self-care, and the ability to interact with others effectively and independently. It is appropriate for use up to 89 years of age.

- **Health Questionnaire** (30 min)

Physical development, medical comorbidity and service usage will be recording using an online questionnaire developed by IMAGINE ID. Data include: birth, physical development and anomalies, metabolic systems, sensory abnormalities, psychomotor development, communication skills, services and intervention, medical history. Free text entry is available. Ethnicity and immigration status will also be recorded (the latter a recently identified risk factor for child mental health).

- **Draw-a-Person: Quantitative Scoring System** (DAP:QSS, 10 min)

The draw a person test is a non-verbal test to evaluate intelligence in children. Participating children were asked to complete 3 drawings: a picture of a man, a woman and themselves. The instructions are minimal and easy to understand: "I want you to make a picture of a person. Make the very best picture that you can. Take your time and work very carefully. Try very hard and see what a good picture you can make." For each picture the child is asked to draw a full person (e.g. head to feet). There is no time limit, but children rarely take longer than 10-15 minutes to complete all 3 drawings. The DAP:QSS is both valid and reliable (Goodenough, 1963; Naglieri, 1988; Naglieri and Maxwell,

1981; Jolley, 2010) and correlates with face to face IQ measures including the WISC-R and WISC-III (Abell, Wood, & Liebman, 2001).

Workstream 2 (subset of cohort with additional face to face assessments):

Baseline assessments conducted during ***IMAGINE-1*** (2014-2019) included:

Questionnaire-assessed child psychopathology, prenatal factors and pubertal development, self-report psychopathology

The main-caregiver will provide information on the child and their environment, including:
1. Family size and structure, social class, pregnancy and child birth (age at birth, birth weight, ante- and perinatal health problems, smoking and alcohol use, as collected by with the modified Lewis scale) (Lewis et al., 1987).
2. Life Events Checklist to screen for possible traumatic events experienced by the child (Johnson et al., 1980).
3. Family relationship quality i.e. overall family relationship quality (Family Environment Scale; Moos et al., 2013) and parent child relationship quality (warmth and hostility)(Iowa Family Interaction Rating Scales; Melby et al., 1997).
4. Child prosocial and antisocial behaviour, ADHD and emotional symptoms by completing the Strengths and Difficulties Questionnaire (SDQ; Goodman et al., 2011).
5. Child development and behavioural problems with the Developmental Behaviour Checklist (DBC) which was developed specifically for children with intellectual disability.
6. The Social Communication Questionnaire (SCQ; formerly Autism Screening Questionnaire (ASQ)) will be used to screen for autism.
7. Child pubertal development will be obtained by Peterson assessment.
8. Development Coordination Disorder using the Development Coordination Disorder Questionnaire (Einfeld et al., 2002) and the Children's Physical Activity Questionnaire (cPAQ) (Corder, 2009).
9. Child eating style and behaviour, with the Child Eating Behaviour Questionnaire (CEBQ; Carnell et al., 2007) and the Hyperphagia Questionnaire (HQ) (Fehnel, 2015).
10. Epilepsy and seizures using the Epilepsy screening questionnaire (Ottman et al., 2010).
11. Record of medication, operations, contact details of GP, school and screening questions about current state of health.

Interview-assessed child psychopathology:

- Child and Adolescent Psychiatric Assessment (P-CAPA; Angold et al., 1995): will be conducted with the main-caregiver. The CAPA (duration 2-3 hours) provides DSM-IV and ICD-10 diagnoses of all behavioural and psychiatric problems (including detailed assessment of psychotic symptoms), except autism. A child self-report version of the CAPA (C-CAPA) will used with the children to ascertain psychotic symptoms, mood and anxiety symptoms
- Structured interview for Prodromal Symptoms (SIPS; Miller et al., 2002): conducted with older children to obtain information on prodromal psychosis symptoms
- Autism Diagnostic Interview–Revised (ADI-R; Rutter et al., 2003): will be conducted where screening by SCQ is positive (duration 1-2 hours). If probands screen positive for autism, in combination with the ADI-R interview conducted with the parents, we will offer the parent the possibility to conduct an observational assessment of the child, to establish autism, using the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1989). The ADOS is a semi-structured, standardised assessment of communication, social interaction and play. It provides a series of standardised contexts in which the child's social, communication and repetitive, stereotyped behaviours can be observed. Standardised toys and activities are used to present opportunities for social and communicative interaction with the examiner.

Interview-assessed own and partner psychopathology:

- The 'Family Structure and function' section of the CAPA will be conducted with the primary caretaker regarding any psychiatric problems faced by themselves and the second caretaker, if applicable. This section provides DSM-IV and ICD-10 diagnoses of the following psychopathology: depression, anxiety, panic disorders, eating disorders, drug or alcohol use and psychosis.

Teacher reports:

- Teachers will be asked to complete a consent form agreeing to complete a questionnaire about their pupils if the participant agrees that the teacher can be approached. We provide a consent form for teachers. Once agreed teachers are asked to complete a brief teacher version of the Strengths and Difficulties questionnaire (SDQ) and further information on child development specifically suited for cognitively impaired children with the Developmental Behaviour Checklist (DBC).

Neurocognitive assessment of children:

- Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler et al., 1981): to assess children's IQ
- Wisconsin Card Sorting Test (WCST; Heaton et al., 1981): to assess executive function
- Cambridge Neuropsychological Test Automated Battery (CANTAB)

5.5 Subsequent Visits

Workstream 1 (*full cohort - online*):

Completed by: Caregivers/parents will be asked to complete short questionnaires on an annual basis and more in-depth questionnaires at a 5 year follow up (Figure 2).
Completion time: Short annual follow up ~25mins; once only 5-year follow-up assessment ~3h. Questionnaire answers will be automatically saved. Participants will be encouraged to complete the questionnaires at their pace and convenience. They will be able to complete the questionnaires in multiple sittings.
Location: Families can complete the questionnaires online at home. Should families not have access to the internet, the questionnaires will be sent in paper form by post or administered over the phone. Previous experience indicates this provision applies to less than 1 in 10 participants.
Online tools: Questionnaires will be sent to the participant via a RedCap link sent by the researcher team. The link takes them to the questionnaires. These can be 'saved' and do not need to be completed in one go. Participants can contact the researchers and full support will be offered to participants encountering any issues whilst completing the questionnaires.

IMAGINE-2					
Year recruited	2020	2021	2022	2023	2024
Follow up	Wave 1	Wave 2	Wave 3	Wave 4	Wave 5
2014/2015 N= 552	DAWBA + ABAS-3	Annual Follow-up	Annual Follow-up	Annual Follow-up	Annual Follow-up
2016 N= 621	Annual Follow-up	DAWBA + ABAS-3	Annual Follow-up	Annual Follow-up	Annual Follow-up

2017 N= 803	Annual Follow-up	Annual Follow-up	DAWBA + ABAS-3	Annual Follow-up	Annual Follow-up
2018 N= 900	Annual Follow-up	Annual Follow-up	Annual Follow-up	DAWBA + ABAS-3	Annual Follow-up
2019 N= 526	Annual Follow-up	Annual Follow-up	Annual Follow-up	Annual Follow-up	DAWBA + ABAS-3

Figure 2: Assessment schedule based on year of recruitment

Annual follow-up assessments:

All consenting participants will be followed up annually to complete an online survey. The survey will be comprised of four short questionnaires. The survey will be administered using the RedCap online data collection tool which is hosted on the UCL Data Safe Haven. The annual assessments combined will take no longer than 30 minutes to complete. The assessments have been shown to be acceptable to families as part of IMAGINE-1:

1. ***Strengths and Difficulties Questionnaire*** (SDQ,5 min)

The SDQ will allow us to understand the trajectory of behavioural adjustment of their child over a 5 year period. The SDQ is a brief behavioural screening questionnaire about 4-18 year olds (Goodman et al., 2011). Many child and adolescent mental health clinics now use the SDQ as part of the initial assessment.

2. ***Everyday Feelings Questionnaire*** (EFQ, 5 min)

The EFQ is a short 10-item measure of psychological wellbeing and distress in adults. It is widely used and well-validated (Uher and Goodman, 2009; Goodman and Goodman, 2009).

3. ***Family Life Questionnaire***

The Family Life Questionnaire (FLQ) is a brief 14-item measure of family functioning. It differs from other family function assessments by measuring the experience of family in relation to a single child (Last, Miles, Wills, Brownhill, & Ford, 2012).

4. ***Wessex scales*** (5 min)

The Wessex Scales will allow us to measure adaptive function and severity of the intellectual disability (Kushlick, Blunden & Cox, 1973). The measure assesses self-help skills, literacy, mobility and incontinence. The different domains can be summed to derive a 'Social and Physical Incapacity' score and 'Speech, Self-Help and Literacy' score. It is widely used in studies of intellectual disability.

5. ***Demographic updates*** (10 min)

This questionnaire will allow us to understand changes in circumstances over the 5 year period. The questionnaire will include questions on changes in the child's address, mental health diagnoses, schooling and support received (Appendix B).

Feedback to families:

In IMAGINE-1 parents were sent a report summarising their child's strengths and difficulties. After every annual follow up during IMAGINE-2 parents will receive a report summarising their child's current strengths and difficulties (Appendix C). Participants will be emailed a copy of their report within a month of having completed the questionnaire.

5 year follow up assessment:

Participants will also be asked to complete the DAWBA and the ABAS, 5 years after baseline completion.

- **Development and Wellbeing Assessment** (DAWBA; 2-2.5h parent-report)

The DAWBA will be used to collect information on the child's behavioural adjustment and mental health. The DAWBA has been used both in UK national and international surveys (Ford et al., 2003; Green et al., 2004; Heiervang et al., 2008; Emerson et al., 2007).

This methodology has been used successfully to gather data of high quality by parental on-line report. We will use a validated automated diagnostic algorithm system devised for this purpose, compatible with ICD-10/DSM-V. The DAWBA is available in 26 languages (http://www.dawba.com/) and we do not intend to exclude families on the basis of ethnicity or inability to speak/understand English.

- ***Adaptive Behavior Assessment System, Second Edition*** (ABAS-3; 30 min)

The ABAS-3 is a measure of adaptive function (Harrison and Oakland, 2003). It covers three broad domains (conceptual, social and practical). Within these domains, it assesses 10 skill areas. Items focus on practical, everyday activities required to function, meet environmental demands, provide self-care, and the ability to interact with others effectively and independently. It is appropriate for use up to 89 years of age.

Exceptional assessment amendment – for Wave 1 only:

We wish to collect some feedback on the impact of IMAGINE-1 for families as part of our study monitoring and evaluation. During this exceptional time, we also wish to understand the impact of COVID-19 on our cohort. We will exceptionally be administering additional short questionnaires at the first follow up timepoint (wave 1 only):

- ***The CoRonavIruS Health Impact Survey (CRISIS, 10 min)***

We will use a subset of the parent/caregiver CRISIS questionnaire created by the NIH (Appendix B). This information will help us interpret the SDQ data collected during the global pandemic.

- ***Study Impact Questionnaire (5 min)***

Short questionnaire collecting information on the behavioural, clinical, social and psychological impact of taking part in IMAGINE-1 (Appendix B).

Workstream 2 (subset of cohort assessed during face to face visits):

In Workstream 2 there will be one intensive follow-up face-to-face assessment, ~5 years after our initial research visit. The same detailed wide-ranging and multi-informant assessments we used in IMAGINE-1 will be employed, providing optimal opportunities for longitudinal analysis and understanding of the children's development. We will also re-assess the unaffected (control) siblings. As a thank you to families for taking part, a £30 online gift voucher will be sent to parents/consultee. The assessments have been shown to be acceptable to families as part of IMAGINE-1:

Questionnaire-assessed child psychopathology, prenatal factors and pubertal development, self-report psychopathology

The main-caregiver will provide information on the child and their environment, including:

1. Family size and structure, social class, pregnancy and childbirth (age at birth, birth weight, ante- and perinatal health problems, smoking and alcohol use, as collected by the modified Lewis scale).
2. Life Events Checklist to screen for possible traumatic events experienced by the child (Johnson et al., 1980).
3. Family relationship quality i.e. overall family relationship quality (Family Environment Scale; Moos et al., 2013) and parent child relationship quality (warmth and hostility)(Iowa Family Interaction Rating Scales; Melby et al., 1997).
4. Child prosocial and antisocial behaviour, ADHD and emotional symptoms by completing the Strengths and Difficulties Questionnaire (SDQ; Goodman et al., 2011).
5. Child development and behavioural problems with the Developmental Behaviour Checklist (DBC; Einfeld et al., 2002) which was developed specifically for children with intellectual disability and will not be completed for the unaffected siblings.
6. The Social Communication Questionnaire (SCQ; formerly Autism Screening Questionnaire (ASQ); Berument et al., 1999) will be used to screen for autism.

7. Child pubertal development will be obtained by Peterson assessment (Peterson, 1988).
8. Physical activity and Development Coordination Disorder using the Development Coordination Disorder Questionnaire (DCDQ; Wilson et al., 2009) and the and the Children's Physical Activity Questionnaire (cPAQ) (Corder, 2009)
9. Repetitive Behavior Scale Revised (RBSR; Bodfish et al., 2000)
10. Child eating style and behaviour, with the Child Eating Behaviour Questionnaire (CEBQ; Carnell et al, 2007)) and the Hyperphagia Questionnaire (HQ) (Fehnel, 2015).
11. Epilepsy and seizures using the Epilepsy screening questionnaire (Ottman et al., 2010).
12. Record of medication, operations, contact details of GP, school and screening questions about current state of health.
14. Identify the presence and severity of social impairment using the Social Responsiveness Scale, 2nd Edition (SRS-2; Constantino et al., 2005)
15. Screening for eating disorders: a) anorexia nervosa and bulimia using the Eating Disorder Examination (self-rated) Adolescent Questionnaire (EDE-A, Fairburn et al 2014, which can be adapted for parent-report by substituting "your child" for "you" (Lydecker & Grilo 2017)); b) screening for Avoidant Restrictive Food Intake Disorder (ARFID) using a questionnaire that combines the PARDI-AR-Q (Bryant-Waugh et al 2019 - based on the Pica, ARFID, and Rumination Disorder Interview, PARDI), the ARFID-BS (ARFID brief screener, Dinkler et al 2021), and the NIAS (Nine Item ARFID screen, Zickgraf et al 2018).

The questionnaires will be sent to the research participants prior to the home visit via an online link [REDCap], and will contain a consent procedure.

Interview-assessed child psychopathology:

- The Child and Adolescent Psychiatric Assessment (P-CAPA; Angold et al, 1995): will be conducted with the main-caregiver. The CAPA (duration 2-3 hours) provides DSM-IV and ICD-10 diagnoses of all behavioural and psychiatric problems (including detailed assessment of psychotic symptoms), except autism. A child self-report version of the CAPA (C-CAPA) will used with the children to ascertain psychotic symptoms, mood and anxiety symptoms
- Structured interview for Prodromal Symptoms (SIPS; Miller et al., 2002): conducted with older children to obtain information on prodromal psychosis symptoms.
- Autism Diagnostic Interview–Revised (ADI-R; Rutter et al., 2003): will be conducted where screening by SCQ is positive (duration 1-2 hours). If probands screen positive for autism, in combination with the ADI-R interview conducted with the parents, we will offer the parent the possibility to conduct an observational assessment of the child, to establish autism, using the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1989). The ADOS is a semi-structured, standardised assessment of communication, social interaction and play. It provides a series of standardised contexts in which the child's social, communication and repetitive, stereotyped behaviours can be observed. Standardised toys and activities are used to present opportunities for social and communicative interaction with the examiner.
- Where appropriate, an interview section [completed via parent and/or child self-report depending on clinical context and child's verbal ability] about eating disorders will be conducted using the Eating Disorder Examination Child version (Bryant-Waugh et al 1996) and the PARDI (Bryant-Waugh et al 2019, The Pica, ARFID (Avoidant Restrictive Food Intake Disorder), and Rumination Disorder Interview).

Interview-assessed own and partner psychopathology:

- The 'Family Structure and Function' section of the CAPA will be conducted with the primary caretaker regarding any psychiatric problems faced by themselves and the second caretaker, if applicable. This section provides DSM-IV and ICD-10 diagnoses of the following

psychopathology: depression, anxiety, panic disorders, eating disorders, drug or alcohol use and psychosis. Where appropriate, additional information on eating disorders may be assessed using adult self-report questionnaires (the Eating Disorder Examination Questionnaire (Fairburn et al 2014) and the PARDI-AR-Q (Bryant-Waugh et al 2019)).

Neurocognitive assessment

Children's' IQ will be assessed using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler et al, 1999) and the Computerised Neurocognitive Battery (CNB; Moore et al., 2015) to assess cognition.

Weschler Abbreviated Scale of Intelligence (WASI)

This is an individually administered intelligence test suitable for individuals aged 6-89. The WASI comprises four subtests (vocabulary, block design, similarities and matrix reasoning) and provides the following intelligence quotient (IQ) scores:

- **Verbal IQ score** - a measure of acquired knowledge, verbal reasoning, and attention to verbal information.
- **Performance IQ scores –** a measure of fluid reasoning, spatial processing, attentiveness to detail and visual-motor integration.
- **Full Scale IQ score** - the overall estimate of an individual's general level of intellectual functioning.

Computerised Neurocognitive Battery (CNB)

The tests of the CNB measure accuracy and speed of performance and response time, allowing assessment of processing efficiency. The areas of cognition included are: executive-control, episodic memory, complex cognition, social cognition and sensorimotor skills.

The following domains will be assessed with child appropriate versions:

- Abstraction and mental flexibility (ABF)
- Penn Conditional Exclusion Test (PCET), which is a measure of abstraction and concept formation. Subjects decide which of 4 objects does not belong with the other 3, based on one of three sorting principles, which change and feedback is used (4 min)
- Attention (ATT): The Penn Continuous Performance Test (PCPT). Participants respond to a set of 7-segment displays whenever they form a digit or letter (5 min)
- Working Memory (WM): The Letter N-back Test displays sequences of uppercase letters with a stimulus duration of 500 ms (ISI 2,500 ms.) In the 0-back condition, participants respond to a single target (i.e., X). In the 1-back condition they respond if the letter is identical to that preceding it. In the 2-back condition, they respond if the letter is identical to that presented two trials back (9 min)
- Verbal Memory (VMEM): The Penn Word Memory Test presents 20 target words that are then mixed with 20 distractors equated for frequency, length, concreteness and low imageability (3 min)
- Face Memory (FMEM): The Penn Face Memory Test presents 20 digitized faces that are then mixed with 20 distractors equated for age, gender and ethnicity (4 min)
- Spatial Memory (SMEM): The Visual Object Learning Test (VOLT) uses Euclidean shapes as stimuli with the same paradigm as the word and face (2 min)
- Language and Analogical Reasoning (LAN): The Penn Verbal Reasoning Test consists of verbal analogy problems (3 min)
- Spatial Processing (SPA): Penn Line Orientation Test (PLOT) presents two lines at an angle, and participants click on a button that makes one line rotate until it has the same angle as the other (5 min)

- Emotion Processing (EMO): Facial displays of 4 emotions (Happy, Sad, Anger, Fear) and Neutral faces, 8 each, are presented and the subject identifies the emotion in a multiple-choice format. The facial stimuli are balanced for gender, age, and ethnicity (2 min)
- Sensory-motor Processing Speed (S-M): The task requires moving the mouse and clicking on a green square that disappears after the click. The square gets increasingly small and appears in unpredictable locations (2 min).
- Motor Speed (MOTOR): In the Computerized Finger-Tapping Test, participants tap the spacebar as many times as they can in 5 seconds. Three trials each alternate between dominant and non-dominant hands. (4 min).

Teacher reports:

- Teachers will be asked to complete a consent form agreeing to complete a questionnaire about their pupils if the participant agrees that the teacher can be approached. We provide a consent form for teachers. Once agreed teachers are asked to complete a brief teacher version of the Strengths and Difficulties questionnaire (SDQ) and further information on child development specifically suited for cognitively impaired children with the Developmental Behaviour Checklist (DBC).

Body measurements

We will measure height, weight and head circumference of children and their sibling(s) (if present). Height will be measured using a height measure. Weight will be measured using scales. Head circumference will be measured using a cloth tape. Measurements will be collected using standardized procedures to ensure measurement technique is consistent

Biological Samples

Blood/Saliva: We will take 4 EDTA tubes of blood (approximately 40ml) from each participant (proband, sibling, and parents) using venepuncture, if this is not possible, we can take a saliva sample using an Oragene saliva collection tube. Some of the probands may find both these procedures difficult and so we offer an option of a saliva swab. This method will be used only with participants who will struggle with either the venepuncture or saliva collection tube.

Hair root samples (on a subset of cohort): Samples of hair-root keratinocytes will be taken from the children with CNVs and their siblings where possible. We would pluck a few hairs from the scalp so that hair root is sampled from which keratinocytes can be collected at the base of the follicle. Prior to doing this, we shall wash a small area of scalp at the back of the neck with a disinfectant solution (HiBiSCRUB; chlorhexidine glutonate 4% w/v), then the area will be rinsed thoroughly with saltwater, a few hairs will then be plucked using sterile forceps. Once the samples are collected, they shall be placed directly into a cell preservative containing an antibiotic to prevent bacteria growing. This procedure should cause only minor discomfort; however, due to the nature of our sample we are aware that some children may be uncomfortable with this. If so, samples will not be collected.

COVID-19 Pandemic adjustments to Face-to-Face assessments – Online Assessment

Our face-to-face assessment protocol has had to be adapted to allow the study to continue during the COVID-19 pandemic. Most measures have now been implemented online and we will be able to conduct our interviews using Microsoft teams, Cardiff Enterprise Zoom or by phone, depending on the preference of the participants (see ref 12 for data security measures). Biological sample collection, however, would need to take place at another time, when it is safe again to see families face to face.

We will offer a reduced selection of the above measures to our participants whom we now cannot visit at their homes. This will able us to maintain contact our cohort keeping us connected during

these times where face to face research is restricted. The CAPA interview and questionnaire pack are adaptable to being used online. Saliva sample collection may continue via remote contact, and we will collect blood samples at a later date once restrictions have been lifted.

For other assessments that would usually be included in the usual face-to-face protocol but cannot be completed remotely, participants will be asked if we can visit them at a future date to complete these assessments. If this is impossible we will offer the participants the option to have their face-to-face assessments conducted at Cardiff University in the clinic at the Hadyn Ellis Building.

Avoiding assessment duplication between workstreams 1 & 2:
We are aware that the online and face-to-face protocols include some potential duplication of assessment procedures. Data collection for both workstreams will be conducted based on information from a centralised database. The decision tree about data collection is based on RedCap. Branching logic within RedCap will ensure that participants who wish to take part in both workstreams 1 and 2 are not asked to complete the same assessment twice.

5.6 Study Duration

IMAGINE-2 was funded for 54 months and was due to end in December 2024. Due to the coronavirus pandemic the timeline of the study has started later and will probably extend until December 2025.

5.7 Discontinuation/Withdrawal of Participants from Study

Every participant has the right to withdraw from the study at any time; we will remove participants from the study at any time if it becomes necessary for any reason. Withdrawal from the study will not result in exclusion of the data for that participant from analysis. Participants will be offered two levels of withdrawal options:

"No further contact": This means that IMAGINE-ID would no longer contact the participant, but would retain permission to keep and use information and/or samples provided previously, and to obtain and use data from the participant's health (Hospital Episode Statistics) and school (National Pupil Database) records.

"No further use": This means that, in addition to no longer contacting the participant or obtaining further information, any information (and samples) collected previously would no longer be available to researchers. IMAGINE-ID would destroy the participant's samples (although it may not be possible to trace all distributed sample remnants) and would only hold participant contact information for archival audit purposes. Such a withdrawal would prevent information from contributing to further analyses. However, it is not possible to remove previously gathered data (IMAGINE-1) from public databases (the UK Data Archive), or data that have been shared with other researchers outside our organization.

The reason for withdrawal will be recorded in the CRF.

5.8 Definition of End of Study

The end of study is the date of the last assessment follow up of the last participant (e.g. wave 5).

6 Statistics

6.1 Statistical methods to be employed (plan of analysis)

Workstream 1:

The analytic framework we will use in Workstream 1 aims to detect risk and protective factors; we seek to identify variables (at the biological, psychological and social level) that are associated with better or worse outcomes, using a two-step analytic strategy.

As a first step, our analysis in Workstream 1 would define groups characterized by distinct developmental trajectories of generalized emotional/behavioural problems defined by the total SDQ score at each time-point. Follow-up data are to be sought for all people (n~3000) recruited in IMAGINE-1, for whom we have baseline measures. The differences of the wellbeing and mental health state of the IMAGINE and control cohorts will be investigated using the IMAGINE-1 research (DAWBA/SDQ/ABAS) and MHCYP data, considering the fixed effects of age, gender, ethnicity and index of multiple deprivation. All analyses will be performed in RStudio and Mplus.

Following an analytic strategy that was employed by a comparable longitudinal study of behavioural adaptation with the SDQ we will describe trajectories of internalizing and externalizing problems and adaptive functioning over the period of follow-up by fitting a parallel-process growth mixture model (GMM). The growth parameters, i.e., the slope and intercept, will be estimated for each of the repeatedly measured variables (SDQ/ABAS). A latent class variable will be estimated, defined by the growth parameters of the parallel processes.

We will estimate models with a small number of potential classes and compare model fit with four commonly used goodness of fit indices[5]:
(1) the Bayesian information criterion (BIC);
(2) the sample size-adjusted BIC (SSA-BIC);
(3) the Akaike information criterion (AIC);
(4) the entropy of each model.

Lower BIC, AIC and SSA-BIC values indicate better fit to the data. Entropy ranges from 0 to 1, with higher values indicating that the latent classes are clearly distinguishable (values ≥ 0.80 are considered adequate). Solutions with extremely small classes (≤ 1% of the sample) or with several small classes (< 2% of the sample) will be disregarded.

The GMM will be carried out using the maximum likelihood with robust standard errors estimator, which is robust to non-normality in the data. Full information maximum likelihood (FIML) will be used to accommodate missing data in problem behaviour and adaptive functioning. Under the assumption that the data are missing at random (MAR), FIML can estimate parameters using any available information that is contained in the dataset. FIML is also considered superior to other techniques used to handle missing data in terms of bias and the sampling variability of the parameter estimates produced. To avoid model convergence to local maxima, we may increase the number of random starts. We will follow a classic three-step analysis whereby, upon selection of the optimal latent class model, the latent class variable is extracted and used as an observed variable for further testing. We note that one-step approaches whereby the latent class variable is extracted and examined in terms of its associations with covariates and outcomes in the same analytical step are frequently used, but they can be problematic when examining a large number of covariates.

In addition, simulations have shown that in models with high entropy values, the covariates do not influence class assignment to a large extent. Upon examination of the distribution of the covariates

across the extracted classes, we will run regression models to measure the associations between class membership and outcomes at the final follow-up assessment (e.g. worsened/improved/no change). We will use linear, logistic, ordered logistic and multinomial regression models, depending on the scale of measurement of each outcome. Potential moderators of risk include: environmental variables (Index of Multiple Deprivation, ethnicity, parental education); biological variables including age, sex, medical history (including treatments for neurodevelopmental disorders); and genotypic variables such as whether the genetic anomaly was inherited or *de novo*, and mutational burden (e.g. sum of the lengths of CNVs containing neurodevelopmental genes).

From the HES data, the control cohort will be matched to the IMAGINE-2 study group in age range, gender, ethnicity and index of multiple deprivations. Patterns of healthcare usage will be identified and their association with developmental trajectories of mental health will be evaluated, revealing any differences between cohorts. Incidence rates of the hospital episodes will be derived by age (from birth) and analysed using negative binomial or Poisson regression, allowing for a random intercept per child to account for longitudinal nature of the HES data.

We will identify clusters of similar usage and test the extent to which the composition of clusters is influenced by genetic, familial and environmental factors in IMAGINE-2 cohort. They also will be grouped according to how they interact with healthcare facilities and their healthcare use trajectories using group based multi-trajectory model / sequence analysis. Mixed model regression and latent class analysis will be employed to compare domain-specific trajectories between the IMAGINE-2 and control cohorts. Specific patterns of NHS facility usage associated with the trajectories will be determined, accounting for child's age, sex, demographic variables (including age of genetic diagnosis) and health characteristics (genetic condition, medical or surgical interventions, mental health problems). As a result of these analyses, points of strength and weakness in hospital services can be identified in both cohorts.

At the second step of our analysis, we will be examining predictors of onset of events, primarily new psychiatric disorders, based both on intermediate measures (SDQ/ABAS-3) and on diagnostic data from the DAWBA administered at the 5-year follow-up. An analytic framework suitable for predictions such as this, which incorporate state (diagnosis at outcome) and trait (the intermediate) risk factors, including genetic risk factors, has recently been described. We are particularly interested in studying transition to psychosis, as many of the genetic anomalies identified by IMAGINE-1 convey an enhanced risk in late adolescence and early adulthood (up to 21% incidence between 14-19 years). Our approach would test predictions based on the three step analysis described in step one of this analytic plan, using the latent classes in a logistic regression for a distal binary outcome (e.g. psychosis/no psychosis). The comparison of IMAGINE-2 cohort with the MHCYP data enables the identification of differences in vulnerability to mental health conditions.

In a separate set of analyses, we are planning to make use of the substantial free-text commentaries by families in the DAWBA interviews. We will employ natural language processing (e.g., Sentiment analysis and support vector clustering) to derive new measures of clinical severity, in collaboration with our collaborator at the Institute of Health Informatics (UCL), Dr Spiros Denaxas. Preliminary work to establish proof of principle has proved promising.

Workstream 2: Data analytic strategy

The approach we propose for the longitudinal investigation is based on our findings from the IMAGINE-1 study, as well as our longitudinal studies of children with rare CNV. These have indicated that longitudinal follow-up of children with pathogenic CNVs is feasible and informative and that specific childhood factors predict adverse outcomes in adolescence (risk of psychotic disorder). Our analysis indicates that CNV genotype, when included as a factor in our models, explained only 6-22%

of variance in phenotypic outcome, depending on trait. Thus, the majority of the phenotypic variation is not attributable to the CNV but to other factors. It therefore will be important for better understanding of variability in phenotypic outcomes to study the extent to which other genetic variation and environmental risk factors play a role.

Previous work by our group, including a study in collaboration with the 22q11.2DS IBBC, has indicated that Polygenic Risk Scores (PRS) for schizophrenia (derived from a study of patients with that condition) can be used to predict the risk of schizophrenia as an outcome in people possessing pathogenic CNVs. In addition to extrinsic genetic sources of phenotypic variability, the study of characteristics intrinsic to each CNV will also be informative (i.e., CNV size and gene content). For example, previous studies have provided evidence that the number of constrained genes within a CNV may contribute cumulatively to variability in cognitive outcome. Furthermore, there is evidence that the specific gene content of a CNV may also influence risk. Our findings from IMAGINE-1 indicate that children carrying inherited genetic variants are more likely to have neurodevelopmental, emotional and behavioural disorders than children who carry a *de novo* variant. Inherited mutations were associated with higher multiple social deprivation scores, suggesting that the worse outcomes in this group might be reflect the impact of parental mutation (carrier) on the psychosocial environment of these families. Thus, the study of salient environmental factors affecting risk is also likely to be fruitful.

i) We will model the trajectories for the psychopathological and neurocognitive measures using mixed models via an accelerated longitudinal design. We will test several models of longitudinal development including linear and non-linear effects. We have found evidence of considerable psychiatric comorbidity in children with pathogenic CNVs as well as between psychiatric and other neurodevelopmental traits (e.g., motor coordination). We therefore propose to use data reduction strategies as part of our analytical approach, combining highly correlated traits to create phenotypic clusters. We will reduce measures to critical developmental domains by applying principal components analysis to the individual-specific random effects for trajectory generated for each phenotypic measure in the mixed model analysis. This is similar to the approach successfully applied by our team's collaborators to derive measures of disease progression in Huntington Disease and has two main benefits: firstly, defining a more informative phenotypic measure, and secondly, reducing the multiple testing burden.

ii) The domain-specific trajectory measures will be compared between children with pathogenic CNV and their unaffected siblings using regression analysis.

iii) A similar regression analysis will be used to test for differences in trajectories between the 13 different CNVs.

iv) The regression models in ii) will be expanded to include a) polygenic risk scores (PRS), which will be generated using the publicly available summary statistics from large GWAS of schizophrenia, ADHD, ASD and IQ. Each PRS will be regressed against each trajectory measure as described above. These regression models will also consider the effects of environmental factors (e.g., inheritance status of CNV, whether *de novo* or inherited), family socio-economic adversity, family and parent-child relationship quality, parental psychopathology, and experiences of bullying). The effects of environmental factors on the trajectory measures will be tested directly in the regression analyses and we will also be able to include a factor representing change over time in an environmental risk factor. For factors with significant effects (after accounting for multiple testing), their influence in modifying the effects of CNV status on trajectory will be tested by including a CNV*environmental factor interaction term in the regression. Information on second hits and genetic variation intrinsic to the CNV will be examined in individual models for each CNV only. Where appropriate, we will

investigate whether specific factors influence the analysis above, including family socio-economic status and child history of physical health problems and medication use.

v) Key adolescent outcomes, including prodromal risk for psychosis, internalising disorder and persistence of neurodevelopmental disorders, will be extracted via data linkage, as discussed earlier. The effects of trajectory (and CNV status) on these outcomes will be assessed by logistic regression, considering relevant environmental factors.

Power

Our previous studies have shown that CNV status accounts for up to 38% of the variation in the range of phenotypic outcome measures we have studied (i.e., psychiatric conditions, other neurodevelopmental problems, including motor coordination, cognitive function, social and other behaviour, and sleep disturbance). However, we have a power of 80% to detect differences in trajectory between 500 children with pathogenic CNV and 150 siblings at a significance level of 0.01 (corrected for 5 trajectories) for CNV effects accounting for as little as 2% of variance. Our work indicates that the different CNV genotypes account for up to 22% of the variance of these individual phenotypes. For a sample of 500 affected individuals, we have power of 80% to detect differences in trajectory between 13 different CNVs at a significance level of 0.01 (corrected for 5 trajectories) for CNV effects accounting for as little as 5% of variance. We have 80% power to detect an effect of PRS accounting for 3% of variance in trajectory in 500 participants at a significance level of 0.0025 (corrected for 5 trajectories and 4 PRS). Such effects are reasonable, given that 7% of the variance in schizophrenia liability is accounted for by PRS.

7 Data Management

7.1 Source Documents

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.
All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

7.2 Direct Access to source data / documents

Only members of the study research team and authorised representatives from the sponsor will have direct access to the source data and study documentation. All source data and study documentation will also be available to external auditors if and when required, and inspectors in the event of regulatory inspection. Access to the final data set will remain with the chief investigator.

7.3 Data Recording and Record Keeping

Identifiable information will be stored in the Data Safe Haven and linked to a unique study ID (allocated as part of IMAGINE-1). Data will be collected with questionnaires created on Redcap and linked to a secure database on the UCL Data Safe Haven (DSH). The participants will be identified by a unique study specific number in any database. The name and any other identifying detail will NOT be included in any study data electronic file. The NPD data will be accessed through the Office for National Statistics Secure Research Service (ONS SRS). The HES data will be processed and stored on the UCL DSH, and will be flowed onto ONS SRS for analysis with the NPD according to the

agreements with the DfE and NHS Digital. Anonymised data will be kept after the study has ended and made accessible to *bona fide* and authorised medical researchers.

Paper documents will be stored securely and only accessible by study staff and authorised personnel. Samples will be stored in a secure manner and in accordance with the Data Protection Act 1998, GDPR and HTA. We may send anonymized data collected as part of the study (e.g. questionnaire responses, genetics, interview recording, biological samples) outside the European Economic Area (EEA). The information will only be used by organisation and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research. The participant information could be used for research in any aspect of health or care and could be combined with information about the participant from other sources held by researchers (in the UK or abroad), the NHS or government.

7.3.1 Archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. Essential documents will be retained for a **minimum** of 20 years after completion of the study in line with the UCL data retention schedule and MRC research practice principles and guidelines (MRC GRP B.3).

8 Patient Confidentiality & Data Protection

The participants will be identified only by initials and a participant ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

Contacting participants using video-conferencing software: We will use Microsoft Teams (UCL and Cardiff) and Zoom enterprise (Cardiff) with participants that wish to be contacted using video-conferencing software.

Microsoft Teams: To ensure that confidentiality is maintained, participants will be advised that it is their responsibility to ensure they have adequate anti-virus protection on their computers. They will be made aware that the video-conferencing sessions are recorded and stored in the Local University researcher's Team account. They will be advised that only members of the research team and auditors from Microsoft will have access to these recordings. They will also be made aware that some personal information from their Microsoft Teams account is stored locally on the computer (this is particularly important if participants intend to use public or shared computers). They will also be advised to logout of their Microsoft Teams account when not in use.

Zoom: Cardiff University holds an 'Enterprise' account with Zoom, thus interviews conducted by Zoom will be protected by Cardiff University data securities. However, In order to ensure the security of the online meeting when we set up the meetings we will:

- Password protect the meeting
- Meeting ID will be randomly generated
- Disable 'join before host' and enable 'waiting room'
- Once the participant is on the call the meeting will be 'locked' to prevent unauthorised access
- Disable 'screen sharing'

To ensure that confidentiality is maintained, participants will be advised that the platforms calls are encrypted, but it is their responsibility to ensure they have adequate anti-virus protection on their computers. They will be made aware that some personal information from their Zoom account is stored locally on the computer (this is particularly important if participants intend to use public or shared computers). They will also be advised to logout of their Microsoft Zoom account when not in use.

The meeting will be recorded and saved locally on password-protect files on Cardiff University servers. This will allow the researchers at Cardiff to score the psychiatric symptoms and code the psychiatric diagnosis and also to discuss complicated symptoms in consensus meetings led by a Child and Adolescent Psychiatrists in order to achieve the best-suited diagnosis.

Managing, storing and curating data: Assessments in this cohort study will be online using commercial software and that software adheres to rigorous standards, both here and in the United States. There will be pseudonymization of all data, with codes to allow linkage to identifiable data which is kept securely and separately. Information necessary to administer recruitment to the study was kept on a designated secure computer network. IMAGINE patient data is held in CiviCRM, which is an open-source patient management software, and stored in AIMES secure hosted environment licensed to University of Cambridge. This database will be transferred to the UCL Data Safe Haven at the outset of IMAGINE-2. Research data will be collated and stored in the UCL Data Safe Haven, transferred securely from the originating source (secure server for online assessment data or secure storage at University of Cardiff for offline testing). Data will be held in a MySQL database within the UCL Data Safe Haven, linked through unique identifiers. Institutional guidance on research data management will be used to ensure adherence to guidelines and best practice, and researchers will contribute to development of institutional strategy.

All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so. Assessments in this cohort study will be online using commercial software and that software adheres to rigorous standards, both here and in the United States. There will be pseudonymization of all data, with codes to allow linkage to identifiable data which is kept securely and separately. Information necessary to administer recruitment to the study was kept on a designated secure computer network. Phenotypic Research data will be collated and stored in the MRC Centre for Neuropsychiatric Genetics & Genomics under the Data Protection Act protected in Cardiff University's secure environment. Biological samples will be stored in the laboratory in the University of Cardiff MRC Centre for Neuropsychiatric Genetics & Genomics in adherence with the Human Tissue Act.

Formal information/data security standards: Data collected using US servers will comply with US laws - the HITECH Act of 2009 and the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and all subsequent amendments. Data at rest will be encrypted and site security addressed multiple times per day. In the UK, we will work to the principle that information governance is about providing legitimate access to these data whilst protecting information from unauthorized access, disclosure and loss. All database providers are aware of the need to identify and assess potential risks to the security of the information within the project and are developing appropriate procedures, policies and security systems. The work in this package will be guided by the appropriate sections of the NHS IG Toolkit, ISO27001, data protection legislation (GDPR/DPA 2018), the Information Commissioner Office recommendations and best practice in IT security technologies.

Sample Collection, Storage, Transfer and Analysis

Sample Collection
Sample collection will take place either in the participant's home, or in the clinic at the Hadyn Ellis Building at Cardiff University and then stored in the laboratory in the Hadyn Ellis Building (MRC Centre for Neuropsychiatric Genetics & Genomics.

Biological sample analysis
The procedures undertaken on the biological samples will be: Whole Genome Sequencing (WGS), cell signalling proteomic analysis, and induced Pluripotent Stem Cell (iPSC) generation to create cell lines and brain organoids. These procedures will all be performed using blood samples. If a participant has provided a saliva sample, we use this to perform genetic analysis including clarifying the presence or absence (in family members of child with a CNV) of a CNV as well as WGS. However, saliva samples cannot be used to investigate cell signalling or for iPSC generation.

From the DNA collected we will conduct:

Whole Genome Sequencing*:* This will be performed using the Illumina HiSeqX (150 bp paired end) at coverage of >30X. Variant Call Files will be generated from BWA-MEM alignments using the GATK4 haplotype caller by the TCAG sequencing facility, using a structural variant (SV) calling pipeline. This short-read pipeline is a composite of 4 complementary methods for detection of deletions, duplications, balanced rearrangements and mobile element insertions (MEIs). Short and long tandem repeat (TR) variants will be typed using *hipSTR* and GangSTR respectively. We will ensure that all alignment and calling of WGS data for all subjects, existing and new, will be performed using the same methodology.

We recognize that each individual CNV has distinct effects and a characteristic spectrum of clinical outcomes, and factors that explain variability in clinical outcome may also differ between CNVs. We will define components of secondary genetic risk including rare coding and non-coding variants and PRS. We will investigate the contributions of secondary rare variants and common variation to clinical outcome/dimensions across four CNV alleles at two loci.

ERK Pathway Analysis: We aim to collect blood samples from these individuals in order to screen for peripheral alterations in signalling components, including, among others, those belonging the ERK and the mTOR pathways. By conducting the same analysis in participating siblings of these individuals, we will be able to establish the degree to which these CNVs affect cell signalling, where we expect that those carrying the deletion will have higher overall ERK activity in the brain than controls, whereas those with the duplication will have lower overall levels than controls. This data will then be linked to the relevant phenotypic information we will collect (neurodevelopmental, psychiatric and cognitive function). Specifically, we aim to demonstrate that MAPK3/ERK1 genetic alterations in individuals with specific CNVs for which these pathways are implicated (e.g., those with 16p11.2 deletion or duplication or 22q11.2 deletion or duplication) are reflected in corresponding biochemical changes in blood samples, thus validating peripheral cell signalling changes as potential biomarkers

Cell Signalling Analysis: This will be performed on the same subset of individuals with CNV which can affect the ERK pathway to demonstrate in humans that genetic alterations in these CNVs are reflected in corresponding biochemical changes, as we have already found to be the case in mouse models. These analyses will be led by Professor Brambilla, who is an international expert on cell signalling pathways and take place in the laboratory of the Neuroscience and Mental Health Research Institute (NMHRI) / School of Biosciences at Cardiff University.

Induced Pluripotent Stem (iPS) Cells: Induced pluripotent stem cells (iPSCs) will be used to better understand how CNV lead to neuronal and glial alterations at the cellular level. We will generate factor-free iPS cell colonies that are more applicable to the establishment of human disease models and screening for biomarkers. We will derive neural stem cells from Peripheral Blood Mononuclear Cells (PBMCs) which will be extracted from a participant's blood sample. The PBMCs will be reprogrammed using the Cytotune-iPS 2.0 reprogramming kit. This process can take between 9 and 28 days to complete and at the end of this process live staining highlights undifferentiated iPSCs; the healthiest undifferentiated iPSCs are moved to a fresh culture dish for passage. We will characterize and define the neural phenotype associated with the disorder related cells and compare these to normal neurons and glial cells using a variety of techniques including receptor and cell surface antibodies, immunocytochemistry, morphology, functional analysis and electrophysiology. The generation of iPSCs will be led by Professor Li, who is an international expert on iPSCs and take place in the laboratory of the Neuroscience and Mental Health Research Institute (NMHRI) / School of Biosciences in at Cardiff University.

Brain organoids*:* Cerebral organoid or Brain organoids represent a new model system for deciphering mechanisms of human brain development at a considerable level of detail outside the human body. They provide the relevant human background and the complex 3D arrangement of cells in a tissue context. As technology can bridge the gap between non-human animal models and reductionist human two-dimensional monolayer cell culture techniques, it is becoming model of choice for drug discovery. The method for the generation of homogeneous and reproducible organoids from induced pluripotent stem cells (iPSC) involves:

1) the generation of embryoid bodies from iPSC,
2) The induction of anterior cortical neuroectoderm,
3)the embedding of neuroectodermal aggregates in a matrix scaffold (Matrigel),
4) the generation of forebrain-type organoids from neuroectodermal aggregates; and
5) the fixation and validation of forebrain-type organoids.

Further, the organoids protocol can be further optimized to derive more oligodendrocytes or microglia to study effect of myelin or inflammation on brain development. Following generation of the organoids, the organoids will be assessed for their size, maturity, cellular heterogeneity and cortical layer formation. The two big limitations of the current protocol are
1) organoids lack externally recognizable body axes that guide their gross morphogenesis that can aid the phenotypic analysis,
2) Heterogeneity among the organoids from different batches.

Keratinocyte-iPS Analysis: Keratinocytes will be cultured using a defined, serum-free, feeder-independent medium; from this culture iPS cells will be generated using a non-viral reprogramming method. This will involve transfection of a transposon-based vector call piggyBac encoding the five reprogramming factors (c-Myc, Klf4, Oct4, Sox2 and Lin28). The vector can be removed once reprogramming has been achieved without leaving 'footprint mutations.' This method therefore allows for the generation of factor-free iPS cell colonies that are more applicable to the establishment of human disease models and screening for biomarkers and drug targets. The iPS cell colonies will then be selected on their morphologic appearance, their expression markers of pluripotency, and the capacity for generate all three germ-cell types. To confirm that the generated iPS cell lines are genetically matched to their parental somatic lines, and to rule out the possibility of cross contamination from existing cultures, PCR and DNA fingerprint analysis will be used. We expect to successfully generate iPS cells from each participant and derive neural stem cells from these iPS lines; we also expect to successfully derive neurons with an identical genotype. We will characterize and define the neural phenotype associated with the disorder related cells and compare these to

normal neurons using a variety of techniques including receptor and cell surface anti-bodies, immunocytochemistry, morphological analysis and electrophysiology.

Sample transfer
We may send anonymized data collected as part of the study (e.g. questionnaire responses, genetics, interview recording, biological samples) outside the European Economic Area (EEA). The information will only be used by organisation and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

9 Financial Information and Insurance

The study is funded by the Medical Research Council.

No-fault compensation insurance cover for any non-negligent harm will be provided by University College London.

10 Publications Policy

All individuals who have made substantial intellectual, scientific and practical contributions to the study and the manuscript should, where possible, be credited as authors; all individuals credited as authors should deserve that designation. It is the responsibility of the Chief Investigator and co-PI and, ultimately, the Sponsors to ensure that these principles are upheld. The status of manuscripts in preparation will be reviewed by the chief Investigator and sponsor if requires. In all cases where journal policies permit, all investigators who contribute patients to the study will be acknowledged.

The results of the study will be reported and disseminated as follows:

- Peer reviewed scientific journals
- Internal report, plus possible article on Institute web pages (publicly accessible)
- Conference presentations
- Written feedback to patient support groups.

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12 Appendix A: Transcript of consent video

Thank you for your interest in the IMAGINE-2 follow-up study. The IMAGINE-1 study recruited over 3,000 families with a child with a rare genetic disorder. Thanks to your contribution it's the largest study of its kind in the world. We've collected lots of detailed information about you and your family's health and wellbeing.

The purpose of our new project is to find out how the children who took part in IMAGINE-1 have changed as they've grown up. We'd like to know about your successes and your difficulties.

We will be inviting you to complete an online survey once a year for the next five years.
We will also ask for your permission to access your child's health and education data held by NHS Digital and the National Pupil Database. This means we'll be able to find out how many times your child goes to hospital and their educational attainment, without having to ask you to complete more questionnaires.

If you took part in face-to-face interviews, we would like to visit your family again. If we visit you again we'll also ask whether your child's sibling and schoolteacher are interested in taking part too.

If you're happy to take part, please answer the questions below. Depending on the answers you give we may ask your child to complete a consent form to take part in the study.

The next screen will take you to an information sheet. Please take your time to read the information sheet and ask questions about the study. If appropriate we'd encourage you to speak to your child about the study too.

You can also consent to taking part in the study over the phone, if you'd like to do this, please contact us using the telephone or email addresses below.

Appendix B: *Demographic updates, Study Impact Questionnaire & Covid Impact Questionnaire*

Demographic Updates

Thank you for completing the IMAGINE Questionnaires. We'd like to find out if anything has changed since you last completed some questionnaires:

1. **What is your age:**

2. **Your partner's age (if applicable):**

3. **Your child's age:**

4. **Ethnicity:**

□ White British
□ White Irish
□ Any other white background
□ Black or Black British Caribbean

□ Black or Black British African
□ Any other Black background
□ Mixed White and Black Caribbean
□ Mixed White and Black African
□ Mixed White and Asian
□ Any other mixed background
□ Indian
□ Pakistani
□ Bangladeshi
□ Chinese
□ Any other Asian background
□ Any other ethnic group
□ Unknown

5. **What is the name of your child's school?**

6. **What is your current postcode?**

7. **What is your highest education level?**

□ Left school before exams
□ O-levels or GCSEs
□ A-levels or Highers
□ University degree
□ Higher or postgraduate degree
□ Vocational training
□ Not known

8. **What is your current employment status/ situation?**

□ Full time paid employment
□ Part time paid employment
□ Currently unemployed
□ Full time training or education
□ Part time training or education
□ Voluntary work
□ Other (please specify)

9. **What is your yearly household income? "**Household income" means the money brought in by you and/or your spouse and/or another adult you live with, with whom you share finances. Don't count the income from anybody whose finances are independent of yours.

□ Less than £16,000 a year (£310 a week)
□ £16,000-£29,999 a year (£310 - £579 a week)
□ £30,000-£59,999 a year (£580 - £1149 a week)
□ £60,000-89,999 a year (£1500 - £1729 a week
□ £90,000-119,999 a year (£1730 - £2299 a week)
□ More than £120,000 a year (£2300 a week)
□ Prefer not to say

10. In the past year, have you or your child had help or advice on his emotions, concentration or behaviour from any of the following?

□ Someone in your family or a close friend
□ Books or magazines
□ The internet
□ Telephone help-line
□ Self-help group

11. In the past year, have any of the following professionals been involved in the care of your child?

□ A teacher (such as a class teacher, head of year, special educational needs coordinator)
□ Special educational needs staff in school (e.g. learning support assistant)
□ Educational psychologist
□ Your GP, family doctor, health visitor
□ Someone specializing in young people's general health (such as a paediatrician, school nurse, □ school doctor, or speech therapist)
□ Someone specializing in mental health (such as a counsellor, psychologist or psychiatrist)
□ □ Someone from social services (such as a social worker or family support worker)
Someone else

12. A. Does your child have a diagnosis of the following: (Please tick all that apply)

□ Autism Spectrum Disorder
□ Attention Deficit Hyperactivity Disorder
□ Conduct Disorder/Oppositional Defiant Disorder
□ Anxiety Disorder
If yes: Social Phobia, Generalized Anxiety Disorder
□ Mood disorder
□ Attachment Disorder
□ Tourette's Disorder/Tic disorder
□ Seizures/Epilepsy
□ □ Specific Learning Disability
Intellectual Disability
□ Developmental Delay
□ Other:

B. We'd like to know whether your child has received any new diagnoses since you completed the Imagine-1 DAWBA questionnaire. Were any of these new diagnoses?

13. Is there another child living at home?

□ Yes
□ No

If yes, does your child's sibling (half, full or adopted) have any of the following diagnoses: Please tick all that apply

□ Autism Spectrum Disorder
□ Attention Deficit Hyperactivity Disorder
□ Conduct Disorder/Oppositional Defiant Disorder
□ Anxiety Disorder
If yes: Social Phobia, Generalized Anxiety Disorder

□ Mood disorder
□ Attachment Disorder
□ Tourette's Disorder/Tic disorder
□ Seizures/Epilepsy
□ □ Specific Learning Disability
Intellectual Disability
□ Developmental Delay
□ Other:

14. **At present, roughly what sort of age level is he/she at in her school work and ability to reason things out?**

15. **At present, roughly what sort of age level is he/she at in her use and understanding of language?**

Study Impact and Feedback

As part of IMAGINE-ID online study we sent you a report summarising your child's strengths and difficulties. We'd like to ask you a few questions about the report, to find out whether it had an impact and find out how to improve it. We'd also like to ask you a few questions about your experiences of taking part in the study in general.

Behavioural impact

Did you show your summary report to anyone? (Please tick all that apply)
□ I did not show anyone the report
□ Other members of my family
□ A teacher (such as a class teacher, head of year, special educational needs coordinator)
□ Special educational needs staff in school (e.g. learning support assistant)
□ Educational psychologist
□ Your GP, family doctor, health visitor
□ Someone specializing in young people's general health (such as a paediatrician, school nurse, school doctor, or speech therapist)
□ Someone specializing in mental health (such as a counsellor, psychologist or psychiatrist)
□ Someone from social services (such as a social worker or family support worker)
□ Someone else – please specify:

Clinical impact

Receiving the IMAGINE-ID Summary report led to… Please tick the appropriate boxes	**Yes**	**No**	**Not applicable**
improvements in my child's treatment and/or care plan			
improvements in my child's access to physical health care			
improvements in my child's access to mental health care			
improvements in my child's access to behavioural support			
improvements in our communication with medical professionals			
getting in touch with a patient support group			
a referral for autism spectrum disorder assessment			
a referral for attention deficit hyperactivity disorder			

assessment			
a referral for any other assessment or appointment			

Please use the space below to add any further comments:

Social impact

Did you use the report as supporting evidence to access services? (Please tick all that apply)

□ No

□ Yes

If yes:

□ Disability Benefits

□ Special Educational Needs Support

□ Educational Health Care Plan

□ Other (please specify):

Psychological impact

For each statement please circle the number from 1 to 5 that best describes how you feel

Did the summary report help you to understand your child's strengths and difficulties compared to other children?

Not helpful 1 2 3 4 5 Very helpful

Did the summary report change the way you thought about your child's behaviour?

No change 1 2 3 4 5 Change

Did the summary report help/empower you to seek additional support for your child?

Not helpful 1 2 3 4 5 Very helpful

Did the summary report help you to feel more in control of your child's behaviour?

Not helpful 1 2 3 4 5 Very helpful

Attitudes towards feedback

For each statement please circle the number from 1 to 5 that best describes how you feel

For me and my child, receiving the summary report was:

Not helpful 1 2 3 4 5 Very helpful

For me and my child, taking part in the Imagine study was:

Not helpful 1 2 3 4 5 Very helpful

Feedback

Do you feel the report accurately represented your child's strengths and difficulties?

□ Yes
□ No
□ Don't know

Any further comments on the report:

Is there anything we could do to improve the report?

□ Yes
□ No
□ Don't know

Any further comments on the report:

Is there anything we could do to improve your experience of taking part in the Imagine study?

□ Yes
□ No
□ Don't know

Please use the space below to add any further comments on taking part in the study:

The impact of the Coronavirus/ COVID-19 pandemic on your family

The Coronavirus/ COVID-19 pandemic has been difficult for many families. The following questions will help us understand what has happened in your family and how your child with a Rare Genetic Condition has coped during this crisis. There are no right or wrong answers.

Interviewer –
Child's name –
Participant/relative's ID number –

Family questions (to be asked *once* if sibling and proband have the same family).

1. **During the Coronavirus/ COVID19 pandemic has anyone in your child's family been diagnosed with Coronavirus/ COVID-19? (check all that apply)**
    a. Yes, member of household
    b. Yes, non-household member
    c. No

2. **During the Coronavirus/ COVID19 pandemic have any of the following happened to your child's family members because of Coronavirus/ COVID-19: (check all that apply)**
    a. Fallen ill physically
    b. Hospitalized
    c. Put into self-quarantine with symptoms
    d. Put into self-quarantine without symptoms (e.g., due to possible exposure)
    e. Lost job
    f. Reduced ability to earn money
    g. Passed away
    h. Does not apply

3. **During the Coronavirus/ COVID-19 pandemic to what degree have changes related to the Coronavirus/COVID-19 crisis in your area created financial problems for your family?**
    a. Not at all
    b. Slightly
    c. Moderately
    d. Very
    e. Extremely

4. **How stressful have you found life during the Coronavirus/ COVID-19 pandemic?**
    a. Not at all
    b. Slightly
    c. Moderately
    d. Very
    e. Extremely

Please explain___

5. **During the Coronavirus/ COVID19 pandemic has your child with a Rare Genetic Condition been exposed to someone likely to have Coronavirus/ COVID-19? (check all that apply)**
    a. Yes, someone with positive test
    b. Yes, someone with medical diagnosis, but no test
    c. Yes, someone with possible symptoms, but no diagnosis by doctor
    d. No

6. **During the Coronavirus/ COVID19 pandemic has your child with a Rare Genetic Condition been suspected to have Coronavirus/ COVID-19 infection?**
    a. Yes, has tested positive
    b. Yes, medical diagnosis, but no test
    c. Yes, has had some possible symptoms, but no diagnosis by doctor
    d. No symptoms or signs

7. **People who are at very high risk of severe illness coronavirus/ COVID-19 infection have been advised to shield. Shielding means minimising all interaction with others (even those one lives with). Has your child shielded during the Coronavirus/ COVID19 pandemic?**
    a. Yes, based on guidance from the NHS (my child received a letter/we were advised by our GP or hospital clinician)
    b. Yes, because other family members were advised to shield
    c. Yes, this was our personal decision
    d. No

8. **In general, during the Coronavirus/COVID19 pandemic how worried has your child been about being infected?**
    a. Not at all
    b. Slightly
    c. Moderately
    d. Very
    e. Extremely
    f. Cannot tell

9. **In general, during the Coronavirus/COVID19 pandemic how worried has your child been about friends or family being infected?**
    a. Not at all
    b. Slightly
    c. Moderately
    d. Very
    e. Extremely
    f. Cannot tell

10. **In general, during the Coronavirus/COVID19 pandemic how worried has your child been about their *physical health* being influenced by Coronavirus/ COVID-19?**
    a. Not at all
    b. Slightly
    c. Moderately
    d. Very
    e. Extremely
    f. Cannot tell

11. **In general, during the Coronavirus/COVID19 pandemic has your child's behavior changed in a <u>positive</u> way due to Coronavirus/ COVID-19? (Check all that apply)**
    a. No positive changes
    b. Yes, more relaxed
    c. Yes, happier
    d. Yes, more confident
    e. Other, please explain___

12. **In general, during the Coronavirus/COVID19 pandemic has your child's behavior changed in a <u>negative</u> way due to Coronavirus/ COVID-19? (Check all that apply).**
    a. No negative changes
    b. Yes, more irritable
    c. Yes, more restless
    d. Yes, less energetic
    e. Other, please explain___

13. **In general, during the Coronavirus/COVID19 pandemic how worried has your child been about their *mental/ emotional health* being influenced by Coronavirus/COVID-19?**
    a. Not at all
    b. Slightly

c. Moderately
d. Very
e. Extremely
f. Cannot tell

14. During the Coronavirus/ COVID-19 pandemic has your child's school building been closed?

a. **Yes**
b. **No**
c. **Child no longer in school (skip to question 17).**

If no,

- Have classes been in session? Y/N
- Did your child attend classes in-person? Y/N
- **Please explain___**

If yes,

- Were classes resumed online? Y/N
- Has your child had easy access to the internet and a computer? Y/N
- Have there been assignments for your child to complete? Y/N

15. If your child no longer attends school, but is working, training, or volunteering, has the Coronavirus/COVID19 pandemic affected these activities? Y/N

If yes, please explain___

16. How well has your child managed to cope with these physical changes to learning/working?

a. Not at all
b. Slightly
c. Moderately
d. Very
e. Extremely
f. Does not apply

17. During the Coronavirus/ COVID-19 pandemic how much time has your child spent away from the home (e.g., going to stores, parks, etc.)?

a. No time
b. Rarely
c. Occasionally
d. Often
e. A lot of the time

18. During the Coronavirus/ COVID-19 pandemic how stressful have the restrictions on leaving home been for your child?

a. Not at all
b. Slightly
c. Moderately

d. Very
e. Extremely

19. During the Coronavirus/ COVID-19 pandemic has the quality of the relationships between your child and members of his/her family changed?

a. A lot worse
b. A little worse
c. About the same
d. A little better
e. A lot better

20. During the Coronavirus/ COVID-19 pandemic how stressful have these changes in family contacts been for your child?

a. Not at all
b. Slightly
c. Moderately
d. Very
e. Extremely
f. Does not apply

21. During the Coronavirus/ COVID-19 pandemic has the quality of your child's relationships with their friends changed?

a. A lot worse
b. A little worse
c. About the same
d. A little better
e. A lot better
f. Does not apply

22. During the Coronavirus/ COVID-19 pandemic how stressful have these changes in social contacts been for your child?

a. Not at all
b. Slightly
c. Moderately
d. Very
e. Extremely
f. Does not apply

23. During the Coronavirus/ COVID-19 pandemic has cancellation of important events (such as holidays, prom, birthday parties etc.) in your child's life been difficult for him/her?

a. Not at all
b. Slightly
c. Moderately
d. Very
e. Extremely
f. Not applicable/ Cannot tell

g. Does not apply

24. During the Coronavirus/ COVID-19 pandemic to what degree has your child been concerned about the stability of your living situation?

a. Not at all
b. Slightly
c. Moderately
d. Very
e. Extremely
f. Cannot tell

25. During the Coronavirus/ COVID-19 pandemic has your child worried whether your food would run out because of a lack of money?

a. Not at all
b. Slightly
c. Moderately
d. Very
e. Extremely
f. Cannot tell

26. During the Coronavirus/COVID19 pandemic, what was the biggest challenge for your family?

a. Finances
b. Childcare
c. Family tension
d. Adapting to new routines
e. No challenges
f. Other, please explain ___

27. During the Coronavirus/COVID19 pandemic, what was the biggest challenge for your child?

a. Low mood
b. Anxiety
c. Social distancing
d. Loneliness
e. No challenges
f. Other, please explain___

SUPPORTS

28. Have any supports for your child been disrupted because of the Coronavirus/ COVID-19 pandemic (check all that apply)

a. Additional learning support

b. Mentoring programs
c. After school activity programs
d. Volunteer programs
e. Psychotherapy
f. Psychiatric care
g. Occupational therapy
h. Physical therapy
i. Speech/language therapy
j. Sporting activities
k. Medical care for chronic illnesses
l. Other, please explain_____

29. Has the Coronavirus/COVID-19 crisis led to any positive changes in your child's life?

a. Not at all
b. Only a few
c. Some
d. A lot
e. Extremely
f. Does not apply

30. If answered b, c or d to question 29, please specify: ____

ADDITIONAL COMMENTS

Please describe anything else that concerns you about the impact of Coronavirus/COVID-19 on your child with a Rare Genetic Condition.

IMAGINE-2 Online Annual SDQ Report
IMAGINE-2 Online 5 year DAWBA Follow-up Report
IMAGINE-2 Face to Face 5 year Follow-up report

IMAGINE-2 Online Annual SDQ Report

IMAGINE 2

Intellectual Disability and Mental Health:
Assessing Genomic Impact on Neurodevelopment

Programme Directors:
Professor David Skuse
Professor Marianne van den Bree
Professor Jeremy Hall
Professor Sir Michael Owen

Strengths and Difficulties Report 2021

[Date]

Name: [full name of child]
Age: [XXX] years
Study ID: [123456]

Thank you for taking part in the first IMAGINE-2 annual survey. We are gathering this information to track changes in your child's health, wellbeing and behaviour as they grow up, and we want to share our assessment of those changes with you. So, over the next few years, we will be sending you reports on your child's progress, to keep you up to date.

You have already completed the **Strengths and Difficulties Questionnaire (SDQ)** on a couple of occasions, first during the original IMAGINE-ID study and again during IMAGINE-2. Questionnaires like the SDQ are a helpful guide to show how a child's behaviour compares with typically developing children in the UK. We call those comparisons our 'ratings'; they indicate the extent to which your child is similar, or different, to [girls and boys of a similar age.] [young people up to the age of 17. We do not have information that would allow a comparison to be made with young adults of a similar age.]

Our analysis is based entirely on the information you provided to us, because we have not had the opportunity to meet your child. Consequently, it is not a substitute for a clinical examination. It may, however, prove useful in identifying areas of need. On the basis of our analysis, the report may suggest there is a need for further assessment and clinical or educational management. On the other hand, it is important to bear in mind that, since no questionnaire is perfect, there is a risk that our analysis of your answers to the questionnaire will have exaggerated or underestimated your child's strengths and difficulties.

We will keep you updated about the study's progress with our online Research Newsletters. For live updates please follow us on social media (search for @imagineidnews on Twitter and @imagineid.study on Facebook). You can also keep up to date on the IMAGINE-ID website at www.imagine-id.org. If you have any questions please don't hesitate to contact us on ich.imagineid@ucl.ac.uk or ring us on 020 8138 7768.

The assessment has been obtained for research purposes. Please do not use this report as a substitute for a clinical assessment.

MRC Medical Research Council | Medical Research Foundation | UCL | youthinmind

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Intellectual Disability and Mental Health:
Assessing Genomic Impact on Neurodevelopment

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Professor Sir Michael Owen

How to interpret the score ratings

The ratings in this report compare your answers with the answers we have collected from large numbers of other parents across the UK. For ease of interpretation, we group the comparison scores into four ranges, as shown in the figure below. The position of the needle indicates how similar your child or young person is (in terms of their behaviour or emotional adjustment) to an average child of similar age.

Close to average

In the general population most children and young people (roughly 80%) are in the 'close to average' category. For example, if your child scores in this range for 'Emotional distress', it means their emotional wellbeing is about average.

Slightly raised

In the general population many children and young people (roughly 10%) are in the 'slightly raised' category. For example, if your child scores in the 'slightly raised' range for 'Difficulties getting along with other children'; this means they find it a bit harder making friends than the average.

High

Just one in twenty childrenand young people score in the 'high' category. For instance, if your child's 'Hyperactivity and concentration' score falls in the 'high' range, it means they have many more ADHD symptoms than average.

Very high

About one in twenty children and young people score in the 'very high' category. If our analysis suggests a rating is in the 'very high' range it implies this in an area of serious concern.

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Intellectual Disability and Mental Health:
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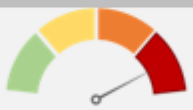
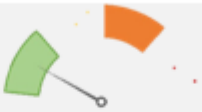
YOUR 2021 QUESTIONNAIRE RATINGS: Strengths and Difficulties Questionnaire (SDQ)

Your child's ratings for 2021:

SDQ Scale score	Rating	
Emotional distress		VERY HIGH
Behavioural difficulties		VERY HIGH
Hyperactivity and concentration difficulties		Slightly raised
Difficulties getting along with other children		HIGH
Helpful behaviour		Close to average

These ratings are based entirely on information you gave us. We did a computerized analysis that compared the description of your own child with the average in the UK. High scores might be a 'false alarm', so you need to use your own judgement when deciding if they make sense. They do not necessarily imply a problem that needs treating. Some difficulties do get better by themselves.

Everything measured by the SDQ is rated on a scale that goes from 'not at all' to 'very high'. Some children have difficulties that are so subtle that people outside the family may think that everything is fine. We know that many families whose child has an intellectual disability may struggle to cope. If your child does have scores in the 'very high' range, it is usually wise to seek professional advice on their management, if you are not already receiving help.

The assessment has been obtained for research purposes. Please do not use this report as a substitute for a clinical assessment.

IMAGINE 2

Intellectual Disability and Mental Health:
Assessing Genomic Impact on Neurodevelopment

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Changes in the Strengths and Difficulties Questionnaire (SDQ) scores over time

The table below tracks changes in your child's strengths and difficulties profile over time. Every year, as you complete questionnaires for the IMAGINE 2 Study, we'll add a new set of ratings to this table.

SDQ Subscale score	2018 (IMAGINE 1)	2021	2022	2023	2024	2025
Emotional distress	HIGH	VERY HIGH	–	–	–	–
Behavioural difficulties	HIGH	VERY HIGH	–	–	–	–
Hyperactivity and concentration difficulties	Slightly raised	Slightly raised	–	–	–	–
Difficulties getting along with other children	HIGH	HIGH	–	–	–	–
Helpful behaviour	VERY LOW	Close to average	–	–	–	–

Strengths

Whilst other sections of the report focus mainly on areas of possible difficulties and problems, this section allows us to acknowledge X's strengths and good points. Here are some of X's strengths based on what you have told us they are like and what they do that really pleases you:

- Generous
- Lively
- Keen to learn
- Affectionate
- Reliable and responsible
- Easy going
- Good fun, good sense of humour
- Interested in many things
- Caring, kind-hearted
- Bounces back quickly after setbacks
- Grateful, appreciative of what they get
- Independent
- Helps around the home
- Gets on well with the rest of the family
- Does homework without needing to be reminded
- Good at reative activities: art, acting, music, making things
- Likes to be involved in family activities
- Takes care of her appearance
- Good at school work
- Polite
- Good at sport
- Keeps bedroom tidy
- Good with friends
- Well behaved
- [If family provide open text response insert here]

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Share your report

If you are concerned and maybe surprised by our analysis, is there someone you could ask whose opinion you would trust? This report could help you explain your concerns and ask for advice – for example, you might want to show this report to a family member, to your child's school or to your doctor.

Stay in touch

We will keep you updated about the study's progress with our online Research Newsletters. For live updates please follow us on social media. If you have any questions please don't hesitate to contact us on ich.imagineid@ucl.ac.uk or ring us on 020 8138 7768.

www.facebook.com/imagineid.study

www.twitter.com/imagineidnews

http://www.imagine-id.org

The assessment has been obtained for research purposes. Please do not use this report as a substitute for a clinical assessment.

IMAGINE-2 Online 5 year DAWBA Follow-up Report

IMAGINE 2

Intellectual Disability and Mental Health:
Assessing Genomic Impact on Neurodevelopment

Programme Directors:
Professor David Skuse
Professor Marianne van den Bree
Professor Jeremy Hall
Professor Sir Michael Owen

[Date]

Re:
Age: XXX
DAWBA ID: XXX

Thank you for taking part in the IMAGINE-2 study and completing the DAWBA questionnaire. You have already completed the Development and Wellbeing Assessment (DAWBA) as part of the IMAGINE-1 study. This report summarizes information about a range of common behavioural and emotional difficulties of childhood. You may want to compare this IMAGINE-2 report to the one we sent you as part of the IMAGINE-1 study.

Questionnaires like the DAWBA are usually a helpful guide to children's stress levels, behaviour, concentration and friendships. But since no questionnaire is perfect, there is a risk that we'll exaggerate or underestimate your child's strengths and difficulties. We use computer programs to calculate how your child behaves, according to the information you have given us, compared with all the other children we have assessed with the DAWBA. We call the comparisons our "ratings" and they might be similar, or different, to [girls and boys of a similar age.] [young people up to the age of 17. We do not have information that would allow a comparison to be made with young adults of a similar age.]

This report relies on parental information and is not a substitute for a clinical examination. It may, however, prove useful in identifying areas of need in terms of further assessment and clinical or educational management.

We will keep you updated about the study's progress with our online Research Newsletters. For live updates please follow us on social media (search for @imagineidnews on Twitter and @imagineid.study on Facebook) or you can keep up to date on the Imagine ID website at www.imagine-id.org. If you have any questions please don't hesitate to contact us on ich.imagineid@ucl.ac.uk or ring us on 0207 905 2168.

The assessment from the DAWBA questionnaire has been obtained for research purposes. Please do not use this report as a substitute for a clinical assessment.

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How to interpret the ratings

These ratings compare your answers with the answers we have collected from large numbers of other parents across the UK. Many parents find this sort of comparison helpful, but it is obviously not the same as an assessment by an expert. If you have serious concerns about your child's behaviour, you may wish to consult with a doctor, psychologist or other expert.

For ease of interpretation, we group the comparison scores into four categories. The similarity of your child's psychological difficulties to those of other children is different in each category:

Close to average

In the general population most children and young people (roughly 80%) are in the "close to average" category. For example, if your child scores in this category for "sleep difficulties problems", it means their sleep is about average.

Slightly raised

If your child scores in the "slightly raised" category for "fears and worries"; this means their fears and worries are slightly higher than average.

High

Just one in twenty children and young people score in the "high" category. This means that, if your child's "hyperactivity and attention" problems fall in the "high" category, their behaviour is more severe than average.

Very high

One in twenty children and young people score in the "very high" category. If they have problems in the "very high category" those problems appear to be more severe than we find in 95 out of every 100 children.

The rating is only a rough guide. A high rating can be a "false alarm", so you need to use your own judgement. Not all difficulties need treating. Some difficulties get better by themselves, particularly if they are mild or if they have only been there for a short time. It's not "all or nothing".

Most strengths and difficulties lie on a spectrum. There will be children and young people at each end of the spectrum, but most will fall somewhere in between. Sometimes this results in difficulties that are subtle and severe at the same time. They are subtle enough that people outside the family often think that everything is fine; and yet severe enough for the child's life to be seriously affected by their difficulties.

IMAGINE 2

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Your 2021 DAWBA questionnaire ratings

The Development and Wellbeing Assessment (DAWBA) collects information about a range of common behavioural and emotional difficulties in children and young people, and analyses this information to produce a report of possible disorders of clinical significance.

Your child's ratings:

- Close to average / Slightly raised / HIGH / VERY HIGH for problems with language, routines, play, and social ability
- Close to average / Slightly raised / HIGH / VERY HIGH for over-activity and attention difficulties
- Close to average / Slightly raised / HIGH / VERY HIGH for troublesome behaviour
- Close to average / Slightly raised / HIGH / VERY HIGH for fears and worries
- Close to average / Slightly raised / HIGH / VERY HIGH for obsessions or compulsions
- Close to average / Slightly raised / HIGH / VERY HIGH for unusual movements or possible tics
- Close to average / Slightly raised / HIGH / VERY HIGH for low mood and loss of interest
- Close to average / Slightly raised / HIGH / VERY HIGH for feeding difficulties
- Close to average / Slightly raised / HIGH / VERY HIGH for sleep difficulties
- Close to average / Slightly raised / HIGH / VERY HIGH for difficulties with toilet training

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IMAGINE 2
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What next?

There are many good resources out there, covering everything from practical advice to inspiring stories. We've put together a list of resources that we think you might find useful below.

Please note that these websites are run by independent organisations and as such, we do not take any responsibility for their content.

Unique Charity provides support for individuals with rare chromosome or rare genomic disorders and their families. We recommend their disorder-specific information guides, which are family-friendly and medically-verified.
www.rarechromo.org

The **Genetic Disorders UK** charity is a source of information and support for both those affected by a genetic disorder, and the charities and patient groups that support them.
www.geneticdisordersuk.org

The **Genetic Alliance UK** charity produces booklets about genetics and genetic testing.
www.geneticalliance.org.uk

The **FIND Resources** website summarises findings from research studies into genetic syndromes.
www.findresources.co.uk

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Cerebra
Positively Different

The **Cerebra** charity provides health and social care information for children with neurological conditions. Their guides for parents section contains booklets on a variety of topics ranging from Educational Health Care Plans to transitioning to adult services.
www.cerebra.org.uk

contact a family
for families with disabled children

Contact a Family is a national charity for families with disabled children. They provide information, advice and support.
www.cafamily.org.uk

The Challenging Behaviour Foundation

The Challenging Behaviour Foundation charity supports people with severe learning disabilities whose behaviour challenges.
www.thecbf.org.uk

mencap
The voice of learning disability

Mencap works with people with a learning disability to change laws, challenge prejudice and support them to live their lives as they choose.
www.mencap.org.uk

Boosting the positive

How could you encourage positive behaviour? Most parents find that simply telling their child to be nicer doesn't work. Often it is more helpful to notice when they do kind and helpful things and then praise or thank them. (But don't go to extremes - praise won't work if it embarrasses them or sounds as though you don't mean it.) And, of course, young people learn by example, so you and the rest of the family can be on the lookout for opportunities to be kind and helpful to them.

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Share your report

If you are still concerned, is there someone you could ask whose opinion you would trust? This report could help you explain your concerns and ask for advice – for example, you might want to show this report to a family member, to your school or to your doctor.

Stay in touch

We will keep you updated about the study's progress with our online Research Newsletters. For live updates please follow us on social media. If you have any questions please don't hesitate to contact us on ich.imagineid@ucl.ac.uk or ring us on 020 8138 7768.

www.facebook.com/imagineid.study

www.twitter.com/imagineidnews

http://www.imagine-id.org/newsevents

The assessment from the DAWBA questionnaire has been obtained for research purposes. Please do not use this report as a substitute for a clinical assessment.

IMAGINE-2 Face to Face 5 year Follow-up report

IMAGINE 2

Intellectual Disability and Mental Health:
Assessing Genomic Impact on Neurodevelopment

Programme Directors:
Professor David Skuse
Professor Marianne van den Bree
Professor Jeremy Hall
Professor Sir Michael Owen

<ADDRESS> <DATE>

Participant Report

This document is strictly confidential and must not be disclosed, photocopied or reproduced for any other purpose without the consent of the writer.

Name: [full name of child]
DOB: [XXXXX]
Study ID: [123456]

Dear <PARENT/CG NAME>,

Thank you for taking part in the IMAGINE-2 study. Your involvement is greatly appreciated and will contribute towards research into the phenotype of individuals with <SYNDROME>. During your assessment, you have completed a Child and Adolescent Psychiatric Assessment about <NAME>. Also, some neurocognitive assessments were completed by <NAME>. The results from the interviews and the Wechsler Abbreviated Scale of Intelligence (WASI) are attached.

Please note the psychiatric interviews and cognitive assessments observed in this report have been obtained for research purposes only. Consequently, it is not a substitute for a clinical assessment.

We will keep you updated about the study's progress with our online Research Newsletters. For live updates please follow us on social media (search for @imagineidnews on Twitter and @imagineid.study on Facebook). You can also keep up to date on the IMAGINE-ID website at www.imagine-id.org. If you have any questions please don't hesitate to contact us directly at imagineID@cardiff.ac.uk or phone us on 02920 688065 and 02922 512286.

Yours sincerely,

Professor. Marianne van den Bree, Principal Investigator

<NAME>, Psychology Assistant

www.facebook.com/imagineid.study
www.twitter.com/imagineidnews
http://www.imagine-id.org

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Professor Sir Michael Owen

RESULTS AND TEST DETAILS

Psychiatric Assessments

Child and Adolescent Psychiatric Assessment

The Child and Adolescent Psychiatric Assessment is an interviewer-based structured diagnostic interview which collects data on the onset, duration, frequency, and intensity of symptoms of a wide range of psychiatric disorders including ADHD, mood and anxiety disorders, and psychosis. *<NAME OF CHILD> had symptoms of <INSERT DISORDER>. It may be beneficial for them to have a full clinical assessment to further evaluate these findings.*
OR IF NO SYMPTOMS PRESENT REMOVE THIS SECTION

Neurocognitive Assessment

Wechsler Abbreviated Scale of Intelligence (WASI)

The WASI is a general intelligence, or IQ test designed to assess specific and overall cognitive capabilities. It is a battery of three subtests: Vocabulary, Similarities and Matrix Reasoning. The Vocabulary and Similarities subtests are combined to yield a Verbal IQ score, and when combined with the Matrix Reasoning subtest this provides a Full Scale IQ Score.

The WASI provides the following intelligence quotient (IQ) scores:

- **Estimated Verbal IQ score:** A measure of acquired knowledge, verbal reasoning, and attention to verbal information.
- **Estimated Full Scale IQ score**: The overall estimate of an individual's general level of intellectual functioning).

IQ Score	<NAME>'s Score
Estimated Verbal IQ Score	
Estimated Full Scale IQ Score	

Each child's scores are compared with those of others of the same age. The average range for an IQ score at any age is between 90 and 109. This means that <NAME>'s IQ is <below average/average/above average.>

Please note that this is an abbreviated measure of intelligence obtained for research purposes. It does not have the validity of a full-scale IQ assessment conducted by an educational psychologist.