Guideline for the Investigation of Moderate / Severe Early Developmental Impairment & Intellectual Disability

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Target Audience:

People who need to know about this document in detail	Paediatricians (acute and community)
People who need to have a broad understanding of this document	Professionals involved in the assessment of children and young people presenting with EDI / ID, to include those processing and interpreting tests e.g. biochemistry

Disclaimer:
If the review date of this document has passed, please ensure that the version you are using is the most up to date version either by contacting the author.

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1. INTRODUCTION

Early developmental impairment (EDI) and Intellectual Disability (ID) are common reasons for referral to Paediatric Outpatient Departments. EDI is also known as Global Developmental Delay (GDD), but there is a growing preference amongst professionals working in Community Child Health to use EDI as a descriptor term. The term GDD can be misleading for parents, who often think their child will "catch up" with peers, which leads to unrealistic expectations in relation to their child's developmental trajectory.

In the general population, the prevalence of EDI / ID is between 1-3%.[1] There is a wide range of causes for EDI / ID, the commonest being chromosomal and structural brain abnormalities.[1,2] Approximately 1% of children with EDI / ID will have an underlying inherited metabolic disease (IMD). These children most commonly present with EDI / ID in addition to associated features,[3] and do not usually present with EDI / ID in isolation. However, it is important to remember that there are some rare IMDs which are treatable and present with isolated EDI / ID, and missing these diagnoses can have potentially devastating consequences.

Investigation of EDI / ID can be challenging and should be tailored according to the history and examination findings. Most often EDI / ID presents in isolation, i.e. no clinical clues in the history or examination findings to suggest a specific aetiology.

Clinical practice across the UK regarding EDI / ID investigation varies considerably. In 2014, a Steering Group in the East Anglia region consisting of adult and paediatric ID teams, and experts in laboratory testing and genetics published guidance on the efficient investigation of a child with early developmental impairment.[1] Following this, a review article was published in Archives of Disease in Childhood in 2019.[2]

As a team of paediatricians in Cwm Taf Morgannwg UHB, we reviewed the East Anglia guidance, along with the most recent guidelines from Cardiff and Vale UHB.[4] Further consultation was sought with Dr Graham Shortland, Consultant Paediatrician with Special interest in Inherited Metabolic Disease and previous chair of Rare Diseases Implementation Group (RDIG) as part of a working group with Consultant Geneticists and Clinical Biochemists. Joint collaborative working across Wales was gratefully received, namely input and resources from Betsi Cadwaladr UHB guideline[6]. Collaboration with the All Wales Community Child Health Network has further developed this guideline into an All Wales guidance document.

We have created this guideline in accordance with our consensus opinion and the available resources.

2. POLICY STATEMENT AND SCOPE

This guideline is for paediatricians (acute and community based), who assess children and young people referred for an assessment of their early developmental impairment and / or intellectual disability. This guidance is not for health visitors or General Practitioners, who should refer to community paediatrics if they have concerns about a child presenting with developmental impairment.

3. AIMS AND OBJECTIVES

3.1. outline an approach for isolated EDI / ID where a thorough history and examination does *not* lead to targeted testing

3.2. prioritise investigations with higher diagnostic yields and tests for rare, but potentially treatable causes.

3.3. improve diagnostic efficiency and equity of access to diagnostic testing through implementation of a standardized approach

3.4. minimise "pathway fatigue" – the negative effects of prolonged and extensive investigations on children and parents

This guideline does *not* provide a comprehensive list of investigations that should be considered when a child presents with EDI / ID in association with other clinical features or red flags, as this is beyond the scope of this guidance. However, there is a summary of possible investigations for EDI / ID *plus other clinical features* provided in Appendix 2, which clinicians may find useful as a reference.

4. RESPONSIBILITIES

It is the responsibility of the clinician to ensure appropriate use of this guideline, which includes selecting the appropriate clinical context for its use e.g. correct identification of moderate / severe EDI / ID; correctly identifying other clinical features which would indicate more targeted testing is required. All staff should report any issues, errors or near-misses via the usual channels.

5. DEFINITIONS

Early developmental impairment (EDI) is defined as significant delay (2 SD below the mean) in *two or more* of the following developmental domains: *gross motor, fine motor / vision, speech and language, cognition, and personal social skills affecting activities of daily living*. EDI can be categorised from mild to severe, and is identified as the directly observable and measurable impairment in the acquisition of skills when compared with the typical developmental progression of a child. EDI is usually used to describe children < *age 5 years* because formal psychological testing of intellectual and adaptive functioning is less reliable, and *not all children with EDI* will meet criteria for ID as they grow older.

Intellectual Disability (ID) involves impairments of general mental abilities that impact adaptive functioning in three domains: *conceptual, social, and practical*. Although ID does not have a specific age requirement, it is usually used to describe children *aged > 5 years* when formal cognitive assessments can be more reliably performed.

For many children referred for an assessment of their EDI / ID, the results of a formal assessment will clearly quantify the severity of their impairment e.g.

- Ruth Griffiths report – evidence of moderate to severe if impairment (score <5th centile) in two or more domains tested

- Schedule of Growing Skills (SOGS): suggestive of moderate to severe impairment if scores are two boxes below chronological age in two or more domains
- Educational Psychology report: IQ or GCA <70
- Other equivalent scores in tests: e.g. Bayley Scales, ASQs etc.

However, when results of a direct / formal assessment is not available, clinical acumen *must* be used. The clinician will take a thorough history and examination, seek information from other professionals e.g. therapists, colleagues in education, to formulate an opinion as to how significantly the child is impaired in comparison to their chronological age in all developmental domains. It is also important to assess the impact of their delay on *day to day functioning*, and indeed there is a growing acknowledgement that this is a better reflection of a child's ability rather than an IQ test performed on a single day. A child who requires a *Specialist School for educational provision could be considered to have moderate / severe EDI / ID*. *Those children attending a Special Unit should be considered on a case by case basis.*

6. GUIDELINE

6.1. History and examination

Investigations for moderate / severe EDI / ID should only be considered *after* a detailed history and examination has been undertaken.

The following **"red flags"** for IMDs / genetic / structural aetiology should be identified, as they may indicate the need for ***targeted*** **testing** and / or specialist referral.

- **Full development history**: signs of regression of speech and language or motor skills following a period of normal development
- **Vision and hearing**: must be assessed (low threshold for referral to audiology and / or ophthalmology)
- **Pregnancy and birth history:** prematurity, history of unexplained neonatal or sudden infant death, recurrent miscarriages, maternal ill-health e.g. HELLP syndrome (Haemolysis, Elevated Liver enzymes and Low Platelets syndrome), AFLP (Acute Fatty Liver disease of Pregnancy), perinatal TORCH infections (Toxoplasma, Other, Rubella, Cytomegalovirus, Herpes Simplex Virus) history of prenatal alcohol or drug exposure, medications during pregnancy
- **Family history** (at least 3 generations): history of consanguinity, family history of developmental delay / ID / neurodevelopmental disorders or seizures
- **Past medical history:** results of newborn bloodspot screening, significant symptoms such as unexplained hypoglycaemia in neonatal period or childhood, severe peri-natal or childhood infection (e.g. meningitis), seizures, encephalopathy, self-injurious behaviour, psychiatric symptoms, cardiomyopathy
- Consider influences of **environment** e.g. neglect, lead toxicity

- **Examination:** abnormal head circumference, growth, dysmorphic features, skin features (e.g. café au lait, severe eczema, angiofibroma), organomegaly, hypotonia, unusual head hair (e.g. kinky, coarse), eyes (e.g. cataract, nystagmus, abnormal fundi), focal neurology

NB. Developmental regression or static development warrants urgent investigation and referral to appropriate specialists.

It is important to consider if the child was born in another country as they may not have been screened or tested for conditions such as phenylketonuria or congenital hypothyroidism. This is routine practice in the UK as part of the newborn bloodspot screening. However, this is not mandatory and parents in the UK can opt out. It is crucial not to miss treatable causes, especially congenital hypothyroidism.

6.2. First line investigations

We recommend the following first line investigations (Table 1) for children with *isolated* moderate / severe early developmental impairment or intellectual disability. Any associated clinical features should prompt targeted investigations, some of which are suggested at the end of this guideline (see Appendix 2). Consider onward referral to allied specialties if additional features are identified.

Second line investigations are discussed later in this guideline. The assessing clinician may opt to do some / all of the second line tests simultaneously with the first-line investigations depending on local arrangements.

IMPORTANT
Ensure all relevant clinical information is entered on the lab request forms to assist with interpretation of results. This includes providing detail in relation to which areas of development are impaired, and the severity e.g. Bayleys / SOGS / Ruth Griffiths / Educational Psychology results and how it is affecting their daily function e.g. how much support is required in nursery / school / home. This information will also assist with auditing of results against the phenotype of the CYP.

NB. Please refer to the National Pathology handbook to check sample requirements for **your local laboratory,** as there can be variation in sample requirement **(https://wphtrak.wales.nhs.uk/).**

Table 1 - First line investigations for isolated EDI / ID

Test required	Specimen	Bottle colour
FBC + blood film	**Blood**: 2x EDTA	2x Purple top
+/- Lead (consider if high risk in geographical area)		
Urea & electrolytes (NB. Low creatinine is also significant. See notes below)	**Blood**: 2x SST **or** 1x LiH **+** 1x SST	2x Adult Yellow / Paeds red top **or,** 1x Yellow + 1x Green top
Liver function test		
Bone profile		
Thyroid function test		
Urate (NB. low and high urate is potentially significant)		
Creatinine Kinase (CK) for girls and boys		
Genetics: SNP array and Fragile X *(*please read section 6.4 prior to obtaining signed consent on genetics blood request form. Further details in Appendix 3 – 5)*	**Blood**: 1x EDTA	1x Purple top

6.3. Second line investigations

If all first line investigations are normal, the next step is to **review and reconsider the history and REPEAT the clinical assessment.** The family will need to be made aware that it may take approximately 4-6 months for the genetic test in the first line investigations to be analysed and reported. Unless there is clinical change in that time i.e. additional clinical features arise, then it would be best to wait for the first line investigations to be complete before pursuing the second line tests.

Following repeat assessment, you may decide on one of the following two courses of action:

1. *No further testing and "watch and wait" approach:*

This guideline is for moderate / severe EDI / ID therefore if the impairment is *mild*, the child is demonstrating reasonable developmental progress over time i.e. not static / regressing, and there are *no new or additional features,* we think it is reasonable to adopt a "watch and wait" approach. If they develop other features i.e. multi-system involvement or additional features, then targeted testing would be indicated at that point. If the child continues to make slow, but steady progress then the clinician may decide to end the investigation pathway and continue with supportive management. Decision should be made in conjunction with parental discussion.

2. *Second-line investigations and specialist discussion for moderate to severe EDI / ID:*

If the child presents with moderate or severe EDI / ID *without* clinical features to assist targeted testing, second line blood and urine tests (Table 2) should be considered and discussed with the parents. The aim is to identify rare IMDs, which can present with isolated EDI / ID, for which treatment is available. For example, the most common cerebral creatine deficiency syndrome is X-linked creatine transporter deficiency, which has been reported in 1% of males with ID of unknown aetiology and novel treatments are in development.[2] Rarer creatine synthesis defects are amenable to treatment with creatine supplementation.

However, it is important to remember that the diagnostic yield of the secondary investigations is low and many of these tests are complex and labour intensive. In addition, some of the analytes tested for are unstable e.g. the urine sample required to analyse creatine and guanidinoacetate (testing for cerebral creatine deficiency syndromes) needs to be frozen within 1-2 hours of collection, and paired with the blood test. This increases the risk of sampling error and the need to repeat samples, which leads to a potentially distressing experience for the child / young person and parents.

Urine organic acids and glycosaminoglycans (GAG) are easier samples to obtain, as they require fresh non-sterile samples, i.e. do not require freezing. Evidence to date suggests that the diagnostic yield for these investigations requested in children with EDI is very low. Out of 699 participants, urine GAG analysis did not contribute to a diagnosis, while for urine organic acids, three participants had diagnostic results (two of whom had abnormal plasma amino acids).[5] A further review of 8,500 urine organic acids over a ten-year period detected no children with an IMD presenting with isolated EDI / ID.[1]

We recommend:

1. Clinicians should decide based on their clinical assessment, and in conjunction with the parents +/- specialist advice, whether *some or all* of the following second line investigations should be requested.

2. Medical Genetics referral (to consider a gene panel / exome / whole genome sequencing) to assist with investigation for:
   - those with moderate to severe EDI / ID
   - those with mild EDI with additional features

NB: A child with mild EDI / ID *without* additional features is unlikely to benefit from genetics referral as there are limited further testing options for them.

Table 2 - Recommended second line investigations for consideration following above guidance

Test required	**Specimen**	**Bottle colour**
Creatine and guanidinoacetate *Urine and blood samples need to be frozen within 1-2 hours of collection, therefore need to reach lab promptly*	**Blood:** 1x Lithium Heparin *Paired (collected within 24-48hrs of each other)* ***with*** **Urine**	1x Green top **AND** White universal urine container (NOT red boric)
Organic acids Glycosaminoglycans **NB: Strongly consider in children with normal early development up to 1 year old**	**Urine**: Universal container *NB. <u>Fresh</u> sample to reach lab within 2 hours*	White universal urine container
Amino acids	**Blood:** 1x Lithium Heparin, ideally fasted sample	1x Green top

6.4. Supplementary Notes regarding tests:

Genetics

Comparative Genomic Hybridisation (*CGH*) array has a diagnostic yield of around 10-20%. Single Nucleotide Polymorphism (SNP) array has replaced CGH array and is considered a better test, which will hopefully lead to increased diagnostic yield.[2] For more specific information in relation to SNP array, please see Appendix 4.

The East Anglian article created a summary of the implications of genetic testing that families need to be made aware of (see Appendix 3).[1] Incidental findings are a serious, but fortunately rare complication of genetic testing, whereas *variants of uncertain significance (VOUS)* are a common problem. The SNP array has the ability to identify whether the biological parents are first degree relatives so this information needs to be included in the pre-test counselling for parents. Please provide patients / parents / carers with SNP array patient information leaflet.
We recommend that **any child with a confirmed genetic cause for their EDI / ID should be offered a referral to Medical Genetics** for genetic counselling and testing of relatives.

Lead
Some areas around Wales have high lead levels. Cwm Taf Morgannwg UHB has recently had some cases of children with early developmental impairment who had elevated blood lead levels. We therefore recommend for lead levels to be tested as first line if the child is living in a high risk area.

Lactate and ammonia
These are *<u>not</u>* advised in children who are otherwise well, i.e. seen in an outpatient setting. However, they should be considered if a child presents acutely unwell with seizures, lethargy +/- background of developmental impairment. *NB: Ammonia must be transported to the lab urgently <u>on ice</u> and processed as soon as possible to prevent errors.*

Urea & Electrolytes (U+E)
Low creatinine can be significant as it can indicate a cerebral creatine deficiency syndrome. This would warrant further discussion with a Clinical Scientist and testing for plasma / urine creatine and guanadinoacetate may be considered.

Thyroid function tests (TFTs)
These are included as a first line investigation as the UK newborn bloodspot screening programme does not detect secondary hypothyroidism, and some children may not have been tested previously if they were born outside the UK or parents declined newborn bloodspot screening.

6.5. Neuroimaging

The probability of MRI identifying the aetiology in children with isolated EDI / ID without other features such as microcephaly or focal neurology is 0-2%.[2] However, the East Anglian group comment that many investigations on the diagnostic pathway are low yield, and that many parents may have strong feelings about the necessity of a scan. In their experience, a discussion about low yield of diagnostic results, the trauma and risks of undergoing general anaesthetic or sedation, and the low likelihood that the result will change management almost always results in the family deciding against a scan.[2]

7. REFERENCES

7.1. PHG Foundation. A guide to the investigations of intellectual disability / developmental delay in East Anglia (2014). Available online at: www.phgfoundation.org

7.2. Coysh T, et al. Fifteen-minute consultation: Efficient investigations of the child with early developmental impairment in the era of genomic sequencing. *Archives of Disease in Childhood Education and Practice Edition 2020; 105: 13-18.*

7.3. Hogg S. Best Practice Guidelines for the Biochemical Investigation of Global Developmental Delay for Inherited Metabolic Disorders. *MetBioNet 2019.*

7.4. Skone K and Moat S. Guidelines for investigation of developmental delay. *Cardiff and Vale UHB (*2017*).*

7.5. Hart A, et al. Aetiological investigations in early developmental impairment: are they worth it? *Archives of Disease in Childhood 2017; 102: 1004-1013.*

7.6. Parker. S, et al. Medical assessment of Early Developmental Impairment (Global Developmental Delay) in children under 5 years. *BCUHB (2022).*

8. GETTING HELP

Metabolic Biochemistry Laboratory at Cardiff & Vale UHB
To discuss testing strategies and interpretation of metabolic results:
Stuart Moat - Stuart.Moat@wales.nhs.uk
Claire Gallagher - Claire.Gallagher2@wales.nhs.uk
Thomas Lewis - Thomas.Lewis5@wales.nhs.uk

Clinical Metabolic
Generic email address for all queries: Paedsimd.cavservice@wales.nhs.uk

Genetics
Generic email address for all referrals: se.genetics@wales.nhs.uk

Further comments or to discuss these guidelines
Dr Bethan McMinn: bethan.mcminn@wales.nhs.uk

9. ACKNOWLEDGEMENTS

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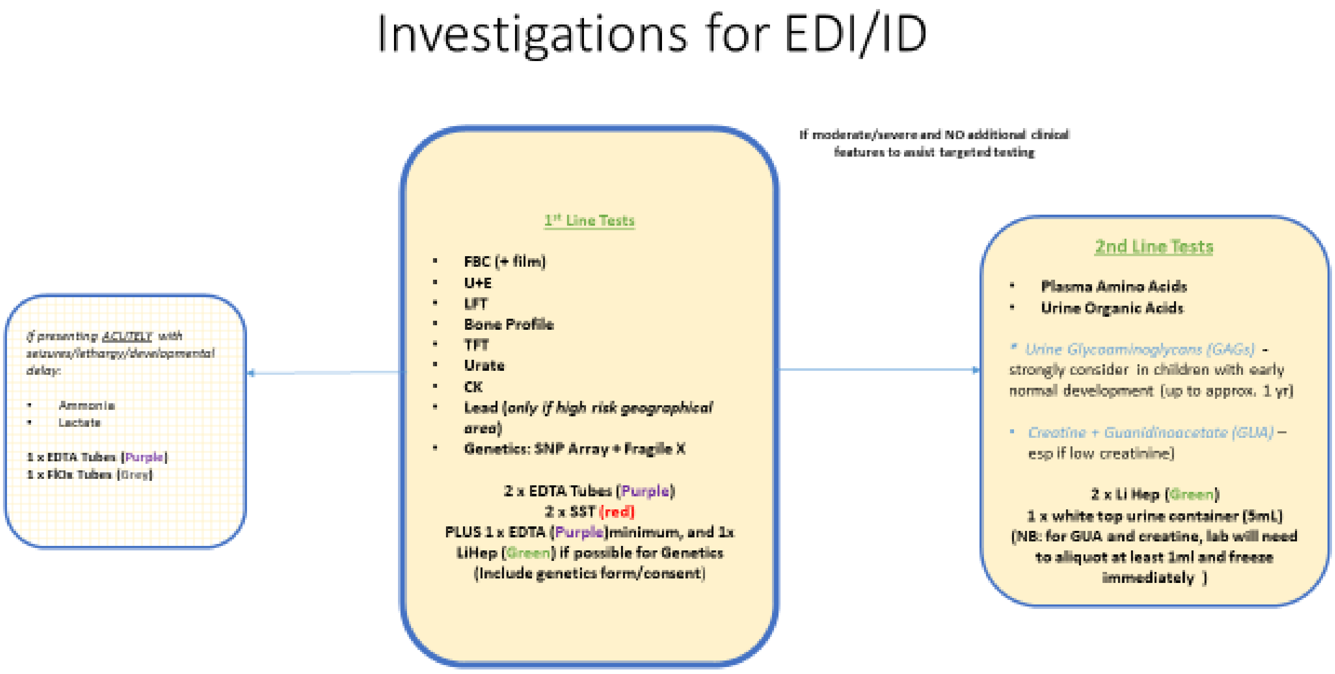
Appendix 1: Flowchart summarising samples required for 1st and 2nd line tests



Please refer to table 2 for details on how samples are processed

NB – The LOCAL biochemistry laboratory must be contacted prior to sample collection for second line tests, as samples have to be referred to specialist laboratories for analysis.

Appendix 2: Clinical features found in addition to EDI / ID which should prompt targeted testing and specialist referral (in addition to first line tests)[2,3]

Clinical feature	Refer to	Possible disorders	Suggested tests
Acute encephalopathy	Metabolic	Amino acidopathies Organic acidaemia Fatty acid disorders	Ammonia *(*transport on ice + process ASAP),* glucose, plasma amino acids Urine organic acids acylcarnitines
Dysmorphic features	Clinical genetics		Syndrome dependent
Coarse facial features	Metabolic	Lysosomal storage disorders	White cell enzymes, urine GAG typing
Growth failure	Metabolic Endocrine	Hypothyroidism Many IMDs – organic acidaemias and amino acidopathies	TSH, fT4 and fT3 Glucose, ammonia, lactate, urine organic acids, orotic acid, acylcarnitines, amino acids
Eczema (severe); alopecia	Dermatology	Biotinidase deficiency	Biotinidase
Eye signs (incl. corneal clouding, cataracts, cherry red spots, severe myopia)	Ophthalmology +/- neurology +/- clinical genetics	Homocystinuria Lysosomal storage disorders Wilson's disease Congenital disorders of glycosylation Cholesterol precursor disorders	Plasma total homocysteine, *see above* Copper, caeruloplasmin Transferrin isoforms 7-dehydrocholesterol
Hearing loss	Audiology	Beta mannosidosis Mucopolysaccharidoses	Oligosaccharides, white cell enzymes Urine GAG
Hypotonia	Neurology	Organic acidaemia Peroxisomal disorders Biotinidase deficiency Purine / pyrimidine disorder Creatinine synthesis defect Fatty acid oxidation defect Neurotransmitter deficiencies	*See above* VLCFA *see above* urine purines + pyrimidines Urine and plasma guanidinoacetate and creatine Acylcarnitines Test as guided by neurology

Neurological regression	Neurology (urgently)	Lysosomal storage disorders Organic acidaemias Mitochondrial disorders X-linked adreno-leukodystrophy (peroxisomal)	*See above* & White cell enzymes *See above* Plasma and CSF lactate, biotinidase, acylcarnitines and organic acids VLCFA
Multisystem involvement	Neurology / Metabolic / Endocrine	Mitochondrial disorders Congenital disorders of glycosylation	*See above* *See above*
Hepato-spleno-megaly	Gastro-enterology+/- metabolic	Lysosomal storage disorders Glycogen storage disorders Nieman Pick Type C	*See above* Glucose, lactate, urate, lipids, erythrocyte and leukocyte glycogen studies Oxysterols and fibroblast filipin staining
Seizures / Epileptic encephalopathy and/or movement disorders	Neurology	GLUT-1 deficiency Biotinidase deficiency Organic acidaemias Peroxisomal Congenital disorders of glycosylation Purine and pyrimidine Pterin defects	Plasma and CSF glucose *See above* *See above* *See above* *See above* *See above* CSF neurotransmitter metabolites
Acute encephalopathy / ataxia	Metabolic Neurology	Amino acidopathies Organic acidaemias Fatty acid disorders Urea cycle defects	Glucose, ammonia, plasma amino acids, urine organic acids and orotic acid, acylcarnitines. *NB results may be normal when well*
Severe expressive language delay	SALT Neurology	Creatinine synthesis defect Succinic semialdehyde dehydrogenase deficiency	Urine and plasma creatine and guanidinoacetate Urine organic acids

Appendix 3: Important implications of genetic testing to discuss with families (taken from East Anglian guidance[2])

Table 1 Issues surrounding testing

Issue	
True positives	▶ A true positive result may be distressing; often no curative treatment is available. ▶ Diagnosis can aid prognostication, provide closure to the family and help with family planning choices. ▶ The result may have direct implications for the health of asymptomatic family members: – e.g. Fragile X testing identifies premutations, which can result in maternal fragile X tremor/ataxia syndrome in later life.
False positives	▶ e.g. An innocent variant is mistakenly judged to be disease-causing.
True negatives	▶ Where tests fail to identify a cause, this does not mean all disorders are excluded: – e.g. A negative comparative genomic hybridisation (CGH) or unremarkable urine organic acid may be interpreted by families to mean that their child cannot have a genetic/metabolic disorder.
False negatives	▶ Genetic testing may be initially reported as normal, but as knowledge/panels of genes tested expands, subsequently a disease-causing variant may be identified.
Non-diagnostic results	▶ Results may be reported with a change of unknown significance, eg, many smaller duplications in array CGH or subtle changes in organic acids. ▶ There may currently be insufficient data to tell whether the variant is disease-causing.
Turnaround times	▶ More advanced tests can have lengthy turnaround times, eg, whole genome sequencing.

14 Coysh T, *et al*. *Arch Dis Child Educ Pract Ed* 2020;**105**:13–18. doi:10.1136/archdischild-2018-315123

Appendix 4: Information / resources in relation to SNP array

SNP array service information and eligibility criteria:

https://medicalgenomicswales.co.uk/images/awmgsdownload/PD-GEN-INFSNPArray2.pdf

SNP Array and Fragile X Test Request form:

https://medicalgenomicswales.co.uk/images/awmgsdownload/PD-GEN-DevDelReq5.pdf

More information about the change from array CGH to SNP array:

https://medicalgenomicswales.co.uk/images/awmgsdownload/PD-GEN-SNParrayUpdate.pdf

Appendix 5: SNP array Patient / Parent Leaflet – AWMGS (see overleaf)

This might include things like having an increased risk of cancer or other health problem in the future. This could also be important for other family members. Your healthcare professional will discuss this type of result with you and they may suggest that you are seen by AWMGS.

An uncertain result

The SNP array may detect changes of uncertain significance. We call these variants of uncertain significance (VUS). This means that currently there is not enough evidence available to know whether this change is significant or not. For instance, the change might never have been seen before and not much is known about that part of the chromosome.

Sometimes we might suggest testing parents to see if they have the change. This might help our understanding. If parents are tested, and depending upon the testing method used, it is possible the test might reveal whether the individual is biologically related to one or both of their parents.

Close family relationships

The test might also reveal if a person's biological parents are very closely related to one another. This will only usually be reported if the test shows the parents might be first degree relatives. For example, the test shows the biological parents are siblings, or a parent and another child.

When will I get the results?

SNP array results usually take about 2-3 months. If the person having the test is in hospital, or a close relative is pregnant, the test might be completed in a few weeks. Sometimes results may take longer. A problem with the sample or test can delay the result. In some cases, the test may fail. In this event you/your child might need to have another sample taken.

Where can I get more information?

All Wales Medical Genomics Service (AWMGS)

AWMGS provides genetic testing and Clinical Genetics services for patients across Wales. More information about AWMGS and the tests they offer can be found on our website. www.medicalgenomicswales.co.uk

Wales Gene Park

Wales Gene Park has a range of information tailored for the public and health professionals. They also have information about where families with rare genetic conditions can find additional support. www.walesgenepark.cardiff.ac.uk

UNIQUE

UNIQUE offers support and information for individuals and family members that might have a rare chromosome disorder.

AWMGS Genetics Team Version 1.0

Date of issue: May 2022

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AWMGS
All Wales Medical Genomics Service

Single Nucleotide Polymorphism (SNP) array test

Patient Information Leaflet

Why is this test being offered to me?

There are a number of reasons why you / your child might be offered a SNP array test. Please ask the health care professional who is looking after you why they think the test will be helpful for you / your child.

Understanding your genetic code

Our genetic code is made up of a series of chemical letters; this is our DNA. We inherit half of our DNA from each of our parents. Our DNA forms thousands of genes which instruct our body on how to grow, function and develop. These genes are packaged into structures called chromosomes.

One way to think about this, is to think of our genetic code as being a library of instructions for making us. In this library, our chromosomes are like bookshelves holding thousands of instruction manuals (our genes).

Usually, we have 46 chromosomes in 23 pairs. We inherit one copy of each pair from each parent. The chromosome pairs are numbered from 1 to 22. The final pair are called the sex chromosomes. Our biological sex is largely determined by our sex chromosomes. Females typically, but not always, have two ‘X’ chromosomes (XX). Males usually, but not always, have an “X” and a “Y” chromosome (XY).

What is a SNP?

We all have variation in our DNA. Most of this does not contribute in any meaningful way to our health or learning abilities. This can sometimes be called natural genetic variation. Some of this variation is very small and involves only one of the letters is our DNA. These are SNPs. Different people will have a unique mixture of SNPs.

What is a SNP array?

This variation allows us to detect thousands of SNPs at various locations along each of the chromosomes. A SNP array shows if there is any chromosome material missing (deleted) o if there is any extra chromosome material present (duplicated). Having too much or too little chromosome material can cause problems with growth and development, or cause health issues. It is a very broad genetic test. It will not look for very small genetic changes which might affect how genes work.

How is the test carried out?

It usually involves having a blood sample taken This is then sent to the laboratory for testing. Sometimes it is helpful to test other body tissues, like saliva.

What are the possible test results?

There are a number of possible outcomes from genetic testing. Unfortunately, you may not ge a clear answer from testing.

No significant change is found

This means the test did not find a significant chromosome change. This result does not exclude a genetic diagnosis. Your healthcare team might suggest further genetic testing will be helpful.

A significant change is found

This means that the SNP array has found a change that is likely to cause health and/or learning problems. It may have implications for other family members. Your healthcare professional will discuss this result with you. They might suggest that seeing a specialist at the All Wales Medical Genomics Service (AWMGS) will be helpful.

It is important to remember that not everybody with the same type of genetic change is affected in the same way. This is especially true for chromosome changes which can affect a person’s learning ability. Some people in a family might have significant problems associated with the genetic change. Other family members might only be mildly affected or not have any symptoms at all.

An unexpected result

Sometimes a chromosome change is found that is associated with other health problems which are unrelated to the reason for having the test. This means they do not explain your/your child’s health and/or learning issues, but they could have other implications for the person having the test.

Appendix 6.1: Parent / Carer Information Leaflet (Parker. S, et al BCUHB. 2022) – English version[6]

Developmental Difficulties in Young Children
Parent / Carer Information Leaflet

If you require this leaflet in large print, another language or format please ask your paediatrician or health visitor.

What is developmental delay?

'Developmental delay' is a phrase used when children are slower to reach milestones than is expected for their age. They may have problems with:

- Movement
- Eye-hand coordination
- Communication - speech and understanding
- Play, social skills, learning and behaviour

Children may have difficulties in one of these areas, or in more than one area. The term 'early developmental impairment' is now used when children have difficulty in two or more aspects of their development. In the past, this was often called 'global developmental delay.'

Some delays in development are temporary and with help and support children can meet their milestones and develop along with others their age. For other children delays continue much longer. They may be the first sign of a long-term condition for which your child may need specialised intervention, treatment or support. Some children with early developmental impairment at pre-school age go on to have learning difficulty or learning (intellectual) disability when they are older.

What is a developmental milestone?
Milestones represent what an average child can do around a particular age. They involve physical, social, emotional, problem solving and communication skills that children learn as they develop and grow. Examples of milestones include rolling over, sitting upright and taking their first steps.

What causes developmental difficulties?

For many children the specific cause or factors involved in their developmental difficulties are never known. For some children, there may be an underlying cause, for example a genetic or medical reason.

Although a specific cause for developmental impairment is often not found, it is important to investigate for the following reasons:

- To know if there are any treatment options
- To monitor for known complications if a diagnosis is made

- To know about the likely progression of any conditions which are diagnosed
- To provide condition-specific child and family support
- To know if future children are likely to have the condition

Some families are disappointed or frustrated if no cause is found, but others are reassured that many serious medical conditions have been ruled out for their child.

Investigation of Early Developmental Impairment

The investigation of developmental difficulty first involves a review by a children's doctor (Paediatrician). The doctor will ask questions about your child's health and their development, and will do a physical medical examination. The doctor will also measure your child's height, weight and head size.

Next, the doctor may arrange tests to look into the cause of developmental difficulty. Not every child will require these tests and the doctor will always seek permission (parental consent) to request tests for your child. These may include referring your child to Ophthalmology (eye clinic) or Audiology. They may also arrange blood and/or urine tests. Urine tests are collected at home. You will be provided with a container to collect the urine and should bring it to the place you have been asked. Blood tests happen in a hospital or outpatient clinic. You will receive an appointment for this investigation.

What happens next?

In most cases, these tests are not urgent. Results can take several months, and your doctor will write or speak to you when the results are available.

Children with developmental difficulties should receive therapies and support to help them achieve their potential. Access to these services does not require blood results or a specific medical cause for the developmental difficulties.

Depending on your child's needs, they may have input from Physiotherapy, Occupational Therapy, Speech and Language Therapy, Early Years Nurses, Play Specialists or Multi-agency Child Development Teams. As a parent, the best way you can help your child is to use the ideas from these professionals in your everyday routine, and spend time talking and playing with your child.

Children with persistent developmental impairment often benefit from ongoing Community Paediatric input. These doctors are skilled at working with professionals in health, education and social care who may support you and your child.

Where can I get more information?

After reading this leaflet, if you would like more information please speak to your Paediatrician or Health Visitor.

You can also access further information regarding what you can do to support your child's development on the following website: https://gov.wales/parenting-give-it-time.

Appendix 6.2: Parent Information Leaflet (Parker. S, et al BCUHB. 2022) – Welsh Version[6]

Anawsterau Datblygiadol mewn Plant lfanc

Taflen Wybodaeth i Rieni neu Ofalwyr

Os oes angen y daflen hon mewn print bras, iaith neu fformat arall, gofynnwch i'ch paediatregydd neu'ch ymwelydd iechyd.

Beth yw oedi datblygiadol?

Mae 'oedi datblygiadol' yn ymadrodd a ddefnyddir pan fa plant yn arafach yn cyrraedd cerrig milltir na'r hyn a ddisgwylir ar gyfer eu hoedran. Efallai y bydd ganddynt broblemau gyda'r canlynol:

- Symud
- Cyd-drefniant rhwng y llygad a'r llaw
- Cyfathrebu - lleferydd a dealltwriaeth
- Chwarae, sgiliau cymdeithasol, dysgu ac ymddygiad

Gall plant gael anhawster yn un o'r meysydd hyn, neu mewn mwy nag un maes. Mae'r term 'nam datblygiadol cynnar' yn cael ei ddefnyddio bellach pan mae plant yn cael anhawster gyda dwy agwedd neu fwy ar eu datblygiad. Yn y gorffennol, gelwid hyn yn aml yn 'oedi datblygiadol hollgynhwysol'.

Mae rhywfaint o oedi mewn datblygiad dros dro a gyda chymorth a chefnogaeth gall plant gwrdd a'u cerrig milltir a datblygu ar y cyd ag eraill o'u hoedran. I blant eraill mae oedi'n para yn llawer hirach. Fe all fad yr arwydd cyntaf o gyflwr hirdymor lie gall fad angen ymyrraeth, triniaeth neu gymorth ar eich plentyn. Mae rhai plant gyda nam datblygiadol cynnar oedran cyn-ysgol yn mynd ymlaen i ddatblygu anawsterau dysgu neu anabledd dysgu (deallusol) pan maen nhw yn hyn.

Beth yw carreg filltir ddatblygiadol?
Mae cerrig milltir yn cynrychioli'r hyn y gall plentyn cyffredin ei wneud o gwmpas oedran arbennig. Maen nhw'n cynnwys sgiliau corfforol, cymdeithasol, emosiynol, datrys problemau a chyfathrebu y mae plant yn eu dysgu fel y maen nhw'n datblygu a thyfu. Mae enghreifftiau o gerrig milltir yn cynnwys rowlio drosodd, eistedd yn unionsyth a chymryd eu camau cyntaf.

Beth sy'n achosi anawsterau datblygiadol?

I lawer o blant, nid yw'r achos neu'r ffactorau penodol ynghlwm wrth eu hanawsterau byth yn cael eu hadnabod. I rai plant, gall fod achos sylfaenol er enghraifft, rheswm geneteg neu feddygol.

Er nad yw'r achos penodol am nam datblygiadol yn aml wedi ei ddarganfod, mae'n bwysig ymchwilio am y rhesymau canlynol:

- Gwybod a oes unrhyw opsiynau o ran triniaeth

- Monitro ar gyfer cymhlethdodau hysbys os gwneir diagnosis
- Gwybod ynghylch datblygiad tebygol unrhyw gyflyrau lie gwnaed diagnosis
- Darparu cymorth yn ymwneud a chyflyrau penodol ar gyfer plant a theuluoedd
- Gwybod a fydd plant yn y dyfodol yn debygol o gael y cyflwr.
- Mae rhai teuluoedd yn siomedig neu'n rhwystredig os na chanfyddir achos, and mae eraill yn dawel eu meddwl bod llawer o gyflyrau meddygol difrifol wedi eu diystyru i'w plentyn.

Archwilio Nam Datblygiadol Cynnar

I ddechrau, mae archwilio anhawster datblygiadol yn golygu adolygiad gan feddyg plant (Paediatregydd). Bydd y meddyg yn gofyn cwestiynau am iechyd eich plentyn a'u disobliged, a bydd yn gwneud archwiliad meddygol corfforol. Bydd y meddyg hefyd yn mesur taldra eich plentyn, pwysau a maint y pen.

Nesaf, efallai y bydd y meddyg yn trefnu profion i edrych i mewn i achos yr anhawster datblygiadol. Ni fydd angen y profion hyn ar bob plentyn a bydd y meddyg bob amser yn gofyn caniatad (cydsyniad rhieni) i wneud cais am brofion i'ch plentyn. Gally rhain gynnwys cyfeirio eich plentyn at Offthalmoleg (clinig llygaid) neu Awdioleg. Efallai y bydd yn trefnu profion gwaed a/neu wrin hefyd. Cesglir profion wrin gartref. Cewch gynhwysydd i gasglu'r wrin a dylech ddod ag o i'r man y gofynnwyd i chi. Mae profion gwaed yn digwydd mewn ysbyty neu glinig cleifion allanol. Byddwch yn derbyn apwyntiad ar gyfer yr archwiliad hwn.

Beth sy'n digwydd nesaf?

Yn y rhan fwyaf o achosion, nid yw'r profion hyn yn rhai brys. Gall canlyniadau gymryd sawl mis, a bydd eich meddyg yn ysgrifennu atoch neu'n siarad a chi pan fydd y canlyniadau ar gael.

Dylai plant sydd ag anawsterau datblygiadol dderbyn theraprau a chymorth i'w helpu nhw i gyrraedd eu potensial. Nid oes angen canlyniadau profion gwaed nae achos meddygol penodol dros yr anawsterau datblygiadol i gael mynediad at y gwasanaethau hyn.

Yn dibynnu ar anghenion eich plentyn, efallai y bydd yn derbyn cymorth gan Ffisiotherapi, Therapi Galwedigaethol, Therapi laith a Lleferydd, Nyrsys y Blynyddoedd Cynnar, Arbenigwyr Chwarae neu Dimau Datblygiad Plentyn Aml asiantaethol. Fel rhiant, y ffordd orau y gallwch chi helpu eich plentyn yw defnyddio syniadau gan y gweithwyr proffesiynol hyn yn eich arferion bob dydd, a threulio amser yn siarad a chwarae gyda'ch plentyn.

Mae plant sydd a nam datblygiadol parhaus yn aml yn elwa ar gymorth parhaus Paediatregydd Cymunedol. Mae'r meddygon hyn yn fedrus mewn gweithio gyda gweithwyr proffesiynol mewn iechyd, addysg a gofal cymdeithasol a all eich helpu chi a'ch plentyn.

Ble caf i fwy o wybodaeth?

Ar 61 darllen y daflen hon, os hoffech fwy o wybodaeth siaradwch a'ch Paediatregydd neu'ch Ymwelydd lechyd. Gallwch hefyd gael mynediad at wybodaeth bellach ynghylch beth y gallwch ei wneud i gefnogi datblygiad eich plentyn ar y wefan ganlynol: https://llyw.cymru/magu-plant-rhowch-amser-iddo

Appendix 7: Table for the Record of Investigations of Early Development Impairment / Intellectual Disability

PATIENT DETAILS / STICKER
Patient name:
DOB:
Hospital / NHS number:

	Investigation	Date of request	Date of result	Comments
Genetics	SNP array			
	Fragile X			
Bloods	FBC			
	Blood film			
	Lead (if required)			
	Urea & electrolytes			
	Bone profile			
	Thyroid function test			
	Creatinine Kinase			
	Urate (Uric Acid)			

PATIENT DETAILS / STICKER

Patient name:

DOB:

Hospital / NHS number:

	Investigation	Date of request	Date of result	Comments
Additional investigations				