

Cambridge University Hospitals NHS Foundation Trust

# A guide to the investigation of intellectual disability / developmental delay in East Anglia



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### The diagnostic pathway

This flowchart is intended as the clinician's guide to the investigation of intellectual disability (ID) and developmental delay (DD) in the East Anglia region. The evidence which underpins this diagnostic rationale is described in the accompanying document.



\*array CGH - array comparative genomic hybridisation; ALP - alkaline phosphatase; ALT - alanine transaminase; CK - creatine kinase; FRX - fragile X

### Introduction

In 2006 our group, including parent representatives, clinical geneticists, paediatricians and laboratory scientists, reviewed the investigation of children with intellectual disability (ID) and developmental delay (DD) within the Eastern region of the UK. We found variation in practice amongst community paediatricians. In light of our results we produced a <u>consensus statement</u> with <u>guidelines for investigation</u> and an <u>explanatory document for families</u> with the aim of improving standards and consistency of care. These documents are available at <u>www.phgfoundation.org/reports/4968</u>.

Over the last seven years, there have been significant advances in the ability to identify the causes of ID/DD with modern genetic techniques including array comparative genomic hybridisation (array CGH) and more recently exome/ genome sequencing.

In 2013, an online questionnaire was emailed to 37 consultant community paediatricians in our region. Respondents were asked if they accessed guidelines to appropriately tailor investigations of children with developmental delay. They were asked to select investigations for this scenario:

"A 3-year old boy with global developmental delay attends your clinic. He is just starting to walk. He uses pincer grip, but does not point at objects or scribble with a pencil. He is just starting to use single words appropriately; he can drink from a cup with two hands, but cannot use a spoon and does not imitate activities. There are no dysmorphic features and no neurological signs; growth is steady around the 60th centile for height and weight and 50th centile for head circumference. Previous medical, perinatal and family history are unremarkable. All routine newborn screening tests were normal."

Responses were received from 25 (68%) of those surveyed. 52% accessed regional guidelines. 56% accessed other guidelines. Figure 1 shows the survey results.



#### Figure 1 Results of survey of current practice in East Anglia Region

In light of these findings, indicating continued variation and divergence from recommended practice, we felt it was necessary to review the evidence base for investigation, looking at the principal modalities used in ID/DD: identification of cases and relevant history, examination yield, radiological, biochemical and genetic investigations.

A principal strength of the previous guideline development process was its engagement with families affected by ID/DD, and again our process has involved families at all stages including the production of this evidence document, which incorporates a diagnostic flowchart for clinicians (page 4) and a separate explanatory guide for families. We hope that the involvement of families affected by ID/DD makes our guidelines both more relevant and effective.

Whilst reviewing the investigation of ID/DD, we have emphasised the importance of considering yield and complexity (in terms of cost, processing and potential trauma to the individual/family) of the investigation. However, we were unanimous in our agreement that using yield, in terms of the simple percentage, as a criterion for test inclusion was unhelpful particularly when considering low yield tests for some of the rare but devastating ID-linked disorders which can however, be successfully treated if detected sufficiently early in life. Nevertheless, sensitivity and specificity of the relevant investigations have been assessed, to inform our evaluation of the suitability of tests in clinical practice.

#### A note on terminology

The guide is aimed at younger children with developmental delay (DD) as well as older children with intellectual disability (ID). For older children, we have used the term 'intellectual disability' in our report, to reflect its widespread use, following the latest revision of the American Psychiatric Association (APA) Diagnostic Manual for DSM-5 (2013), which replaces the term mental retardation with the term 'intellectual disability' and the sub-category 'intellectual developmental disorder' to reflect deficits in cognitive capacity beginning in the developmental period. This brings DSM terminology in line with other classification systems such as that used by WHO. The term 'learning disability' is also mentioned in our guide as a number of sources have used this phrase.

### Parents' viewpoint

### Assessment, investigation, diagnosis and beyond - the parental perspective

Before proceeding with assessment, investigation and diagnosis, take time to consider the parental perspective. What do they understand by the terms developmental delay, learning or intellectual disability? If parents did not initiate the referral, are they aware of the implications of their child's delay, and how best can you help them through the process of assessment?

Once assessment is underway, consider why finding a precise diagnosis and cause of their child's difficulties may be important to them, and what the implications might be for their family in terms of siblings and future births.

In 2006, the guideline development group set up an online discussion forum. Through interviews and focus groups it explored why finding a cause for their child's learning disability was important to the parents. The key points raised were:

#### Box 1 Parents' reasons for seeking a diagnosis

- "Just to know" to seek an answer to uncertainty, to provide confirmation that there is something wrong, to be reassured that they are not to blame, to have a name for their child's condition.
- To understand the future likely needs of the child, anticipate problems and hope for the best scenarios
- To understand what the condition means for the rest of the family
- To provide an end to the diagnostic quest
- To find others affected by the same condition
- To help the child find support and services

These and other benefits and potential problems of a genetic diagnosis are described in detail in the 2006 CGKP report <u>'Parents as Partners'</u> which can be downloaded from the PHG Foundation website.

Investigation of DD/ID can be a lengthy process and an incredibly anxious period for families. Emphasis should be on ongoing support alongside any investigation. Referrals to early intervention services such as Portage, education and therapy services should be considered, as well as directing parents to their own support groups.

<u>The Parents' Guide</u> (www.phgfoundation.org/file/16328) may be helpful in your discussion with parents and includes a list of parent support groups and organisations.

## Epidemiology

#### Definitions

Intellectual disability (ID) is a neurodevelopmental disorder with multiple aetiologies that encompass a broad spectrum of functioning, disability, and skills. ID involves impairments of general mental abilities that impact adaptive functioning in three domains.

These domains determine how well an individual copes with everyday tasks.

- The conceptual domain includes skills in language, reading, writing, maths, reasoning, knowledge and memory.
- The social domain refers to empathy, social judgement, interpersonal communication skills, the ability to make and retain friendships.
- The practical domain centres on self-management in areas such as personal care, job responsibilities, money management, recreation and organising school and work tasks.

While ID does not have a specific age requirement, an individual's symptoms must begin during the developmental period and are diagnosed based on the severity of deficits in adaptive functioning. The disorder is considered chronic and may be associated with other medical problems such as low mood, attention deficit hyperactivity disorder and autism spectrum disorder<sup>1</sup>.

The term 'global developmental delay' (GDD) rather than ID is usually used to describe children younger than age five with significant cognitive deficits, because testing of intellectual and adaptive functioning is less reliable in this age group and because not all children with GDD will meet criteria for ID as they grow older.

The following measures are often used to categorise the severity of GDD:

- Mild if functional age is less than 33% below chronological age
- Moderate if functional age is 34-66% below chronological age
- Severe if functional age is more than 66% below chronological age

#### **Prevalence of ID**

The reported prevalence of ID varies between studies and comparisons are confounded by issues such as sample size, definitions of ID and systems for reporting, but the most cited prevalence figures are in the region of 1-3% of the general population<sup>2-6</sup>. Table 1 presents prevalence figures from the literature. In the UK, the Learning Disabilities Observatory estimates the prevalence to be around 2%<sup>7</sup> but emphasises the difference in numbers of patients known to specialist services (the administrative prevalence of 0.46%) and the true prevalence, which results in part from differences in service use amongst people with different severity of ID, and under-reporting once individuals move beyond formal education .

#### Table 1 ID prevalence estimates

	Source	Population	Prevalence estimate (% and numbers)
	WHO (1989) <sup>4</sup>	Global	3%
	Roeleveld (1997) <sup>3</sup>	Global	1-3%
	Maulik (2011) <sup>2</sup>	Global	1.04%
Pe	Holland (BILD), (2011) <sup>6</sup>	UK	2%
ited tru lence	Emerson & Hatton, CeDR (2008) <sup>8</sup>	UK	2% 157,000 children 828,000 adults
Estima preva	Department of Health (2001)⁵	UK	2.5% mild/moderate LD 0.42% severe LD
	Emerson & Hatton LDO (2004) <sup>9</sup> Based on local health & social care data	UK	2%
rative ce	Emerson & Hatton LDO (2004) <sup>9</sup> People known to local services	UK	0.46%
nisti alen	LDO website (2014) <sup>7</sup> GP data	UK	0.42%
Admi preva	LDO website (2014) <sup>7</sup> School data Children aged 7-15 yrs	UK	3.6% moderate LD 0.47% severe LD 0.12% profound LD

#### **Aetiology of ID**

People with ID constitute a highly heterogeneous clinical group, with variation in the severity and scope of disability and the presence of concomitant clinical features. The aetiological factors are varied but, in broad terms, the causes of ID may be grouped into biological, environmental and genetic factors which may impact before, during or after birth. In many cases the cause will be multifactorial. Biological factors include infections in the antenatal or postnatal period; environmental factors include exposure to fetal teratogens or toxins in the postnatal period and genetic factors range from whole chromosome or partial aneuploidies, to mutations in single genes associated with brain function.

Large variations in the numbers of patients with a definitive diagnosis are reported but the most often quoted figure is around 40-60%<sup>10</sup>, therefore approximately half of further ID cases are usually described as idiopathic.

Recent advances in diagnostic genomic technologies (array CGH and exome/ whole genome sequencing) are proving useful in the investigation of undiagnosed ID, and reports in the literature describe increments in diagnostic rates in patients with idiopathic ID resulting from the application of such technologies<sup>11</sup>. Estimates of the relative contribution of different aetiological factors in ID are difficult to calculate, and are inevitably influenced by the sample population and sensitivity and extent of diagnostic methods. However, in industrialised countries, studies indicate that prematurity, prenatal and genetic factors predominate as the underlying aetiology<sup>12</sup>.

#### **Genetic causes of ID**

Genetic factors are identified or presumed as the cause of ID in the greatest proportion of cases. A spectrum of genetic abnormalities has been identified in ID. Whole chromosome or partial aneuploidies may arise *de novo* or as a result of inheritance of unbalanced chromosome rearrangements (translocations and inversions). Smaller imbalances may also arise *de novo*, or in inherited form and

can be identified with array CGH or targeted fluorescent *in situ* hybridisation (FISH) studies. More rarely, syndromic ID such as that seen in Prader-Willi syndrome, may arise from abnormal gene expression following inheritance of imprinted alleles arising from uniparental disomy. The most common inherited form of ID, Fragile X syndrome, results from expansion of a repeat sequence in the Fragile X mental retardation 1 gene which can be detected by PCR. Small rearrangements within genes such as point mutations, substitutions, insertions and deletions, can be detected by DNA sequencing. Recent technological developments in this field, which are enabling analysis on an exome- or genome wide scale, are beginning to contribute significantly to the elucidation of the aetiological basis of ID.

### **Entry Criteria**

#### Assessment of patients with ID and DD

The target population for this guide are those with moderate to severe ID or DD. The literature suggests the criteria outlined on page 8 may be a useful guide to determining whether a child meets these definitions, but we have found clinical acumen must also be used.

Outlined below are some key scenarios which would prompt investigation of ID/DD.

1. Developmental concerns regarding preschool children (under five years)

The developmental concerns may have been identified through history taking from the parents, direct observation of the child and a developmental screening tool such as a schedule of growing skills. Community paediatricians are skilled at assessing the developmental needs of children and work closely with multidisciplinary teams such as physiotherapists, occupational and speech therapists. By undertaking an accurate history/ examination they formulate a view as to how significantly the child is delayed in relation to their chronological age in all developmental domains. They also assess impact on day to day functioning.

2. Children who exhibit a widening gap between functional and chronological age.

All children should be reviewed to assess their rate of developmental progress. If the developmental gap from chronological age widens with time, then this also highlights the need for investigation.

3. Children who exhibit no other clinical features on history taking which could point to the aetiology.

This guide may be useful for those children where there are no clues on history taking or physical examination of an underlying pathology.

4. Older children who are referred with possible ID.

For this group of children, other sources of information particularly from education, will also be valuable in determining severity. There should be an emphasis on how functioning is affected. For example, difficulty understanding and following simple instructions; experiencing great difficulty following the curriculum despite receiving suitable help and intervention<sup>13</sup>. Genetic testing may be considered in this group with moderate difficulties.

#### History taking and examination technique

Particular attention needs to be taken to look out for conditions which might be identified through specific testing and those that are amenable to disease modification therapy for example some inherited metabolic conditions, which are treatable with dietary modification.

#### **History**

Full history of the pregnancy, perinatal period and early development should be noted. A careful family history should be recorded, including siblings, specifically asking for a history of miscarriage or stillbirth. Particular issues that would alter the plan of first and second line investigations include consanguinity and encephalopathy.

#### **Examination**

The growth (WHO charts) including head circumference (UK90 charts) should be both measured and carefully plotted, looking for parameters that are discordant with other measurements, and those outside the normal range *e.g.* microcephaly. The assessment for dysmorphic features should include the face, but also hair, skin, nails, eyes, ears, genitalia, hands, feet, digits and fat distribution. Systemic conditions such as anaemia, that may cause delay in development should be considered, as well as endocrine malfunction particularly hypothyroidism, and abnormality of the heart, lungs and viscerae. Neurological examination should exclude any focal signs.

### First line tests

#### First line genetic testing Array CGH

Array comparative genomic hybridisation (array CGH) should be the first line investigation in all children and adults with unexplained ID/DD. Array CGH testing has replaced G-banded karyotype analysis and targeted fluorescence *in situ* hybridisation (FISH) testing for the majority of ID referrals. The resolution of current array CGH platforms is on average 25-30 times higher compared to standard G-banded karyotype analysis with average genome-wide resolution of latest array platforms of about 200 kilobases (kb). The result of this is that whilst the detection rates of G-banding in combination with targeted FISH analysis for specific microdeletion syndromes ranges from 3-5%, array CGH offers pathogenic abnormality detection rates between 10-15% in ID referrals.

Here we outline current reporting practice regarding first line genetic testing, using protocols and data from our regional genetics laboratory.

In addition to clearly pathogenic abnormalities, in a further 10-15% of cases variants of unknown clinical significance (VOUS) are detected by array CGH and reported. Such VOUS may require further investigations, such as testing of parental samples, depending on the clinical presentation of the proband, referral reasons and the family history. In some cases, while the current state of knowledge is insufficient to determine whether the copy number variant (CNV) is pathogenic, as the literature advances the interpretation may become clearer, allowing the CNV to be redefined as pathogenic or benign.

CNVs detected by array CGH in our diagnostic laboratory are classified into one of five categories that describes their pathogenicity:

#### Box 2 Categories of copy number variants (CNVs)

- 1. Benign variants with high population prevalence.
- 2. Likely benign variants with overlapping CNVs identified in the general population and previously recorded in the laboratories as CNVs inherited from unaffected parents.
- 3. VOUS with population prevalence of < 1 in 1000 individuals and no known association with disease phenotypes.
- 4. Likely pathogenic variants containing dosage sensitive genes and/ or reported in national or international databases in association with overlapping clinical problems.
- Pathogenic variants containing known disease genes and with strong published evidence of pathogenicity in cases with overlapping clinical problems.

Regardless of the genomic size of a CNV, all category 4 and 5 CNVs are reported after confirmation by a second method (such as FISH or quantitative PCR (QF-PCR). Such clinical reports will always include the genomic coordinates of the reported CNV, start and end positions and genes together with a list of OMIM disease genes when appropriate. Most reports will also include a request for parental follow up samples to determine the recurrence risks in the family and recommendation of a referral to clinical genetics when appropriate.

A small proportion (around 1-5%) of category 4 and 5 CNVs will be pathogenic, but incidental to the reason for referral. These incidental findings may include well known recurrent CNVs including for example *PMP22* gene (associated with Charcot-Marie-Tooth disease, type 1A or Hereditary neuropathy with liability to pressure palsies), *STS* gene (associated with X-linked Ichthyosis), *DMD* gene (associated with Duchenne and Becker muscular dystrophies) or very rarely DNA losses including known tumour suppressor genes which would indicate predisposition to certain types of cancer. As most of the incidental findings will be familial, genetic counselling should be considered in all such cases before further family follow up investigations are initiated.

Category 1 and 2 CNVs will not be reported unless they are likely to affect both copies of a gene and as such would result in a complete loss of gene function.

Category 3 CNVs are the most difficult to assess clinically, and it is essential that sufficient clinical information is provided at the time of referral for array CGH.

#### Box 3 Clinical information to provide on referral for array CGH

The clinical information provided should include:

- All main clinical features
- All unusual clinical features
- Brief family history of same or unrelated clinical problems
- Information about siblings when appropriate

The sensitivity of the platform currently used in our regional genetics service is outlined below. The SNP array platforms used will detect:

- All numerical chromosomal abnormalities
- All clinically relevant unbalanced chromosomal rearrangements
- All clinically relevant subtelomeric deletions and duplication syndromes
- All known recurrent microdeletion and duplication syndromes
- All category 3-5 CNVs which are greater than 200 kilobases (kb)

- Most cases of uniparental disomy (UPD) including UPD15 associated with Prader-Willi / Angelman syndromes, maternal and paternal UPD14, maternal UPD7 associated with Silver-Russell syndrome and paternal UPD6 associated with transient neonatal diabetes
- Up to 10% mosaicism for DNA imbalances (losses or gains) greater than 5000 kb

Consequently, many of the genetic diagnoses which in the past have fallen under second or third line specialist referrals/investigations can now be diagnosed as part of the first line testing which could significantly improve the time to diagnosis.

#### **Biochemistry**

There is a paucity of information on the clinical utility and effectiveness of biochemical testing in isolated ID/DD, with recommendations mainly being based on expert opinion<sup>14-20</sup>. There is some consensus between groups; however the guidelines are often misleading as they include children with additional clinical features rather than ID alone. Information on the sensitivity and specificity of the various tests is also lacking.

Inborn errors of metabolism (IEMs) are rare diseases and therefore the yield will inevitably be low, but given their devastating impact, they need to be considered. Poplawski et al.<sup>21</sup>, reporting on urine amino acid and organic acid analysis, found a similar yield for isolated ID/DD(1.0%) and ID/DD with additional features (1.1%), however the clinical details were gleaned from the request cards and may not have been complete. Sempere et al.<sup>22</sup> examined a cohort of 944 patients with unexplained "mental retardation" (age range 5-84 years) and found seven patients (0.8%) with IEMs (three with cerebral creatine deficiency, one with adenylosuccinate lyase deficiency and three with phenylketonuria (PKU)) all of whom had other symptoms such as epilepsy, spastic tetraparesis or deafness. The three adults with PKU all had microcephaly and abnormal brain MRI in addition to psychiatric disturbances. Michelson et al.<sup>23</sup> reported a yield for IEM of up to 5% but included children where there was clinical suspicion of an underlying diagnosis. The Cambridge laboratory (serving Norfolk, Suffolk and Cambridgeshire with a population of 2.4 million) has analysed approximately 8,500 urine organic acids over a ten year period and detected no children with an IEM presenting with ID/DD alone. Similarly, analysis of approximately 5,500 plasma amino acids has identified no cases, but given the ease of sample taking, the potential for detecting markers for broader metabolic conditions e.g. mitochondrial disorders, and potentially devastating impact of the conditions, it was agreed to include plasma amino acids as a first line investigation.

### First line biochemical tests (including haematological investigations)

The first line tests are based on the following assumptions/considerations:

- The child has isolated ID/DD
- The child has undergone newborn screening (including phenylketonuria and congenital hypothyroidism)
- Venepuncture will be undertaken for microarray
- Obtaining a fresh urine sample from a child seen in the community may be difficult

The tests chosen reflect the consensus from the reports cited above together with local expert opinion. They comprise 'broad brush', relatively non-specific screens aimed at detecting a range of conditions and/or clues to an underlying pathology in the first instance.

## Full blood count, calcium, liver function tests (albumin, bilirubin, alkaline phosphatase and alanine transaminase): aimed at detecting underlying systemic illness and/or anaemia.

**Creatine kinase in boys:** boys with Duchenne muscular dystrophy may present with speech delay and delayed motor milestones and/or global delay.

**Plasma amino acids:** these may provide clues as to lactic acidaemia (raised alanine and proline), hyperammonaemia (raised glutamine) and may detect some cases of classical homocystinuria (on the basis of a raised methionine).

#### Other considerations

Children born in the UK should have been tested for congenital hypothyroidism on the newborn blood spot screen. If this result was normal (recommend confirmation from child health record) repeat investigation is not required unless there are clinical signs suggestive of hypothyroidism. However, it is important to exercise more caution with children originating from countries where newborn screening is not in place, particularly with regard to congenital hypothyroidism and phenylketonuria. Other clues such as consanguinity and/or a significant family history should accelerate second line biochemistry testing. This guide is not aimed at children with symptoms and signs suggestive of a metabolic disorders (*e.g.* microcephaly, macrocephaly, hepatosplenomegaly, episodic attacks, regression) who should be referred to specialist teams - see Appendix 1, Table 1.)

### Second line tests

#### Second line genetic investigations

ID/DD may be present in a child with or without additional clinical features and thus the child may be categorised as syndromic or non-syndromic. This classification has been used to aid diagnosis as where there are additional clinical or syndromic features the number of candidate genes that cause the disease is more limited. In an era where the analysis of DNA was cost- and time-limited, this triaging of cases for testing to the more syndromic cases was effective. However with the advent of next generation sequence analysis the availability of panels of >100 genes that can be tested simultaneously is now possible. This means that many genes can be simultaneously interrogated at an affordable cost and the diagnostic yield for cases where ID/DD is present alone should increase significantly as access to tests for individual disease genes implicated in isolated ID has been severely limited to date. The use of whole exome analysis for diagnosis of severe non-syndromic ID/DD has yielded a diagnosis in 30-40%<sup>24, 25</sup> of cases in the research context and with the advent of whole genome sequence analysis within clinical care the likelihood is that diagnostic yields will increase to 40-60%<sup>26.</sup>

#### **Fragile X**

Fragile X syndrome (FXS) is a relatively common inherited form of ID with approximately 1 in 4000 males affected by this condition. The physical features of the syndrome are subtle and may include an increased head size, typically in the >50th centile range, long face with high forehead and large ears. Boys with FXS typically present with moderate to severe delay in development and ID, autistic features, and different types of repetitive behaviour. Girls with confirmed FXS often have more subtle clinical presentation with milder ID, communication problems and social anxiety.

The diagnosis of FXS is typically excluded by PCR using primers flanking the CGG repeat in 5'-UTR region of the *FMR1* gene. This method is used to determine the CGG copy number in normal range (< 50 copies), intermediate range (50-58 copies) and premutation range (59-200). Full mutation and methylation status of the 5'-UTR region is established by a method called southern blotting which is very labour intensive, but highly sensitive.

An audit of Fragile X testing in 2003 from a subset of UK laboratories indicated that up to 180 such tests were performed per million population<sup>27</sup>. When used as an exclusion test, a full mutation is detected in around 1% of Fragile X tests. Occasionally alleles within premutation ranges are identified in the course of the 'exclusion' testing. *FMR1* premutation carriers are mostly asymptomatic, with some reports indicating an increased risk of autism spectrum disorder, attention deficit problems in males or social avoidance in females, *i.e.* this result is unlikely to explain a significant ID. It is of note that all female *FMR1* premutation carriers are at risk of having an offspring with a full mutation and there are also consequences for unaffected relatives who may also carry an *FMR1* premutation. Female *FMR1* premutation carriers also have an increased risk of ovarian failure (POF) before the age of 40. Up to 40% of male and occasionally female carriers of *FMR1* premutation who are older than 50 years of age develop Fragile X-associated tremor/ataxia syndrome (FXTAS).

It is important that all *FMR1* expansions above the normal range are referred to clinical genetics to co-ordinate advice, and predictive testing for all at-risk relatives as well as prenatal testing for full *FMR1* mutations when appropriate.

#### X-associated ID

Since the identification of Fragile X, over 100 further genes have been identified on the X chromosome in which mutation can cause ID. Where there is a significant family history of ID, families should be referred to clinical genetics for further evaluation and genetic testing. In a family with two or more males with intellectual disability the chance that this is due to a familial X linked intellectual disability (XLID) gene is high.

#### **Further genetic investigations**

Where array CGH and Fragile X testing has failed to identify the cause of disease, further evaluation by clinical genetics would be indicated if the child has moderate to profound intellectual disability.

Referral to clinical genetics is therefore indicated if a child has moderate or severe ID/DD when first line investigations have proved negative.

The list below highlights other related circumstances outside the scope of this guide which would warrant referral to clinical genetics:

- Diagnosis: a child with problems such as DD, ID, congenital anomalies (*e.g.* heart defect, deafness) may be referred if there is concern that there may be a genetic basis to the child's condition. If a child has multiple problems, the geneticist may be asked to assess whether there is a unifying genetic diagnosis.
- Issues related to genetic testing: a genetic test *e.g.* array CGH, arranged by a paediatrician has given an abnormal/atypical/unusual result or has diagnosed a genetic disorder. Genetic counselling is recommended for all patients and their families who received an abnormal result by genetic testing. If the result is clearly pathogenic, the natural history of the disease will be explained as well as the patterns of inheritance, the risk of disease in a wider family context, reproductive choices for the parents as well as support and treatment options for the patients themselves. Referral should also be made following detection of incidental findings and some variants of uncertain significances to provide expert counselling of patients.
- A new diagnosis of a genetic disorder in a child.
- Teenager/young adult with a genetic problem that was diagnosed in early childhood may need referral for an explanation about the genetic basis of their disorder, and discussion about their reproductive risks and options for prenatal diagnosis.
- Reproductive advice: parents of a child with a genetic condition, or a condition that may have a genetic cause, wish advice about the likelihood of similar problems recurring in a future pregnancy.

#### **Current research studies**

To improve the practice of clinical genetics and our understanding of genes affecting child development, a national project called Deciphering Developmental Disorders (DDD project) was jointly funded by the Welcome Trust and the UK Department for Health in 2009 and will be completed in 2015. It is a collaborative project between professionals from regional clinical genetics departments throughout the UK and Republic of Ireland, with scientists at the Wellcome Trust Sanger Institute. The aim of the project is to enable genetic diagnosis for thousands of UK families, discover new developmental disease genes, and help establish good practice for implementation of genome-wide testing in clinical practice.

Another national research project designed to enable broader translation of whole genome sequencing into diagnostic practice was recently established by the UK Department of Health. The project is run by Genomics England to supply whole genome sequencing for a number of clinical specialties, including rare developmental disorders. The aim of this project is to drive and facilitate mainstreaming of genome-wide technologies for improved personalised care by creating large population datasets of sequences matched with clinical data.

It is envisaged that the above initiatives and a drive towards wider access to genome-wide testing will lead to significantly improved diagnosis and management of developmental disorders in the next five years. Discussion with clinical genetics colleagues can provide information on current research studies.

#### Second line biochemical tests

Many inborn errors of metabolism (IEMs) have an ID/DD component, but presentation with isolated ID/DD is rare and additional features are usual. A very small number of conditions have been described that occasionally present with isolated ID/DD, including classical homocystinuria (cystathionine betasynthase deficiency)<sup>28</sup>, mucopolysaccharidosis type III (MPS III)<sup>29, 30</sup> and succinic semialdehyde dehydrogenase deficiency. Biotinidase deficiency is mentioned in reviews<sup>15, 20</sup> but there is little evidence in the literature to suggest that this condition presents with ID/DD alone. Mild forms of adenylosuccinate lyase deficiency may present in this way, but this disorder is extremely rare<sup>31</sup> and, as yet, there is no available treatment. Homocystinuria is to be added to the UK newborn blood spot screening panel in 2015, but the proposed methodology may not detect vitamin responsive forms of the condition so this disorder should still be considered even in screen-negative children. MPS III may present between the ages of 1 and 4 years with ID/DD alone, particularly with speech delay, although typically this occurs after an initial period of normal development<sup>29, 30</sup>. Human clinical trials of genistein aglycone are currently in progress, making earlier diagnosis considerably more important<sup>32, 33</sup>.

Cerebral creatine deficiency syndromes should also be considered. Clark *et al.*<sup>34</sup> reported a frequency of the X-linked creatine transporter defect in sporadic cases of male ID of at least 0.8%, whereas Arias *et al.*<sup>35</sup> found a lower value of 0.3%. Although treatment for the transporter defect is currently not available, clinical trials of cyclocreatine are underway<sup>36, 37</sup>. The autosomal recessive creatine synthesis defects (arginine:glycine amidinotransferase and guanidinoacetate methyltransferase deficiencies) are less common, but are more amenable to treatment with creatine supplementation.

There are a number of rare defects in thyroid hormone cell membrane transport and metabolism where the phenotypic spectrum has yet to be delineated<sup>38-40</sup>. It is not clear whether presentation may include isolated ID so, pending more definitive information, assessment of thyroid function (thyroid stimulating hormone (TSH), free thyroxine (fT4)and free triiodothyronine (fT3)) has been included in the second line investigations. These simple tests will identify the majority of these disorders together with central hypothyroidism, which is not detected on newborn screening in the UK. The second line biochemical tests are outlined below.

Plasma / urine creatine and guanidinoacetate\* to detect cerebral creatine deficiency disorders. Urine creatine is a useful marker of the X-linked creatine transporter defect in boys, but requires freshly frozen urine and is prone to false positives<sup>35</sup>. Plasma creatine and guanidinoacetate will detect the synthesis disorders and are more stable, making sample handling easier.

Urine glycosaminoglycans typing: urine glycosaminoglycans (GAG) quantitation provides a screening test only. False positives are common and false negatives may occur, particularly in patients with Morquio disease and less often in MPS III. While GAG typing is a labour-intensive test for the laboratory, it is more reliable and should be considered in children with early normal development, up to the age of approximately 1 year.

<sup>\*</sup> Approximately 1 mL urine is required (in a plain white-topped universal), which should be sent to laboratory as soon as possible after collection (preferably within 1 to 2 hours). This should be frozen as soon as possible and transported on dry ice to the specialist laboratory (*e.g.* Addenbrooke's regional biochemical genetics laboratory). Samples collected under less than ideal conditions can be analysed but may give falsely raised creatine values, necessitating a repeat sample.

Urine organic acids: to detect organic acidaemias, including succinate semialdehyde dehydrogenase deficiency (4-hydroxybutyric aciduria).

**Plasma total homocysteine:** this is a more reliable, sensitive test of disordered homocysteine metabolism than a plasma amino acid profile.

Thyroid functions tests: TSH, fT4 and fT3.

If the second line biochemistry and genetic tests also fail to reach a diagnosis, continue to monitor keeping in mind signs and symptoms of metabolic disorders. If the phenotype evolves with additional features developing, consider other biochemical tests (see Appendix 1,Table 1) and refer to specialist teams as appropriate. The table is not intended to be an exhaustive list of metabolic tests but rather conditions that may develop on a background of ID.

### Neuroradiology as a diagnostic tool

#### **Summary**

Analysis of recent literature indicates that neuroradiological investigations are unlikely to provide a diagnosis in cases of non-syndromic ID/DD where other investigations have failed to find a cause. Studies utilising both magnetic resonance imaging (MRI) and computerised tomography (CT) cite high yields of up to 42%, but this must be interpreted with caution for reasons outlined below. Studies on MRI, where data was available, suggest that the yield is around 0-1.9% in patients with ID alone<sup>41-43</sup>. If other signs or symptoms are present such as microcephaly, abnormal neuroradiological examination, or presence of seizures, diagnostic yield with MRI may increase to around 5-8%<sup>41-43</sup>. Hydrogen magnetic resonance spectroscopy (HMRS) is of limited use as a diagnostic tool in ID/DD. We propose that the decision on whether to undergo neuroradiological investigations should be made after discussion with parents and in particular their understanding of the yield and risks *e.g.* general anaesthesia.

#### **Evidence from the literature**

A literature search was conducted to determine the current use of neuroradiology (MRI, CT and HMRS) in the diagnosis of ID/DD. The specific focus was the use of MRI and CT when the diagnosis is still unknown after patient and family history taking, physical examination and genetic and metabolic testing. Variation in diagnostic yield between studies may reflect:

- Differing definitions of abnormality and different use of technology, which may provide different level of detail on scans, leading to variation in the proportion of cases with abnormalities observed on scan.
- Differences in diagnostic approach prior to neuroradiological examination.
- Differences in attributing the scan to the diagnostic success. Some may
  consider a supportive scan counts towards yield (the phrase 'useful in
  finding aetiology' is used often) whereas others may only have counted it
  as diagnostic yield if the diagnosis could not be made without the scan.

Our review looked at eight studies on MRI and ID over the past 10 years, two studies examining the use of MRI and CT together and a further two studies on HMRS (see Appendix 2 for summary of data and discussion)

### Next steps

This guide outlines the key features in the assessment and diagnosis of intellectual disability, based on currently available tests. Diagnostic technologies and aetiological understanding are continually evolving and referring clinicians should be alert to this along with the needs and wishes of families, when considering a case review.

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## Appendix 1

### Table 1 Key metabolic disorders to be considered in ID/DD plus other features (in addition to first line tests)

Clinical	Refer to	Disorders	Additional Biochemical tests
Prominent expressive		Creatine synthesis and transport defects	Urine & plasma creatine & guanidinoacetate
language delay		Succinic semialdehyde dehydrogenase deficiency	Urine organic acids
Growth failure		Hypothyroidism	TSH, fT4 and fT3, consider reverse T3
		Many IEMs – organic acidaemias and amino acidopathies	Glucose, ammonia, lactate, urine organic acids & orotic acid, acylcarnitines, acid- base
Multisystem involvement	Neurology / metabolic/ endocrine	Mitochondrial disorders	Plasma & CSF lactate, biotinidase, acylcarnitines and organic acids
		Congenital defects in glycosylation	Transferrin glycoforms
Regression	Neurology (urgently)	Lysosomal storage disorders (inc MPS)	White cell enzymes, urine GAG typing
		X-linked adrenoleukodystrophy	Very long chain fatty acids
		Organic acidaemias	Urine organic acids
		Mitochondrial disorders	See above
Epileptic	Neurology	GLUT-1 deficiency	Plasma & CSF glucose
Encephalopathy and / or movement		Biotinidase deficiency	Plasma biotinidase
disorders		Organic acidaemias	Urine organic acids
		Mitochondrial disorders	See above
Pterin defects		Pterin defects	CSF neurotransmitter metabolites
Acute encephalop- Metabolic athy/ ataxia		Amino acidopathies Organic acidaemias Fatty acid disorders	Glucose, ammonia, plasma amino acids, urine organic acids & orotic acid, acylcarnitines
		Urea cycle defects	Note: results may be normal when well
Eye signs	Ophthalmology	Homocystinuria	Plasma total homocysteine
	+/-neurology/ clinical genetics	Lysosomal storage disorders	See above
		Mitochondrial disease	See above Note: tests guided by ophthalmology report
Hepato(sple-	Gastroenterology +/- metabolic	Lysosomal storage disorders (inc MPS)	See above
no)-megaly		Glycogen storage disorders	
		Niomann Pick Type C	Glucose, lactate, urate, lipids, erythrocyte and leukocyte glycogen studies
		Memanin Fick Type C	Oxysterols and fibroblast filipin staining
Dysmorphic features	Clinical genetics +/- metabolic	Lysosomal storage disorders (inc MPS)	See above

### Appendix 2

#### Literature review of neuroradiology as a diagnostic tool in ID/DD

#### Studies on MRI in ID/DD

Eight studies in the past 10 years have looked at either the percentage of abnormalities found in MRI scans or the percentage of individuals in which MRI led to or was useful in finding the cause of ID (Table 1). Decobert et al.<sup>41</sup> compared the percentage of abnormalities found in individuals with ID compared to age matched controls without an intellectual disability and without a history of developmental delay. The percentage of brain abnormalities in this control group was 17% compared to 53% in the children with ID. One study by Unal et al. (2009)<sup>44</sup> looked only at individuals with both a pervasive developmental disorder (PDD), such as autism, Asperger's syndrome or PDD-NOS, and ID and found the percentage of brain abnormalities to be 12.3%; not significantly different from individuals without either PDD and ID in that population. In the rest of the studies, the percentage of abnormalities found on an MRI scan varied from 30-90% 41,42, 43, 45-48 in those with a developmental delay or intellectual disability of unknown origin. In the four studies that looked at whether MRI was useful in finding the cause of ID, three of the studies suggest MRI was of low yield in individuals with ID of an unknown cause with an aetiology found in 5.4%, 8.3% and 5% as a whole <sup>41-43</sup>.

In patients where the only presenting symptom or sign was isolated ID or developmental delay, the aetiological yield fell to 1.9%, 0% and 1% <sup>41, 43, 45.</sup> In the most recent study (Jain *et al.* 2013)<sup>45</sup>,"findings consistent with a specific aetiology" were found in almost 40% of the 73 participants. 48 of the 73 MRI scans were done on an indicated basis (due to seizures, abnormal neurological signs, microcephaly or perinatal asphyxia) and 56.2% of these patients had MRI scans that contributed to their diagnosis. In comparison, of the other 25 participants who received an MRI, only 8% were defined as useful in establishing the cause of their ID. In the study conducted by Verbruggen *et al.*<sup>42</sup>, 80 of the 109 participants had an MRI scan due to indications such as seizures, abnormal neurological examination or a head circumference over 2 standard deviations from the average: it too had a slightly higher aetiological yield than the two other studies <sup>41,43</sup>.

Verbruggen *et al.*<sup>42</sup> also state in their paper that all of the patients who received a diagnosis due to an MRI scan, had an abnormal neurological examination as well as ID, hence MRI scan alone did not identify the aetiology in individuals presenting with solely ID (n=29). In their study of 410 people, Engbers *et al.*<sup>43</sup> found that an abnormal MRI scan was significantly more likely to occur in individuals with pyramidal movement disorders, head circumference 2 standard deviations from normal (either microcephaly or macrocephaly) or epilepsy. Very few participants in this study with isolated ID received a diagnosis (1.9%). Aetiology was established in just 1% of people in the trial using MRI conducted by Decobert *et al.*<sup>41</sup> if they presented with no other signs (an abnormal neurological examination for example). Table 1 MRI studies and the percentage of abnormalities on scans of individuals with ID and the percentage of scans that contributed to finding the cause of the ID

Study	Number of participants	Participants with abnormalities on MRI (%)	Participants where cause was found due to MRI (%)	Patients with no other presenting symptoms and/ or signs where aetiology was established (%)	Notes
Jain <i>et al.</i> (2013) <sup>45</sup>	73	52.73	39.7	n/a	MRI done on indicated basis* in the majority of cases
Engbers <i>et al.</i> (2010) <sup>43</sup>	410	30.0	5.4	1.9%	Unknown ID post genetic and metabolic testing
Verbruggen <i>et al.</i> (2008) <sup>42</sup>	109	86.2	8.3	0%	Majority of scans done on an indicated basis*
Decobert <i>et al.</i> (2005) <sup>41</sup>	100	53.0	5.0	1%	All participants had previously unexplained ID (after genetic testing <i>etc.</i> )
Unal <i>et al.</i> (2009) <sup>44</sup>	81	12.3	n/a	n/a	Only individuals with pervasive developmental disorders and ID in trial
Da Rocha (2006) <sup>46</sup>	146	51.4	n/a	n/a	Aetiology not looked at on scans
Soto-Ares <i>et al.</i> (2003) <sup>47</sup>	30	90.0	n/a	n/a	Percentage of scans useful for aetiology was not evaluated
Tanaka <i>et al.</i> (2003) <sup>49</sup>	124	41.1	n/a	n/a	Aetiology not looked at in relation to use of MRI

\* Indications for performing an MRI include: head circumference 2-3 standard deviations from the mean, seizures and abnormal neurological examination

#### Studies on MRI and CT in ID/DD

There is very little available information on use of CT scans in establishing a definitive diagnosis of ID in the past 10 years. This is probably because MRI has a higher acuity and contains more details than a CT scan, hence in certain studies, they found a greater percentage of abnormalities on an MRI scan compared to a CT scan. Data from recent studies suggests that aetiology may be established from MRI and CT in up to 42.4% of patients. However in some studies it is unclear whether the scans were fundamental or just useful to the diagnostic procedure. The diagnostic yield increases if MRI scans are done on an additional indicated basis: microcephaly or macrocephaly, epilepsy or an abnormal neurological examination for example.

Two studies examined both neuroimaging MRI and CT, while another focused only on CT (Table 2). The percentages of abnormalities found on scans were 55.9% (CT only)<sup>49</sup>, 63.8%<sup>50</sup> and 79.8%<sup>12</sup>. In the two papers where diagnostic yield

from neurological imaging was assessed, it was found to be high (40.3% and 42.4%)<sup>12,50</sup>. However, both papers suggested that neuroradiology contributed to diagnosis, but that the scans may not have been crucial in establishing it. In the study conducted by Jauhari *et al.* <sup>12</sup> all individuals in the trial received a CT scan, an MRI scan or both as well as multiple other investigations (including a full physical examination and a medical history). Pandey *et al.*<sup>50</sup> found that individuals with microcephaly, increased severity of the intellectual disability or other neurological signs and symptoms were more likely to be diagnosed with neuroimaging as a whole.

Table 2 Neuroimaging studies and the percentage of abnormalities of participants with ID/DD and number of scans contributing to or making the basis of aetiological diagnosis\*

\* included children with abnormal neurological signs.

Study	Number of participants	Participants with abnormalities on scan (%)	Participants where aetiology found due to scan (%)	Notes
Jauhari P <i>et al.</i> (2011) <sup>12</sup>	122	79.8	40.3	'aetiological findings 40.3%' 103CT, 42MRI, 31 both
Pandey A <i>et al</i> . (2004) <sup>50</sup>	47	63.8	42.4	'42.4 useful in arriving at aetiology'
Tanaka K <i>et al</i> . (2003) <sup>49</sup>	34	55.9	n/a	CT scan abnormalities

#### Hydrogen magnetic resonance spectroscopy (HMRS) and ID

Two studies looked at HMRS and aetiology of ID. One study<sup>42</sup> found that in 109 patients, aetiology could only be established with one patient using HMRS, and another three using HMRS in conjunction with MRI. The other study found<sup>48</sup> had 48 individuals with varying severities of ID and 23 matched controls. They established that all brain metabolites tested using HMRS were within 'normal' concentration limits in the individuals with ID and there was no statistically significant difference detected using HMRS between the individuals with ID and the controls.

# Appendix 3

All in the group were involved in the production and review of this document, and where stated, with the following sections specifically:

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