BMJ Paediatrics Open

Towards an agreed approach to investigate children with developmental regression

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To cite: Furley K, Hunter M, Gawade G, *et al*. Towards an agreed approach to investigate children with developmental regression. *BMJ Paediatrics Open* 2025;**9**:e003594. doi:10.1136/bmjpo-2025-003594

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjpo-2025-003594).

Received 21 April 2025
Accepted 15 August 2025

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ABSTRACT

Aim Children presenting with developmental regression are inconsistently investigated, leading to unacceptable delays to diagnosis for some children. This study sought global expert opinion to develop an agreed approach to investigate children presenting with developmental regression.

Method A Delphi survey collected clinician participant choice of investigations in response to case scenarios of children presenting with developmental regression and differing presenting features. Participants responded to two surveys, and consensus was achieved at 70% agreement. Results were analysed using descriptive statistics (number of responses and percentage agreement). Fifty participants completed the first-round survey, and 31 completed round two. Forty-eight percent of participants who completed both rounds had over 20 years of experience in caring for children with developmental regression. They represented four different clinician specialties and worked across five countries.

Results For each of the four scenarios, there was agreement to recommend haematological, biochemical and genetic investigations as first investigations. Endocrine, metabolic and neurophysiological investigations reached consensus for scenarios based on presentation differences.

Interpretation Participants agreed on first investigations to recommend for children presenting with developmental regression. This is an important initial step towards an agreed approach to investigate children with developmental regression needed to reduce inconsistencies in current care.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Developmental regression during childhood is concerning and may be an early sign of a serious underlying condition. Currently, there is no agreed approach to investigating children presenting with developmental regression. Consequently, investigation practice is inconsistent, with a risk of over- or under-ordering and delays in receiving important results with consequences for child and family outcomes.

WHAT THIS STUDY ADDS

⇒ Children with developmental regression may present to general paediatricians or sub-specialists. Using the Delphi method, experts from five countries and four specialties reached agreement on first-choice investigations.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Consistency in investigative approach is vital to reduce the diagnostic odyssey that families experience and to tailor interventions to improve child and family outcomes. A consistent approach to first line investigations will assist decision-making about further investigations and advance our understanding of the causal mechanisms for developmental regression.

INTRODUCTION

Developmental regression refers to a loss of established developmental skills in children and may be an early sign of a serious underlying disorder that warrants early identification and diagnostic pursuit. Although there is a lack of an universally agreed definition to operationalise developmental regression, when considered broadly, disorders diagnosed during childhood that may present with developmental regression include developmental epileptic encephalopathies (DEE), neurodegenerative and neurodevelopmental conditions. Children may present at different ages and with varying trajectories of decline and pre loss abilities. The domains of skills lost and the presence of co-occurring features may also differ.[1] Acknowledging the heterogeneity in clinical presentation and variations in access to clinicians and services, children with symptoms of developmental regression may be referred to health professionals across a range of specialties, including psychiatry, neurology, genetics and general or developmental paediatrics. Each clinician may or may not have training or experience in supporting children with developmental regression and may order many or few investigations, resulting in important variations in care. Currently, there are no investigation guidelines for children with developmental

regression. This increases the risk of inconsistencies in care, as well as both delayed diagnosis and requests for tests that are unnecessarily invasive or have low diagnostic yield.[2] Inconsistent investigation may prolong the diagnostic odyssey for these vulnerable children and delay opportunities to intervene with diagnosis-specific care and establish essential child and family support.[3] Diagnostic clarification allows for anticipatory care and optimised holistic management and support for the child and family and may inform future reproductive planning.[4] Parents value diagnostic clarification to enhance their ability to respond to the health, education and disability needs of their children and to help them navigate and anticipate care needs and outcomes.[1]

The DEE can present with developmental regression at different ages and developmental stages and alter neurology and neurodevelopment globally or selectively, depending on the areas of epileptic activity.[5 6] A child diagnosed with a DEE may regain skills with seizure control,[6] be diagnosed with a metabolic disorder that may be amenable to targeted treatment[7] or be found to have gene variants that can be therapeutically targeted.[8] Therapeutic interventions, including initiation of a ketogenic diet, can modify the disease trajectory for children diagnosed with a childhood onset progressive neurological condition, such as glucose transport type 1 deficiency.[9 10] An example of a DEE is Landau Kleffner syndrome (LKS), a rare condition that presents in children who have usually achieved early developmental milestones without delay. Regression of receptive and later expressive language skills typically occurs between 3 and 8 years of age and can be accompanied by cognitive and social regression and symptoms of poor attention and concentration.[11–13]

Neurodegenerative conditions that feature developmental regression and progressive skill loss may be grouped under umbrella terms that share core clinical criteria, such as childhood dementia (CD)[14] or progressive intellectual and neurological deterioration (PIND).[15] CD and PIND conditions are individually rare with underlying metabolic, genetic or mitochondrial causal mechanisms proposed that are degenerative and characterised by the development of abnormal neurological signs. Yet, the collective prevalence of CD is not uncommon, with recent estimates reporting 1:2800 children born with conditions that can lead to CD.[14] Currently, there are only a few treatment options for CD or PIND conditions that alter the disease progression.[16] Therapeutic discoveries are contingent on a greater understanding of the genes and biological processes that underlie developmental regression. Therefore, diagnostic discovery is vital to advance towards translating precision medicine systems that are known to feature developmental regression. Neurodevelopmental conditions may feature developmental regression, and autism spectrum disorder is one of the most studied.[17–25] First described by Kanner in the 1940s,[26] regression was initially described as a distinct subtype of autism; however, recent reports postulate that regression may be a common feature of an autistic phenotype.[27 28] Despite decades of research to search for a biological marker for autistic regression, the results remain inconclusive.[29] It is possible that next generation sequencing (NGS) will advance our understanding with recent reports of regressive autism candidate genes.[30]

Recognising that developmental regression may be an early presentation, before additional and sometimes defining clinical features emerge that suggest a specific diagnosis, an agreement among clinicians on the most appropriate first-choice investigations is important. The objective of this consensus-seeking research is to seek global expert opinion toward an agreed investigative approach.

In this study, we focus specifically on developmental regression, which is distinct from the criteria used to diagnose other conditions including CD or PIND in children. While CD and PIND encompasses a broader range of neurodegenerative conditions characterised by progressive loss of intellectual and neurological functions with at least 3 months of progressive decline,[15] developmental regression refers to the loss of previously acquired developmental skills without necessarily meeting the criteria for CD or PIND at the onset of regression.

Our approach aims to address the diagnostic challenges unique to developmental regression, which may present as an early symptom of various underlying disorders. Unlike CD or PIND, which often includes a wider spectrum of progressive neurological signs, early signs of developmental regression can occur in isolation or with minimal additional neurological findings.

While comprehensive resources exist for broader categories such as developmental delay and intellectual disability, and criteria for conditions like CD or PIND are well-established, there remains a need for a focused and consistent approach to investigate symptoms of developmental regression

METHODS

The Delphi process is an established consensus-seeking method used to solicit expert opinion among clinicians and healthcare providers on priority questions.[31 32] The Delphi method was chosen to reach out to national and international clinicians from a range of specialities.

Patient and public involvement: For the purpose of obtaining expert opinions on clinical investigations, members of the public and patients were not contacted for this Delphi project, and no patients were involved. A future project will focus on engaging families with lived experience of developmental regression.

Using electronic dissemination over two rounds (rounds 1 and 2), we recruited expert clinicians to select first-choice investigations for children presenting with developmental regression. The consensus process was developed in accordance with the standards for quality improvement reporting excellence,[33] and CREDES.[34] The survey was created using Qualtrics XM (*Qualtrics*

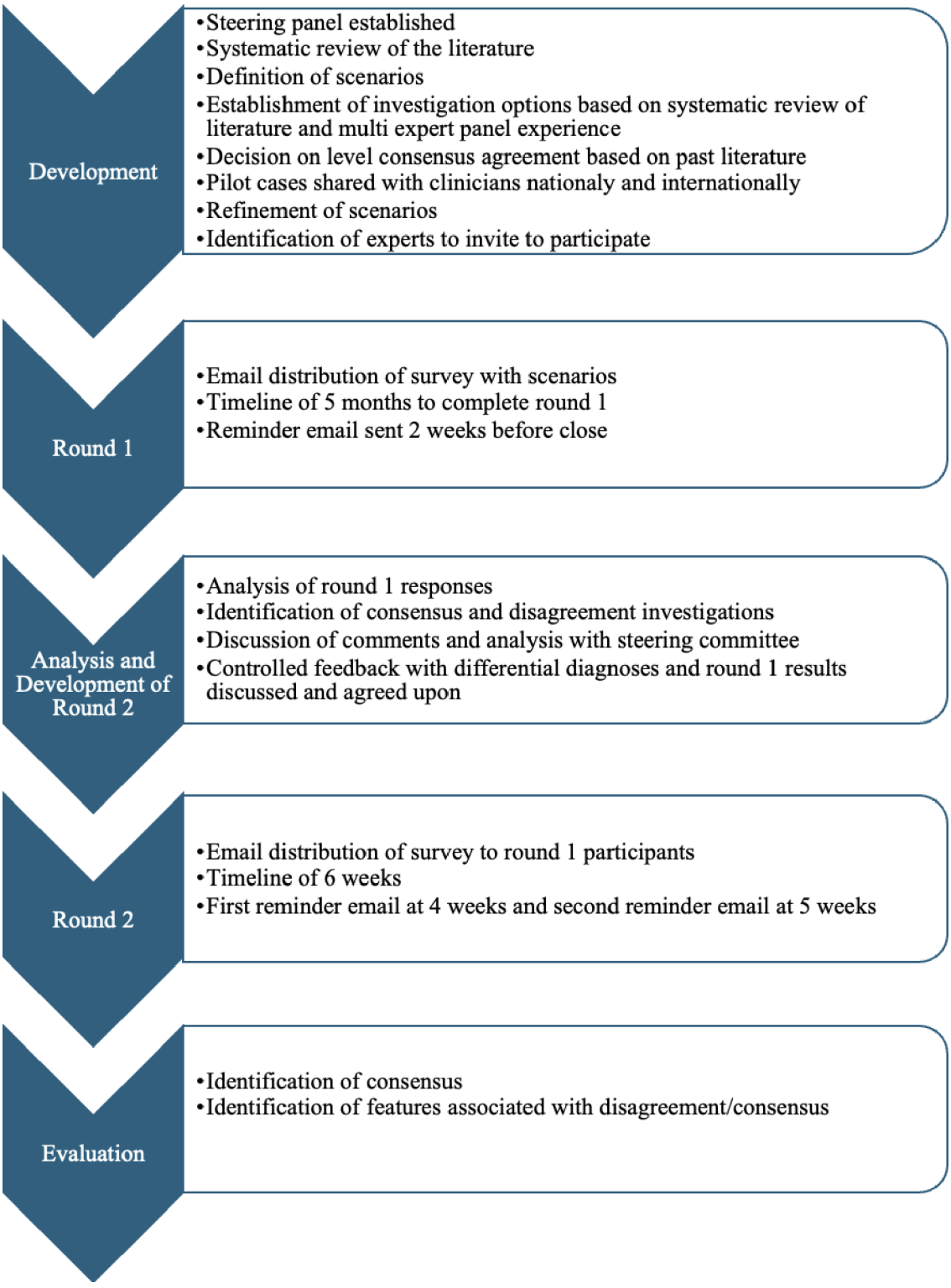

Figure 1 The Delphi process workflow.

XM - Experience Management Software, 2015), and 70% agreement was chosen a priori to represent consensus.[32] Figure 1 reports the Delphi process workflow. This project was approved by Human Research Ethics at Monash University, Melbourne, Australia (project ID 37623).

The rounds 1 and 2 surveys for this study presented information about four hypothetical case scenarios and offered possible investigations to select. The scenarios were developed by a panel of four expert clinicians from neurology, genetics and paediatrics. The panel systematically reviewed the literature for studies reporting investigations and/or diagnostic yield data for children with symptoms of developmental regression without an existing explanatory diagnosis (search strategy for systematic review in online supplemental material). Using this information and clinical expertise, case scenarios were

designed to be undifferentiated with no prior diagnosis nor specific physical examination findings and represent a broad spectrum of clinical presentations. Scenarios were peer-reviewed by national and international colleagues from a range of specialities as a pilot process, with feedback incorporated into the round 1 survey.

Participants were asked to select 'first-choice' tests (ie, the first investigations the clinician would request) from a list of investigation types (haematological; biochemical; endocrine; infective/immune; neurophysiology; neuroimaging; genetic (blood, saliva, other); and metabolic (blood and/or urine)). Participants were asked to assume they had access to any listed investigation and to select any preferred first-choice investigations. Participants could add free-text entries to provide details on selection choices.

Distribution for the round 1 survey commenced on 15 August 2023 through emails to professional contacts, online forums of professional associations (eg, Australasian Society of Developmental and Behavioural Paediatrics, Australian and New Zealand Child Neurology Society, Royal Australasian College of Paediatricians), organisational websites (eg, Asperger/Autism Network, CD initiative) and snowball sampling, whereby participants were encouraged to share the recruitment letter with others they believed may be interested.[35] The round 1 survey was open for five months. Development of round 2 was an iterative process involving controlled feedback to round 1 participants (ie, provision of group responses, summary of key features from case and potential diagnoses). Round 2 was open for 6 weeks. Participants from round 1 received two individualised email reminders before the close of round 2. Percent agreement was measured to assess consensus.[36]

RESULTS

Fifty clinicians completed round 1, and 31 completed both round 1 and round 2 (table 1). Participants who completed both rounds were from five countries and four different specialities. Most were from Australia. Representation from each specialty, apart from psychiatry, continued from rounds 1 to 2. Participant years of expertise across both rounds were similar, with over 70% having more than 10 years' experience and nearly half having more than 20 years.

In round 1, participants reached consensus to recommend biochemical tests for all scenarios and haematological tests for scenarios 2–4 (table 2). Consensus for metabolic tests was reached for scenarios 2 and 3, genetic tests for scenario 1, and endocrine and neurophysiology tests for scenario 2 only.

In round 2, participants reached consensus for genetic tests for genetic, haematology and biochemistry tests for all scenarios. Consensus for metabolic tests was reached for 2–4 and neurophysiology for scenario 2.

There was a change in consensus towards ordering genetic tests for scenarios 2 to 4, haematology tests for scenario 1, and metabolic and endocrine tests for scenario 4. There was also an increase in the proportion of participants who reported they would order neuroimaging in case 4, but not to the level of consensus. There was a change in consensus away from ordering endocrine tests for scenario 2 following controlled feedback.

Table 1 Participant characteristics for rounds one and two

		Round 1 n=50 No. (%)	Round 2 n=31 No. (%)
Specialty	Neurology	13 (26.0)	11 (35.5)
	General paediatrics	13 (26.0)	10 (32.3)
	Developmental paediatrics	17 (34.0)	9 (29.0)
	Genetics	5 (10.0)	1 (3.2)
	Psychiatry	2 (4.0)	0 (0)
Country of practice	Australia	42 (84.0)	24 (77.4)
	New Zealand	2 (4.0)	1 (3.2)
	UK	4 (8.0)	4 (12.9)
	USA	1 (2.0)	1 (3.2)
	Canada	1 (2.0)	1 (3.2)
Years of experience	<5 years	5 (10.0)	3 (9.7)
	5–10 years	9 (18.0)	6 (19.4)
	10–15 years	6 (12.0)	3 (9.7)
	15–20 years	7 (14.0)	4 (12.9)
	More than 20 years	23 (46.0)	15 (48.4)

DISCUSSION

The objective of this study was to reach an agreed first-choice approach to investigate children presenting with developmental regression without accompanying neurological signs, or a clear diagnosis at the time of assessment. Developmental and general paediatricians, neurologists and geneticists from five different countries, and with many years of experience provided expert opinion on their preferred first-choice investigations. They agreed that children should be referred for haematological, biochemical and genetic tests as initial investigations, with agreement just below consensus (69% agreement) to add endocrine testing, which from free text responses was predominantly thyroid-function testing. For the children described in the first three scenarios, the proportion of participants who suggested each investigation was similar or increased between the first and second rounds of the survey, likely in response to information provided about potential diagnoses in the latter round (autistic regression, LKS and MPS, respectively). There was a more marked increase in investigation choice between the first and second round for the older child described in scenario 4, with declining school performance and withdrawal as presenting symptoms. For scenario 4, more participants agreed to investigate in round 2 following

Table 2 Case summaries and participant agreement on choice of requested investigations

	Scenarios							
	Child 1		**Child 2**		**Child 3**		**Child 4**	
Age at onset of regression	18 months old		5 year 10 months old		2 year 8 months old		9 year 10 months old	
Developmental domains impacted	Language (expressive), social (interest in social interaction)		Language (receptive), school performance		Language (expressive), functional (velcro shoes on/off)		School performance	
Co-occurring features	Repetitive and restrictive behaviours, and sensory sensitivities		Increasingly poor attention and concentration		Sleep and behavioural deterioration		Increasingly poor attention and concentration	
Potential diagnosis provided in round 2	Autistic regression		Landau Kleffner syndrome		Mucopolysaccharidoses type III		X- linked adrenoleukodystrophy	
Investigation type	Round 1	Round 2	Round 1	Round 2	Round 1	Round 2	Round 1	Round 2
One or more tests no. (%)	24 (85.6)	29 (100.0)	28 (100.0)	29 (100.0)	29 (96.7)	30 (96.7)	17 (56.7)	31 (100.0)*
Genetic no. (%)	23 (82.1)	26 (89.7)	19 (67.9)	22 (75.9)*	18 (62.1)	29 (96.7)*	4 (23.5)	24 (77.4)*
Biochemistry no. (%)	20 (71.4)	22 (75.9)	25 (89.3)	26 (89.7)	26 (89.7)	28 (93.3)	17 (100.0)	31 (96.8)
Haematology no. (%)	19 (67.9)	22 (75.9)*	21 (75.0)	23 (79.3)	25 (86.2)	29 (96.7)	15 (88.2)	29 (93.5)
Metabolic no. (%)	17 (60.7)	18 (62.1)	21 (75.0)	26 (89.7)	27 (93.1)	30 (100.0)	6 (35.3)	31 (100.0)*
Endocrine no. (%)	15 (53.6)	17 (58.6)	20 (71.4)	20 (69.0)	19 (65.5)	19 (63.3)	11 (64.7)	25 (83.3)*
Neurophysiology no. (%)	11 (39.3)	9 (31.0)	24 (85.7)	26 (89.7)	12 (41.4)	8 (26.7)	4 (23.5)	10 (32.2)
Imaging no. (%)	6 (21.4)	4 (13.8)	19 (67.9)	19 (65.5)	20 (69.0)	20 (66.7)	7 (41.2)	19 (61.3)
Infective/immune no. (%)	3 (0.7)	1 (3.4)	10 (35.7)	6 (20.7)	8 (27.6)	1 (3.3)	5 (29.4)	6 (19.4)

Green= >70%–100% agreement = consensus reached; orange= 50–<70% agreement; red= <50% agreement.
*Change to consensus over rounds.

feedback of a potential diagnosis of X-linked adrenoleukodystrophy (X-ALD). Additional first-choice investigation choices were selected in response to key features of the presented scenarios. These included electroencephalograms (EEG) for the child with suspected LKS, metabolic investigations for the children presented in scenarios 2 to 4 with MPS III, LKS and X-ALD and endocrine investigations (adrenal function) for the child with X-ALD.

There are no existing guidelines or consensus on investigations specific for children with developmental regression, hence the crucial rationale for this study. To consider whether the investigations reported in our Delphi survey aligned with current practice for children with neurodevelopmental conditions including global developmental delay (GDD), developmental delay (DD), intellectual disability (ID) or learning difficulties (LD, which, for some, is a preferred synonym for ID), we searched for national and international past and current guidelines. Our reasoning was that implementation to clinical practice will require recognition of similarities and differences to existing recommendations for children with neurodevelopmental presentations. Publications presented in online supplemental Table(i) in the supplementary material are position statements, guidelines, or recommended practice papers over the last 10 years from 2013 to 2023 that reference investigations to recommend. As shown in online supplemental Table(i), most publications made specific recommendations if risk factors were identified. For example, if a child was eating poorly, investigating for vitamin B12 deficiency was recommended,[37 38] or if a child was at risk of lead exposure, lead was an additional recommended investigation.[39] Bone profile bloods were recommended in one publication,[40] to look for reduced total resorption of phosphate associated with mitochondrial disorders, and calcium was recommended in one publication.[41] Recommendations varied depending on whether newborn screening had been performed.[42] Recommendations for neuroimaging depended on whether children had abnormal neurological signs or symptoms[43] or features suggestive of seizures or abnormal head size.[40] In one

publication, neurophysiology was recommended when risk factors, including regression or episodic symptoms, were identified.[43]

Developmental regression may be a symptom of a metabolic disorder. Most publications recommend metabolic testing to investigate children with GDD, ID or LD; however, there are different specific recommendations for first-choice metabolic tests (online supplemental Tablei). Urine metabolic screening, including glycosaminoglycans (GAGs) and organic acids (OA), was the most often recommended urine tests. Metabolic blood/plasma tests were more varied, with amino acids (AA) recommended by most publications and other specific tests recommended less frequently (online supplemental Tablei). NGS can identify metabolic conditions and is becoming an increasingly important diagnostic tool for children with undifferentiated symptoms.[44] Metabolic conditions, with a known genetic aetiology in coding and established non-coding regions, can be diagnosed using NGS. However, NGS gene panels, exome sequencing and genome sequencing may miss variants including mitochondrial variants, non-coding variants, complex structural variants, short tandem repeats and epigenetic variants involving metabolic genes. Survey participants agreed to refer all the children for metabolic investigations except for the toddler with regression of skills and a potential diagnosis of autism, hereby described as autistic regression. Recent reports draw causal relationships between autism and inborn errors of metabolism and mitochondrial function, especially for autistic children who regress.[45] Furthermore, there are overlapping clinical features between autistic children who regress in speech and social abilities and children diagnosed with Mucopolysaccharidoses type III.[46]

All current guidance recommends chromosomal microarray (CMA) as a first-choice genetic test, with or without Fragile X, based on clinical or family risk.[39 47] Other guidelines recommend early consideration of NGS as first or second choice.[48] Information about the diagnostic yield of NGS for developmental regression is emerging, with recent reports of moderate diagnostic yields, up to 51%,[49] with similar diagnostic yields for children who experience developmental regression with and without a pre-existing ID or autism diagnosis. Survey participants agreed that all children should be referred for genetic/genomic testing, in line with recommendations for children with DD, GDD and ID as shown in online supplemental Table (i).

Only one publication listed in online supplemental Table (i) recommended EEG as a first-choice investigation for symptoms that are episodic or regressive. EEG investigations for children with GDD and ID may be included in recommendations as second tier[50 51] or not recommended based on low diagnostic yields.[52] Scenario 2 in our survey described a 5-year and 10-month old boy who regressed in receptive language abilities with deteriorating focus and attention is a well-recognised presentation of LKS. EEG investigations may be suggestive for DEE; however, for other conditions, the clinical usefulness is less certain. For children with regression and later diagnoses of autism, there are mixed reports about the significance of EEG findings, with some studies reporting an increase in paroxysmal abnormalities,[52 53] and other studies reporting no associations.[54 55]

Table 3 synthesises the information from this Delphi survey, expert opinion and recommendations for children with ID, GDD and LD to propose first-choice investigations for children presenting with symptoms of developmental regression (without neurological symptoms). Access to country-specific newborn screening and investigation availability will further inform and refine decisions about first-choice investigations. As shown, first-choice tests include haematological, biochemical and metabolic (urine metabolic screening including glycosaminoglycans, organic acids and plasma amino acids). Ammonia and lactate are added to proposed recommendations (table 3) to identify urea cycle disorders and other inborn errors of metabolism that may feature developmental regression. Additional tests may be requested as first choice if clinical features suggest a specific condition which may become more apparent over time. Brain MRI should be considered for developmental regression when there are additional risks such as abnormal head size, seizures or neurological signs, and EEG should be recommended when DEE or seizures are suspected.

LIMITATIONS

Despite multiple attempts to individually invite participants from round 1 to complete round 2, only 62% completed the final round. Results need to be considered in the context of relatively small numbers. Nonetheless, the high level of experience among participant experts adds validity to results.[31] Despite attempting to gain global perspectives, participants were predominantly from Australia, though proportionately less so in round two. Recognising that resource equity and access to certain investigations may be limited in some countries is important.[56] This is especially relevant when recommending NGS that may be inaccessible in some settings.[57] Future research is needed to evaluate the health economics of investigating children with developmental regression in relation to diagnostic and management outcomes.

Participants were invited to add free text comments to describe specific tests within each investigation category; however, as this was optional very few participants added free text comments. Such information is especially important for metabolic investigations given the inconsistency of included tests within current guidelines for children with ID, GDD and LD. Future research is needed to gain further detail on the specific investigations within each investigation type and the rationale for each test based on diagnostic yield, or screening for associated conditions and complications.

These four scenarios illustrate conditions known to feature developmental regression. There are other

Table 3 Proposed first-choice investigations

Investigation type	Specific first-choice investigations to consider
Haematology	► Complete blood count ► Blood film
Biochemistry	► Electrolytes ► Glucose ► Urea ► Creatinine ► Renal function ► Liver function ► Creatine kinase ► Vitamin D3 ► Calcium (bone profile if risks) ► Active vitamin B12 ► Ferritin/iron studies ► Lead (if risk factors)
Genetic	► Chromosomal microarray ► Fragile X (if risk factors) ► Targeted gene panels when specific condition suspected ► Whole exome sequencing (when available) ► Whole genome sequencing (when available)
Endocrine *	► Thyroid function† ► Consider adrenal function if suspect ALD
Metabolic*	Urine ► Metabolic screen ► Organic acids ► Glycosaminoglycans Plasma ► Amino acids ► Ammonia ► Lactate
Sleep deprived/ routine EEG*	► When DEE suspected/seizures
MRI-brain*	► When abnormal neurological exam, abnormal head size or seizures

*Optional for autistic regression depending on additional features.
†Especially if newborn screening not completed (eg, not included on newborn screening or not accessible).
ALD, adrenoleukodystrophy; DEE, developmental epileptic encephalopathy; EEG, electroencephalograms.

conditions that have similar yet different clinical characteristics. The Delphi survey scenarios were intentionally presented without neurological examination findings, which may trigger specific investigation pathways. Consequently, making recommendations on an agreed investigative approach for children with developmental regression with neurological examination findings is beyond the scope of this Delphi survey. Furthermore, whether children with an ID/GDD/LD and developmental regression and children with developmental regression from a background of typical development should be recommended the same first-choice investigations requires further scrutiny as none of the cases described in this Delphi had moderate or severe ID/GDD or LD.

SUMMARY OF MAJOR FINDINGS

An agreed initial investigative approach for children presenting with symptoms of developmental regression without neurological signs is proposed and includes haematological, biochemical and genetic testing with a low threshold to add thyroid function testing. Based on these Delphi results and literature review, we propose first-choice investigations as shown in table 3. We recommend NGS as first choice where possible, or second choice after non-diagnostic CMA and Fragile X (if clinically indicated). These proposed first choice investigations for children presenting with undifferentiated developmental regression allow for consistency in clinical approach.

Reaching an agreed investigative approach is an important first step towards future guidelines development. This must occur in parallel with an agreed method to measure and define developmental regression to ensure consistency in identifying and investigating developmental regression, which is essential to improve child and family outcomes.

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Contributors All authors have been involved in the editing of versions and conception of study. KF, KW, MH, GG and MF with support from MA, RGK and CM designed the scenarios. KF led first and revised drafts of manuscript with review by all authors including revised submission. KF is responsible for the overall content (as guarantor).

Funding KF received a Ph.D. stipend from Monash University and from Monash Health, Australia. There are no grant numbers for these stipend scholarships. This research formed part of KF's thesis programme of work.

Competing interests No, there are no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication No patients were involved in this study. For the purposes of gaining expert opinion on clinical investigations, members of the public and patients were not contacted for this Delphi project. A future project will focus on reaching families with lived experience.

Ethics approval This study involved human participants and was approved by the Human Research Ethics at Monash University, Melbourne, Australia (project ID 37623). Participants were invited expert clinicians (not patient or public involvement). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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REFERENCES

1 Furley K, Mehra C, Goin-Kochel RP, *et al*. Developmental regression in children: Current and future directions. *Cortex* 2023;169:5–17.
2 Zurynski Y, Deverell M, Dalkeith T, *et al*. Australian children living with rare diseases: experiences of diagnosis and perceived consequences of diagnostic delays. *Orphanet J Rare Dis* 2017;12:68.
3 Pavisich K, Jones H, Baynam G. The diagnostic odyssey for children living with a rare disease – Caregiver and patient perspectives: A narrative review with recommendations. *Rare* 2024;2:100022.
4 Parikh S, Goldstein A, Karaa A, *et al*. Patient care standards for primary mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genet Med* 2017;19:1380–97.
5 Specchio N, Wirrell EC, Scheffer IE, *et al*. International League Against Epilepsy classification and definition of epilepsy syndromes with onset in childhood: Position paper by the ILAE Task Force on Nosology and Definitions. *Epilepsia* 2022;63:1398–442.
6 Scheffer IE, Liao J. Deciphering the concepts behind “Epileptic encephalopathy” and “Developmental and epileptic encephalopathy”. *Eur J Paediatr Neurol* 2020;24:11–4.
7 Stenshorne I, Syvertsen M, Ramm-Pettersen A, *et al*. Monogenic developmental and epileptic encephalopathies of infancy and childhood, a population cohort from Norway. *Front Pediatr* 2022;10:965282.
8 Soto D, Olivella M, Grau C, *et al*. L-Serine dietary supplementation is associated with clinical improvement of loss-of-function *GRIN2B*-related pediatric encephalopathy. *Sci Signal* 2019;12:586.
9 Aaltio J, Etula A, Ojanen S, *et al*. Genetic etiology of progressive pediatric neurological disorders. *Pediatr Res* 2024;95:102–11.
10 Warmerdam HAG, Termeulen-Ferreira EA, Tseng LA, *et al*. A Scoping Review of Inborn Errors of Metabolism Causing Progressive Intellectual and Neurologic Deterioration (PIND). *Front Neurol* 2019;10:1369:1369:.
11 Muzio MR, Cascella M, Khalili YA. Landau-kleffner syndrome. In: *StatPearls*. 2024.
12 Almeida G. Landau-Kleffner syndrome: A systematic review and two illustrative cases. *Revista Chilena de Neurocirugía: Órgano Oficial de La Sociedad de Neurocirugía de Chile* 2021;47:67.
13 Tharpe AM, Olson BJ. Landau-Kleffner syndrome: acquired epileptic aphasia in children. *J Am Acad Audiol* 1994;5:146–50.
14 Djafar JV, Johnson AM, Elvidge KL, *et al*. Childhood Dementia: A Collective Clinical Approach to Advance Therapeutic Development and Care. *Pediatr Neurol* 2023;139:76–85.
15 Verity C, Baker E, Maunder P, *et al*. Differential diagnosis of progressive intellectual and neurological deterioration in children. *Dev Med Child Neurol* 2021;63:287–94.
16 Schulz A, Specchio N, de Los Reyes E, *et al*. Safety and efficacy of cerliponase alfa in children with neuronal ceroid lipofuscinosis type 2 (CLN2 disease): an open-label extension study. *Lancet Neurol* 2024;23:60–70.
17 Parr JR, Le Couteur A, Baird G, *et al*. Early developmental regression in autism spectrum disorder: evidence from an international multiplex sample. *J Autism Dev Disord* 2011;41:332–40.
18 Thompson L, Gillberg C, Landberg S, *et al*. Autism With and Without Regression: A Two-Year Prospective Longitudinal Study in Two Population-Derived Swedish Cohorts. *J Autism Dev Disord* 2019;49:2281–90.
19 Rogers. Developmental regression in ASD. *Medical Research and Dev Dis* 2004.
20 Thurm A, Manwaring SS, Luckenbaugh DA, *et al*. Patterns of skill attainment and loss in young children with autism. *Dev Psychopathol* 2014;26:203–14.
21 Lord C, Shulman C, DiLavore P. Regression and word loss in autistic spectrum disorders. *J Child Psychol Psychiatry* 2004;45:936–55.
22 Werner EB. *Regression in the early developmental course of autism spectrum disorders: validation of the phenomenon using parent report and home video tapes* [Dissertation Abstracts International: Section B: The Sciences and Engineering]. 2003.3946.
23 Kumar S, Karmakar P, Mohanan A. Language regression in children with Autism Spectrum Disorders. *Int J Pediatr Otorhinolaryngol* 2014;78:334–8.
24 Luyster R, Richler J, Risi S, *et al*. Early regression in social communication in autism spectrum disorders: a CPEA Study. *Dev Neuropsychol* 2005;27:311–36.
25 Boterberg S, Van Coster R, Roeyers H. Characteristics, Early Development and Outcome of Parent-Reported Regression in Autism Spectrum Disorder. *J Autism Dev Disord* 2019;49:4603–25.
26 Kanner L. Autistic disturbances of affective contact. *Nerv Child* 1943;2:217–50.
27 Lainhart JE, Ozonoff S, Coon H, *et al*. Autism, regression, and the broader autism phenotype. *Am J Med Genet* 2002;113:231–7.
28 Iosif O. Changing conceptualisations of Regression: What prospective studies reveal about the onset of ASD. *Neurosci Biobehav Rev* 2019.
29 Jensen AR, Lane AL, Werner BA, *et al*. Modern Biomarkers for Autism Spectrum Disorder: Future Directions. *Mol Diagn Ther* 2022;26:483–95.
30 Yin J, Chun C-A, Zavadenko NN, *et al*. Next Generation Sequencing of 134 Children with Autism Spectrum Disorder and Regression. *Genes (Basel)* 2020;11:853.
31 Shang Z. Use of Delphi in health sciences research: A narrative review. *Medicine (Baltimore)* 2023;102:e32829.
32 Nasa P, Jain R, Juneja D. Delphi methodology in healthcare research: How to decide its appropriateness. *World J Methodol* 2021;11:116–29.
33 Ogrinc G, Davies L, Goodman D, *et al*. SQUIRE 2.0 (Standards for QUality Improvement Reporting Excellence): revised publication guidelines from a detailed consensus process. *BMJ Qual Saf* 2016;25:986–92.
34 Jünger S, Payne SA, Brine J, *et al*. Guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care: Recommendations based on a methodological systematic review. *Palliat Med* 2017;31:684–706.
35 Albarqouni L, Hoffmann T, Straus S, *et al*. Core Competencies in Evidence-Based Practice for Health Professionals: Consensus Statement Based on a Systematic Review and Delphi Survey. *JAMA Netw Open* 2018;1:e180281.
36 Sumsion T. The Delphi Technique: An Adaptive Research Tool. *British Journal of Occupational Therapy* 1998;61:153–6.
37 Silove N, Collins F, Ellaway C. Update on the investigation of children with delayed development. *J Paediatr Child Health* 2013;49:519–25.
38 van Karnebeek CD, Stockler-Ipsiroglu S. Early identification of treatable inborn errors of metabolism in children with intellectual disability: The Treatable Intellectual Disability Endeavor protocol in British Columbia. *Paediatr Child Health* 2014;19:469–71.
39 Mithyantha R, Kneen R, McCann E, *et al*. Current evidence-based recommendations on investigating children with global developmental delay. *Arch Dis Child* 2017;102:1071–6.
40 O’Byrne JJ, Lynch SA, Treacy EP, *et al*. Unexplained developmental delay/learning disability: guidelines for best practice protocol for first line assessment and genetic/metabolic/radiological investigations. *Ir J Med Sci* 2016;185:241–8.
41 Midlands N. Fifteen minute consultation: Approach to a school age child with suspected learning disability. *Arch Dis Child Educ Pract Ed* 2024;109:13–8.
42 Merino Elia A, Coghill J. A practical guide to assessing and investigating developmental delay. *Paediatr Child Health (Oxford)* 2021;31:335–9.

43 Shapiro KA. Assessment of learning difficulty and cogntive delay. *BMJ Best Practice* 2023.
44 Kubaski F, de Oliveira Poswar F, Michelin-Tirelli K, *et al*. Diagnosis of Mucopolysaccharidoses. *Diagnostics (Basel)* 2020;10:172.
45 Frye RE, Cakir J, Rose S, *et al*. Early life metal exposure dysregulates cellular bioenergetics in children with regressive autism spectrum disorder. *Transl Psychiatry* 2020;10:223.
46 Heon-Roberts R, Nguyen ALA, Pshezhetsky AV. Molecular Bases of Neurodegeneration and Cognitive Decline, the Major Burden of Sanfilippo Disease. *J Clin Med* 2020;9:344.
47 Carter MT, Srour M, Au P-YB, *et al*. Genetic and metabolic investigations for neurodevelopmental disorders: position statement of the Canadian College of Medical Geneticists (CCMG). *J Med Genet* 2023;60:523:523–32:.
48 Manickam K, McClain MR, Demmer LA, *et al*. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 2021;23:2029–37.
49 Furley K, Hunter MF, Fahey M, *et al*. Diagnostic findings and yield of investigations for children with developmental regression. *Am J Med Genet A* 2024;194:e63607.
50 Stacey A, Bélanger J. Mental health and developmental disabilities committee, evaluation of the child with global developmental delay and intellectual disability. *Paediatr Child Health* 2018;23:403–10.
51 Moeschler JB, Shevell M, Committee on Genetics. Comprehensive evaluation of the child with intellectual disability or global developmental delays. *Pediatrics* 2014;134:e903–18.
52 Tuchman RF, Rapin I. Regression in pervasive developmental disorders: seizures and epileptiform electroencephalogram correlates. *Pediatrics* 1997;99:560–6.
53 Oslejsková H, Dusek L, Makovská Z, *et al*. Complicated relationship between autism with regression and epilepsy. *Neuro Endocrinol Lett* 2008;29:558–70.
54 Canitano R, Luchetti A, Zappella M. Epilepsy, electroencephalographic abnormalities, and regression in children with autism. *J Child Neurol* 2005;20:27–31.
55 Baird G, Robinson RO, Boyd S, *et al*. Sleep electroencephalograms in young children with autism with and without regression. *Dev Med Child Neurol* 2006;48:604–8.
56 Veugelers R, Gaakeer MI, Patka P, *et al*. Improving design choices in Delphi studies in medicine: the case of an exemplary physician multi-round panel study with 100% response. *BMC Med Res Methodol* 2020;20:156.
57 Jenkins SM, Palmquist R, Shayota BJ, *et al*. Breaking barriers: fostering equitable access to pediatric genomics through innovative care models and technologies. *Pediatr Res* 2025;97:1261–8.