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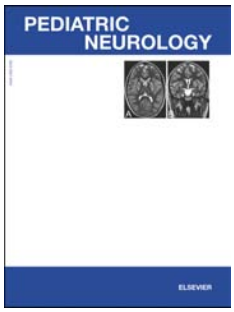

A Refined Approach to Evaluating Global Developmental Delay for the International Medical Community

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Title Page

A Refined Approach to Evaluating Global Developmental Delay for the International Medical Community

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INTRODUCTION

Developmental disabilities are a growing cause of morbidity in the modern world. This has become a diagnostic and therapeutic challenge especially in the context of cost-containment brought about by recent socioeconomic crises.[1, 2] Isolated developmental delays (motor, speech) pose a specific diagnostic challenge but their management is more contained than that of global developmental delay. Global developmental delay is generally defined as significant delay in two or more domains of development[3] (where "significant" is defined as two or more standard deviations below the mean reference norms for age), and usually confined to children up to the age of 5. This very definition brings forth many caveats, from the misunderstanding of its implications (as a continuum of "delay" rather than a disability, or the variability of the blanket term "global")[4, 5] to its allocation as a diagnosis rather than the manifestation of an underlying etiology.

Several studies have sought to define the causes that bring about global developmental delay. Although etiologic diagnosis many times remains a mystery (anywhere from 20% to 62% undetermined in the literature),[6, 7] identified etiologies have been grouped into several main causes[8](table 1). The identification of the etiology of global developmental delay is a time and resource-intensive process that has gained attention in the current economic climate. Disorganized and "shotgun" approaches to diagnosis have been discouraged[9] in favor of structured diagnostic algorithms proposed by scholars and major academic associations in the English-speaking world.[3, 10-12] These have largely homogenized the approach from a level of etiologic suspicion as incited by a full history and physical and leading down pathways of neuroimaging, metabolic or genetic testing (figure 1). Indices of suspicion, alongside the existence of newborn screens (that rule out many major and/or treatable causes) have been acknowledged in every step of the proposed flow charts; however, it is common that the end point always requires advanced testing.

Several studies recognize the history and physical exam as the most important elements in the diagnostic process in global developmental delay,[13-15] with others identifying checklists and focused approaches that enhance the diagnostic yield of tests for specific etiologies commonly associated to global developmental delay.[16-18] There is growing support for a conservative, observative and empirical approach to the evaluation, focusing more directly on the treatment of the delays themselves rather than the underlying etiologies in light of cost- and time-effectiveness; however, this approach remains under dispute.[19, 20] In order to address this controversy, we reviewed the existing literature, via electronic resources (such as the PubMed database) on the topic of global developmental delay to identify its most common etiologies and the current diagnostic approach and management outcomes. We therein offer a targeted, empirical approach in the context of a likely etiology which may not be readily evident in a first clinical visit. Five major etiologic groups were selected for review on the basis of existing literature to encompass the most common causes of undetermined global developmental delay (table 2).[6, 7, 13, 14, 21-26] Major and commonly preventable causes readily detected by a standardized newborn metabolic screen were not included, but should be considered in settings where such screens

are unavailable. Critical appraisal of literature for the diagnostic process and therapeutic management for each cause was conducted.

COMMON ETIOLOGIES OF GLOBAL DEVELOPMENTAL DELAY

Perinatal asphyxia

Asphyxia neonatorum is the result of a constellation of intrauterine and perinatal events that preclude the fetal brain from obtaining adequate blood (and therefore oxygen) flow. The events that characterize the cerebral response and lead to neonatal encephalopathy or hypoxic-ischemic encephalopathy are best described elsewhere.[27-29] Asphyxia neonatorum and hypoxic ischemic encephalopathy/neonatal encephalopathy represent up to 55% of the diagnostic yield in the literature for the diagnosed causes of global developmental delay.

The degree of resulting hypoxic ischemic encephalopathy/neonatal encephalopathy relates to the risk of significant neurodevelopmental comorbidities.[30, 31] While asphyxia neonatorum and subsequent hypoxic ischemic encephalopathy/neonatal encephalopathy do not have a pathognomonic clinical presentation, survivorship is usually preceded by an extensive course of care in the neonatal intensive care unit. Improving peripartum care has increased said survivorship, and in spite of the significant benefits of established interventions such as therapeutic cooling,[32-34] hypoxic ischemic encephalopathy still presents significant risk for developmental disability.[35, 36] Therefore, thoroughly investigating the perinatal and neonatal history could yield possible hallmarks such as non-reassuring fetal tracings while in utero/intrapartum, low APGAR scores at 5 and 10 minutes and cord blood gases demonstrating significant metabolic acidosis or base deficit.[27, 37-39] Such items contribute to an abnormal perinatal history which has been identified as a marker enhancing etiologic yield by Srour et al.[7] In the absence of suggestive events in the pre- and perinatal history, management should include ongoing multidisciplinary assessment of the persistent delays and may not require additional testing, unless an indication develops (i.e., seizures) for which a focused assessment is necessary.

Toxin exposure

Maternal substance abuse has been identified as a cause for global developmental delay with up to 21% of the diagnostic yield. Studies most frequently indicate alcohol/ethanol as the culprit, which has been thoroughly studied and described as specific phenotypes across the spectrum of the diagnosis (Fetal Alcohol Spectrum Disorder and its subsets-Complete/Partial Fetal Alcohol Syndrome, Alcohol Related Neurodevelopmental Disorders, Alcohol Related Birth Defects).[40, 41]

A significant past medical history[15, 24], notable for maternal substance abuse should prompt diagnostic suspicion. However, in many cases historical events may be difficult to elucidate, whether because these children have been removed from parental care,[42] or because of maternal underreporting due to fear or guilt.[43] Withdrawal is rare and a significant neonatal intensive care unit course may not be documented.

Some authors have advocated for diagnostic criteria even without a significant history, reliant on the physical exam and/or traits for early diagnosis[40-42] based on the specific, common features of fetal alcohol spectrum disorder. However, studies demonstrate conflicting evidence over the yield of the physical exam/dysmorphism in global developmental delay,[13, 15, 24, 44] and specific diagnosis in fetal alcohol spectrum disorder may be difficult to determine at an early age. Novel detection mechanisms, such as 3D laser are not widely available; and while specific prenatal/neonatal screening techniques (such as immunoassay for Ethyl Glucuronide and/or prenatal ultrasound parameters) are in development, existing biomarkers are time and labor intensive.[45]

Diagnosis for other common substances, however, is not clearly accompanied by a typical phenotype. In the case of cocaine, some authors have suggested features of a "fetal cocaine syndrome" that have been questioned.[46] Although specific findings have been described in the literature (stroke, cognitive impairment, etc.) studies remain conflicting in regards to global developmental delay.[47, 48] No less complicated is the study of outcomes in heroin/opioid exposure, given the substantial factors present- i.e. psychosocial factors (described below)- that confound the causal relationship. Therefore, in the context of suspicion provoked by history and/or physical exam findings, referral for early intervention, and reevaluation of an evolving phenotype may allow prevention of secondary disability and/or directed diagnostic assessment for comorbidities.

Cerebral dysgenesis

Cerebral dysgenesis refers to a group of malformations of the neuronal tissue during the various stages of embryonic and fetal brain development (segmentation, cleavage, cell proliferation, migration and differentiation). These malformations represent as much as 28% of the diagnosed causes of global developmental delay and in nature, propose a wide range of presentations (variable, overt and subtle), associated findings, clinical significance and etiology (isolated vs. syndromic). Dysgenesis poses a particular diagnostic challenge in the clinical context when present in isolation (i.e., without identifiable clinical signs) and without a significant history. However, several findings may offer clues to amount to the suspicion and improve the diagnostic yield. A study by Pandey et al[49] in a small cohort suggested the presentation of delay with neurologic features associated with a higher incidence of findings both on CT and MRI (notably atrophy, morphologic abnormalities such as polymicrogyria or holoprosencephaly, and white matter disorders) This study and others [22] including the American Academy of Neurology/Child Neurology Society guidelines in 2003[3] additionally supported the value of imaging in abnormalities of head circumference (both micro- and macrocephaly). One review[50] looked at the different aberrations in development according to stages of embryogenesis and suggested clinical clues that may correlate with radiologic findings (such as midline defects and holoprosencephaly), which could guide suspicion for diagnostic imaging. Additionally, links between radiologic abnormalities and associated etiologies (i.e., polymicrogyria

and/or white matter disorders in metabolic diseases) or secondary disabilities (i.e., hypothalamic/endocrine abnormalities in septo-optic dysplasia) are described as added values of radiologic imaging which may alter overall management.

The challenge remains in the context of global developmental delay without syndromic features, in which radiologic findings can be categorized as "overt" (related to ventral induction, migrational abnormalities or aberrant white matter development) or "subtle" (persistence of cavum septum pellucidum, open operculum, colpocephaly, etc.).[51] Questions remain as to whether to obtain imaging (to change the outcome) and *when* to obtain it (i.e., before developing secondary disabilities). Moreover, *what* to obtain is also questionable- recommendations such as those put forth by the American Academy of Neurology/Child Neurology Society favor MRI over CT scan whenever available, but studies in resource limited settings[22, 49] suggest that in spite of superior technical quality of the MRI, CT may prove sufficient.

Genetic disorders

Genetic conditions are the most common identified cause of global developmental delay, accounting for as much as 47% of the etiology in diagnosed cases; as ongoing improvement and availability of tests expands, it is anticipated the diagnostic yield will also increase among the cases with an unidentified cause.[10] The span of genetic conditions associated with global developmental delay and intellectual disability is extremely broad making a targeted review challenging. It is important to acknowledge the difference between what can be a clear, syndromic condition (such as trisomy 21); non-syndromic conditions with specific dysmorphisms (or phenotypic expressions); and- what poses the broader challenge- conditions with minor, unclear or absent dysmorphic features, presenting with global developmental delay.

The underlying debate relates to whether confirmatory testing is warranted and improves or modifies outcomes. Even when considering the value of a precise diagnosis when there is high suspicion for a specific condition (as outlined by Schaefer and Bodensteiner),[52] current practice guidelines and suggested algorithms are conflicting regarding confirmatory testing, upheld by some[3, 10] and non-specific or unsupported by others.[11-13] Patients presenting with global developmental delay and dysmorphisms without a clear syndromic presentation warrant clinical evaluation prior to etiologic testing. It is generally agreed that a thorough clinical assessment, including a family and genetic history and an exhaustive exam is essential and may yield up to 39% of the etiologic diagnoses (table 3).[13, 15, 22-24, 26] Equally important within this evaluation is establishing the nature of the delay- whether it is static, progressive or regressive.

In spite of this, subsequent confirmatory testing is usually the mainstay. It is generally agreed that a "shotgun" approach is inefficient in establishing an etiology. Several studies have detailed clinical history and exam features (or absence thereof) that improve diagnostic yield in assessment of global developmental delay.[15, 44] Srour et al identified the presence of male gender, abnormal perinatal history, microcephaly, dysmorphic features and an abnormal neurologic exam, as well as absence of autistic features, to increase diagnostic yield.[7] Wong and Chung, through likelihood ratios

identified the severity of the delay, facial dysmorphisms, neurologic deficits and absent behavioral traits to increase the post-test probability to up to 96%.[13]

In a more targeted manner, several studies have sought to identify traits that directly suggest common causative etiologies to therefore specifically test for these conditions. One such example is Fragile X syndrome: Giangreco et al[16] and de Vries et al[17] developed checklists for traits identified during evaluation (family history, elongated face, macroorchidism among others) that allow exclusion from unnecessary testing in as many as 86% of patients without missing cases. In another example, de Vries et al[18] developed a five-item checklist for subtelomeric rearrangements with however a much lesser overall successful pick up rate. This suggests that continued research in identifying and improving clinical criteria and checklists would be beneficial and may aid a more targeted diagnostic assessment, or potentially preclude confirmatory testing altogether.

In addition, it is important to acknowledge the existence of evolving phenotypes and the chronologic nature of the diagnostic process. Some suggest the probability of a diagnosis increases over subsequent visits.[53] Curry et al,[54] in the 1997 American College of Medical Genetics recommendations, lists syndromes where a recognizable phenotype evolves over time (among others, Rett, Prader Willi, Angelman and Fragile X syndrome). In light of this, the nature of an aggressive diagnostic approach may be revisited on a more individualized basis. Conflicting opinions in regards to the overall value of diagnosis have also been documented in the literature. While some advocate for *answers* that provide families with due counseling,[55-57] it is also known that, in the case of global developmental delay due to genetic conditions, diagnosis only occasionally leads to specific therapeutic changes,[58] and variations in outcomes have not been thoroughly studied. One study by Samm et al showed array comparative genomic hybridization (aCGH) information changed medical management in 13 of 48 patients and led to avoid further testing for 17/48. [59]

The changing availability of diagnostic tools is, nonetheless, affecting the abovementioned dilemmas. Several studies have shown the growing yield of tests such as aCGH in comparison to more limited techniques such as karyotype or FISH.[60, 61] The International Standard Cytogenomic Array Consortium (ICSA) has issued a statement advocating for microarrays to become 'first-tier' investigations.[62] More recently, an evidence report by the American Academy of Neurology/Child Neurology Society[58] deferred preferentially for the microarray. Furthermore, some have advocated for a "genotype first" diagnosis in light of the expanding utility of microarrays.[63] As technology expands and ongoing research, such as the Deciphering Developmental Disorders (DDD) study[64] yield results, the applications of these technologies (including whole genome/exome sequencing) will continue to be promising.

However, microarray technology is not without limitations. First, there are restrictions in diagnostic capacity in balanced translocations and inversions, and a high number of copy number variations of undetermined significance[65, 66] means many false positives which may potentially add to the anxiety of families. A 'genotype first' approach by primary

care providers (using aCGH as a screening tool) has already evolved into a heated debate over the utility of the clinical genetic evaluation[67, 68] and- given the implied costs- the economic burden that this may bring on the health system and families.[19, 20]

Neglect/psychosocial

Psychosocial factors have been documented to be as much as 11% of the etiology of diagnosed global developmental delay, and is a risk factor for neurologic conditions beyond global developmental delay.[69] These encompass a broad range of factors, both involuntary (eg., poverty, poor parental education, cultural expectations) or voluntary (maltreatment by commission or omission), that hinder the development of the child. The underlying pathophysiology denotes both mechanosensory deprivation and investment of the child's own resources in defensive/self-preserving behaviors.[70, 71]

The diagnostic process may prove especially difficult and warrant a multidisciplinary/multifactorial evaluation. However specific traits of neglect (dishevelment, malnutrition) may provide hints; mother-child and mother-father interactions are also important, and parents may demonstrate poor level of concern towards the ongoing investigation.[72] Past history may show delayed medical care; associations to apparent life-threatening episodes have also been described and should heighten awareness.[73] Behavioral traits have been described as negative predictors of diagnostic yield in several studies,[7, 13] However, they deserve mention in the context of psychosocial deprivation. These children may manifest specific externalizing or internalizing behaviors[74, 75] such as hypervigilance, aggression or withdrawal which may provide clue to the examiner in the context of this diagnostically complex situation.

Parental lack of awareness may not necessarily stem off neglect. Cultural traits may alter developmental expectations across societies and genders.[76, 77] These may also alter stimulation/deprivation patterns in a culturally sensitive manner: for example, lower educational attainment in women or availability of domestic aids serve as limitations not as often seen in western, industrialized contexts.[78] Providers may themselves lack awareness and allocate no value to developmental delay in the context of normal growth[79] or even allocate growth concerns to 'constitutional' factors.[72] The team should assess factors such as maternal age, parental level of education, socioeconomic level, employment stability, housing among others that may explain or contribute to global developmental delay or that may condition access to intervention or treatment.[79-83]

The diagnosis provides a particular challenge in adopted children with unclear family and social history, especially in the current context of international adoptions. Close, frequent re-evaluations and adequate interventions should demonstrate "catch-up" based on the child's *potential*; many times the diagnosis is evidenced only by *recovery.*[72, 75, 84-86] This will thus define requirement for any further testing. It is worth mentioning that physical abuse/non-accidental trauma can also lead to impaired development and global developmental delay.[87] A host of radiologic findings can be associated (intra- or extraparenchymal hemorrhages, axonal injury, hypoxic-ischemic changes).[87] It is generally expected that all

healthcare providers be actively vigilant for signs/symptoms of physical and sexual abuse that are beyond the scope of this review.

A word on metabolic disorders

Albeit a relevant topic in the practice of pediatrics and child neurology, metabolic disorders represent a small and extremely heterogeneous proportion of cases of global developmental delay, especially in countries or regions with universal metabolic screening at birth. With the advent of Tandem Mass Spectrometry, a broad and cost-effective process of screening has been widely implemented, and even many low and middle income countries, such as Colombia, already have nationally recognized practice guidelines that detect a host of metabolic etiologies at birth.[88] Clinical suspicion, as outlined by Michelson et Al and Silove et al,[11, 58] should contemplate family history (consanguinity), chronologic factors (developmental regression, food aversion and vomiting, episodic decompensation) or suggestive features on physical exam (coarse facies, organomegalies). Additional factors (as outlined by Curry et al[54]) such as deafness, failure to thrive, ataxia and skin, hair or bone abnormalities should also raise suspicion. Targeted evaluation may ensue; the yield of *screening*, however, remains very low. Limited screening, such as thyroid studies, urine organic acids, serum amino acids and creatine kinase are often advocated as initial studies,[11, 12] but their low yield and common, non-specific findings should limit them to a case-by-case use.

PROPOSED IMPROVED APPROACH

In making use of the existing practice parameters proposed in the US and elsewhere,[3, 10-12] and in contemplation of the many limitations that otherwise present with largely resource-intensive algorithms, we present an improved approach to the diagnosis of global developmental delay (figure 2). The existing literature has supported an ever more conservative and cost-containing, rational approach. However, the recommendations- ever more reliant on ongoing research, but still much dependent on expert consensus- advocate for many tests and processes that to date have do not necessarily have a formal, direct influence on the *medical* management of global developmental delay.

Our approach seeks to assist in recognition and rationalization of the diagnosis in global developmental delay allowing individual clinical practices and healthcare systems- with their existing infrastructure and resource limitations- to formulate a more conservative and treatment focused approach. It allows the use of likelihood ratios or checklists to *include*, *exclude* or *preclude* diagnostic testing; and when necessary, it allows the managing team to ask *how* said testing will change the management, and whether diagnosis could be deferred to follow-up visits, allowing comprehensive management in the interim. It also seeks to serve as a catalyst for alternative research, spanning beyond diagnostic yield and into *therapeutic yield* as well as *global* cost-containment.

DISCUSSION

Several arguments can be made in favor of a limited, conservative diagnostic approach. Although the literature broadly recognizes the value of the clinical evaluation with thorough history-taking and examination, guidelines continue to advocate for precise etiologic diagnosis, even in light of studies demonstrating near equivalence of this diagnostic approach.[14, 89] Utilizing methodologies that may indicate the yield of diagnostic, such as likelihood ratios[90] or checklists, for global developmental delay in general or for specific entities such as Fragile X (as mentioned above) may altogether eliminate the need for diagnostic tools in more obvious cases, or spare unnecessary testing when insufficiently helpful. In the developed world this could assist in cost-containment as suggested by Duker et al[91] and potentially facilitate an selective approach to diagnostics in global developmental delay favoring outcomes, as suggested by Trevathan.[19, 20] In low and middle income countries, reaffirming the value of immediate resources at hand can empower providers to act on diagnoses otherwise ignored and allow them, as suggested by Scherzer et al[76] to "Think Developmentally and Refer Early".

Assessing the potential changes in *medical* outcome should also be a routine practice of any provider, and should come in contemplation of the *patient's* best interest: Whether a strict diagnosis needs to be in place to address comorbidities is necessary; whether diagnostic timing will delay referral and, as described by Ehrmann et al[92] affect the quality of life of the patient; whether the use of a 5-minute CT scan vs. a 45-minute MRI will significantly change the diagnosis so that the costs are to be incurred by the families;[22] whether there can be strict, established follow-up in place for an unexplained global developmental delay while clinical interventions take place. All are important questions, especially in light of the value of early intervention in patients with developmental delay.[93]

Finally, understanding the limitations of existing diagnostic tools is extremely important. As discussed, advances in technology such as microarrays or whole exome/genome sequencing should be taken with cautious excitement. Many findings that represent genotypic variations without clinical consequences may otherwise lead to misdiagnosis (or misattribution of the diagnosis). In a recent review, Tirosh et al[94] reflected on the consequences of erroneous results (even within expected error) that lead to unnecessary tests and stress to the families; going further, Moynihan et al[95] in a recent opinion article, assessed the drivers of overdiagnosis. They identified among them that newer technologies- through higher sensitivity- correlated with higher prevalence by including those without evolving clinical significance; they also noted that changing definitions and thresholds sustain overdiagnosing- and overtreatment- of pathologies beyond global developmental delay. These opinions, while still in debate, uphold our belief that we must be rational and commensurate in the employment of our available resources.

There are limitations to a conservative approach. The pursuit of a definitive etiologic cause will always be of significant medical interest and existing literature supports that, by establishing an etiology, additional outcomes- such as risk assessment and family counseling- ensue. The definitive diagnosis may also be in the interest of care providers in

adapting therapeutic management to the traits of a specific condition; nonetheless, insufficient studies have focused on assessing these changes or adaptations based on diagnostic outcomes. These concerns are shared and have been expressed by current experts on global developmental delay.[58] Our review acknowledges said concerns and encourages further research in answering the outstanding questions in the diagnostic pathway. Additionally, a conservative approach should not seek to trump ongoing research on newer diagnostic tools that may in future change the highly dynamic process of evaluating and treating global developmental delay, nor should it seek to limit the role of subspecialty services that currently play a leading role in the diagnostic process (e.g., developmental pediatricians, pediatric geneticists). Our approach, instead, encourages actively seeking the best *clinical* diagnostic tools as much as those that are *paraclinical*, in a cost-effective manner, and is cognizant of the limited availability of material resources as of subspecialized manpower in underserved regions throughout the world. Utilization of said resources should be proactive but rational whenever available, and when not delaying the referral to early intervention. We did not contemplate particularities of countries/regions without standardized metabolic screens that may account for the diminishing presentation of metabolic diseases as global developmental delay. This pertains the field of public health, with its due regional variations, in eliciting locally pertinent etiologies that justify the selected conditions to be screened for in national programs where nonexistent. It should be a goal in healthcare planning for nations to universally implement such programs and their due referral and management protocols- similar case as for infection or prematurity, to name other examples. Our review, however, acknowledges variations in resources to provide regional alternatives to care of an otherwise global condition.

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Table 2

Title: Etiologies in global developmental delay

Reference	Location	Percentage of those diagnosed						% Undiagnosed
		Genetic	Metabolic	Dysgenesis	Toxins	Asphyxia/NE*	Psychosocial	
Koul et al. (2010)	Oman	12.7	16.5	15.2		32.9		28.2
Wong and Chun (2011)	Hong Kong	47.1		5.5	3.9†	15.4	7.2‡	47
Jauhari et al. (2010)	India	25.7 (grouped as prenatal)				54.5		46
Tikaria et al. (2010)	India	46.6	9.6 §	15.1	1.4	20.5		27
Srour et al. (2005)	Canada	24.6	2 §	16.3	7.1	22.4	11.2	62
Ozmen et al. (2005)	Turkey	19	12.7 §	27.8		32.9		36
Chun Chen et al. (2002) **	Taiwan	34		25.8 ¶		17.3 #	0.7	19.2
Shevell et al. (2000)	Canada	18.2		22.7	20.5	20.5	6.8	56
Stromme et al. (2000)	Norway	44		9.7		5.6	3.4	20

Majnemer et al. (1995)	Canada	21	7.9	26.3	13.2	15.8		36.7

* NE, neonatal encephalopathy

** Listed as 'Risk factors'

† All external prenatal causes (as per Wilska et al., ref. 8)

‡ All postnatal causes (as per Wilska et al., ref. 8)

§ Includes hypothyroidism

¶ Includes other insults, such as intracranial hemorrhage, hydrocephalus, hypoxic-ischemic encephalopathy, seizures.

Includes other insults, such as infantile spasms and hyperbilirubinemia post-exchange transfusion.

Table 3

Title: Etiologic diagnosis determined exclusively with history and physical exam

Study	Percentage based on history and physical exam
Wong and Chung (2011)	36%
Tikaria et al. (2010)	27%
Van Karnebeek et al. (2005)	33%
Ozmen et al. (2005)	12.5%
Shevell et al. (2000)	38.6%
Majnemer et al. (1995)	34%

Table 1

Title: Causes of global developmental delay

Group	Causes
Prenatal intrinsic	Genetic/metabolic disorders
	CNS malformations
Prenatal extrinsic	Teratogens/toxins
	Infectious
Perinatal	Asphyxia
	Prematurity
	Neonatal Complications
Postnatal	Infectious
	Psychosocial
	Traumatic
	Toxins

Modified from Wilska et al., ref 8

Figure 1 Legend

Currently accepted diagnostic algorithm for global developmental delay with concerns

Figure 1

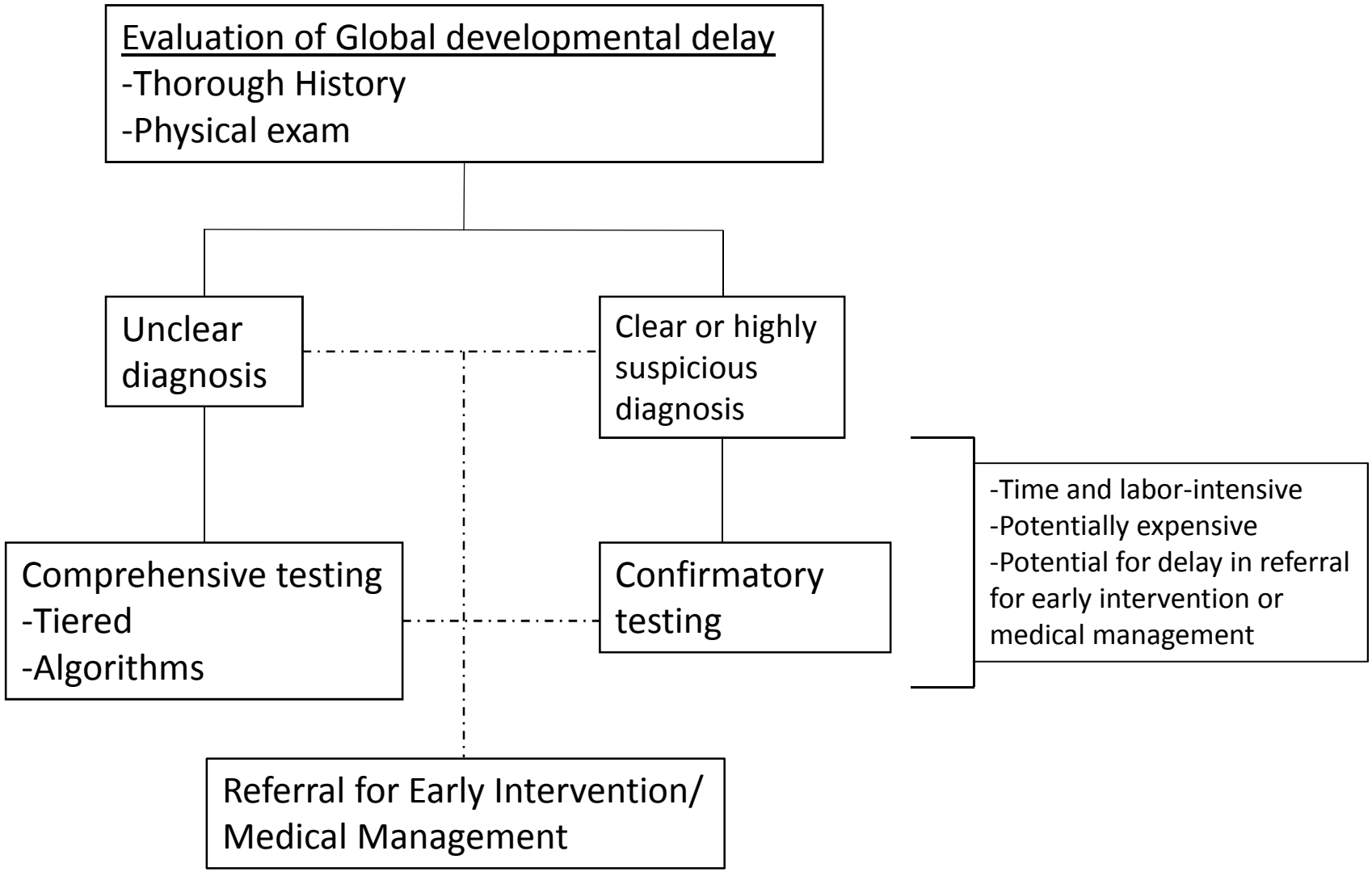

Figure 2 Legend

Proposed improved approach for the evaluation of global developmental delay

ure 2: proposed improved approach for the evaluation of global developmental delay