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Topical Review

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

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ABSTRACT

BACKGROUND: Global developmental delay is usually defined as significant delay in two or more domains of development. Etiologic diagnosis generally proves difficult and the etiology remains undetermined in up to 62% of these children. Those in whom an etiology is established generally undergo an exhaustive and costly diagnostic evaluation, even though this may not change the medical or therapeutic management of the delay. The history and physical examination may provide up to 40% of etiologic diagnoses if adequately conducted. **METHODS:** We performed a critical review of the literature on global developmental delay via PubMed. **RESULTS:** Five major etiologic categories for global developmental delay were identified and traits of the history and physical examination suggestive for their diagnosis were described. Additionally, current diagnostic tools and their benefits and limitations were appraised. **CONCLUSIONS:** We propose an improved approach to enhance clinical diagnosis in both resource-rich and resource-limited settings favoring early intervention and management.

Keywords: global developmental delay, etiologic yield, global health, pediatrics

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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 concerns.[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] (in which "significant" is defined as two or more standard deviations below the mean reference norms for age) and usually limited 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 and the variability of the blanket term "global")[4,5] to its characterization as a diagnosis rather than the manifestation of an underlying etiology.

Several studies have sought to define the causes of global developmental delay. Although an etiologic diagnosis often remains a mystery (anywhere from 20% to 62% are undetermined in the literature),[6,7] identified etiologies have been grouped into several main causes (Table 1).[8] 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 (Fig 1). Indices of suspicion, alongside the existence of newborn screens (that eliminate many major and/or treatable causes) have

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TABLE 1.
Causes of global developmental delay

Group	Causes
Prenatal intrinsic	Genetic/metabolic disorders
	Central nervous system malformations
Prenatal extrinsic	Teratogens/toxins
	Infectious
Perinatal	Asphyxia
	Prematurity
	Neonatal complications
Postnatal	Infectious
	Psychosocial
	Traumatic
	Toxins

Adapted, with permission, from Wilska et al.[8]

been acknowledged in every step of the proposed flow charts; however, this end point often requires advanced testing.

Several studies recognize the history and physical examination 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] 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 offer a targeted, empirical approach in the context of a likely etiology that 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 have not been performed. 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 represent up to 55% of the diagnostic yield in the literature for the diagnosed causes of global developmental delay.

The severity of hypoxic-ischemic encephalopathy relates to the presence and severity of significant neurodevelopmental comorbidities.[30,31] Although asphyxia neonatorum and subsequent hypoxic-ischemic encephalopathy do not have a pathognomonic clinical presentation, survivorship is often preceded by an extensive course of care in the neonatal intensive care unit. Improving peripartum care has increased this 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, thorough investigation of the perinatal and neonatal history could yield worrisome clues such as nonreassuring intrauterine fetal tracings, low Apgar scores at 5 and 10 minutes, or

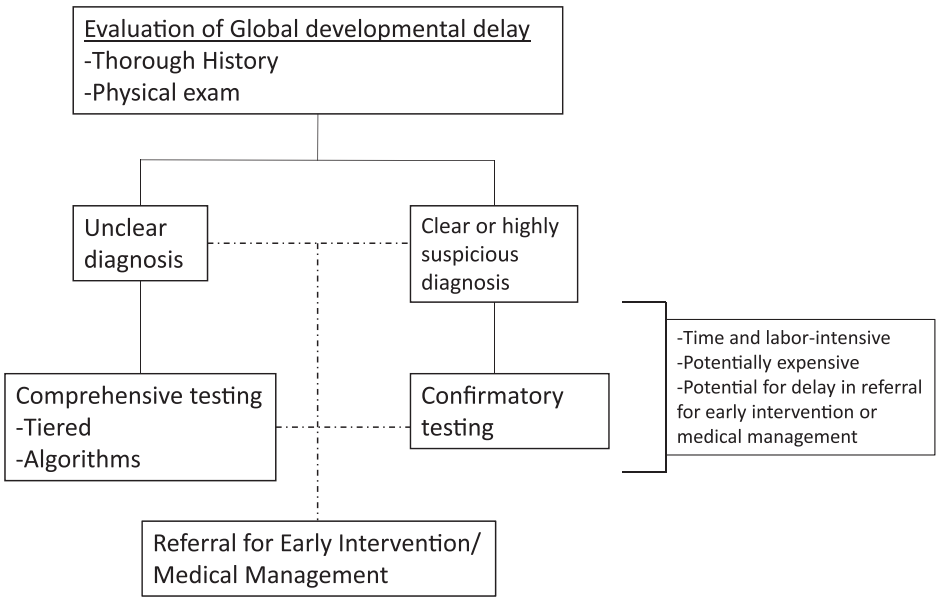

FIGURE 1.
Currently accepted diagnostic algorithm for global developmental delay with concerns.

TABLE 2.
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

Abbreviation:
NE = Neonatal encephalopathy
[*] Listed as "risk factors."
[†] All external prenatal causes (as per Wilska et al.).[8]
[‡] All postnatal causes (as per Wilska et al.).[8]
[§] Includes hypothyroidism.
[‖] Includes other insults, such as intracranial hemorrhage, hydrocephalus, hypoxic-ischemic encephalopathy, and seizures.
[¶] Includes other insults, such as infantile spasms and hyperbilirubinemia postexchange transfusion.

cord blood gases demonstrating significant metabolic acidosis or base deficit.[27,37-39] Such abnormal perinatal factors may constitute markers that could enhance the etiologic yield.[7] In the absence of suggestive events in the pre- and perinatal history, management may include ongoing multidisciplinary assessment of persistent delay and may not require additional testing unless an indication for a focused assessment develops (e.g. seizures).

Toxin exposure

Maternal substance abuse has been identified as a cause of global developmental delay, accounting for up to 21% of the diagnostic yield. Studies most frequently indicate alcohol as the culprit. Alcohol has been thoroughly studied and a number of specific phenotypes across the spectrum of the diagnosis have been described (fetal alcohol spectrum disorder and its subsets complete/partial fetal alcohol syndrome, alcohol-related neurodevelopmental disorders, and alcohol-related birth defects).[40,41]

A significant medical history[15,24] of 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 out of 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 in the absence of a significant history, relying on the physical examination and/or traits for early diagnosis[40-42] based on the specific, common features of fetal alcohol spectrum disorder. However, there is conflicting evidence on the yield of the physical findings and dysmorphic features in global developmental delay,[13,15,24,44] and it may be difficult to confirm the diagnosis of fetal alcohol spectrum disorder at an early age. Novel detection mechanisms such as three-dimensional laser are not widely available, and although 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]

Other common toxins, however, do not produce a characteristic phenotype. Some authors have suggested a "fetal cocaine syndrome," but others have questioned its validity.[46] Although specific findings have been described (eg, stroke, cognitive impairment), the data are conflicting in regard to global developmental delay.[47,48] No less complicated is the study of outcomes after heroin/opioid exposure, given the substantial psychosocial factors (described later in this article) that confound the causal relationship. Therefore, in individuals with appropriate history or physical findings, early evaluation of an evolving phenotype may facilitate prevention of secondary disability and help to direct the assessment for comorbidities.

Cerebral dysgenesis

Cerebral dysgenesis refers to a group of malformations of the neuronal tissue during various stages of embryonic and fetal brain development (segmentation, cleavage, cell proliferation, migration, and differentiation). These malformations account for as much as 28% of the diagnosed causes of global developmental delay. These disorders exhibit an array of phenotypes, associated findings, and etiologies (isolated versus syndromic).

Dysgenesis poses a particular diagnostic challenge when it occurs in isolation (ie, without identifiable clinical signs) and without a significant history. However, several findings provide clues to the diagnosis and improve the diagnostic yield. A small study by Pandey et al.[49] suggested that the presentation of delay with neurological features is associated with a higher incidence of findings both on computed tomography (CT) and magnetic resonance imaging (MRI) (notably atrophy, morphologic abnormalities such as polymicrogyria or holoprosencephaly, and white matter disorders). This study and others,[22] along with the American Academy of Neurology/Child Neurology Society guidelines in 2003,[3] supported imaging studies in abnormalities of head circumference (both micro- and macrocephaly). One

review[50] compared the different aberrations in development to the stages of embryogenesis and suggested clinical clues that may correlate with radiologic findings (such as midline defects and holoprosencephaly), and guide diagnostic imaging. Additionally, links between radiologic abnormalities and associated etiologies (ie, polymicrogyria and/or white matter disorders in metabolic diseases) or secondary disabilities (ie, hypothalamic/endocrine abnormalities in septo-optic dysplasia) may constitute an added values of imaging that may alter overall management.

Assessing global developmental delay without syndromic features can be challenging. 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).[51] Questions remain about whether to obtain imaging (to change the outcome) and *when* to obtain it (before the onset of secondary disabilities). Moreover, *what* study to obtain is also debatable. Recommendations by the American Academy of Neurology and Child Neurology Society favor MRI when it is available, but studies in resource-limited settings[22,49] suggest that CT may be adequate in spite of superior technical quality of MRI.

Genetic disorders

Genetic conditions are collectively the most common identified cause of global developmental delay, accounting for as much as 47% of the diagnosed patients. As the improvement and availability of testing expand the diagnostic yield is likely to increase.[10] The array of genetic conditions associated with 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); nonsyndromic 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 question is whether confirmatory testing is warranted and improves or modifies the outcome. 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 nonspecific or unsupported by others.[11-13] Patients with global developmental delay and dysmorphisms without a clear syndromic designation may warrant clinical evaluation before etiologic testing. It is generally agreed that a thorough clinical assessment, including a family and genetic history and an exhaustive examination, is essential and may yield up to 39% of the etiologic diagnoses (Table 3).[13,15,22-24,26] Equally important is establishing the nature of the delay, whether it is static, progressive, or regressive.

Nevertheless, confirmatory testing is usually the mainstay. It is generally agreed that a "shotgun" approach is inefficient in establishing an etiology. Several studies have detailed the clinical history and examination 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, an abnormal neurological examination, and the absence of autistic features to increase diagnostic yield.[7] Wong and Chung, through likelihood ratios, identified the severity of the delay, facial dysmorphisms, neurological deficits, and absent behavioral traits to increase the post-test probability to up to 96%.[13]

TABLE 3.
Etiologic diagnosis based on history and physical examination

Study	Percentage of Patients
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

In a more targeted manner, several studies sought to identify traits that suggest common etiologies to and 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, and macroorchidism among others) that allow exclusion from unnecessary testing in as many as 86% of patients without overlooking diagnoses. In another example, de Vries et al.[18] developed a five-item checklist for subtelomeric rearrangements, although with a lower overall success rate. This suggests that continued research in identifying and improving clinical criteria and checklists might be beneficial and promote a more targeted diagnostic assessment, or potentially avoid confirmatory testing altogether.

In addition, it is important to acknowledge the existence of evolving phenotypes and the chronologic nature of the diagnostic process. The probability of a diagnosis may increase 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 syndromes). In light of this, the diagnostic approach may be revisited on a more individualized basis. There are sometimes conflicting opinions about the overall value of diagnosis. Specific diagnoses may facilitate family counseling,[55-57] but, in the case of global developmental delay from genetic conditions, diagnosis only occasionally leads to specific therapeutic changes,[58] and variations in outcomes have not been thoroughly studied. Samm and colleagues showed that array comparative genomic hybridization (aCGH) information changed medical management in 13 of 48 patients and avoidance of further testing in 17 of 48.[59]

The changing availability of diagnostic tools is, nonetheless, affecting these dilemmas. Several studies have demonstrated the growing yield of tests such as aCGH in comparison to more limited techniques such as karyotype or fluorescent *in situ* hybridization.[60,61] An International Standard Cytogenomic Array Consortium statement advocates microarrays as "first-tier" investigations.[62] More recently, an evidence-based analysis by the American

Academy of Neurology and Child Neurology Society[58] favored the microarray. Furthermore, some have advocated 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 study,[64] yield results, the applications of these technologies (including whole genome/exome sequencing) will continue to evolve.

However, microarray technology is not without limitations. First, there are limitations in the diagnostic capacity for balanced translocations and inversions, and a high number of copy number variations of undetermined significance[65,66] results in many false positives that add to the anxiety of families. A genotype-first approach by primary care providers (using aCGH as a screening tool) has sparked controversy over the utility of the clinical genetic evaluation[67,68] and, given the implied costs, the economic burden that this testing may add to the health system and the families.[19,20]

Neglect/psychosocial

Psychosocial factors account for up to 11% of the diagnosed global developmental delay and may also contribute to other neurological conditions.[69] This category includes an array 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 suggests 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 indications of neglect (dishevelment, malnutrition) may provide hints. Mother–child and mother–father interactions are also important, and parents may demonstrate poor level of concern toward the ongoing investigation.[72] The history may document delayed medical care; apparent life-threatening episodes 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 that may provide clues in the context of this diagnostically complex situation.

Parental lack of awareness does not always suggest 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 lack awareness and allocate no value to developmental delay in the context of normal growth[79] or even attribute growth concerns to "constitutional" factors.[72] The team should assess factors such as maternal age, parental level of education, socioeconomic level, employment stability, and housing that may explain or contribute to global developmental delay or that may condition access to intervention or treatment.[79-83]

The diagnosis of psychosocial dysfunction can be particularly challenging in adopted children whose family and social history are unclear, especially in the context of international adoptions. 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/nonaccidental 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 health care providers be actively vigilant for signs/symptoms of physical and sexual abuse that are beyond the scope of this review.

Metabolic disorders

Metabolic disorders account for 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 already have nationally recognized practice guidelines that detect a host of metabolic disorders at birth.[88] Clinical suspicion should consider family history (consanguinity), chronologic factors (developmental regression, food aversion and vomiting, episodic decompensation), and suggestive physical features (coarse facies, organomegaly.[11,58]). 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, nonspecific findings should limit them to a case-by-case use.

Proposed improved approach

In making use of the existing practice parameters proposed in the United States and elsewhere,[3,10-12] and in view of the limitations that otherwise present with largely resource-intensive algorithms, we propose a modified approach to the diagnosis of global developmental delay (Fig 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 very dependent on expert consensus—advocate for many tests and processes that do not directly alter the *medical* management of global developmental delay.

Our approach seeks rationalize the diagnosis of global developmental delay, allowing individual clinical practices and health care 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. When necessary, it allows the managing

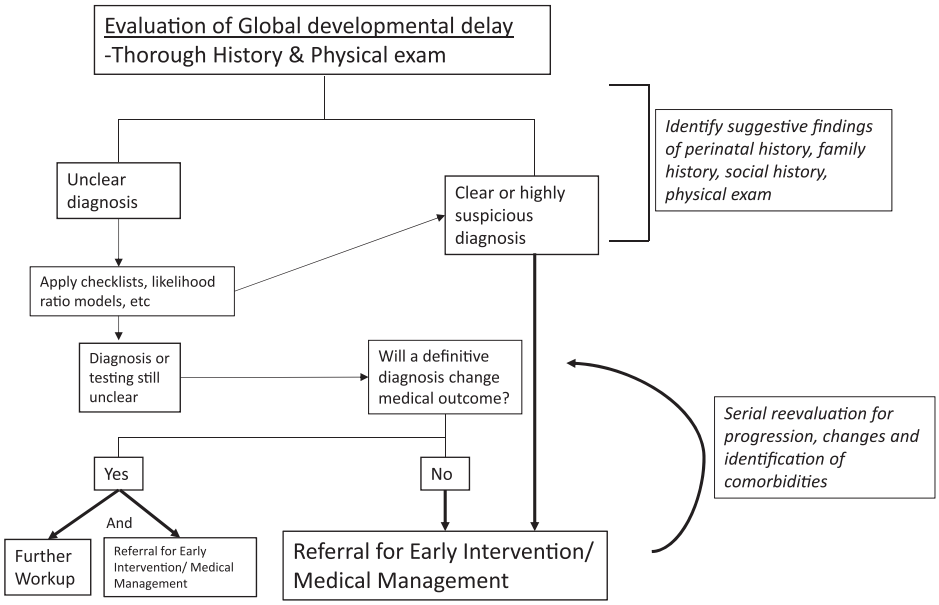

FIGURE 2.
Proposed improved approach for the evaluation of global developmental delay.

team to ask *how* the 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 catalyze alternative research, extending beyond diagnostic yield 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 precise etiologic diagnosis, even in light of studies demonstrating near equivalence of this diagnostic approach.[14,89] Using methodologies that may indicate the yield of diagnostic criteria, such as likelihood ratios[90] or checklists, for global developmental delay in general or for specific entities such as fragile X may 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.[91] and potentially facilitate a 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 contemplate the *patient's* best interest: Whether a strict diagnosis needs to be in place to address comorbidities; 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 versus a 45-minute MRI will significantly alter the diagnosis so that the costs are to be incurred by the families[22]; and whether there can be strict, established follow-up in place for an unexplained global developmental delay while clinical interventions take place. These are important questions, especially in light of the value of early intervention in individuals with developmental delay.[93]

Finally, understanding the limitations of existing diagnostic tools is extremely important. Advances in technology such as microarrays or whole exome/genome sequencing should be taken with cautious excitement. Genotypic variations without clinical consequences may 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] assessed the drivers of overdiagnosis. They observed 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. Although still debated, these concepts support 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. A definitive diagnosis may also assist care providers in adapting therapeutic management to the traits of a specific condition. Nevertheless, too few studies have focused on assessing these changes or adaptations in light of the diagnostic outcomes. These concerns have also been expressed by experts on global developmental delay.[58] Our review acknowledges these 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 (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. Use of resources should be proactive but rational whenever available and when not delaying 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 to public health, with its regional variations, in eliciting locally pertinent etiologies that justify screening for selected conditions in national programs where nonexistent. It should be a goal in health care planning for nations to universally implement such programs and related referral and management protocols, as with similar case 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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