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Guidance for the Clinician in Rendering Pediatric Care

CLINICAL REPORT

Comprehensive Evaluation of the Child With Intellectual Disability or Global Developmental Delays

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ABBREVIATIONS

AAP—American Academy of Pediatrics
CMA—chromosome microarray
CNS—central nervous system
CNV—copy number variant
CT—computed tomography
FISH—fluorescent in situ hybridization
GAA—guanidinoacetate
GDD—global developmental delay
ID—intellectual disability
XLID—X-linked intellectual disability

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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abstract

FREE

Global developmental delay and intellectual disability are relatively common pediatric conditions. This report describes the recommended clinical genetics diagnostic approach. The report is based on a review of published reports, most consisting of medium to large case series of diagnostic tests used, and the proportion of those that led to a diagnosis in such patients. Chromosome microarray is designated as a first-line test and replaces the standard karyotype and fluorescent in situ hybridization subtelomere tests for the child with intellectual disability of unknown etiology. Fragile X testing remains an important first-line test. The importance of considering testing for inborn errors of metabolism in this population is supported by a recent systematic review of the literature and several case series recently published. The role of brain MRI remains important in certain patients. There is also a discussion of the emerging literature on the use of whole-exome sequencing as a diagnostic test in this population. Finally, the importance of intentional comanagement among families, the medical home, and the clinical genetics specialty clinic is discussed. *Pediatrics* 2014;134:e903–e918

The purpose of this clinical report of the American Academy of Pediatrics (AAP) is to describe an optimal medical genetics evaluation of the child with intellectual disability (ID) or global developmental delays (GDDs). The intention is to assist the medical home in preparing families properly for the medical genetics evaluation process. This report addresses the advances in diagnosis and treatment of children with intellectual disabilities since the publication of the original AAP clinical report in 2006[1] and provides current guidance for the medical genetics evaluation. One intention is to inform primary care providers in the setting of the medical home so that they and families are knowledgeable about the purpose and process of the genetics evaluation. This report will emphasize advances in genetic diagnosis while updating information regarding the appropriate evaluation for inborn errors of metabolism and the role of imaging in this context. The reader is referred to the 2006 clinical report for background information that remains relevant, including the roles of the medical home or pediatric primary care provider.

This clinical report will not address the importance of developmental screening in the medical home, nor will it address the diagnostic

evaluation of the child with an autism spectrum disorder who happens to have ID as a co-occurring disability. (For AAP guidance related to Autism Spectrum Disorders, see Johnson and Myers.[2])

For both pediatric primary care providers and families, there are specific benefits to establishing an etiologic diagnosis (Table 1): clarification of etiology; provision of prognosis or expected clinical course; discussion of genetic mechanism(s) and recurrence risks; refined treatment options; the avoidance of unnecessary and redundant diagnostic tests; information regarding treatment, symptom management, or surveillance for known complications; provision of condition-specific family support; access to research treatment protocols; and the opportunity for comanagement of patients, as appropriate, in the context of a medical home to ensure the best health, social, and health care services satisfaction outcomes for the child and family. The presence of an accurate etiologic diagnosis along with a knowledgeable, experienced, expert clinician is one factor in improving the psychosocial outcomes for children and with intellectual disabilities and their families.[3–5] Although perhaps difficult to measure, this "healing touch" contributes to the general well-being of the family. "As physicians we have experience with other children who have the same disorder, access to management programs, knowledge of the prognosis, awareness of research on understanding the disease and many other elements that when shared with the parents will give them a feeling that some control is possible."[5]

TABLE 1 The Purposes of the Comprehensive Medical Genetics Evaluation of the Young Child With GDD or ID

1. Clarification of etiology
2. Provision of prognosis or expected clinical course
3. Discussion of genetic mechanism(s) and recurrence risks
4. Refined treatment options
5. Avoidance of unnecessary or redundant diagnostic tests
6. Information regarding treatment, symptom management, or surveillance for known complications
7. Provision of condition-specific family support
8. Access to research treatment protocols
9. Opportunity for comanagement of appropriate patients in the context of a medical home to ensure the best health, social, and health care services satisfaction outcomes for the child and family

Makela et al[6] studied, in depth, 20 families of children with ID with and without an etiologic diagnosis and found that these families had specific stated needs and feelings about what a genetic diagnosis offers:

1. Validation: a diagnosis established that the problem (ID) was credible, which empowered them to advocate for their child.
2. Information: a diagnosis was felt to help guide expectations and management immediately and provide hope for treatment or cure in future.
3. Procuring services: the diagnosis assisted families in obtaining desired services, particularly in schools.
4. Support: families expressed the need for emotional companionship that a specific diagnosis (or "similar challenges") assisted in accessing.
5. Need to know: families widely differed in their "need to know" a specific diagnosis, ranging from strong to indifferent.
6. Prenatal testing: families varied in their emotions, thoughts, and actions regarding prenatal genetic diagnosis.

For some families in the Makela et al[6] study, the clinical diagnosis of autism, for example, was sufficient and often more useful than "a rare but specific etiological diagnosis." These authors report that "all of the families would have preferred to have an [etiologic] diagnosis, if given the option," particularly early in the course of the symptoms.

As was true of the 2006 clinical report, this clinical report will not address the etiologic evaluation of young children who are diagnosed with cerebral palsy, autism, or a single-domain developmental delay (gross motor delay or specific language impairment).[1] Some children will present both with GDD and clinical features of autism. In such cases, the judgment of the clinical geneticist will be important in determining the evaluation of the child depending on the primary neurodevelopmental diagnosis. It is recognized that the determination that an infant or young child has a cognitive disability can be a matter of clinical judgment, and it is important for the pediatrician and consulting clinical geneticist to discuss this before deciding on the best approach to the diagnostic evaluation."[1]

INTELLECTUAL DISABILITY

ID is a developmental disability presenting in infancy or the early childhood years, although in some cases, it cannot be diagnosed until the child is older than ~5 years of age, when standardized measures of developmental skills become more reliable and valid. The American Association on Intellectual and Developmental Disability defines ID by using measures of 3 domains: intelligence (IQ), adaptive behavior, and systems of supports afforded the individual.[7] Thus, one cannot rely solely on the measure of IQ to define ID. More recently, the term ID has been suggested to replace "mental retardation."[7,8] For the purposes of this clinical report, the American Association on Intellectual and Developmental Disability definition is used: "Intellectual disability is a disability characterized by

significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social and practical adaptive skills. The disability originates before age 18 years."[7] The prevalence of ID is estimated to be between 1% and 3%. Lifetime costs (direct and indirect) to support individuals with ID are large, estimated to be an average of approximately $1 million per person.[9]

Global Developmental Delay

Identifying the type of developmental delay is an important preliminary step, because typing influences the path of investigation later undertaken. GDD is defined as a significant delay in 2 or more developmental domains, including gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living and is thought to predict a future diagnosis of ID.[10] Such delays require accurate documentation by using norm-referenced and age-appropriate standardized measures of development administered by experienced developmental specialists. The term GDD is reserved for younger children (ie, typically younger than 5 years), whereas the term ID is usually applied to older children for whom IQ testing is valid and reliable. Children with GDD are those who present with delays in the attainment of developmental milestones at the expected age; this implies deficits in learning and adaptation, which suggests that the delays are significant and predict later ID. However, delays in development, especially those that are mild, may be transient and lack predictive reliability for ID or other developmental disabilities. For the purposes of this report, children with delays in a single developmental domain (for example, isolated mild speech delay) should not be considered appropriate candidates for the comprehensive genetic evaluation process set forth here. The prevalence of GDD is estimated to be 1% to 3%, similar to that of ID.

Diagnosis

Schaefer and Bodensteiner[11] wrote that a specific diagnosis is that which "can be translated into useful clinical information for the family, including providing information about prognosis, recurrence risks, and preferred modes of available therapy." For example, agenesis of the corpus callosum is considered a sign and not a diagnosis, whereas the autosomal-recessive Acrocallosal syndrome (agenesis of the corpus callosum and polydactyly) is a clinical diagnosis. Van Karnebeek et al[12] defined etiologic diagnosis as "sufficient literature evidence…to make a causal relationship of the disorder with mental retardation likely, and if it met the Schaefer-Bodensteiner definition." This clinical report will use this Van Karnebeek modification of the Schaefer–Bodensteiner definition and, thus, includes the etiology (genetic mutation or genomic abnormality) as an essential element to the definition of a diagnosis.

Recommendations are best when established from considerable empirical evidence on the quality, yield, and usefulness of the various diagnostic investigations appropriate to the clinical situation. The evidence for this clinical report is largely based on many small- or medium-size case series and on expert opinion. The report is based on a review of the literature by the authors.

Highlights in This Clinical Report

Significant changes in genetic diagnosis in the last several years have made the 2006 clinical report out-of-date. First, the chromosome microarray (CMA) is now considered a first-line clinical diagnostic test for children who present with GDD/ID of unknown cause. Second, this report highlights a renewed emphasis on the identification of "treatable" causes of GDD/ID with the recommendation to consider screening for inborn errors of metabolism in all patients with unknown etiology for GDD/ID.[13]

Nevertheless, the approach to the patient remains familiar to pediatric primary care providers and includes the child's medical history (including prenatal and birth histories); the family history, which includes construction and analysis of a pedigree of 3 generations or more; the physical and neurologic examinations emphasizing the examination for minor anomalies (the "dysmorphology examination"); and the examination for neurologic or behavioral signs that might suggest a specific recognizable syndrome or diagnosis. After the clinical genetic evaluation, judicious use of laboratory tests, imaging, and other consultations on the basis of best evidence are important in establishing the diagnosis and for care planning.

CHROMOSOME MICROARRAY

CMA now should be considered a first-tier diagnostic test in all children with GDD/ID for whom the causal diagnosis is not known. G-banded karyotyping historically has been the standard first-tier test for detection of genetic imbalance in patients with GDD/ID for more than 35 years. CMA is now the standard for diagnosis of patients with GDD/ID, as well as other conditions, such as autism spectrum disorders or multiple congenital anomalies.[14–24] The G-banded karyotype allows a cytogeneticist to visualize and analyze chromosomes for chromosomal rearrangements, including chromosomal gains (duplications) and losses (deletions). CMA performs a similar function, but at a much "higher resolution," for genomic imbalances, thus increasing the sensitivity substantially. In their recent review of the CMA literature,

Vissers et al[25] report the diagnostic rate of CMA to be at least twice that of the standard karyotype. CMA, as used in this clinical report, encompasses all current types of array-based genomic copy number analyses, including array-based comparative genomic hybridization and single-nucleotide polymorphism arrays (see Miller et al[15] for a review of array types). With these techniques, a patient's genome is examined for detection of gains or losses of genome material, including those too small to be detectable by standard G-banded chromosome studies.[26,27] CMA replaces the standard karyotype ("chromosomes") and fluorescent in situ hybridization (FISH) testing for patients presenting with GDD/ID of unknown cause. The standard karyotype and certain FISH tests remain important to diagnostic testing but now only in limited clinical situations (see Manning and Hudgins[14]) in which a specific condition is suspected (eg, Down syndrome or Williams syndrome). The discussion of CMA does not include whole-genome sequencing, exome sequencing, or "next-generation" genome sequencing; these are discussed in the "emerging technologies" section of this report.

Twenty-eight case series have been published addressing the rate of diagnosis by CMA of patients presenting with GDD/ID.[28] The studies vary by subject criteria and type of microarray technique and reflect rapid changes in technology over recent years. Nevertheless, the diagnostic yield for all current CMA is estimated at 12% for patients with GDD/ID.[14–29] CMA is the single most efficient diagnostic test, after the history and examination by a specialist in GDD/ID.

CMA techniques or "platforms" vary. Generally, CMA compares DNA content from 2 differentially labeled genomes: the patient and a control. In the early techniques, 2 genomes were cohybridized, typically onto a glass microscope slide on which cloned or synthesized control DNA fragments had been immobilized. Arrays have been built with a variety of DNA substrates that may include oligonucleotides, complementary DNAs, or bacterial artificial chromosomes. The arrays might be whole-genome arrays, which are designed to cover the entire genome, or targeted arrays, which target known pathologic loci, the telomeres, and pericentromeric regions. Some laboratories offer chromosome-specific arrays (eg, for nonsyndromic X-linked ID [XLID]).[30] The primary advantage of CMA over the standard karyotype or later FISH techniques is the ability of CMA to detect DNA copy changes simultaneously at multiple loci in a genome in one "experiment" or test. The copy number change (or copy number variant [CNV]) may include deletions, duplications, or amplifications at any locus, as long as that region is represented on the array. CMA, independent of whether it is "whole genome" or "targeted" and what type of DNA substrate (single-nucleotide polymorphisms,[31] oligonucleotides, complementary DNAs, or bacterial artificial chromosomes),[32] identifies deletions and/or duplications of chromosome material with a high degree of sensitivity in a more efficient manner than FISH techniques. Two main factors define the resolution of CMA: (1) the size of the nucleic acid targets; and (2) the density of coverage over the genome. The smaller the size of the nucleic acid targets and the more contiguous the targets on the native chromosome are, the higher the resolution is. As with the standard karyotype, one result of the CMA test can be "of uncertain significance," (ie, expert interpretation is required, because some deletions or duplications may not be clearly pathogenic or benign). Miller et al[15] describe an effort to develop an international consortium of laboratories to address questions surrounding array-based testing interpretation. This International Standard Cytogenomic Array Consortium[15] (www.iscaconsortium.org) is investigating the feasibility of establishing a standardized, universal system of reporting and cataloging CMA results, both pathologic and benign, to provide the physician with the most accurate and up-to-date information.

It is important for the primary care pediatrician to work closely with the clinical geneticist and the diagnostic laboratory when interpreting CMA test results, particularly when "variants of unknown significance" are identified. In general, CNVs are assigned the following interpretations: (1) pathogenic (ie, abnormal, well-established syndromes, de novo variants, and large changes); (2) variants of unknown significance; and (3) likely benign.[15] These interpretations are not essentially different than those seen in the standard G-banded karyotype. It is important to note that not all commercial health plans in the United States include this testing as a covered benefit when ordered by the primary care pediatrician; others do not cover it even when ordered by the medical geneticist. Typically, the medical genetics team has knowledge and experience in matters of payment for testing.

The literature does not stratify the diagnostic rates of CMA by severity of disability. In addition, there is substantial literature supporting the multiple factors (eg, social, environmental, economic, genetic) that contribute to mild disability.[33] Consequently, it remains within the judgment of the medical geneticist as to whether it is warranted to test the patient with mild (and familial) ID for pathogenic CNVs. In their review, Vissers et al[25] reported on several recurrent deletion or duplication syndromes with mild disability and commented on the variable penetrance of the more common CNV conditions, such as 1q21.1

microdeletion, 1q21.1 microduplication, 3q29 microduplication, and 12q14 microdeletion. Some of these are also inherited. Consequently, among families with more than one member with disability, it remains challenging for the medical geneticist to know for which patient with GDD/ID CMA testing is not warranted.

Recent efforts to evaluate reporting of CNVs among clinical laboratories indicate variability of interpretation because of platform variability in sensitivity.[34,35] Thus, the interpretation of CMA test abnormal results and variants of unknown significance, and the subsequent counseling of families should be performed in all cases by a medical geneticist and certified genetic counselor in collaboration with the reference laboratory and platform used. Test variability is resolving as a result of international collaborations.[36] With large data sets, the functional impact (or lack thereof) of very rare CNVs is better understood. Still, there will continue to be rare or unique CNVs for which interpretation remain ambiguous. The medical geneticist is best equipped to interpret such information to families and the medical home.

SCREENING FOR INBORN ERRORS OF METABOLISM

Since the 2006 AAP clinical report, several additional reports have been published regarding metabolic testing for a cause of ID.[13,37–40] The percentage of patients with identifiable metabolic disorders as cause of the ID ranges from 1% to 5% in these reports, a range similar to those studies included in the 2006 clinical report. Likewise, these newer published case series varied by site, age range of patients, time frame, study protocol, and results. However, they do bring renewed focus to treatable metabolic disorders.[13] Furthermore, some of the disorders identified are not included currently in any newborn screening blood spot panels. Although the prevalence of inherited metabolic conditions is relatively low (0% to 5% in these studies), the potential for improved outcomes after diagnosis and treatment is high.[41]

In 2005, Van Karnebeek et al[40] reported on a comprehensive genetic diagnostic evaluation of 281 consecutive patients referred to an academic center in the Netherlands. All patients were subjected to a protocol for evaluation and studies were performed for all patients with an initially unrecognized cause of mental retardation and included urinary screen for amino acids, organic acids, oligosaccharides, acid mucopolysaccharides, and uric acid; plasma concentrations of total cholesterol and diene sterols of 7- and 8-dehydrocholesterol to identify defects in the distal cholesterol pathway; and a serum test to screen for congenital disorders of glycosylation (test names such as "carbohydrate-deficient transferrin"). In individual patients, other searches were performed as deemed necessary depending on results of earlier studies. This approach identified 7 (4.6%) subjects with "certain or probable" metabolic disorders among those who completed the metabolic screening (n = 216). None of the 176 screening tests for plasma amino acids and urine organic acids was abnormal. Four children (1.4%) with congenital disorders of glycosylation were identified by serum sialotransferrins, 2 children had abnormal serum cholesterol and 7-dehydrocholesterol concentrations suggestive of Smith-Lemli-Opitz syndrome, 2 had evidence of a mitochondrial disorder, 1 had evidence of a peroxisomal disorder, and 1 had abnormal cerebrospinal fluid biogenic amine concentrations. These authors concluded that "screening for glycosylation defects proved useful, whereas the yield of organic acid and amino acid screening was negligible."

In a similar study from the Netherlands done more recently, Engbers et al[39] reported on metabolic testing that was performed in 433 children whose GDD/ID remained unexplained after genetic/metabolic testing, which included a standard karyotype; urine screen for amino acids, organic acids, mucopolysaccharides, oligosaccharides, uric acid, sialic acid, purines, and pyrimidines; and plasma for amino acids, acylcarnitines, and sialotransferrins. Screenings were repeated, and additional testing, including cerebrospinal fluid studies, was guided by clinical suspicion. Metabolic disorders were identified and confirmed in 12 of these patients (2.7%), including 3 with mitochondrial disorders; 2 with creatine transporter disorders; 2 with short-chain acyl-coenzyme A dehydrogenase deficiency; and 1 each with Sanfilippo IIIa, a peroxisomal disorder; a congenital disorder of glycosylation; 5-methyltetrahydrofolate reductase deficiency; and deficiency of the GLUT1 glucose transporter.

Other studies have focused on the prevalence of disorders of creatine synthesis and transport. Lion-François et al[37] reported on 188 children referred over a period of 18 months with "unexplained mild to severe mental retardation, normal karyotype, and absence of fragile X syndrome" who were prospectively screened for congenital creatine deficiency syndromes. Children were from diverse ethnic backgrounds. Children with "polymalformative syndromes" were excluded. There were 114 boys (61%) and 74 girls (39%) studied. Creatine metabolism was evaluated by using creatine/creatinine and guanidinoacetate (GAA)-to-creatine ratios on a spot urine screen. Diagnosis was further confirmed by using brain proton magnetic resonance spectroscopy and mutation screening by DNA sequence analysis in

either the SLC6A8 (creatine transporter defect) or the *GAMT* genes. This resulted in a diagnosis in 5 boys (2.7% of all; 4.4% of boys). No affected girls were identified among the 74 studied. All 5 boys also were late to walk, and 3 had "autistic features." The authors concluded that all patients with undiagnosed ID have urine screened for creatine-to-creatinine ratio and GAA-to-creatine ratio. Similarly, Caldeira Arauja et al[38] studied 180 adults with ID institutionalized in Portugal, screening them for congenital creatine deficiency syndromes. Their protocol involved screening all subjects for urine and plasma uric acid and creatinine. Patients with an increased urinary uric acid-to-creatinine ratio and/or decreased creatinine were subjected to the analysis of GAA. *GAMT* activity was measured in lymphocytes and followed by *GAMT* gene analysis. This resulted in identifying 5 individuals (2.8%) from 2 families with *GAMT* deficiency. A larger but less selective study of 1600 unrelated male and female children with GDD/ID and/or autism found that 34 (2.1%) had abnormal urine creatine-to-creatinine ratios, although only 10 (0.6%) had abnormal repeat tests and only 3 (0.2%) were found to have an SLC6A8 mutation.[42] Clark et al[43] identified *SLC6A8* mutations in 0.5% of 478 unrelated boys with unexplained GDD/ID.

Recently, van Karnebeek and Stockler reported[13,42] on a systematic literature review of metabolic disorders "presenting with intellectual disability as a major feature." The authors identified 81 treatable genetic metabolic disorders presenting with ID as a major feature. Of these disorders, 50 conditions (62%) were identified by routinely available tests (Tables 2 and 3). Therapeutic modalities with proven effect included diet, cofactor/vitamin supplements, substrate inhibition, enzyme replacement, and hematopoietic stem cell transplant. The effect on outcome (IQ, developmental performance, behavior, epilepsy, and neuroimaging) varied from improvement to halting or slowing neurocognitive regression. The authors emphasized the approach as one that potentially has significant impact on patient outcomes: "This approach revisits current paradigms for the diagnostic evaluation of ID. It implies treatability as the premise in the etiologic work-up and applies evidence-based medicine to rare diseases." Van Karnebeek and Stockler[13,42] reported on 130 patients with ID who were "tested" per this metabolic protocol; of these, 6 (4.6%) had confirmed treatable inborn errors of metabolism and another 5 (3.8%) had "probable" treatable inborn error of metabolism.

This literature supports the need to consider screening children presenting with GDD/ID for treatable metabolic conditions. Many metabolic screening tests are readily available to the medical home and/or local hospital laboratory service. Furthermore, the costs for these metabolic screening tests are relatively low.

GENETIC TESTING FOR MENDELIAN DISORDERS

For patients in whom a diagnosis is suspected, diagnostic molecular genetic testing is required to confirm the diagnosis so that proper health care is implemented and so that reliable genetic counseling can be provided. For patients with a clinical diagnosis of a Mendelian disorder that is certain, molecular genetic diagnostic testing usually is not required to establish the diagnosis but may be useful for health care planning. However, for carrier testing or for genetic counseling of family members, it is often essential to know the specific gene mutation in the proband.

For patients with GDD/ID for whom the diagnosis is not known, molecular genetic diagnostic testing is necessary, under certain circumstances, which is discussed in the next section.

MALE GENDER

There is an approximate 40% excess of boys in all studies of prevalence and incidence of ID.[44,45] Part of this distortion of the gender ratio is attributable to X-linked genetic disorders.[46] Consequently, genetic testing for X-linked genes in boys with GDD/ID is often warranted, particularly in patients whose pedigree is suggestive of an X-linked condition. In addition, for several reasons, research in X-linked genes that cause ID is advanced over autosomal genes,[46,47] thus accelerating the clinical capacity to diagnose XLID over autosomal forms.

Most common of these is fragile X syndrome, although the prevalence of all other X-linked genes involved in ID

TABLE 2 Metabolic Screening Tests

Specimen[a]	Test	Notes
Blood	Amino acids	See Table 3
	Homocysteine	
	Acylcarnitine profile	
Urine	Organic acids	
	GAA/creatine metabolites	
	Purines and pyrimidines	
	Mucopolysaccharide screen	
	Oligosaccharide screen	

See Fig 1.

[a] Serum lead, thyroid function studies not included as "metabolic tests" and to be ordered per clinician judgment.

TABLE 3 Metabolic Conditions Identified by Tests Listed

PAAs	P-HCY	Acylcarn	UOA	UPP	UGAA/Cr	UMPS	UOligo
Argininosuccinic aciduria[a]	Cobalamin C deficiency	Cobalamin C deficiency	β-ketothiolase deficiency	Pyrimidine 5′nucleotidase superactivity	AGAT deficiency	Hurler	α-mannosidosis
Citrullinemia[a]	Cobalamin D deficiency	Cobalamin D deficiency	Cobalamin A deficiency	Molybdenum cofactor type A deficiency	GAMT deficiency	Hunter	Aspartylglucosaminuria
Citrullinemia, type II[a]	Cobalamin F deficiency	Cobalamin F deficiency	Cobalamin B deficiency		Creatine transporter defect	Sanfilippo A, B, C	
CPS deficiency[a]	Cobalamin E deficiency	Ethylmalonic encephalopathy	Cobalamin C deficiency			Sly (MPS VI)	
Argininemia[a]	Cobalamin G deficiency	Isovaleric acidemia[a]	Cobalamin D deficiency				
HHH syndrome	MTHFR deficiency[a]	3-methylcrotonyl glycinuria	Cobalamin F deficiency				
Maple syrup urine disease, variant	Homocystinuria	PPA[a]	Ethylmalonic encephalopathy				
NAGS deficiency[a]		Tyrosinemia, type II	GA, type I				
MTHFR deficiency[a]			GA, type II				
OTC deficiency[a]			HMG-CoA Lyase deficiency				
PKU			Holocarboxylase synthetase deficiency				
PDH complex deficiency			Homocystinuria				
Tyrosinemia, type II			Isovaleric acidemia[a]				
			3-methylcrotonyl glycinuria				
			3-methylglutaconic aciduria				
			MMA[a]				
			MHBD deficiency				
			PPA[a]				
			SCOT deficiency				
			SSADH deficiency				
			Tyrosinemia, type II				

Adapted from van Karnebeek and Stockler.[41]

Acylcarn, acylcarnitine profile; CPS, carbamyl phosphate synthetase; GA, glutaric acidemia; HHH, hyperornithinemia-hyperammonemia-homocitrullinuria; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; MHBD, 2-methyl-3-hydroxybutyryl CoA dehydrogenase; MMA, methylmalonic acidemia; MTHFR, methylenetetrahydrofolate reductase; NAGS, N-acetylglutamate synthase; OTC, ornithine transcarbamylase; PAA, plasma amino acids; PDH, pyruvate dehydrogenase; P-HCY, plasma homocysteine; PKU; phenylketonuria; PPA, propionic acid; SCOT, succinyl-CoA:3-ketoacid CoA transferase; SSADH, succinic semialdehyde dehydrogenase; UGAA/creat; urine guanidino acid/creatine metabolites; UMPS, urine mucopolysaccharides qualitative screen (glycosaminoglycans); UOA, urine organic acids; UOGS, urine oligosaccharides; UPP, urine purines and pyrimidines.

[a] Late-onset form of condition listed; some conditions are identified by more than 1 metabolic test.

far exceeds that of fragile X syndrome alone.[46] Fragile X testing should be performed in all boys and girls with GDD/ID of unknown cause. Of boys with GDD/ID of uncertain cause, 2% to 3% will have fragile X syndrome (full mutation of *FMR1*, >200 CGG repeats), as will 1% to 2% of girls (full mutation).[48]

GENETIC TESTING FOR NONSPECIFIC XLID

Stevenson and Schwartz[49] suggest 2 clinical categories for those with XLID: syndromal and nonsyndromal. Syndromal refers to patients in whom physical or neurologic signs suggest a specific diagnosis; nonsyndromal refers to those with no signs or symptoms to guide the diagnostic process. Using this classification has practical applicability, because the pediatric primary care provider can establish a specific XLID syndrome on the basis of clinical findings. In contrast, nonsyndromal conditions can only be distinguished on the basis of the knowledge of their causative gene.[50] In excess of 215 XLID conditions have been recorded, and >90 XLID genes have been identified.[46,50]

To address male patients with GDD/ID and X-linked inheritance, there are molecular genetic diagnostic "panels" of X-linked genes available clinically. These panels examine many genes in 1 "test sample." The problem for the clinical evaluation is in which patient to use which test panel, because there is no literature on head-to-head performance of test panels, and the test panels differ somewhat by genes included, test methods used, and the rate of a true pathogenic genetic diagnosis. Nevertheless, the imperative for the diagnostic evaluation remains the same for families and physicians, and there is a place for such testing in the clinical evaluation of children with GDD/ID. For patients with an X-linked pedigree, genetic testing using one of the panels is clinically indicated. The clinical geneticist is best suited to guide this genetic testing of patients with possible XLID. For patients with "syndromal" XLID (eg, Coffin-Lowry syndrome), a single gene test rather than a gene panel is indicated. Whereas those patients with "nonsyndromal" presentation might best be assessed by using a multigene panel comprising many of the more common nonsyndromal XLID genes. The expected rate of the diagnosis may be high. Stevenson and Schwartz[46] reported, for example, on 113 cases of nonspecific ID testing using a 9-gene panel of whom 9 (14.2%) had pathogenic mutations identified. de Brouwer et al[51] reported on 600 families with multiple boys with GDD/ID and normal karyotype and *FMR1* testing. Among those families with "an obligate female carrier" (defined by pedigree analysis and linkage studies), a specific gene mutation was identified in 42%. In addition, in those families with more than 2 boys with ID and no obligate female carrier or without linkage to the X chromosome, 17% of the ID cases could be explained by X-linked gene mutations. This very large study suggested that testing of individual boys for X-linked gene mutations is warranted.

Recently, clinical laboratories have begun offering "high-density" X-CMAs to assess for pathogenic CNVs (see previous discussion regarding microarrays) specifically for patients with XLID. Wibley et al[30] (2010) reported on CNVs in 251 families with evidence of XLID who were investigated by array comparative genomic hybridization on a high-density oligonucleotide X-chromosome array platform. They identified pathogenic CNVs in 10% of families. The high-density arrays for XLID are appropriate in those patients with syndromal or nonsyndromal XLID. The expected diagnostic rate remains uncertain, although many pathogenic segmental duplications are reported (for a catalog of X-linked mutations and CNVs, see http://www.ggc.org/research/molecular-studies/xlid.html).

Whole exome sequencing and whole-genome sequencing are emerging testing technologies for patients with nonspecific XLID. Recently, Tarpey et al[52] have reported the results of the large-scale systematic resequencing of the coding X chromosome to identify novel genes underlying XLID. Gene coding sequences of 718 X-chromosome genes were screened via Sanger sequencing technology in probands from 208 families with probable XLID. This resequencing screen contributed to the identification of 9 novel XLID-associated genes but identified pathogenic sequence variants in only 35 of 208 (17%) of the cohort families. This figure likely underestimates the general contribution of sequence variants to XLID given the subjects were selected from a pool that had had previous clinical and molecular genetic screening.[30]

BOYS WITH SUSPECTED OR KNOWN XLID

Table 4 lists some common XLID conditions. In cases in which the diagnosis is not certain, molecular genetic testing of patients for the specific gene is indicated, even if the pedigree does not indicate other affected boys (ie, cannot confirm X-linked inheritance).[46]

FEMALE GENDER AND MECP2 TESTING

Rett syndrome is an X-linked condition that affects girls and results from *MECP2* gene mutations primarily (at least 1 other gene has been determined causal in some patients with typical and atypical Rett syndrome: *CDKL5)*. Girls with mutations in the

MECP2 gene do not always present clinically with classic Rett syndrome. Several large case series have examined the rate of pathogenic *MECP2* mutations in girls and boys with ID. The proportion of *MECP2* mutations in these series ranged from 0% to 4.4% with the average of 1.5% among girls with moderate to severe ID.[53–62] *MECP2* mutations in boys present with severe neonatal encephalopathy and not with GDD/ID.

ADVANCES IN DIAGNOSTIC IMAGING

Currently, the literature does not indicate consensus on the role that neuroimaging, either by computed tomography (CT) or MRI, can play in the evaluation of children with GDD/ID. Current recommendations range from performing brain imaging on all patients with GDD/ID,[63] to performing it only on those with indications on clinical examination,[12] to being considered as a second-line investigation to be undertaken when features in addition to GDD are detected either on history or physical examination. The finding of a brain abnormality or anomaly on neuroimaging may lead to the recognition of a specific cause of an individual child's developmental delay/ID in the same way that a dysmorphologic examination might lead to the inference of a particular clinical diagnosis. However, like other major or minor anomalies noted on physical examination, abnormalities on neuroimaging typically are not sufficient for determining the cause of the developmental delay/ID; the underlying precise, and presumably frequently genetic in origin, cause of the brain anomaly is often left unknown. Thus, although a central nervous system (CNS) anomaly (often also called a "CNS dysgenesis") is a useful finding and indeed may be considered, according to the definition of Schaefer and Bodensteiner,[11] a useful "diagnosis." However, it is frequently not an etiologic or syndromic diagnosis. This distinction is not always made in the literature on the utility of neuroimaging in the evaluation of children with developmental delay/ID. The lack of a consistent use of this distinction has led to confusion regarding this particular issue.

Early studies on the use of CT in the evaluation of children with idiopathic ID[64] indicated a low diagnostic yield for the nonspecific finding of "cerebral atrophy," which did not contribute to clarifying the precise cause of the ID.[65] Later studies that used MRI to detect CNS abnormalities suggested that MRI was more sensitive than CT, with an increased diagnostic yield.[10,66] The rate of abnormalities actually detected on imaging varies widely in the literature as a result of many factors, such as subject selection and the method of imaging used (ie, CT or MRI). Schaefer and Bodensteiner,[63] in their literature review, found reported ranges of abnormalities from 9% to 80% of those patients studied. Shevell et al[10] reported a similar range of finding in their review. For example, in 3 studies totaling 329 children with developmental delay in which CT was used in almost all patients and MRI was used in but a small sample, a specific cause was determined in 31.4%,[67] 27%,[68] and 30%[69] of the children. In their systematic review of the literature, van Karnebeek et al[12] reported on 9 studies that used MRI in children with ID. The mean rate of abnormalities found was 30%, with a range of 6.2% to 48.7%. These investigators noted that more abnormalities were found in children with moderate to profound ID versus those with borderline to mild ID (mean yield of 30% and 21.2%, respectively). These authors also noted that none of the studies reported on the value of the absence of any neurologic abnormality for a diagnostic workup and concluded that "the value for finding abnormalities or the absence of abnormalities must be higher" than the 30% mean rate implied.

If neuroimaging is performed in only selected cases, such as children with an abnormal head circumference or an abnormal focal neurologic finding, the rate of abnormalities detected is increased further than when used on a screening basis in children with a normal neurologic examination except for the documentation of developmental delay. Shevell et al[68] reported that the percentage of abnormalities were 13.9% if neuroimaging was performed on a "screening basis" but increased to 41.2% if performed on "an indicated basis." Griffiths et al[70] highlighted that the overall risk of having a specific structural abnormality found on MRI scanning was 28% if neurologic symptoms and signs other than developmental delay were present, but if the developmental delay was isolated, the yield was reduced to 7.5%. In a series of 109 children, Verbruggen et al[71] reported an etiologic yield on MRI of 9%. They noted that all of these children had neurologic signs or an abnormal head circumference. In their practice parameter, the American Academy of Neurology and the Child Neurology Society[10] discussed other studies on smaller numbers of patients who showed similar results, which led to their recommendation that "neuroimaging is a recommended part of the diagnostic evaluation," particularly should there be abnormal findings on examination (ie, microcephaly, macrocephaly, focal motor findings, pyramidal signs, extrapyramidal signs) and that MRI is preferable to CT. However, the authors of the American College of Medical Genetics Consensus Conference Report[10] stated that neuroimaging by CT or MRI in normocephalic patients without focal neurologic signs should not be considered a "standard of

TABLE 4 Common Recognizable XLID Syndromes

Syndrome	Common Manifestations	Gene, Location
Aarskog syndrome	Short stature, hypertelorism, downslanting palpebral fissures, joint hyperextensibility, shawl scrotum	*FGD1,* Xp11.21
Adrenoleukodystrophy	Variable and progressive vision and hearing loss, spasticity, neurological deterioration associated with demyelination of the central nervous system and adrenal insufficiency	*ABCD1,* Xq28
Aicardi syndrome	Agenesis of the corpus callosum, lacunar chorioretinopathy, costovertebral anomalies, seizures in females	_____, Xp22
Allan–Herndon syndrome	Generalized muscle hypoplasia, childhood hypotonia, ataxia, athetosis, dysarthria, progressing to spastic paraplegia	*MCT8* (SLC16A2), Xq13
ARX-related syndromes (includes Partington, Proud, West, XLAG syndromes and nonsyndromal XLMR)	Partington: dysarthria, dystonia, hyperreflexia, seizures. West: infantile spasms, hypsarrhythmia. Proud: microcephaly, ACC, spasticity, seizures, ataxia, genital anomalies. XLAG: lissencephaly, seizures, genital anomalies	*ARX,* Xp22.3
ATRX syndrome (includes ARTX, Chudley–Lowry, Carpenter–Waziri, Holmes–Gang, and Martinez spastic paraplegia syndromes and nonsyndromal XLMR)	Short stature, microcephaly, hypotonic facies with hypertelorism, small nose, open mouth and prominent lips, brachydactyly, genital anomalies, hypotonia, in some cases hemoglobin H inclusions in erythrocytes	*XNP,* (XH2) Xq13.3
Christianson syndrome	Short stature, microcephaly, long narrow face, large ears, long straight nose, prominent mandible, general asthenia, narrow chest, long thin digits, adducted thumbs, contractures, seizures, autistic features, truncal ataxia, ophthalmoplegia, mutism, incontinence, hypoplasia of the cerebellum, and brain stem	*SLC9A6,* Xq26
Coffin–Lowry syndrome	Short stature, distinctive facies, large soft hands, hypotonia, joint hyperextensibility, skeletal changes	*RSK2,* Xp22
Creatine transporter deficiency	Nondysmorphic, autistic, possibly progressive	*SLC6A8,* Xq28
Duchenne muscular dystrophy	Pseudohypertrophic muscular dystrophy	*DMD,* Xp21.3
Fragile X syndrome	Prominent forehead, long face, recessed midface, large ears, prominent mandible, macroorchidism	*FMR1,* Xq27.3
Hunter syndrome	Progressive coarsening of face, thick skin, cardiac valve disease, joint stiffening, dysostosis multiplex	*IDS,* Xq28
Incontinentia pigmenti	Sequence of cutaneous blistering, verrucous thickening, and irregular pigmentation. May have associated CNS, ocular abnormalities	*NEMO* (IKB6KG), Xq28
Lesch–Nyhan syndrome	Choreoathetosis, spasticity, seizures, self-mutilation, uric acid urinary stones	*HPRT,* Xq26
Lowe syndrome	Short stature, cataracts, hypotonia, renal tubular dysfunction	*OCRL,* Xq26.1
MECP2 duplication syndrome	Hypotonia, progressing to spastic paraplegia, recurrent infections	*MECP2,* Xq28
Menkes syndrome	Growth deficiency, full cheeks, sparse kinky hair, metaphyseal changes, limited spontaneous movement, hypertonicity, seizures, hypothermia, lethargy, arterial tortuosity, death in early childhood	*ATP7A,* Xpl3.3
Pelizaeus–Merzbacher disease	Nystagmus, truncal hypotonia, progressive spastic paraplegia, ataxia, dystonia	*PLP,* Xq21.1
Renpenning syndrome (includes Sutherland–Haan, cerebropalatocardiac, Golabi–Ito–Hall, Porteous syndrome	Short stature, microcephaly, small testes. May have ocular or genital abnormalities	*PQBP1,* Xp11.3
Rett syndrome	XLMR in girls, cessation and regression of development in early childhood, truncal ataxia, autistic features, acquired microcephaly	*MECP2,* Xq28
X-linked hydrocephaly-MASA spectrum	Hydrocephalus, adducted thumbs, spastic paraplegia	*L1CAM,* Xq28

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practice" or mandatory and believed that decisions regarding "cranial imaging will need to follow (not precede) a thorough assessment of the patient and the clinical presentation." In contrast, van Karnebeek et al[12] found that MRI alone leads to an etiologic diagnosis in a much lower percentage of patients studied. They cited Kjos et al,[72] who reported diagnoses in 3.9% of patients who had no known cause for their ID and who did not manifest either a progressive or degenerative course in terms of their neurologic symptomatology. Bouhadiba et al[73] reported diagnoses in 0.9% of patients with neurologic symptoms, and in 4 additional studies, no etiologic or syndromic

diagnosis on the basis of neuroimaging alone was found.[65,69,74,75] The authors of 3 studies reported the results on unselected patients; Majnemer and Shevell[67] reported a diagnosis by this typed unselected investigation in 0.2%, Stromme[76] reported a diagnosis in 1.4% of patients, and van Karnebeek et al[40] reported a diagnosis in 2.2% of patients.

Although a considerable evolution has occurred over the past 2 decades in neuroimaging techniques and modalities, for the most part with the exception of proton magnetic resonance spectroscopy, this has not been applied or reported in the clinical situation of developmental delay/ID in childhood. Proton resonance spectroscopy provides a noninvasive mechanism of measuring brain metabolites, such as lactate, using technical modifications to MRI. Martin et al[77] did not detect any differences in brain metabolite concentrations among stratifications of GDD/ID into mild, moderate, and severe levels. Furthermore, they did not detect any significant differences in brain metabolite concentration between children with GDD/ID and age-matched typically developing control children. Thus, these authors concluded that proton resonance spectroscopy "has little information concerning cause of unexplained DD." Similarly, the studies by Martin et al[77] and Verbruggen et al[71] did not reveal that proton magnetic resonance spectroscopy was particularly useful in the determination of an underlying etiologic diagnosis in children with unexplained developmental delay/ID.

All of these findings suggest that abnormal findings on MRI are seen in ~30% of children with developmental delay/ID. However, only in a fraction of these children does MRI lead to an etiologic or syndromic diagnosis. The precise value of a negative MRI result in leading to a diagnosis has not yet been studied in detail. In addition, MRI in the young child with developmental delay/ID invariably requires sedation or, in some cases, anesthesia to immobilize the child to accomplish the imaging study. This need, however, is decreasing with faster acquisition times provided by more modern imaging technology. Although the risk of sedation or anesthesia is small, it still merits consideration within the decision calculus for practitioners and the child's family.[63,78,79] Thus, although MRI is often useful in the evaluation of the child with developmental delay/ID, at present, it cannot be definitively recommended as a mandatory study, and it certainly has higher diagnostic yields when concurrent neurologic indications exist derived from a careful physical examination of the child (ie, microcephaly, microcephaly, seizures, or focal motor findings).

RECOMMENDED APPROACH

The following is the recommended medical genetic diagnostic evaluation flow process for a new patient with GDD/ID. All patients with ID, irrespective of degree of disability, merit a comprehensive medical evaluation coordinated by the medical home in conjunction with the medical genetics specialist. What follows is the clinical genetics evaluation (Fig 1):

1. Complete medical history; 3-generation family history; and physical, dysmorphologic, and neurologic examinations.
2. If the specific diagnosis is certain, inform the family and the medical home, providing informational resources for both; set in place an explicit shared health care plan[80] with the medical home and family, including role definitions; provide sources of information and support to the family; provide genetic counseling services by a certified genetic counselor; and discuss treatment and prognosis. Confirm the clinical diagnosis with the appropriate genetic testing, as warranted by clinical circumstances.
3. If a specific diagnosis is suspected, arrange for the appropriate diagnostic studies to confirm including single-gene tests or chromosomal microarray test.
4. If diagnosis is unknown and no clinical diagnosis is strongly suspected, begin the stepwise evaluation process:
   a. Chromosomal microarray should be performed in all.
   b. Specific metabolic testing should be considered and should include serum total homocysteine, acyl-carnitine profile, amino acids; and urine organic acids, glycosaminoglycans, oligosaccharides, purines, pyrimidines, GAA/creatine metabolites.
   c. Fragile X genetic testing should be performed in all.
5. If no diagnosis is established:
   a. Male gender and family history suggestive X-linkage, complete XLID panel that contains genes causal of nonsyndromic XLID and complete high-density X-CMA. Consider X-inactivation skewing in the mother of the proband.
   b. Female gender: complete *MECP2* deletion, duplication, and sequencing study.
6. If microcephaly, macrocephaly, or abnormal findings on neurologic examination (focal motor findings, pyramidal signs, extrapyramidal signs, intractable epilepsy, or focal seizures), perform brain MRI.
7. If brain MRI findings are negative or normal, review status of diagnostic evaluation with family and medical home.
8. Consider referrals to other specialists, signs of inborn errors of metabolism

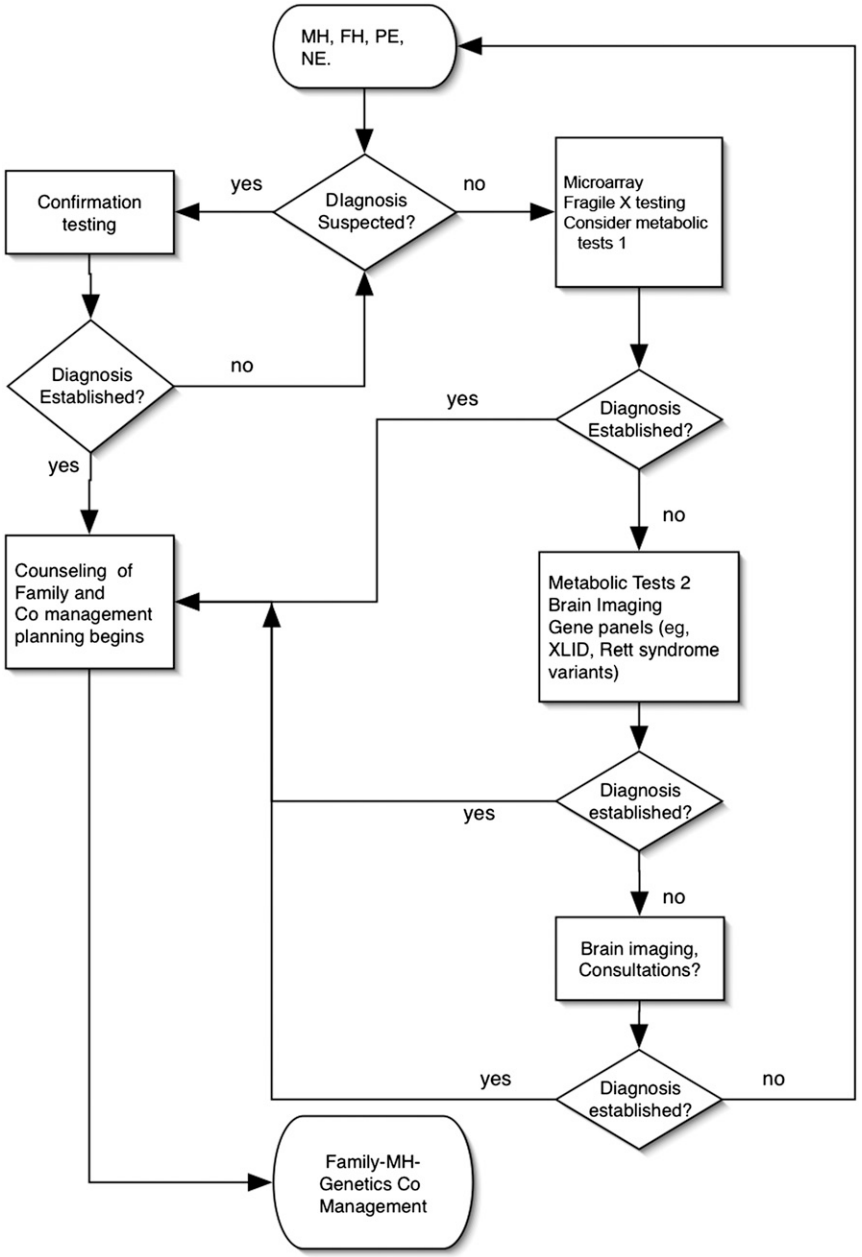

FIGURE 1

Diagnostic process and care planning. Metabolic test 1: blood homocysteine, acylcarnitine profile, amino acids; and, urine organic acids, glycosaminoglycans, oligosaccharides, purines, pyrimidines, GAA/creatine metabolites. Metabolic test 2 based on clinical signs and symptoms. FH, family history; MH, medical history; NE, neurologic examination; PE, physical and dysmorphology examination.

for which screening has not yet been performed, etc.

9. If no further studies appear warranted, develop a plan with the family and medical home for needed services for child and family; also develop a plan for diagnostic reevaluation.

THE SHARED EVALUATION AND CARE PLAN FOR LIMITED ACCESS

Health care systems, processes, and outcomes vary geographically, and not all of what is recommended in this clinical report is easily accessible in all regions of the United States.[21,81–84] Consequently, local factors affect the process of evaluation and care. These arrangements are largely by local custom or design. In some areas, there may be quick access and intimate coordination between the medical home and medical genetics specialist, but in other regions, access may be constrained by distance or by decreased capacity, making for long wait times for appointments. Some general pediatricians have the ability to interpret the results of genetic testing that they may order. In addition, children with GDD or ID are often referred by pediatricians to developmental pediatricians, child neurologists, or other subspecialists. It is appropriate for some elements of the medical genetic evaluation to be performed by physicians other than medical geneticists if they have the ability to interpret the test results and provide appropriate counseling to the families. In such circumstances, the diagnostic evaluation process can be designed to address local particularities. The medical home is responsible for referrals of the family and child to the appropriate special education or early developmental services professional for individualized services. In addition, the medical home can begin the process of the diagnostic evaluation if access is a problem and in coordination with colleagues in medical genetics.[80,85] What follows is a suggested process for the evaluation by the medical home and the medical genetics specialist and only applies where access is a problem; any such process is better established with local particularities in mind:

Medical home completes the medical evaluation, determines that GDD/ID is present, counsels family, refers to educational services, completes a 3-generation family history, and completes the physical examination and addresses the following questions:

1. Does the child have abnormalities on the dysmorphologic examination?

   a. If no or uncertain, obtain microarray, perform fragile X testing, and consider the metabolic testing listed previously. Confirm that newborn screening was completed and reported negative. Refer to medical genetics while testing is pending.
   b. If yes, send case summary and clinical photo to medical genetics center for review for syndrome identification. If diagnosis is suspected, arrange for expedited medical genetics referral and hold all testing listed above. Medical geneticist to arrange visit with genetic counselor for testing for suspected condition.
2. Does the child have microcephaly, macrocephaly, or abnormal neurologic examination (listed above)? If "yes," measure parental head circumferences and review the family history for affected and unaffected members. If normal head circumferences in both parents and negative family history, obtain brain MRI and refer to medical genetics.
3. Does child also have features of autism, cerebral palsy, epilepsy, or sensory disorders (deafness, blindness)? This protocol does not address these patients; manage and refer as per local circumstances.
4. As above are arranged and completed and negative, refer to medical genetics and hold on additional diagnostic testing until consultation completed. Continue with current medical home family support services and health care.
5. Should a diagnosis be established, the medical home, medical geneticist, and family might then agree to a care plan with explicit roles and responsibilities of all.
6. Should a diagnosis not be established by medical genetics consultation, the medical home, family, and medical geneticist can then agree on the frequency and timing of diagnostic reevaluation while providing the family and child services needed.

EMERGING TECHNOLOGIES

Several research reports have cited whole-exome sequencing and whole-genome sequencing in patients with known clinical syndromes for whom the causative gene was unknown. These research reports identified the causative genes in patients with rare syndromes (eg, Miller syndrome,[86] Charcot-Marie-Tooth disease,[87] and a child with severe inflammatory bowel disease[88]). Applying similar whole-genome sequencing of a family of 4 with 1 affected individual, Roach et al[86] identified the genes for Miller syndrome and primary ciliary dyskinesia. The ability to do whole-genome sequencing and interpretation at an acceptable price is on the horizon.[87,89] The use of exome or whole-genome sequencing challenges the field of medical genetics in ways not yet fully understood. When a child presents with ID and whole-genome sequencing is applied, one will identify mutations that are unrelated to the question being addressed, in this case "What is the cause of the child's intellectual disability?" One assumes that this will include mutations that families do not want to have (eg, adult-onset disorders for which no treatment now exists). This is a sea change for the field of medical genetics, and the implications of this new technology have not been fully explored. In addition, ethical issues regarding validity of new tests, uncertainty, and use of resources will need to be addressed as these technologies become available for clinical use.[90,91]

CONCLUSIONS

The medical genetic diagnostic evaluation of the child with GDD/ID is best accomplished in collaboration with the medical home and family by using this clinical report to guide the process. The manner in which the elements of this clinical protocol are applied is subject to local circumstances, as well as the decision-making by the involved pediatric primary care provider and family. The goals and the process of the diagnostic evaluation are unchanged: to improve the health and well-being of those with GDD/ID. It is important to emphasize the new role of the genomic microarray as a first-line test, as well as the renewal of efforts to identify the child with an inborn error of metabolism. The future use of whole-genome sequencing offers promise and challenges needing to be addressed before regular implementation in the clinic.

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