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## CLINICAL REPORT

# Clinical Genetic Evaluation of the Child With Mental Retardation or Developmental Delays

John B. Moeschler, MD, Michael Shevell, MD, and the Committee on Genetics

Guidance for the Clinician in Rendering  
Pediatric Care

## ABSTRACT

This clinical report describes the clinical genetic evaluation of the child with developmental delays or mental retardation. The purpose of this report is to describe the optimal clinical genetics diagnostic evaluation to assist pediatricians in providing a medical home for children with developmental delays or mental retardation and their families. The literature supports the benefit of expert clinical judgment by a consulting clinical geneticist in the diagnostic evaluation. However, it is recognized that local factors may preclude this particular option. No single approach to the diagnostic process is supported by the literature. This report addresses the diagnostic importance of clinical history, 3-generation family history, dysmorphic examination, neurologic examination, chromosome analysis ( $\geq 650$  bands), fragile X molecular genetic testing, fluorescence in situ hybridization studies for subtelomere chromosome rearrangements, molecular genetic testing for typical and atypical presentations of known syndromes, computed tomography and/or magnetic resonance brain imaging, and targeted studies for metabolic disorders.

## INTRODUCTION

The purpose of this clinical report of the American Academy of Pediatrics (AAP) Committee on Genetics is to describe an optimal clinical genetics evaluation of the child with developmental delays or mental retardation (DD/MR). Developmental surveillance is an integral component of a primary care medical home, and much is written about the importance of early identification and referral of children with developmental delays. For example, in "Developmental Surveillance and Screening of Infants and Young Children," the AAP Committee on Children With Disabilities discusses the importance of early identification and referral of infants with developmental delays by the primary care pediatrician and the importance of the pediatrician's responsibility to "determine the cause of delays or refer to appropriate consultant for determination."<sup>1</sup> No AAP statement has addressed the elements that constitute an optimal diagnostic evaluation of the infant or young child with DD/MR. This clinical report focuses on the diagnostic evaluation once the primary care pediatrician or other health care professional determines that there is a developmental delay. The goal of this diagnostic evaluation is to identify the etiology of the disability, including any medical genetic cause. The medical genetics diagnostic evaluation takes place within the context of a comprehensive evaluation of a child's neurodevelopmental status, which is designed to address

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### Key Words

developmental delay, mental retardation, medical home, diagnostic evaluation, dysmorphism, medical genetics, chromosome, fragile X, molecular genetics, inborn errors of metabolism, central nervous system malformations

### Abbreviations

AAP—American Academy of Pediatrics  
DD/MR—developmental delays or mental retardation  
CNS—central nervous system  
EEG—electroencephalography  
CT—computed tomography  
FISH—fluorescence in situ hybridization  
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the child's developmental management needs and guide the etiologic evaluation process.<sup>2-5</sup> The primary care pediatrician has a role in determining whether neurologic, developmental pediatrics, audiologic, or ophthalmologic evaluations, as well as other rehabilitative services, are needed in the child's neurodevelopmental diagnosis. Many primary care pediatricians will initiate aspects of the diagnostic evaluation; others will seek specialty consultation before embarking on the diagnostic evaluation. It is appropriate for the individual pediatrician to determine the diagnostic approach that is optimal for a particular child and family.

The type of developmental delay identified is an important preliminary step, because such typing influences the path of investigation that is undertaken later. The focus of this report is the child with cognitive developmental delays rather than those with motor delays or language delays solely. Such delays require accurate documentation using norm-referenced and age-appropriate standardized measures of development by experienced pediatricians or developmental specialists whenever feasible.<sup>6,7</sup> The term "developmental delay" is usually reserved for younger children (typically younger than 5 years), and the term "mental retardation" is usually applied to older children when IQ testing is valid and reliable.<sup>8</sup> Children with developmental delays are those who present with delays in the attainment of developmental milestones at the expected age. Developmental delays imply deficits in learning and adaptation,<sup>2</sup> which may be significant and predict later cognitive or intellectual disability. However, delays in development, especially those that are mild, may be transient and lack predictive reliability for mental retardation or other developmental disabilities.

Mental retardation (often referred to as "intellectual disability" and "cognitive disability") is a lifelong disability that presents in infancy or the early childhood years but cannot be diagnosed until the child is older than 5 years, when standardized measures of intelligence become reliable and valid. The American Association on Mental Retardation defines mental retardation by measures of 3 domains: intelligence (IQ), adaptive behavior, and systems of supports. Thus, one cannot rely solely on the measure of IQ to define mental retardation.<sup>9</sup>

The prevalence of developmental delay is estimated at 1% to 3% based on the rate often quoted for mental retardation.<sup>2</sup> However, this may be an overestimate.<sup>10,11</sup> The US Department of Education data from 1993 indicated a rate of 1.14%, although there are state-to-state variations in rates.<sup>12</sup> Developmental disabilities, taken together, affect 5% to 10% of all children.<sup>13</sup>

Developmental surveillance is one important component of a primary care medical home. The AAP Committee on Children With Disabilities states: "All infants and young children should be screened for developmental delays. Screening procedures should be incorporated

into the ongoing health care of the child as part of the provision of a medical home, as defined by the Academy."<sup>1</sup> Developmental screening or surveillance identifies those who may need further evaluation and referral for services. Of those who are screened and identified with developmental delays, only a subset of the whole will be diagnosed with developmental delays that indicate the presence of a cognitive disability and for which this suggested diagnostic evaluation is warranted. The proportion of children who will have developmental delays detected on screening depends on the psychometric characteristics of the screening method used, including sensitivity and specificity of the screening test.<sup>14</sup>

The diagnosis of mental retardation cannot be made accurately or reliably until the child is at least 5 years of age; therefore, many children will continue with the diagnosis of developmental delay until 5 years or older. Thus, developmental delay might be considered as a set of symptoms and signs (a "phenotype") for which a variety of etiologies are known.

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). Some children present with both developmental delay and 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.

Pediatricians are key in the process that ultimately leads to making a diagnosis of DD/MR. Pediatricians often are charged with explaining the etiology of the child's DD/MR to the family as one role in providing a medical home.<sup>1</sup> The primary care pediatrician, by providing the medical home, is key in translating diagnostic results to help families develop an integrated, anticipatory plan including health care, education, and eventual transition planning.<sup>15</sup>

The yield of etiologic evaluations of children with DD/MR vary widely (10% to 81%).<sup>2-5</sup> The wide variation reflects many factors, such as study population differences, extent of the diagnostic evaluation, era during which the study was completed, and improving diagnostic technologic advances over time. There is also wide variation in the category of reported causes of mental retardation: 18.6% to 44.5% of cases have exogenous causes, such as teratogen exposure or infection, and 17.4% to 47.1% have genetic causes.<sup>11,16-18</sup>

For the purposes of this clinical report, we have adopted the definition of "etiology" proposed by Schaefer and Bodensteiner<sup>19</sup>: "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 a finding or sign and not a diagnosis, whereas Down syndrome is a clinical diagnosis, and when confirmed by a routine chromosome study, there is certainty that the clinical diagnosis is correct and indication as to how the patient came to have trisomy 21 (eg, nondisjunction versus translocation).

Pediatricians are expected to know the elements that constitute an optimal clinical genetics diagnostic evaluation for the cause of DD/MR. Families of children with DD/MR expect and deserve to know, whenever possible, the underlying etiology of their child's diagnosis. Pediatricians often refer such patients to consultants, including clinical geneticists, to assist with diagnosis and management and would benefit from knowing what represents an optimal evaluation. Knowing what is likely to be involved in the clinical genetics diagnostic evaluation will assist pediatricians in preparing the family for what to expect during the course of the evaluation and in integrating a diagnosis into the care provided to the child and family (Table 1).

Recently, the American College of Medical Genetics<sup>3</sup> and the American Academy of Neurology and Child Neurology Society<sup>2</sup> published statements on the evaluation of children with DD/MR. This clinical report will refer to these statements and to more recent literature to support this description of an optimal medical genetics evaluation for DD/MR. The AAP recognizes that the evaluation of a child is tailored to the specific facts of that

child's situation as defined by the child, family, and referring pediatrician and that the consulting clinical geneticist will use clinical judgment in devising the most appropriate diagnostic evaluation schema. As Curry et al<sup>3</sup> stated, "there was no uniform consensus regarding the 'right' or 'wrong' approach. No unifying or single algorithm was found appropriate for every patient or every situation. A large number of variables currently affect the physician's evaluation process." And although Shevell et al<sup>2</sup> suggested a diagnostic algorithm, they acknowledge that there are few systematic studies of the process of evaluation. Cost savings are documented<sup>20</sup> when the evaluation process suggested by Shevell et al<sup>2</sup> is used, compared with that of a group of specialists not following a particular process; the diagnostic rate was no different. The AAP Committee on Genetics favors an approach modified from that suggested by van Karnebeek et al,<sup>4</sup> because it emphasizes the importance of the clinical history, family history, and diagnostic skill of the clinical geneticist (Fig 1).

#### EXPECTED OUTCOMES OF A MEDIAL GENETICS EVALUATION

There is no systematic study of the benefits (or harms) of a comprehensive evaluation of the child with DD/MR. However, there are recurring statements of likely benefits for parents and patients in the literature.<sup>3,21-24</sup> For example, Shevell<sup>21</sup> indicated that the "etiologic diagnosis in the young child has immediate implications with respect to recurrence risks and therapeutic imperatives, possessing the potential to modify management and expected outcomes" and that "future medical challenges and the actual prognosis for the disabled child can be more accurately addressed." The family of a child with DD/MR often experiences the feeling of a loss of control,<sup>25</sup> and a diagnosis can contribute to the family feeling in control once more. "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"<sup>23</sup> (Table 2).

#### KEY COMPONENTS OF THE GENETICS EVALUATION

The referring pediatrician and the family will benefit from knowing what to expect from the medical genetics consultation and evaluation. The approach to a child with DD/MR includes the clinical history (including prenatal and birth histories), family history and construction of a pedigree of 3 generations or more, and physical and neurologic examinations, emphasizing the examination for minor anomalies and neurologic or behavioral signs that might suggest a specific recognizable syndrome or diagnosis (Table 3). After this clinical consultation, judicious use of laboratory tests, imaging, and

**TABLE 1** What Families Might Expect From the Clinical Genetics Evaluation

Before visit	Request for child's medical charts; neurodevelopmental test results; all medical test results; copies of MRI, CT, or other imaging studies Request to bring photographs of child and family members Asked about the family history Asked to set aside sufficient time for prolonged consultation
At the visit	Clarify the purpose of the visit Review the child's medical history and neurodevelopmental status Review family history ( $\geq 3$ generations) Complete physical and neurologic examinations Geneticist's initial impressions discussed
After the visit	Clinical photographs Laboratory studies (blood and/or urine tests) Arrangements for MRI or CT studies Arrangements for other consultations (eg, neurology, developmental pediatrics, ophthalmology, etc) Arrangements for ongoing communication and follow-up visits

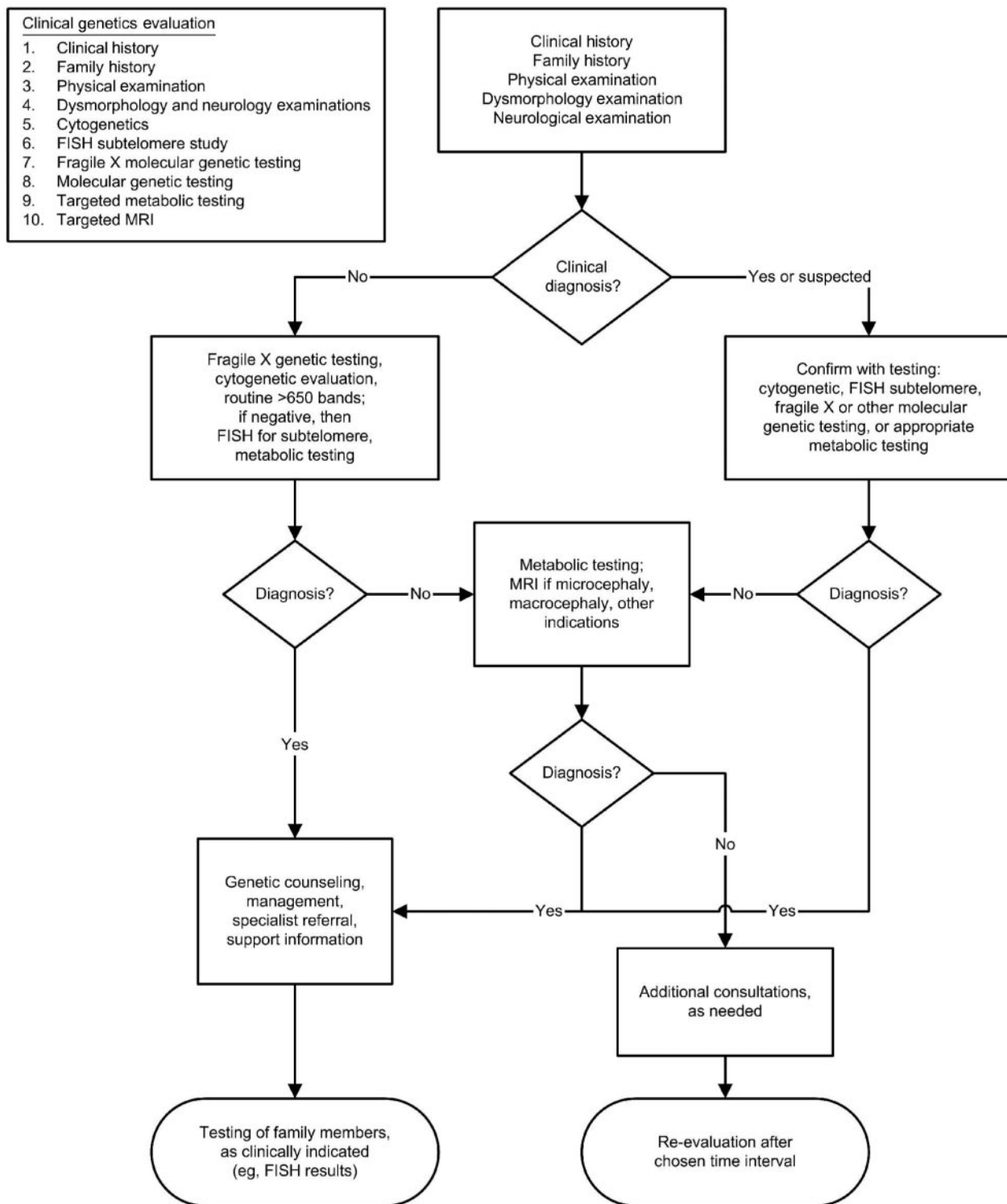


FIGURE 1  
Approach to the clinical genetics evaluation for DD/MR.

other consultant services can be anticipated with most patients.

### Family History

An optimal medical genetics evaluation starts with a comprehensive history and physical examination, in-

cluding a 3-generation family history with particular attention to family members with mental retardation, developmental delays, psychiatric diagnoses, congenital malformations, miscarriages, stillbirths, and early childhood deaths. The medical and family history allows for the clinical geneticist to suspect an etiology and helps in

**TABLE 2** Expected Benefits of Evaluation for DD/MR<sup>3</sup>

For parents	Questions addressed What is the cause of my child's delays? How did this happen? Are there medical complications? What can we expect in the future? Is there treatment? Will this happen again in future children? Can it be prevented in future children? Can we test for it in future pregnancies? Are others in my family at risk? How can I learn more? What support resources are available?
For pediatricians	Clarification of etiology, prognosis, genetic mechanism(s), recurrence risks, treatment options Avoidance of unnecessary tests Information regarding management or surveillance and family support Research/treatment protocols Co-management of appropriate patients

**TABLE 3** Selected Clinical Findings or Laboratory Abnormalities Suggesting a Metabolic Disorder<sup>3</sup>

Failure of appropriate growth
Recurrent unexplained illness
Seizures
Ataxia
Loss of psychomotor skills
Hypotonia
"Coarse" appearance
Eye abnormalities (cataracts, ophthalmoplegia, corneal clouding, abnormal retina)
Recurrent somnolence/coma
Abnormal sexual differentiation
Arachnodactyly
Hepatosplenomegaly
Metabolic/lactic acidosis
Hyperuricemia
Hyperammonemia
Low cholesterol
Structural hair abnormalities
Unexplained deafness
Bone abnormalities (dysostosis, occipital horns, punctuate calcifications)
Skin abnormalities (angiokeratoma, "orange-peel" skin, ichthyosis)

guiding the diagnostic evaluation; it does not stand alone and is important only in the context of the clinical examination. The family history can help in suggesting a diagnosis, particularly when other family members are affected similarly. This is important especially in the case of male patients who have male relatives with DD/MR, related through females who are not mentally retarded. Such a pedigree suggests an X-linked genetic cause of DD/MR and requires special attention (see section on fragile X testing later in this report).

### The Dysmorphologic Examination

Pediatricians and families can expect that an optimal clinical genetics evaluation will include a thorough ex-

amination for minor anomalies that might suggest an etiology or contribute to the recognition of a particular diagnostic pattern—a dysmorphologic examination.<sup>26–28</sup> Schaefer and Bodensteiner<sup>19</sup> state that the "association of mental retardation and congenital malformations has long been recognized" and that "a necessary component of the evaluation of the child with idiopathic mental retardation is a comprehensive dysmorphologic examination."

Several studies of etiology of mental retardation suggest that the dysmorphologic examination and syndrome recognition by an experienced clinical geneticist is the critical diagnostic modality. An early study of the co-occurrence of mental retardation and minor anomalies was that of Smith and Bostian.<sup>29</sup> The authors examined 50 children with mental retardation of unknown cause for the numbers and kinds of minor anomalies; controls consisted of 100 children without mental retardation. They found that 42% of the children with DD/MR had 3 or more minor anomalies, compared with none of the controls. They concluded that the etiology of the mental retardation was abnormal development of the central nervous system (CNS) heralded by the presence of the minor anomalies on the surface examination. Hunter<sup>18</sup> completed a retrospective study of the diagnostic evaluation of 411 children with mental retardation referred to a university-based genetics center between 1986 and 1997. He found that "physical findings in the patient were the most important factors in determining whether or not a diagnosis was made. . . A diagnosis was significantly more likely when a patient was noted to have an unusual appearance (sic) and, although the numbers are small, the presence of a major malformation did not increase the diagnostic rate. Half the diagnoses were made on the basis of a key finding (eg, velopharyngeal incompetence) or the Gestalt of the patient."

In a prospective study of patients referred to a university hospital clinical genetics center in Amsterdam, Netherlands, for diagnostic evaluation for DD/MR, van Karnebeek et al<sup>5</sup> studied 281 children prospectively and made etiologic diagnoses in 150 (54%). One third of these diagnoses were made on the basis of history and examination alone; in another one third, history and examination provided essential clues to the diagnosis, later confirmed by additional studies; and laboratory studies alone provided diagnoses in the remaining one third. For example, in patients with Prader-Willi syndrome, these authors felt the history and examination were contributory to the diagnosis and the molecular genetic analysis was essential for the diagnosis. Using these definitions, they found that the dysmorphologic examination was contributory to the diagnosis in 79% of cases and essential in 62%. This study found that on the basis of clinical history alone, a diagnosis could be estab-

lished in 1 of 20 patients, and on the basis of physical examination alone, a diagnosis could be established in 1 of 30 patients. On the basis of history and examination together, a diagnosis was made in 1 of 3 patients. In addition, the clinical history and examination provided essential guidance to the clinician regarding which additional investigations should be performed. The additional investigations (laboratory and consultation) allowed for diagnosis in another one third of the patients in the study.

Similarly, Battaglia and Carey<sup>30</sup> found that a "pathogenetic diagnosis" could be identified in 80% of all patients; of these, half were diagnosed by history and physical examination alone. Majnemer and Shevell<sup>7</sup> found that a diagnosis was made in 63.3% of patients with "global developmental delays"; of this total, the diagnosis was made by history and physical examination alone in 18.4%. Shevell et al<sup>22</sup> studied 99 children with global developmental delays prospectively, and in 44, an etiology was determined. Of these 44, 15 (38.6%) had diagnoses made by history and physical examination alone. It is emphasized that Wood lamp examination for neurocutaneous disorders, such as tuberous sclerosis, is an essential component of the diagnostic evaluation. Thus, the dysmorphic examination by the experienced clinical geneticist is a key element of the diagnostic evaluation.

### Neurologic Examination

Like the dysmorphic examination, the neurologic examination (defined as the physical examination focused on detecting neurologic abnormalities) is considered essential in the evaluation of every child with DD/MR. However, there are few systematic studies of the utility of the neurologic examination in establishing a diagnosis. For example, in their review, Majnemer and Shevell<sup>7</sup> included in this category the utility of electroencephalography (EEG) and neuroimaging by computed tomography (CT) or magnetic resonance imaging (MRI). The role of the neurologic examination itself is addressed by van Karnebeek et al<sup>4</sup> in their systematic review. They included 5 studies that addressed the neurologic examination alone<sup>18,31-34</sup> and reported that the total yield of etiologic diagnoses in all studies was 42.9%, which means that 42.9% of patients presenting with DD/MR had abnormalities, which typically included cerebral palsy, muscle weakness, spasticity, paresis, and microcephaly. Finding such abnormalities on neurologic examination assisted in determining the need for additional studies, such as EEG, neuroimaging or molecular genetic testing, or referral to other specialists.

### Cytogenetic Studies

Cytogenetic studies in the evaluation of children with DD/MR are to be expected in all children for whom the etiology of DD/MR is unknown. The reported frequency

of chromosome anomalies detected by high-resolution karyotyping (ie,  $\geq 650$  bands) in patients evaluated for DD/MR varies between 9% and 36%.<sup>35</sup> In a recent review of the frequency of cytogenetic abnormalities in the evaluation of patients with mental retardation by van Karnebeek et al,<sup>5</sup> the authors found the median frequency of detected chromosome abnormalities was nearly 1 in 10 patients investigated. Their review noted a wide range of reported frequencies of chromosome abnormalities causing mental retardation—from 2% to 50% depending on the variation in the study design among published reports. They found that chromosome abnormalities were present in all categories of mental retardation (mild to profound) and in both genders. The authors concluded that cytogenetic studies are a "valuable diagnostic technique" in the evaluation of children with DD/MR. In a recent prospective study of the etiology of mental retardation in which karyotyping was performed in 266 children in Amsterdam, van Karnebeek et al<sup>31</sup> found that 21 children (8.3%) had abnormalities (8 numerical, 13 structural). These authors found that there was a relationship between the number of minor anomalies and the likelihood of a chromosomal abnormality: a higher number of anomalies (more than 6) indicated a significantly higher likelihood to find a chromosomal abnormality. They concluded that all patients with no known cause for the DD/MR should have chromosome analysis performed.

Likewise, a review by Shevell et al<sup>2</sup> reported the range of chromosomal abnormalities found on routine cytogenetic analysis to be 2.93% to 11.6%, with a median of 3.7%. They concluded that "routine cytogenetic testing is indicated in the evaluation of the child with developmental delay even in the absence of dysmorphic features or clinical features suggestive of a syndrome." They cite Graham and Selikowitz,<sup>36</sup> who found that 4 of 10 patients with mental retardation attributable to chromosomal abnormalities had no dysmorphic features. Curry et al<sup>3</sup> state that "chromosome analysis in the individual with mental retardation is generally regarded as a mainstay in the overall evaluation process." van Karnebeek et al<sup>4</sup> found that approximately 10% of all patients with DD/MR had a chromosomal abnormality and recommended routine karyotyping in all patients for whom the etiology of the DD/MR was unknown. It is key that the cytogenetic study be reviewed by the clinical geneticist during the evaluation of a particular child. At times, a clinical geneticist may request a second chromosomal analysis for a number of reasons, ranging from high clinical suspicion of a certain chromosomal diagnosis to a desire to have a chromosomal study of sufficient bands to find smaller rearrangements, such as a 700-band study. Thus, pediatricians and families can anticipate that a routine chromosome analysis will be recommended for those patients in whom an etiology is not recognized after the clinical history and examination.

### Submicroscopic Subtelomeric Rearrangements

Approximately half of all structural chromosomal abnormalities (“segmental aneusomies”) include the telomere of the chromosome. A test for the absence of the functional end of the chromosome (subtelomere region) will effectively evaluate many potential abnormalities of that chromosome and, thus, the cause of the DD/MR. Many deletions of the telomeres are visible by standard techniques, and the syndromes caused by such deletions are often clinically recognizable (eg, cri-du-chat syndrome, which is caused by the deletion of the telomere of the short [p] arm of chromosome 5). However, deletions of other subtelomeric regions lead to a phenotype that is not recognized easily, and the deletions often go undetected by routine karyotyping.

Recently, fluorescence in situ hybridization (FISH) techniques have been applied to examine the subtelomeric regions of each chromosome for abnormalities that are known to cause mental retardation.<sup>37–44</sup> Since a complete set of FISH probes has become available clinically, the utility of these probes has been demonstrated by the numerous reports of patients with mental retardation who have had a previously normal routine karyotype, suggesting that subtelomeric abnormalities (deletions or duplications of chromosome regions) are second only to Down syndrome as the most common cause of mental retardation.<sup>41,45</sup> Some deletions and duplications of clinically significant chromosome material at the telomeres are not visible by standard karyotype analytic techniques; these are often referred to as “cryptic” subtelomeric chromosome anomalies (ie, they are not detectable by routine cytogenetic testing). The newer FISH techniques have allowed more sensitive analysis of the telomeres for clinically significant abnormalities.

The application of the FISH technique to examine the subtelomere region of each chromosome has led to the recognition that approximately 7.4% of children with moderate to severe mental retardation who have had normal results of routine chromosome analysis have an abnormality detected (either a deletion or duplication, sometimes both) by the FISH technique to explain their mental retardation. Also, 0.5% of children with mild mental retardation of previously unknown etiology have been found to have cryptic telomere rearrangements as the etiology.<sup>41,45</sup> Only a few subtelomeric syndromes have been delineated to date (Table 4).

Most subtelomeric abnormalities detected by FISH cause mental retardation syndromes that have not been fully delineated, thus making recognition and selection of patients for such testing challenging and counseling families regarding the natural history of their child’s diagnosis difficult.

There have been apparent subtelomere deletions detected by FISH techniques that have been proven to be benign familial “variations” and not the cause of the child’s DD/MR. Such “false positives” are thought to be

**TABLE 4** Recognizable Syndromes Caused by Subtelomeric Abnormalities Detected by FISH Technique

Chromosome Syndrome	Key Features
1pter deletion	Growth retardation; mental retardation; seizures; visual problems; large anterior fontanelle; asymmetric and low-set, dysplastic ears; deep-set eyes; depressed nasal bridge; pointed chin; and fifth finger clinodactyly <sup>72,73</sup>
1p36.3 deletion	Ebstein anomaly; mental retardation <sup>72–74</sup>
1qter deletion	Microcephaly; growth and mental retardation; corpus callosum abnormalities; cardiac anomalies; hypospadias; characteristic facial features <sup>75</sup>
22qter deletion	Developmental delay; hypotonia; absent speech; and normal growth or somatic overgrowth <sup>76–79</sup>

rare<sup>31</sup> but complicate the evaluation of patients and their families by requiring parental samples for confirmation.

Biesecker<sup>45</sup> reviewed 14 studies involving 1718 subjects who were selected on the basis of mental retardation, growth retardation, major and minor anomalies, exclusion of known diagnosis, and familial versus sporadic occurrence. It is notable that even with the variation in subject selection criteria from study to study, there was a relatively constant yield of subtelomere abnormalities detected by FISH of approximately 6%. The presence of major and minor physical anomalies did not affect the yield; however, the yield was higher among familial cases compared with sporadic cases. de Vries et al<sup>47</sup> have proposed a 5-item checklist designed to increase the yield of FISH subtelomere studies; using a score of  $\geq 3$  as a cutoff for subtelomere testing, the authors note that approximately 20% of cases could be excluded from testing without missing a subtelomeric case.

Thus, when the standard karyotype is normal, a FISH study for subtelomere rearrangements is an important diagnostic component in the evaluation of the child with DD/MR.

The use of microarray comparative genomic hybridization in the evaluation of children with DD/MR might be considered best as “emerging technology.”<sup>47</sup> This methodology promises to detect abnormal copy numbers of DNA sequences—deletions and duplications of very small segments of the entire chromosomes. Currently, this testing technique samples many known clinically important loci simultaneously in addition to the subtelomeres and pericentric regions of all chromosomes. Some clinical geneticists have begun to take advantage of this testing technique in patients with undiagnosed DD/MR because it is an efficient method for subtelomere testing and can be used to confirm clinical suspicion on certain diagnoses (eg, Williams syndrome). It appears that this method will increase the clinician’s ability to determine the cause of DD/MR, particularly in cases with minor anomalies. There are currently insufficient published reports of the use of this technology in the evaluation of the child with DD/MR. At the time of



this writing, a few clinical laboratories are offering this type of testing.

### **Molecular Genetic Diagnostic Testing and Fragile X Syndrome**

Molecular genetic diagnostic testing is used to establish the genetic etiology for DD/MR when the diagnosis is considered established clinically (eg, a girl who fulfills established clinical diagnostic criteria for typical Rett syndrome) or suspected clinically (a young boy with nonspecific mental retardation suspected to have fragile X syndrome).

#### *Fragile X Syndrome*

Fragile X syndrome is said to be the most common genetic cause of DD/MR,<sup>2</sup> yet reviews suggest that only approximately 2.0% of patients with mental retardation (both genders) will be found to have a mutation in this gene (with prevalence ranging from 0% to 28.6%).<sup>4</sup> In their comprehensive review of the literature, van Karnebeek et al<sup>4</sup> found that those with more significant mental retardation are more likely to have positive results of fragile X testing (4.1%), compared with those with milder delays or borderline intelligence testing results (1.0%). In a large study of unselected school-aged patients with mental retardation, de Vries et al<sup>48,49</sup> reported a prevalence of fragile X diagnosed by molecular genetic testing to be 0.7%, with a higher prevalence among boys (1.0% for boys, 0.3% for girls). There have been a number of studies using clinical checklists aimed at improving identification of patients for whom fragile X testing is warranted. For example, de Vries et al<sup>49</sup> found that a 7-item clinical checklist increased the molecular genetic diagnostic yield to 7.6% without the loss of cases identified. This checklist included positive family history of mental retardation, long jaw or high forehead, large and/or protuberant ears, hyperextensible joints, soft and velvety palmar skin with redundancy on the dorsum of the hands, testicular enlargement, and behaviors of initial shyness and lack of eye contact followed by friendliness and verbosity. Other checklists designed to increase the efficiency of fragile X genetic testing have been used with results that are generally positive.<sup>50-54</sup> However, the design of such checklists varies, and comparisons among them are difficult. Generally, they included male gender, a positive family history for mental retardation, and absence of microcephaly.

At a consensus conference convened by the American College of Medical Genetics, it was recommended that fragile X testing be “strongly considered in both males and females with unexplained mental retardation especially in the presence of a positive family history, a consistent physical and behavioral phenotype and absence of major structural abnormalities.”<sup>3</sup> Likewise, the Child Neurology Society and American Academy of Neurology advise in a practice parameter that fragile X testing be “considered in the evaluation of the child with

global developmental delay” and that “clinical preselection may narrow the focus of who can be tested without sacrificing diagnostic yield.”<sup>2</sup> van Karnebeek et al<sup>4</sup> recommend that all boys with unexplained mental retardation have molecular genetic testing for fragile X syndrome but caution that routine testing of girls is not warranted unless there are indications of increased risk (eg, a positive family history).

Pediatricians and families can expect that clinical geneticists are likely to recommend testing for fragile X syndrome in any child with undiagnosed DD/MR, particularly if there are findings in the history or examination suggestive of this diagnosis. Molecular genetic testing for fragile X is highly sensitive and specific and is considered the diagnostic standard for fragile X syndrome.<sup>55</sup>

#### *Other Molecular Genetic Testing*

There are situations in which the clinical geneticist may establish a clinical diagnosis and use genetic testing to confirm it (much in the same way that the clinical diagnosis of Down syndrome is confirmed by karyotyping). In addition to confirming the clinical diagnosis, genetic testing may be important for describing the genetic mechanism for the diagnosis and for improving the precision of genetic counseling. For example, Angelman syndrome might be attributable to one of several genetic mechanisms (interstitial deletion of the critical region of chromosome 15q, uniparental disomy, an imprinting mutation, or a mutation in the gene *UBE3A*), the knowledge of which becomes important for genetic counseling as well as for confirming the clinical diagnosis.<sup>56</sup>

In other situations, the clinical geneticist may consider molecular genetic testing for the patient who presents with “atypical features” of a known syndrome, as is the case for those suspected to have a mutation in the *MECP2* gene, which causes Rett syndrome in patients who do not fulfill the diagnostic criteria. There are now case reports of girls with milder presentations consistent with DD/MR who have mutations in *MECP2*<sup>57</sup> as well as males with X-linked mental retardation syndromes.<sup>58</sup> (Also see Laumonnier et al<sup>59</sup> for discussion of *NGLN4* gene mutations and X-linked mental retardation and autism.) Thus, in certain circumstances, the clinical geneticist may suggest testing for *MECP2* mutations when the patient does not fulfill the clinical diagnostic criteria for the syndrome in question (in this example, Rett syndrome) but when deemed appropriate to address the question of an “atypical presentation” of the known clinical syndrome. There is not yet sufficient data to suggest that this be part of the optimal genetics evaluation, but it does serve as an example of a likely trend in clinical genetics.

#### **MRI and CT**

The literature does not indicate universal agreement on the role that brain imaging by CT or MRI plays in the

evaluation of children with DD/MR. Recommendations range from performing brain imaging on all patients with DD/MR<sup>60</sup> to performing it only on those with indications on clinical examination.<sup>4</sup> Major or minor malformations of the brain are known to be an important finding in patients with DD/MR. The finding of a brain abnormality may lead to the recognition of the specific cause for a particular child's DD/MR in the same way that a dysmorphic examination might lead to a clinical diagnosis. However, like other major or minor anomalies noted on physical examination, abnormalities on brain imaging typically are not sufficient for determining the cause of the DD/MR; the cause of the brain anomaly is often unknown. Thus, although a CNS anomaly (often called "CNS dysgenesis") is a useful finding (and considered, according to the definition by Schaefer and Bodensteiner,<sup>19</sup> a useful "diagnosis"), it is frequently not an etiologic or "syndrome" diagnosis. This distinction is not always made in the literature on the utility of MRI in the evaluation patients with DD/MR.

Early studies of the use of CT in the evaluation of patients with idiopathic mental retardation<sup>61</sup> indicated a low diagnostic yield or the nonspecific finding of "cerebral atrophy," which did not contribute to clarifying the cause of the mental retardation.<sup>62</sup> Later studies that used MRI to detect CNS abnormalities suggested that MRI is more sensitive than CT, with increased yield.<sup>2,63</sup> The rate of abnormalities detected on imaging varies widely in the literature as a result of many factors such as subject selection criteria and method of imaging (CT, MRI, whether quantitative methods were used). Schaefer and Bodensteiner,<sup>60</sup> in their literature review, found reported ranges of abnormalities from 9% to 80% of those patients studied. Shevell et al<sup>2</sup> reported a similar range of findings in their review.<sup>2</sup> For example, in 3 studies of a total of 329 children with developmental delay in which CT was used in almost all patients and MRI was used in a small sample, a specific cause was determined in 31.4%,<sup>7</sup> 27%,<sup>22</sup> and 30% of the children.<sup>64</sup> In their systematic review, van Karnebeek et al<sup>4</sup> reported on 9 studies of the use of MRI in children with mental retardation. The mean rate of abnormality found was 30%, with a range of 6.2% to 48.7%, and more abnormalities were found in children with moderate to profound mental retardation versus borderline to mild mental retardation (means of 30% and 21.2%, respectively). These authors also noted that none of the studies reported on the value of the absence of any neuroradiologic 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 implies.

If neuroimaging is performed in only selected cases with abnormal head circumference or an abnormal focal neurologic finding, the rate of abnormalities detected is increased. Shevell et al<sup>22</sup> reported that the percentage of

abnormalities was 13.9% if performed on a "screening basis" but increased to 41.2% if performed on an "indicated basis." In their practice parameter, the American Academy of Neurology and Child Neurology Society<sup>2</sup> discussed other studies on smaller numbers of patients that showed similar results, which led to the recommendation that "neuro-imaging is a recommended part of the diagnostic evaluation," particularly should there be abnormal findings on examination (microcephaly, focal motor findings), and that MRI is preferable to CT. However, in the American College of Medical Genetics consensus conference report,<sup>3</sup> the authors state that neuroimaging by CT or MRI in the normocephalic patient without focal neurologic signs should not be considered "standard of practice" or mandatory. These authors felt that the 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<sup>4</sup> found that MRI alone leads to an etiologic diagnosis in a much lower percentage of patients studied. They cited Kjos et al,<sup>65</sup> who reported diagnoses in 3.9% of patients who had no known cause for their mental retardation and followed no progressive or degenerative course. Bouhadiba et al<sup>66</sup> reported diagnoses in 0.9% of patients with neurologic symptoms, and in 4 additional studies, no etiologic or syndrome diagnosis on the basis of neuroimaging alone was found.<sup>18,62,64,67</sup> The authors of 3 studies reported the results of unselected patients: Majnemer and Shevell<sup>7</sup> reported a diagnosis by this type of investigation in 0.2% of patients, Stromme<sup>34</sup> reported a diagnosis in 1.4% of patients, and van Karnebeek et al<sup>31</sup> reported a diagnosis in 2.2% of patients.

Abnormal findings on MRI are seen in approximately 30% of patients with DD/MR. However, MRI leads to an etiologic or syndrome diagnosis in 0% to 3.9% of patients studied. The value of a negative MRI result in leading to a diagnosis has not been studied. In addition, MRI in the young child with DD/MR invariably requires sedation or anesthesia to immobilize the child to accomplish the study. Although this poses a small risk for the child, it merits appropriate consideration by the clinicians and family.<sup>60</sup> Thus, although MRI is often useful in the evaluation of the child with DD/MR, it is not a mandatory study and has a higher diagnostic yield when indications exist (eg, microcephaly, focal motor findings on neurologic examination).

### Metabolic Studies

Inborn errors of metabolism are a rare cause of DD/MR (approximately 1%), particularly when there are no other signs or symptoms suggestive of a metabolic disorder. Although rare, the effect of proper diagnosis and treatment of a metabolic disorder on the patient's prognosis may be substantial.

Shevell et al<sup>2</sup> found that "routine metabolic screen-

ing" of patients with DD/MR has a diagnostic yield of less than 1% and that a stepwise evaluation (on the basis of clinical indicators) will increase the diagnostic yield (on the basis of the single report of Papavasiliou et al<sup>68</sup>). Curry et al<sup>3</sup> found an "extremely low yield for unselected metabolic screening" and concluded that metabolic testing should be selective and "targeted at the suspected category of disorder" on the basis of the history and examination. In their systematic literature review, van Karnebeek et al<sup>4</sup> identified 16 studies that addressed the metabolic evaluation of patients with DD/MR. They reported diagnostic yield from metabolic studies of 0.2% to 8.4%, with a median of 1.0% of patients. The higher rates were from countries in which a specific metabolic disorder is common (eg, aspartylglycosaminuria in Finland) or from a study that included targeted screening of highly inbred populations. van Karnebeek et al<sup>4</sup> also found that comparison between studies was not possible given the lack of uniformity of metabolic testing from study to study.<sup>4</sup> These authors suggest that the need for any metabolic studies be determined by the history and examination findings and that, to standardize and study the approach, checklists be used to guide the metabolic evaluation of patients with DD/MR. Hunter<sup>18</sup> accepted "a metabolic screen . . . in any child under a year of age or who showed apparent deterioration" in his review of his center's evaluation process. Hunter reported that 37.5% of his patient sample had a metabolic screening of urine amino acids, mucopolysaccharides, nitroprusside, ketones, reducing substances, phenylhydrazide, and ferric chloride, and 7.1% had an organic acid screening. Using criteria that screening was justified if there were signs of a specific biochemical disease or the child had unexplained mental retardation and was younger than 1 year or there was evidence of apparent deterioration, Hunter<sup>18</sup> concluded that 75.3% of the metabolic screens and 69% of the organic acid studies were unnecessary. van Karnebeek et al<sup>3</sup> stated that "metabolic studies should not be performed as the first diagnostic study in each child, but in the absence of clues for other causes the yield is still of sufficiently high level to allow testing." Thus, there is a range of expert opinion regarding what constitutes the optimal metabolic screening pathway for patients who present with nonspecific DD/MR. More study in this area is needed.

Routine metabolic screening of all patients with DD/MR is not required; targeted metabolic studies are expected in patients on the basis of findings in the history or examination or if the clinical geneticist judges them necessary. Curry et al<sup>3</sup> have listed selected clinical findings or laboratory abnormalities that may indicate the need for further metabolic investigations (Table 3). Even in the absence of such indicators, some experts recommend routine metabolic testing of patients with nonspecific DD/MR.

Tandem mass spectrometry for screening for inborn

**TABLE 5 Clinical Genetics Evaluation of the Child With DD/MR**

1. Clinical history
2. Family history
3. Dysmorphic examination
4. Neurologic examination
5. Karyotype
6. FISH for subtelomere abnormalities
7. Fragile X molecular genetic testing
8. Molecular genetic testing
9. Brain imaging (MRI)
10. Metabolic testing

errors of metabolism in newborn infants is an example of a recent technology that may affect the ability to screen patients with DD/MR for inborn errors of metabolism. Many metabolic conditions appear to be identifiable with relatively little cost<sup>69,70</sup> and a small sample of blood. However, there is insufficient literature on the clinical application at this time to judge its appropriateness in the evaluation of the child with DD/MR. Because the technology is used for newborn screening programs, the clinical utility in other settings, such as the evaluation of children who might be clinically symptomatic, is being discussed.<sup>69,71</sup> Studies addressing the optimal metabolic evaluation of patients with DD/MR are needed.

#### SUMMARY

The aim of this clinical report was to describe what pediatricians and patients can anticipate as an optimal clinical genetics evaluation of the child with DD/MR (Table 5) and the anticipated benefits and outcome of such an evaluation. The literature supporting the clinical genetics diagnostic evaluation has been provided, as has a description of what pediatricians and families can anticipate. It is important to note that many patients will not have an etiologic diagnosis as a result of a complete diagnostic consultation. These patients and families deserve occasional reevaluations by the clinical geneticist as new diagnostic testing becomes available that might address the etiology of the child's DD/MR. The interval between diagnostic evaluations or the indications for reconsidering the evaluation timing (eg, new signs or symptoms) are topics that have not been systematically studied. It is important that the consulting clinical geneticist, primary care pediatrician (medical home), and family discuss the interval between evaluations and any signs or symptoms that might prompt an earlier return to the clinical geneticist.

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## Clinical Genetic Evaluation of the Child With Mental Retardation or Developmental Delays

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