Complete Summary

GUIDELINE TITLE

Clinical genetic evaluation of the child with mental retardation or developmental delays.

BIBLIOGRAPHIC SOURCE(S)

Moeschler JB, Shevell M, American Academy of Pediatrics Committee on Genetics. Clinical genetic evaluation of the child with mental retardation or developmental delays. Pediatrics 2006 Jun;117(6):2304-16. [79 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

All clinical reports and policy statements from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Developmental delays
- Mental retardation

GUIDELINE CATEGORY

Diagnosis
Evaluation

CLINICAL SPECIALTY

Family Practice
Medical Genetics
Neurology
Pediatrics

INTENDED USERS

Allied Health Personnel
Physicians

GUIDELINE OBJECTIVE(S)

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

TARGET POPULATION

Children with developmental delays or mental retardation

INTERVENTIONS AND PRACTICES CONSIDERED

1. Clinical history
2. Family history (3 generations or more)
3. Dysmorphologic examination
4. Neurologic examination
5. Karyotype
6. Fluorescence in situ hybridization (FISH) for subtelomere abnormalities
7. Fragile X molecular genetic testing
8. Molecular genetic testing
9. Brain imaging (magnetic resonance imaging [MRI]) if indicated
10. Targeted metabolic testing

MAJOR OUTCOMES CONSIDERED

Sensitivity and specificity of the methods of clinical genetic evaluation

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Published cost analyses were reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

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 (see Table titled "What Families Might Expect from the Clinical Genetics Evaluation," below).

Table. 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 magnetic resonance imaging (MRI), computed tomography (CT), or other imaging studies • Request to bring photographs of child and family members • Ask about the family history • Ask 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 (e.g., neurology, developmental pediatrics, ophthalmology, etc.) • Arrangements for ongoing communication and follow-up visits

The approach to a child with developmental delays/mental retardation (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 (see Table titled "Selected Clinical Findings or Laboratory Abnormalities Suggesting a Metabolic Disorder," below). After this clinical consultation, judicious use of laboratory tests, imaging, and other consultant services can be anticipated with most patients.

Table. Selected Clinical Findings or Laboratory Abnormalities Suggesting a Metabolic Disorder

• 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)

Family History

An optimal medical genetics evaluation starts with a comprehensive history and physical examination, including 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 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 summary).

The Dysmorphologic Examination

Pediatricians and families can expect that an optimal clinical genetics evaluation will include a thorough examination for minor anomalies that might suggest an etiology or contribute to the recognition of a particular diagnostic pattern—a 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. In an early study, 50 children with mental retardation of unknown cause were examined for the numbers and kinds of minor anomalies; controls consisted of 100 children without mental retardation. It was found that 42% of the children with DD/MR had 3 or more minor anomalies, compared with none of the controls. It was 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.

In a prospective study of patients referred to a university hospital clinical genetics center in Amsterdam, Netherlands, for diagnostic evaluation for DD/MR, etiologic diagnoses were made in 54% of cases. 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.

Thus, the dysmorphologic examination by the experienced clinical geneticist is a key element of the diagnostic evaluation.

Neurologic Examination

Like the dysmorphologic 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.

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 (i.e., $\geq$650 bands) in patients evaluated for DD/MR varies between 9% and 36%. In a recent review of the frequency of cytogenetic abnormalities in the evaluation of patients with mental retardation, 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.

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 (e.g., 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. 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. 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 (i.e., 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. Only a few subtelomeric syndromes have been delineated to date (see Table 4 in the original guideline document).

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 rare but complicate the evaluation of patients and their families by requiring parental samples for confirmation.

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." This methodology promises to detect abnormal copy numbers of DNA sequences—deletions and duplications of very small segments of the entire 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 (e.g., 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.

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 (e.g., 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, 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%).

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, one group of researchers 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. 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." 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."

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.

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.

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* as well as males with X-linked mental retardation syndromes. 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 computed tomography (CT) or magnetic resonance imaging (MRI) plays in the evaluation of children with DD/MR. Recommendations range from performing brain imaging on all patients with DD/MR to performing it only on those with indications on clinical examination. 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 dysmorphologic 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 central nervous system (CNS) anomaly (often called "CNS dysgenesis") is a useful finding, it is frequently not an etiologic or "syndrome" diagnosis.

Early studies of the use of CT in the evaluation of patients with idiopathic mental retardation indicated a low diagnostic yield or the nonspecific finding of "cerebral atrophy," which did not contribute to clarifying the cause of the mental retardation. Later studies that used MRI to detect CNS abnormalities suggested that MRI is more sensitive than CT, with increased yield. 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).

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.

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. 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 (e.g., 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.

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. Selected clinical findings or laboratory abnormalities that may indicate the need for further metabolic investigations are listed in the Table titled "Selected Clinical Findings or Laboratory Abnormalities Suggesting a Metabolic Disorder," above. 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 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 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. 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 (see Table 5 in the original guideline document) 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 (e.g., 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.

CLINICAL ALGORITHM(S)

An algorithm is provided in the original guideline document for "Approach to the Clinical Genetics Evaluation for Developmental Delay/Mental Retardation."

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting each recommendation is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate clinical genetic evaluation of the child with mental retardation or developmental delays

POTENTIAL HARMS

- There have been apparent subtelomere deletions detected by fluorescence in situ hybridization (FISH) techniques that have been proven to be benign familial "variations" and not the cause of the child's developmental delay/mental retardation (DD/MR). Such "false positives" are thought to be rare but complicate the evaluation of patients and their families by requiring parental samples for confirmation.
- Magnetic resonance imaging (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.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- 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.
- The American Academy of Pediatrics (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.
- There are few systematic studies of the utility of the neurologic examination in establishing a diagnosis of developmental delays/mental retardation (DD/MR).
- There are currently insufficient published reports of the use of microarray comparative genomic hybridization in the evaluation of children with DD/MR.
- The literature does not indicate universal agreement on the role that brain imaging by computed tomography (CT) or magnetic resonance imaging (MRI) plays in the evaluation of children with DD/MR. Recommendations range from

performing brain imaging on all patients with DD/MR to performing it only on those with indications on clinical examination.

- Tandem mass spectrometry for screening for inborn 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. 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.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Moeschler JB, Shevell M, American Academy of Pediatrics Committee on Genetics. Clinical genetic evaluation of the child with mental retardation or developmental delays. Pediatrics 2006 Jun;117(6):2304-16. [79 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Jun

GUIDELINE DEVELOPER(S)

American Academy of Pediatrics - Medical Specialty Society

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American Academy of Pediatrics

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

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GUIDELINE AVAILABILITY

Electronic copies: Available from the American Academy of Pediatrics (AAP) Policy Web site.

Print copies: Available from American Academy of Pediatrics, 141 Northwest Point Blvd., P.O. Box 927, Elk Grove Village, IL 60009-0927.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

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