Abstract—Objective: To make evidence-based recommendations concerning the evaluation of the child with a nonprogressive global developmental delay. Methods: Relevant literature was reviewed, abstracted, and classified. Recommendations were based on a four-tiered scheme of evidence classification. Results: Global developmental delay is common and affects 1% to 3% of children. Given yields of about 1%, routine metabolic screening is not indicated in the initial evaluation of a child with global developmental delay. Because of the higher yield (3.5% to 10%), even in the absence of dysmorphic features or features suggestive of a specific syndrome, routine cytogenetic studies and molecular testing for the fragile X mutation are recommended. The diagnosis of Rett syndrome should be considered in girls with unexplained moderate to severe developmental delay. Additional genetic studies (e.g., subtelomeric chromosomal rearrangements) may also be considered in selected children. Evaluation of serum lead levels should be restricted to those children with identifiable risk factors for excessive lead exposure. Thyroid studies need not be undertaken (unless clinically indicated) if the child underwent newborn screening. An EEG is not recommended as part of the initial evaluation unless there are historical features suggestive of epilepsy or a specific epileptic syndrome. Routine neuroimaging, with MRI preferred to CT, is recommended particularly if abnormalities are found on physical examination. Because of the increased incidence of visual and auditory impairments, children with global developmental delay may undergo appropriate visual and audiometric assessment at the time of diagnosis. Conclusions: A specific etiology can be determined in the majority of children with global developmental delay. Certain routine screening tests are indicated and depending on history and examination findings, additional specific testing may be performed.
a clinical presentation that has a heterogeneous etiologic profile and is associated with age-specific deficits in adaptation and learning skills. Those deficits are evident in comparison with the skills attainment of chronological peers. Significant delay is defined as performance two standard deviations or more below the mean on age-appropriate, standardized norm-referenced testing. The term global developmental delay is usually reserved for younger children (i.e., typically less than 5 years of age), whereas the term mental retardation is usually applied to older children when IQ testing is more valid and reliable.4-13

A child with the clinical picture of global developmental delay is not necessarily destined to be mentally retarded. Infants and children may have global developmental delay owing to conditions such as cerebral palsy, certain neuromuscular disorders, and other conditions such as early environmental deprivation, yet when they are old enough to measure cognitive level they do not score in the mentally retarded range. The diagnosis of mental retardation, according to the American Association of Mental Retardation8 and the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision,11 requires accurate and valid assessment of intelligence, which is generally not possible in infants and young children8 in addition to deficits in adaptive function. Available valid instruments for assessing intelligence (such as the Stanford-Binet or Wechsler Preschool Primary Scale of Intelligence) are not generally applicable under age 3 years.12

The precise prevalence of global developmental delay is unknown. Estimates of 1% to 3% of children younger than 5 years are reasonable given the prevalence of mental retardation in the general population.14 Based on approximately 4 million annual births in the United States and Canada, between 40,000 and 120,000 children born each year in these two countries will manifest global developmental delay.

Developmental surveillance is recognized as an integral component of pediatric care.15 Professional organizations dedicated to the medical care of children recommend routine monitoring of a child’s developmental progress.15,16 Formal screening, together with reliance on parental reporting measures, constitutes the primary means by which children with global developmental delay are identified.17 In addition, children possessing either biologic or social risk factors for later developmental delay are often targeted through specific follow-up programs that incorporate routine periodic assessments evaluating developmental performance.18 Environmental influences such as culture, parental skills, neglect, and opportunity may modify the cause’s expression as well as the detection and diagnosis of global developmental delay. Accumulating evidence also demonstrates the benefits of early intervention through a variety of programs (e.g., Head Start) with respect to short-term outcomes19 and suggests that early diagnosis of a child with global delay may improve outcome.

Initial screening is important not only in identifying children with developmental delay but also is the first step in determining whether a child has global delay, a language disorder, or an autistic spectrum disorder. This parameter is focused specifically on the child who has global developmental delay. Previous parameters have reviewed the evaluation of children and adolescents with language disorders20 and autistic spectrum disorders.21

Identification of a globally delayed young child by routine pediatric screening in the first years of life mandates a careful search for an underlying etiology.22 This search is usually initiated by the primary care physician and frequently requires referral to either a child neurologist or developmental pediatrician.7,23 Accurate etiologic determination, despite the fact that many disorders have no specific therapeutic interventions, has specific implications regarding treatment, prognosis, ongoing medical management of associated conditions, assessment of recurrence risk, counseling of families if there is a risk of recurrence, and implementation of prevention programs.7,14,24 Determining causality also empowers the affected family in planning for their child and limits further unnecessary testing.25

Estimates of the etiologic yield (10% to 81%) in children with global developmental delay/mental retardation are highly variable.7,14,24-29 The reported variability in diagnostic yield can be attributed to differences in a variety of factors including sample population characteristics, severity of delay in the children studied, extent of diagnostic investigations, and technological advances over time, especially with respect to genetic and neuroimaging techniques. Considerable uncertainty exists among practitioners evaluating young children with global developmental delay with respect to the appropriate extent of laboratory investigations and referral for ancillary services.24,30,31 Laboratory investigations should be undertaken only after a comprehensive history and physical examination are undertaken. One prospective (17.2% yield) and two retrospective (19.1%, 34.2%) studies have shown that the etiology of developmental delay can be established on the basis of the history and examination.7,28,29

This practice parameter reviews available evidence concerning the value of diagnostic testing in the initial evaluation of a young child with a global developmental delay that is static, nonprogressive, and has no clear etiology. Based on this evidence, specific recommendations for each testing modality are provided.

Description of process. Literature searches were conducted with the assistance of the University of Minnesota Biomedical Information Services for relevant articles published from 1980 to 2000. Databases searched included MEDLINE, Healthstar, ERIC, and CINAHL. Depending on the particular diagnostic test/ancillary service of interest, key words/phrases included the following: mental retardation, developmental delay, developmental disability, neurodevel-
neurological and psychiatric evaluation. Searches were restricted to the English language under the subheading of infant and child.

Individual committee members reviewed titles and abstracts so identified for content and relevance. Articles dealing with investigations in developmental delay with reference to determining a possible etiology were selected for further detailed review. From the bibliographies of several articles selected for review, additional articles thought to be relevant were identified at the discretion of committee members. A bibliography of the 160 articles identified and reviewed for preparation of this parameter is available at the American Academy of Neurology website (http://www.aan.com/). Relevant position papers were also sought from professional organizations, including the consensus statement of the American College of Medical Genetics on the evaluation of mental retardation.

Each article was reviewed, abstracted, and classified by a committee member. A four-tiered classification scheme for diagnostic evidence recently approved by the Quality Standards Subcommittee was utilized as part of this assessment (Appendix 2). Depending on the strength of this evidence it was decided whether specific recommendations could be made, and if so, the level of strength of these recommendations (Appendix 3). Evidence pertinent to each diagnostic test followed by the committee’s evidenced-based recommendations are presented. The committee selected a value of 1% as a clinically meaningful cutoff point for diagnostic yield. Thus if the diagnostic yield of a test was less than 1% it was felt that this test should not be performed on a routine basis whereas tests with yields greater than 1% should be considered.

What is the diagnostic yield of metabolic and genetic investigations in children with global developmental delay? Evidence. Laboratory investigations relevant to the possible ascertainment of an underlying etiology include metabolic studies that screen for specific inborn errors of metabolism, cytogenetic and molecular tests that employ various techniques, and screening for chronic lead poisoning and hypothyroidism.

Metabolic studies. Two class III studies (table 1) involving 2,655 patients have evaluated the diagnostic yield of screening for metabolic disorders in institutionalized populations of individuals with presumed significant global developmental delay or mental retardation. A diagnostic yield of 0.6%34 and 1.3%35 was obtained utilizing nonsyndrome screening protocols. A class II population-based study from Israel36 and a class IV study of heterogeneous North American children with global developmental delay7 highlighted that the diagnostic yield for metabolic testing was about 1% even within the context of a history or examination suggestive of a possible underlying metabolic disorder. A more recent class II prospective study from the same group of investigators confirmed a yield of less than 5% even on an indicated (i.e., family history, parental consanguinity) basis. Typically metabolic screening in these studies involved amino and organic acids together with a determination of serum ammonia and lactate levels.

Neonatal screening programs for metabolic disorders (varying in testing but typically involving amino and organic acids and thyroid function) identify infants with conditions that are associated with global developmental delay. These have decreased the number of children who present with undiagnosed global developmental delay and thus decrease the yield of metabolic testing in this particular population done later in life. The advent of tandem mass spectrometry has further increased the yield of neonatal screening programs (i.e., universal newborn screening). Although the yield from metabolic testing is low, one issue that needs consideration is whether a treatable condition that was not detected using a neonatal screening program would be missed. Most children with an inborn error of metabolism have other symptoms (e.g., failure to thrive, developmental regression, episodic decompensation) or physical findings (e.g., hepatosplenomegaly, coarse facial features) that prompt diagnostic testing, making the likelihood of not diagnosing a treatable condition presenting just with symptoms of global developmental delay quite low. In addition, nonspecific and nondiagnostic abnormalities are fre-

<table>
<thead>
<tr>
<th>Reference</th>
<th>Class</th>
<th>N</th>
<th>Results (% patients with abnormal screening)</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>II</td>
<td>151</td>
<td>26% for mild delay; 77% for severe delay; genetic etiology in 28%, 5% were metabolic disorders</td>
</tr>
<tr>
<td>34</td>
<td>III</td>
<td>1,087</td>
<td>0.6%; standardized biochemical screening</td>
</tr>
<tr>
<td>35</td>
<td>III</td>
<td>1,568</td>
<td>1.3%; standardized biochemical screening</td>
</tr>
<tr>
<td>7</td>
<td>III</td>
<td>60</td>
<td>63% with all testing but less than 1% for metabolic testing</td>
</tr>
<tr>
<td>36</td>
<td>III</td>
<td>281</td>
<td>&lt;5%; nonstandardized evaluation; etiologic yield of 72% for whole group</td>
</tr>
<tr>
<td>28</td>
<td>III</td>
<td>99</td>
<td>&lt;5% even on an indicated basis</td>
</tr>
<tr>
<td>37</td>
<td>III</td>
<td>118</td>
<td>13.6% using stepwise rather than routine screening protocol</td>
</tr>
</tbody>
</table>

Table 1 Metabolic testing in children with global developmental delay
quently found when routine metabolic screening is performed and often lead to additional extensive and expensive laboratory testing.32

Also to be considered is the potential role of doing focused, selective, or sequential (i.e., based on results of prior testing) rather than routine metabolic screening.32 Using this approach, tests would be ordered if there were specific features in the history or examination to suggest a specific group of metabolic disorders (i.e., focused or selective evaluation) or, if tests were ordered, based on doing those with the greatest yield first and then if negative ordering the next level of testing that has a lower diagnostic yield (sequential). Few data are available that address this question except for a recent class III report of 118 children that used a stepwise rather than a routine screening approach. This study found a diagnostic yield of 13.6%, which is much higher than that reported using routine screening of all patients with undiagnosed global developmental delay.37 Findings on physical (dysmorphology, organomegaly), neurologic, and ophthalmologic examination as well as the results of basic laboratory screening tests were used to decide additional targeted tests that were performed.

Conclusions. Routine screening for inborn errors of metabolism in children with global developmental delay has a yield of about 1% that can, in particular situations such as relatively homogeneous and isolated populations or if there are clinical indicators, increase up to 5%. When stepwise screening is performed the yield may increase to about 14%.

Cytogenetic studies. Six class III studies (table 2, top) have addressed the yield of cytogenetic testing (karyotype) in individuals with global developmental delay/mild to moderate mental retardation. These studies, encompassing 3,672 patients, in almost all of whom the etiology of developmental delay was not evident, documented a frequency of cytogenetic abnormalities of 2.93%,41 3.9%,42 4.7%,43 5.4%,44 7.1%,28 and 11.6%.29 The overall yield was 3.7% and some of the more common cytogenetic abnormalities found included Down syndrome, sex chromosome aneuploidies (47, XXY), fragile X syndrome, and unbalanced translocations/deletion syndromes. In one of these studies, the presence of two or more dysmorphic features was associated with a higher yield of cytogenetic abnormalities (20%).42 One of these class III studies28 involving 99 children found a similar yield whether testing was performed on an indicated or screening basis. Two retrospective class IV studies involving 230 children identified yields of 3.5%45 and 10%7 on routine cytogenetic testing in children with global developmental delay. Technical issues related to the type and resolution of specific cytogenetic studies have been reviewed in the 1997 American College of Medical Genetics consensus report.32

Fragile X studies. Fragile X syndrome, due to a mutation of the FMR1 gene, represents the most common inherited disorder causing global developmental delay and merits special diagnostic attention.

Four forms of the CGG trinucleotide repeat have been described: normal (6 to 40 repeats), intermediate (41 to 60 repeats), premutation (61 to 200 repeats), and full mutation (>200 to 230 repeats). Prevalence of the full mutation associated with developmental delay ranges from 1 per 3,717 to 8,918 males in the general population whereas prevalence of the premutation is approximately 1 per 1,000. In females, prevalence of the full mutation based on large population studies has not yet been reported but the premutation or carrier rate is estimated to be between 1 per 246 to 468 individuals in the general population.46

Table 2 summarizes data on clinical studies related to the prevalence of fragile X syndrome. Two class III studies totaling 2,877 patients with undiagnosed developmental delay found incidences of FMR1 mutations in 2.3%28 and 2.61%41 of these populations. One class IV comprehensive analysis of 16 studies evaluating 4,940 males with mental retardation and/or autistic features found a pooled average incidence of 5.3% for fragile X syndrome using older methods of laboratory study.46 Prevalences in this study ranged from 0 to 19.5%. A class III prospective study of 103 males with moderate to severe learning

<table>
<thead>
<tr>
<th>Reference</th>
<th>Class</th>
<th>N</th>
<th>Results*</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>III</td>
<td>2,757</td>
<td>2.93% (2.61% also had FraX)</td>
</tr>
<tr>
<td>42</td>
<td>III</td>
<td>256</td>
<td>3.9%</td>
</tr>
<tr>
<td>43</td>
<td>III</td>
<td>274</td>
<td>4.7% (9.1% also had FraX)</td>
</tr>
<tr>
<td>44</td>
<td>III</td>
<td>166</td>
<td>5.4%</td>
</tr>
<tr>
<td>28</td>
<td>III</td>
<td>99</td>
<td>7.1%</td>
</tr>
<tr>
<td>29</td>
<td>III</td>
<td>120</td>
<td>11.6% (2.3% also had FraX)</td>
</tr>
<tr>
<td>47</td>
<td>II</td>
<td>1,581</td>
<td>0.7% FraX overall with 1.0% in males, 0.3% in females, and 7.6% in males with clinically pre-selected criteria</td>
</tr>
<tr>
<td>48</td>
<td>II</td>
<td>80</td>
<td>0% females with FraX</td>
</tr>
<tr>
<td>49</td>
<td>II</td>
<td>29</td>
<td>0% females with FraX</td>
</tr>
<tr>
<td>50</td>
<td>II</td>
<td>278</td>
<td>0.3% females with FraX</td>
</tr>
<tr>
<td>51</td>
<td>II</td>
<td>128</td>
<td>3.9% females with FraX</td>
</tr>
<tr>
<td>52</td>
<td>II</td>
<td>56</td>
<td>4.0% females with FraX</td>
</tr>
<tr>
<td>53</td>
<td>II</td>
<td>194</td>
<td>4.1% females with FraX</td>
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<td>54</td>
<td>II</td>
<td>35</td>
<td>11.4% females with FraX</td>
</tr>
<tr>
<td>55</td>
<td>III</td>
<td>103</td>
<td>3.9% FraX</td>
</tr>
<tr>
<td>56</td>
<td>IV</td>
<td>4,940</td>
<td>5.3% FraX</td>
</tr>
</tbody>
</table>

* For references 7, 28, 29, and 41–45 (top of table), % of patients with abnormal results on cytogenetic studies; for references 48–56 (bottom of table), % of patients with fragile X (FraX).
difficulties yielded a 3.9% incidence among males for the \textit{FMR1} mutation using molecular techniques.\textsuperscript{35} Pooled data (see table 2, bottom) from seven studies involving 785 females with varying degrees of mental retardation found an incidence of the fragile X mutation of 2.5%.\textsuperscript{48-54} In a more recent study of 2,757 individuals with mental retardation, 2.6% had fragile X mutations and one-third of these individuals were female.\textsuperscript{41} Sisters of fragile X males are also more likely to have the fragile X mutation and if so are more likely to exhibit cognitive impairment, prominent ears, shyness, and poor eye contact.\textsuperscript{57}

Molecular screening of the \textit{FMR1} gene in a population of individuals derived from residential institutions, special schools, sheltered workshops, and group homes with mental retardation of unknown cause (1,581 individuals—896 males, 685 females) resulted in a new diagnosis in 11 cases (0.7%) (class II study).\textsuperscript{57} In this study, utilizing a simple seven-item checklist of clinical features in the males would have eliminated from molecular analysis 86% of the sample without loss of any newly diagnosed cases. These seven items included a family history of mental retardation, facial features including either a long jaw or high forehead, large and/or protuberant ears, hyperextensible joints, soft and velvety palmar skin with redundancy on the dorsum of the hand, enlargement of the testes, and personality attributes with initial shyness and lack of eye contact followed by friendliness and verbosity. Thus, clinical preselection increased the efficiency of molecular testing in males to a 7.6% yield.

\textbf{Testing for Rett syndrome.} Rett syndrome is currently believed to be one of the leading causes of global developmental delay/mental retardation in females and is caused by mutations in the X-linked gene encoding methyl-CpG-binding protein 2 (\textit{MECP2}).\textsuperscript{32} About 80% of patients with Rett syndrome have \textit{MECP2} mutations; however, \textit{MECP2} mutations can occur without clinical features of this disorder. Patients with classic Rett syndrome appear to develop normally until 6 to 18 months of age, then gradually lose speech and purposeful hand use, and develop abnormal deceleration of head growth that may lead to microcephaly. Seizures, autistic-like behavior, ataxia, intermittent hyperventilation, and stereotypic hand movements occur in most patients. The prevalence of Rett syndrome in the general population is approximately 1 to 3 individuals per 10,000 live births\textsuperscript{58,61} and it has been estimated that there are approximately 10,000 individuals in the United States with this disorder.\textsuperscript{62} In institutionalized individuals with mental retardation, the incidence has been estimated at 2.5%.\textsuperscript{63} Rett syndrome was initially believed to occur primarily in females with severe developmental delay. Recent studies have shown that milder forms of this disorder occur in females and that males with more severe global delay have features similar to Rett syndrome seen in females.\textsuperscript{58,64} Currently there are insufficient data to estimate the prevalence of Rett syndrome variants in milder affected females or in males.

\textbf{Molecular screening for subtelomeric chromosomal rearrangements.} The value of molecular rather than cytogenetic screening for chromosomal rearrangements has been shown in a number of recent studies. Following an initial report\textsuperscript{65} that up to 6% of children with moderate to severe developmental delay might have small rearrangements involving the ends of chromosomes (subtelomeric rearrangements), there has been considerable interest in determining whether molecular screening should become routine in cases of idiopathic developmental delay.\textsuperscript{66,67} Data from 11 class I and II studies involving 1,952 children are summarized in table 3.

Nine studies used fluorescence in situ hybridization (FISH) of subtelomeric probes to detect chromosomal rearrangements\textsuperscript{68-70,72,74-76} and two studies used microsatellite markers.\textsuperscript{71,73} The latter approach is able to detect uniparental disomy (inheritance of both copies of one chromosome from the same parent). However, this technique makes only a small contribution (0.7%) to the etiology of idiopathic developmental delay.

FISH screening of patients with moderate or severe developmental delay has demonstrated a relatively high yield. Abnormalities were detected in 6.8% of 840 patients with moderate or severe developmental delay compared to only 1.1% of 379 patients with mild retardation and 0.9% of 225 controls (see table 3). The presence of chromosomal abnormalities in control patients raises the possibility that a proportion of these abnormalities may not be the cause of mental retardation. In most cases this has been excluded by investigating the parents and observing whether the chromosomal anomaly segregates with the developmental delay.

Diagnostic yield in detecting subtelomeric chromosomal rearrangements may also be improved by selective screening. In a study of 29 patients with subtelomeric abnormalities, it was demonstrated that a five-item checklist (family history of developmental delay, prenatal onset of growth retardation, presence of two or more facial dysmorphic features, postnatal growth abnormalities [micro or macrocephaly, short or tall stature], and nonfacial and congenital abnormalities) increased the diagnostic yield.\textsuperscript{79}

Conclusions. The accumulated data suggest that cytogenetic studies will be abnormal in 3.7% of children with global developmental delay, a yield that is likely to increase in the future as new techniques are employed. In mixed populations (both males and females), a yield of between 0.3% and 5.3% (average yield of 2.6%) has been demonstrated for fragile X testing. The higher range of this yield exists for testing among males. There is a suggestion that clinical preselection for the fragile X syndrome among males may improve diagnostic testing beyond routine screening. After Down syndrome, Rett syndrome is believed to be the most common cause of developmental delay in females.\textsuperscript{58} Although milder variants in females and more severe phenotypes in males recently have been recognized, estimates of their prev-
Subtelomeric chromosomal rearrangements have been found in 6.6% (0 to 11.1%) of patients with idiopathic moderate to severe developmental delay.

Recommendations.
1. Given the low yield of about 1%, routine metabolic screening for inborn errors of metabolism is not indicated in the initial evaluation of a child with global developmental delay provided that universal newborn screening was performed and the results are available for review. Metabolic testing may be pursued in the context of historical (parental consanguinity, family history, developmental regression, episodic decompensation) or physical examination findings that are suggestive of a specific etiology (or in the context of relatively homogeneous population groups) in which the yield approaches 5% (Level B; class II and III evidence). If newborn screening was not performed, if it is uncertain whether a patient had testing, or if the results are unavailable, metabolic screening should be obtained in a child with global developmental delay.

2. Routine cytogenetic testing (yield of 3.7%) is indicated in the evaluation of the child with developmental delay even in the absence of dysmorphic features or clinical features suggestive of a specific syndrome (Level B; class II and III evidence).
3. Testing for the fragile X mutation (yield of 2.6%), particularly in the presence of a family history of developmental delay, may be considered in the evaluation of the child with global developmental delay. Clinical preselection may narrow the focus of who should be tested without sacrificing diagnostic yield. Although screening for fragile X is more commonly done in males because of the higher incidence and greater severity, females are frequently affected and may also be considered for testing. Because siblings of fragile X patients are at greater risk to be symptomatic or asymptomatic carriers, they can also be screened (Level B; class II and class III evidence).

4. The diagnosis of Rett syndrome should be considered in females with unexplained moderate to severe mental retardation. If clinically indicated, testing for the MECP2 gene deletion may be obtained. Insufficient evidence exists to recommend testing of females with milder clinical phenotypes or males with moderate or severe developmental delay (Level B; class II and class III evidence).

5. In children with unexplained moderate or severe

Table 3 Subtelomeric probe testing in children with global developmental delay

<table>
<thead>
<tr>
<th>Reference</th>
<th>Class</th>
<th>Level of mental retardation</th>
<th>N</th>
<th>No. (%) of patients with significant rearrangements</th>
</tr>
</thead>
<tbody>
<tr>
<td>68</td>
<td>I</td>
<td>Controls</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild</td>
<td>182</td>
<td>1 (0.55)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate/severe</td>
<td>284</td>
<td>21 (7.39)</td>
</tr>
<tr>
<td>69</td>
<td>I</td>
<td>Controls</td>
<td>150</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unspecified</td>
<td>61</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild</td>
<td>82</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate/severe</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>70</td>
<td>II</td>
<td>Unspecified</td>
<td>27</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>71</td>
<td>II</td>
<td>Moderate/severe</td>
<td>29</td>
<td>2 (6.89)</td>
</tr>
<tr>
<td>72</td>
<td>II</td>
<td>IQ &lt; 60</td>
<td>254</td>
<td>13 (5.12)</td>
</tr>
<tr>
<td>73</td>
<td>II</td>
<td>Unspecified</td>
<td>120</td>
<td>5 (4.17)</td>
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<td>II</td>
<td>Mild</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate/severe</td>
<td>117</td>
<td>13 (11.11)</td>
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<tr>
<td>75</td>
<td>II</td>
<td>Mild</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate/severe</td>
<td>28</td>
<td>1 (3.57)</td>
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<td>76</td>
<td>II</td>
<td>Unspecified</td>
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<td>3 (6.0)</td>
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<td>77</td>
<td>II</td>
<td>Mild</td>
<td>80</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate/severe</td>
<td>82</td>
<td>7 (8.5)</td>
</tr>
<tr>
<td>78</td>
<td>II</td>
<td>Unspecified</td>
<td>250</td>
<td>9 (3.6)</td>
</tr>
</tbody>
</table>

Abnormalities were classified as significant if there was evidence that they caused retardation and nonsignificant when they appeared to be a polymorphism devoid of phenotypic consequences.

* Two patients had nonsignificant rearrangements.
† One additional patient had uniparental disomy.

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developmental delay, additional testing using newer molecular techniques (e.g., FISH, microsatellite markers) to assess for subtelomeric chromosomal rearrangements (6.6%) may be considered (Level B; class II and class III evidence).

**What is the role of lead and thyroid screening in children with global developmental delay? Lead screening; evidence.** Lead is the most common environmental neurotoxin. Studies over the past several decades have shown a relation between marked elevations in serum lead levels, clinical symptoms, and cognitive deficits (but not definitively mental retardation), which prompted extensive efforts to reduce exposure to environmental lead. As a result, average blood lead levels in the United States have fallen dramatically from 15 μg/dL in the 1970s to 2.7 μg/dL in 1991 through 1994. It is estimated that there are still about 900,000 children in the United States between the ages of 1 and 5 years who may have blood lead levels equal to or greater than 10 μg/dL.

Because of these low lead levels and the environmental safeguards currently in place, it is unlikely at the present time for a child to have symptomatic high-level lead exposure that would cause moderate to severe global developmental delay. Even in the classic studies of Byers and Lord, published in 1943, which focused attention on the issue of chronic lead exposure and development, the mean IQ score of 19 children with lead poisoning was 92 ± 10.5, values that would not fall within the range of mental retardation. Low-level lead exposure remains possible, and it has been estimated that each 10 μg/dL increase in blood lead level may lower a child’s IQ by about 1 to 3 points. However, the relation and clinical significance of mildly elevated but nontoxic levels (i.e., those that do not require medical intervention) to developmental status remains controversial. In a cohort of young children (age 12 to 36 months) identified on routine screening at an urban public hospital, elevated lead levels (10 to 25 μg/dL) resulted in a 6.2-point decline in scores on the Mental Developmental Index when compared to children with lead levels below 10 μg/dL (class II study). In a study of data drawn from the Third National Health and Nutrition Examination Survey (NHANES III), an inverse relation between blood lead concentration at subtoxic levels and scores on four measures of cognitive functioning was demonstrated (class III study). The clinical status of the children in these studies (i.e., delayed or not) was not provided.

In a consecutive series of 72 children referred to a child developmental center with developmental and/or behavioral problems compared to controls, a significantly higher distribution of lead concentrations was demonstrated, with 12% of the sample possessing a concentration greater than 10 μg/dL (class II study). However, in a study of children drawn from a population at low risk for lead exposure, a series of 43 children with either developmental delay or attention deficit hyperactivity disorder did not demonstrate elevated lead levels compared to controls (class II study).

Current consensus guidelines with respect to lead testing in children recommend a strategy of targeted screening of all children with identifiable risk factors. These risk factors emphasize potential sources of environmental exposure and socioeconomic disadvantage. Developmental delay alone is not presently recognized as a risk factor within these guidelines. Targeted (rather than universal) screening is recommended in communities where <12% of children have blood lead levels >10 μg/dL or where <27% of houses were built before 1950. According to the recently published guidelines of the American Academy of Pediatrics, other candidates for targeted screening include children 1 to 2 years of age living in housing built before 1950 situated in an area not designated for universal screening, children of ethnic or racial minority groups who may be exposed to lead-containing folk remedies, children who have emigrated (or been adopted) from countries where lead poisoning is prevalent, children with iron deficiency, children exposed to contaminated dust or soil, children with developmental delay whose oral behaviors place them at significant risk for lead exposure, victims of abuse or neglect, children whose parents are exposed to lead (vocationally, avocationally, or during home renovation), and children of low-income families.

**Thyroid screening; evidence.** Unrecognized congenital hypothyroidism is a potentially treatable cause of later developmental delay. Delay in diagnosis and treatment beyond the newborn period and early infancy has been clearly linked to later, often substantial, neurodevelopmental sequelae. Implementation of newborn screening programs has been extremely successful in eliminating such sequelae, with very few cases reported in which the diagnosis was not established. In some countries, where comprehensive newborn screening programs are not yet in place, congenital hypothyroidism has been found to be responsible for 17/560 (3.8%) cases of cognitive delay evaluated in a pediatric neurology clinic (class II study). Many of these children also had prominent systemic symptoms.

**Conclusions.** Low-level lead poisoning is associated with mild cognitive impairments but not with global developmental delay. Approximately 10% of children with developmental delay and identifiable risk factors for excessive environmental lead exposure may have an elevated lead level. In the absence of systematic newborn screening, congenital hypothyroidism may be responsible for approximately 4% of cases of cognitive delay.

**Recommendations.**

1. Screening of children with developmental delay for lead toxicity may be targeted to those with known identifiable risk factors for excessive envi-
2. In the setting of existing newborn screening programs for congenital hypothyroidism, screening of children with developmental delay with thyroid function studies is not indicated unless there are systemic features suggestive of thyroid dysfunction (Level B; class II evidence).

What is the diagnostic yield of EEG in children with global developmental delay? Evidence. Given the higher incidence of epilepsy and behavioral disorders in children with global developmental delay, EEG is often considered at initial evaluation. The utility of EEG from a diagnostic perspective in this population has rarely been addressed. The vast majority of articles on EEG and global developmental delay are class IV studies on small cohorts of children with an already established diagnosis (e.g., subacute sclerosing panencephalitis or progressive myoclonic epilepsy) that is often a progressive encephalopathy rather than a static encephalopathy such as global developmental delay.

Two class III studies involving 200 children with global developmental delay who had EEG have been reported. In one study, the EEG did not contribute to determining the etiology of developmental delay. In the second study, 10 of 120 children were found to have epileptic syndromes (Lennox-Gastaut, severe myoclonic epilepsy, epilepsy with myoclonic-astatic seizures, symptomatic generalized epilepsy, partial symptomatic epilepsy, and epilepsy undetermined). Although not stated in the article, it is likely that all of these children already had overt seizures and a recognized epilepsy for which an abnormal EEG result is expected. Another class III prospective study of 32 children with significant developmental dysphasia with or without associated global developmental delay revealed nonspecific epileptic abnormalities in 13 of 32 children (40.6%), a finding of unclear etiologic significance. A retrospective class IV study of 80 children with global developmental delay, 83% of whom had EEG, yielded an etiologic diagnosis based on the EEG results in 2.0% of the cohort (specifically one child with ESES—electrographic status epilepticus during slow wave sleep). Although the yield on routine testing is negligible, if there is a suspected epileptic syndrome that is already apparent from the history and physical examination (e.g., Lennox-Gastaut syndrome, myoclonic epilepsy, Rett syndrome), the EEG has confirmatory value.

Conclusions. Available data from two class III studies and one class IV study determined an epilepsy-related diagnosis in 11 of 250 children (4.4%). However, the actual yield for a specific etiologic diagnosis occurred in only 1 patient (0.4%).

Recommendations.

1. An EEG can be obtained when a child with global developmental delay has a history or examination features suggesting the presence of epilepsy or a specific epileptic syndrome (Level C; class III and IV evidence).

2. Data are insufficient to permit making a recommendation regarding the role of EEG in a child with global developmental delay in whom there is no clinical evidence of epilepsy (Level U; class III and IV evidence).

What is the diagnostic yield of neuroimaging in children with global developmental delay? Evidence. Advances in neuroimaging have had a significant impact on the clinical practice of child neurology during the past 25 years. Studies utilizing cranial CT scanning have documented an increasing etiologic yield for global developmental delay that parallels improved imaging technology (table 4). Although early studies (1981, 1982) did not appear to justify CT imaging on a widespread screening basis, more recent studies suggest that about one-third of children will have abnormalities that likely explain their developmental disorder. Three class III studies totaling 329 children with global developmental delay, utilizing CT in almost all patients and MRI in a small sample, found a specific cause in 31.4%, 27%, and 30% of children. In one of these studies, the yield on neuroimaging when done on an indicated basis (e.g., microcephaly, focal motor findings) was almost threefold greater than when done on a screening basis (41.2% vs 13.9%). Two additional class III retrospective studies of 196 children...
found that physical examination findings consistent with cerebral palsy together with global developmental delay increased the yield of CT to between 63% and 73%.103,104

The value of MRI has also been documented in this clinical context (see table 4). A recent class III retrospective study found MRI abnormalities in 109 of 224 (48.6%) children with global developmental delay.105 These included nervous system malformations (n = 55); cerebral atrophy (12); white matter disease, delayed myelination, or other white matter abnormalities (42); postischemic lesions (10); widened Virchow-Robin spaces (3); and phakomatoses (2). Other studies have shown that MRI appears to be more sensitive than CT in detecting abnormalities. In one class III retrospective study of 170 children with global developmental delay, MRI abnormalities were detected in 65.5% (19/29) compared to 30% (51/170) of those who underwent CT scanning.45 When physical findings consistent with cerebral palsy coexist with global delay, an additional yield of MRI beyond that obtained by CT scanning alone has been found in one class III retrospective study of 40 children106 and a retrospective class IV small case series involving three children.107 MRI is also more sensitive for the detection of specific cerebral malformations108 and the degree of white matter abnormality observed on MRI also appears to correlate with the degree of cognitive disability in one class III study of children with spastic diplegia.109

Conclusions. Available data primarily from class III studies show that CT contributes to the etiologic diagnosis of global developmental delay in approximately 30% of children, with the yield increasing if physical examination findings are present. MRI is more sensitive than CT, with abnormalities found in 48.6% to 65.5% of children with global delay with the chance of detecting an abnormality increasing if physical abnormalities, particularly cerebral palsy, are present.

Recommendations.

1. Neuroimaging is recommended as part of the diagnostically evoked evaluation of the child with global developmental delay (Level B; class III evidence). As the presence of physical findings (e.g., microcephaly, focal motor findings) increases the yield of making a specific neuroimaging diagnosis, physicians can more readily consider obtaining a scan in this population (Level C; class III evidence).

2. If available, MRI should be obtained in preference to CT scanning when a clinical decision has been made that neuroimaging is indicated (Level C; class III evidence).

Are vision and hearing disorders common in children with global developmental delay? In the past decade, guidelines for vision110-112 and hearing113 screening in infants and children have been proposed and methods of assessment of these modalities have also been refined.114,115 It is suspected that children with global developmental delay are at greater risk to have vision and/or auditory sensory impairments and evaluation for such impairments is an important component of the initial management of the child with global developmental delay. These impairments interfere with developmental progress or rehabilitation effects. Often these impairments are correctable and their correction may improve developmental outcome. Detection of a specific type of sensory deficit may also help establish the etiology of a child’s developmental disorder.

Evidence. One class IV study in adults from a large institutional population found a tenfold higher incidence of vision impairment in individuals with developmental disabilities compared to those without disabilities.116 In two class III studies totaling 365 children with global developmental delay, abnormalities on vision screening were found in 13%,117 to 25%-118 of children. Refractive errors (24%), strabismus (8%), and a number of organic oculardiseases (8%) were also detected in one of these reports.118 Supporting these findings is a class IV retrospective review that estimated the frequency of primary visual sensory impairment in children with global developmental delay to range between 20% and 50%114. There also appears to be an increased prevalence of additional visual developmental disability among individuals with syndromes featuring significant sensory impairment.119

Because speech and language delay is often a feature of global developmental delay and may be the result of a hearing loss, audiologic testing is often undertaken. Children with global developmental delay are at higher risk for hearing loss.120 In one class III study of 260 children with severe global developmental delay in whom vision and audiologic screening were performed, 18% of children were found to be deaf.121 Another class III study involving 96 children with global developmental delay and clinically suspected hearing loss found that 91% had hearing loss as detected by behavioral audiometry or brainstem auditory evoked response testing.121

The feasibility of utilizing transient evoked otoacoustic emissions, compared to standard audiometry, to screen for hearing impairment in children has been demonstrated (class II study).122 Its use has not yet been reported specifically in a group of children with developmental delay. However, retrospective analysis of a statewide (Rhode Island) legally mandated universal newborn screening program (53,121 newborns over 4 years) demonstrated the utility of a two-stage otoacoustic emission evaluation process in accurately detecting early hearing loss in a population not amenable to audiometric testing (class II study).123

Conclusions. Several class III studies have shown that children with global developmental delay are at risk to have primary sensory impairments of vision and hearing. Estimates of vision impairment or other visual disorders range from 13% up to 50% whereas significant audiologic impairments occur in about 18% of children based on data in one series of patients.
Recommendations.

1. Children with global developmental delay may undergo appropriate vision and audiometric assessment at the time of their diagnosis (Level C; class III evidence).

2. Vision assessment can include vision screening and a full ophthalmologic examination (visual acuity, extra-ocular-movements, funduscopic) (Level C; class III evidence).

3. Audiometric assessment can include behavioral audiometry or brainstem auditory evoked response testing when feasible (Level C; class III evidence). Early evidence from screening studies suggests that transient evoked otoacoustic emissions should offer an alternative when audiometry is not feasible (Level A; class I & II evidence).

Recommendations for a staged approach to the evaluation of the child with global developmental delay. Although there is insufficient evidence to recommend the optimal sequence of tests to determine the etiology of global developmental delay, taking into account diagnostic yield and potential treatability, we propose the following consensus-based schedule of testing as outlined in the algorithm (figure). Consensus-based recommendations relate to the order and timing of testing but not to the relative diagnostic yield of the specific tests themselves (table 5).

All children should undergo a detailed history and physical examination, which may in itself suggest specific diagnostic possibilities. For all children with global developmental delay, auditory and visual in-
universal newborn screening.

Metabolic testing usually consists of urine organic acids, serum amino acids, serum lactate, ammonia level, and a capillary blood gas.

TSH = thyroid stimulating hormone; T4 = thyroxine; UNS = universal newborn screening.

tegrity should be ascertained. If a child was born in a locale without universal newborn screening, a screening metabolic evaluation including capillary blood gas, serum lactate and ammonia levels, serum amino acids and urine organic acids, and thyroid function studies (T4 and thyroid stimulating hormone) may be considered. If a history of events suggestive of possible seizures, paroxysmal behaviors, or an underlying epilepsy syndrome is elicited, one can consider an EEG. In addition, screening for autism or a language disorder should be considered in any child presenting with GDD. If there is a family history of a close family member (sibling, aunt/uncle, or first cousin) with global developmental delay or a language disorder should be considered in any child presenting with GDD. If there is a family history of unexplained developmental delay, cytogenetic testing (which may include testing for subtelomeric rearrangements) may be obtained.

In the absence of a familial history of global developmental delay, specific historical or physical findings can be utilized to direct testing. Observed dysmorphic features may prompt specific testing for such entities as Down syndrome (karyotype), fragile X (FMR1), Rett syndrome (MECP2), Prader-Willi/Angelman (FISH), or hypothyroidism. Historical documentation of intrapartum asphyxia or ascertainment of physical findings such as microcephaly, cerebral palsy, or focal findings or focal seizures may suggest acquired CNS injury or an underlying cerebral malformation and thus prompt neuroimaging study (MRI preferable to CT). Risk factors for lead exposure or findings suggestive of lead intoxication mandate lead screening.

Parental consanguinity, documentation of loss or re- gression of developmental milestones, or unexplained prior parental loss of a child are likely to be caused by a definable disease process and thus a comprehensive evaluation may be considered. This can include careful metabolic evaluation together with neuroimaging studies, EEG, cytogenetic studies, and genetic and ophthalmologic consultations.

The absence of any clinical features that suggest a specific diagnosis is less likely to be associated with a definable disease and thus a stepwise approach is recommended. This may include initial neuroimaging (MRI preferred) and cytogenetic and fragile X screening. If these tests are negative, consideration may be given to metabolic evaluation, testing for subtelomeric rearrangements, and genetic consultation.

Future research

1. Further prospective studies on the etiologic yields of various diagnostic tests need to be undertaken on large numbers of young children with global developmental delay including control subjects. These should include newer molecular genetic and MRI technologies. With this information, prospective testing of specific evaluation paradigms would be possible.

2. Features (i.e., markers) present on the history and physical examination at intake need to be identified that will improve specific evaluation strategies and enhance etiologic yield.

3. The timing of actual testing in children with global developmental delay needs to be addressed. Specifically, it should be determined at what age and on what basis one can be certain that a child has a global developmental delay sufficient to justify testing as well as at what age the yield from testing will be optimal.

4. Alternative strategies of conducting testing simultaneously or sequentially need to be critically assessed. This should help reduce unnecessary testing and provide cost-effective evaluations and more accurate diagnostic yields.

5. Additional studies are needed to evaluate the role of EEG in a child with global developmental delay in whom there is no clinical evidence of epilepsy.

6. Additional studies are needed to better characterize visual and auditory deficits in children with global developmental delay. Further investigation of the sensorimotor impairments of children with global delay are also needed to better determine how early intervention therapies might improve the overall function of children who are likely to have multiple needs.

7. Issues related to quality of life and social support of families who have children with developmental delay need further study. Included in this should be the benefits that medical testing confer by re-

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**Table 5 Diagnostic yield of tests in children with global developmental delay**

<table>
<thead>
<tr>
<th>Test</th>
<th>Diagnostic yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI scan, nonenhanced</td>
<td>55.3</td>
</tr>
<tr>
<td>CT scan</td>
<td>39.0</td>
</tr>
<tr>
<td>Genetic studies†</td>
<td></td>
</tr>
<tr>
<td>Routine cytogenetic studies</td>
<td>3.7</td>
</tr>
<tr>
<td>Subtelomeric deletion</td>
<td>6.6</td>
</tr>
<tr>
<td>Fragile X screen</td>
<td>2.6</td>
</tr>
<tr>
<td>MECP2</td>
<td>Unknown</td>
</tr>
<tr>
<td>Metabolic testing†</td>
<td>~1</td>
</tr>
<tr>
<td>Thyroid screen (serum TSH, T4)</td>
<td>Near 0 if UNS; ~4 if no UNS</td>
</tr>
<tr>
<td>Serum lead level</td>
<td>Unknown</td>
</tr>
<tr>
<td>EEG (routine)</td>
<td>~1</td>
</tr>
</tbody>
</table>

Based on data from studies listed in table 4,* tables 2 and 3,† and table 1.§

† Metabolic testing usually consists of urine organic acids, serum amino acids, serum lactate, ammonia level, and a capillary blood gas.

§ Metabolic testing usually consists of urine organic acids, serum amino acids, serum lactate, ammonia level, and a capillary blood gas.

* Metabolic testing usually consists of urine organic acids, serum amino acids, serum lactate, ammonia level, and a capillary blood gas.
ducing parental concerns related to determining a specific etiology and by providing important information regarding prognosis, genetic counseling, alleviation of parental anxiety, and planning future educational and treatment needs.

Disclaimer. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The American Academy of Neurology recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

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Appendix 1

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Appendix 2

AAN evidence classification scheme for a diagnostic article

Class I: Evidence provided by a prospective study in a broad spectrum of persons with the suspected condition, using a “gold standard” for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.

Class II: Evidence provided by a prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by “gold standard”) compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriated tests of diagnostic accuracy.

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation.

Class IV: Any design where test is not applied in blinded evaluation or evidence provided by expert opinion alone or in descriptive case series (without controls).

Appendix 3

AAN system for translation of evidence to recommendations

<table>
<thead>
<tr>
<th>Translation of evidence to recommendations</th>
<th>Rating of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies</td>
<td>A = Established as useful/predictive or not useful/predictive for the given condition in the specified population</td>
</tr>
<tr>
<td>Level B rating requires at least one convincing class II study or overwhelming class III evidence</td>
<td>B = Probably useful/predictive or not useful/predictive for the given condition in the specified population</td>
</tr>
<tr>
<td>Level C rating requires at least two convincing class III studies</td>
<td>C = Possibly useful/predictive or not useful/predictive for the given condition in the specified population</td>
</tr>
<tr>
<td></td>
<td>U = Data inadequate or conflicting. Given current knowledge, test, predictor is unproven</td>
</tr>
</tbody>
</table>

References
