CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Genetic Evaluation of the Child With Intellectual Disability or Global Developmental Delay: Clinical Report

Lance H. Rodan, MD,[1,2] Joan Stoler, MD, FAAP,[1] Emily Chen, MD, PhD,[3] Timothy Geleske, MD, FAAP,[4] and the Council on Genetics

Genetic neurodevelopmental disorders are common in the pediatric population, and establishing a specific diagnosis early provides multiple benefits including prognostication, surveillance for disorder-related complications, accurate recurrence risk, and specific management. This report provides an approach to the genetic evaluation of developmental delay/intellectual disability for the general pediatrician. When possible, genetic testing should be selected by phenotype, and typical distinguishing clinical features to facilitate this are presented. If a specific disorder or group of disorders cannot be ascertained by phenotype, an agnostic (or hypothesis-free) approach is utilized. Recommendations are provided for this agnostic approach based on diagnostic yield and also practical considerations such as test complexity and impact on management. The general guidance in this report for genetic testing does not preclude further evaluation by relevant subspecialists as necessary, including neurologists, developmental pediatricians, and clinical geneticists.

INTRODUCTION

Global developmental delay (GDD)/intellectual disability (ID) has an estimated global prevalence of 1% to 3%.[1] Further, in pediatric primary care, neurodevelopmental disorders are the most common chronic medical condition, with a combined prevalence of approximately 17%.[2] Neurodevelopmental disorders have a considerable impact at individual, family, and societal levels. Global developmental delay is defined in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) as the failure to meet expected developmental milestones in several areas of intellectual functioning in an individual younger than 5 years who

abstract

[1]*Division of Genetics and Genomics, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts;* [2]*Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts;* [3]*Department of Genetics, Kaiser Permanente, San Francisco, California; and* [4]*Northwestern University Feinberg School of Medicine, Chicago, Illinois*

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cannot undergo systematic assessment of intellectual functioning, including children too young to participate in standardized testing. This evaluation necessitates reassessment after a period of time.[3] Intellectual disability is defined in the DSM-5 as significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills in individuals 5 years or older.[4] Children with GDD and ID are often first evaluated in the general pediatric setting, so it is pertinent for the general pediatrician to have an initial approach to the evaluation of these patients.

GDD/ID has diverse etiologies, including prenatal injury or developmental disorders (eg, in utero infection, teratogens, toxins, vascular disruption, developmental brain malformations); perinatal/postnatal insult (eg, hypoperfusion injury, asphyxia, infections, trauma, neglect, toxins); and genetic disorders. Genetic disorders account for up to 50% of diagnosed etiologies.[5,6]

Genetic causes can be broadly categorized as:

- chromosomal
- monogenic
- imprinting defects
- oligo/polygenic

Chromosome disorders are commonly associated with GDD/ID. Chromosome disorders may be *numerical*, in which an entire chromosome or multiple chromosomes are added to or missing from the normal pair (eg, trisomy 21), or *structural*, in which a part of a chromosome is deleted (eg, 22q11.2 deletion), duplicated, or rearranged, such as with a translocation. Because chromosome disorders affect multiple contiguous genes, they may also be associated with dysmorphic features, multiple congenital anomalies, and abnormalities of growth.[7] Some chromosome disorders may be inherited from unaffected or more mildly affected parents. Supplementary Table 1 summarizes more common and phenotypically identifiable chromosome disorders. Most chromosome disorders can be identified on chromosome microarray testing, with the main exception being balanced structural chromosome abnormalities, such as translocations and ring chromosomes, which require a karyotype. Some exome sequencing platforms currently offer chromosome (copy number) analysis as well, although sensitivity is lower than with chromosome microarray.

Monogenic disorders are caused by variation in a single gene. There are approximately 20 000 protein-coding genes in the human genome, and more than 1300 causative genes and 1100 candidate genes have thus far been implicated in neurodevelopmental disorders, with this number rapidly increasing.[8] Monogenic disorders may be caused by single nucleotide variants, small insertions or deletions (indels), larger exon-level deletions or duplications, or expansion of an inherently repeating genetic sequence (ie, trinucleotide repeat disorders). Inheritance of monogenic disorders may be X-linked, autosomal dominant, autosomal recessive, or even maternally inherited.[9] Some forms of mitochondrial disorders can be inherited in an autosomal recessive manner, and others are maternally inherited (with rare exceptions).[10] Supplementary Table 2 summarizes a number of phenotypically identifiable monogenic neurodevelopmental disorders. Diagnosis of monogenic disorders can be facilitated by targeted gene testing if the disorder is clinically suspected or can be diagnosed in an agnostic manner with gene panels or exome sequencing.

Mosaicism refers to cell lines with differing genotypes. Mosaicism can involve chromosomes (eg, mosaic Turner syndrome, mosaic trisomy 9) or single genes (eg, *PIK3CA* related overgrowth disorders, McCune-Albright syndrome). The diagnosis of mosaicism may require testing in cultured skin fibroblasts or other affected tissue, because the abnormalities may be difficult to detect or even absent in white blood cells or buccal swab. Pigmentary mosaicism of the skin, typically appearing as a whorled pattern of hypo- or hyperpigmentation following Blaschko lines, can occasionally be a clue to a mosaic disorder.

Imprinting disorders are caused by molecular changes affecting imprinted chromosomal regions and genes. Imprinting refers to the expression of genes in a parent-of-origin specific manner (ie, genes only expressed from either the maternally or paternally inherited allele, but not from both). The prototypical imprinting disorders associated with GDD/ID are Prader-Willi syndrome and Angelman syndrome.[11] A summary of imprinting disorders associated with GDD/ID can be found in Table 1. The genetic diagnosis of imprinting disorders typically requires targeted testing for the specific disorder.

Polygenic disorders are caused by the interaction of a number of genes, with each gene contributing partially to the phenotype. If there are only 2 genes involved, this is termed digenic inheritance. Oligogenic inheritance is when there are several genes involved, less than in polygenic inheritance. Examples of these would be modifier genes in which a second gene variant influences the expression/penetrance of the condition, such as in Bardet Biedl syndrome.[12] In general, polygenic inheritance is difficult to delineate in clinical practice, because the ability to assess the additive or cumulative effects of multiple gene variants on phenotype is limited.

Reasons to Pursue Specific Genetic Diagnosis for GDD/ID

Pursuing genetic diagnosis for GDD/ID allows for accurate prognostication, facilitates surveillance for potential disorder-related complications, provides accurate recurrence risk in families interested in having additional children, and allows for prenatal diagnostic testing and preimplantation genetic diagnosis (PGD). This will also

TABLE 1. Imprinting Disorders Associated With Global Developmental Delay and Intellectual Disability		
Disorder	**Genetic Etiology**	**Clinical Features**
Angelman syndrome	Abnormal methylation at 15q11.2-q13 (including UBE3A gene) – maternally imprinted	Feeding difficulties, progressive microcephaly, seizures, ataxia/tremulousness, epilepsy behavioral peculiarities (happy disposition, fascination with water), variable developmental delay/intellectual disability[13]
Prader-Willi syndrome	Abnormal methylation of 15q11.2-q13 – paternally imprinted	Severe feeding difficulties in infancy followed by obesity in childhood, severe hypotonia, hypogonadism, short stature, behavioral abnormalities, global developmental delay/intellectual disability[14]
Temple syndrome	Abnormal methylation of 14q32.2 – paternally imprinted	Intrauterine growth restriction, short stature, feeding difficulties in infancy followed by obesity later in childhood, precocious puberty, hypotonia, variable developmental delay/intellectual disability[15]

have reproductive implications for the child him- or herself when they are of reproductive age, as having a genetic diagnosis can help inform their own reproductive decisions. It can directly impact treatment (ie, inborn errors of metabolism) or identify as candidates for future treatments (eg, gene therapy); reduce further unnecessary diagnostic testing; allow access to developmental therapies/services, appropriate disease-specific support networks, or clinical trials; and provide positive psychological impact on parents/caregivers.[16]

The diagnostic yield of genetic testing is influenced by the severity of GDD/ID. In severe ID, as defined in DSM-5, a genetic etiology may be discovered in approximately 80% of cases, whereas in mild ID, the diagnostic yield is closer to 20%.[17] The genetic diagnostic yield is also increased if there are dysmorphic features, congenital anomalies, or neurological comorbidities. The genetic evaluation of GDD and ID requires a thoughtful and systematic evaluation. This evaluation includes a detailed medical history, family history, clinical examination, and use of corollary investigations such as neuroimaging, vision assessment, and hearing assessment.

GDD/ID can be divided into syndromic and nonsyndromic forms. Syndromic refers to clinical features beyond GDD/ID that may suggest a specific disorder or category of disorders, whereas nonsyndromic GDD/ID lacks such features.[18] Up to two-thirds of GDD/ID is considered nonsyndromic.

If the patient has features suggestive of a syndromic form of GDD/ID, when possible, a phenotype-driven diagnostic approach is useful to make the clinical diagnosis or to refer for more targeted genetic testing to improve testing accuracy as well as to save cost and time. When a specific diagnosis is not suspected, or in cases of nonsyndromic GDD/ID, an agnostic, or "hypothesis-free," approach may be utilized.

PHENOTYPE-DRIVEN APPROACH TO DIAGNOSTIC EVALUATION

Following history and examination, the etiology of GDD/ID can be established in up to 17.2% to 34.2% of cases.[19]

Medical History

The evaluation includes taking a full developmental history, including gross motor, fine motor, language, social-emotional, and self-help skills. Developmental delay isolated to the motor domains may suggest a central (eg, brain) or peripheral (eg, neuromuscular) disorder. Abnormalities in language and social domains raises concern for autism spectrum disorder (ASD). Although the genetic etiologies of ASD may overlap with those associated with GDD/ID, the genetic diagnostic approach to ASD will not be covered further in this review.

It is useful to establish the trajectory of the individual's development to assess whether there is developmental regression. Developmental regression may suggest a neurodegenerative disorder or acquired process necessitating a prompt urgent referral to a neurologist and/or geneticist. The diagnostic evaluation for developmental regression will not be covered in this review.

Comorbid behavioral abnormalities are important to elicit in the child with GDD/ID and can suggest a specific diagnosis. For example, severe self-injurious behaviors can be seen in Lesch-Nyhan syndrome and Cornelia-de-Lange syndrome.[20,21] Some genetic disorders are associated with unique behavioral peculiarities, such as fascination with water or crinkly items in Angelman syndrome, skin picking and hyperphagia in Prader-Willi syndrome, midline stereotypies and intense eye contact in Rett syndrome, and episodic hyperventilation and breath-holding in Pitt-Hopkins syndrome.[13,14,22,23]

In addition to the developmental history, it is useful to establish whether there are any additional health concerns. It is often these features that can allow for the differential diagnosis to be narrowed based on phenotype. Additional health concerns can include other neurological symptoms (eg, seizures, movement disorder, weakness, nystagmus, hypotonia, spasticity, dystonia, hyperreflexia, ataxia, focal neurological findings); vision loss; hearing loss; feeding difficulties; organomegaly; and abnormalities of the gastrointestinal, dermatologic, dental, respiratory, cardiovascular, musculoskeletal, or endocrine systems. Occasionally, history of an unusual odor may prompt evaluation for an

inborn error of metabolism, such as the maple syrup odor to urine or ear wax in maple syrup urine disease.[24]

Family History

Obtaining a 3-generation pedigree (asking specific questions about siblings, parents, grandparents, aunts, and uncles) provides important information. Additional family history of GDD/ID may suggest a specific mode of inheritance. Absence of other affected individuals may suggest autosomal recessive inheritance, a de novo autosomal dominant disorder, or an X-linked disorder. A history of psychiatric disorders and/or seizures is another potential indicator of genetic disorders in patients with GDD/ID, because some genetic disorders associated with GDD/ID can manifest with psychiatric symptoms and/or epilepsy in other family members as the result of incomplete penetrance and variable expressivity. In addition, psychiatric conditions can indicate genetic predisposition in their children. A family history of premature ovarian failure or ataxia/tremor may suggest fragile X syndrome.[25] A family history of 3 or more miscarriages in an individual may suggest a balanced chromosome rearrangement in a parent, predisposing to an unbalanced structural chromosome abnormality in offspring. Advanced paternal age may suggest a de novo dominant disorder, whereas advanced maternal age (>35 years) may suggest an aneuploidy. In vitro fertilization is associated with an increased risk of imprinting disorders, such as Prader-Willi syndrome and Angelman syndrome.[26,27]

Clinical Examination

Accurate assessment of height, weight, and head circumference is important, because these may inform the differential diagnosis. With respect to head circumference, analysis of growth velocity using a standardized growth curve will identify microcephaly (noting whether the microcephaly is congenital or postnatal), plateauing head circumference, and progressive microcephaly or macrocephaly. It is important to assess weight gain and growth to assess for failure to thrive.

Notation of dysmorphic features and other congenital anomalies, such as limb defects, will indicate the need for referral of the patient to a geneticist for further dysmorphology evaluation. For example, dysmorphic craniofacial features may include abnormal head shape, abnormally spaced or upslanting/downslanting eyes, epicanthal folds, depressed nasal bridge, unusual nasal configuration, long philtrum, and ear abnormalities.

Examination of the skin for neurocutaneous stigmata, such as café au lait macules, other hypo- or hyperpigmented skin regions, or vascular skin markings may indicate specific disorders. Rarely, hair or nail abnormalities also may suggest a specific disorder. A precordial examination may detect a murmur indicative of underlying congenital heart disease. Hepatosplenomegaly can be a feature of genetic overgrowth disorders and some inborn errors of metabolism (eg, lysosomal disorders). Cryptorchidism can be associated with some genetic neurodevelopmental disorders. Vision and hearing screening can also be performed by the pediatrician. A complete neurologic examination may detect abnormalities of muscle tone, weakness, or a movement disorder.

Corollary Testing: Neuroimaging, Vision, Hearing

In children with GDD/ID, evaluation by an ophthalmologist should be considered, both for diagnostic and therapeutic purposes. Retinal and optic nerve abnormalities may provide insight into an underlying genetic disorder. In children with language delay, hearing evaluation is also important. In addition to facilitating treatment, the finding of sensorineural hearing loss may offer a phenotypic clue.[28]

Neuroimaging with magnetic resonance imaging (MRI) is indicated in children with GDD/ID and abnormal head circumference, focal neurological signs or symptoms, seizures, increased tone or developmental regression.[5,29] It may also be considered in moderate to severe GDD/ID, if a specific disorder with abnormal neuroimaging is suspected, or if no etiology is identified following other diagnostic evaluations including genetic studies.[19] Neuroimaging may demonstrate relatively nonspecific findings, such as underrotated hippocampi, abnormally contoured and enlarged ventricles, reduced cerebral volume, delayed myelination, or dysgenesis of corpus callosum. It may also demonstrate more specific structural abnormalities, such as polymicrogyria, lissencephaly, periventricular nodular heterotopia, holoprosencephaly, or cerebellar malformations. There may also be signal abnormalities of the cerebral white matter or basal ganglia that can occasionally suggest a specific disorder based on the pattern.[30] Magnetic resonance spectroscopy may be useful in the evaluation for some inborn errors of metabolism, including disorders of creatine metabolism.[31]

AGNOSTIC APPROACH TO DIAGNOSTIC EVALUATION

If the medical history, family history, clinical examination, and corollary testing do not lead to a suspected diagnosis, then a hypothesis-free algorithmic approach could be pursued. This approach considers diagnostic yield, cost and complexity of the test, and the potential impact of the test results. Previously published agnostic approaches include a prior iteration from the American Academy of Pediatrics (AAP), and recommendations from the American Academy of Neurology (AAN), Canadian Pediatric Society (CPS), and the Treatable Intellectual Disability Endeavor (TIDE) protocol.[1,5,32] The AAP proposes the following updated tiered agnostic approach based on diagnostic yield and practical considerations (see Figure 1). Depending on comfort level, the pediatrician may opt to refer to a geneticist at any point in the genetic diagnostic evaluation. If a geneticist is not available, higher-order evaluation from neurologists

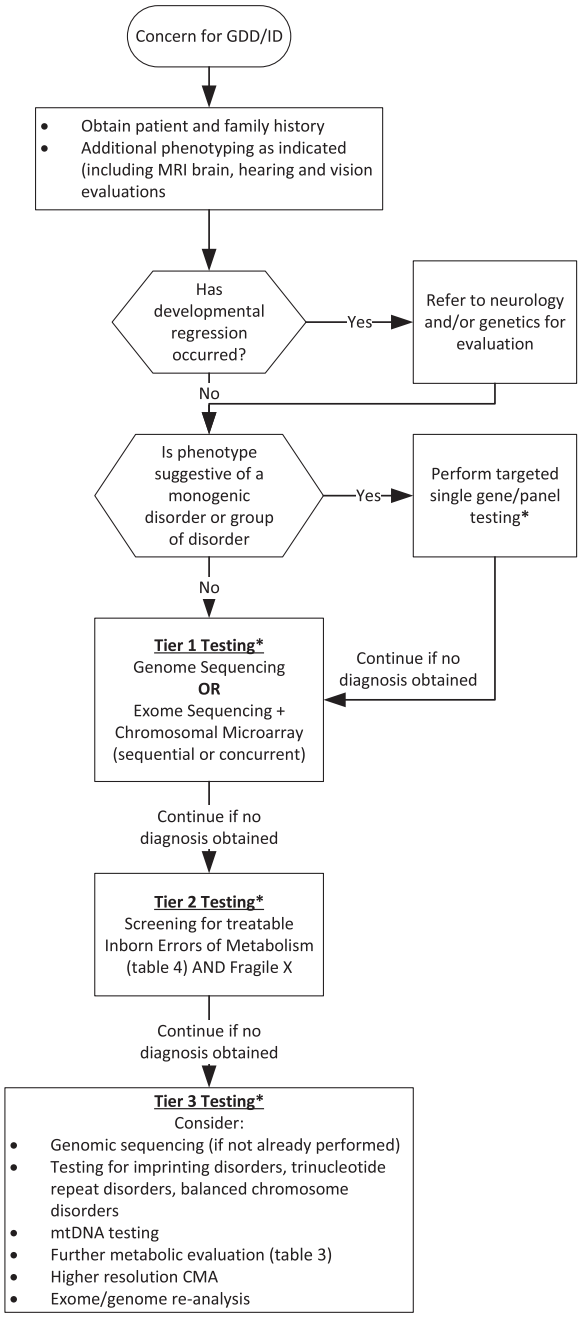

FIGURE 1.
Tiered agnostic approach to diagnostic evaluation.
*Refer to genetics for help with genetic testing.
Abbreviations: CMA, chromosome microarray; GDD, global developmental delay; ID, intellectual disability; MRI, magnetic resonance imaging.

and/or experienced pediatricians including developmental specialists may be considered.

Tier 1: Genome Sequencing or Exome Sequencing + Chromosome Microarray

The American College of Medical Genetics and Genomics (ACMG) recently recommended exome/genome sequencing for pediatric patients with GDD/ID or congenital anomalies as a first- or second-tier test.[33] The AAP recommends exome/genome sequencing as a first-tier test for GDD/ID in most circumstances because of superior diagnostic yield and higher cost-effectiveness if pursued earlier in the diagnostic process. Exome sequencing utilizes high throughput (next generation) sequencing to evaluate the entirety of protein coding exons in the human genome. Some exome sequencing platforms are also able to detect chromosome copy number variation and larger intragenic deletions and duplications (typically 3 exons in size or larger). The reported yield of exome sequencing for GDD/ID ranges from 28% to 43%.[33–35] Genome sequencing is a technique that evaluates almost the entire genome, including intronic and noncoding elements that are not assessed by exome sequencing. It also has the potential to detect copy number variation and structural rearrangements. Genome sequencing has been demonstrated to provide an approximately 10% to 20% higher diagnostic yield than exome sequencing, so it is preferable but currently may be less accessible to providers to order than exome sequencing.[33–35] Genome sequencing may utilize short-read (hundreds of base pairs) or long-read (thousands of base pairs) sequencing. Long-read sequencing has the advantage of being potentially better able to detect structural variations such as large insertions, deletions/duplications, inversions, repeats, translocations, and highly variable or repetitive elements; however, it is more costly and time consuming than short-read sequencing period.[36]

Gene variants reported on exome/genome sequencing are characterized according to the ACMG and the Association for Molecular Pathology (ACMG-AMP) system for variant classification. This classification system utilizes a score based on strict criteria to establishes 5 "classes" of variants: benign, likely benign, variant of unknown significance (VUS), likely pathogenic, and pathogenic.[37] In cases in which the significance of a variant is not definitive (ie, variants that are classified as neither benign nor pathogenic), the clinician must use their best clinical judgement to interpret the clinical significance. Depending on the situation, testing additional affected or unaffected family members for further segregation data may be useful. In addition, there may be a functional test (eg, metabolic testing) or further phenotyping data that can be obtained (eg, specific neuroimaging abnormalities) that can help to confirm or exclude a genetic diagnosis. Finally, the significance of a variant may be reinterpreted over time on the basis of accrued data. Since the interpretation of these results can be challenging, especially when there are variants of uncertain significance, the geneticist should help to provide as much clarification as possible to the family and the pediatrician (who may be asked for their opinion). It must be stressed that in some cases the classification of variants of uncertain significance may change over time.

Pretest genetic counseling should include discussion of variants of uncertain significance and the potential to detect

incidental or secondary findings and nonpaternity or nonmaternity. With regard to incidental findings, the ACMG has specified 81 genes that are regarded as clinically actionable, including genes related to increased risk of cancer, cardiomyopathy, cardiac conduction disorders, connective tissue disorders, and metabolic disorders.[38] Pathogenic variants in these genes are included by default in clinical exome reports, although the patient and family may choose to opt out of these findings. There may be implications of such findings on future insurability such as disability, life, and long-term insurance. The diagnostic yield of exome/genome sequencing is improved if a trio sample is sent (proband and both parents), because this can determine de novo variants and can establish the phase of biallelic variants. Limitations of exome/genome sequencing include inability to diagnose repeat disorders and methylation abnormalities.[39] In addition, exome sequencing may have poor coverage of certain genomic regions, reduced sensitivity at detecting intragenic deletions (particularly those less than 3 exons in size) and will not detect balanced chromosome abnormalities. It is also important to note that the laboratory interpretation of exome/genome is very much dependent on the phenotype provided to the laboratory by the ordering clinician. Artificial intelligence is being studied to help with the automation of interpretation of genome sequencing for putative candidate variants.[40] In cases in which the family desires more targeted testing for concern of identifying candidates in less well understood genes, more variants of uncertain significance, or incidental findings, then a focused GDD/ID panel using similar sequencing technology as exome sequencing, but limited to a set of targeted genes, may be utilized. There is no uniformity with such testing, so the specific genes included and methodologies used differ significantly between performing laboratories. One possible benefit, based on the specific laboratory and test utilized, may be improved coverage of the included genes and better detection of intragenic deletions and duplications compared with exome sequencing, but the provider is encouraged to evaluate this on the basis of the specific panel test. In general, targeted GDD/ID panels have a lower diagnostic yield than exome/genome sequencing and are not preferred except in certain situations as noted previously. If a more targeted GDD/ID panel is nondiagnostic, then exome/genome sequencing may be considered next. The involvement of a geneticist or genetic counselor is recommended in these cases to assist in the selection of appropriate testing.

Chromosome Microarray

Genome-wide chromosome microarray (CMA) has been considered a first-line diagnostic test in the evaluation of the child with GDD/ID by the AAP, AAN, CPS, and the ACMG.[1,5,39,41,42] The AAP continues to recommend CMA in the first-tier agnostic evaluation for GDD/ID along with exome sequencing (sequential or concurrent). CMA is a test that quantitatively evaluates for chromosome gains and losses. It can occasionally detect smaller intragenic deletions or duplications. The specific resolution of the CMA varies depending on the platform used. If the CMA utilizes single nucleotide polymorphism (SNP)-based technology, it may also detect genomic regions of homozygosity, which can help to facilitate diagnosis of an autosomal recessive disorder or an imprinted disorder (in cases of uniparental isodisomy). The CMA cannot detect balanced chromosome rearrangements (eg, balanced translocations or balanced ring chromosomes).[16] It is estimated that the diagnostic yield of this test in the child with GDD/ID is between 15% and 20%.[42] Because the CMA screens for copy number variants genome-wide in an unbiased manner, there is the possibility that a CMA may detect copy number variants of uncertain significance, consanguinity, or incidental findings (eg, deletion of a gene implicated in cancer), and so pretest genetic counseling is indicated.

Pretest genetic counseling involves discussion of possible results such as benign, likely benign, pathogenic, likely pathogenic variants, or variants of uncertain significance. The laboratory uses data to determine these classifications, and in some cases, there are not enough data to determine whether a variant is disease causing or not, resulting in designation of a variant of uncertain significance. Identification of carrier status is possible if a deletion is found that includes a gene causing a recessive disorder. Incidental findings such as deletion of a cancer-causing gene may be reported. There may be implications of such findings on future insurability, such as disability, life, and long-term insurance. Areas of homozygosity (in which areas of both copies of the chromosome pair are the same) could indicate possible consanguinity.

Although CMA has a lower diagnostic yield overall than exome/genome sequencing, it can be superior to exome sequencing at detecting chromosome deletions/duplications, including small intragenic copy number variants. CMA also generally has a faster turnaround time and simpler pretest counseling. Pediatricians and other non-geneticist providers may elect to begin with a CMA first on the basis of available resources (eg, access to genetic counselors) and comfort level with genetic testing, while facilitating referral to a geneticist for possible exome/genome sequencing. A CMA may also be performed prior to exome/genome sequencing on the basis of the individual case and patient or clinician preference. Alternatively, CMA can be performed concurrently or following negative exome sequencing for superior coverage of copy number variation. If genome sequencing is initially performed, there is typically adequate evaluation of copy number variation, so CMA can be deferred in most cases.

Tier 2: Fragile X Testing and Metabolic Testing

Fragile X Testing

Fragile X syndrome is caused by *CGG* expansions in the 5′ untranslated region of the *FMR1* gene, and diagnosis required targeted testing that measures repeat length (ie, will *not* be detected on exome/genome sequencing or CMA).[25] Fragile X testing has historically been considered in the first-line agnostic diagnostic evaluation of the male with GDD/ID, including the prior position statements of the AAP, AAN, and CPS.[1,5,28] However, fragile X testing has a diagnostic yield of only approximately 1% in both males and females, and some authors have suggested that it should no longer be included in the first-tier evaluation of GDD/ID in the absence of clinical suspicion.[43] On the basis of the low diagnostic yield, the AAP recommends fragile X testing in the second-tier evaluation in both males and females with apparently nonsyndromic GDD/ID after exome/genome sequencing and CMA. If there are specific clinical features or family history consistent with fragile X syndrome, then it should be pursued earlier in the diagnostic evaluation (see section on phenotype-driven approach).

Screening for Treatable Inborn Errors of Metabolism

Inborn errors of metabolism (IEMs) are monogenic disorders associated with enzymatic defects or abnormal transport of metabolites. They represent the largest *treatable* cause of intellectual disability. With early diagnosis and treatment, there is the potential for improved outcome.

Many newborn screening programs evaluate for a number of IEMs, although the specific disorders screened for and testing methodologies vary based on location. It is also important to distinguish between screening and diagnostic evaluation and potential for missed diagnoses on newborn screening.[44,45]

Karnebeek et al performed a systematic literature review of treatable inborn errors of metabolism presenting with intellectual disability as a predominant feature. They reported 81 total treatable IEMs across 14 different disease categories. Fifty of 81 were diagnosable with routine blood and urine tests, whereas for the remaining disorders, more specialized testing was required, including specific enzyme testing, cerebrospinal fluid studies, or genetic testing.[32]

IEMs often present as syndromic GDD/IDD; however, IEMs may present as nonsyndromic GDD/ID in the earlier stages of illness. Red flags that may suggest an IEM include:

- Developmental regression
- Neurological signs – epilepsy, spasticity, movement disorder
- Multisystem involvement
- Abnormal body odor
- Basic biochemical abnormalities (eg, acidosis, hypoglycemia, etc)
- Abnormal MRI – atrophy, white matter abnormalities, deep gray structures symmetrically affected, abnormal spectroscopy (eg, elevated lactate or glycine, reduced creatine)
- Family history of IEM, or consanguinity

The diagnostic yield of metabolic evaluation in children with GDD/ID has been estimated to be 1% to 5%.[46] Further, this testing has a relatively low cost, prompt turnaround time, and the potential impact on outcome if one of these disorders is identified. The 2014 AAP recommendations[1] and 2018 CPS position statement[5] both suggest metabolic screening in the first tier evaluation of GDD/ID; however, given the very low yield in nonsyndromic GDD/ID, the AAP recommends testing in the second-tier evaluation after exome/genome sequencing and CMA unless there are specific clinical indications of a metabolic disorder (see "red flags" for an IEM and phenotype-driven approach). Further, CMA and exome/genome sequencing will detect most IEMs, including IEMs without clinically measurable biochemical abnormalities. See Table 2 for recommended initial evaluation for *treatable* IEMs. In addition to these specialized biochemical evaluations, general screening with a complete blood cell count, chemistry panel, liver function tests, and thyroid function tests may be considered. A baseline creatine phosphokinase can screen for some genetic muscle disorders (eg, muscular dystrophies, some metabolic myopathies), particularly in individuals with motor delays, hypotonia, and/or weakness (see phenotype-driven approach).

Tier 3 Evaluation

The third tier in the agnostic genetic evaluation for GDD/ID is aimed at identifying genetic etiologies that may have been missed in the first 2 tiers. The third tier includes consideration of: genome sequencing if exome sequencing was previously performed; an imprinting disorder; trinucleotide disorder (which may be missed on panel testing or exome/genome, depending on methodology used); mitochondrial DNA (mtDNA) testing if not included with prior testing; potential further biochemical evaluation for an IEM beyond laboratory tests in tier 2 (see Table 3); karyotype to evaluate for balanced chromosome rearrangements such as ring chromosomes; and broad screening for intragenic deletion/duplications that may have been missed on exome sequencing. The latter may be accomplished with a targeted GDD/ID deletion and duplication panel test, a higher-resolution CMA with specific exon-level coverage of disease-associated genes, or genome sequencing.

If negative, exome/genome sequencing may be clinically reanalyzed every 1 to 2 years following the initial test.[47] Some clinical laboratories offer a one-time complementary reanalysis if requested. It is very important for the ordering clinician to provide any updated phenotype data for the

TABLE 2. Treatable Inborn Errors of Metabolism Associated With Global Developmental Delay and Intellectual Disability for Tier 2 Evaluation

Disorder (Gene)	Clinical Features (Untreated)	Biochemical Evaluation
Phenylketonuria (*PAH*)	Developmental delay/intellectual disability, autism, eczema, reduced skin and hair pigmentation, epilepsy[48]	Plasma amino acids (increased phenylalanine)
Classic homocystinuria *(CBS1)*	Developmental delay/intellectual disability, marfanoid habitus (tall stature, scoliosis, pectus excavatum), eye lens dislocation and/or high myopia, increased risk of thrombosis[49]	Total homocysteine (increased), plasma amino acids (increased methionine)
Organic acidurias	Developmental delay/intellectual disability, metabolic acidosis, hyperammonemia, failure to thrive, epilepsy, movement disorder, metabolic stroke[24]	Urine organic acids, plasma acylcarnitines, ammonia
Urea cycle disorders	Episodes of hyperammonemic encephalopathy, protein aversion[50]	Ammonia, plasma amino acids (abnormal citrulline and/or arginine), urine organic acids (+/− increased orotic acid)
Creatine deficiency syndromes *(AGAT, GAMT, SLC6A8)*	Developmental delay/intellectual disability, autism, epilepsy[51]	Urine creatine/creatinine, plasma creatine, urine and plasma guanidinoacetate
Lesch-Nyhan syndrome *(HPRT1)*	Developmental delay/intellectual disability, autism, spasticity, movement disorder, uric acid nephropathy[20]	Plasma uric acid (increased), urine purine and pyrimidines
Mucopolysaccharidoses	Developmental delay, behavioral abnormalities, coarse facial features, hepatosplenomegaly, ophthalmological findings, orthopedic anomalies (eg, progressive spine deformities)[52]	Urine glycosaminoglycans
Biotinidase deficiency	Developmental delay/regression, hypotonia, ataxia, epilepsy, hearing and vision loss, skin rash, alopecia[53]	Biotinidase enzyme activity (if not included on newborn screening or clinical suspicion)

TABLE 3. Additional Tier 3 Screening Evaluation for Inborn Errors of Metabolism Associated With Global Developmental Delay and Intellectual Disability

Disorder	Clinical Features	Biochemical Evaluation
Congenital disorders of glycosylation (CDG)	Highly variable phenotype, may include developmental delay/intellectual disability, abnormal tone, epilepsy, blood clotting abnormalities (both pro- and antithrombotic), liver disease, lipodystrophy (abnormal fat distribution)[54]	CDG transferrin testing, N-glycans, O-glycans, urine oligosaccharides, and free glycans
Lysosomal disorders	Highly variable phenotype, may include developmental delay/regression, epilepsy, coarse features, hepatosplenomegaly, skeletal anomalies, corneal or retinal abnormalities, hearing loss[55]	Urine mucopolysaccharides, urine oligosaccharides, lysosomal enzyme screening panel
Peroxisomal disorders	Highly variable phenotype, includes developmental delay/regression, hypotonia, epilepsy, neuropathy, craniofacial dysmorphisms, enlarged anterior fontanelle, skeletal abnormalities (eg, rhizomelia, chondrodysplasia punctata), liver disease, renal disease, hearing loss, retinal disease[56]	Plasma very long chain fatty acids, red blood cell plasmalogens
Smith-Lemli-Opitz syndrome *(DHCR7)*	Craniofacial dysmorphisms, short stature, 2/3 toe syndactyly, failure to thrive, microcephaly, congenital heart defects, CAKUT[57]	7-dehydrocholesterol levels
Purine and pyrimidine disorders (other than Lesch-Nyhan syndrome)	Highly variable phenotype, includes developmental delay/regression, movement disorder, epilepsy[58]	Urine purines/pyrimidines
Menkes syndrome *(ATP7A)*	Sparse and wiry hair, pale complexion, lax skin and joints, severe hypotonia, microcephaly, global developmental delay, epilepsy[59]	Serum copper and ceruloplasmin

Abbreviation: CAKUT, congenital anomalies of the kidneys and urinary tract.

reanalysis, because these data may influence the interpretation of the exome/genome sequencing. Some academic centers may also have the capacity for research-based exome reanalysis. The additional diagnostic yield of this iterative approach to exome analysis has been previously demonstrated.[60]

OTHER TESTING

Some genetic neurodevelopmental disorders are associated with abnormal DNA methylation at a single locus (see imprinted disorders discussed previously), whereas other disorders are associated with the abnormal methylation of multiple gene loci. This specific pattern of methylation

abnormalities across multiple loci, or "methylation signature," can be syndrome-specific and exploited for diagnostic purposes. Recently, such genome-wide methylation signature testing has become clinically available, although it is still only able to evaluate for a relatively small number of disorders, limiting its utility primarily to the evaluation of variants of uncertain significance in these genes or as a screening evaluation following otherwise nondiagnostic testing as above.[61]

Finally, various facial recognition computer software programs are now available that have been designed to better recognize genetic disorders based on dysmorphology, but it remains to be seen what the clinical utility of such programs is.[62] Also, these facial recognition programs are not routinely available in clinical practice.

ETHICAL ISSUES

There are ethical issues associated with genetic testing, potential harm from genetic testing (privacy concerns, misattributed parentage) and inequities in access to genetic testing. These issues are beyond the scope of this paper and the reader is referred to the AAP policy statement "Ethical and Policy Issues in Genetic Testing and Screening of Children."

CONCLUSIONS/RECOMMENDATIONS

Genetic neurodevelopmental disorders are common in the pediatric population, and it is vital for the general pediatrician to have an approach for their initial evaluation. Establishing a genetic diagnosis early provides multiple benefits. If possible, genetic testing should be selected by phenotype, but in many cases, an agnostic approach may be utilized. The AAP provides recommendations for this agnostic approach based on diagnostic yield and also practical considerations such as test complexity and impact on management. These recommendations for initial testing do not preclude further evaluation by relevant subspecialists as necessary, including neurologists, developmental pediatricians, and clinical geneticists. These recommendations are provided throughout the report and are summarized in Figure 1.

LEAD AUTHORS

Lance H. Rodan, MD
Joan Stoler, MD, FAAP
Emily Chen, MD, PhD
Timothy Geleske, MD, FAAP

COUNCIL ON GENETICS EXECUTIVE COMMITTEE 2024–2025

Samantha Vergano, MD, FAAP (chair)
Ingrid A. Holm, MD, FAAP
Kelly Jones, MD, FAAP
Jennifer Kalish, MD, FAAP
Danielle C. Monteil, MD, FAAP
Amanda Barone Pritchard, MD, FAAP
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Bianca Russell, MD, FAAP
Stephanie L. Santoro, MD, FAAP
Pamela Trapane, MD, FAAP
Kathryn Nicole Weaver, MD, FAAP

PARTNERSHIP FOR POLICY IMPLEMENTATION

Juan D. Chaparro, MD, MS, FAAP

LIAISONS

Lynne M. Bird, MD, FAAP - American College of Medical Genetics and Genomics
Steven J. Ralston, MD - American College of Obstetricians & Gynecologists (ACOG)

STAFF

Paul Spire

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REFERENCES

1. Moeschler JB, Shevell M, Moeschler JB, et al; Committee on Genetics. Comprehensive evaluation of the child with intellectual disability or global developmental delays. *Pediatrics*. 2014;134(3):e903–e918. PubMed doi: 10.1542/peds.2014-1839
2. Zablotsky B, Black LI, Maenner MJ, et al. Prevalence and trends of developmental disabilities among children in the United States: 2009–2017. *Pediatrics*. 2019;144(4):e20190811. PubMed doi: 10.1542/peds.2019-0811
3. Shevell M, Ashwal S, Donley D, et al; Practice Committee of the Child Neurology Society. Practice parameter: evaluation of the child with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society. *Neurology*. 2003;60(3):367–380. PubMed doi: 10.1212/01.WNL.0000031431.81555.16
4. Schalock RL, Luckasson RA, Shogren KA. The renaming of mental retardation: understanding the change to the term intellectual

disability. *Intellect Dev Disabil.* 2007;45(2):116–124. PubMed doi: 10.1352/1934-9556(2007)45[116:TROMRU]2.0.CO;2

5. Bélanger SA, Caron J. Evaluation of the child with global developmental delay and intellectual disability. *Paediatr Child Health.* 2018; 23(6): 403–410. DOI: https://doi.org/10.1093/pch/pxy093
6. Srour M, Shevell M. Genetics and the investigation of developmental delay/intellectual disability. *Arch Dis Child.* 2014;99(4):386–389. PubMed doi: 10.1136/archdischild-2013-304063
7. Theisen A, Shaffer LG. Disorders caused by chromosome abnormalities. *Appl Clin Genet.* 2010;3:159–174. DOI: 10.2147/tacg.s8884
8. Kochinke K, Zweier C, Nijhof B, et al. Systematic phenomics analysis deconvolutes genes mutated in intellectual disability into biologically coherent modules. *Am J Hum Genet.* 2016;98(1):149–164. PubMed doi: 10.1016/j.ajhg.2015.11.024
9. Chiurazzi P, Pirozzi F. Advances in understanding - genetic basis of intellectual disability. *F1000 Res.* 2016;5:F1000. PubMed doi: 10.12688/f1000research.7134.1
10. Luo S, Valencia CA, Zhang J, et al. Biparental inheritance of mitochondrial DNA in humans. *Proc Natl Acad Sci U S A.* 2018;115(51): 13039–13044. PubMed doi: 10.1073/pnas.1810946115
11. Eggermann T, Perez de Nanclares G, Maher ER, et al. Imprinting disorders: a group of congenital disorders with overlapping patterns of molecular changes affecting imprinted loci. *Clin Epigenetics.* 2015;7(1):123. PubMed doi: 10.1186/s13148-015-0143-8
12. Kousi M, Katsanis N. Genetic modifiers and oligogenic inheritance. *Cold Spring Harb Perspect Med.* 2015;5(6):a017145. PubMed doi: 10.1101/cshperspect.a017145
13. Bird LM. Angelman syndrome: review of clinical and molecular aspects. *Appl Clin Genet.* 2014;7:93–104. PubMed doi: 10.2147/TACG.S57386
14. Angulo MA, Butler MG, Cataletto ME. Prader-Willi syndrome: a review of clinical, genetic, and endocrine findings. *J Endocrinol Invest.* 2015;38(12):1249–1263. DOI: 10.1007/s40618-015-0312-9
15. Ioannides Y, Lokulo-Sodipe K, Mackay DJG, Davies JH, Temple IK. Temple syndrome: improving the recognition of an underdiagnosed chromosome 14 imprinting disorder: an analysis of 51 published cases. *J Med Genet.* 2014;51(8):495–501. PubMed doi: 10.1136/jmedgenet-2014-102396
16. Savatt JM, Myers SM. Genetic testing in neurodevelopmental disorders. *Front Pediatr.* 2021;9:526779. PubMed doi: 10.3389/fped.2021.526779
17. Shaffer LG; American College of Medical Genetics Professional Practice and Guidelines Committee. American College of Medical Genetics guideline on the cytogenetic evaluation of the individual with developmental delay or mental retardation. *Genet Med.* 2005; 7(9):650–654. PubMed doi: 10.1097/01.gim.0000186545.83160.1e
18. Kaufman L, Ayub M, Vincent JB. The genetic basis of non-syndromic intellectual disability: a review. *J Neurodev Disord.* 2010;2(4):182–209. PubMed doi: 10.1007/s11689-010-9055-2
19. O'Byrne JJ, Lynch SA, Treacy EP, et al. Unexplained developmental delay/learning disability: guidelines for best practice protocol for first line assessment and genetic/metabolic/radiological investigations. *Ir J Med Sci.* 2016;185(1):241–248. PubMed doi: 10.1007/s11845-015-1284-7
20. Jinnah HA. HPRT1 disorders. In: *GeneReviews [Internet].* University of Washington; 1993–2021. 2000 Sep 25 [Updated 2020 Aug 6]
21. Kline AD, Moss JF, Selicorni A, et al. Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. *Nat Rev Genet.* 2018;19(10):649–666. PubMed doi: 10.1038/s41576-018-0031-0
22. Weaving LS, Ellaway CJ, Gécz J, Christodoulou J. Rett syndrome: clinical review and genetic update. *J Med Genet.* 2005;42(1): 1–7. PubMed doi: 10.1136/jmg.2004.027730
23. Goodspeed K, Newsom C, Morris MA, Powell C, Evans P, Golla S. Pitt-Hopkins syndrome: a review of current literature, clinical approach, and 23-patient case series. *J Child Neurol.* 2018;33(3): 233–244. doi: 10.1177/0883073817750490
24. Vaidyanathan K, Narayanan MP, Vasudevan DM. Organic acidurias: an updated review. *Indian J Clin Biochem.* 2011;26(4):319–325. PubMed doi: 10.1007/s12291-011-0134-2
25. Gallagher A, Hallahan B. Fragile X-associated disorders: a clinical overview. *J Neurol.* 2012;259(3):401–413. PubMed doi: 10.1007/s00415-011-6161-3
26. Odom LN, Segars J. Imprinting disorders and assisted reproductive technology. *Curr Opin Endocrinol Diabetes Obes.* 2010;17(6): 517–522. PubMed doi: 10.1097/MED.0b013e32834040a3
27. Vermeiden JPW, Bernardus RE. Are imprinting disorders more prevalent after human in vitro fertilization or intracytoplasmic sperm injection? *Fertil Steril.* 2013;99(3):642–651. PubMed doi: 10.1016/j.fertnstert.2013.01.125
28. American Academy of Neurology, Child Neurology Society. *Evaluation of the Child with Global Developmental Delay.* American Academy of Neurology; 2011. Accessed April 9, 2024. https://www.aan.com/globals/axon/assets/2603.pdf
29. Noritz GH, Murphy NA, Murphy NA, et al; Neuromotor Screening Expert Panel. Motor delays: early identification and evaluation. *Pediatrics.* 2013;131(6):e2016–e2027. PubMed doi: 10.1542/peds.2013-1056
30. Ali AS, Syed NP, Murthy GSN, et al. Magnetic resonance imaging (MRI) evaluation of developmental delay in pediatric patients. *J Clin Diagn Res.* 2015;9(1):TC21–TC24. PubMed doi: 10.7860/JCDR/2015/11921.5478
31. Rajvanshi N, Bhakat R, Saxena S, et al. Magnetic resonance spectroscopy in children with developmental delay: time to look beyond conventional magnetic resonance imaging (MRI). *J Child Neurol.* 2021;36(6):440–446. PubMed doi: 10.1177/0883073820978006
32. van Karnebeek CD, Stockler-Ipsiroglu S. Early identification of treatable inborn errors of metabolism in children with intellectual disability: The Treatable Intellectual Disability Endeavor protocol in British Columbia. *Paediatr Child Health.* 2014;19(9): 469–471. PubMed doi: 10.1093/pch/19.9.469
33. Manickam K, McClain MR, Demmer LA, et al; ACMG Board of Directors. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an

evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2021;23(11):2029–2037. PubMed doi: 10.1038/s41436-021-01242-6

34. Srivastava S, Love-Nichols JA, Dies KA, et al. Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders. *Genet Med.* 2019;21(11):2413–2421. doi: 10.1038/s41436-019-0554-6
35. Ewans LJ, Minoche AE, Schofield D, et al. Whole exome and genome sequencing in mendelian disorders: a diagnostic and health economic analysis. *Eur J Hum Genet.* 2022;30(10):1121–1131. PubMed doi: 10.1038/s41431-022-01162-2
36. Oehler JB, Wright H, Stark Z, Mallett AJ, Schmitz U. The application of long-read sequencing in clinical settings. *Hum Genomics.* 2023;17(1):73–85. PubMed doi: 10.1186/s40246-023-00522-3
37. Riggs ER, Andersen EF, Cherry AM, et al. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). *Genet Med.* 2020;22(2):245–257. PubMed doi: 10.1038/s41436-019-0686-8
38. Miller DT, Lee K, Abul-Husn NS, et al; ACMG Secondary Findings Working Group. Electronic address: documents@acmg.net. ACMG SF v3.2 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2023;25(8):100866. PubMed doi: 10.1016/j.gim.2023.100866
39. Savatt JM, Myers SM. Genetic testing in neurodevelopmental disorders. *Front Pediatr.* 2021;9:526779. DOI: 10.1002/humu.23607
40. De La Vega FM, Chowdhury S, Moore B, et al. Artificial intelligence enables comprehensive genome interpretation and nomination of candidate diagnoses for rare genetic diseases. *Genome Med.* 2021;13(1):153–171. PubMed doi: 10.1186/s13073-021-00965-0
41. Manning M, Hudgins L; Professional Practice and Guidelines Committee. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genet Med.* 2010;12(11):742–745. PubMed doi: 10.1097/GIM.0b013e3181f8baad
42. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet.* 2010;86(5):749–764. PubMed doi: 10.1016/j.ajhg.2010.04.006
43. Borch LA, Parboosingh J, Thomas MA, Veale P. Re-evaluating the first-tier status of fragile X testing in neurodevelopmental disorders. *Genet Med.* 2020;22(6):1036–1039. PubMed doi: 10.1038/s41436-020-0773-x
44. Therrell BL Jr, Padilla CD. Newborn screening in the developing countries. *Curr Opin Pediatr.* 2018;30(6):734–739. PubMed doi: 10.1097/MOP.0000000000000683
45. Fabie NAV, Pappas KB, Feldman GL. The current state of newborn screening in the United States. *Pediatr Clin North Am.* 2019;66(2):369–386. PubMed doi: 10.1016/j.pcl.2018.12.007
46. Tirosh E, Jaffe M. Global developmental delay and mental retardation—a pediatric perspective. *Dev Disabil Res Rev.* 2011;17(2):85–92. PubMed doi: 10.1002/ddrr.1103
47. Ji J, Leung ML, Baker S, Deignan JL, Santani A. Clinical exome reanalysis: current practice and beyond. *Mol Diagn Ther.* 2021;25(5):529–536. PubMed doi: 10.1007/s40291-021-00541-7
48. Mitchell JJ, Trakadis YJ, Scriver CR. Phenylalanine hydroxylase deficiency. *Genet Med.* 2011;13(8):697–707. PubMed doi: 10.1097/GIM.0b013e3182141b48
49. Morris AAM, Kožich V, Santra S, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. *J Inherit Metab Dis.* 2017;40(1):49–74. PubMed doi: 10.1007/s10545-016-9979-0
50. Mew NA, Simpson KL, Gropman AL, Lanpher BC, Chapman KA, Summar ML.Urea cycle disorders overview. In: *GeneReviews [Internet]*. University of Washington; 1993–2021. 2003 Apr 29 [Updated 2017 Jun 22]
51. Mercimek-Andrews S, Salomons GS. Creatine deficiency syndromes. In: *GeneReviews [Internet]*. University of Washington; 1993–2021. 2009 Jan 15 [Updated 2015 Dec 10]
52. Muenzer J. Overview of the mucopolysaccharidoses. *Rheumatology (Oxford).* 2011;50(5)(suppl 5):v4–v12. PubMed doi: 10.1093/rheumatology/ker394
53. Wolf B. Biotinidase deficiency. In: *GeneReviews [Internet]*. University of Washington; 1993–2021. 2000 Mar 24 [Updated 2016 Jun 9]
54. Witters P, Morava E. Congenital disorders of glycosylation (CDG): review. *eLS.* November 3, 2016. DOI: 10.1002/9780470015902.a0026783
55. Platt FM, d'Azzo A, Davidson BL, Neufeld EF, Tifft CJ. Lysosomal storage diseases. *Nat Rev Dis Primers.* 2018;4(1):27. PubMed doi: 10.1038/s41572-018-0025-4
56. Braverman NE, D'Agostino MD, Maclean GE. Peroxisome biogenesis disorders: biological, clinical and pathophysiological perspectives. *Dev Disabil Res Rev.* 2013;17(3):187–196. doi: 10.1002/ddrr.1113
57. Nowaczyk MJM, Irons MB. Smith-Lemli-Opitz syndrome: phenotype, natural history, and epidemiology. *Am J Med Genet C Semin Med Genet.* 2012;160C(4):250–262. PubMed doi: 10.1002/ajmg.c.31343
58. Nyhan WL. Disorders of purine and pyrimidine metabolism. *Mol Genet Metab.* 2005;86(1-2):25–33. PubMed doi: 10.1016/j.ymgme.2005.07.027
59. Kaler SG. ATP7A-related copper transport diseases-emerging concepts and future trends. *Nat Rev Neurol.* 2011;7(1):15–29. PubMed doi: 10.1038/nrneurol.2010.180
60. Shashi V, Schoch K, Spillmann R, et al; Undiagnosed Diseases Network. A comprehensive iterative approach is highly effective

in diagnosing individuals who are exome negative. *Genet Med*. 2019;21(1):161–172. PubMed doi: 10.1038/s41436-018-0044-2

61. Cerrato F, Sparago A, Ariani F, et al. DNA Methylation in the diagnosis of monogenic diseases. *Genes (Basel)*. 2020;11(4): 355. PubMed doi: 10.3390/genes11040355

62. Dudding-Byth T, Baxter A, Holliday EG, et al. Computer face-matching technology using two-dimensional photographs accurately matches the facial gestalt of unrelated individuals with the same syndromic form of intellectual disability. *BMC Biotechnol*. 2017;17(1):90. PubMed doi: 10.1186/s12896-017-0410-1