DOI: 10.32481/djph.2021.03.004

# Intellectual Developmental Disabilities:

## Definitions, Diagnosis, and Delivery of Care

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## Introduction

Intellectual developmental disability (IDD) is a developmental condition characterized by significant deficiencies in intellectual functioning and adaptive behavior. Some definitions specify an onset before age 22. Other definitions[1–3] stress the specific areas of disability: reasoning, planning, judgment, abstract thinking and experiential learning.[4] In the absence of a specific biomarker (IQ alone having been appropriately discarded along with the outdated term mental retardation), the determination or diagnosis of IDD is established on "clinical grounds." "Clinical" implies a sophisticated and comprehensive evaluation, not simply one person's impression. It includes an evaluator with a degree of clinical training and expertise capable of a thorough review and analysis.[1] Similarly, a comprehensive clinical care team ensures health for the individual throughout life.

## Frequency

It is difficult to report a specific prevalence of IDD, because of clinical heterogeneity of the condition, variations of age of subjects in reported studies, and variations in methods of diagnosis/determination. A recent CDC report quotes a prevalence of adults with cognitive disability in Delaware as 14%, while other sources quote figures in the 1 to 3% range.[3,5,6] In any case, the prevalence is substantial and of public health importance.

## Comorbidities

Frequently, individuals with IDD have accompanying comorbidities, such as autism spectrum disorder, seizure disorder, attention deficit disorder, anxiety, cerebral palsy, vision disorders, hearing loss, and depression. In other cases, there may be extensive physical and developmental features outside of the nervous system consistent with a syndromic IDD such as Down Syndrome.

## Causes

A precise determination of cause in an affected person is often not determined.[1,5] However, consideration of causes can be important to families and in estimating prognosis. A useful approach is to consider possible causes related to environment and others to genetics with an acknowledgment that there is also a third category: "unknown" or, optimistically, "to be determined" or "multifactorial."[3]

Environmental causes can be prenatal, perinatal and postnatal. Examples of prenatal causes include poor maternal health, maternal infection with organisms known to be teratogenic (e.g. ru-

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bella, cytomegalovirus, varicella, Zika, toxoplasmosis); high dose of radiation; maternal use of drugs/medications such as anti-metabolites, warfarin, anticonvulsants, isotretinoin, tobacco, alcohol and others.

Possible perinatal causes or risk factors include low birth weight, prematurity, complications of labor and delivery, neonatal asphyxia, perinatal infections, newborn multiple congenital anomalies, infant infections such as Herpes, meningitis, neonatal sepsis and structural brain anomalies (microcephaly, hydrocephalus, schizencephaly) as well as other major congenital anomalies such as diaphragmatic hernia or complex congenital cardiac anomalies.

Potential postnatal environmental causes of IDD include serious infections, meningitis, acknowledged environmental toxins, traumatic brain injury and adult onset of degenerative nervous system disorders (e.g Parkinson's, Alzheimer's, Huntington's, and many others).

There are numerous genetic causes of IDD. Genetic disorders include variations of chromosome number (e.g. Down Syndrome), relatively large duplications or deletions of parts of a chromosome (e.g. Cri du Chat Syndrome, due to the deletion of part of the short arm of chromosome number 5), and single gene disorders. Single gene disorders include (but are not limited to) inborn errors of metabolism (e,g. PKU), lysosomal storage disorders, peroxisomal disorders, fatty acid oxidation disorders, disorders of energy metabolism (mitochondrial disorders) and a number of syndromes with multiple congenital anomalies including the central nervous system.[6,7]

The Online Mendelian Inheritance in Man (OMIM)[8] is a comprehensive, authoritative compendium of human genes and disorders related to mutations. Recently OMIM reported that about 1091 genetic loci have identified mutations which may be associated with an intellectual developmental disorder.[8]

## Evaluation

Determining a specific cause of an intellectual, developmental disability can assist a family in working with an affected individual. A specific determination might result in better understanding of how an IDD occurred and an idea of whether progression is likely to occur. Specific determination is not likely, at this time, to suggest specific interventions, but could help families and individuals understand risks to the individual, and likelihood of presentation in other family members. Genetic counselling is a useful tool to navigate risks to other and future family members.

In a diagnostic setting, medical history is important with specific attention to pre- and perinatal history, as well as a family history, including a three generation family pedigree taking into account history of early death, infertility, and consanguinity. A physical exam could be helpful in identifying minor congenital variants that could assist in determining a genetic disorder. For example, detecting minor variants in extremities could assist in identifying a chromosome disorder, or detecting certain subtle skin variants could suggest tuberous sclerosis complex.

Appropriate blood and urine studies – such as measurement of amino acids, organic acids, fatty acids, and lactate/pyruvate ratios – may lead to an identification of an underlying inborn error of metabolism. These are most often part of a pediatric developmental/genetic evaluation, though in recent years, late-onset inborn errors of metabolism have been proven to be more common than thought previously.

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Karyotyping ("routine" chromosome analysis) has been available for decades and has been valuable in confirming certain clinically suspected syndromes - most notably Down Syndrome (in most cases due to Trisomy 21), but also confirming other trisomies such as Trisomy 13 and Trisomy 18 - as well as detecting relatively large chromosome deletions. Routine karyotype may be adequate in identifying variants in a suspected sex chromosome anomaly. As part of the evaluation of a person with congenital anomalies and/or IDD, newer technologies have replaced karyotype except in situations noted above.

Chromosome microarray (CMA) in its simplest explanation is a technology in which parts of an individual's DNA are compared to a standard.[9] There are other similar technologies involving single nucleotide variants with similar sensitivities. These technologies can identify copy number variants (CNV) in a subject with resolution to as few as 60,000 nucleotides. This means the technology can reliably detect disorders characterized by small deletions or duplications, including some relatively well known syndromes: Williams, DiGeorge, Smith Magenis, 1p36 deletion and others. It may also detect other deletions and/or duplications that could explain the IDD.[9] Occasionally the technique will detect a deletion or duplication not previously known to be pathogenic. These are known as variants of uncertain significance, or VUS. Parental studies could be helpful in interpretation of VUS if one of the unaffected parents has the same CNV. Though sometimes it can be confusing to interpret VUS, in a study of hundreds of persons with IDD, CMA resulted in up to 25% of selected persons having a diagnosis made.[9]

Many single gene disorders can be confirmed by specific mutation analysis. For example, if there is a clinical suspicion of Fragile X syndrome this can be confirmed at a number of available laboratories. In this situation, the lab looks specifically for mutations at the Fragile X locus. No other genes are studied.

Recently, nucleic acid sequencing technologies (so called next generation sequencing) have become clinically available. These allow for relatively prompt determination of the number and sequence of part of the DNA in a patient's genome. Genes are made up of exons and introns. The exons are the parts of the gene that code for a specific protein. The next generation sequencing can be set up to study all (or almost all) of the exons known as the exome. The technology (called whole exome sequencing, WES) is relatively expensive, though often comparable to the cost associated with step by step evaluations.[10] Generating substantial amounts of information, WES can reliably detect singe gene variants throughout the exome.[10–14] Fifteen to forty percent of persons with IDD who have WES will have a detectable mutation and a molecular diagnosis or determination made.

The next technology step, whole genome sequencing (WGS), is currently clinically available in some situations and will be generally available soon. This form of next generation sequencing "looks" at the entire (or almost entire) genome and can reliably deject single gene variants in exons AND introns. These new technologies at times can require complex interpretations. WGS can identify mutations in genes that were not being studied, so called Secondary Results. Appropriate responses to VUS or Secondary Results of sequencing are under investigation with particular attention to ethical issues.

## Conclusion

New genetic technologies contributing to the understanding of the etiology of IDD are becoming available to persons with IDD and their families. This availability is expected to be beneficial for

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those individuals and families who wish to pursue a specific diagnosis with the guidance of a genetic counselor, and for the health care providers caring for the individual and his or her family throughout a lifetime.

## Companion Pearl

Whether or not the specific etiology of IDD is known, an appropriate clinical team should be comprehensive and multidisciplinary, and based in collaborative primary and specialty care. Health disparities between adults with IDD and the general population result for a variety of reasons: fragmented access to primary and preventive care,[15] social and medical stigma,[16] and marginalization.[17] So, too, can there be increased morbidity from the associated conditions, with an all-cause mortality almost three times higher than in the general population.[18] Black race, Latinx ethnicity, low income status, and female gender accentuate the disparity.[19]

To empower adults with IDD, their caregivers, and their clinical teams, the goals of effective health care engagement follow:

1. **Get specific!** If genetic testing is warranted, pursue the diagnosis to better direct care. Searching for a genetic cause can be helpful, but not necessary. If a particular genetic syndrome is known, visit foundation websites and refer to guidelines of care that are syndrome-specific. The most common congenital etiologies of IDD are Down Syndrome, Fragile X Syndrome, and fetal alcohol syndrome (FAS). All three disorders have strong advocacy organizations and frequently updated guidelines for diagnosis and care accessible by secondary data sources like Uptodate or Medscape. For these and less known congenital causes, additional use of a research database like Pubmed or Medline can also direct care and demonstrate clinical experts familiar with the disorder who may be willing to collaborate.
2. **Routine health care** should include age-appropriate cancer screening, infection screening, immunizations, and periodic dental evaluation. For those in congregate living arrangements like group homes or facilities, evaluations should include screening for infectious diseases like tuberculosis. Frequent evaluation of common problems will focus on brain disorders (mental illness, seizure disorder), bowel complaints (from oral hygiene to dysphagia and constipation), and behaviors (both adaptive and maladaptive). On demand health services may be insufficient in those who have difficulty with communication, so routine health examinations at least every six months are advised.
3. **Address sexuality** and the need for birth control and infection screening among adults with IDD. Address the possibility of abuse. Those with IDD are at increased risk of experiencing interpersonal violence of all forms.[20]
4. **Communicate!** Encourage addressing the patient first and frequently during clinical encounters no matter how the particular individual communicates. Additional bidirectional communication is necessary among clinical team and both local and family caregivers who may be in different geographic locations and varying proximity to the patient. Provide written communication accessible by all. Clarify whether the patient speaks for him or herself and if not, who does. Sometimes there is a need to establish supported decision making or guardianship, especially

when a patient is anticipated to need a procedure. This process can take time and money. The guardian may be a relative or state-appointed official.

**5.** Implement **e**thical care. Establishing goals of care in patients with IDD is no different that establishing goals of care in the general population. The diagnosis of IDD alone does not signify the type of procedures an individual may have nor resuscitation status. Understanding the patient's and family's wishes, in addition to the nature of terminal illnesses and likelihood of resuscitation success, should guide shared decision making. Check biases to ensure appropriate care delivery unfettered by discrimination.

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