Approach to Genetic Diagnosis in Developmental Delay

Introduction
- This document does not replace input from a clinical geneticist, but given that many regions are underserved by clinical genetics, this document may assist primary care providers in conducting an initial diagnostic evaluation.
- Patients with new-onset seizures, developmental regression, concern for increased intracranial pressure or other acute concerns should be referred to the appropriate specialty.
- This document will change over time with new developments in genetic testing.

Initial considerations
- The American Academy of Pediatrics has published their statement on appropriate genetic evaluation of children with developmental delay: see Moeschler et al Pediatrics 2014.
- Much of the following is adapted from that source, with updates based on changing technology for genetic testing in the intervening years.
- Reasons to pursue diagnostic genetic testing:
  - A definitive diagnosis (reduced uncertainty, access to support groups, reduction in invasive diagnostic testing)
  - Ability to provide a more detailed prognosis for the child
  - Potential for treatment or management specific to the diagnosis
  - Determination of recurrence risk for the parents and other family members
- History and physical examination
  - Is there a known family history of a specific genetic condition?
  - Does the history or physical exam implicate a specific genetic diagnosis based on physical features or characteristic history (e.g. Down Syndrome, Prader Willi)?
  - Is there an aspect of the history that makes a genetic diagnosis less likely (e.g. extreme prematurity, prenatal exposure to alcohol, history of traumatic brain injury, history of meningitis)?
    - A reference for non-genetic considerations for etiological diagnosis in patients with developmental delay can be found in the attached documents.
  - If targeted testing is indicated then can contact genetics for advice on the logistics of testing or refer at that time.
  - If no specific diagnosis is considered likely then consider the untargeted approach presented below.
- MRI of the brain
  - Not necessarily indicated in all patients with developmental delay
  - Higher yield for providing actionable information in the following settings:
    - Epilepsy
    - Macrocephaly
    - Microcephaly
- Focal neurological findings (e.g. asymmetry, ataxia, hypertonia, dystonia, concern for elevated intracranial pressure, etc.)
- Developmental regression
  - If MRI findings are specific (e.g. Leigh syndrome, cerebellar atrophy, cortical dysplasias, etc.) then consider targeted testing for that indication with advice from genetics or refer at that time.
  - If MRI is not obtained or if findings are normal or nonspecific then consider the untargeted approach presented below.

Untargeted approach to genetic testing for developmental delay

- Tier 1
  - Chromosomal microarray
    - Provides copy number of most clinically significant genes (e.g. deletion, duplication, triplication); can diagnose aneuploidy
    - Roughly two-week turnaround time
    - Insurance authorization should be obtained prior to sending (or use a lab that will complete insurance authorization for you).
    - Informed consent for the following should be discussed prior to testing:
      - Diagnostic yield for the indication of developmental delay is about 10%-30% depending on the setting
      - Test will reveal if parents are related to one another
      - Test may have clearly diagnostic, clearly normal or ambiguous results
      - Ambiguous results may require testing of parents or other family members for follow-up; in other cases ambiguity cannot be resolved
      - May have secondary findings that are clinically-significant but unrelated to the reason for testing (e.g. cancer predisposition)
  - Fragile X trinucleotide repeat expansion analysis
    - Caused by a trinucleotide repeat that cannot be detected by methods other than targeted testing
    - X-linked disorder, but symptomatic females are not uncommon and thus testing is indicated in both sexes
    - Insurance authorization and informed consent should be obtained prior to testing
    - Diagnostic yield is 1%-2% in boys, lower in girls
    - Informed consent:
      - With diagnostic results, mother may be a full mutation or premutation carrier, results may have implications for her fertility and potential for adult-onset neurological disease in premutation carriers

- Tier 2
  - Large gene sequencing panel of developmental delay-associated genes
Ideally trio-based including both biological parents to reduce the likelihood of uncertain variants; if not trio testing initially, then parental samples are likely to be needed subsequently for confirmation of diagnosis.

Insurance authorization and informed consent should be obtained prior to testing (or use a lab that will complete insurance authorization for you).

Informed consent includes:

- Any time child and parents are tested, there is the possibility to reveal that one of the parents is not the biological parent of the child.
- Diagnostic yield is probably about 30%, but depends on many factors.
- Ambiguous findings are common; some can be resolved with further testing, others cannot.
- Secondary findings are possible - detection of a diagnosis that does not account for the patient’s entire presentation but still has clinical relevance.
- A parent could also receive the same diagnosis as the child as a result of testing.

- Tier 3
  - Whole exome or whole genome sequencing can be considered.
  - See www.treatable-id.org for a testing algorithm and information on diagnoses that have specific management and can be detected with biochemical testing.
  - Samples should ideally be obtained 3-4 hours after eating.
  - Informed consent:
    - There are often abnormal but nonspecific findings in metabolic testing and further testing is often required as a result.
    - Algorithm includes:
      - Serum amino acids
      - Serum homocysteine
      - Urine creatine metabolites
      - Urine organic acids
      - Urine purines and pyrimidines
      - Urine oligosaccharides
      - Urine mucopolysaccharides

Genetic testing laboratories that currently offer patient insurance benefit verification service:

- Patient insurance benefit verification may be available at other labs as well and the availability of this service may change.
- Some laboratories have subsidies available to limit out of pocket cost to families.
- We recommend assessing the availability of these services with the specific lab that will be used at the time that testing is obtained.
- Most genetic tests can now be performed with buccal swab sample kits from the labs.
  - GeneDx
Return of results

- Labs will classify each reported genetic variant as either benign, likely benign, variant of uncertain significance (VUS), likely pathogenic or pathogenic.
- Likely pathogenic or pathogenic results can usually be reported as diagnostic to families if clinical features are compatible with that diagnosis.
- A VUS may require interpretation from a geneticist and additional testing of the child and family members.
- If there are questions about the significance of a result, then we recommend discussion with a geneticist prior to disclosing to the family.

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