Arizona approach to Genetic Services in children with Developmental Delay

**Primary care providers may consider initiating genetic diagnostic testing for patients with developmental delay when access to genetic services is limited or wait time is long.**

* The American Academy of Pediatrics has published their statement on appropriate genetic evaluation of children with developmental delay: see Moeschler et al Pediatrics 2014.
* Ensure that acute neurological concerns are addressed with appropriate evaluation and not deferred until after genetic testing.
* Referrals for developmental therapies and services that address developmental concerns should be made concurrently with a genetic evaluation.

Tiered recommendations are as follows:

**Tier 1**

***Molecular testing***

1. Chromosomal microarray
   * Provides copy number of most clinically significant genes (eg deletion, duplication, triplication); can diagnose aneuploidy
   * Roughly two-week turnaround time
2. Fragile X trinucleotide repeat 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

***Biochemical testing***

1. Plasma amino acids
2. Urine organic acids
3. Plasma total homocysteine
4. Serum carbohydrate deficient transferrin

**Tier 2**

***Molecular testing***

1. 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

***Biochemical testing***

1. Urine & plasma creatine and guanidinoacetate
2. Urine purines and pyrimidines
3. Plasma very long chain fatty acids
4. WBC lysosomal enzyme panel

**Tier 3**

1. Whole exome sequencing may be considered
2. See [www.treatable-id.org](http://www.treatable-id.org) for a testing algorithm and information on diagnoses that have specific treatment and can be diagnosed with biochemical testing.

**Additional considerations:**

Families should undergo appropriate informed consent specific to the test that is planned before completing genetic testing (see attached document).

Ensure that insurance approval is obtained prior to testing to avoid large out-of-pocket expenses; this may be performed by the provider’s office or as a benefits investigation by the lab performing the testing (if that service is offered by the lab; see attached document).

Most genetic tests can be performed on a buccal swab rather than a blood sample.

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 to determine clinical significance and may require follow up testing of the child and other family members.

Visit <https://www.mountainstatesgenetics.org/projects/current-projects/developmentaldelay/> for additional information on developmental delay and genetic resources

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