# Diagnostic Exome Sequencing (DES) provides a diagnosis for 23% of adult patients

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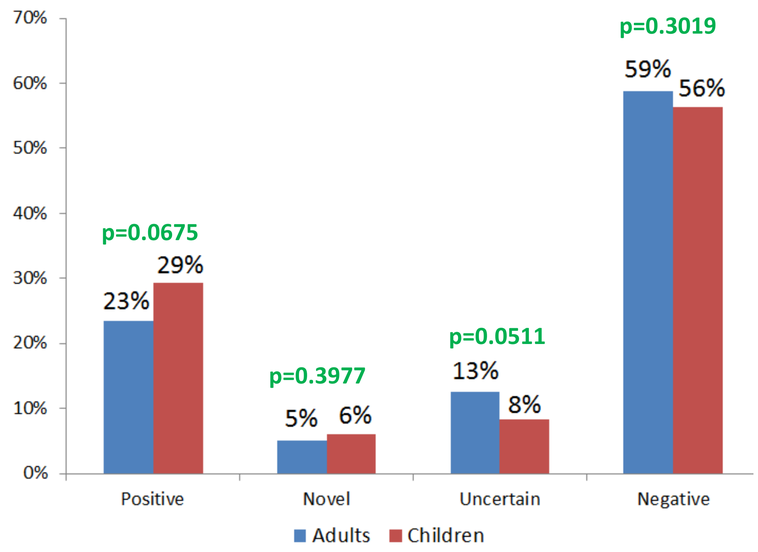
## BACKGROUND

- Diagnostic exome sequencing (DES) is successful in solving the diagnostic odyssey for roughly 30% of undiagnosed patients with a broad range of underlying Mendelian disorders.
- Reaching a diagnosis results in an end to the expensive, time consuming, and potentially invasive diagnostic odyssey which poses a heavy burden both for families and on the healthcare system (Beaulieu, 2014; Farwell, 2014; Iglesias, 2014; Srivastava, 2014).
- Pediatric neurologic manifestations are the most common DES referral indication. However, DES has also been successful in diagnosing adult patients undergoing the diagnostic odyssey.
- The aim of this study was to determine the diagnostic yield of exome sequencing for adult patients in a cohort of 1000 families referred for DES at a single clinical diagnostic laboratory.

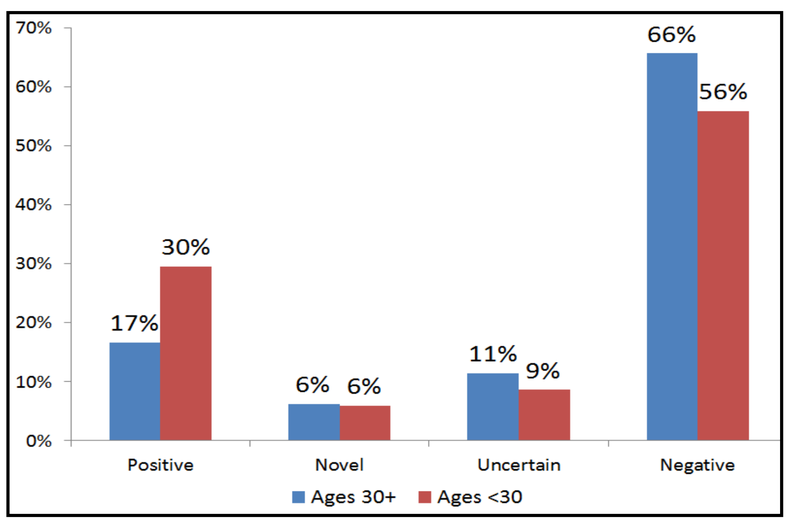
## METHODS

- **Patients/study population:** Genomic deoxyribonucleic acid (gDNA) was isolated from whole blood from probands and relatives referred to Ambry Genetics (Aliso Viejo, CA) for diagnostic exome sequencing (DES). Informed consent was obtained from all family members involved in the testing process.
- **Whole exome sequencing and data analysis:** Samples were prepared using the SeqCap EZ VCRome 2.0 (Roche NimbleGen, Madison, WI). The enriched exome libraries were sequenced using paired-end, 100-cycle chemistry on the Illumina HiSeq 2000 (Illumina, San Diego, CA). Data analysis were performed as previously described (Farwell *et al.* 2014).
- **Targeted Sanger sequencing** was performed to confirm the alterations and determine co-segregation in this family.
- **Data curation:** Data regarding the primary exome test ordered, patient age, diagnosis and/or clinical description, and exome sequencing results were also curated. Data on results included gene(s), alteration(s), gene category (novel or characterized), alteration interpretation (pathogenic, likely pathogenic, uncertain, likely benign), and clinical overlap of gene-association and patient phenotype (positive, uncertain, or partial).
- **Statistical analyses** were computed by Fisher's Exact Test.

## FIGURE 1. Adults and children were equally likely to have a positive finding.




## FIGURE 2. Among all adults and children, positive finding was significantly more likely for patients <30 vs ≥30 years of age (p=4.125e-3).

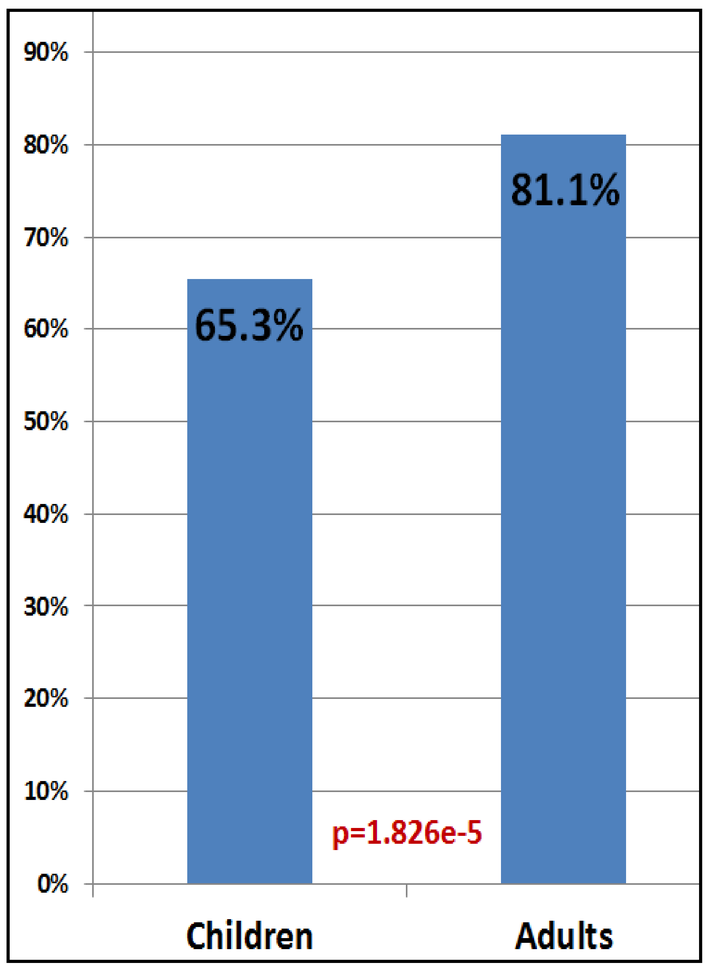



## TABLE 1. Inheritance patterns were similar among adults and children; however, *de novo* alterations were significantly higher among children.

| | AD | AR | XL | Mito | % de novo |
|---|---|---|---|---|---|
| ADULTS | 52.6% | 35.1% | 12.3% | 0% | 18% |
| CHILDREN | 57.3% | 28.3% | 14.1% | 0.2% | 44% |
| | | | | | p=5.278e-5 |

AD = autosomal dominant, AR = autosomal recessive, XL = X-linked, Mito = mtDNA

## FIGURE 3. Adult patients were more likely than children to have a significant family history.




## TABLE 2. Detection rates by primary referral

| Primary Referral Indication | Adult Patients Referred | Positive, Characterized Gene | | Novel Genetic Etiology | |
|---|---|---|---|---|---|
| Single organ system: Ocular | 3 | 3 | 100.0% | 0 | 0.0% |
| Single organ system: Integumentary | 3 | 2 | 66.7% | 0 | 0.0% |
| NM: Muscular dystrophy | 5 | 3 | 60.0% | 0 | 0.0% |
| ND: Intellectual disability | 7 | 4 | 57.1% | 0 | 0.0% |
| Single organ system: Renal | 2 | 1 | 50.0% | 0 | 0.0% |
| Single organ system: Cardiovascular | 7 | 3 | 42.9% | 0 | 0.0% |
| Neurodevelopmental NOS (+/- minor dysmorphic features) | 15 | 6 | 40.0% | 2 | 13.3% |
| Multiple Congenital Anomalies (+/- Neurodevelopmental symptoms) | 23 | 8 | 34.8% | 0 | 0.0% |
| ND: Seizures | 3 | 1 | 33.3% | 0 | 0.0% |
| NM: Ataxia/spasticity | 10 | 3 | 30.0% | 1 | 10.0% |
| Single organ system: Brain | 8 | 2 | 25.0% | 0 | 0.0% |
| Neuromuscular NOS | 12 | 2 | 16.7% | 0 | 0.0% |
| Single organ system: Connective tissue | 7 | 1 | 14.3% | 2 | 28.6% |
| Single organ system: Skeletal | 14 | 1 | 7.1% | 0 | 0.0% |
| Cancer Susceptibility | 25 | 1 | 4.0% | 3 | 12.0% |
| ND: ASD (autism) | 2 | 0 | 0.0% | 0 | 0.0% |
| ND: Psychiatric | 2 | 0 | 0.0% | 0 | 0.0% |
| NM: Abnormal Muscle Biopsy | 1 | 0 | 0.0% | 0 | 0.0% |
| NM: Neuropathy | 6 | 0 | 0.0% | 0 | 0.0% |
| NM: Other Movement Disorder | 2 | 0 | 0.0% | 0 | 0.0% |
| Single organ system: Endocrine | 3 | 0 | 0.0% | 0 | 0.0% |
| Single organ system: Gastrointestinal | 1 | 0 | 0.0% | 0 | 0.0% |
| Single organ system: Hematologic | 1 | 0 | 0.0% | 0 | 0.0% |
| Single organ system: Immune | 5 | 0 | 0.0% | 1 | 20.0% |
| Single organ system: Metabolic | 5 | 0 | 0.0% | 0 | 0.0% |
| Single organ system: Respiratory | 3 | 0 | 0.0% | 0 | 0.0% |

## RESULTS

- Among the first 1000 reported DES families, 175 (17.5%) adult patients (≥18 years old) were referred for testing .
- Among adults tested, 79 (45.1%) were between 18-29 years old, 50 (28.6%) were between 30-49 years old, and 46 (26.3%) were between 50-79 years old.
- The most common referral indication among adult patients was cancer susceptibility (25, 14.3%), followed by multiple congenital anomalies (23, 13.1%), neurodevelopmental anomalies (15, 8.6%), skeletal anomalies (14, 8.0%), and ataxia/spasticity (10, 5.7%) (**TABLE 2**).
- Positive findings were uncovered in 23.4% of adults (41 of 175), compared to 29.3% of children (242 of 825) and a novel genetic etiology was proposed for 9 families (5.1%) (**FIGURE 1**).
- Among all patients (adults and children), the diagnostic rate among patients ≤30 years old (29.5%) is significantly higher than among patients greater than 30 years old (16.7%) (p=4.125e-3) (**FIGURE 2**).
- Significant family history was more common among adult patients (81.1%) than children (65.3%) (p=1.826e-5) (**FIGURE 3**).
- Among the 41 adults with positive results, over half of the gene findings were autosomal dominant (23, 56.1%), 12 (29.3%) were autosomal recessive, and 6 (14.6%) were X-linked (**TABLE 1**).
- Overall, the rate of *de novo* and likely *de novo* findings among adult patients (17.5%) was much lower than among children (44.4%) (p=5.278e-5) (**TABLE 1**).
- The highest diagnostic yields were observed among patients with ocular anomalies (3/3, 100%), integumentary anomalies (2/3, 66.7%), muscular dystrophy (3/5, 60%), intellectual disability (4/7, 57.1%), and renal anomalies (1/2, 50%), (**TABLE 2**).

## TAKE-HOME POINTS

- While there is no difference in diagnostic rates between adults (≥18 years old) and children (<18 years old), there is a significantly higher likelihood for a positive finding among patients <30 vs patients ≥30 years of age.
- These data, including the high DES diagnostic rate of 23% among adult patients, highlight the potential medical-economics savings to patients as well as payers given that achieving a diagnosis abrogates the expensive, time-consuming, and often invasive diagnostic odyssey.

### References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