The Likelihood of Positive Results from Diagnostic Exome Sequencing is Not Predicted by Ordering Physician Specialty

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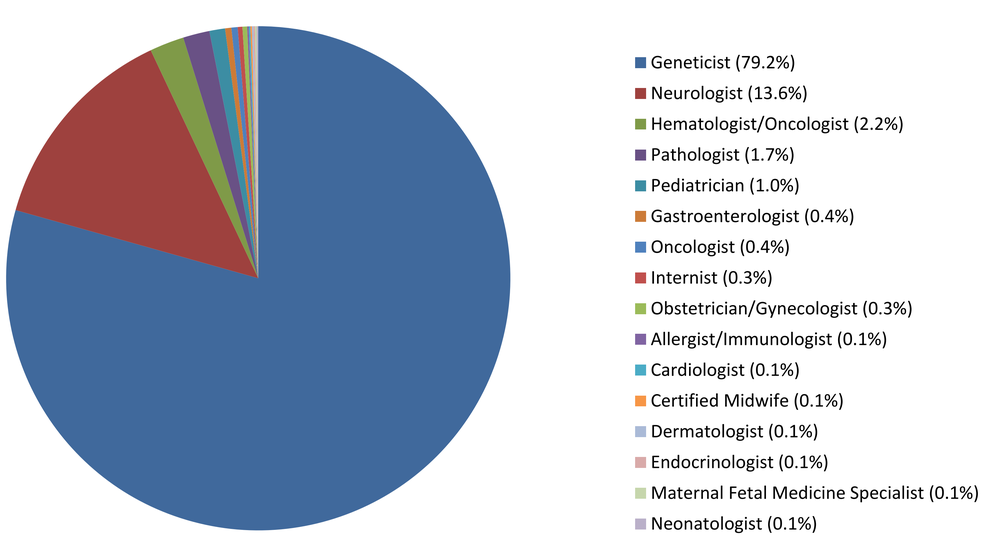
BACKGROUND

- Diagnostic exome sequencing (DES) is an efficient molecular diagnostic tool for previously undiagnosed cases where the underlying cause is believed be genetic.
- Recent algorithms have been proposed to aid clinicians in efficient and cost effective utilization of DES for various indications.
- While a variety of clinicians order DES, it is uncertain if the ordering clinician's specialization increases the likelihood of a positive result.
- Herein, we performed a retrospective analysis of the first 715 DES cases received at Ambry Genetics to determine if clinicians with a specific specialization are more apt at identifying cases that will have a positive result.

METHODS

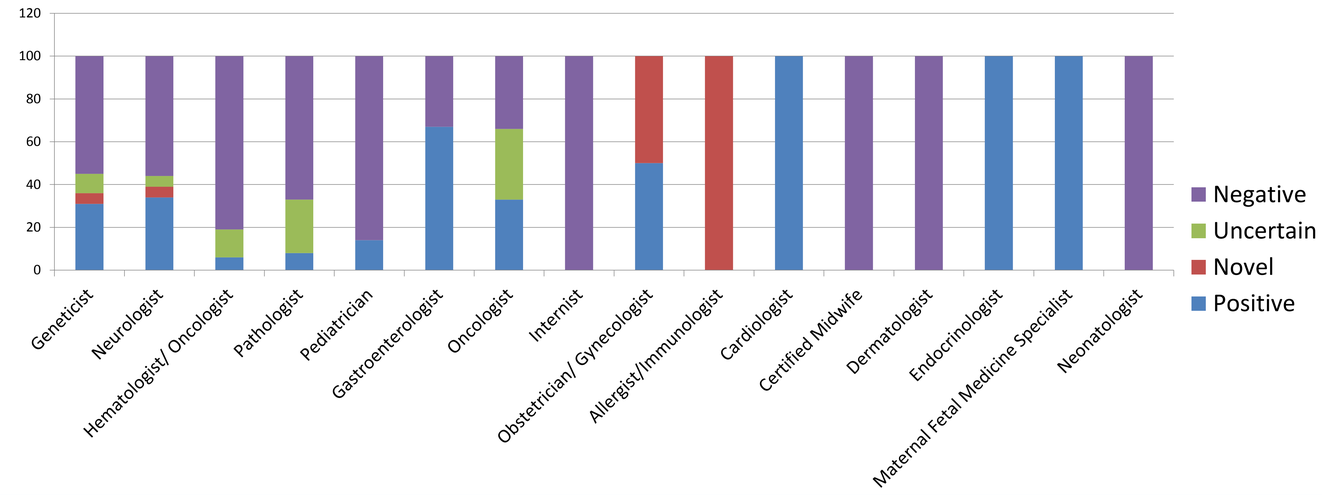
- **Patients/study population:** Genomic deoxyribonucleic acid (gDNA) was isolated from whole blood from probands and relatives referred to Ambry Genetics (Aliso Viejo, CA) for diagnostic exome sequencing (DES). Informed consent was obtained from all family members involved in the testing process.
- **Whole exome sequencing:** Samples were prepared using the SureSelect Target Enrichment System (Agilent Technologies, Santa Clara, CA) or 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).
- **Exome library preparation**, sequencing, bioinformatics, and data analysis were performed as previously described (Farwell et al. 2014).
- **Statistical analyses** were computed by chi^2 goodness of fit tests and Fisher's Exact Probability.

PERCENTAGE OF DES CASES ORDERED BY CLINICAL SPECIALTY

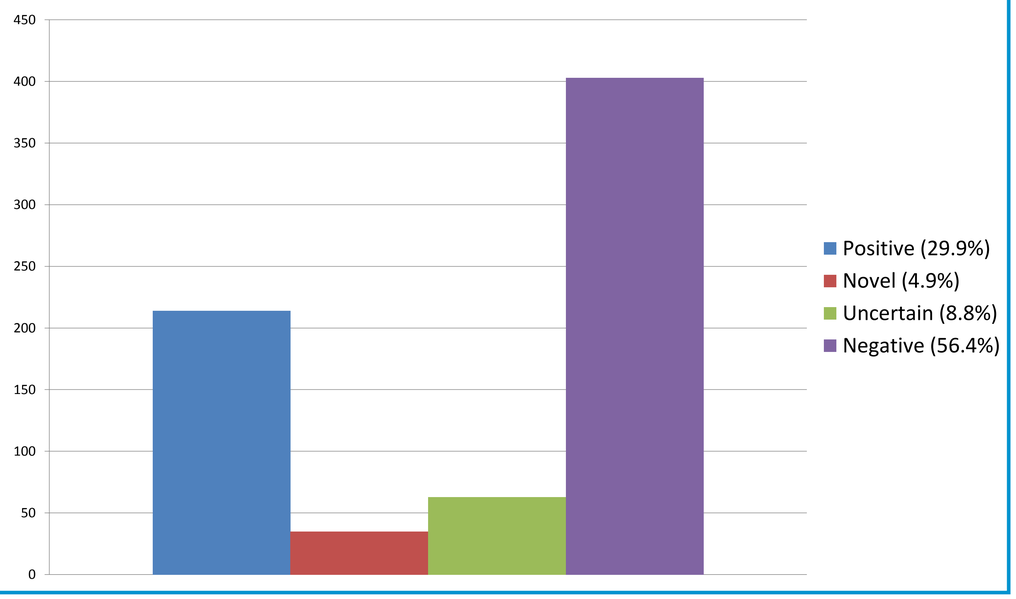


PERCENTAGE OF POSITIVE, NOVEL, UNCERTAIN AND NEGATIVE RESULTS BY ORDERING PHYSICIAN SPECIALTY

Statistical analysis of the 715 cases received for DES demonstrated that the type of ordering physician was not found to affect the likelihood of a positive result (proportion test, p-values > 0.06).



RESULTS OF 715 DES CASES



TAKE-HOME POINTS

- These results suggest that at this time, neither geneticists nor other specialists most familiar with DES are more proficient determining which cases are more likely to test positive.
- This data is dependent on accurate reporting of the ordering provider's medical specialty on the test requisition form and may not reflect important information about other members of the patient's care team.
- It is recommended that patients and their families be referred to clinicians who, regardless of their medical specialty, have experience in the complexities of DES and its results.

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