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Exome Reanalysis Results in an 8% Reclassification Rate

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BACKGROUND

- Diagnostic exome sequencing (DES) has the potential to end expensive, invasive, time-consuming testing and lead to changes in patient care.[1-7]
- Upon initial analysis, ~25% of patients with underlying Mendelian diseases receive a diagnosis via DES.[1-2,8-13]
- A major advantage of DES is the ability to reanalyze the same data set and benefit from new gene-disease discoveries, new variant information, and changes in the patient's medical/family history.
- Reclassifications may result from a client request for reanalysis or proactively from the laboratory.

METHODS

- We analyzed a cohort of patients who underwent DES at a commercial lab between January 2016 and August 2018, and for whom a client-initiated exome reanalysis was subsequently requested.
- A reclassification was defined as any change to the overall results category among the following 4 groups:[1,2]
  - Positive/likely positive
  - Uncertain findings within characterized genes
  - Candidate findings within uncharacterized genes
  - Negative
- Cases were categorized by the clinical information included in the reanalysis request.
  - No new clinical features reported
  - New organ system involvement
  - New feature(s) as denoted by one or more new HPO terms
- Reclassifications from candidate or uncertain to negative, or positive/likely positive to any other category were considered downgrades; all other changes were upgrades.

RESULTS

- From January 2016 through August 2018, a total of 436 patients had ≥1 client-initiated reanalysis request. A second request was received for some patients, bringing the total number of reanalysis/reclassification reports issued to 451.
- **Overall, the rate of reclassification from client requested reanalysis was 8% (36/436) (FIGURE 1).**
- **Among the 36 reclassified reports, there were 34 (94.4%) upgraded and 2 (5.6%) downgraded reports (FIGURE 2).**
- 20 reclassifications (46.5%) led to a change in clinical utility when a negative or uncertain result was upgraded to positive or likely positive.
- **Among the 36 reclassified reports, 8 (22.2%) were due to variant reclassification, 13 (36.1%) were due to gene reclassification, and 15 (41.7%) were due to new clinical information allowing for an upgrade in clinical overlap (FIGURE 3).**
- All reports with an initial positive/likely positive conclusion were unchanged after reanalysis.
- No difference was seen in sex or age between the reanalysis requests that resulted in upgrades or those that remained unchanged.
- **64% (289/451) of client-driven reanalysis requests included updated clinical information. 9.3% of requests with new clinical information resulted in an upgrade, while only 4.9% of requests without new clinical information were upgraded (FIGURE 1).**
- Among the 34 upgraded reports following client-initiated reanalysis, **79.4% included new clinical information. Reanalysis requests that included additional family history and/or updated testing results were significantly more likely to result in an upgrade ($p<0.05$). (FIGURE 4).** Examples of changed testing or family history included new biochemical test results and updated affected status of a relative.

FIGURE 1: Rates of Reanalysis-driven Reclassification

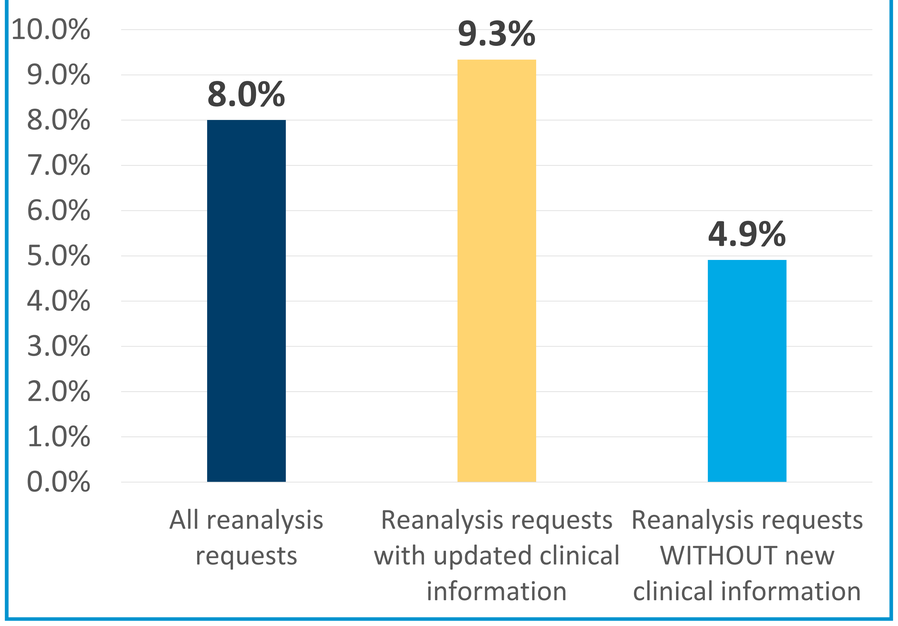


FIGURE 2: Direction of Reanalysis-driven Reclassifications

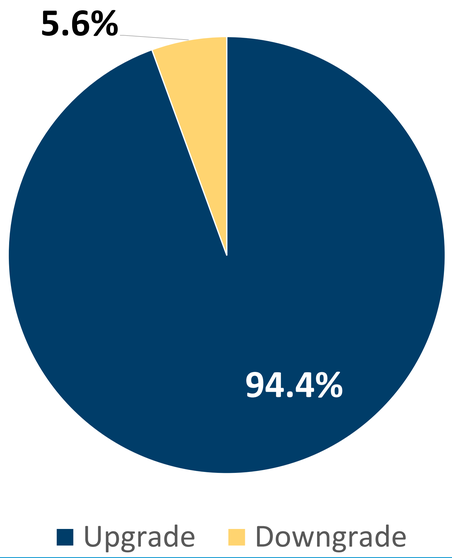


FIGURE 3: Reason for Reanalysis-driven Reclassification

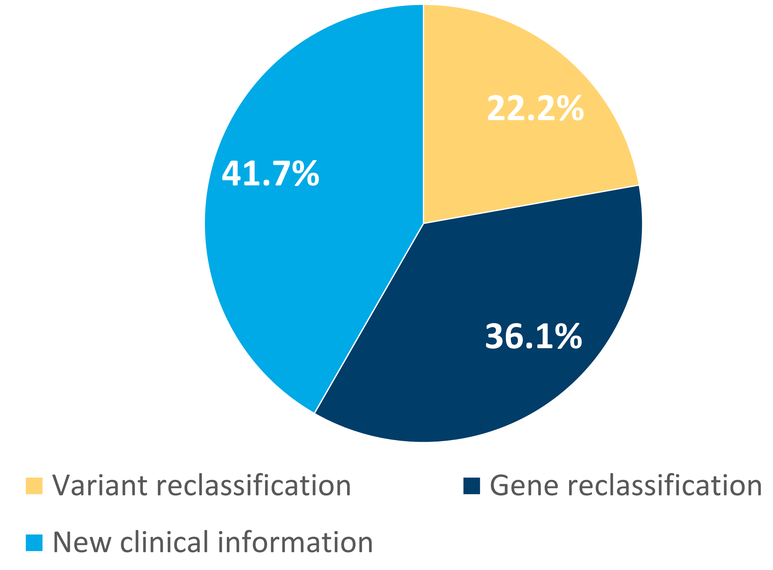
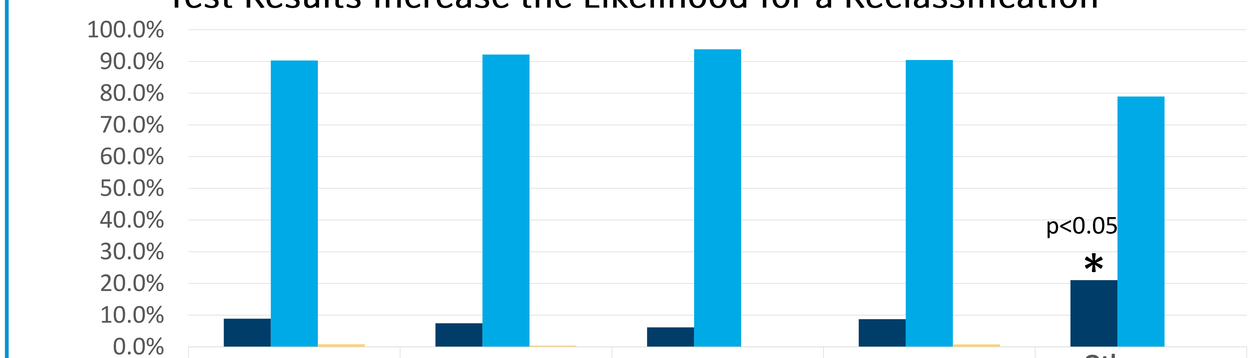


FIGURE 4: Reanalysis Requests with Additional Family History or Updated Test Results Increase the Likelihood for a Reclassification



	New organ system	Any New HPO Term	New HPO term without new organ system	New HPO with new organ system	Other new clinical update (testing hx, family hx, etc)
Upgrades	8.87%	7.42%	6.15%	8.73%	21.05%
Unchanged	90.32%	92.19%	93.85%	90.48%	78.95%
Downgrades	0.81%	0.39%	0.00%	0.79%	0.00%

TAKE-HOME POINTS

- Overall, 8% of clients ordering a reanalysis received a reclassified report.
- New test results or new family history details resulted in a significantly higher likelihood of a reclassification.
- These data highlight the utility of DES in providing a comprehensive and timely molecular diagnosis with the ability to continually assimilate new information.
- The ability to continually reanalyze exome data adds to the economic value of the test compared to traditional testing methods.
- The data emphasize the importance of counseling patients about the likelihood of a result reclassification in the future.

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