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Variable Rates of Reclassification Based on Clinical Indication among Patients Referred for Diagnostic Exome Sequencing

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BACKGROUND

- Diagnostic exome sequencing (DES) is successful in providing a molecular diagnosis for ~25% of patients with underlying Mendelian diseases.
- DES has the potential to end the expensive, invasive, time-consuming testing and lead to changes in patient care.
- A major benefit of DES is the simultaneous interrogation of virtually all genes, including those recently characterized as disease causing.
- Reclassification of DES reports occur due a variety of reasons including subsequent familial co-segregation analysis, new patient clinical information, bioinformatics pipeline upgrades, variant reclassification, and new gene-disease information.
- Publications about gene-disease discoveries occur every two to three days on average, making reclassification due to new gene information the most common reason for a reclassification DES report.

METHODS

- We calculated overall reclassification rates among 6,027 DES patients.
- Patients are grouped into one of 29 clinical indication categories prospectively as they arrive for testing.
- A reclassification was defined as any change to the overall results category among the following four groups:[1,2]
  - *Positive/likely positive*
  - *Uncertain findings within characterized genes*
  - *Candidate findings within uncharacterized genes*
  - *Negative*
- Reclassifications from candidate or uncertain to negative or positive/likely positive to any other category were considered downgrades and all other changes were considered upgrades.

RESULTS

- Among 6027 DES patients, 2.3% (136) received a reclassification report (FIGURE 1):
  - 2.0% (121) of which were upgraded
  - 0.3% (17) were downgraded
- The highest rates of reclassification were among patients with primary indications of:
  - Hypotonia (6/80; 7.5%), abnormal muscle biopsy (1/17; 5.9%), ataxia/spasticity (5/103; 4.9%), cancer susceptibility (3/71; 4.2%), skeletal disorders (7/187; 3.7%), and intellectual disability (14/380; 3.7%) (TABLE 1).
- More complex primary indications were statistically significantly more likely to undergo reclassification (p=0.008; TABLE 1).

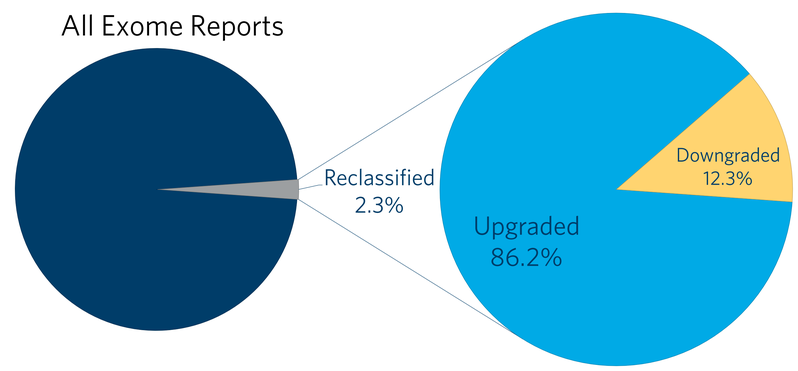
TABLE 1: Reclassification Rate by Primary Indication for Testing

	Primary Indiciation For Testing	Total Patients	% Upgraded	% Downgraded	% Reclassified
Complex Phenotypes	**Neurodevelopmental (+/- minor dysmorphic features):** Hypotonia	**80**	6.3%	1.3%	**7.5%**
	Neuromuscular: Abnormal Muscle Biopsy	**17**	5.9%	0.0%	**5.9%**
	Neuromuscular: Ataxia/ spasticity	**103**	4.9%	0.0%	**4.9%**
	Neurodevelopmental (+/- minor dysmorphic features): Intellectual disability	**380**	3.2%	0.5%	**3.7%**
	Multiple Congenital Anomalies (+/- Neurodevelopmental symptoms)[a]	**858**	3.0%	0.2%	**3.3%**
	Cancer Susceptibility	**71**	2.8%	0.0%	**2.8%**
	Neuromuscular: Neuromuscular NOS[b]	**275**	2.2%	0.4%	**2.5%**
	Neurodevelopmental (+/- minor dysmorphic features): Neurodevelopmental NOS	**1830**	2.0%	0.2%	**2.2%**
	Neurodevelopmental (+/- minor dysmorphic features): ASD	**233**	1.7%	0.0%	**1.7%**
	Neuromuscular: Other Movement Disorder	**112**	0.9%	0.0%	**0.9%**
	Neuromuscular: Neuropathy	**55**	0.0%	1.8%	**1.8%**
	Neurodevelopmental (+/- minor dysmorphic features): Seizures	**375**	0.8%	0.3%	**1.1%**
	Neuromuscular: Muscular dystrophy	**44**	0.0%	0.0%	**0.0%**
	Sub-total:	**4433**	**2.3%**	**0.3%**	**2.6%**[c]
Less complex phenotypes	**Disorder or feature primarily affecting one organ system:** Renal	**33**	3.0%	0.0%	**3.0%**
	Disorder or feature primarily affecting one organ system: Skeletal	**187**	3.2%	0.5%	**3.7%**
	Disorder or feature primarily affecting one organ system: Immune	**100**	2.0%	0.0%	**2.0%**
	Disorder or feature primarily affecting one organ system: Metabolic	**155**	1.9%	0.6%	**2.6%**
	Disorder or feature primarily affecting one organ system: Integumentary	**58**	1.7%	0.0%	**1.7%**
	Disorder or feature primarily affecting one organ system: Ocular	**73**	1.4%	0.0%	**1.4%**
	Disorder or feature primarily affecting one organ system: Brain	**224**	0.9%	0.9%	**1.8%**
	Disorder or feature primarily affecting one organ system: Connective tissue	**158**	0.6%	0.0%	**0.6%**
	Disorder or feature primarily affecting one organ system: Cardiovascular	**126**	0.0%	0.8%	**0.8%**
	Disorder or feature primarily affecting one organ system: Hematologic	**33**	0.0%	0.0%	**0.0%**
	Disorder or feature primarily affecting one organ system: Endocrine	**78**	0.0%	0.0%	**0.0%**
	Disorder or feature primarily affecting one organ system: Respiratory	**41**	0.0%	0.0%	**0.0%**
	Disorder or feature primarily affecting one organ system: Gastrointestinal	**63**	0.0%	0.0%	**0.0%**
	Disorder or feature primarily affecting one organ system: ENT	**41**	0.0%	0.0%	**0.0%**
	Growth Disorder: Undergrowth/FTT	**113**	0.9%	0.0%	**0.9%**
	Growth Disorder: Overgrowth	**58**	0.0%	0.0%	**0.0%**
	Neurodevelopmental (+/- minor dysmorphic features): Psychiatric	**53**	0.0%	0.0%	**0.0%**
	Sub-total:	**1594**	**1.1%**	**0.3%**	**1.4%**[c]
	TOTAL	**6027**	2.0%	0.3%	**2.3%**

[a]**>2 major or >3 minor malformations**
[b]NOS = Not otherwise specified
[c]p=0.008

Yellow highlight indicates reclassificaiton rate above 0.

FIGURE 1: Total Reclassification Rate



TAKE-HOME POINTS

- This dataset represents the largest group of DES patients analyzed for rates of reclassification to date.
- The higher rates of reclassification among patients with more complex phenotypes are likely due to recent gene-disease discoveries resulting from a forward-genetics approach which allow identification of diseases with low clinical recognizability and high clinical complexity.
- The data highlight the utility of clinical exome sequencing in providing a comprehensive and timely molecular diagnosis with the ability to continually assimilate new gene discoveries.
- The data also emphasize the importance of counseling patients about the likelihood of a result reclassification in the future, especially among patients with more complex phenotypes.

REFERENCES

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