Two Approaches to Reclassifying Results from Previously Reported Diagnostic Exome Sequencing

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BACKGROUND

- New gene disease relationships are published at an increasing rate and these findings could result in genetic diagnosis for patients with previously negative diagnostic exome sequencing.
- Our diagnostic laboratory has offered clinician request DES reanalysis since February, 2013.
- More recently we began to issue laboratory-Initiated reclassification reports for patients with relevant findings in newly reported gene-disease relationships.
- Overall, 2.6% of DES results have been reclassified.
- Reclassification efforts have increased positive diagnostic rate 1.5% (from 23.7% to 25.3%).

METHODS

- DES was performed as published (Farwell et al, 2015)

59 Reports with Changed Overall Conclusions Were Issued in 2016

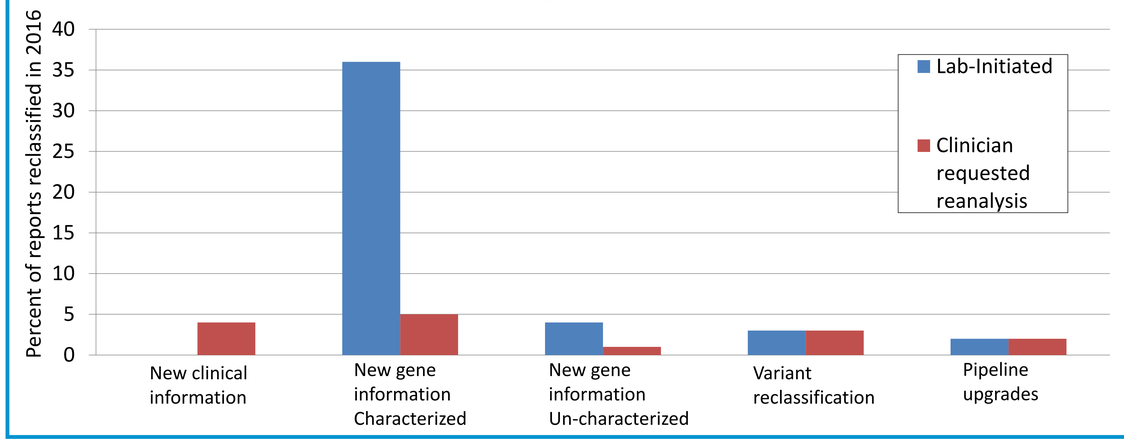
Clinician Requested Reanalysis
13/108= 12%

46 Laboratory Initiated

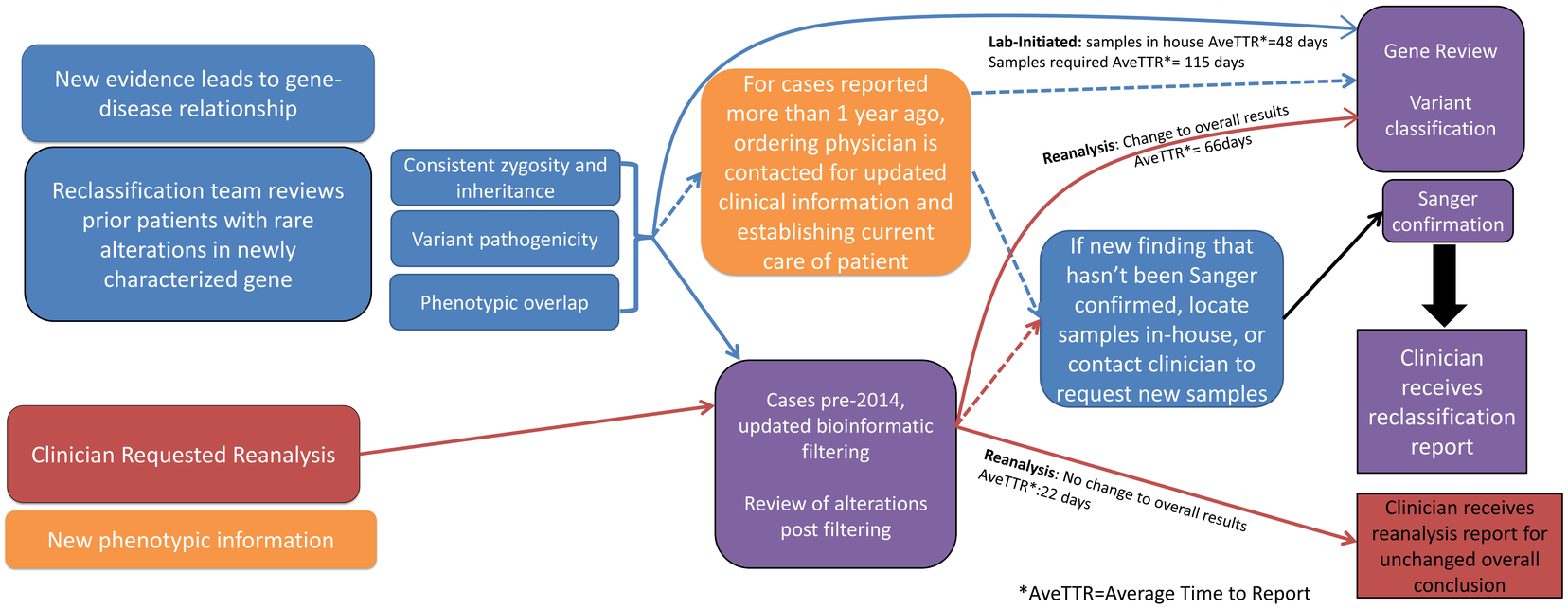
Overall Result Change	#
Negative to positive	7
Negative to uncertain	4
Uncertain to negative	2
Candidate to characterized	0

Overall Result Change	#
Negative to positive	15
Negative to uncertain	15
Uncertain to negative	4
Candidate to characterized	12

Lab-initiated Reclassification Mostly Due to New Gene Information, while Reclassification of Reanalysis Requests Is for Varied Reasons



Reclassification Methods: Lab-initiated and Reanalysis Requests



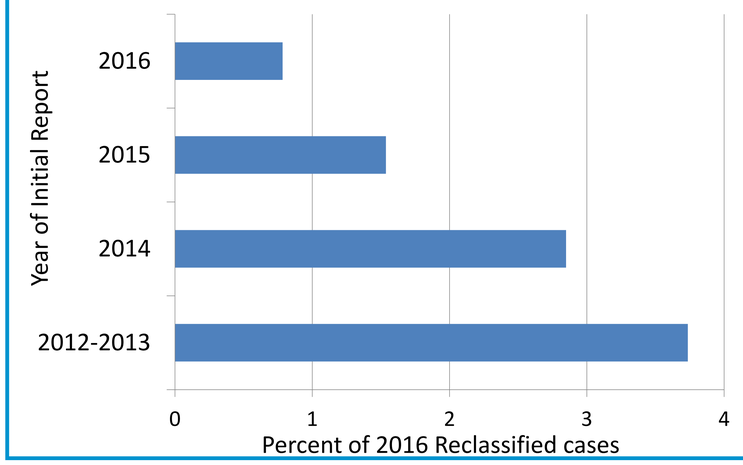
*AveTTR=Average Time to Report

Laboratory-Initiated Reclassification Reports Follow Gene Characterization

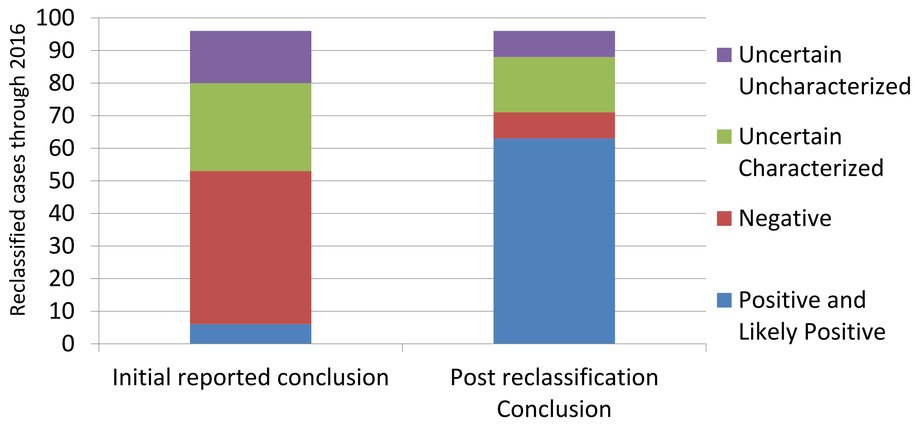
Gene	Associated syndrome/phenotypic findings
TAF6	Cornelia de Lange like syndrome
HECW2	Neurodevelopmental disorder
USP9X	XLD Neurodevelopmental disorder
EMC1	Cerebellar atrophy, visual impairment, and psychomotor retardation
*RERE**	Neurodevelopmental disorder
*GNB1**	Neurodevelopmental disorder
*ZBTB18**	Neurodevelopmental disorder
KAT6A	Neurodevelopmental disorder
PIGT	Multiple congenital abnormalities, hypotonia, and seizures
SAMD9	MIRAGE
*ARV1**	Epileptic encephalopathy
PPP1CB	Neurodevelopmental disorder
ECHS1	Exercise induced paroxysmal attacks without metabolic abnormalities
IARS	Neurodevelopmental disorder with hepatopathy
*SIN3A**	Neurodevelopmental disorder
CREBBP	Neurodevelopmental disorder without typical RTS gestalt
*RORB**	Neurodevelopmental disorder with epilepsy
CHD4	Sifrim-Hitz-Weiss syndrome
*HNRNPH2**	XLD Neurodevelopmental disorder
*TIMM50**	Mitochondrial epileptic encephalopathy
*SON**	Neurodevelopmental disorder
SLC25A4	AD Early-onset mitocondrial disorder
PIK3R1	Immunodeficiency

*Previously reported as candidate gene finding

Cases Reported Earlier have Higher Reclassification Rate



Reclassification Increases Patients with Positive Genetic Diagnoses



Overall, 7.2% of Positive and likely positive reports are due to reclassification

TAKE-HOME POINTS

- Clinician requested reanalysis, especially when patient has developed new clinical symptoms, and laboratory-initiated reclassification based on new literature compliment each other and may offer genetic diagnoses for previously undiagnosed patients.
- Clinician requested reanalysis has 12% change in overall DES results conclusion and cases are reclassified for a variety of reasons including new phenotypic information and change in variant classification.
- Laboratory-initiated reclassifications can provide genetic diagnoses for patients in an unbiased way by evaluating all previously sequenced patients for relevant findings in newly characterized genes.
- Laboratory-initiated reclassifications require the help of current clinicians for patients to receive accurate and timely reports. Laboratory-initiated reclassifications require significant effort locating current clinicians and maintaining HIPPA compliance.

REFERENCES

1. Farwell, K.D. *et al* . (2015) *Genet Med* **17(7)**:578-586