

Self-Assessment of

The False Genotype Rate

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- 1) There are dozens of single-gene disorders that affect the structure and function of the retina. The most common of them affects only one in _____ people while the rarest ones affect fewer than _____ people in the United States.
- 2) If we are going to sustainably deliver these treatments to the tens of thousands of people who need them, we will need to be able to do it for less than _____ per patient.
- 3) To help design a strategy for treating everyone with one of these conditions, investigators at the University of Iowa studied _____ consecutive families diagnosed with inherited retinal disease at the University of Iowa.
- 4) The most important goal of the project was to devise a way to use clinical information to overcome the huge amount of _____ in the genome.
- 5) As part of the battle against this under-appreciated _____, we wanted to come up with a statistic that would make it more understandable to practicing clinicians. We call this statistic the _____.
- 6) Using a tiered testing approach, we identified mutations in _____ of the _____ families.
- 7) _____ of these genotypes were found with a focused test that was chosen based on the patients' clinical findings, and _____ of these were mutations that would have been missed by _____.
- 8) The average cost of the testing was _____ per family despite the fact that some families had multiple tests performed on them. This

is because many of the clinically focused tests are much less expensive than _____.

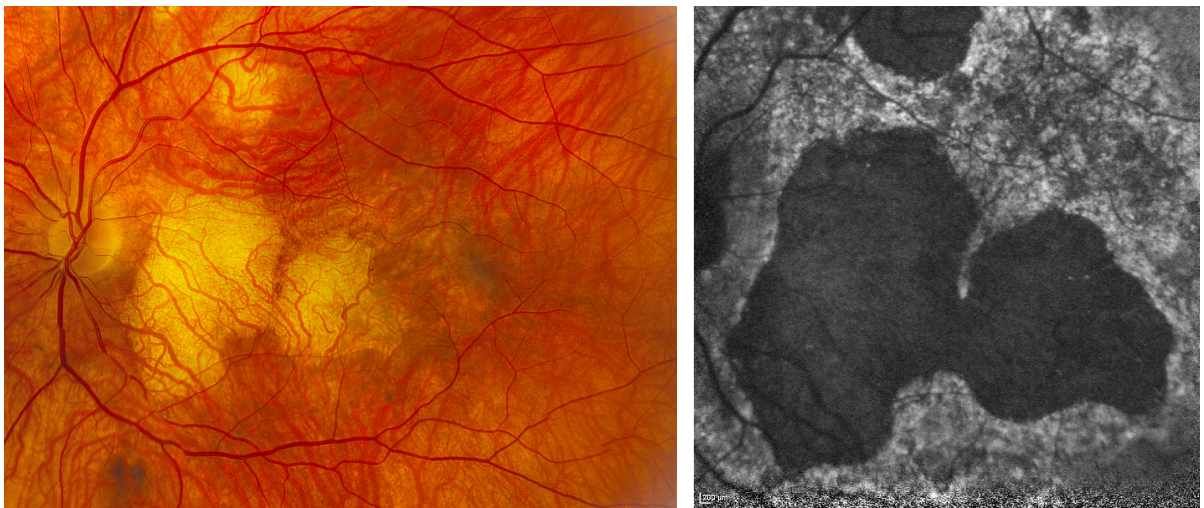
9) The mutations we found were distributed across more than _____ different genes.

10) Some genes were much more common than others – ABCA4 caused disease in _____ families while _____ of the genes each caused disease in fewer than 1% of the cohort.

11) Most people are relatively unaware that every person's genome is riddled with variants that are rare enough and damaging enough to be a plausible explanation for their disease. The opportunity to observe one or more _____ by chance increases as the number of genes tested goes up.

12) A 305 gene panel is over _____ times more likely to yield one or more _____ than a clinically focused approach. More than half of the families in our _____ family cohort were assigned to a clinical category whose focused test had a false genotype rate of less than _____% while the average _____ rate for a 305 gene retinal disease panel is _____% -- meaning an average patient tested in this way will be found to have _____ false genotypes in addition to their true disease-causing genotype.

13)



This 48 year old woman first had some retinal abnormalities noticed on a routine eye exam at age 33. She is now 20/20 in the right eye and 20/60 in the left. She was diagnosed with diabetes at age 32 and started wearing hearing aids at age 46.

One of the weaknesses of whole exome sequencing is that it doesn't assess the _____ genome. So, to get the correct molecular diagnosis for this lady, you have to know that bilateral atrophic macular lesions in a patient with diabetes and hearing loss suggests a _____ condition caused by a specific point mutation at position _____ of the _____ genome.

14) The false genotype rate can only be reduced by _____ – there is no technical improvement in the sequencing itself that can do so.

15) If you encounter multiple possibilities despite a narrow _____, you can usually identify the correct one by _____.

16) _____ and the methodical examination of your patients' _____ are both very important factors in arriving at a correct molecular diagnosis and will remain so even as the cost of next generation sequencing continues to fall.