

Optimizing Diagnostic Potential: Impact of Familial Sample Configurations on Exome Sequencing



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BACKGROUND

- Exome sequencing (ES) requires assessment of hundreds of potentially relevant variants
- Trio-based ES that involves complete sequencing of both biological parents (“parental trio”) increases the diagnostic potential of ES
- Real-time inheritance information may clarify variants of uncertain significance (VUS)
- Collection of parental trios can be challenging for a variety of reasons

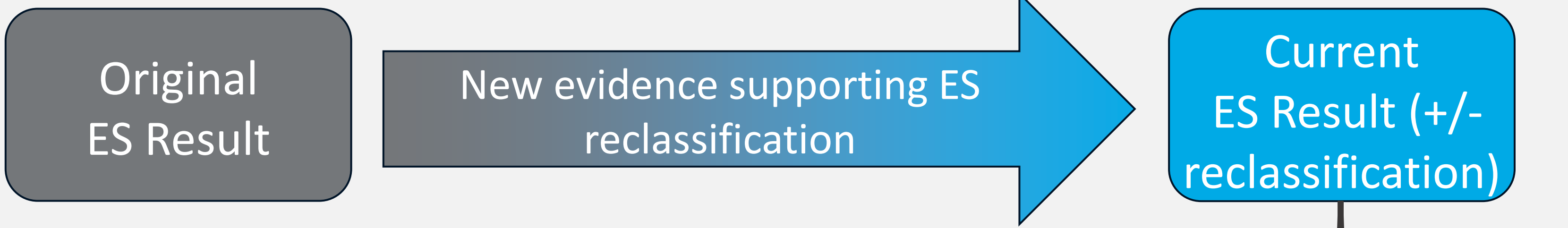
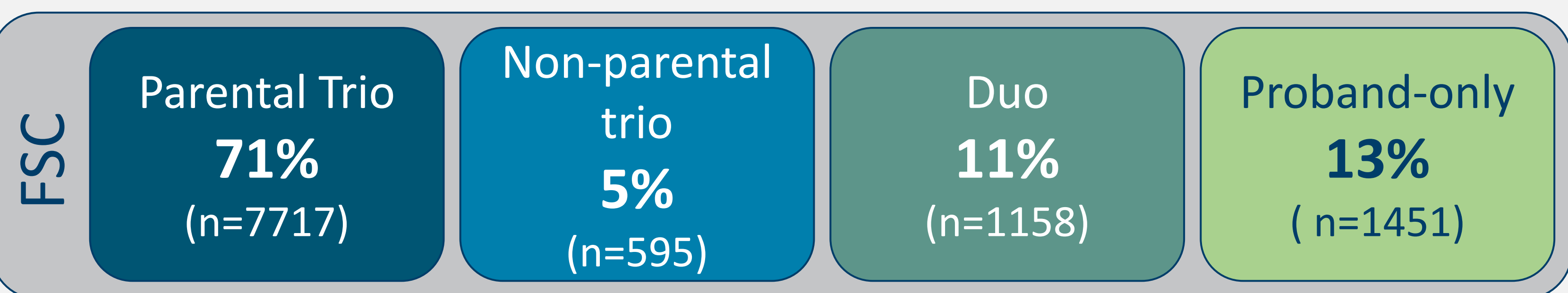
Aims: Investigate how different familial sample configurations (FSC) impact the clinical utility and reclassification of ES

TAKE HOME POINTS

- Ongoing assessment of new evidence can aid in closing the gap for diagnostic differences between FSC
- Evidence-driven reclassification increased diagnostic yield for all FSC
 - Primary drivers were new GDRs and familial co-segregation studies
 - >25% were due to other evidence sources, underscoring the importance of ongoing, dynamic variant assessment
- When available, parental trios maximize the clinical utility of ES
 - 30% of ES cases in this cohort were not a parental trio

METHODS

10,921 ES between 2011 - 2021



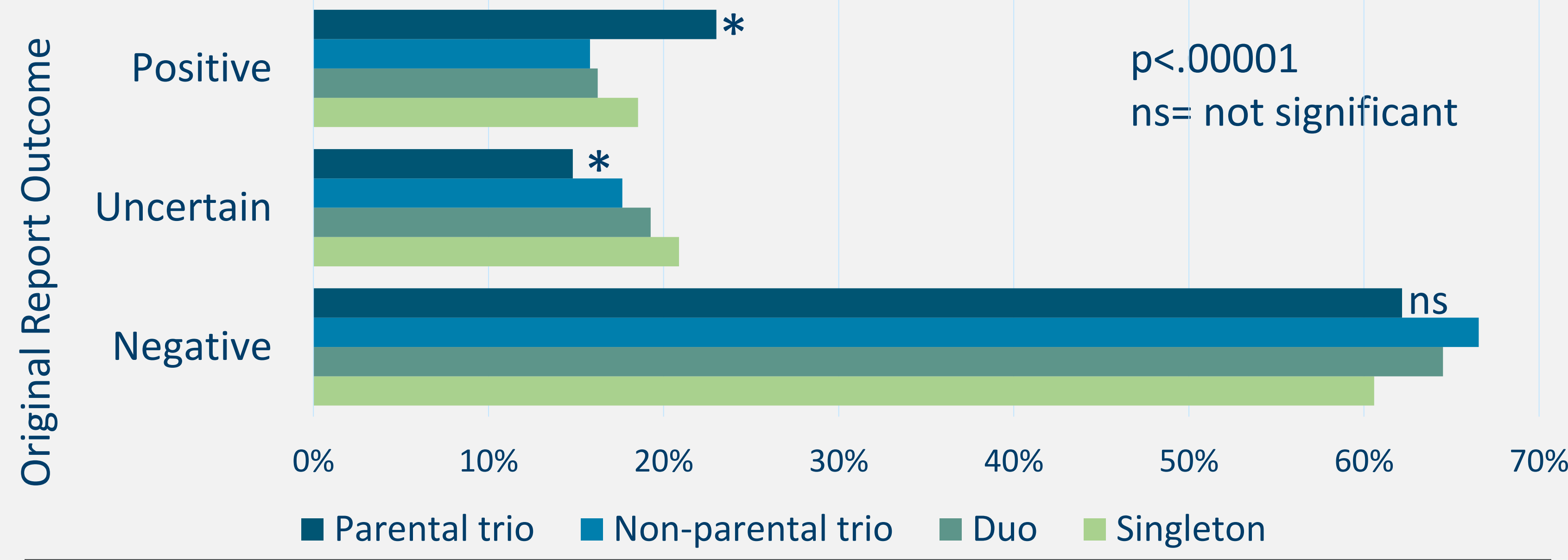
Analyses for this study

- Evidence used for reclassification
- Reclassification rates across FSC categories
- Statistical analysis by chi-square tests

RESULTS

- Parental trios exhibited significantly higher diagnostic rates and lower VUS rates compared to other FSC [Figure 1]
- Over time, diagnostic yield increased across all FSC due to ES reclassification (range 2% to 4%) [Figure 2]
- New gene-disease relationships (GDR) were the most impactful of 37 different types of evidence used for reclassification [Figure 3]

FIGURE 1: DIAGNOSTIC RATES BY FSC



Negative rates were similar across FSC, suggesting appropriate variant reporting, but a lack of segregation evidence leads to more VUS

FIGURE 2: CHANGES IN DIAGNOSTIC RATES BY FSC

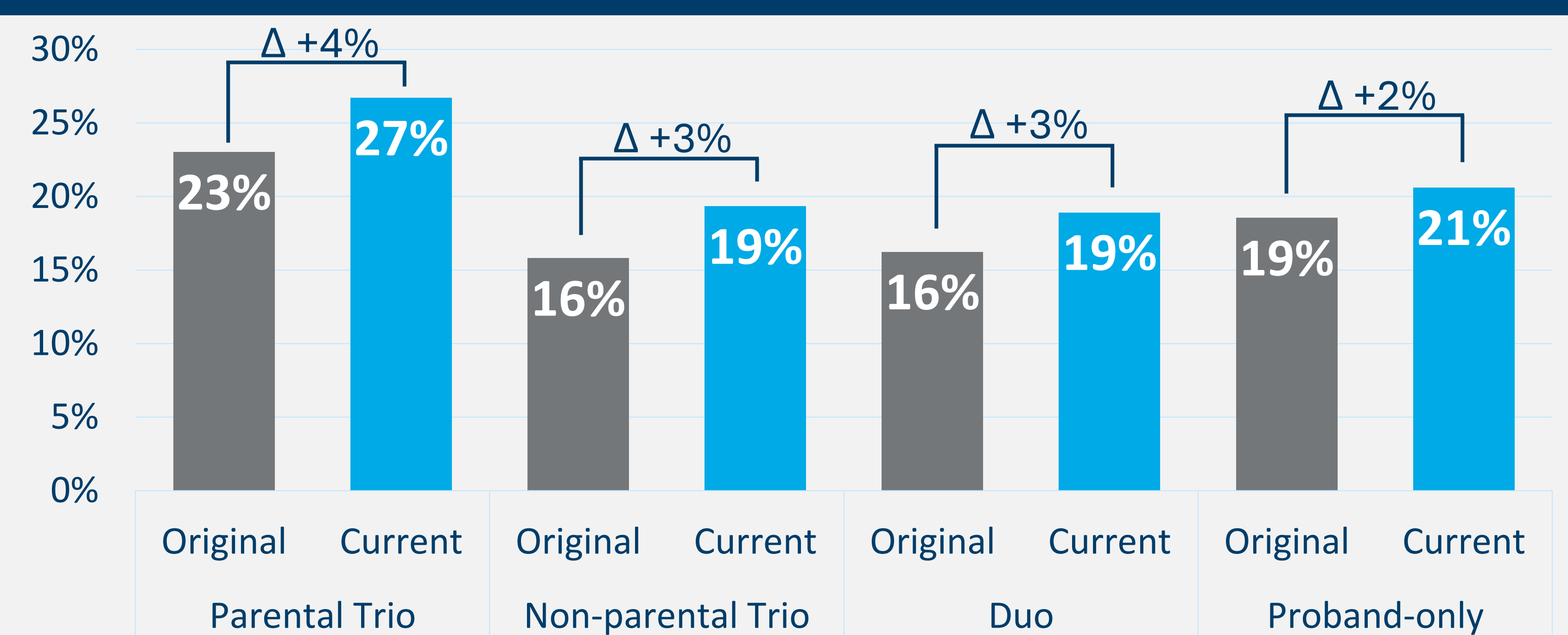


FIGURE 3: EVIDENCE USED IN RECLASSIFICATIONS

