# PGT-M for Variants of Uncertain Significance (VUSs): One PGT Laboratory's Experience

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## Objective

To determine the frequency of PGT-M cases involving a variant of uncertain significance (VUS) at a single PGT laboratory.

## Methods

All submitted, non-canceled PGT-M orders between 1/1/24 and 12/31/25 were reviewed, totaling 921 unique cases.

Case details reviewed include gene of interest, inheritance pattern, family member statuses, and available clinical documentation.

ClinVar reviewed to confirm whether variant was exclusively a VUS or if other classifications reported as well

## Case Examples

Case #5: Patient identified as a carrier on routine carrier screening. Partner's testing ordered via clinical testing instead of carrier screening and VUS reported.

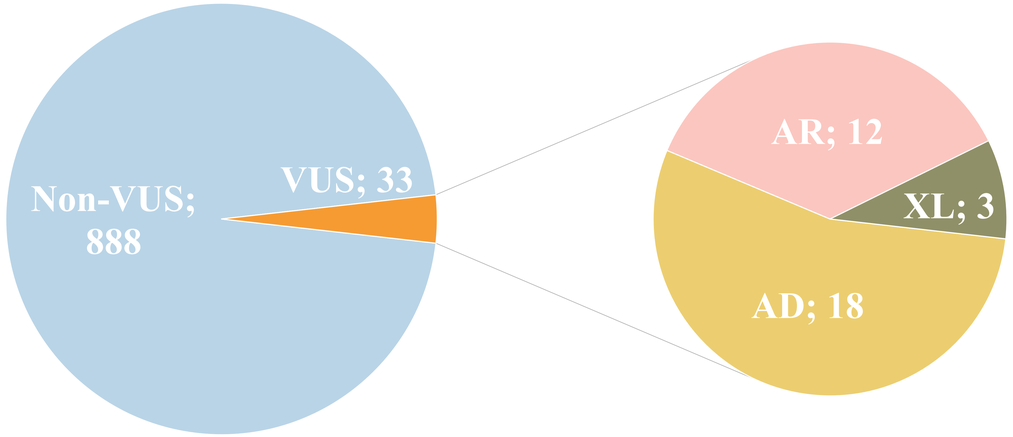
Case #7: NBS identified couple's affected child (one pathogenic and one VUS). Partner found to be affected with one pathogenic variant and the same VUS.

Case #26: Patient identified as an XL carrier after mother's diagnosis (with other findings noted as well). Following test creation, VUS downgraded to likely benign. Couple has opted to forego PGT-M for the time being.

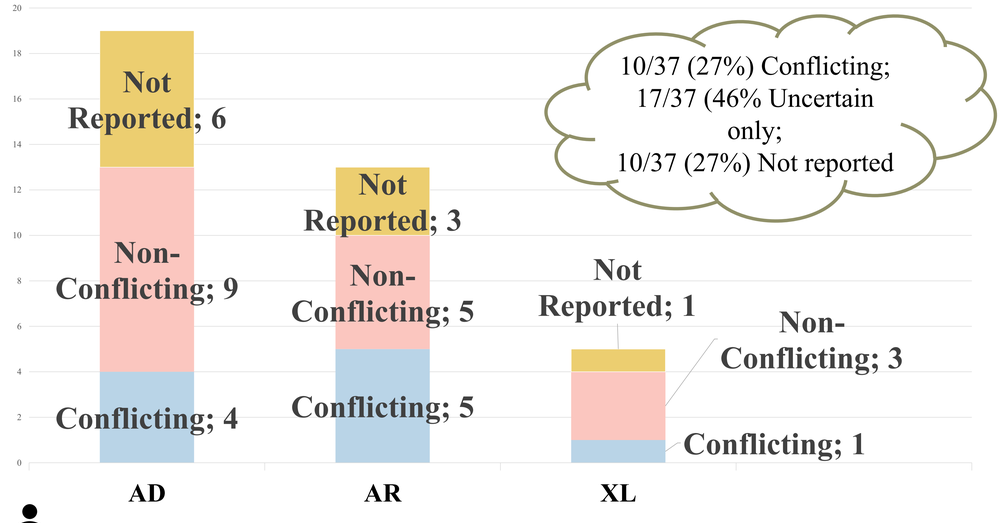
## Results

| Case | Gene | Inheritance | Affected Child | ClinVar Conflicting Classifications |
|---|---|---|---|---|
| 1 | 10q22.1q22.1 Deletion | AD | Yes | Not reported |
| 2 | 2p25.3 Duplication | AD | Yes | Not reported |
| 3 | *ACTA2* | AD | No | Yes |
| 4 | *CFTR* | AR | Yes | Yes |
| 5 | *CFTR* | AR | No | No |
| 6 | *F8* | XL | No | No, Yes |
| 7 | *GAA* | AR | Yes | Yes |
| 8 | *GCH1* | AD | No | Not reported |
| 9 | *GPC3* | AD | Yes | Not reported |
| 10 | *IDUA* | AR | Yes | Yes |
| 11 | *IDUA* | AR | No | No |
| 12 | *INS* | AD | Yes | No |
| 13 | *KRT6B* | AD | No | Not reported |
| 14 | *LZTR1* | AD | No | No |
| 15 | *MED12, HUWE1* | XL, XL | No | No, No |
| 16 | *MMP21* | AR | Yes | No |
| 17 | *MTM1* | AD | Yes | No |
| 18 | *MYH7* | AD | No | No |
| 19 | *NARS2* | AR | Yes | Not reported |
| 20 | *NOTCH2* | AD | No | Not reported |
| 21 | *PKD1* | AD | No | No |
| 22 | *PKD1* | AD | No | Yes |
| 23 | *PKD1* | AD | Yes | Yes, Yes |
| 24 | *POMGNT2* | AR | Yes | No |
| 25 | *PRRT2* | AD | Yes | No |
| 26 | *RPGR* | XL | No | Not reported |
| 27 | *SARS2* | AR | Yes | Yes |
| 28 | *SIX5* | AD | Yes | No |
| 29 | *TBCK* | AR | Yes | Yes |
| 30 | *TSEN54* | AR | Yes | Not reported |
| 31 | *TUBB4B* | AD | Yes | No |
| 32 | *WDR11* | AD | No | No |
| 33 | *WWOX* | AR | Yes | No, Not reported |

### Reviewed PGT-M Cases and Inheritance Patterns




### ClinVar Classifications Review




**19 (19/33, 57.6%) report an affected pregnancy/child**

## Conclusions

33/888 (3.7%) of unique PGT-M cases involved at least one VUS. 57.6% involved an affected child/pregnancy, and only 46% of these findings had non-conflicting pathogenicity reports.

The varying complexity of a VUS case, including potential conflicting pathogenicity classifications, dictates the need for a clear VUS review process for any laboratory performing PGT-M.