

RNA Genetic Testing in Hereditary Cancer Improves Variant Classification and Patient Management

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BACKGROUND

- DNA genetic testing (DGT) for hereditary cancer is becoming widespread; however, variant interpretation remains a challenge.
- Alterations predicted to impact splicing are frequently classified as uncertain (VUS) and likely pathogenic (VLP), as confirmation of the impact requires RNA analysis.
- We aimed to determine the impact RNA genetic testing (RGT) on variant classification of these alterations and clinical management of patients.

METHODS

- 64 splice variants detected by DGT in genes associated with hereditary breast and ovarian cancer (HBOC), Lynch syndrome (LS), and hereditary diffuse gastric cancer (HDGC) were selected for supplemental RGT (Figure 1).
- RGT was performed by CloneSeq, as previously described¹.
- Subsequent classification review was done following ACMG/AMP guidelines².
- A follow-up survey was sent to all medical providers who received a reclassification report for these variants to assess the impact of RGT on the clinical management of these patients.
- To quantify the potential impact of RGT on a larger scale, we queried a cohort of 307,812 patients undergoing DGT for hereditary cancer susceptibility for identified variants predicted to affect splicing.

RESULTS

- Among the 64 putative splice variants identified in 13 genes RGT data clarified the classification for (Figure 2):
 - 90% of HBOC germline DNA variants in *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *PALB2*, *RAD50*, *RAD51C*, *RAD51D*
 - 100% of LS germline variants in *MLH1*, *MSH2*, *MSH6*, *PMS2*, with 70% being reclassified as clinically actionable.
 - 70% of HDGC germline DNA variants in *CDH1*
- RGT resulted in reclassification of 85.9% of all tested variants in hereditary cancer genes (Figure 2):
 - 50% upgraded to clinically actionable variants
 - 35.9% downgraded to benign.
- Results from a clinician follow-up survey demonstrated RGT resulted in changes to the clinical management of these patients (Figure 3).

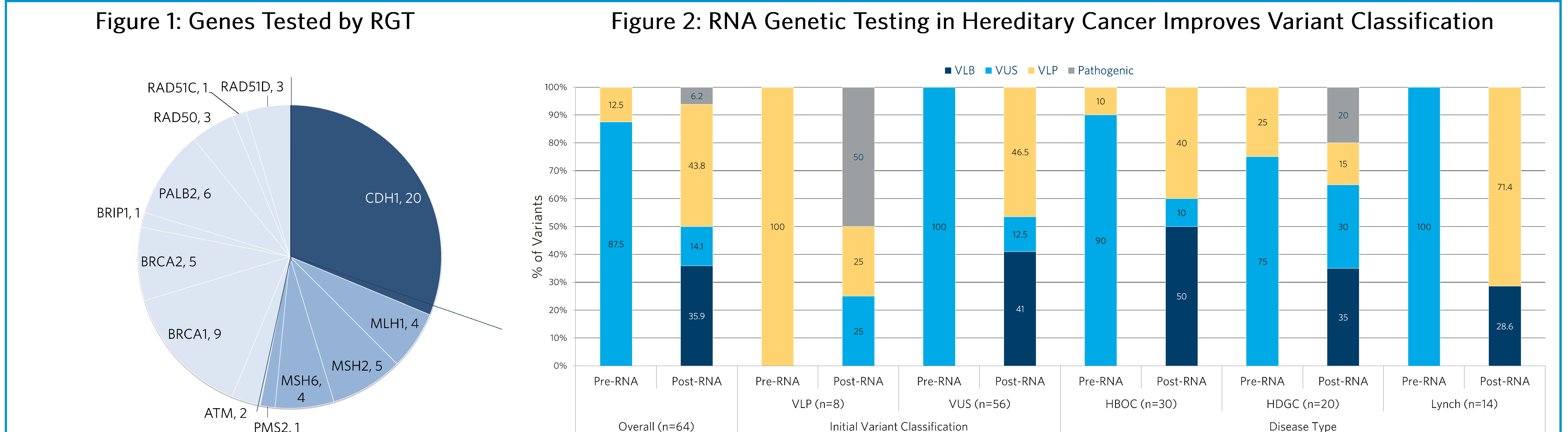
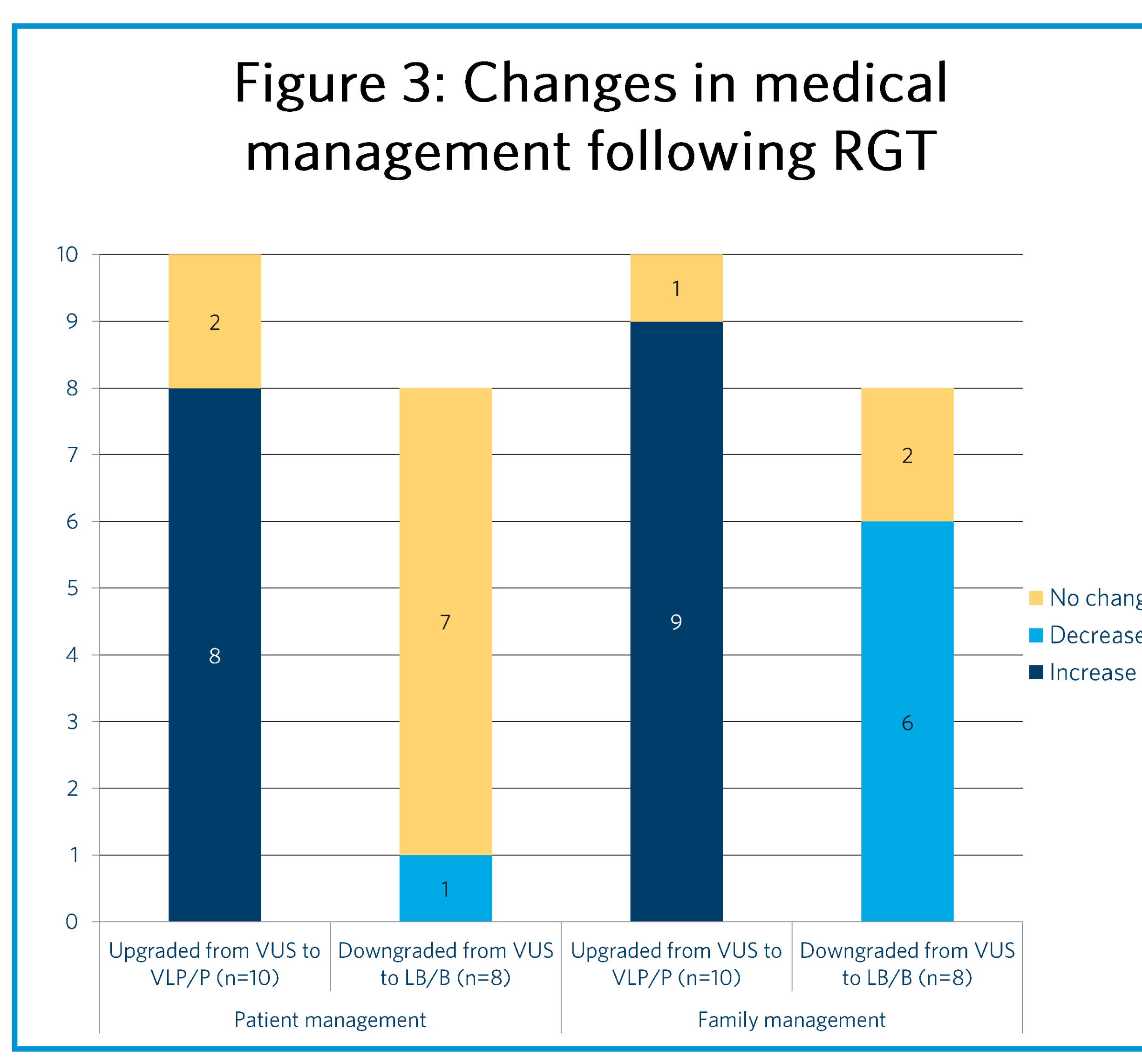
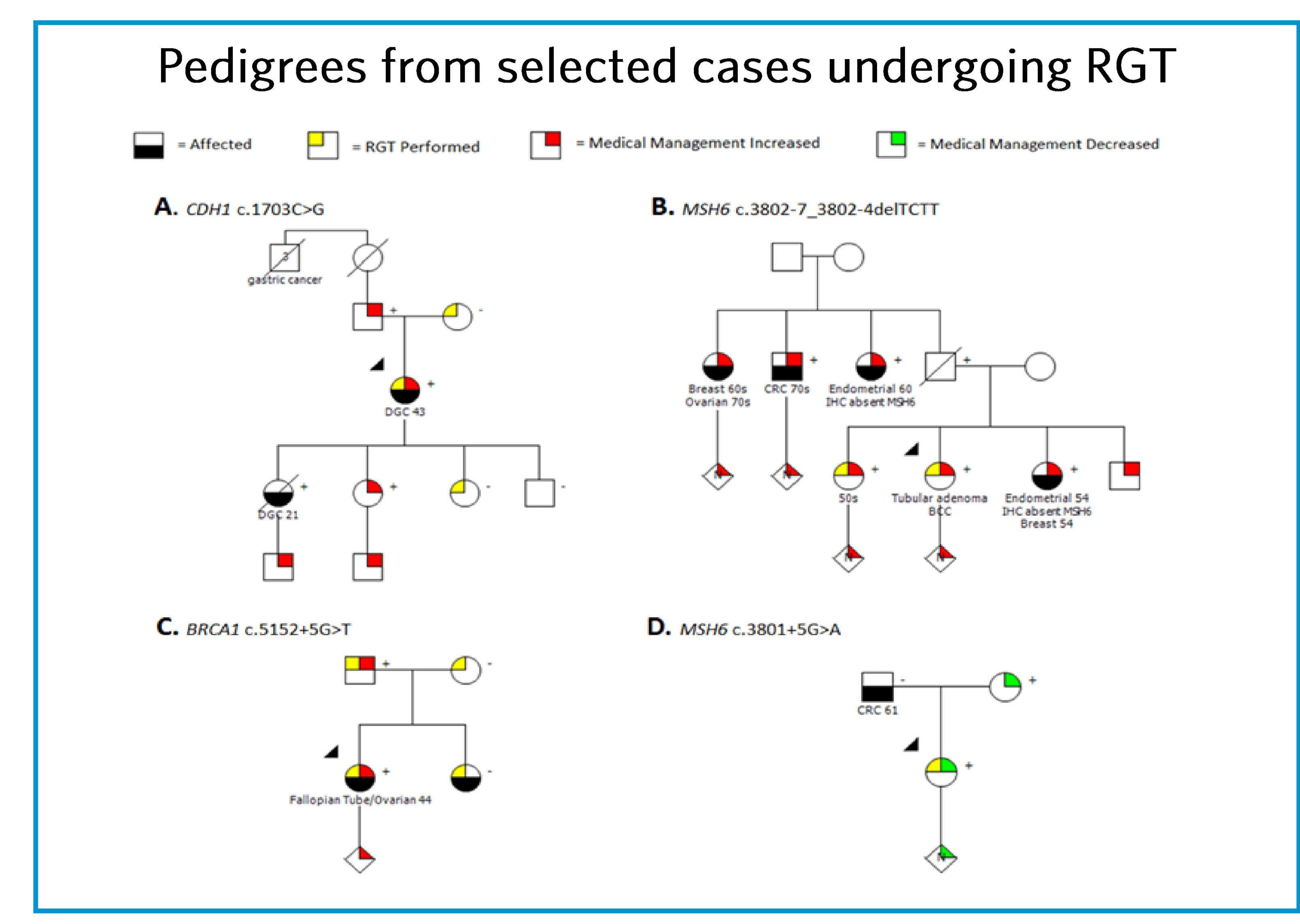


Figure 3: Changes in medical management following RGT



Management Type	Upgraded from VUS to VLP/P (n=10)	Downgraded from VUS to LB/B (n=8)
Patient management	8 (Increase), 2 (No change)	7 (No change), 1 (Decrease)
Family management	9 (Increase), 1 (No change)	6 (Decrease), 2 (No change)

Pedigrees from selected cases undergoing RGT



TAKE-HOME POINTS

- RGT as a supplement to DGT improves the classification of variants identified in hereditary cancer predisposition genes
- RGT-based variant reclassifications impacted management for both patients and their family members, with increased screening and/or more aggressive risk-reducing interventions recommended in most instances of VUS reclassification to VLP.
 - While patient management recommendations were unlikely to change when VUSs were downgraded to VLB, screening recommendations for family members were reduced in the majority of these cases.
- RGT is expected to affect medical management in *at least* 1 in 50 patients.

REFERENCES

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