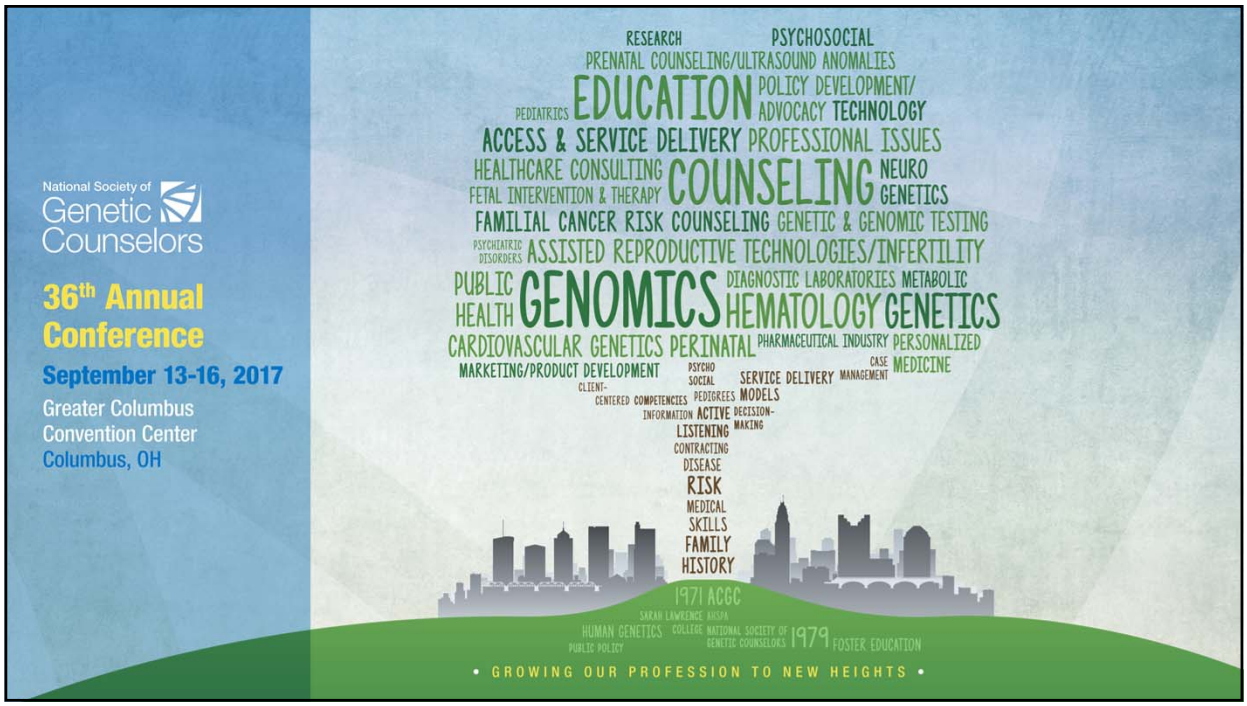

National Society of Genetic Counselors

36th Annual Conference
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Greater Columbus Convention Center
Columbus, OH

Variant Reclassification in a Clinical Cohort: A Decade of Experience

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COI Disclosure

I am employed by Myriad Genetic Laboratories, Inc.

My involvement with this study is based on my previous role at UT Southwestern Medical Center. My current role at Myriad Genetic Laboratories is unrelated to this study.

Background and Objective

- Little data exist regarding the frequency and clinical impact of reclassification to inform how providers counsel and manage patients after genetic testing.
- Here we assessed variant reclassification in a large cohort of patients tested at a single commercial laboratory (Myriad Genetic Laboratories).
- The subset of patients tested at UT Southwestern Medical Center was also evaluated separately.
  - Evaluate a single institution's experience
  - Clinical follow-up for patients with a reclassified variant

Laboratory Process for Variant Classification and Reporting

Variant Identified During Testing

- Classified based on all available evidence
  - Benign (B)
  - Likely Benign (LB)
  - VUS
  - Likely Pathogenic (LP)
  - Pathogenic (P)
  - Special Interpretation
- Initial report sent to provider

New Information Available

- Automated systems to monitor evidence daily
- Classification re-evaluated immediately upon identification of new information

Variant Reclassified

- Amended report sent to notify provider of reclassification
  - Includes amended reports for downgrades from VUS to B/LB

Full Clinical Cohort

1.45 Million Tested Individuals

- Individuals who received an initial and/or an amended test report as part of hereditary cancer genetic testing (Myriad Genetic Laboratories) between 2006 and 2016.
  - Included clinical single-syndrome and pan-cancer panel testing (2013–2016)
  - 95.6% female, 51.9% European, median age of testing 49 years
  - 56.6% had a personal history of cancer at the time of testing

Full Clinical Cohort

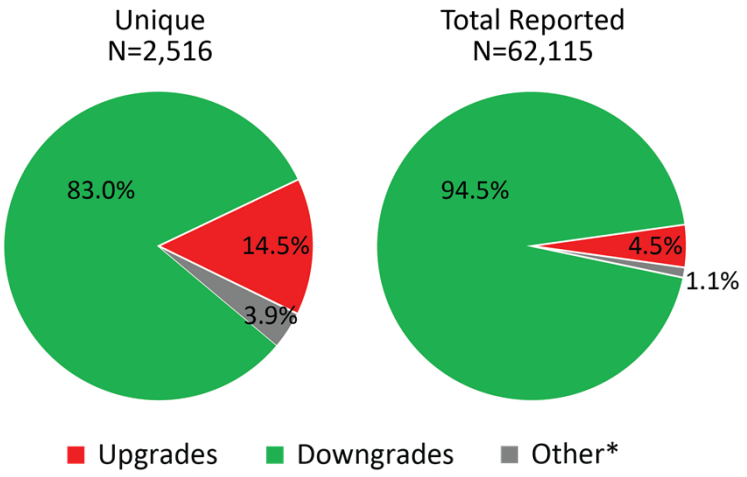
1.45 Million Tested Individuals → **1.67 Million Initial Reports**

- Some individuals had > 1 genetic test
  - i.e. single-syndrome and panel testing, multiple single-syndrome tests
- 5.8% of tested individuals were positive for a P/LP variant (initial classification)

Full Clinical Cohort

1.45 Million Tested Individuals → **1.67 Million Initial Reports** → **59,942 Amended Reports**

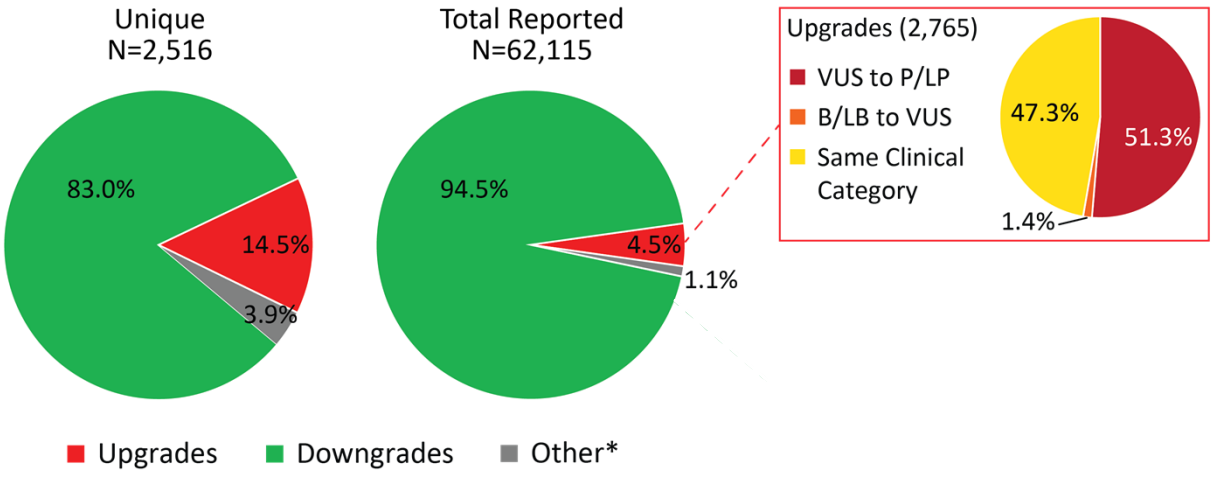
Full Clinical Cohort Reclassifications



- 6.9% (**2,516**/36,264) unique variants were reclassified
- 19.3% (56,731/ 293,496) reported variants were reclassified
  - **62,115** classification changes

*Changes to or from special interpretation; Variants that were upgraded and downgraded

Full Clinical Cohort Reclassifications



*Changes to or from special interpretation; Variants that were upgraded and downgraded

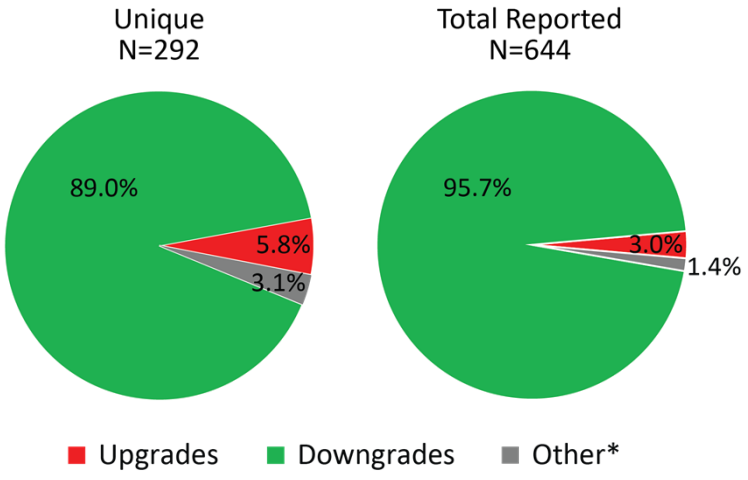
UT Southwestern Subset

8,427 Tested Individuals → **9,545 Initial Reports** → **579 Amended Reports**

- Similar demographics as full clinical cohort
- 71.5% had a personal history of cancer

- 1,694 unique variants
- 2,728 total variants
- 7.8% positive rate

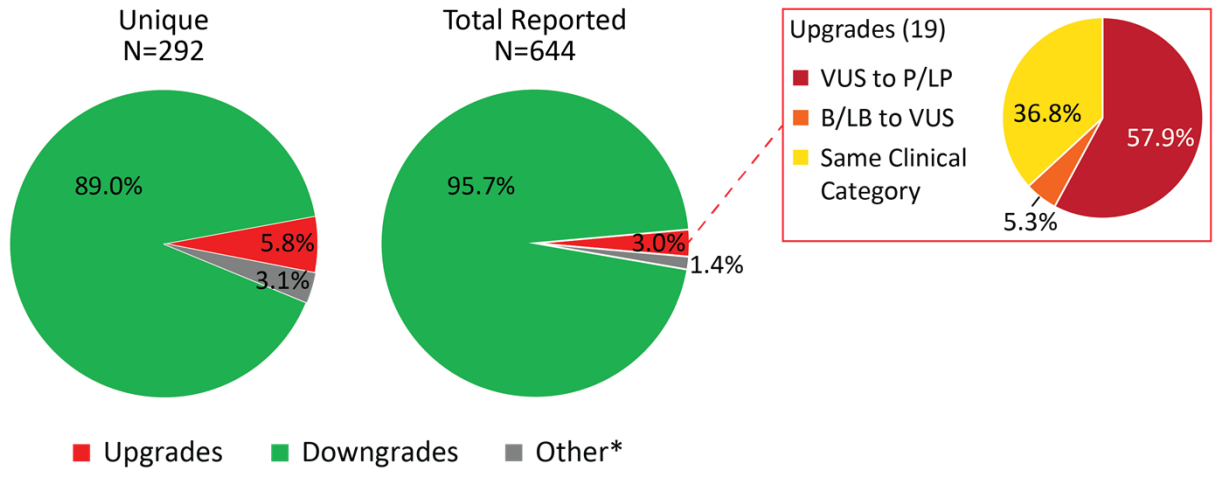
UT Southwestern Reclassifications



- 17.2% (**292**/1,694) unique variants were reclassified
- 22.5% (614/ 2,728) reported variants were reclassified
  - **644** classification changes

*Changes to or from special interpretation; Variants that were upgraded and downgraded

UT Southwestern Reclassifications



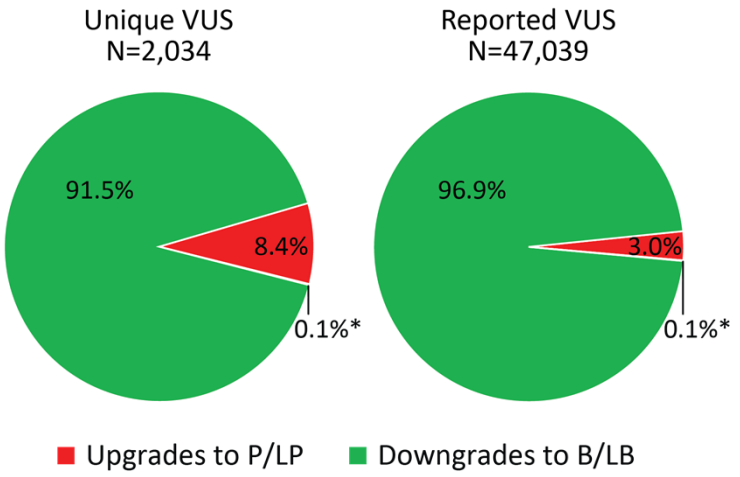
*Changes to or from special interpretation; Variants that were upgraded and downgraded

Downgrades from Pathogenic to VUS

- Only 3 variants in the UTSW cohort were downgraded from P/LP to VUS

	BRCA1	***TP53***	***BRIP1***
Personal Cancer History	Unilateral Breast Cancer at age 58	Unilateral Breast Cancer at age 39	None
Notes	TAH-BSO prior to first appointment		Also carries *APC* c.3920T>A (I1307K)
Time to Amended Report	65 months	8 months	9 months
Medical Management	• Bilateral Mastectomy following genetic testing • Familial Cascade Testing (No medical intervention among positive family members)	• Bilateral Mastectomy following genetic testing	• GI management based on *APC* finding • High risk breast cancer surveillance (continued after reclassification based on strong family cancer history)

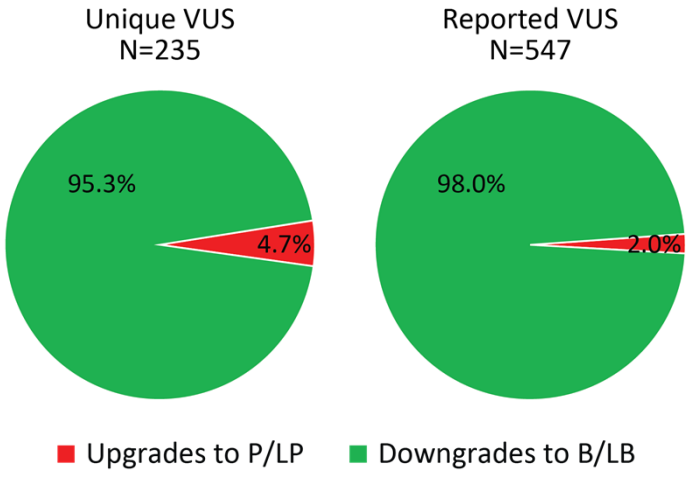
VUS Reclassifications: Full Cohort



*Changes to or from Special Interpretation

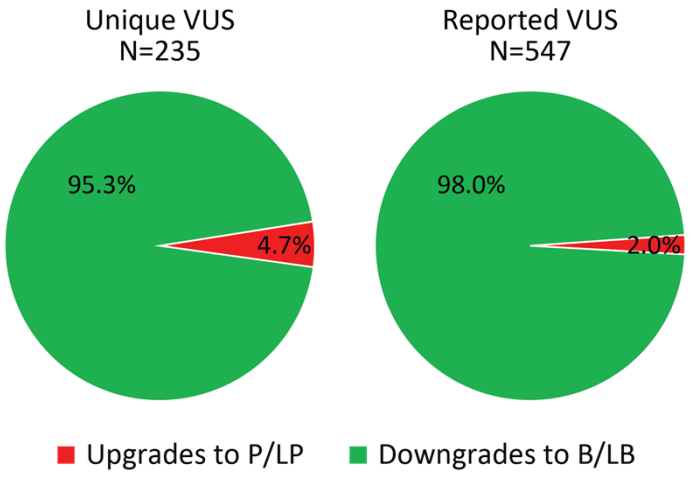
- 7.6% (**2,034**/26,605) unique variants initially classified as VUS were reclassified.
- 24.9% (**47,039**/188,621) total reported VUS were reclassified.

VUS Reclassifications: UTSW Subset



- 19.7% (**235**/1,195) unique variants initially classified as VUS were reclassified.
- 24.5% (**547**/2,231) total reported VUS were reclassified.

VUS Reclassifications: UTSW Subset



- 11 variants upgraded from VUS to P/LP.
  - *BRCA1* (4), *BRCA2* (3), *CDH1* (1), *CHEK2* (1), *MLH1* (1), *MSH6* (1)
- No known interim cancers diagnosed prior to reclassification.

Conclusions

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- When a comprehensive classification approach is employed, variant reclassification is relatively common in genetic testing for hereditary cancer risk.
- Upgrades to a more severe clinical category (i.e. VUS to P/LP) accounted for about 1:15 unique variants and about 1:40 total variants reclassified in this 10 year period.
- This type of reclassification can have significant impact on clinical management and highlights the need for accurate and timely reclassification and notification.
- The ultimate goal is for all variants to have a definitive classification, which requires a robust and timely approach to variant classification and reclassification.