Cardiogenetics			
Paper	Methods	Results	Clinical implications
Westphal et al., 2022 [64]	Retrospective review of genetic test reports from 2009 – 2019 using 2015 ACMG/AMP guidelines (n=167)	126 patients had genetic test reports. 45 variants were identified in 71 patients. 13 out of 45 variants were reclassified (28.9%). 9 of the 13 reclassified variants were from VUS to LB*. 3 variants were reclassified from P** to VUS. One variant was reclassified from LB to VUS.	Management unchanged as patients had clinical diagnoses.
Cherny et al., 2021 [9]	Retrospective review of genetic test reports from 2006 – 2017 using ClinVar (n=583)	583 patients from 337 families from had genetic tests. 422 variants out of 914 variants were investigated . 330 variants out of 422 variants that were examined were reclassified (78.1%) after investigation. 9 out of 330 reclassifications (2.7%) were from VUS to P/LP***; 25 out of 330 reclassifications were from P/LP to VUS (7.6%). Overall, 22% of total variants were reclassified.	Approximately 10% of variants had a reclassification that would change clinical interpretation.
Costa et al., 2021 [3]	Retrospective review of medical records of patients with clinical diagnoses and genetic testing from 1998 – 2019 using 2015 ACMG/AMP guidelines (n=79)	79 patients had clinical diagnoses and genetic testing. 80 unique variants were identified on testing. 47 variants out of 80 unique variants were reclassified (58.8%).	33 reclassified variants out of 80 originally classified variants (41.3%) were deemed clinically relevant. 13 family members had familial testing. 5 family members had a variant reclassified from P/LP to VUS or B/LB~.

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Davies et al. 2021 [70]	Retrospective review of genetic test reports from 2006 – 2017 using 2015 ACMG/AMP guidelines (n=131)	131 patients had genetic test reports. Of the 340 variants reported on the test reports, 211 were originally classified as B/LB, 36 variants were classified as P/LP, 93 variants were classified as VUS. 20 VUS out of 93 VUS were reclassified as B/LB (22%), 7 VUS out of 93 VUS were reclassified as P/LP (8%). Overall, 30% of VUS were reclassified. Out of 23 variants originally classified as P, 5 were reclassified to VUS, 5 were reclassified to B/LB.	40 patients out of 131 patients (31%) had variant reclassification that was clinically significant.
Richmond et al., 2021 [16]	Retrospective review of genetic test reports from 2013 – 2017 using 2015 ACMG/AMP guidelines and ClinGen *MYH7* specific guidelines (n=52)	52 patients had genetic tests reporting 54 variants. 43 unique variants were classified on the test reports. 17 variants out of 43 unique variants (39%) were reclassified using ACMG/AMP guidelines. 13 variants out of 43 unique variants (30%) were reclassified using ClinGen criteria.	19% of variant reclassifications were clinically actionable using ACMG/AMP guidelines. 15% of variant reclassifications were clinically actionable using ClinGen criteria. 19 proband reports were reclassified using ClinGen criteria. Of the 19 reclassified proband reports, 9 (47%) were issued to families where cascade testing had already been initiated.

Cardiogenetics			
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VanDyke et al., 2021 [74]	Retrospective review of genetic test reports from January 2004 – December 2015 using 2015 ACMG/AMP guidelines (n=237)	237 patients had genetic test reports. 223 unique variants were identified on the test reports. 79 variants out of 223 unique variants were reclassified (35.4%). 21% of reclassified VUS were downgraded to B/LB; 12% were upgraded to P/LP.	Medical management recommendations changed for 38/237 (16%) patients based on variant reclassification.
Quiat et al., 2020 [19]	Retrospective review of medical records of patients with clinical diagnoses from January 2008 – January 2018. Variants reported on genetic tests were reclassified using 2015 ACMG/AMP guidelines (n=118)	118 patients had a clinical diagnosis. Genetic testing was performed in 63 patients. 116 variants were classified on 63 genetic test reports. 26 VUS of 90 variants that were originally classified as VUS (28.9%) were reclassified as B/LB.	Medical management unchanged as patients had clinical diagnoses.
Bennett et al., 2019 [66]	Retrospective review of genetic test reports from 2007 – 2017 using 2015 ACMG/AMP guidelines (n=116)	116 genetic test reports were reviewed. P/LP and VUS were identified in 47 reports out of 116 reports (40.5%). 24 reports out of 116 reports (20.1%) had VUS classification (23 unique VUS in 12 genes were identified). 45 reports did not show any clinically relevant variants (38.8%). 12 VUS out of 23 unique VUS initially reported were reclassified. 8 VUS were reclassified to P; 4 VUS were reclassified to B~~~.	Medical management unchanged as patients had clinical diagnoses. Predictive genetic testing available for family members of patients who had VUS reclassified to P/LP.

Cardiogenetics			
Paper	Methods	Results	Clinical implications
Westphal et al., 2019 [56]	Retrospective review of diagnostic genetic test reports from December 2001 – November 2018 using 2015 ACMG/AMP guidelines (n=127)	127 patients had genetic testing. There were 84 different variants initially classified as P/LP in 127 patients. 12 variants out of 84 unique variants (14.3%) originally reported as P/LP were downgraded to VUS.	The reclassification of 12 P/LP variants to VUS affected 19 patients. Clinical management outcome of the reclassification not reported.
Cancer genetics			
Paper	Methods	Results	Clinical implications
Makhnoon et al., 2023 [6]	Retrospective review of diagnostic genetic tests reporting VUS from 2013 – 2019. Reclassification reported by the performing laboratory. (n=2,715)	2,715 patients had a VUS classified on initial genetic test report. 3,261 unique VUS were reported across 2,715 individual patients. 240 VUS out of 3,261 VUS were reclassified (7.36%). 88.7% of VUS were downgraded to B/LB . 11.3% of VUS were upgraded to P/LP .	11.3% of all reclassified VUS resulted in clinically actionable findings. Clinical management was changed for 125 patients (4.6%).
Muir et al., 2022 [72]	Retrospective chart review to identify reclassified variants that were reported from January 1997 – December 2020 (n=2,503)	2,503 reclassified variants were identified by chart review. 211 out of 2,503 variants were reclassified once (8.4%). 21 of these 211 reclassified variants (9.9%) were then reclassified a second time.	21 reclassifications (21/232; 9.1%) led to a change in recommended clinical management. 17 reclassifications changed recommendations for familial testing and screening recommendations. 4 reclassifications led to a change in recommendations for familial testing.

Cancer genetics			
Paper	Methods	Results	Clinical implications
Chiang et al., 2021 [7]	Retrospective review of diagnostic genetic test reports from February 2014 – March 2020 using 2015 ACMG/AMP guidelines (n=1,695)	1,695 patients underwent diagnostic genetic testing. 1,412 unique variants were classified on initial genetic reports. 94 variants out of 1,412 variants (6.7%) were reclassified. Of the 94 variants that were reclassified, 85 VUS and 9 P/LP variants were reclassified. No B/LB variants were reclassified. 80 VUS out of 85 VUS (94%) were reclassified as B/LB. 5 VUS were reclassified as P/LP (5.9%). 6 P/LP reclassifications out of 9 P/LP variants were reclassified within the same pathogenic category.	99 patients had a variant detected on initial genetic testing reclassified. Variant reclassification affected clinical management in 12 patients out of 99 patients (12.1%) who had a VUS reclassified. 2 patients were started on targeted therapy based on reclassification of their VUS.
Ha et al., 2020 [68]	Retrospective review of genetic test reports from January 2006 – August 2018 using 2015 ACMG/AMP guidelines (n=805)	805 patients had genetic testing. 108 unique VUS were reported on initial classification. Of the VUS that were reclassified, 6 VUS were reclassified as P/LP (5.6%), 30 VUS were reclassified as B/LB (27.8%), 72 VUS were not reclassified (66.7%).	Not reported.
So et al., 2019 [67]	Retrospective review of genetic tests reports from 2010 – 2017 using 2015 ACMG/AMP guidelines (n=423)	75 patients out of 423 had a VUS reported on initial classification. 32 patients out of 75 patients had a VUS reclassified (43.7%): 2 patients had VUS reclassified to LP~~; 8 patients had VUS reclassified to B~~~; 22 patients had VUS reclassified to LB.	30 patients who were initially reported to have a VUS out of 75 patients reported to have a VUS (40%) were discharged from medical surveillance following reclassification.

Cancer genetics			
Paper	Methods	Results	Clinical implications
Macklin et al., 2018 [2]	Retrospective review of variant reclassifications reported to a clinic by a testing laboratory between September 2013 – February 2017 (n=1,103)	40 genetic test results out of 1,103 (3.6%) were reclassified. 29 VUS out of 226 VUS (72.5%) were reclassified as LB~. 2 P/LP variants were reclassified to VUS. 1 VUS was reclassified as LP. 6 variants were classified within their pathogenicity class (e.g. LB to B).	3 of 40 reclassifications (7.5%) altered medical management for patients.
Neurogenetics			
Paper	Methods	Results	Clinical implications
Charnay et al., 2021 [63]	Retrospective analysis of variants reported from 2001 – 2020 using 2015 ACMG/AMP guidelines (n=176)	17 variants (9.7%) initially classified as pathogenic were reclassified to VUS or B/LB.	Not reported.
SoRelle et al., 2019 [5]	Retrospective review of genetic test reports from July 2012 – August 2015 using 2015 ACMG/AMP guidelines (n=185)	VUS were reported in 124 patients, 46 of these VUS (37.1%) were downgraded to B/LB on reclassification; 19 P/LP variants were downgraded in pathogenicity; two VUS were upgraded to P/LP.	67 patients out of 185 patients (36.2%) had a reclassified variant. Of the 67 patients who had a variant reclassified, 21 (31.3%) patients experienced a change in diagnosis based on variant reclassification.

Eye diseases			
Paper	Methods	Results	Clinical implications
Chan et al., 2023 [65]	Retrospective review of genetic test reports from January 2006 – July 2022 using 2015 ACMG/AMP guidelines (n=53)	2 VUS out of 10 VUS reported on initial classification (20%) were reclassified to P/LP.	Medical management unchanged as patients had clinical diagnoses.

Supplementary Table: **Summary of sequence variant reclassification literature.** The literature describing variant reclassification demonstrates diverse results, underscoring the current element of uncertainty that exists in variant reclassification.

* LB = likely benign; ** P = pathogenic; *** P/LP = pathogenic/likely pathogenic; ~ B/LB = benign/likely benign; ~~ LP = likely pathogenic; ~~~ B = Benign