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SYSTEMATIC REVIEW

Variant reclassification and recontact research: A scoping review

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ABSTRACT

Purpose: A primary challenge in clinical genetics is accurate interpretation of identified variants and relaying the information to patients and providers. Inconsistencies around handling variant reclassifications and notifying patients, combined with the lack of prescriptive guidelines on re-evaluation, reanalysis, and return of variants, has created practice challenges. Although relevant empirical work has emerged, the scope and outcomes of this research have not been characterized.

Methods: We conducted a systematic literature review of variant reclassification and recontact research (2013-2023) across subdisciplines of medical genetics. Of the 159 nonduplicate records screened, we summarize findings from 54 included research articles describing variant reclassification frequencies, outcomes, and stakeholder perspectives on recontact.

Results: The included articles reported on active reclassification (n = 20), passive reclassification (n = 13), stakeholder surveys (n = 11), qualitative interviews (n = 7), and reanalysis of published or ClinVar data (n = 3). On average, active and passive approaches yielded different reclassification frequencies—31% and 20%, respectively, which were considerably higher than ClinVar (<0.1%-6.4%). Despite a wealth of data on individual stakeholder perspectives and opinions on reclassification, recontact, and consensus on the need for standardization in this space, opinions differ on how to develop and implement standardized processes.

Conclusion: Many active reclassification studies reapplied standard variant classification guideline to previously reported variants—thus demonstrating the number of variants that would be successfully reclassified if reinterpretation and reanalysis were performed routinely. Research gaps identified include the need for understanding practices and opinions of nongenetics providers and engaging in deliberative democracy exercises to reach consensus on these issues.

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Introduction

Dramatic advances in genome sequencing technologies have improved its accuracy, speed, and cost; the primary challenge now is accurate interpretation of identified variants and relaying the information to patients and providers.[1] Today, reclassification of previously reported variants is a frequently occurring phenomenon.[2] Variant reclassification occurs more often because of multiple new or evolving factors including computational tools, functional data, disease-specific insights, better analytical tools, and greater adherence to variant reclassification guidelines.[3,4] Accurate and definitive variant classification is a critical component of clinical genetic testing, especially because the use of larger gene panels is becoming commonplace. With increasing access to and uptake of germline genetic testing across various fields of medicine,[5] there is an inevitable increase in the number of variants detected in these patient populations and observed reclassifications. In this period of dynamic change in knowledge, a systematic understanding of the variant reclassification literature is imperative to guide future work in this space.

Variant reclassifications may clarify the clinical significance of previously reported variants, and some proportion of these reclassifications may warrant changes in clinical management.[3] Resolving the uncertainty associated with variants of uncertain significance (VUS) is a primary motivation for variant interpretation,[6] and VUS are thus the most frequently reclassified category of variants. Between 2006 and 2018, 24.9% of VUS were reclassified in 1 laboratory (compared with 0.7% pathogenic [P] and 0.2% benign [B] variants).[7] VUS upgrades may make patients suitable for interventions that were not previously recommended, whereas VUS downgrades have little impact on clinical management. Other variant downgrades (P or likely P [P/LP] to VUS/B or likely B [B/LB]) may indicate that a patient no longer meets criteria for specific management guidelines. Variant reclassification may similarly affect the management of family members that underwent cascade genetic testing for a known familial variant and often dramatically changes the risk profile and screening protocols for these relatives.[8] These can lead to confusion and poor follow-up in care.[3] Inconsistencies in clinical practice surrounding the process for handling these reclassifications[9] and notifying patients, combined with the lack of prescriptive guidelines on reevaluation, reanalysis, and return of variants, has created heterogeneity in practice.

A growing body of literature report on variant reclassification—some on the frequencies of observed reclassifications across various clinical cohorts that vary by the method used for reclassification, phenotypes, and variants considered in each study; others report on stakeholder perspectives on issues such as variant reinterpretation, reclassification, and return of reclassified variants assessed through surveys and interviews. The lack of systematic understanding of this diverse body of literature presents a challenge for more diffuse clinical translation of genetic technologies through development of evidence-based practice guidelines and standards. No study has systematically examined the literature on variant reclassification to understand the variation among clinical subgroups, sociodemographic characteristics, and the various methodology used in reclassification. This scoping review aims to examine the published data surrounding variant reclassification, including prevalence of reclassification, process for patient recontact, and stakeholders' prospectives. We point out the areas of strength and identify research gaps.

Materials and Methods

We used recommendations outlined by the Joanna Briggs Institute for the extraction, analysis, and reporting of results in scoping reviews[10] and reported the results using the Preferred Reporting Items for Systematic Reviews and Meta Analysis extension for scoping reviews guidelines.[11]

Information sources and search

A research librarian searched Medline, MEDLINE Epub and InProcess, and Embase on August 22, 2023 to identify the studies published within the last 10 years. The Medline search strategy is provided in Supplemental Table 1. After removing duplicates and screening for English language, 4 authors (A.T., R.S., A.G., and S.M.) screened all 152 citations by title and abstract. Discrepancies, when present, were resolved through discussion and moderation by the senior author (S.M.). Eighty-nine articles were further analyzed by full-text review. Reference lists of pertinent studies were manually searched by S.M. After screening, an additional 7 records were identified from the bibliographies of these articles.

Inclusion and exclusion criteria

Studies that investigated variant reclassification or patient recontact after reclassification were considered for inclusion. Included studies were published in English within the last 10 years; the timeline reflects the publication of the 2015 American College of Medical Genomics and

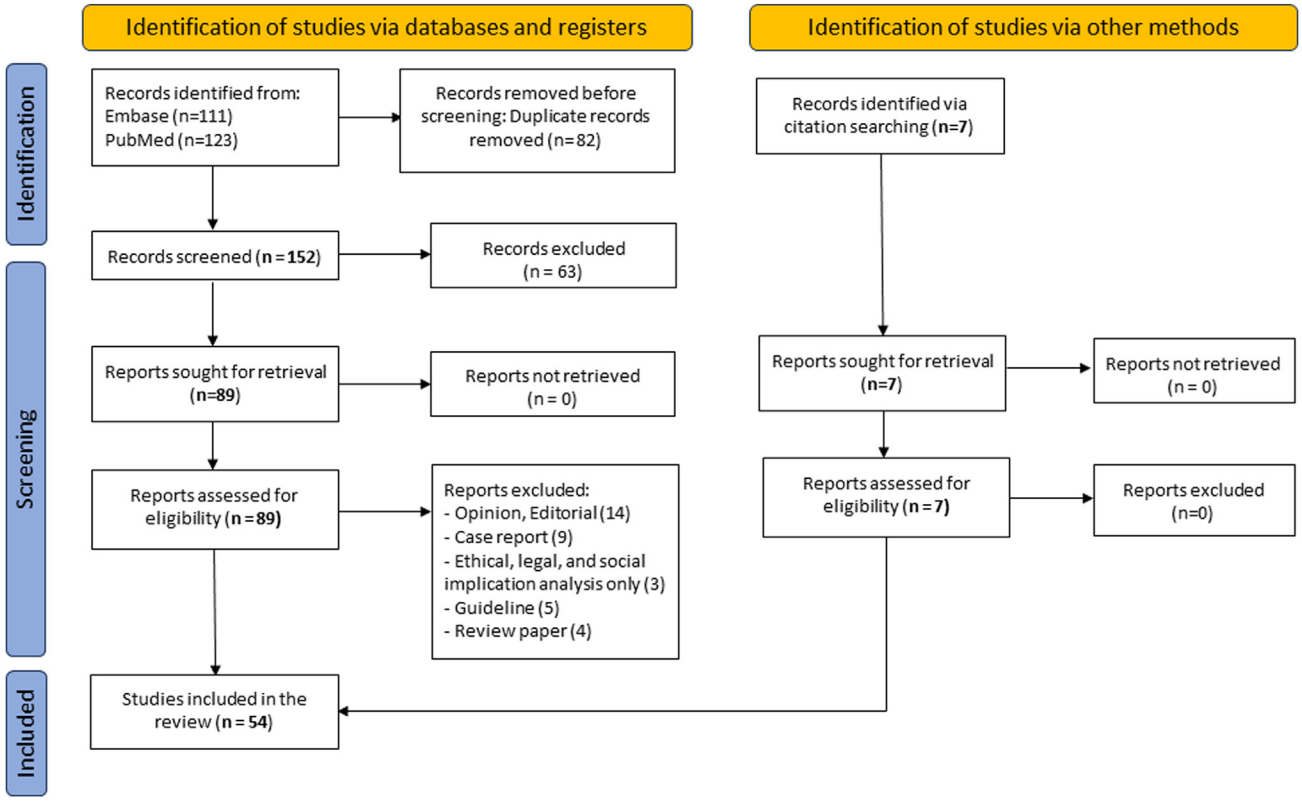

Figure 1 **Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA) flow diagram.**

Genetics (ACMG)/Association for Molecular Pathology (AMP) variant interpretation guidelines, which was published 9 years ago. Duplicate studies were removed, as were articles that were not original studies (ie, opinions, commentary, or review articles). Studies that used or sought to validate novel variant classification methodology using a limited set of variants were also excluded. There were no restrictions placed on the size or demographics of the study population. The reasons for exclusion are listed in Figure 1. Studies were broadly categorized into 1 of 3 themes: active variant classification (variant reclassified through purposeful application of ACMG/AMP criteria to previously classified variants or variant reclassified through the application of new variant reinterpretation tools, methodological approach, or interpretation guidelines), passive variant reclassification (variant reclassified through routine clinical practice), and stakeholder perspectives on reinterpretation and recontact (quantitative and qualitative studies) (Table 1).

Data extraction

In the first round of data extraction from the quantitative articles, 3 authors (A.T., A.G., and R.S.) independently reviewed a randomly selected subset of 26 articles to develop 2 data extraction forms—one focused on reclassification frequencies and another on surveys. Data from each of these 26 articles were independently extracted by 2 authors; discrepancies were identified and resolved through discussion. The codebook was iteratively edited as additional relevant data items were identified within subsequent articles. Data from the 7 qualitative articles were extracted using a different codebook developed by S.M. and an analyst. Extracted data elements included study participant information (sociodemographic and clinical characteristics and sample size), approaches for variant reclassification (passive, active, method of reclassification, and outcome), and stakeholder perspectives (stakeholder type and opinions on reclassification).

Table 1 Criteria used to define studies into active or passive variant reclassification efforts

Definition	
The process by which a variant's classification is updated based on reinterpretation.	Reclassification
Variant reclassified through routine clinical practice.	Passive
Variant reclassified through purposeful application of ACMG/AMP criteria to previously classified variants; OR Variant reclassified through the application of new variant reinterpretation tools, methodological approach, or interpretation guidelines.	Active

Summary measures and synthesis methods

Descriptive statistics (*N*, mean, median, and range) were used to summarize studies. Studies that reported frequency of variant reclassification used a variety of denominators, including total variants, unique variants, number of patients, number of laboratory reports, etc. Here, we report reclassification rates as originally reported in the studies. Prevalence of variant upgrade and downgrade were often reported as a function of all reclassified variants. We report them here as a function of all variants that were included in the analysis.

Results

Overall, 159 unique references were screened for possible inclusion, of which 89 underwent full-text review. Fifty-four studies met the criteria and were included in the scoping review. A flowchart of the study selection process is depicted in Figure 1. These include studies focused on active variant reclassification (n = 20), passive variant reclassification (n = 13), stakeholder surveys (n = 11), qualitative interviews (n = 7), and reanalysis of published data or ClinVar data (n = 3) (Table 2).

Study characteristics

Half (52%) of included studies were conducted in the United States (Table 1). A range of study designs were used, the majority (n = 31) used retrospective, observational designs to report variant reclassification through medical record review and/or analysis of retrospective clinical data; a minority used prospective designs to validate algorithms or new methods for variant reclassification. Eighteen cross-sectional studies conducted stakeholder surveys or semi-structured interviews to explore variant reclassification and recontact. There was large variation in the number of unique variants and patients included in these studies: the median sample size for quantitative studies was 97 variants (range: 13 to 62,842) and 195 patients (27 to 1.9 million). The median sample size was 66 for surveys and 20 for qualitative studies.

Characteristics of study participants

Ten studies reported demographic characteristics of the study participants. On average (unweighted by study sample size), participants were mostly female (77.8%) and non-Hispanic White (71.8%). Some studies only reported the demographic characteristics of a subset of study participants, for example, for participants who had actionable changes in clinical management as a result of variant reclassification.

Active variant reclassification

Twenty[12-31] studies reported reclassification results from proactive variant reinterpretation efforts. Five[5,10,14,17,19] of these studies reported reclassifications of patients and variants, whereas the other 15[2-4,6-9,10-13,15,16,18,27,31] reported only variant reclassifications. These efforts often involved purposeful application of the 2015 ACMG/AMP variant classification guidelines[8] to a specific set of previously reported variants. Others applied newly developed tools or approaches to reclassify variants including in vitro functional evaluation,[24] pre-mRNA splicing,[25] ClinGen's Sequence Variant Interpretation Working Group guidelines,[20,22] family studies,[17] variant segregation studies,[31] and multifactorial likelihood analysis for co-occurrence of variants with personal/family history and tumor characteristics.[4] Some studies only attempted to reclassify P/LP variants[19-21] or VUS,[12,14,31] whereas others included all variants.

The mean frequency of reclassification from proactive efforts was 31% (range: 4.7% to 100%) across studies with 17% downgrade and 14% upgrade. Notably, 4 studies[12,18,25,30] reported higher rates of upgrades than downgrades, which contrasts previous reports in which downgrades are several magnitudes of order higher than upgrades. Two of these studies focused on cardiomyopathy, and the other 2 focused on monogenic conditions. Three of 4 studies only included VUS in their analysis, whereas the fourth included all variants. Another cardiogenetic study that included all variants reported higher frequency of reclassification for P/LP variants than VUS,[23] which is notable because VUS is by far more commonly reclassified.

Passive variant reclassification

Thirteen studies[2,32-41,43] reported the prevalence of passive variant reclassification in routine clinical practice observed within predefined cohorts such as clinical population, genetic testing laboratory, etc. The frequencies of reclassification events by study are reported in Figure 2.

Most studies (10 of 13) were cancer focused, and most (9 of 13) included all types of variants in their analyses, whereas 4 studies analyzed VUS, P/LP, and rare variants only. Average unweighted frequency of variant reclassification across 13 studies was 19.9% with 5% upgrade and 14.2% downgrade. Prevalence of reclassification across the 9 studies that included all variant types was 15.7%, with 3.8% upgrade and 9.7% downgrade. Information on actionable reclassifications that warrant a change in clinical management are in Supplemental Table 2.

For both the total and unique variant reclassifications, VUS downgrades to B/LB were the most common (57.7% and 70.6%, respectively), followed by reclassification of B to/from LB (16.2%), and VUS upgrades to P/LP (7.4%). Reclassifications between B/LB and P/LP were very rare.

Table 2 Studies included in the scoping review ($n = 50$)

Study	Country	Study Timing	Sample Size		Study Design	Disease Type
			Variants	Patients		
Active Reclassification						
Bennett et al[12] (2019)[a]	USA	2007-2017	23 VUS	34	Retrospective	Cardiomyopathy
Esterling et al[13] (2020)[a]	USA	1997-2017	62,842	>1.9 million	Retrospective	Oncology
Lee et al[14] (2018)[a]	South Korea	2007-2013	83 VUS	286	Retrospective	Oncology
So et al[15] (2019)[a]	South Korea	2010-2017	423	75	Retrospective	Oncology
SoRelle et al[16] (2019)[a]	USA	2012-2015	VUS/P/LP	185	Retrospective	Neurology
Tsai et al[17] (2019)[a]	USA	2016-2018	112 VUS	92	Observational	Any
VanDyke et al[18] (2021)[a]	USA	2004-2015	223	237	Retrospective	Cardiomyopathy
Charnay et al[19] (2021)	France	2001-2021	176 P/LP	NA	Retrospective	Musculoskeletal
Westphal et al[20] (2020)	Germany	2001-2018	84 LP	127	Retrospective	Cardiomyopathy
Xiang et al[21] (2020)	China	2019	217 LP/P	NA	Retrospective	Any
Zouk et al[22] (2022)	USA	2016-2018	1,855	NA	Retrospective	Any
Davies et al[23] (2021)	Canada	2004-2021	340	131	Retrospective	Cardiology
Glazer et al[24] (2022)	USA	2016-2018	50 VUS	NA	Retrospective	Arrythmia
He et al[25] (2022)	China	NA	49 VUS	49	Retrospective	Prenatal
Tallis et al[26] (2022)	USA	2010-2019	22 VUS/P/LP	27	Retrospective	Oncology
Haghighi et al[27] (2023)	USA	2020	97 P/LP	NA	Prospective	Nemaline Myopathy
Ravel et al[28] (2023)	France	2010-2017	372 VUS	259	Retrospective	Mendelian
Rossen et al[29] (2023)	USA	2003-2022	92	52	Retrospective	Congenital cataract
Yoon et al[30] (2023)	Korea	2015-2022	61 VUS	69	Retrospective	*FBN1*
Ghorbani et al[31] (2022)	Netherlands	2017	13 VUS	368	Retrospective	Cerebellar Ataxia
Passive Reclassification						
Campuzano et al[32] (2020)	Spain	2010-2019	128 rare	121	Retrospective	Arrythmia Syndromes
Chiang et al[33] (2021)[a]	Singapore	2014-2020	1412	1695	Prospective	Oncology
Ha et al[34] (2020)[a]	South Korea	2006-2018	VUS	195	Retrospective	Oncology
Macklin et al[35] (2019)[a]	USA	2013-2017	1103 reports	226	Retrospective	Oncology
Makhnoon et al[36] (2022)[a]	USA	2013-2019	3574 VUS	2712	Retrospective	Oncology
Mersch et al[2] (2018)[a]	USA	2006-2016	44,777	1,451,533	Retrospective	Oncology
Mighton et al[37] (2019)[a]	Canada	2001-2017	1209	6090	Prospective	Oncology
Muir and Reagle[38] (2022)[a]	USA	1997-2020	2503	NA	Retrospective	Oncology
Quiat et al[39] (2020)[a]	USA	2008-2018	116	63	Retrospective	Cardiomyopathy
Slavin et al[40] (2019)[a]	USA	1996-2016	1816	1743	Retrospective	Oncology
Turner et al[41] (2019)[a]	USA	2012-2017	943	1694	Retrospective	Oncology
Testa 2023[42]	Italy	2003-2021	115 VUS	292	Retrospective	Sotos Syndrome
Ozdemir et al[43] (2022)	Turkey	2016-2017	58	42	Retrospective	Oncology
Other						
Davidson et al[44] (2022)[a]	Australia	2015-2021	179,123	NA	Retrospective	Oncology
Harrison and Rehm[45] (2019)[a]	USA	2016-2019	571,850	NA	Retrospective	Oncology
Slavin et al[46] (2018)[a]	USA	1996-2016	1282	1483	Prospective	Oncology
Surveys						
Berger et al[47] (2022)[a]	USA	2022	1753 stakeholders		Cross sectional	Any
Beunders et al[48] (2018)[a]	Netherlands	2015	47 parents		Cross sectional	Fragile X
Carrieri et al[49] (2017)[a]	UK	2014-2015	23 clinical genetic services		Cross sectional	Any
Richardson et al[9] (2022)[a]	USA/Canada	2020	96 GCs		Cross sectional	Any
Scherr et al[50] (2015)	USA	2013	398 GCs		Cross sectional	Any
Sirchia et al[51] (2018)	EU	2016-2017	105 genetic centers		Cross sectional	Any
Vora et al[52] (2022)[a]	Australia/NZ	2018	45 genetic health professionals		Cross sectional	Any
Chisholm et al[53] (2018)[a]	USA/Canada	2016	8 laboratories		Cross sectional	Any
Makhnoon et al[54] (2023)	USA	2022	634 GCs and oncologists		Cross sectional	Oncology
Sakaguchi et al[55] (2023)	Japan	2021	73 facilities		Cross sectional	Any
Taber et al[56] (2018)	USA	2015	58 higher socioeconomic status study participants		Cross Sectional	Duarte variant galactosemia

(continued)

Table 2 Continued

Study	Country	Study Timing	Sample Size		Study Design	Disease Type
			Variants	Patients		
Interviews						
Fridman et al[57] (2022)	Israel	2022	NA	20	Qualitative	Any
Halverson et al[58] (2020)	USA	2018-2019	NA	20	Qualitative	Oncology
Margolin et al[59] 2021)	USA	2020	NA	15	Qualitative	Pediatric
Wong et al[60] (2019)	Canada, Australia	NA	NA	15	Qualitative	Cardiology
Wedd et al[61] (2023)	Australia	2018-2022	NA	18	Qualitative	Oncology
Tsai, 2020[62]	USA	2017-2018	NA	56	Qualitative	Oncology
Dheensa, 2017[63]	UK	2017	NA	41	Qualitative	Any

GC, genetic counselor; *LP*, likely pathogenic; *P*, pathogenic; *VUS*, variant of uncertain significance.
[a]Studies used to develop data extraction form.

Despite variation in how time to reclassification is reported across studies (eg, median, mean, and prevalence over time), the average time to reclassification was 590 days (range: 13 days to 20 years).

Reclassification in ClinVar

Two studies[44,45] analyzed cancer variants in ClinVar to understand the patterns of reclassification. One study included all variants between 2015 to 2021 and another 2016 to 2019. These retrospective analyses found reclassification rates between <0.1% and 6.4%, which is considerably lower than the 20% to 30% prevalence reported in clinical cohorts within the sections above. Harrison et al[45] included variants that used 1 of the 5 standard ACMG/AMP classification terms in their analysis and reported highest reclassification of LP variants (2.2%) and lowest for benign variants (<0.1%). Davidson et al[44] included all variant terms and reported higher reclassification frequencies (0.6%-6.4%) and a shift in reclassification toward VUS or conflicting interpretations.

Reclassification by race/ethnicity

Self-reported racial and ethnic variation in reclassification, although frequently acknowledged by studies as a cause for concern, was only reported in 2 studies.[36,46] One study reported self-reported maternal and paternal ancestry and another reported race/ethnicity collected from electronic medical records, but neither reported genetic ancestry. In these 2 studies,[36,46] White, Black, and Hispanic patients represented 53.8%, 21.7%, and 13.2% of the reclassification events and 56.6%, 11%, and 16.6% of the overall sample, respectively. Importantly, variant reclassification did not disproportionately affect White individuals because reported reclassification was proportional to their representation in their overall sample, whereas for Black individuals the opposite was true. Slavin et al[46] was the only study designed to investigate variation in reclassification by ancestry and found higher reclassification of nonbenign *BRCA1/2* variants among minorities. Most studies that reported reclassification did not include detailed participant characteristics.

Impact of reclassification for patients

Both quantitative and qualitative data suggest that reclassified results affect uptake of preventive medical management, reproductive planning, and lifestyle behaviors for patients. Most patients could not recall their reclassified results,[60,61] especially those that did not impact management, nor did they have the knowledge that variants can undergo reclassification.[59] Notably, 1 study found that most patients accurately or partially recalled their genetic results but only included patients from high socioeconomic background.[56] On occasion, when patient expectations were unmet, reclassification decreased patients' confidence in medical genetics and negatively affected the patient-provider relationship.[58] Successful delivery of reclassified results strengthened trust in providers as patients understood the dynamic nature of genetic medicine and appreciated being informed.[60,61] In quantitative and qualitative studies,[56,58-60] patients expressed a variety of emotional reactions after recontact, ranging between happiness, acceptance, relief, disappointment, frustration, worry, and neutral/minimal-to-no reaction. Positive and negative emotional outcomes were unrelated to any specific type of variant reclassification.

Stakeholder perspectives of reclassification and recontact

Ten studies[9,47-55] surveyed various stakeholder groups, including genetic professionals (clinical geneticists, genetic counselors, and laboratory geneticists), patients, and other health care providers (primary care physicians, oncologists, cardiologists, and neurologists) on current practices and challenges related to variant reinterpretation, reclassification, and patient recontact. Key findings from these studies are summarized in Table 3.

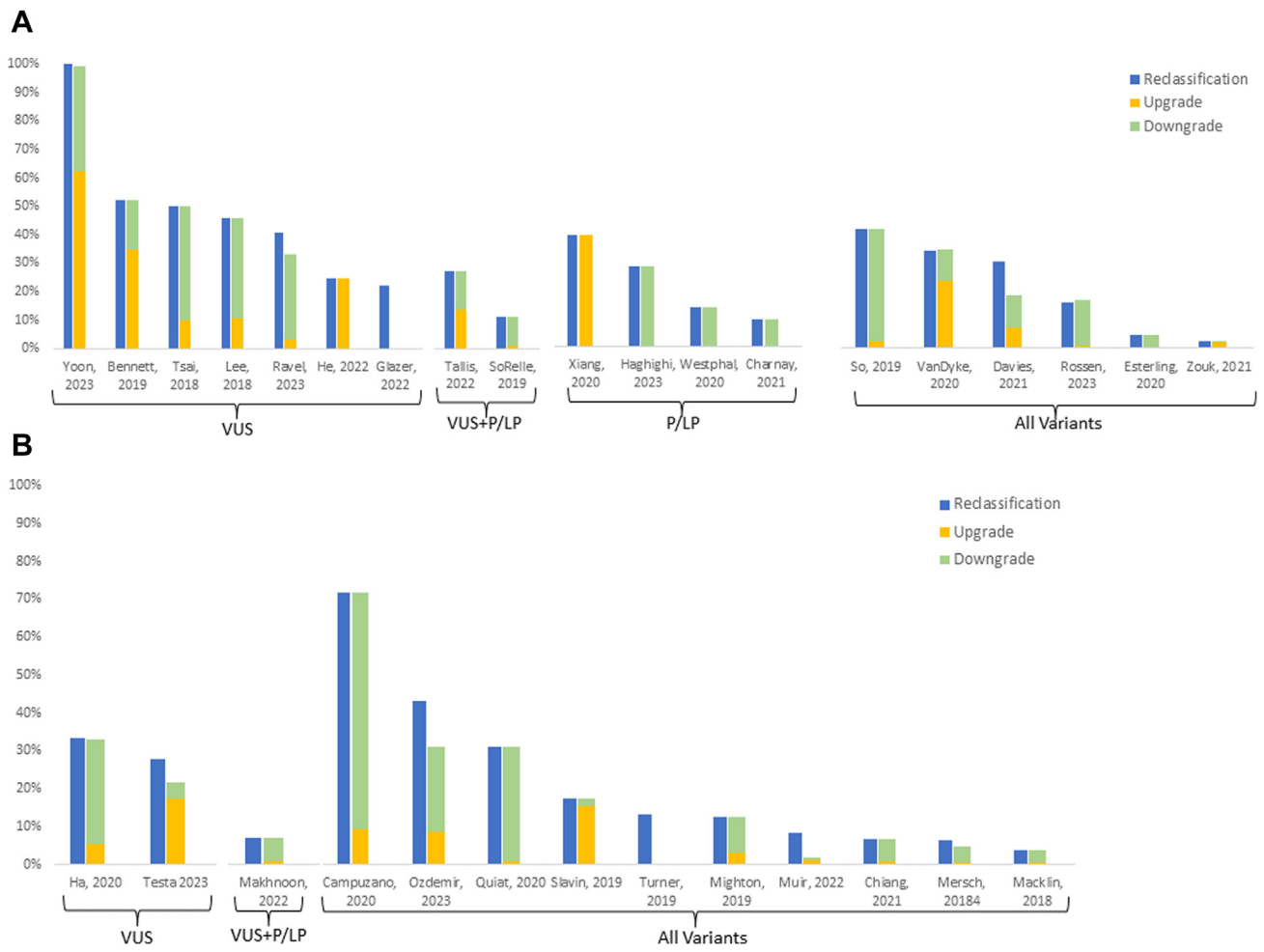

Figure 2 Outcomes of variant reclassification across studies that used (A) active and (B) passive methods of reinterpretation to reclassify variants.

Current recontact practices

Most genetic services (89%-95%)[49,51,55] reported recontacting patients with reclassified results, of which between 8% and 35% routinely engaged in patient recontact. In particular, most genetic professionals (89%-97%)[52,54] reported recontacting patients with reclassified results, as did oncologists (71%),[54] whereas to the best of our knowledge, other nongenetic health care providers were not surveyed on this topic within the selected articles. Standard operating procedures to guide patient recontact were rarely present at various practice settings (0%-37%).[49,51,53,55]

Triggers for patient recontact

Six studies evaluated the triggers for patient recontact after reclassification. Common triggers included clinical actionability, reproductive relevance of reclassified results, and any new update to genetic test results. VUS upgrades were prioritized for recontact as were other clinically significant reclassifications. The majority of laboratory genetic counselors (75%), clinical genetic counselors (68%), and geneticists (58%) supported the idea of recontact after reclassification of all variants, whereas, less than half (45%) of laboratory directors indicated the same.[47] Lack of staffing and clinical resources and lack of up-to-date patient contact information were acknowledged as factors that hinder patient recontact. In qualitative studies in which patients who received reclassified results[58,60,61] and VUS results[59] were interviewed, the overwhelming majority supported recontact for all reclassifications (89%).

Preferred recontact modalities

Genetic professionals used a wide variety of communication mediums for patient recontact (telephone, email, written communication, patient portal, etc) with telephone being the most popular method (either standalone or part of a series of recontact actions). Patients, in contrast, did not indicate preference for any singular method of communication but reported a higher preference for letters (49%) and email (42%) than phone calls (31%).[48]

Responsibility for reinterpretation and recontact

Studies on stakeholder responsibility for reinterpretation and patient recontact report fragmented opinions with no

Table 3 Thematic overview of key stakeholder opinions on recontact after reclassification

Theme	Opinions in Favor	Opinions Against
Patient recontact after reclassification	• Recontact is beneficial for patients and other family members' medical and emotional well-being. • Recontact ensures the provision of up-to-date risk management for patients as guidelines evolve. • Somewhat counterintuitively, recontact was sometimes mentioned as a way to maintain updated patient contact details.	• Recontact is unnecessary as an open-door policy for recontacting providers already exists. Patients can contact genetic services/providers for updated information as needed. • Recontact presents an additional burden to an already stretched health care system: current infrastructure and staffing would not be able to support recontact for all patients. • Recontact is not feasible because providers do not have patients' up-to-date contact details.
Obtaining patient consent for recontact	• Obtaining consent establishes patient trust in the reclassification/recontact process.	• Obtaining consent sets unrealistic patient expectations and implies that recontact will happen; in reality, services cannot commit to recontacting all patients. • Failure to recontact in timely manner after consent could be viewed as medical negligence.
Standardized recontact systems	• Creation of standardized recontact systems will improve quality of patient care by ensuring patients receive accurate medical management. • Such systems will increase patient access to up-to date health information to inform accurate medical decision making. • These systems will allow health care providers to perform their professional duty and recontact patients if clinically actionable results are found.	• Such systems may introduce risk of medical negligence if recontact becomes standard of care. • Such systems would place unlimited duration of responsibility to recontact patients with new information. • These systems are thought to be resource intensive. Currently, we lack clinical resources to support such systems. • The health care system should empower patients to take charge of their genetic health rather than "babysitting" them.
Patients' emotional reactions to reclassification	• Recontact after reclassification does not elicit adverse emotional response in most patients.	• Recontact after reclassification can exacerbate patient anxieties related to medical conditions.
Triggers for patient recontact	• Professional duty for patient recontact is thought to exist if clinically actionable results are found. • Recontact should occur only when reclassification is clinically significant. • Recontact should occur for all reclassified variants.	• Downgraded results would have limited clinical utility and therefore should be deprioritized for recontact.

clear consensus.[9,47,51,54] Although patients and nongenetic providers prefer that referring providers or specialists initiate the process of reinterpretation, clinical and laboratory genetic providers prefer laboratory genetic providers to do so. Patients and providers agree that health care providers, not patients, bear the responsibility for initiating reinterpretation. In contrast to other health care providers, genetic counselors assume most of the responsibility for patient recontact,[50] but it is unclear who assumes responsibility for recontact when genetic counselors are not involved in the testing process. Patients indicate that their own responsibility in the recontact process is lower than the responsibility of the health care providers.

Opinions on routine recontact

Support for a routine recontact system after reclassification among genetic professionals varied widely (20%-69.7%).[9,49,51,54] Oncologists indicated stronger support for routine recontact systems (78.6%).[54] Genetic professionals mentioned the improvement of patient well-being (medical/reproductive/emotional) as an advantage but mentioned lack of time and resources, variability in patient preferences, and liability issues as deterrents for developing routine patient recontact systems. In qualitative interviews,[57] health care and legal experts expressed varied opinions on recontact, stating that responsibility belonged to genetic counselors or laboratory geneticists but should also be shared between patients and providers.

Consent for patient recontact

Consent procedures for patient recontact varied among clinical genetic services. Genetic professionals reported lack of resources, legal liabilities, and lack of time as obstacles for obtaining consent. Genetic professionals reported that if clinically significant results were found, their service might engage in recontact despite patient preference. Both nongenetic providers and patients were ambivalent regarding the need for consent.

Discussion

This scoping review comprehensively examined the published empirical research on variant reclassification and recontact. Of the studies that reported frequencies of variant reclassification; approximately half used a purposeful, active process of reanalysis leading to reclassification, whereas the remainder reported frequencies from passive variant reclassification yielding slightly different reclassification frequencies—31% for active and 20% for passive. These studies varied widely in the variant types included for analysis, methods used to reinterpret variants, and report reclassifications, which prevents comparison across studies. In addition, studies often included only a selected subset of variants in their reclassification efforts, which further skews the reclassification rates. Some only included VUS and/or P/LP variants, whereas others focused on rare variants or all variants, and some only included a limited set of genes (for example, *BRCA1/2* versus panel). There was also significant heterogeneity in how studies reported reclassification events, with some reporting these events as a measure of variants and others as a measure of patients. In addition, there was large variation in sample sizes across studies (tens to millions); thus, the degree to which these studies truly reflect the population is variable. Still, it is worth noting that many of the active reclassification approaches reapplied the standards and guidelines for variant classification issued by the ACMG[8] to previously reported variants, thus demonstrating the number of variants that would be affected if reinterpretation and reanalysis were performed routinely.

The heterogeneity among studies notwithstanding, our findings show a stark difference in the reclassification frequencies reported from the analysis of various clinical cohorts and aggregate analysis of ClinVar data. Frequencies from ClinVar (<0.1%-6.4%) were substantially lower than both active and passive approaches used within specific clinical cohorts. One potential cause is that clinical studies often framed their reclassification rate on a per patient level; whereas, the ClinVar studies framed reclassification rate on a per variant level. Because multiple patients may have the same variant, a single variant reclassification would affect a higher proportion of people and lower proportion of variants. The breadth of the panels used in each study will similarly affect reclassification rate with larger panels including a larger number of less studied genes. ClinVar studies included larger sets of genes, and likely included less studied genes, which are also less likely to be reclassified. Furthermore, these studies were performed on cohorts created after the ACMG/AMP variant classification guidelines were issued and large genome databases were created, which are known to be influential factors for variant reclassification.

It is also possible that the data from clinical settings reflect the sociodemographic and clinical characteristics of the patient populations that they serve. For example, it may be reasonable to expect frequent VUS reclassification in clinics that serve patients from diverse racial/ethnic backgrounds or lower variant reclassification in clinics that commonly order test panels composed of well-studied genes, such as *BRCA1/2*. This review showed some emerging evidence that variant reclassification disproportionately affects racial minorities, likely because of the higher VUS prevalence secondary to fewer reference genomes. However, inconsistent reporting of racial and ethnic information in published studies prevented us from examining this more closely. It is important to note that reclassification is a function of the underrepresentation of certain genetic ancestral populations in genomic databases and not a function of self-reported race and ethnicity. These concepts were often conflated in published studies, perhaps because genetic ancestry is rarely, if ever, reported on clinical genetic tests, whereas self-reported race and ethnicity is routinely available in clinical settings and is convenient to use.

Our findings also show a continuing emphasis in the literature on the use of interview and survey data to understand stakeholder perspectives of variant reinterpretation, reclassification, and recontact. Collectively, the studies indicate that, although reclassification and recontact is considered value added by most, and recontact does occur in practice, it happens on an ad-hoc basis rather than following a systemized method of recontact. Despite consensus on the need for standardization in this space, opinions differ on how to implement standardized methods of reinterpretation, reclassification, and recontact. Deliberation[64] as a method of generating informed opinions and policy suggestions should be considered instead of more and bigger surveys or interviews within homogeneous study samples. Qualitative studies almost exclusively used one-on-one interviews to explore stakeholder perspectives without engaging with others. Participants in deliberative sessions are encouraged to discuss, learn from others, and examine and refine their own views and are particularly well suited to contentious issues such as reclassification and recontact. Stakeholder groups such as patients, patients with reclassified variants, genetics providers including genetic counselors, laboratory geneticists, and oncologists are well represented in the existing literature. In contrast, perspectives of other frequent users of genetic tests, such as obstetricians and gynecologists, have not been studied in the context of variant reclassification or recontact. Although nongenetics providers are often involved in ordering and returning results from germline genetic tests and often do so without the

involvement of genetic counselors, they remain an understudied group in this literature. The field of genetics is rife with discussions of stakeholder responsibilities and duties in variant reinterpretation, reclassification, and recontact. A number of commentaries[65,66] and opinion pieces[67,68] on the ethical, legal, and social implications of reclassification and recontact have called for the development of practice guidelines to delineate stakeholder responsibilities. New tools (variant annotation alert system and patient genetic registry) to support reclassification and recontact systems have been developed but are still in the nascent stages.[69,70] Point-to-consider statements[71] for clinical and research settings have also been published, but none offer definitive guidance on these contentious issues.

The review showed a strong focus on cancer in this literature. In contrast, relatively few articles focused on cardiology, neurology, or pediatrics. Most studies were retrospective analyses of clinical cohorts, which are subject to selection bias and uninformative censoring based on exclusion of records with incomplete data and methods used to calculate time to reclassification. The results of this scoping review are not without its limitations. Because this is a scoping review, we were unable to synthesize the findings from each study to generate weighted overall effect sizes. Instead, our goal was to synthesize the emerging body of literature on variant reclassification and recontact.

In conclusion, this scoping review highlights areas of strength in recent literature on variant reclassification and recontact. In particular, much is known about the individual stakeholder perspectives and opinions on variant reclassification and recontact, as well as reclassification frequencies from various clinical cohorts. Research gaps were also identified, including the need for additional studies on nongenetics health care providers and how they manage recontact after reclassification, deliberative processes to reaching consensus on these issues, understanding variation in reclassification by race/ethnicity, and inclusion of diverse samples with complete description of participant characteristics. Addressing these research gaps can help improve the communication of reclassified variants to patients and to overcome the challenges associated with recontacting patients as science changes.

Data Availability

Data are available upon request from the corresponding author.

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Author Contributions

Conceptualization: S.M., J.M.; Data Curation: A.T., A.G., R.S., S.M.; Formal Analysis: A.T., A.G., R.S., S.M.; Funding Acquisition: S.M.; Methodology: S.M.; Supervision: S.M.; Visualization: S.M., A.G.; Writing-original draft: A.B., J.M., S.M., A.T., A.G., R.S.; Writing-review and editing: A.B., J.M., S.M., A.T., A.G., R.S., G.G., J.A.S., J.P.

Ethics Declaration

Informed consent was not required for this study because it is a review article and does not include any individual level data.

Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

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