	Re-classification				Laboratory management			Clinical management		
	Nature of evidence	**Change in evidence score**	**Direction of re-classification**	**New classification**	**Multicentre MDT review recommended**	**Urgent national re-classification alert**	**Re-issue of laboratory report**	**Proactive re-contact[a] of historic[b] patients and their clinicians/GP**	**Management of new family members from historic families**	**Management of prospectively identified new probands**
Re-classifications that cross the actionability threshold	**New evidence is (i) substantive, non-conflicting, publicly available data or (ii) locally available data [c]**	**Any**	Upgrade	LP, P (ES: ≥ 6)	No	Yes	Yes	Yes	Standard P/LP	Standard P/LP
			Downgrade	B, LB, VUS (ES: ≤5)	Yes	Yes	Yes	Yes	Advise of down classification. As standard for VUS/LB/B: no clinical action	As standard for VUS/LB/B: no clinical action
	New evidence is publicly available data which is conflicting with prior evidence[d] **OR** **Revision to evidence strengths in variant classification framework with no new evidence**	**1-3 points**	Upgrade	Upper-end LP (ES: 8)	No	Yes	Yes	Yes	Standard LP	Standard LP
			Upgrade[e]	Low-end LP (ES: 6-7)	No	Yes	Yes "Potentially changeable classification at actionability threshold"	Yes	Cautious LP management	Cautious LP management
			Downgrade[e,f]	'Warm/Hot' VUS (ES: 4-5)	Yes	Yes	Yes "Potentially changeable classification at actionability threshold"	Immediate systematic proactive re-contact not recommended. Reactive approach only recommended for initial period[g,h]	Advise of changeable down classification. Supply of information as standard for VUS.	As standard for VUS: no clinical action
			Downgrade	'Tepid' VUS (ES: 3)	Yes	Yes	Yes	Yes	Advise of down classification. As standard for VUS: no clinical action	As standard for VUS: no clinical action
		4 or more points	Upgrade	Upper-end LP, P (ES: ≥ 8)	No	Yes	Yes	Yes	Standard P/LP	Standard P/LP
			Upgrade	Low-end LP (ES: 6-7)	No	Yes	Yes	Yes	Cautious LP management	Cautious LP management
			Downgrade	'Warm/Hot' VUS (ES: 4-5)	Yes	Yes	Yes	Yes	Advise of down classification. As standard for VUS: no clinical action	As standard for VUS: no clinical action
			Downgrade	B, LB, 'Ice Cold/Cold/ Cool/Tepid' VUS (ES: ≤3)	Yes	Yes	Yes	Yes	Advise of down classification. As standard for VUS/LB/B: no clinical action	As standard for VUS/LB/B: no clinical action
Re-classifications that DO NOT cross the actionability threshold	**Any**	**Any**	Upgrade from: B, LB, 'Ice Cold/Cold/Cool /Tepid' VUS (ES: ≤3)	to: 'Warm/Hot' VUS (ES: 4-5)	No	No	No	No	As standard for VUS: no clinical action	As standard for VUS: no clinical action
			Downgrade from: 'Warm/Hot' VUS (ES: 4-5)	to: B, LB, 'Ice Cold/Cold/ Cool/Tepid' VUS (ES: ≤3)	No	No	Only if a 'Warm/Hot' VUS report has previously been issued.	No. Exception: communication to patients of down-classification can be considered where patients are known to have previously been informed of the VUS (written communication likely sufficient.)	Advise of down classification. As standard for VUS/LB/B: no clinical action	As standard for VUS/LB/B: no clinical action

Scenarios are separated into reclassifications that cross the actionability threshold and those that do not. Reclassification scenarios that cross the actionability threshold are further separated by nature of evidence that led to reclassification and size of change in evidence score.

B, benign; *ES*, evidence score; *GP*, general practitioner; *LB*, likely benign; *LP*, likely pathogenic; *MDT*, multidisciplinary team; *P*, pathogenic; *VUS*, variant of uncertain significance.

[a]Definition of proactive recontact requires further specification; suggestion: letter explaining situation, proactive scheduling of appointment slot with 1 more attempt to recontact if original appointment not attended.
[b]Historic patients: all current and former patients who have been identified to have the reclassified variant, including former patients, seen in the past, discharged from care, and no longer in an ongoing relationship with the specific health care professional involved.
[c]Substantive new publicly available evidence (eg, functional assay, multifactorial analysis) or locally available evidence (eg, segregation data, RNA analysis) in the absence of previous evidence of that type.
[d]New publicly available evidence conflicting with previous data of the same type (eg, new functional assay conflicting with previous functional assay, new multifactorial analysis conflicting with previous multifactorial analysis); new evidence is of equivalent validity, thus nullifying existing data for that evidence class.
[e]Rows showing reclassification scenarios that produce "potentially changeable classifications at the actionability threshold" which are reclassifications resulting from conflicting evidence or from revision to evidence strengths in the variant classification framework and when the change in evidence score is ≤3 and the new classification is close to the actionability threshold (ES: 4-7).
[f]When sufficient national infrastructure exists, these down-classified variants to remain under active national review.
[g]A reactive approach in this context refers to advising historic patients of down-classification only when they come forward for new intervention.
[h]When national infrastructure exists for active variant monitoring and review, in the absence of further fluctuation in variant class, systematic recontact of historic patients may be considered after a period of ≥1 years.

Version History/Amendments

Revised version	Date	Section	Update	Amended by	Approved by
v1.0	02/09/2022	--	Initial version (as published in Genetics in Medicine)	--	--