|  |  |  |  |
| --- | --- | --- | --- |
|   | **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-contact3 of historic4 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, publically available data or (ii) locally available data 1** | **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 evidence2ORRevision 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** | Low-end LP (ES: 6-7) | No | Yes | Yes "Potentially changeable classification at actionability threshold" | Yes | Cautious LP management | Cautious LP management |
| **Downgrade5** | ‘Hot’ VUS (ES: 4-5) | Yes | Yes | Yes "Potentially changeable classification at actionability threshold" | Immediate systematic re-contact not recommended. Initial reactive approach recommended ie only historic patients coming forward for new intervention should be advised of changeable down classification (and then managed as per VUS status)6 | Advise of changeable down classification. Supply of standard information appropriate to 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** | ‘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, ‘Cold’-‘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, ‘Cold’-‘Tepid’ VUS (ES: ≤3) | to: ‘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: ‘Hot’ VUS (ES: 4-5) | to: B, LB, ‘Cold’-‘Tepid' VUS (ES: ≤3 ) | No | No | Only if a '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 |