UKCGG-National Cancer Genetics MDT meeting February 11th 2021
Clinical considerations of variant classification and reclassification

Exponent Scoring for variant classification – Alice Garrett

Alice presented an overview of the exponent scoring system for variant classification. The slides from the presentation can be found on the CGCV website https://www.cangene-canvaruk.org/uk-clinical-mdt. Alice explained how a variant is classified according to the number of "evidence points" and how this is linked to the probability of pathogenicity, as well as demonstrating combinations of evidence items that are incompatible.

The talk highlighted the continuous scale of variant classification and the possibility of variants shifting back and forth between "uncertain significance" and "likely pathogenic" as new evidence becomes available.

Ellard et al. ACGS Best Practice Guidelines for Variant Classification in Rare Disease 2020

-BRCA variant reclassification case studies -Miranda Durkie

Miranda highlighted some real-world cases, where variants have shifted from benign to pathogenic, pathogenic to benign and likely pathogenic to VUS based on new pieces of evidence and/or changes in variant classification guidelines. The slides from the presentation can be found on the CGCV website https://www.cangene-canvaruk.org/uk-clinical-mdt.

Miranda demonstrated some new suggested template reports which include clear details of the "exponent score/evidence points" used in variant classification, so that clinicians are aware of both the probability of pathogenicity and the evidence used in classification. There was unanimous support from the attendees regarding use of these templates.

Variant details

Gene	Zygosity	HGVS description	Location: GRCh37 (hg37)	*Classification
BRCA1	Heterozygous	NM_007294.3(BRCA1):c.xxxT>G	Chr17(GRCh37):g.xxxxxxA>C	Variant of uncertain significance

Gene-Disease Association	Hereditary cancer susceptibility OMIM 604370 and 614320	
Inheritance	Autosomal Dominant	

Evidence for variant classification using ACMG/AMP guidelines*:		Exponent (Bayesian) score[4]
PM2_mod	Not on gnomad <weblink>	2
PS4_mod	XXX et al 2003 (PMID:XXX); XXX et al 2016 (PMID:xxx)	2
PP3_sup	Revel score 0.808	1
		Total: 5

*Variant classification according to the American College of Medical Genetics and Genomics (ACMG)[1] and Association for Clinical Genomic Science (ACGS) 2020 guidelines[2] and Cancer Variant Interpretation Group-UK consensus specification for Cancer Susceptibility Genes[3] (https://www.cangene-canvaruk.org/canvig-uk)
[1]Richards *et al.* (2015) Genetics in Medicine 17:405-24. (PMID: 25741868)
[2] www.acgs.uk.com/quality/best-practice-guidelines
[3] Garrett et al (2020) J Med Genet (PMID: 32170000)
[4] Exponent (Bayesian) score ranges: VUS: 0-5 (10-90% posterior probability pathogenicity); Likely pathogenic: 6-9 (90-99% posterior probability); Pathogenic: >10 (>99% posterior probability). Points awarded per evidence weighting: sup = 1, mod = 2, str = 4, VStr = 8 (Tavtigian et al 2020 PMID: 32720330; Garrett et al 2020 PMID: 33208383; ACGS 2020 variant guidelines)

-Clinical considerations and consensus on management -Helen Hanson

Helen presented results of a pre-meeting survey. Results from the survey suggest that at present less than half of responders (12/27, 44%) would currently routinely discuss the probability of variant pathogenicity (i.e., how statistically likely that the variant is disease causing) with patients in situations where a variant of uncertain significance, likely pathogenic or pathogenic variant is identified.

Survey results demonstrated strong agreement that for patients with pathogenic variants, responders would offer predictive testing and standard gene specific management including risk reducing surgery and surveillance. Whereas for likely pathogenic variants, a small number of responders (4%, n=1) suggested they would be more cautious about offering risk reducing surgery.

For patients with a variant of uncertain significance (exponent score 5, hot class 3), there was a greater variance in answers. In general responders suggested that management of these patients would be based on family history (22/28, 79%) and likely discussed in an MDT setting. There was agreement from all responders (n=28) that predictive testing should not be offered in these situations.

The meeting then went on to consider the different scenarios where a variant is reclassified.

Scenario 1a. Benign/VUS to pathogenic

In the pre-meeting survey, there was broad agreement that patients should be recontacted and offered an appointment regardless of whether there would be an impact to their immediate or long-term clinical management (28/29, 97%) and that predictive testing and gene carrier specific management should now be discussed and offered, where applicable (28/28, 100%).

Scenario 1b. Benign/VUS to likely pathogenic

In this situation there was more caution about recontacting patients and offering an appointment (25/28, 89% who agreed or strongly agreed to recontact). Clinicians also commented that it was important to request details of the reasons for reclassification and counsel carefully. Although there was clear agreement about offering predictive testing and gene specific surveillance (28/28 respondents), there was more caution about risk reducing surgery, with 10% respondents (3/28) being uncertain as to whether they would offer this.

An in-meeting poll showed that for scenarios 1a and 1b (reclassification from benign to likely pathogenic/pathogenic), there was agreement that;

- *Variant reclassification should be communicated through CAN-VIG.*
  (Yes 52 (95%), No 0 (0%), Not sure 3 (5%))

- *All patients should be contacted to inform them of reclassification.*

  (Yes 46 (84%), No 2 (4%), Not sure 7 (13%))

- *Discussion with patient should include communication about the probability that the variant is pathogenic.*

  (Yes 52 (95%)**,** No 0 (0%)**,** Not sure 3 (5%))

Scenario 2. Pathogenic/Likely pathogenic to cold vus/ benign

In the premeeting survey, there was general agreement that patients should be recontacted and offered an appointment (26/28, 93%) and that no further predictive testing should be offered in the family (28/28, 100%). Most respondents (26/28, 93%) agreed that breast surveillance /risk reducing surgery should now be offered in line with family history.

It was raised that it is important to request details about the rationale for re-classification and likelihood of future changes/strength of evidence and to consider if more extensive panel testing should be performed to exclude another gene responsible for the phenotype in the family.

An in-meeting poll showed that for reclassification from pathogenic/likely pathogenic to cold vus/benign there was agreement that;
- *Variant reclassification should be communicated through CAN-VIG.*
  (Yes 54 (96%), No 1 (2%), Not sure 1 (2%))

- *All patients should be contacted to inform them of reclassification.*
(Yes 53 (95%), No 0 (0%), Not sure 3 (5%))

- *Discussion with patient should include communication about the probability that the variant could still be pathogenic*
(Yes 51 (91%)**,** No 0 (0%)**,** Not sure 5 (9%))

Scenario 3. Pathogenic/likely pathogenic to hot VUS

In the premeeting survey, there was general agreement that patients should be recontacted and offered an appointment, but more caution compared to the previous scenario (23/28, 83%), considering that the evidence could again shift to push back to pathogenic/likely pathogenic.
There was broad but less unanimous agreement that no further predictive testing should be offered in the family (25/26, 96%) and that breast surveillance /risk reducing surgery should now be offered in line with family history, rather than gene specific management (23/27, 85%), compared to the previous scenario.

An in-meeting poll showed that for reclassification from pathogenic/likely pathogenic to a hot vus there was agreement that

- *Variant reclassification should be communicated through CAN-VIG*
(Yes 39 (91%), No 1 (2%), Not sure 3 (7%))

- *There was <u>uncertainty</u> that all patients should be contacted to inform them of reclassification.*

(Yes 23 (53%), No 3 (7%), Not sure 17 (40%))

- *Discussion with patient should include communication about the probability that the variant could still be pathogenic.*

(Yes 40 (93%)**,** No 0 (0%)**,** Not sure 3 (7%))

- *There was some <u>uncertainty</u> about whether management of any family members should now be assessed on the basis of their personal and family history.*

(Yes 26 (60%), No 1 (2%), Not sure 16 (37%))

The in-meeting poll highlighted that this is the most difficult scenario. For variants that are 5/6/7 points and sitting on a borderline of uncertain significance and likely pathogenicity, the classification may more readily change based on publication of new functional data or new evidence as highlighted in the earlier presentations by Alice and Miranda. The in-meeting discussion emphasised how we may need to change our discussion of test results with patients and place more emphasis on the fact that any result is based on current evidence and the possibility of a change in future if further evidence becomes available. It was highlighted that it is helpful to have a summary of evidence and scoring on the genetic test reports, so we can be clearer about the level of uncertainty with patients.

Following the discussion, the appetite for UK CGG guidelines was raised in an in-meeting poll. 95% of attendees indicated they would like national guidance in this area, with

36/40 (90%) guidelines on disseminating information about variant reclassification

28/40 (70 %) guidelines on an approach to recontacting families

33/40 (83%) guidelines on an approach to review of historic variants

24/40 (60%) suggested standard letter/paragraphs

31/40 (78%) suggested standard terminology

Overall Summary

The meeting highlighted a number of themes and areas for further work.

There was agreement that;
- There is a clinical responsibility to inform a patient if a variant reclassified (in either direction).
- Variant reclassification should be based on robust new evidence.
- There should be central communication of any variant reclassification.
- The results discussion needs to evolve to place more emphasis on the fact that any result is based on current evidence and the possibility and probability that this could change in the future if further evidence becomes available.
- The use of "exponent scores" or "evidence points" will be helpful in communicating levels of uncertainty to patients.

Further work

CanGene-CanVar and UKCGG will work together to produce guidance on
1. Communication of variant reclassification nationally
2. Guidelines on recontacting families
3. Key messages for post-test counselling /results