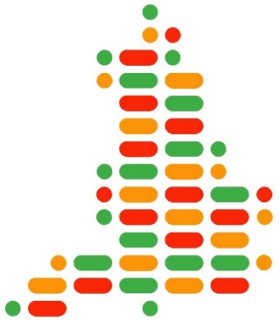
A Reviewers' Guide To PanelApp



PanelApp Release 2.3.0

Reviewers' Guide V1.

Created: 11.12.18, Last Updated: 17.12.18

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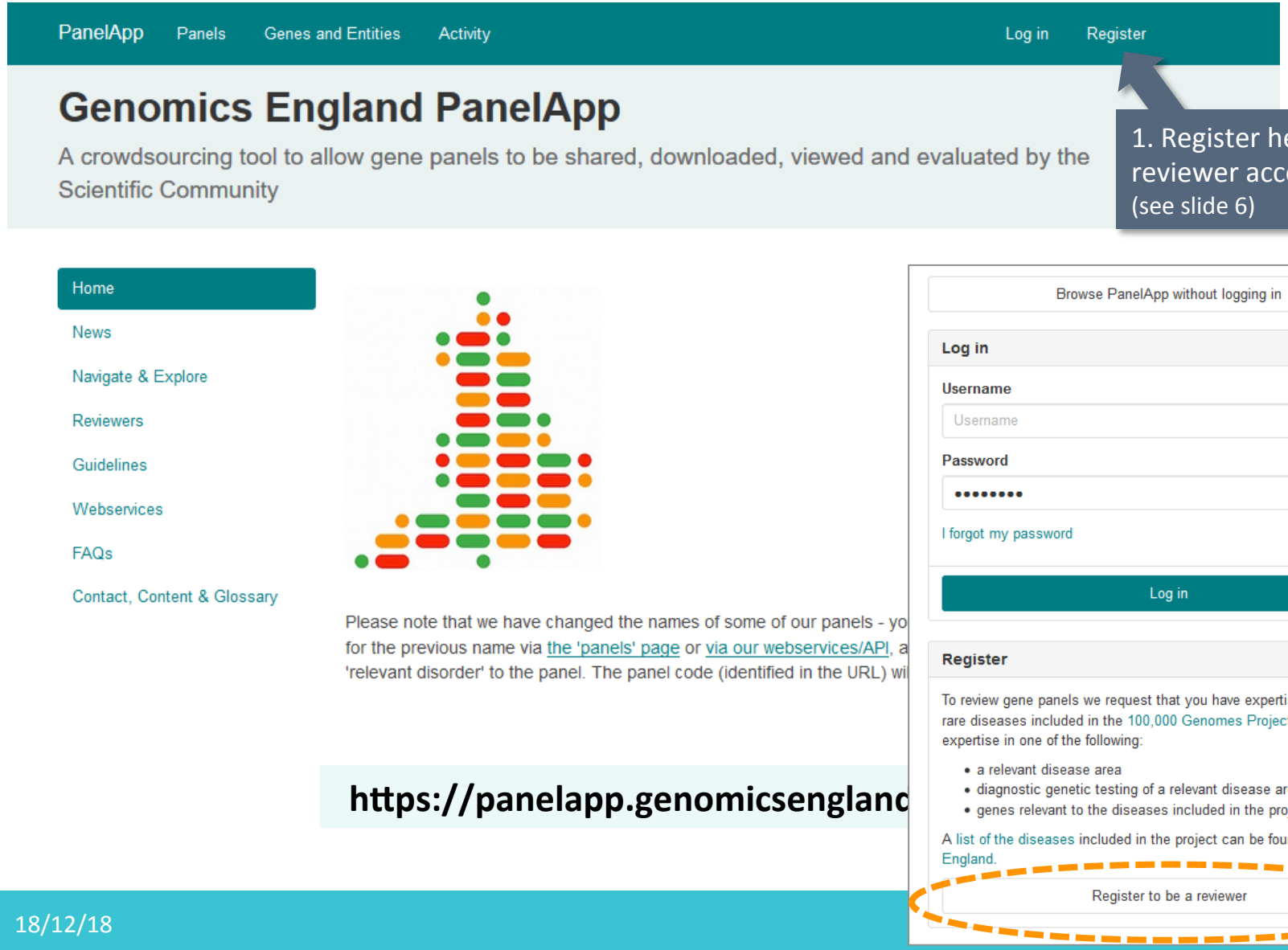
Reviewing Panels in PanelApp

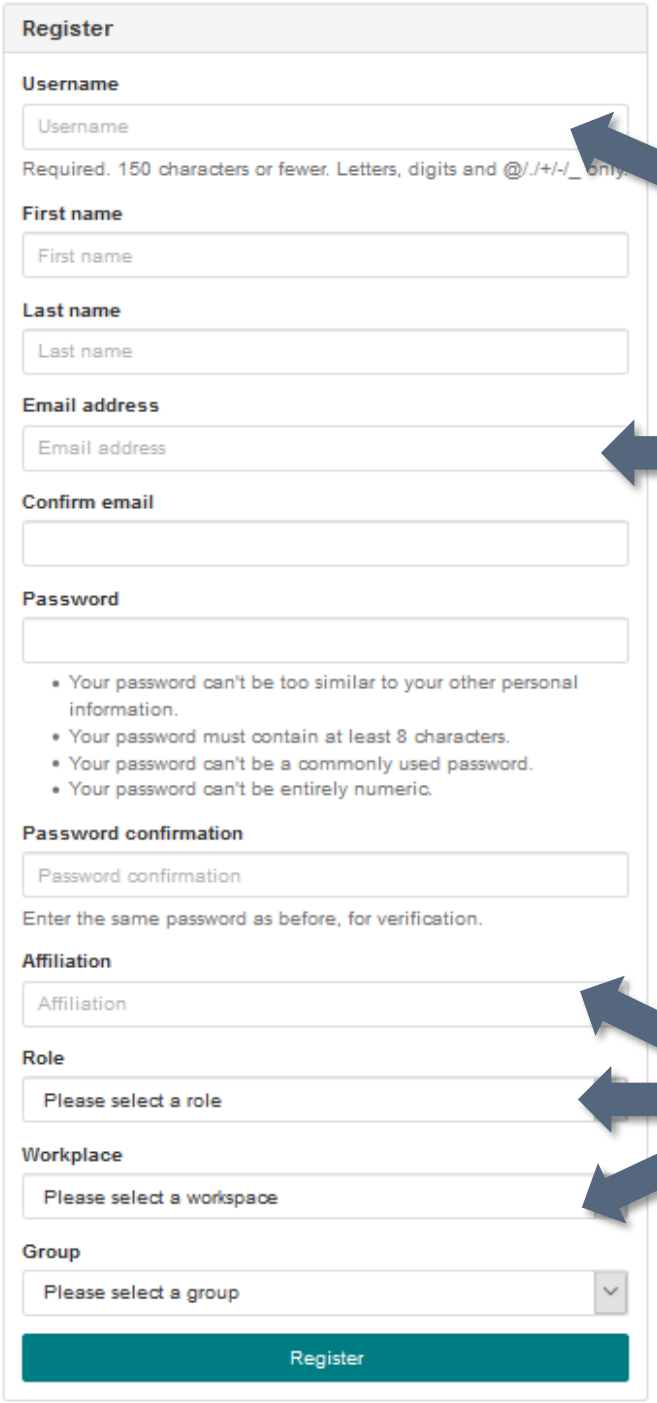
- Expert review of the gene panels is sought to enable a community consensus to be reached on which genes and genomic entities should appear on a diagnostic-grade panel for each disorder.
- We request that reviewers have expertise in a disease area relevant to the panel they are reviewing.
- Reviewers can be based anywhere in the world, and can have an academic, clinical or commercial background.
- This guide highlights the key **Review** functions of PanelApp, in a series of how-to steps. The guide can be used alongside the current PanelApp handbook, which details how to browse PanelApp and leave reviews.
- The accompanying handbook is linked from the Genomics England PanelApp page: **https://panelapp.genomicsengland.co.uk/**

Guide Contents

Creating a PanelApp Reviewer Account, and Logging in

Use the top **PanelApp Toolbar** to Register as a Reviewer:





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- Your Username and password are <u>not visible</u> to the public or other users.
- Please choose a username without spaces, and do not use your email as your username.

- Please use your institutional/work/NHS email address to register.

Fill in your details on the Registration form, and click '**Register**'.

- After registering, you will be sent an email requiring you to verify your email address by visiting a link provided in the email; note that the link expires in 3 days.
- Please click on this link to enable your registration to be processed.
- Your application will be reviewed by a Genomics England curator within 48 hours. If accepted, you will be sent a confirmation email and then you can log in to PanelApp to provide reviews on panels.
- While your application is being processed, you can still browse PanelApp as a public user.

- Your Affiliation, Role and Workplace are collected to help verify your Reviewer account.
- Your Workplace and Group will be displayed on PanelApp.

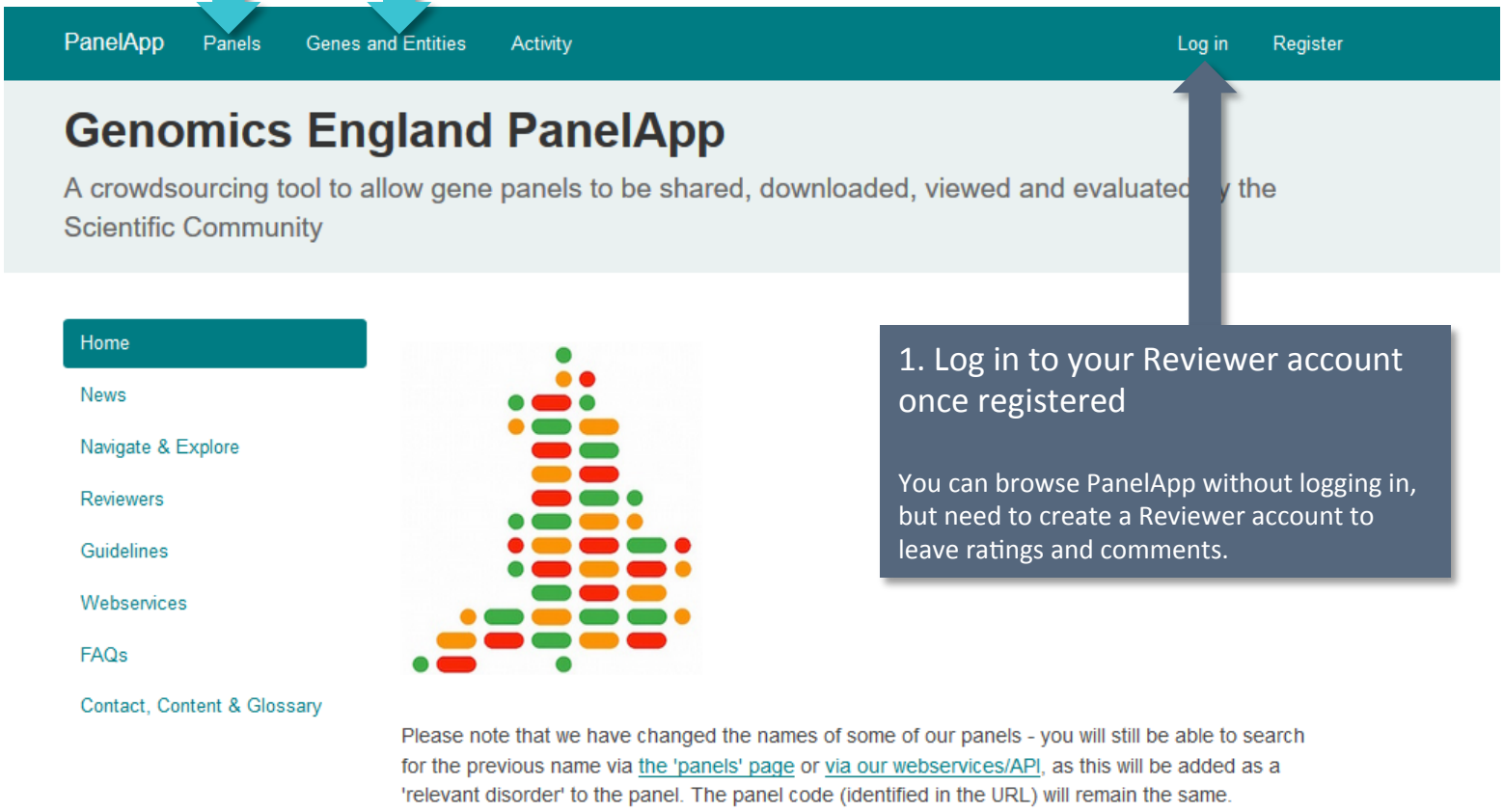
Note: Once registered, if you forget your password, you can reset your account by selecting **I forgot my password** on the PanelApp login page (https://panelapp.genomicsengland.co.uk/accounts/login/) then enter the same email you registered with, and select **Request new password**.

Finding your panel or gene of interest in PanelApp

Use the top **PanelApp Toolbar** to log in to your reviewer account, and search for your panel or gene of interest:

2. To leave a review on a gene, STR or CNV, search PanelApp for a panel or genomic entity (Gene, STR or CNV).

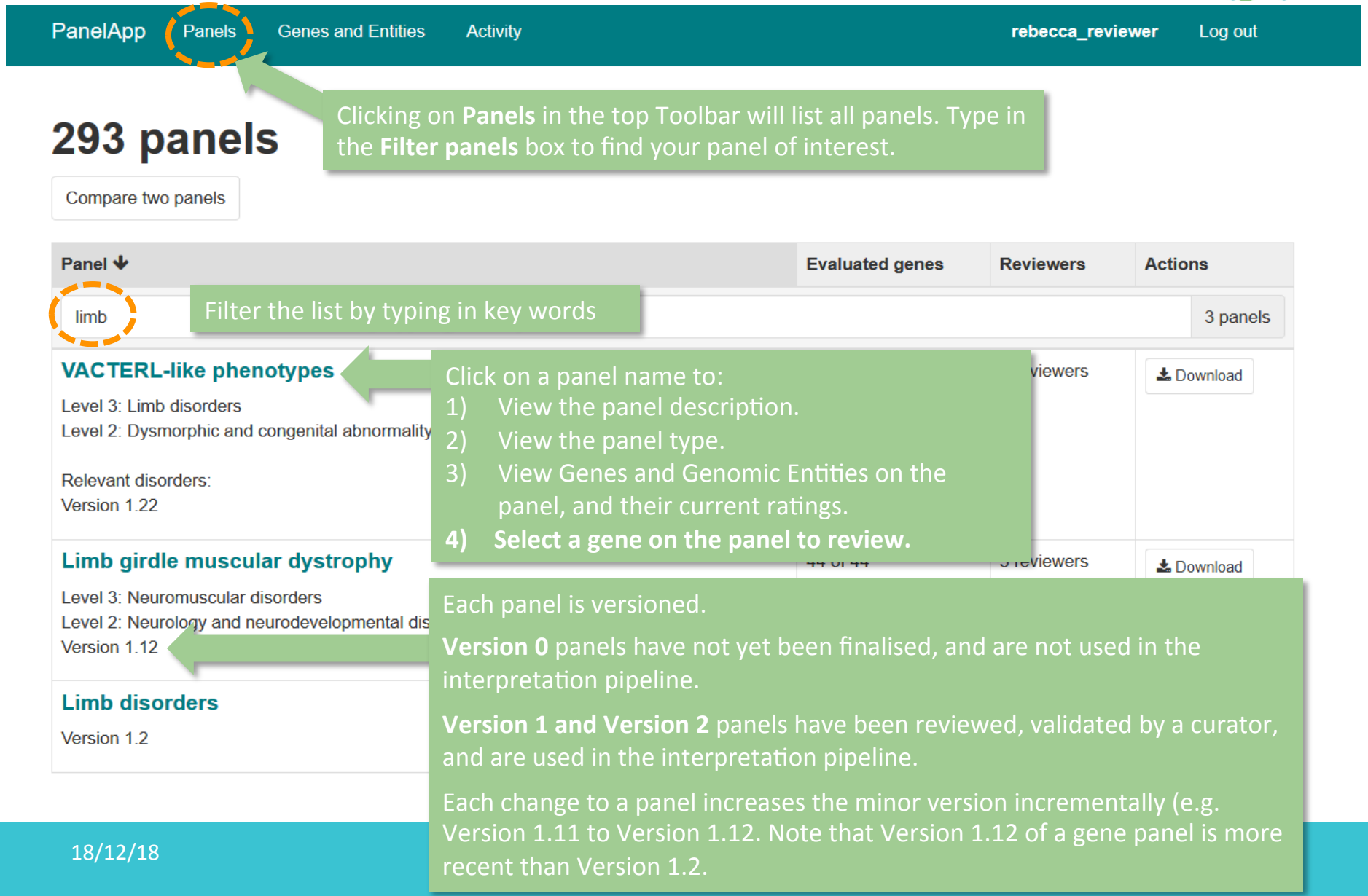
Refer to the PanelApp handbook for more details on searching.



1. Log in to your Reviewer account once registered

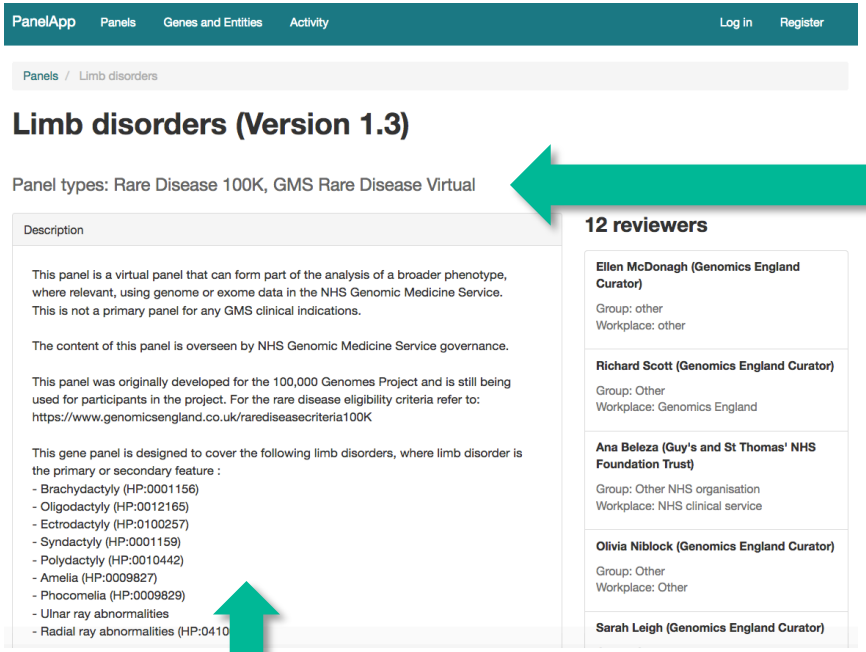
You can browse PanelApp without logging in, but need to create a Reviewer account to leave ratings and comments.

Finding a panel to review:



An overview of information captured on a PanelApp panel

Panel View in PanelApp:

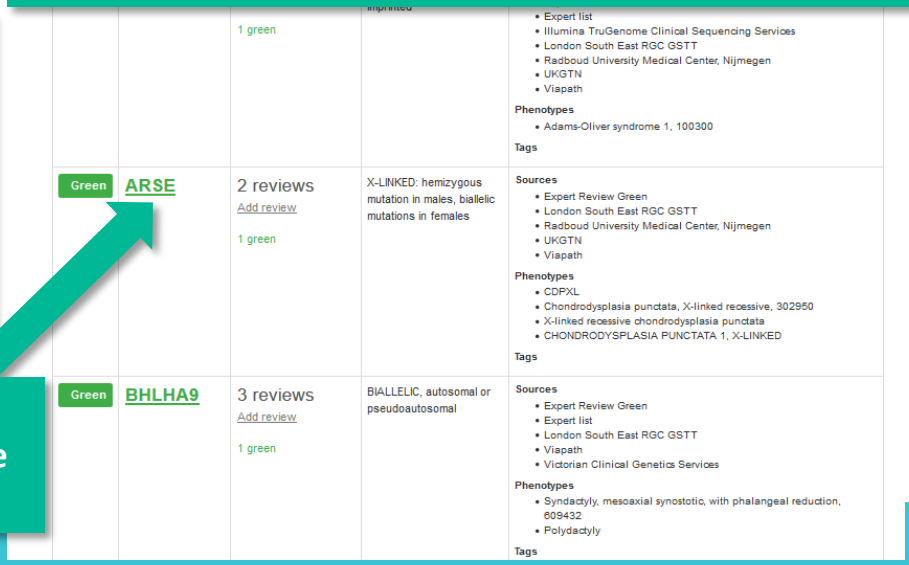


Panel types denote the project(s) the panel is used for, and include:

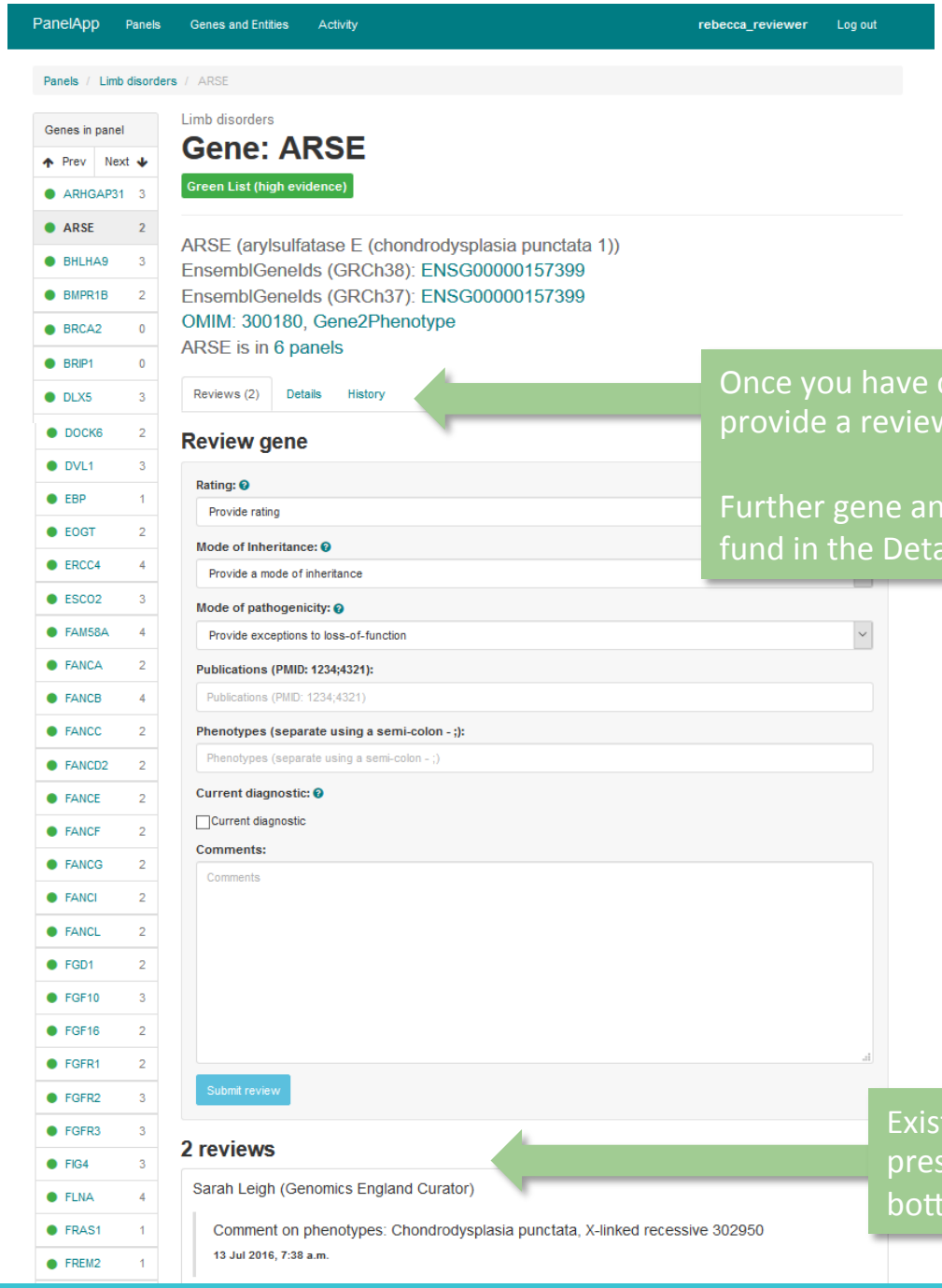
- **Rare Disease 100K:** a panel used for the interpretation pipeline for rare disease genomes from the 100,000 Genomes Project
- **Cancer Germline 100K:** a panel used for the interpretation pipeline for cancer germline genomes from the 100,000 Genomes Project
- **GMS Rare Disease**: a panel developed for the NHS Genomic Medicine Service - may be delivered by WES, large or small 'wet lab' panel or as a virtual panel
- **GMS Rare Disease Virtual:** a panel developed for the NHS Genomic Medicine Service – will be used as a virtual panel for whole genome sequencing indications

Please read the panel Description box before leaving a review. The Description box contains key information which can include:

- Clinical indication
- Governance
- Details on how the panel was created
- Technical considerations



Click on a gene symbol to see further gene details, and **provide a review.**



Once you have clicked on a gene symbol, you can provide a review using the **Reviews** tab.

Further gene and curation information can be fund in the Details and History tabs, respectively.

Existing reviews for the gene (where present) can be viewed at the bottom of the Reviews tab.

Understanding Gene Ratings in PanelApp

Understanding PanelApp Gene Ratings:

STOP: not enough evidence for this gene-disease; this gene should not be used for genome interpretation.

PAUSE: moderate evidence for this gene-disease association, and should not yet be used for genome interpretation.

GO: high level of evidence for this gene-disease association, demonstrates confidence that this gene should be used for genome interpretation.

- Reviewers are asked to rate genes according to this traffic light system.
- Green genes on Version 1+ panels will reflect this evidence system and can be used for genome interpretation.

We classify genes on a panel according to a traffic light system. Genes are rated in terms of the level of evidence to support their association with the phenotypes covered by the gene panel in question.

For rare disease, the criteria for assessing the evidence were developed from a combination of the ClinGen DEFINITIVE and DDG2P CONFIRMED gene evidence levels (set out in full on the next slide). In summary:

- A diagnostic-grade (Green) rating on a Version 1+ panel requires evidence from 3 or more unrelated families OR from 2-3 unrelated families where there is strong additional functional data.
- Genes that do not meet these criteria are rated as Amber (borderline) or Red (low level of evidence), and are not used for genome interpretation/diagnostic testing.

PanelApp Criteria for Diagnostic Grade 'Green' Genes for Rare Diseases:

A. There are plausible disease-causing variants[1] within, affecting or encompassing an interpretable functional region of this gene[2] identified in multiple (3 or more) unrelated cases/families with the phenotype[3].

OR

B. There are plausible disease-causing variants[1] within, affecting or encompassing cis-regulatory elements convincingly affecting the expression of a single gene identified in multiple (3 or more) unrelated cases/families with the phenotype[3].

OR

C. As definitions A or B but in 2 or 3 unrelated cases/families with the phenotype, with the addition of convincing bioinformatic or functional evidence of causation e.g. known inborn error of metabolism with mutation in orthologous gene which is known to have the relevant deficient enzymatic activity in other species; existence of an animal model which recapitulates the human phenotype.

AND

D. Evidence indicates that disease-causing variants follow a Mendelian pattern of causation appropriate for reporting in a diagnostic setting[4].

AND

E. No convincing evidence exists or has emerged that contradicts the role of the gene in the specified phenotype.

[1]Plausible disease-causing variants: Recurrent de novo variants convincingly affecting gene function. Rare, fully-penetrant variants - relevant genotype never, or very rarely, seen in controls.

[2]Interpretable functional region: ORF in protein coding genes miRNA stem or loop.

[3]Phenotype: the rare disease category, as described in the eligibility statement.

[4]Intermediate penetrance genes should not be included.

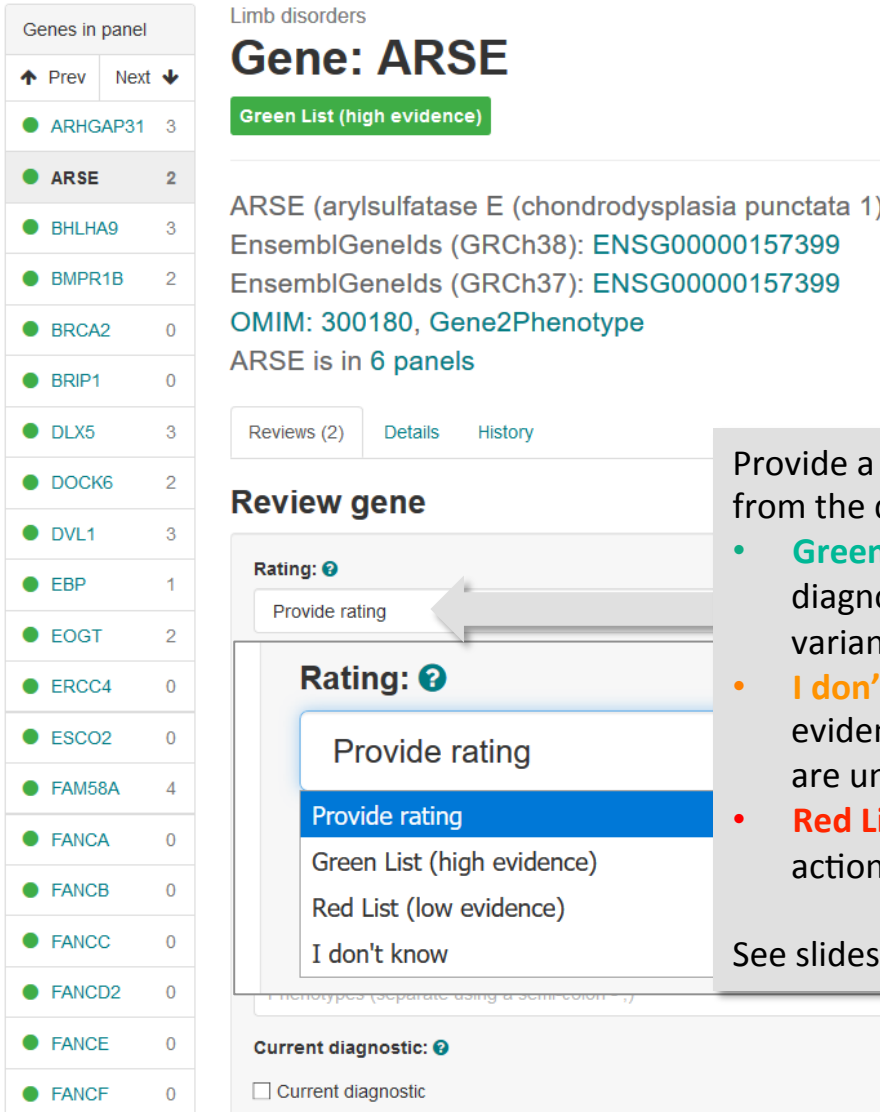
Adapted from references: PMID:28552198 and PMID: 25529582

Leaving a Review in PanelApp

When reviewing a gene or genomic entity, please **rate** whether there is sufficient evidence for the gene or genomic entity to be on a diagnostic panel.

You can also **add the following fields** when reviewing, although they are not compulsory, they are useful when a curator is collating the reviews.

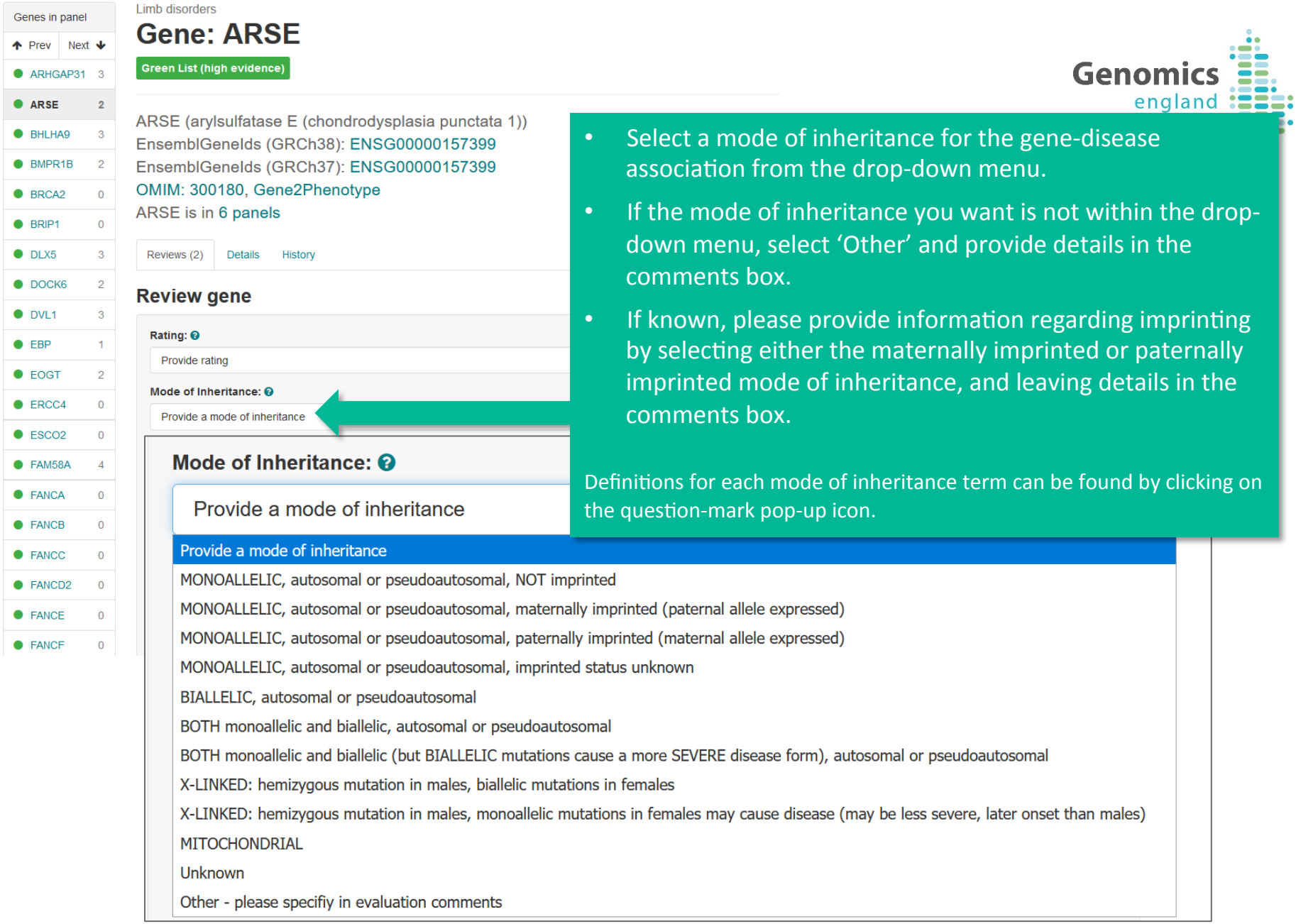
- Mode of inheritance
- Mode of pathogenicity
- Publications
- Phenotypes
- Free-text comments



Provide a rating for a gene or genomic entity by selecting an option from the drop-down menu:

- **Green List (high evidence):** clinically-actionable or diagnostically-reportable pathogenic or likely pathogenic variants.
- **I don't know**: moderate evidence if there is some supportive evidence, but not sufficient for a Green/diagnostic rating, or you are uncertain of the evidence level.
- **Red List (low evidence)**: variants that are not clinically actionable.

See slides 14-16 for guidelines on PanelApp gene ratings.



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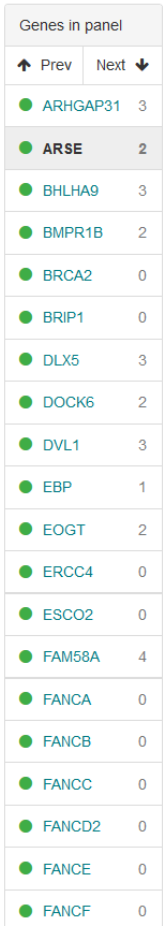
- Select a mode of inheritance for the gene-disease association from the drop-down menu.
- If the mode of inheritance you want is not within the drop-down menu, select ‘Other’ and provide details in the comments box.
- If known, please provide information regarding imprinting by selecting either the maternally imprinted or paternally imprinted mode of inheritance, and leaving details in the comments box.

Definitions for each mode of inheritance term can be found by clicking on the question-mark pop-up icon.



Limb disorders

Gene: ARSE

Green List (high evidence)

ARSE (arylsulfatase E (chondrodysplasia punctata 1))
EnsemblGeneIds (GRCh38): ENSG00000157399
EnsemblGeneIds (GRCh37): ENSG00000157399
OMIM: 300180, Gene2Phenotype
ARSE is in 6 panels

Reviews (2) Details History

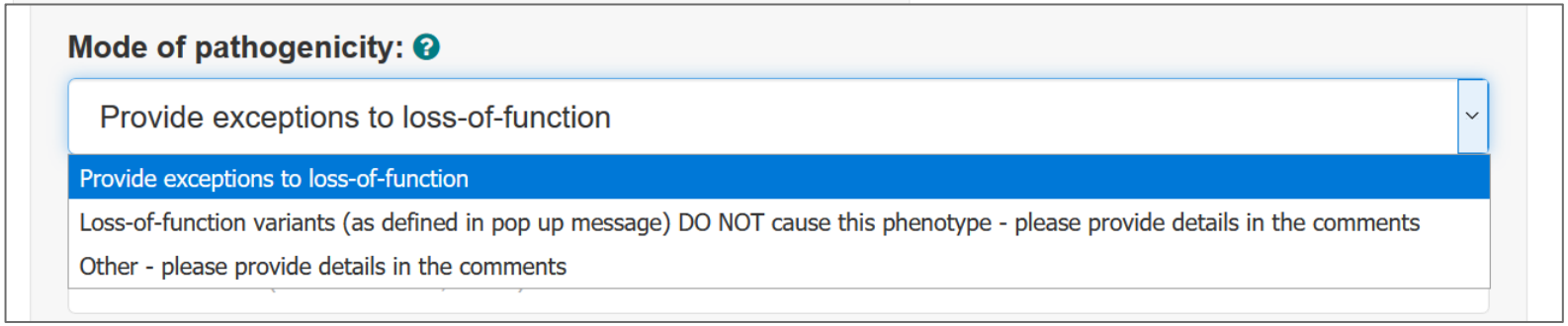
Review gene

Rating:
Provide rating

Mode of Inheritance:
Provide a mode of inheritance

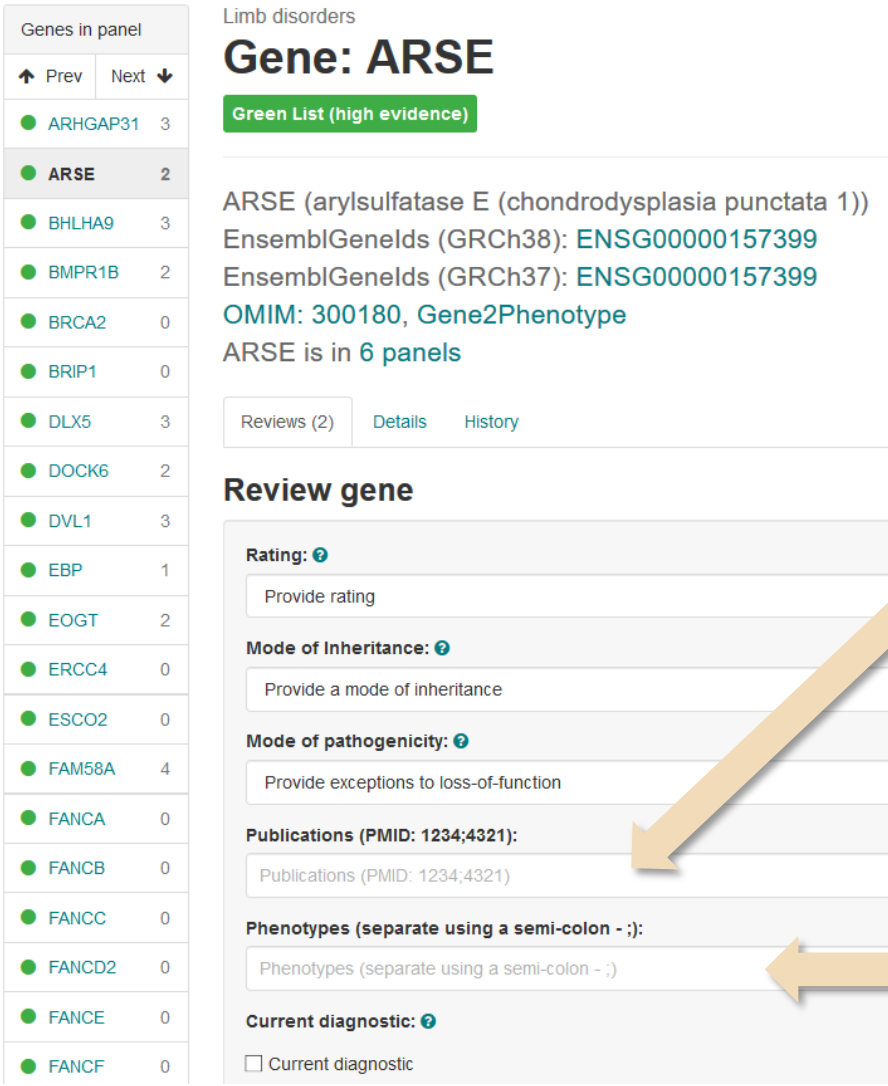
Mode of pathogenicity:
Provide exceptions to loss-of-function

- If loss-of-function variants <u>do not</u> cause the disease phenotype, please select an option in the mode of pathogenicity dropdown menu.
- If providing exceptions to loss-of-function, please leave a free-text comment to explain your selection (e.g. detailing literature or clinical evidence).



In PanelApp, we classify loss-of-function (high impact) variants as those with the sequence ontology (SO) terms:

- transcript_ablation
- splice_acceptor_variant
- splice_donor_variant
- stop_gained
- frameshfit_variant
- stop_lost
- Initiator_codon_variant



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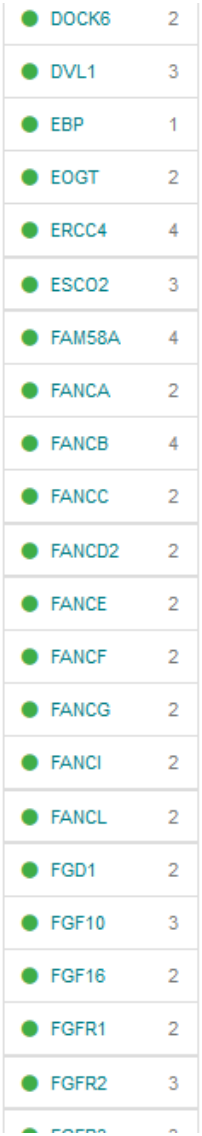
Add any relevant publications.

- Please provide PubMed IDs separated by a semi-colon: E.g. PMID:123456;9876545
- Include publications that provide supporting evidence for your given rating, or publications refuting the gene-disorder association.
- Where the paper doesn't have a PubMed identifier, add in the publication as free text, and these will be subsequently updated by a curator.

Add in phenotypes.

- Separate phenotypes with a semi colon.
- Include relevant identifiers where possible (e.g. OMIM disease IDs and HPO terms). You can also use free text.

E.g. Alport syndrome, 301050; Hearing Loss



Review gene

Rating:

Provide rating

Mode of Inheritance:

Provide a mode of inheritance

Mode of pathogenicity:

Provide exceptions to loss-of-function

Publications (PMID: 1234;4321):

Publications (PMID: 1234;4321)

Phenotypes (separate using a semi-colon - ;):

Phenotypes (separate using a semi-colon - ;)

Current diagnostic:

☐ Current diagnostic

Comments:

Comments

Submit review

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If submitting the gene evaluation on behalf of a clinical laboratory, indicate whether variants in the gene are reported as part of your current diagnostic practice by checking the **Current diagnostic** box.

Provide justifications in the comments box to support your gene rating, particularly when changing the existing rating for a gene or genomic entity.

Any PID information should <u>not</u> be added as the comments will be publically visible.

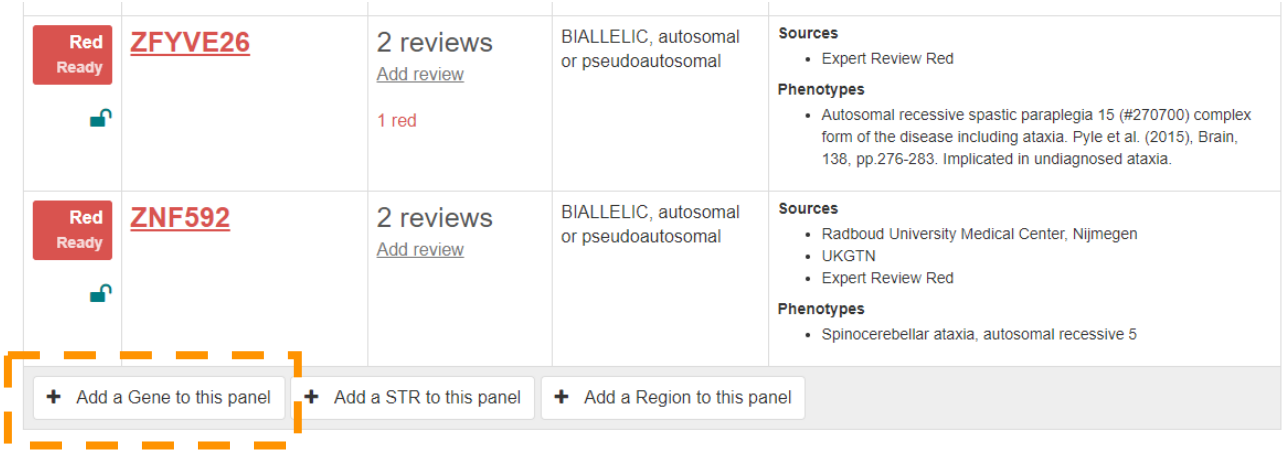
Click **Submit review** when finished.

- To submit a gene list, if you have a large set of genes to review or would prefer to complete your reviews off-line, please contact panelapp@genomicsengland.co.uk and we can provide you with an Excel file to input your reviews.

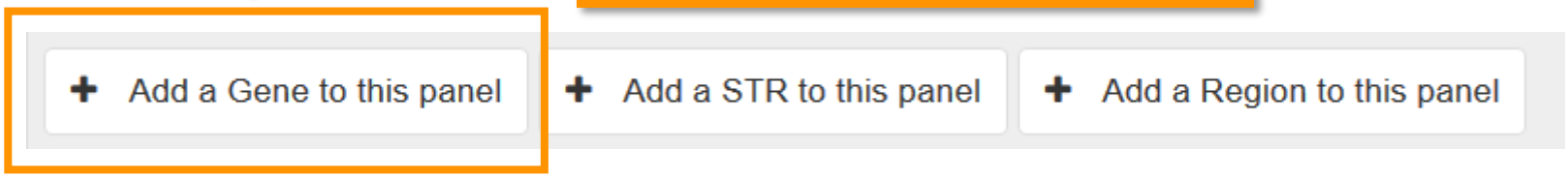
- We also welcome reviews for Short Tandem Repeats (STRs) and Copy Number Variants (CNVs). Please refer to the PanelApp handbook for details on reviewing these genomic entities. The accompanying handbook is linked from the Genomics England PanelApp page: https://panelapp.genomicsengland.co.uk/

Adding Genes to a PanelApp Panel

Adding a **gene** to a Panel:



If any genes are missing from a panel, you can add them using the tool bar below the Entities list:



You can also use this toolbar to add a STR or a region (including CNVs) to the panel. Please refer to the PanelApp handbook for further details, or contact us at panelapp@genomicsengland.co.uk so we can assist you further.

Adding a **gene** to a panel using the **Add gene** tool

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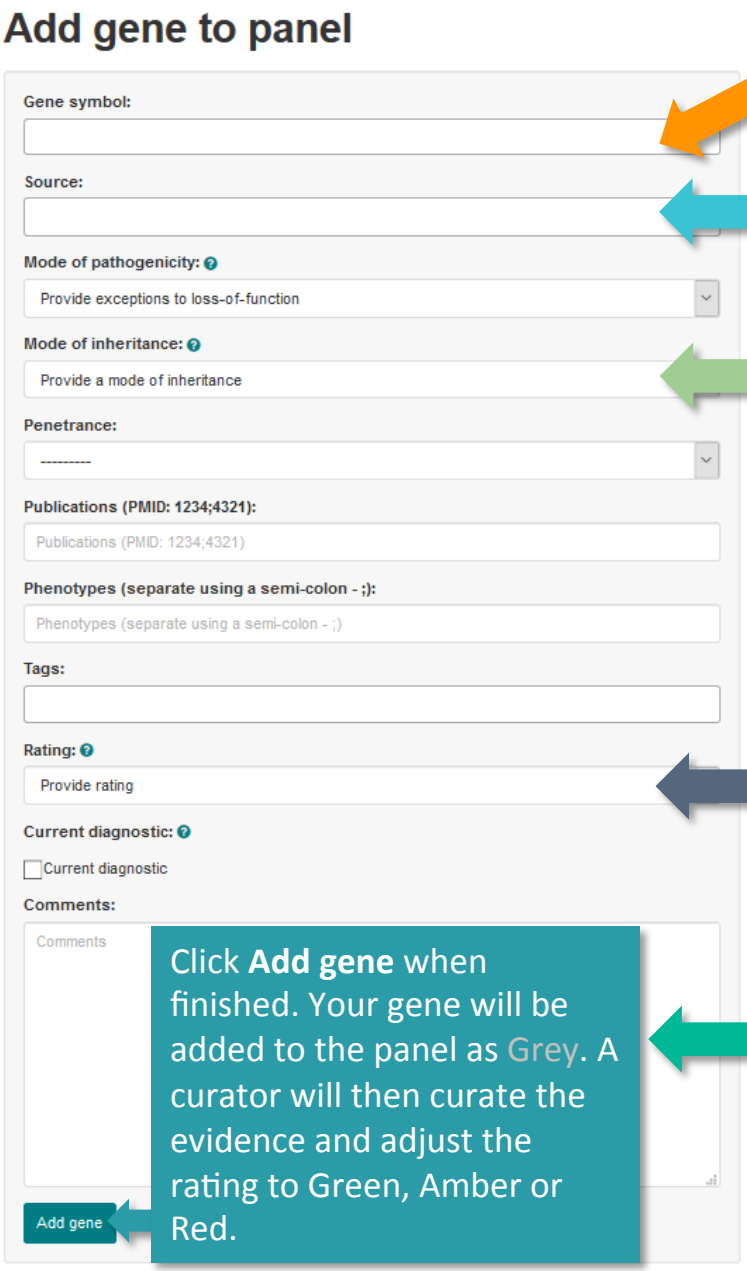


Start typing an HGNC Gene symbol into the top box to select your gene to add to a panel.

You must include a source of information for the gene:disease association. E.g. literature/Expert list.

You must provide a **Mode of inheritance** for the gene-disease association.

You can also add a **Mode of pathogenicity**, **Publications** and **Phenotypes.**

If penetrance is not complete, please denote using the drop down menu in the **Penetrance** field, and provide a comment.

Select a gene **rating** here.

The **Comments** box can be used to leave free-text information about the gene:disorder association and why the gene was added to the panel.

Any PID information should <u>not</u> be added as the comments will be publically visible.

Click **Add gene** when finished. Your gene will be added to the panel as Grey. A curator will then curate the evidence and adjust the rating to Green, Amber or Red.

- If you have a large set of genes and/or genomic entities to upload to PanelApp, please contact **panelapp@genomicsengland.co.uk** and a curator can assist you.

View or Edit your Evaluations

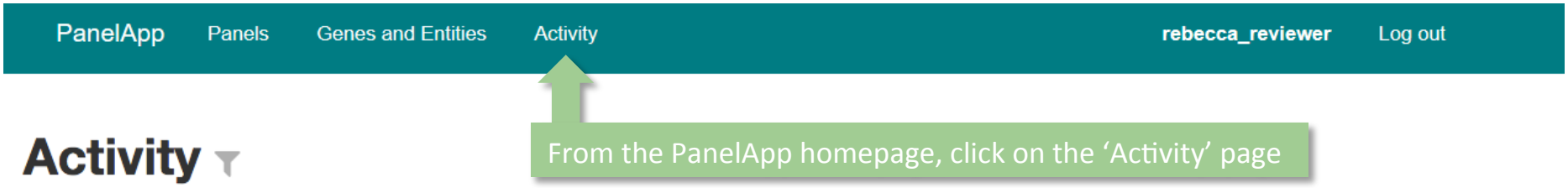
How to view or edit your Reviews:

1. From the PanelApp homepage, click on your username in the top right hand corner to view your user information and a list of your evaluations.

2. Click on the gene or genomic entity symbol to make changes to your evaluation, or click on the panel name to view the entire gene panel.

View Changes to Panels and new reviews

How to view updates or new reviews in PanelApp:



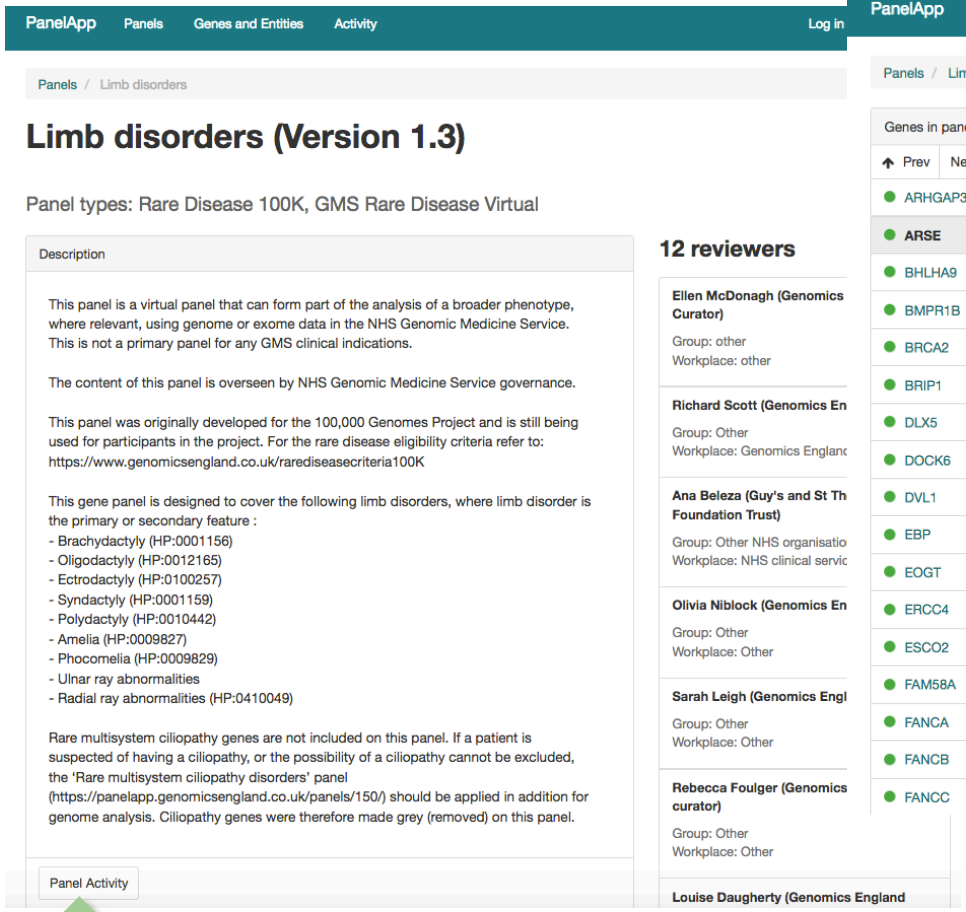
From the PanelApp homepage, click on the 'Activity' page

Activity

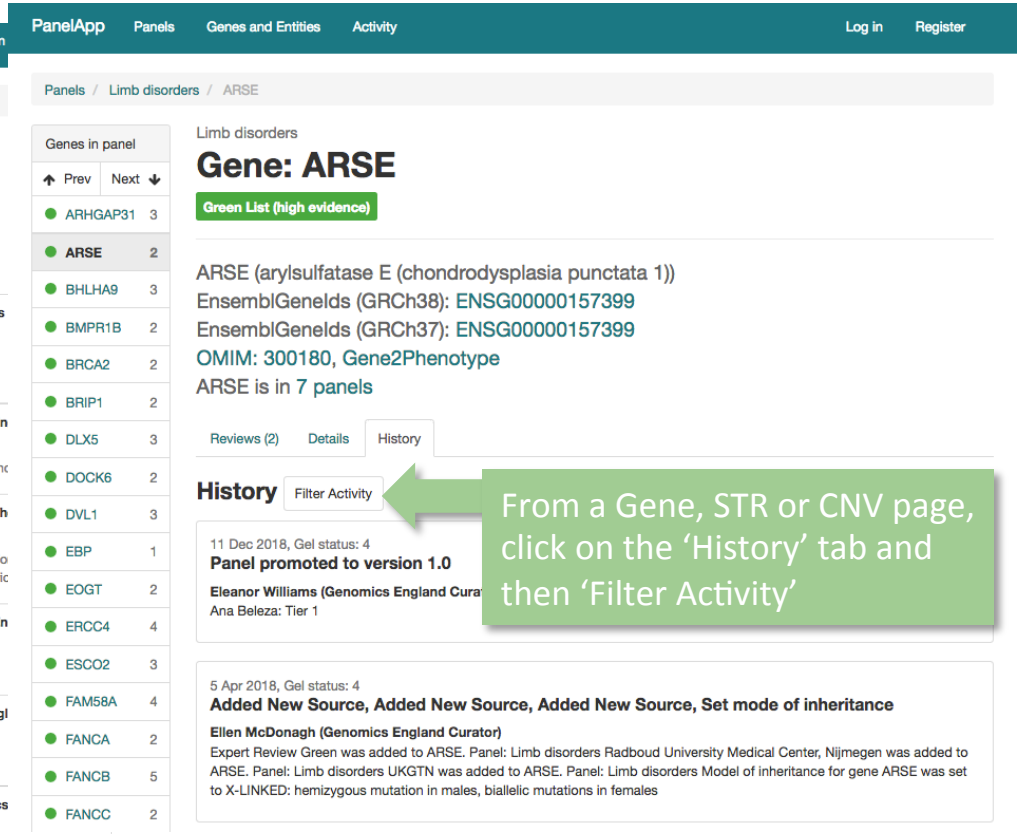
Date	Panel	Item	Activity
Filter activities			3000 actions
17 Dec 2018	Intellectual disability v2.584	ATP8B1	Konstantinos Varvagiannis Deleted their comment
17 Dec 2018	Intellectual disability v2.584	ATP8B1	Konstantinos Varvagiannis commented on gene: ATP8B1: I could not find any evidence that ATP8B1 deficiency is associated with DD/ID. Kinsley et al. (2014 - PMID: 20301474) review the spectrum of the disorder. DD/ID is not among the features and not mentioned among extrahepatic manifestations. The only possibly relevant complication is vitamin E deficiency which can lead to neurologic manifestations (but not of this type).

This will display activity for all panels in PanelApp and can be filtered for date, panel name, version, gene or genomic entity name, activity type, name of Reviewer or Curator

How to view updates on individual Panel or Gene pages:



From a Panel page, click on 'Panel Activity'



From a Gene, STR or CNV page, click on the 'History' tab and then 'Filter Activity'

This will display the relevant activity can be filtered for date, version, activity type, name of Reviewer or Curator

Additional Notes for Reviewers

- Your evaluations and comments will be tagged with your name and affiliation, and are public. Your name and affiliation will appear in the list of reviewers at the top of the panel.
- The date you made your reviewer will appear, along with the version of the panel you reviewed.
- You can make multiple comments for each gene or genomic entity, and edit or delete them individually.
- Changes to the rating, mode of inheritance, mode of pathogenicity and current diagnostic practice will overwrite your initial evaluation.
- Publications and phenotypes will be saved in the evaluation tool and can be added to.
- When you have reviewed a gene or genomic entity, you can see your review under the review tab along with any reviews from other experts.
- For your reviewed genes, a tick will appear in front of the gene in the Genes in panel list. A tick together with **You reviewed** text will also be added to the Reviewed column on the main panel page.
- If you have any issues, please contact us at panelapp@genomicsengland.co.uk.

Acknowledgements

- **Document Authors:** Rebecca Foulger and Ellen McDonagh
- **PanelApp developers:** **Antonio Rueda-Martin**, **Oleg Gerasimenko**, Paul Hayes
- **PanelApp Curators** (past & **present): Ellen McDonagh, Rebecca Foulger, Sarah Leigh, Louise Daugherty, Olivia Niblock, Eleanor Williams, Ivone Leong, Arianna Tucci, Helen Brittain, Anna de Burca,** Rachel Jones**,** Eik Haraldsdottir, Alice Gardham, Ellen Thomas, Richard Scott, Caroline Wright, Emma Baple, Damian Smedley, Chris Boustred, Maria Athanasopoulou, Kirsty McCaffrey, Chris Campbell.
- **Other contributers to PanelApp creation, documentation, outreach:** Augusto Rendon, Katherine Smith, Clare Turnbull, Jo Whittaker, Mina Ryten, Tom Fowler & members of the V&F GeCIP Domain, Mark Caulfield, Verity Fryer, Kristina Ibanez-Garikano, Dalia Kasperaviciute, Corey Johnson, Lisa Carr, Alona Sosinsky, PanelApp collaborators & Users.

Further thanks to:

PanelApp Reviewers and **Participants & Partners of the 100,000 Genomes Project and NHS Genomic Medicine Service.**

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