

# PanelApp Handbook

Version 5.7

Background & Guidance for Public Users and  
Reviewers for PanelApp Release V2.0

# PanelApp Tool

## Background & Guidance for Reviewers

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## 1 Document Purpose & Scope

The purpose of this document is to provide an overview of PanelApp, together with a step-by-step guide for users of PanelApp and reviewers of PanelApp gene panels. This includes guides to *what* information is housed, *where* to find the relevant information and *how* to leave reviews and feedback.

## 2 PanelApp Overview

### 2.1 What is PanelApp?

The Genomics England PanelApp (<https://panelapp.genomicsengland.co.uk/>) is a publically-available knowledgebase that allows virtual gene panels related to human disorders to be created, stored and queried. It includes a crowdsourcing tool that allows genes to be added or reviewed by experts throughout the worldwide scientific community, providing an opportunity for the standardisation of gene panels, and a consensus on which genes have sufficient evidence for disease association. The diagnostic grade 'Green' genes and their modes of inheritance in the PanelApp virtual gene panels are used to direct the variant tiering process for the interpretation of genomes in the 100,000 Genomes Project. As panels in PanelApp are publically available, they can also be utilised by others. For further information, see <https://www.genomicsengland.co.uk/about-genomics-england/panelapp/>.

### 2.2 How Gene Panels are Defined

For the 100,000 Genomes Project, gene panels are mapped to one or more recruitment categories, indicated by the gene panel name (Level 4 Title) and/or listed under 'relevant disorders' for each panel in PanelApp. Gene panels are created in a number of steps described in detail in Appendix A. In summary, for Rare Diseases:

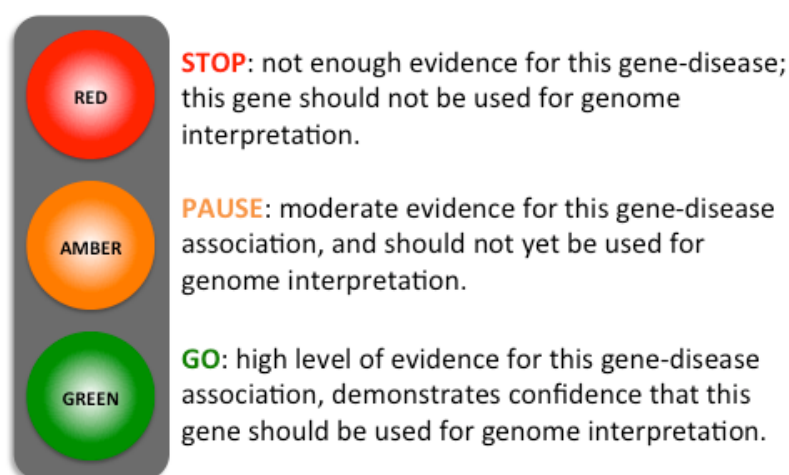
1. **An initial gene list** is drawn up from established sources (UKGTN, Radboud UMC, Emory Genetic Laboratory and Illumina) and from disease area experts. Initial gene panels are Version 0.

2. **Expert review** of each gene is crowdsourced.
3. **Evaluation** of the reviews, further curation and consultation with the Genomics England clinical team results in a finalised panel. The panel will then be promoted to Version 1 and used in the interpretation of participant genomes.

Note that PanelApp gene panels are not used in interpretation until initial expert review and curation has been completed and the panel has been promoted to 'Version 1'. Before this, panels are viewable and can be reviewed but the rating of genes (see Section 2.3) has not been finalised.

### 2.3 Understanding Gene Ratings on a Version 1+ Gene Panel

We classify genes on a panel according to a traffic light system (Figure 1). Genes are rated in terms of the level of evidence to support their association with the phenotypes covered by the gene panel in question. 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 in Appendix B).



- 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.

**Figure 1. A traffic-light system is used to rate genes on a Version 1+ gene panel.**

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 in Tiering.

## 2.4 How Do I Add Genes and Gene Reviews to a Gene Panel?

PanelApp has more than 500 registered reviewers from 25 countries, the majority of whom are experts in rare disease diagnosis from the UK. We encourage experts to contribute their knowledge to update existing panels and help create new diagnostic-grade panels. To find your PanelApp gene panel of interest, see Section 3. For step-by-step instructions on reviewing data in PanelApp, see Section 4.3. To add genes to an existing panel, see Section 4.4.

## 2.5 Uses and Users of PanelApp

The diagnostic grade '**Green**' genes (see Section 2.3) and their modes of inheritance on the Version 1+ PanelApp virtual gene panels are used to direct the Genomics England Rare Disease Tiering process. This Tiering process is to aid NHS GMC evaluation of Rare Disease primary finding results by annotating variants that are plausibly pathogenic based on their segregation in the family, frequency in control populations, effect on protein coding, mode of inheritance and whether they are in a Green gene in the virtual gene panel(s) applied to the family. Variants in diagnostic grade '**Green**' genes can be tiered as Tier 1 or Tier 2.

Gene panels in PanelApp can also be utilised for other projects, clinics and databases. See Appendix F for scenarios describing how PanelApp may be useful to you, depending on your role and interests.

### 3 Navigating PanelApp

There are several different user types of PanelApp (Table 1). You can browse the PanelApp user interface as a Public (anonymous) user without creating an account - all panels and reviewer comments are publicly visible. Individual panels of the desired version can be downloaded from the user interface or queried from WebServices (see Section 3.9 and Appendix D). To provide comments or reviews for a gene panel, you will need to register as a Reviewer.

Action	Public User (Section 3.1)	Reviewer (Section 4)	Curator
View gene panels (Section 3.2)	✓	✓	✓
View gene information (Section 3.3)	✓	✓	✓
Download individual gene panels (Section 3.8)	✓	✓	✓
Query PanelApp WebServices (Section 3.9)	✓	✓	✓
View reviewers' ratings and comments, and who made these (Section 3.4)	✓	✓	✓
Link to external gene sources including Ensembl, OMIM and ClinVar (Section 3.5)	✓	✓	✓
View gene history (Section 3.6)	✓	✓	✓
Rate genes in a gene panel (Section 4.3)	X	✓	✓
Add genes to a gene panel (Section 4.4)	X	✓	✓
Add comments and information (e.g. publications, mode of inheritance) to genes (Section 4.3)	X	✓	✓
View a list of your own evaluations (Section 4.6)	X	✓	✓
Delete genes from a panel	X	X	✓
Change the rating of a gene	X	X	✓
Promote a panel to the next major version	X	X	✓

**Table 1. The PanelApp actions available to public users, reviewers and Genomics England curators. Note that neither public users nor reviewers can delete genes from a panel.**

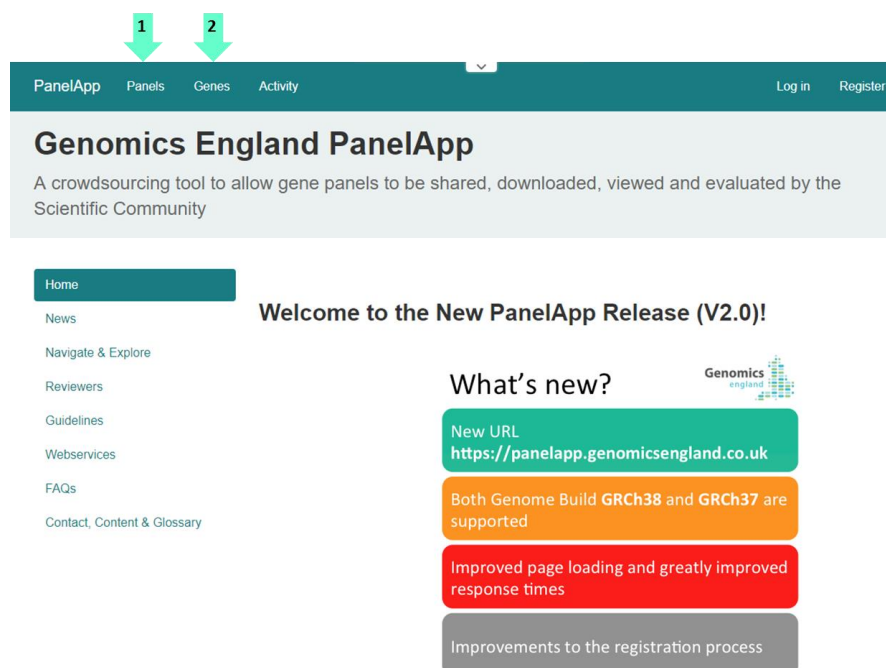
#### 3.1 Browsing PanelApp as a Public User

1. Go to <https://panelapp.genomicsengland.co.uk/>



2. If going from the <https://panelapp.genomicsengland.co.uk/accounts/login/> page, select 'Browse PanelApp without logging in' to be redirected to the homepage.

3. On the homepage you can find out more about PanelApp from the left hand menu. You can browse PanelApp through either a panel-centric or gene-centric route by selecting 'Panels' or 'Genes' from the menu at the top of the homepage.



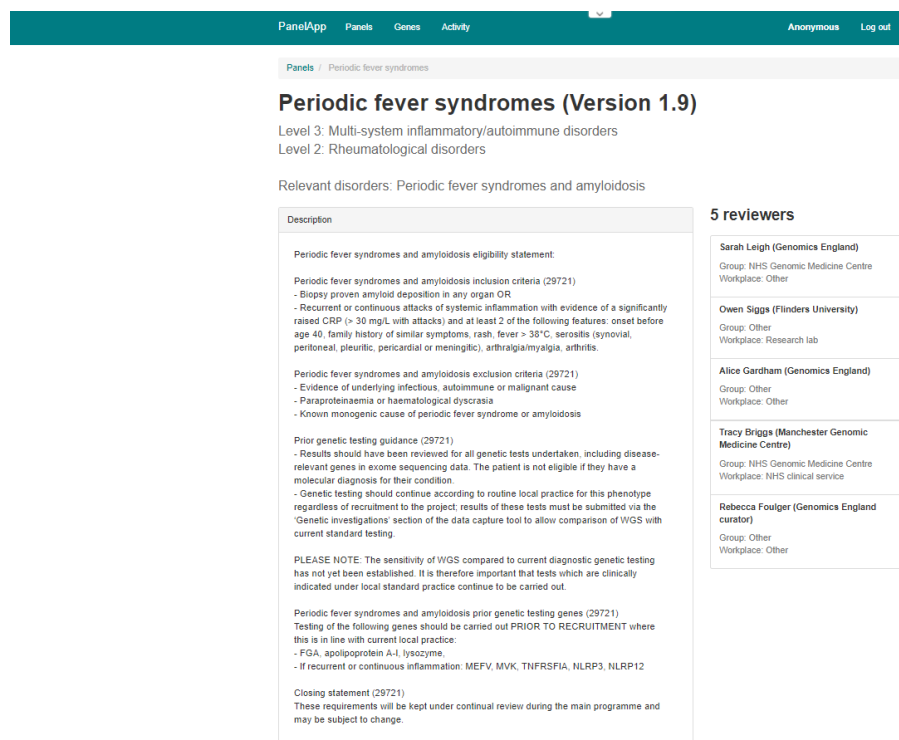
**Figure 2.** The PanelApp homepage. Use the top menu to navigate 'Panels' or 'Genes' within PanelApp (<https://panelapp.genomicsengland.co.uk/>).

### 3.2 Browsing Panels in PanelApp (a Panel-Centric View)

1. Click on 'Panels' in the top bar of the page.

A full list of panels is displayed in alphabetical order. The list can be sorted by panel name, number of evaluated genes or number of reviewers. The 'Filter panels' box allows users to find gene panels of interest, for example; by entering 'immunodeficiency', the list will be filtered to display all panels that fall under this term. To compare two panels, click the 'Compare two panels' button and select the panels for comparison from the drop-down

menu. Once selected, click 'submit' and the genes and their colour rating on each panel will be displayed. For a gene of interest, select 'compare' to see further details regarding the gene on the two panels, including reviews.



**Periodic fever syndromes (Version 1.9)**  
 Level 3: Multi-system inflammatory/autoimmune disorders  
 Level 2: Rheumatological disorders  
 Relevant disorders: Periodic fever syndromes and amyloidosis

**Description**

Periodic fever syndromes and amyloidosis eligibility statement:

Periodic fever syndromes and amyloidosis inclusion criteria (29721)  
 - Biopsy proven amyloid deposition in any organ OR  
 - Recurrent or continuous attacks of systemic inflammation with evidence of a significantly raised CRP (> 30 mg/L with attacks) and at least 2 of the following features: onset before age 40, family history of similar symptoms, rash, fever > 38°C, serositis (synovial, peritoneal, pleuritic, pericardial or meningitic), arthralgia/myalgia, arthritis

Periodic fever syndromes and amyloidosis exclusion criteria (29721)  
 - Evidence of underlying infectious, autoimmune or malignant cause  
 - Paraproteinaemia or haematological dyscrasia  
 - Known monogenic cause of periodic fever syndrome or amyloidosis

Prior genetic testing guidance (29721)  
 - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.  
 - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

Periodic fever syndromes and amyloidosis prior genetic testing genes (29721)  
 Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:  
 - FGA, apolipoprotein A-I, lysozyme  
 - If recurrent or continuous inflammation: MEFV, MVK, TNFRSF1A, NLRP3, NLRP12

Closing statement (29721)  
 These requirements will be kept under continual review during the main programme and may be subject to change.

**5 reviewers**

<b>Sarah Leigh (Genomics England)</b> Group: NHS Genomic Medicine Centre Workplace: Other
<b>Owen Siggs (Flinders University)</b> Group: Other Workplace: Research lab
<b>Alice Gardham (Genomics England)</b> Group: Other Workplace: Other
<b>Tracy Briggs (Manchester Genomic Medicine Centre)</b> Group: NHS Genomic Medicine Centre Workplace: NHS clinical service
<b>Rebecca Foulger (Genomics England curator)</b> Group: Other Workplace: Other

**Figure 3. A gene panel includes a description box detailing the eligibility statement for the rare disease category or a description of the panel.**

2. Click on the **gene panel** name to:

- Read the Genomics England eligibility statement for the disease displayed in the description box (Figure 3).
- View a list of the reviewers (and their affiliations) who have reviewed genes on this panel.
- View the list of genes in the panel and their current status (e.g. **Green**, **Amber**, **Red**) (Figure 4).

- View mode of inheritance (if known), sources the gene was found in, and phenotypes related to the gene.
- View tags attached to genes within a gene panel. These are used by curators to highlight specific information about variants in a gene, for example a ‘nucleotide-repeat-expansion’ tag indicates that nucleotide expansion repeat variations can cause the disorder. See Appendix E for an explanation of gene tags.
- From the links at the bottom of the page, you can download the whole panel or a selection of genes (see Section 3.8).

				<ul style="list-style-type: none"> <li>Hereditary Periodic Fever Syndromes</li> <li>PAPA syndrome</li> <li>Pyogenic sterile arthritis, pyoderma gangrenosum, and acne, 604416</li> </ul>
Green	TNFRSF1A	3 reviews 1 green	MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	<b>Sources</b> <ul style="list-style-type: none"> <li>Emory Genetics Laboratory</li> <li>Eligibility statement prior genetic testing</li> <li>Expert Review Green</li> </ul> <b>Phenotypes</b> <ul style="list-style-type: none"> <li>Hereditary Periodic Fever Syndromes</li> <li>Periodic fever, familial, 142660</li> </ul>
Green	TTR	2 reviews 1 green	MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	<b>Sources</b> <ul style="list-style-type: none"> <li>UKGTN</li> <li>Illumina TruGenome Clinical Sequencing Services</li> <li>Radboud University Medical Center, Nijmegen</li> <li>Expert Review Green</li> </ul> <b>Phenotypes</b> <ul style="list-style-type: none"> <li>Amyloidosis, Hereditary, Transthyretin-Related, 105210</li> <li>Familial Transthyretin Amyloidosis</li> </ul>
Amber	APOC2	2 reviews	MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	<b>Sources</b> <ul style="list-style-type: none"> <li>Literature</li> <li>Expert Review Amber</li> </ul> <b>Phenotypes</b> <ul style="list-style-type: none"> <li>Amyloidosis</li> <li>Hyperlipoproteinemia, type Ib 207750</li> </ul>
Amber	APOC3	1 review	MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	<b>Sources</b> <ul style="list-style-type: none"> <li>Literature</li> <li>Expert Review Amber</li> </ul> <b>Phenotypes</b> <ul style="list-style-type: none"> <li>Amyloidosis</li> </ul>
Amber	TNFAIP3	2 reviews 1 green	MONOALLELIC, autosomal or pseudoautosomal, imprinted status unknown	<b>Sources</b> <ul style="list-style-type: none"> <li>Literature</li> <li>Expert Review Amber</li> </ul> <b>Phenotypes</b> <ul style="list-style-type: none"> <li>Autoinflammatory syndrome, familial, Behcet-like (AISBL) (616744)</li> </ul>
Red	APP	1 review	MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	<b>Sources</b> <ul style="list-style-type: none"> <li>Radboud University Medical Center, Nijmegen</li> <li>Literature</li> <li>Expert Review Red</li> </ul> <b>Phenotypes</b> <ul style="list-style-type: none"> <li>Cerebral amyloid angiopathy, Dutch, Italian, Iowa, Flemish, Arctic variants 605714</li> </ul>
Red	B2M	1 review 1 red	MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	<b>Sources</b> <ul style="list-style-type: none"> <li>Literature</li> <li>Radboud University Medical Center, Nijmegen</li> <li>Expert Review Red</li> </ul> <b>Phenotypes</b> <ul style="list-style-type: none"> <li>Amyloidosis, familial visceral 105200</li> </ul>

Figure 4. A subset of genes on the ‘Periodic fever syndromes’ panel. Gene information including mode of inheritance and phenotypes related to the gene can be viewed from this panel page (<https://panelapp.genomicsengland.co.uk/panels/60/>).

### 3.3 View Gene Information on a Panel

Click on the **gene symbol** to view information about the gene including the HGNC-approved name, and links to gene information on Ensembl, OMIM and Gene2Phenotype. Further gene information is available on three separate tabs (Figure 5):

- I. Reviews of the gene.
- II. Details about the gene including links to ClinVar.
- III. History of when the gene was added, and any changes made to the gene information.

The screenshot shows the PanelApp interface. At the top, there's a navigation bar with 'PanelApp', 'Panels', 'Genes', and 'Activity'. On the right, there are links for 'Anonymous' and 'Log out'. Below the navigation bar, the breadcrumb trail reads 'Panels / Periodic fever syndromes / TTR'. The main content area is divided into two columns. The left column, titled 'Genes in panel', contains a list of genes with their symbols and counts: APOA1 (1), APOA2 (1), ELANE (2), FGA (1), GSN (1), IL1RN (1), IL36RN (1), LPIN2 (2), LVZ (1), MEFV (3), MVK (2), NLRP12 (1), NLRP3 (2), NOD2 (1), OSMR (1), OTULIN (2), PSMB8 (1), PSTPIP1 (2), TNFRSF1A (3), TTR (2), APOC2 (2), APOC3 (1), TNFAIP3 (2), APP (1), and B2M (1). The right column, titled 'Periodic fever syndromes', shows the details for the selected gene, TTR. It includes a 'Green List (high evidence)' badge, the gene symbol 'TTR', the gene name 'transthyretin', and links to Ensembl (ENSG00000118271, LRG\_416), OMIM (176300), and Gene2Phenotype. Below this, there are tabs for 'Reviews (2)', 'Details', and 'History'. The 'Reviews' tab is active, showing two reviews. The first review is by Rebecca Foulger (Genomics England curator) on Jan. 16, 2017, 3:44 p.m., with a comment: 'Comment on mode of inheritance: Mode of inheritance confirmed by OMIM.' The second review is by Alice Gardham (Genomics England) on Jan. 30, 2017, 4:36 p.m., with a comment: 'well recognised as causing hereditary amyloidosis'. Both reviews have a 'Green List (high evidence)' badge. The interface also displays the mode of inheritance as 'MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted' and the phenotypes as 'Amyloidosis, hereditary, transthyretin-related 105210'. The panel version is 0.37.

Figure 5. Each **gene** within a panel contains information in the 'Reviews', 'Details' and 'History' tabs.

### 3.4 View Gene Reviews using the Reviews Tab

Reviews for a gene can be accessed by different routes:

- To see the individual reviews for a given gene, click on the gene symbol and then the Reviews tab. Scroll down to view reviewer's evaluations and comments.

- If you are a reviewer, you can view your own evaluations following instructions in Section 4.6.
- A summary of reviews can also be viewed:
  - On the Panels page (<https://panelapp.genomicsengland.co.uk/panels/>), a summary of the number of evaluated genes, and reviewers for each gene panel is provided in the panel summaries.
  - On each individual panel page, a list of reviewers is provided on the right hand side, and the number of **Red** or **Green** reviews is shown beside each rated gene.

### 3.5 View Gene Information Using the Details Tab

The Details tab on the Gene page contains more information for that gene, including:

- Mode(s) of inheritance for that gene for the relevant disease.
- Sources in which the gene-phenotype association was found.
- Phenotypes collected from the sources, related to the rare disease category.
- A link to the gene page in the OMIM database.
- A link to variants within this gene in the ClinVar database.
- Penetrance (the default is 'complete penetrance', however this field allows collection of information on cases of incomplete penetrance from reviewers and the literature).
- Publications related to the gene-disorder association.
- The mode of pathogenicity for the gene-disorder association (if loss-of-function variants in the gene do not cause the phenotype).
- Other gene panels in PanelApp that this gene appears in.

### 3.6 View Gene History Using the 'History' Tab.

The history tab lists changes made to the gene information, reviews and status.

### 3.7 Browsing Genes in PanelApp (a Gene-Centric View)

1. To browse genes, click on “Genes” in the top bar of the page. A full list of genes will be displayed in alphabetical order.
2. Select the gene of interest, or start typing the gene symbol into the ‘Filter genes’ box to narrow down your selection.

Click on a gene symbol to view information about a gene. You will be able to see:

- HGNC-approved Gene name.
- Links to OMIM and Gene2Phenotype.
- A list of all panels on which the gene occurs, and the panel version.
- The status of the gene (Green, Amber, Red) on each panel.
- The Mode of Inheritance of the gene for each disorder (if known).
- Sources in which the gene-phenotype association was found.
- The relevant phenotypes of the gene for each disorder.

From this page, you can:

- Click on the gene symbol to take you to the gene entry within the listed panel.
- Click on the panel name to view the full panel that contains that gene.

### 3.8 Download a Gene Panel

The download menu is available at the bottom of each panel page. Downloads of gene panels are in .tsv format, which can be opened in a number of applications, including Microsoft Excel. Users have the option of downloading the (i) whole gene panel, (ii) only Green genes, (iii) only Amber genes, (iv) Green and Amber genes, or (v) only Red genes. Users can also download a

previous version of the panel. Downloads of the current panel version are also available from the panel page.

The download file contains the following fields:

- Gene Symbol (HGNC-approved gene symbol)
- Sources (separated by ;)
- Level 4, 3 and 2 title (specific rare disease specific, subgroup and group)
- Mode of inheritance (using PanelApp standardised terms)
- Phenotypes (as collected from the sources)
- OMIM, Orphanet, HPO terms (if available)
- Publications
- Description (not currently populated)
- Flagged
- GEL status (reflects the current gene rating; 3 or 4 = Green, 2 = Amber, 1 or 0 = Red)
- User Ratings (represented as the number of ratings for Green;Amber;Red).
- Version (the gene panel version)
- Ready
- Mode of pathogenicity

### 3.9 Querying PanelApp Through WebServices

Examples for querying the PanelApp API, together with terms available to use for mode of inheritance queries, are listed in Appendix D.

## 4 Reviewing genes in PanelApp

### 4.1 Registering to be a Reviewer

We encourage expert review of the gene panels to reach a community consensus on which genes should appear on a diagnostic-grade gene panel for each disorder. We request that reviewers of the gene panels should have:

- Expertise in a disease area, genes or diagnostic genetic testing relevant to the diseases that are part of the 100,000 Genomes Project.

A full list of the rare diseases that are part of the 100,000 Genomes Project can be found on the Genomics England website: <http://www.genomicsengland.co.uk/library-and-resources/>

The relevant tumour types can be found here:

<https://www.genomicsengland.co.uk/information-for-gmc-staff/cancer-programme/eligibility/>

Reviewers can:

- Be based anywhere in the world.
- Have an academic, clinical and/or commercial background.

To register as a PanelApp reviewer:

1. Go to: <https://panelapp.genomicsengland.co.uk/accounts/login/> and select 'Register to be a reviewer' at the bottom of the panel.

(If you are already browsing the PanelApp as a public user, click on the 'Register' button in the top right hand corner of PanelApp, and you will be redirected to this Login page.)

2. Fill in the information on the Sign up page:



**Username and password:** These are needed to set up and sign in to your reviewer account but are not visible to the public or other reviewers in PanelApp. Please choose a username without spaces and do not use your email address as your username.

**First Name, Last Name and Affiliation:** To encourage openness, all gene evaluations and comments from reviewers are made public. Your full name and affiliation will be added to your reviews. By registering as a reviewer you are agreeing to this condition.

**Role, Workplace and Group:** These details are gathered to provide information about reviewers' backgrounds. Workplace and Group will be displayed on PanelApp.

**Email:** please use your institutional / work email address or NHS email to register if possible. This will allow us to process the reviewer request more effectively. Your confirmation of reviewer status will be sent to this email address. Your email will not be publically visible on PanelApp.

3. Submit your request by clicking 'Register'.

After registering, you will be automatically signed in with your new username, but will temporarily only have public access. Within 48 hours, a Genomics England curator will validate your application and, if accepted, you will be sent an email with confirmation and further instructions. **You will need to click on the link in this email to verify and authenticate your account. This is required to allow full access to the panels and let you leave a review.**

## 4.2 Signing in as a Reviewer

Once registered as a reviewer, to sign-in go to

<https://panelapp.genomicsengland.co.uk/accounts/login/>

If you have forgotten your password, you can reset your account by selecting 'I forgot my password', then enter the same email you registered with and select 'Request new password'.

Please contact [panelapp@genomicsengland.co.uk](mailto:panelapp@genomicsengland.co.uk) if you have any issues signing in or have any questions regarding reviewing.

### 4.3 Instructions for Review of Genes on PanelApp

Once logged in as a reviewer (see Section 4.2), search for the relevant panel or gene you would like to review or comment on, by browsing PanelApp as described in Section 3.

We request that reviewers read the details regarding the panel in the description box. For the rare diseases this will be the eligibility statement for the 100,000 Genomes Project (where available, see Figure 3). The description provides information on the phenotype inclusion for the panel.

- Click on each gene in the panel and provide a review using the 'Reviews' tab. Please leave feedback for each gene on a panel, specifically:
- Provide a rating (**Green**/high evidence/clinically-actionable or diagnostically reportable variants OR **Red**/low evidence/variants that are not clinically actionable). You may also choose **Amber** evidence (I don't know) if it is a borderline case or you are unsure.
  - Guidelines for reviewers for the evidence required for a gene to be rated as '**Green**/high evidence' are available from the PanelApp homepage (on the **Guidelines** tab), and are detailed in this document in Appendix B.
- Would you be confident reporting a pathogenic or likely pathogenic variant within all the genes in the Green list, in relation to the specified disorder?
- Provide a mode of inheritance for the gene-disease association from the drop-down menu.
  - Definitions for the terms are provided in the (?) pop-up box, within this document (See Appendix E) and on the PanelApp homepage within the **Contact, Content & Glossary** tab.

- If the mode of inheritance you want to add is not within the drop down menu, or you know of more than one mode of inheritance pattern, different modes of inheritance for specific phenotypes, or other scenarios, please select 'other' and provide details in the comments box. Please provide information regarding imprinting, if known.
- Add relevant phenotypes.
  - Where possible, please add phenotypes using standardised OMIM, Orphanet or HPO terms/codes if additional phenotypes are known to be associated with this gene relevant to the rare disease category (level 4 title). The phenotypes shown in PanelApp are largely those collected from the sources, with relevance to the panel.
  - Separate phenotypes using a semi-colon e.g. Agammaglobulinemia 7, autosomal recessive; SHORT syndrome.
- Add relevant publications.
  - Please provide PubMed IDs separated by a semi-colon, in the format 1234;4321. Include publications that provide supporting evidence for your given rating e.g. published family pedigree studies supporting the gene-phenotype association, or publications showing a lack of an association between the gene and phenotype.
  - If the publication does not have a PubMed ID (e.g. a recently-accepted article), please include details in free-text and these will be updated by a curator.
- If loss-of-function variants do not cause the disease phenotype, please select an option in the mode of pathogenicity dropdown menu and provide further details as a comment.
  - Loss-of-function variants are defined as variants with the sequence ontology (SO) terms; **transcript\_ablation**, **splice\_acceptor\_variant**, **splice\_donor\_variant**, **stop\_gained**, **frameshift\_variant**, **stop\_lost**, **initiator\_codon\_variant** (see Appendix E).
  - An example where loss-of-function variants are not relevant is for the *PCSK9* gene in hypercholesterolemia, where such variants are associated with increased LDL-cholesterol uptake (PMID:[25911073](#)).

- Provide justifications in the comments box to support your gene rating, particularly when changing the existing rating of a gene. Include information such as the age of disease onset, penetrance, and details of clinical practice.
  - The comments box can also be used to provide comments intended to activate community debate.
- 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 'Clinical diagnostic' box.
- Add any missing genes using the 'Add gene' button found at the bottom of the gene list. See Section 4.4 for further details.

#### 4.4 How to Add a Gene to a Panel

Scroll down to the bottom of the gene panel page to the 'Add a gene to this panel' button.

- Start to type the gene symbol in the 'Gene symbol' box. An automated list of HGNC-approved gene symbols will appear. Select from the list. To check the HGNC-approved gene symbol for a gene or a list of genes, use the symbol checker tool ([http://www.genenames.org/cgi-bin/symbol\\_checker](http://www.genenames.org/cgi-bin/symbol_checker)).
- Select *Expert Review*, *Literature* or *Research* as a source from the drop down menu, depending on which is most suitable.
  - Choose '**Expert Review**' as a source if you test for this gene as part of current clinical practice in the diagnosis of the relevant rare disease category. Using the evaluation tool, please rate the gene '**Green List (high evidence)**' and check the 'Current diagnostic' checkbox. Provide a short explanation in the comments as to why this gene is important to add to the panel.
  - Chose '**Literature**' or '**Expert Review**' as the source if the gene is well established in the disease area. Please rate the gene '**Green List (high evidence)**' and add publications to support the addition of this gene. Please also provide a short

explanation in the comments box as to why this gene is important to add to this panel.

- Choose '**Research**' as the source if the gene is still in research phase, and requires further evidence before it can be used in diagnosis, for example a gene you have identified in your own research. Adding these genes to the panel is useful to source further evidence from other reviewers. You should rate these genes as '**Red List (low evidence)**'. Please provide a short explanation in the comments box for why you think it is important to add.
- Add Mode of Inheritance, Publications and Phenotypes as outlined above, and where applicable, select 'loss-of-function variants in this gene do not cause the phenotype' (mode of pathogenicity).
- If penetrance is not complete, please denote using the drop down menu and provide a comment.
- Provide a rating and comments as to why the gene was added to the list.
- Click *submit*.

The gene will appear at the bottom of the list in Grey to indicate that it has been submitted by a reviewer. The status of the gene will change (to **Green**, **Amber** or **Red**) when evaluated by a Genomics England curator.

If you have a number of genes that you wish to add to a panel, please contact us at [panelapp@genomicsengland.co.uk](mailto:panelapp@genomicsengland.co.uk), and a curator can assist in uploading the genes to a panel.

#### 4.5 Additional Notes for Reviewers

- Your evaluation and comments will be tagged with your name and affiliation, and are public. In addition, your name and affiliation will appear at the top of the panel.
- The date you made your review will appear, along with the version of the panel you reviewed.

- You can make multiple comments for each gene, and edit or delete them individually.
- Changes to the rating, mode of inheritance, mode of pathogenicity and current diagnostic practise using the gene evaluation tool will overwrite your initial evaluation.
- Publications and phenotypes will be saved in the evaluation tool and can be added to; please note that if you delete what has been saved in these boxes, your original submissions of publications and phenotypes will be overwritten.

When you have reviewed a gene, you can see your review under the review tab along with others. A tick will appear against the gene on the left hand side, and on the main panel page genes you have reviewed are also denoted.

If a curated set of known-pathogenic variants is available for this gene-phenotype, please contact us at [panelapp@genomicsengland.co.uk](mailto:panelapp@genomicsengland.co.uk).

#### 4.6 View or Edit your Evaluations

From the PanelApp homepage, click on your username button in the top right hand corner to view your user information and a list of your evaluations. Click on the gene name to make changes to your evaluation, or click on the panel name to view the entire gene panel.

## 5 Contact information

For enquiries related to PanelApp, to give feedback or suggestions or to submit gene lists, please email: [panelapp@genomicsengland.co.uk](mailto:panelapp@genomicsengland.co.uk).

GMC staff can contact the Service Desk via email ([ssd.genomics@hscic.gov.uk](mailto:ssd.genomics@hscic.gov.uk)) or call **0808 2819 535** with any queries about the 100,000 Genomes Project.

## 6 Frequently Asked Questions

### 6.1 Why gene panels?

The finalised 'Green' genes on a Version 1+ gene panel will be used in the tiering of variants in order to aid clinical interpretation of the genomes sequenced as part of the 100,000 Genomes Project. As the virtual gene panels are publically accessible, they are also available for the scientific and clinical community.

### 6.2 Why are you asking experts to review the gene panels?

The aim is to utilise expertise and knowledge from the scientific community to establish consensus gene panels (a defined Green list) for each rare disease category.

### 6.3 As an expert reviewer, how do I rate the genes?

Genes included in a Genomics England gene panel for a rare disease category (Green list) should fit the criteria outlined in the gene panel guidelines (see Appendix B). For step-by-step instructions on rating genes, see Section 4.

### 6.4 Review Scenarios

- *For the congenital hearing impairment (profound/severe) panel:*

**a.** A gene is proven to cause syndromic hearing loss but has not to date been proven to manifest with non-syndromic hearing loss. The level 3 title for the panel is 'Non-syndromic hearing loss' Should it be included in the panel?

> Yes; we feel that these genes should be included because a variant in this gene is likely to be relevant to this individual (for example highlighting additional medical features that should be looked for) and should therefore be reported in the genome interpretation.

**b.** A gene is proven to cause hearing loss, but not congenital profound/severe hearing loss.  
Should it be included in the panel?

> Yes, we feel that these genes should be included because a variant in this gene is likely to be relevant to this individual (even if only partially explaining the phenotype) and should therefore be reported in the genome interpretation.

### 6.5 Who will be able to access the gene panels?

Anyone can view, download or query the gene panels. In addition, registered reviewers can evaluate genes on the gene panels and provide comments.

### 6.6 Will the gene panels change?

Gene panels may change over time as knowledge accumulates and curators become aware of new evidence. This includes the addition of new genes, rating changes to existing genes or gene information. The panels may also be merged or split as appropriate. Each change to a panel increases the minor version (E.g. Version 1.0 to Version 1.1). Previous versions of a gene panel can be downloaded using the tool available at the bottom of a gene panel page or by querying WebServices (see Section 3.9).

The PanelApp 'Activity' tab (displayed from the PanelApp home page) displays the last 1000 key changes to all panels. The 'History' tab for each gene on a gene panel records changes to gene information. Gene reviews are also added with a date-stamp for tracking.

Gene panels <Version 1 are viewable and can be reviewed. Once expert reviews have been collected and evaluated internally by Genomics England Curators, Version 1 of the gene panels are released. Version 2 panels will be launched when significant changes have been made to Version 1 panels.

### 6.7 What is recorded when I make my reviewer evaluation?

When you are logged in as a reviewer, any information you enter using the gene evaluation or new gene tool will be recorded. Your reviewer name (made up of your first name, last name



and affiliation used when you registered to be a reviewer) will be attached to ratings and evaluations. To encourage openness, all gene evaluations and comments you make as a reviewer will be open to anyone to see (the public and other reviewers). The date, time and version of the panel when these actions were carried out is also recorded.

### 6.8 Am I able to change my reviewer evaluations?

As a reviewer, you can log in to PanelApp using your log in details, and view and/or edit your evaluations at any time. To make changes to your evaluations, see Section 4.6.

### 6.9 Who will be assessing the evaluations?

The evaluations will be viewed by Genomics England Curators using internally established rules, and consultation with Genomics England clinicians.

### 6.10 How will reviews be assessed/conflicting reviews resolved?

A set of rules has been established to define different scenarios in order to have a pragmatic review evaluation process. The Validation & Feedback GeCIP (Genomics England Clinical Interpretation Partners) Domain was involved in establishing this process. Comments regarding changes to a gene rating are viewable in PanelApp for transparency.

### 6.11 Can I send the link to others so that they can review/download panels?

Please distribute the PanelApp URL or gene panel URLs to those within the Scientific Community; anyone can view and download the gene panels. We also encourage those with expertise to register as reviewers.

**Please note; if someone else logs in with your review log in details, any evaluations made will over-ride yours, and comments will not be distinguished as being from more than one user. You are therefore responsible for any changes and comments made under your reviewer name.**

### 6.12 When I register to be a reviewer, where are my details kept and who has access?

Information added during the registration process is stored internally and only utilised for uses related to PanelApp and will not be passed to third parties. Your first name, last name, affiliation, Workplace and Group will be visible to the public. Your role may be used to display the demographics of PanelApp reviewers.

You can view your account information by clicking on the “Logged in as: ...” button in the top right hand corner of the screen. Please contact [panelapp@genomicsengland.co.uk](mailto:panelapp@genomicsengland.co.uk) to make any changes to your user information.

### 6.13 Where can I keep up to date with major changes or news regarding PanelApp?

Go to the PanelApp home page, <https://panelapp.genomicsengland.co.uk> and click the **News** tab. Alternatively, select the ‘Activity’ page from the top menu for the latest key updates to panels. Follow @GenomicsEngland #PanelApp on Twitter. News items will also be displayed on the Genomics England website – for more information see <https://www.genomicsengland.co.uk/about-genomics-england/panelapp/>.

### 6.14 Can I submit my own gene panels?

We welcome submission of panels of genes from experts for the rare diseases covered in the 100,000 Genomes Project. If possible, please format the panel using the template available on the PanelApp homepage (**Contact, Content and Glossary** tab), enabling us to capture the information in a standardised manner.

Please submit gene panels by sending an email to [panelapp@genomicsengland.co.uk](mailto:panelapp@genomicsengland.co.uk).

## 7 Key Changes in PanelApp 2

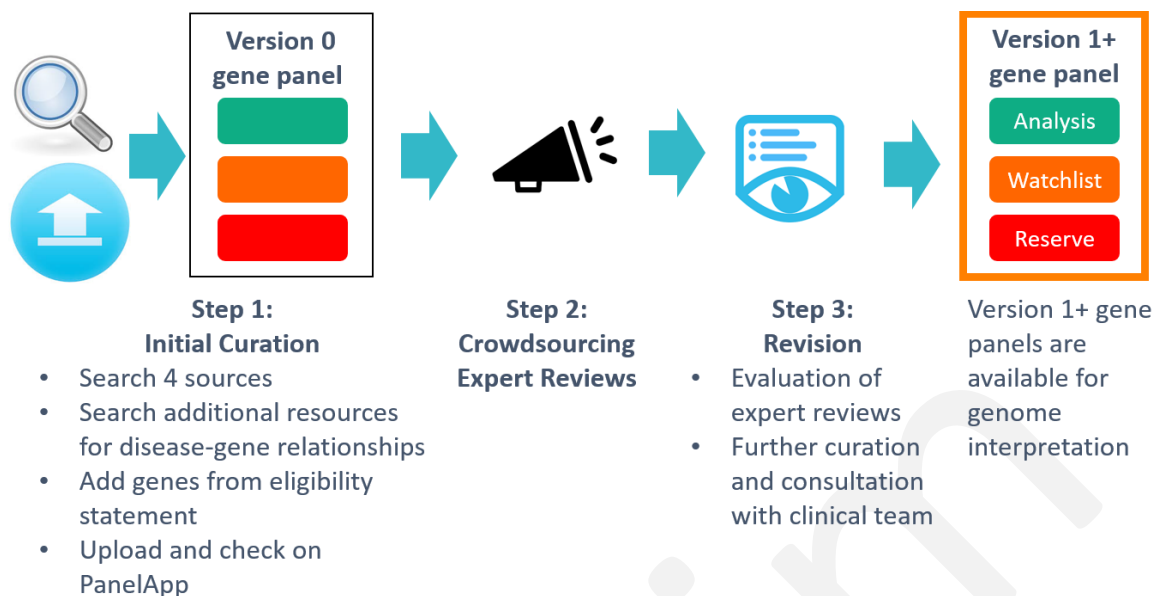
### 7.1 New and Improved Functionality in PanelApp 2

- When users are registering for a PanelApp account, the registration page captures more information, and has better checks.
- It is easier to log-in and log-out of PanelApp, to browse as a reviewer or as a anonymous user.
- Direct URL links to panels or genes are available even if you are not logged in.
- New URL links are simpler.
- The [URL for PanelApp](#) is now linked to Genomics England.
- Curators can download an all-genes list that now includes the panel version, biotype, Ensembl gene ID and genomic locations.
- An `assembly` parameter has been added to the URL for WebServices, so users can retrieve different Ensembl IDs depending on this parameter. By default it will return build 82, and if GRch38 is provided it will return build 90.

## 8 Appendices

### Appendix A: Gene Panel Curation Protocol

#### Creation of an Initial Gene Panel



**Figure 6. The curation process from initial establishment of a Version 0 gene panel, expert review and subsequent revision to form a Version 1 panel.**

For each approved rare disease category within the 100,000 Genomes Project, an initial virtual gene panel is created by a Genomics England Scientific Curator. Each of the following four sources is manually searched for key relevant phenotypic words (e.g. disease category and/or key phenotypes mentioned in the eligibility statement or additional sources summarising the disorder): Radboud University Medical Center, Illumina TruGenome Predisposition Screen, Emory Genetics Laboratory and UKGTN. Genes identified in this way are added to the panel. In addition, genes are added to the panel from gene lists provided by experts in particular disease areas, and genes mentioned in eligibility criteria for disease recruitment for the 100,000 Genomes Project. Curation of scientific publications and other key sources may also be performed to contribute to the initial gene panel (Table 2).

Source displayed in PanelApp	Source Name and URL	Details
Illumina TruGenome Clinical Sequencing Services	Illumina TruGenome Predisposition Screen: <a href="http://www.illumina.com/clinical/illumina_clinical_laboratory/trugenome-clinical-sequencing-services.html#tps">www.illumina.com/clinical/illumina_clinical_laboratory/trugenome-clinical-sequencing-services.html#tps</a>	4 sources used in the initial establishment of gene lists. Genes are given an initial ranking (Green, Amber, Red) depending on how
Emory Genetics Laboratory	<a href="http://www.egl-eurofins.com">www.egl-eurofins.com</a>	

UKGTN	United Kingdom Genetic Testing Network: <a href="https://ukgtn.nhs.uk/">https://ukgtn.nhs.uk/</a>	many of these four sources the gene appears on
Radboud University Medical Center, Nijmegen	<a href="https://order.radboudumc.nl/en/genetics/lab-information/exome-panels">https://order.radboudumc.nl/en/genetics/lab-information/exome-panels</a>	
Expert List	n/a	Gene lists submitted from an expert in the disease area
Eligibility statement prior genetic testing	<a href="http://www.genomicsengland.co.uk/information-for-gmc-staff/rare-disease-documents/rare-disease-eligibility-criteria/">http://www.genomicsengland.co.uk/information-for-gmc-staff/rare-disease-documents/rare-disease-eligibility-criteria/</a>	Prior genetic testing required/advised on the Genomics England Eligibility Statement for each disorder
Eligibility statement exclusion criteria	<a href="http://www.genomicsengland.co.uk/information-for-gmc-staff/rare-disease-documents/rare-disease-eligibility-criteria/">http://www.genomicsengland.co.uk/information-for-gmc-staff/rare-disease-documents/rare-disease-eligibility-criteria/</a>	The gene was included in the exclusion criteria within the eligibility statement
Literature	PubMed: <a href="http://www.ncbi.nlm.nih.gov/pubmed">www.ncbi.nlm.nih.gov/pubmed</a>	Genes are sourced from peer-reviewed published articles
Other	OMIM (Online Mendelian Inheritance in Man): <a href="https://omim.org/">https://omim.org/</a>	Used for some phenotype, gene, or mode of inheritance information. Links to OMIM gene pages are provided in PanelApp
Other	Orphanet: <a href="http://www.orpha.net/consor/cgi-bin/index.php">www.orpha.net/consor/cgi-bin/index.php</a>	Used for some phenotype, gene, or mode of inheritance information
Other	Gene2Phenotype: <a href="http://www.ebi.ac.uk/gene2phenotype">www.ebi.ac.uk/gene2phenotype</a>	Used for some phenotype, gene, or mode of inheritance information. Links to Gene2Phenotype gene pages are provided in PanelApp
Other	NIH Genetics Home Reference: <a href="https://ghr.nlm.nih.gov/">https://ghr.nlm.nih.gov/</a>	Used for some phenotype, gene, or mode of inheritance information
ClinVar	<a href="http://www.ncbi.nlm.nih.gov/clinvar">www.ncbi.nlm.nih.gov/clinvar</a>	Links to ClinVar are provided in PanelApp to aid evaluation of the evidence for an association between the gene and phenotype
ClinGen	<a href="#">ClinGen Home</a> & <a href="#">Gene Validity Classification</a>	ClinGen gene panels can be used to revise and re-evaluate PanelApp gene panels
HGNC	HUGO Gene Nomenclature Committee: <a href="http://www.genenames.org">www.genenames.org</a>	Used to check gene names in order to establish the correct HGNC-approved symbol
Expert Review Green/Amber/Red	n/a	Indicates the rating assigned by a reviewer
BRIDGE study Tier 1 gene	n/a	BRIDGE consortium Tier 1 genes from NIHR BioResource – Rare Diseases Study (NIHRBR-RD)

**Table 2. Key sources used in gene panel curation.**

For the creation of other gene panels, for example for pertinent germline genes for the cancer programme within the 100,000 Genomes Project, genes are identified from a variety of

sources, which will be indicated within the 'Source' section in PanelApp and publications for each gene.

Genes are uploaded to the PanelApp website to create an initial 'version 0' gene panel. Each gene in a version 0 panel will automatically be given an initial level of confidence, based on the number of the 4 sources (Radboud, Illumina, Emory, and UKGTN) that the gene was mentioned in, as indicated by the traffic light system:

- **Green** = highest level of confidence; a gene from 3 or 4 sources.
- **Amber** = intermediate; a gene from 2 sources.
- **Red** = lowest level of confidence; 1 of the 4 sources or from other sources.

### Crowdsourcing Expert Review

Once a panel has been created (Version 0+), review of the evidence and clinical utility for each gene is sought from the worldwide clinical and scientific community from those with relevant expertise. Once registered as a reviewer, experts can utilise the reviewer tool within PanelApp to provide their rating of a gene (see Section 4).

### Revision of the Gene Panel to Establish a List of High-Level Evidence Genes for Genome Interpretation

Based on the expert reviews and additional evidence from other sources (Table 2), Genomics England curators with clinical input revise the gene panel, based on criteria outlined in Appendix B, so that the genes and their ratings reflect a community consensus.

Once completed, the revised panel is promoted to the next major version – i.e. Version 1. The list of **Green** (high confidence) genes on this revised panel have a high level of evidence (diagnostic-grade) for implication in disease causation, and are used within the 100,000 Genomes Project Bioinformatics pipeline for prioritisation of genetic variants. The **Amber**

(moderate level of evidence) and **Red** (low level of evidence) genes on each panel will be maintained as lists of genes that are not currently be used in clinical reporting. These genes may be of interest for research purposes, and may be promoted to **Green** if more evidence for the gene-disease association arises. Gene panels (Version 0 and Version 1+) on PanelApp are dynamic, so genes can be added to the panel by reviewers or curators, and gene ratings may be changed by curators as new evidence arises. These genes may be utilised to prioritise tier 3 variants.

Interim

## Appendix B: PanelApp Criteria for Diagnostic Grade ‘Green’ Genes

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

OR

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

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 mutations follow a Mendelian pattern of causation appropriate for reporting in a diagnostic setting<sup>4</sup>.

AND

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

<sup>1</sup>*Plausible disease-causing mutations: Recurrent de novo mutations convincingly affecting gene function. Rare, fully-penetrant mutations - relevant genotype never, or very rarely, seen in controls.*

<sup>2</sup>*Interpretable functional region: ORF in protein coding genes miRNA stem or loop.*

<sup>3</sup>*Phenotype: the rare disease category, as described in the eligibility statement.*

<sup>4</sup>*Intermediate penetrance genes should not be included.*

### References:

<sup>a</sup> [https://www.clinicalgenome.org/site/assets/files/5967/gene-validity\\_classification.pdf](https://www.clinicalgenome.org/site/assets/files/5967/gene-validity_classification.pdf) and **Evaluating the Clinical Validity of Gene-Disease Associations: An Evidence-Based Framework developed by the Clinical Genome Resource**, PMID:28552198.

<sup>b</sup> <https://decipher.sanger.ac.uk/ddd#ddgenes> and **Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data**. PMID: 25529582.



## Appendix C: Genomics England Gene Panel Principles

- A conservative list of **Green** genes of known clinical utility and scientific validity is required.
- The **Green** genes on a panel should be a conservative (diagnostic grade) set of genes that out of the whole genome should be examined first, as variants within these genes are most likely to cause/explain the disease phenotype. We acknowledge that the panel will therefore be missing genes that have been reported in association with the disease/phenotype but where the level of proof has not reached that required for them to enter use in a diagnostic setting. Variants that have passed the standard filtering criteria but are not within the gene panel for the relevant disease category will be assigned to a separate tier (Tier 3).
- Genes included on a panel may have been screened in a patient previously (for example, may be included within prior-genetic testing before recruitment to the 100,000 Genomes Project); however, variants of interest in genes not well covered by exome sequencing or missed by other methods may be detected by whole genome sequencing and should be included.
- A single gene may appear in multiple gene panels.
- Genes may also be associated with additional phenotypes not indicated in the gene panel.
- The gene panels will be updated as we learn from new published evidence and the 100,000 Genomes Project participant data.

## Appendix D: Example PanelApp WebServices queries, and terms available for Mode of Inheritance queries

Query Description	Query Example
Get a list of the panel names	<a href="https://panelapp.genomicsengland.co.uk/WebServices/list_panels/">https://panelapp.genomicsengland.co.uk/WebServices/list_panels/</a>
Get information about individual panels using the panel name (last version of the panel by default)	<a href="https://panelapp.genomicsengland.co.uk/WebServices/list_panels/?Name=Epileptic%20encephalopathy">https://panelapp.genomicsengland.co.uk/WebServices/list_panels/?Name=Epileptic%20encephalopathy</a>
Get individual panels using the panel identifier (last version of the panel by default)	<a href="https://panelapp.genomicsengland.co.uk/WebServices/get_panel/55940f0e22c1fc4f7d26e965">https://panelapp.genomicsengland.co.uk/WebServices/get_panel/55940f0e22c1fc4f7d26e965</a> <a href="https://panelapp.genomicsengland.co.uk/WebServices/get_panel/67">https://panelapp.genomicsengland.co.uk/WebServices/get_panel/67</a>
Select a specific version of a panel (version=X.X)	<a href="https://panelapp.genomicsengland.co.uk/WebServices/get_panel/Epileptic%20encephalopathy/?version=1.0">https://panelapp.genomicsengland.co.uk/WebServices/get_panel/Epileptic%20encephalopathy/?version=1.0</a>
Filter <b>Green</b> genes by level of confidence	<a href="https://panelapp.genomicsengland.co.uk/WebServices/get_panel/Epileptic%20encephalopathy/?LevelOfConfidence=HighEvidence">https://panelapp.genomicsengland.co.uk/WebServices/get_panel/Epileptic%20encephalopathy/?LevelOfConfidence=HighEvidence</a>
Filter <b>Green</b> and <b>Red</b> genes by level of confidence	<a href="https://panelapp.genomicsengland.co.uk/WebServices/get_panel/Epileptic%20encephalopathy/?LevelOfConfidence=HighEvidence,LowEvidence">https://panelapp.genomicsengland.co.uk/WebServices/get_panel/Epileptic%20encephalopathy/?LevelOfConfidence=HighEvidence,LowEvidence</a>
Filter the genes by biallelic mode of inheritance	<a href="https://panelapp.genomicsengland.co.uk/WebServices/get_panel/Epileptic%20encephalopathy/?LevelOfConfidence=HighEvidence,LowEvidence&amp;modesOfInheritance=biallelic">https://panelapp.genomicsengland.co.uk/WebServices/get_panel/Epileptic%20encephalopathy/?LevelOfConfidence=HighEvidence,LowEvidence&amp;modesOfInheritance=biallelic</a>
Search for panels by gene	<a href="https://panelapp.genomicsengland.co.uk/WebServices/search_genes/BTK/">https://panelapp.genomicsengland.co.uk/WebServices/search_genes/BTK/</a>
Search for a gene in one panel	<a href="https://panelapp.genomicsengland.co.uk/WebServices/search_genes/BTK/?panel_name=Intellectual%20disability&amp;format=json">https://panelapp.genomicsengland.co.uk/WebServices/search_genes/BTK/?panel_name=Intellectual%20disability&amp;format=json</a>
Search by a gene, and pull out information only when it is rated <b>Green</b>	<a href="https://panelapp.genomicsengland.co.uk/WebServices/search_genes/BTK/?&amp;LevelOfConfidence=HighEvidence&amp;format=json">https://panelapp.genomicsengland.co.uk/WebServices/search_genes/BTK/?&amp;LevelOfConfidence=HighEvidence&amp;format=json</a>
Search by gene from a particular source (e.g. UKGTN)	<a href="https://panelapp.genomicsengland.co.uk/WebServices/search_genes/BTK/?&amp;Evidences=UKGTN&amp;format=json">https://panelapp.genomicsengland.co.uk/WebServices/search_genes/BTK/?&amp;Evidences=UKGTN&amp;format=json</a>
Search for all genes in a panel	<a href="https://panelapp.genomicsengland.co.uk/WebServices/search_genes/all/?panel_name=Intellectual%20disability&amp;format=json">https://panelapp.genomicsengland.co.uk/WebServices/search_genes/all/?panel_name=Intellectual%20disability&amp;format=json</a>
Specify the genome build with either GRCh37 (default) or GRCh38 as a value. EnsemblIds will be returned for the specified assembly version: GRCh37	<a href="https://panelapp.genomicsengland.co.uk/WebServices/search_genes/AKT2/?panel_name=Regional%20overgrowth%20disorders&amp;assembly=GRCh38">https://panelapp.genomicsengland.co.uk/WebServices/search_genes/AKT2/?panel_name=Regional%20overgrowth%20disorders&amp;assembly=GRCh38</a>

version 82 or GRch38 version 90 if they exist in the database.	
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## Available Filters

PanelApp Mode of Inheritance	WebServices Query
MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	"monoallelic_not_imprinted"
MONOALLELIC, autosomal or pseudoautosomal, maternally imprinted (paternal allele expressed)	"monoallelic_maternally_imprinted"
MONOALLELIC, autosomal or pseudoautosomal, paternally imprinted (maternal allele expressed)	"monoallelic_paternally_imprinted"
MONOALLELIC, autosomal or pseudoautosomal, imprinted status unknown	"monoallelic"
BIALLELIC, autosomal or pseudoautosomal	"biallelic"
BOTH monoallelic and biallelic, autosomal or pseudoautosomal	"monoallelic_and_biallelic"
BOTH monoallelic and biallelic (but BIALLELIC mutations cause a more SEVERE disease form), autosomal or pseudoautosomal	"monoallelic_and_more_severe_biallelic"
X-LINKED: hemizygous mutation in males, biallelic mutations in females	"xlinked_biallelic"
X-LINKED: hemizygous mutation in males, monoallelic mutations in females may cause disease (may be less severe, later onset than males)	"xlinked_monoallelic"
MITOCHONDRIAL	"mitochondrial"
Unknown	"unknown"

**ModeOfPathogenicity** : comma separated list of modes of pathogenicities, one of the following values:

- loss\_of\_function
- other

**Penetrance** : comma separated list of penetrance values, one of the following:

- unknown
- Complete
- Incomplete

**LevelOfConfidence** : comma separated list of confidence levels, one of the following:

- HighEvidence (green)
- ModerateEvidence (amber)
- LowEvidence (red)

**Evidences**: comma separated list of evidences, one of the following:

- radboud\_university\_medical\_center\_nijmegen
- illumina\_trugenome\_clinical\_sequencing\_services
- emory\_genetics\_laboratory
- ukgt
- other
- export\_list
- export\_review
- literature
- eligibility\_statement\_prior\_genetic\_testing
- research

## Appendix E: Glossary

### Eligibility statement

Eligibility statements for each of the rare diseases have been written and can be found on the Genomics England website (<https://www.genomicsengland.co.uk/information-for-gmc-staff/rare-disease-documents/>). The aim of the eligibility statements is to provide guidance to clinicians regarding the patients most likely to benefit from the opportunity of diagnostic whole genome sequencing and who are therefore eligible for recruitment into the Genomics England Rare Diseases Programme. Each eligibility statement has been informed by at least one clinician specialising in the field and represents a significant effort on the part of the rare disease clinical community.

Each eligibility statement is composed of the following key information:

1. The sub-category (Level 3) and disease (Level 4) titles.
2. Inclusion criteria – the clinical features, characteristics or investigations that probands with a given disease must have in order to be eligible for recruitment.
3. Exclusion criteria - the clinical features, characteristics or investigation findings that participants with a given disease must not have in order to be eligible for recruitment.
4. Prior genetic testing – this sets out both in general terms, and where appropriate more specifically, the genetic testing which participants with a given disease must have performed prior to recruitment.

The relevant eligibility statement is provided in the gene panel *description* box for each rare disease when available. For some gene panels, no eligibility statement is available at the current time. These include disorders within the pilot that were not taken to the main phase of the programme, or Panels encompassing a broader set of diseases, or panels for the cancer programme.

### Level 4 panel title, Level 3 title, Level 2 title

These terms refer to the rare disorder categories and titles e.g. Arrhythmogenic Right Ventricular Cardiomyopathy (level 4 title) is a disease under the Cardiomyopathy sub-category (level 3 title), within Cardiovascular disorders (level 2 title).

### Gene symbol

The HGNC-approved symbol for the gene ().

### Gene description

The HGNC-approved name for the gene.

### GEL Status

The current gene rating:

- 3 or 4 = Green = highest level of confidence
- 2 = Amber = intermediate level of confidence
- 1 or 0 = Red = lowest level of confidence

The 4 sources used in the initial establishment and ratings of genes are listed in Appendix A:

### Mode of inheritance

Standardised terms were used to represent the gene-disease mode of inheritance, and were mapped to commonly used terms from the different sources. Below each of the terms is described, along with the equivalent commonly-used terms.

***MONOALLELIC, autosomal or pseudoautosomal, not imprinted:*** A variant on one allele of this gene can cause the disease, and imprinting has not been implicated.

***MONOALLELIC, autosomal or pseudoautosomal, maternally imprinted (paternal allele expressed):*** A variant on the paternally-inherited allele of this gene can cause the disease, if the alternate allele is imprinted (function muted).

***MONOALLELIC, autosomal or pseudoautosomal, paternally imprinted (maternal allele expressed)***: A variant on the maternally-inherited allele of this gene can cause the disease, if the alternate allele is imprinted (function muted).

***MONOALLELIC, autosomal or pseudoautosomal, imprinted status unknown***: A variant on one allele of this gene can cause the disease. This is the default used for autosomal dominant mode of inheritance where no knowledge of the imprinting status of the gene required to cause the disease is known. Mapped to the following commonly used terms from different sources: autosomal dominant, dominant, AD, DOMINANT.

***BIALLELIC, autosomal or pseudoautosomal***: A variant on both alleles of this gene is required to cause the disease. Mapped to the following commonly used terms from different sources: autosomal recessive, recessive, AR, RECESSIVE.

***BOTH monoallelic and biallelic, autosomal or pseudoautosomal***: The disease can be caused by a variant on one or both alleles of this gene. Mapped to the following commonly used terms from different sources: autosomal recessive or autosomal dominant, recessive or dominant, AR/AD, AD/AR, DOMINANT/RECESSIVE, RECESSIVE/DOMINANT.

***BOTH monoallelic and biallelic (but BIALLELIC mutations cause a more SEVERE disease form), autosomal or pseudoautosomal***: A variant on one allele of this gene can cause the disease, however a variant on both alleles of this gene can result in a more severe form of the disease/phenotype.

***X-LINKED: hemizygous mutation in males, biallelic mutations in females***: A variant in this gene can cause the disease in males as they have one X-chromosome allele, whereas a variant on both X-chromosome alleles is required to cause the disease in females. Mapped to the following commonly used term from different sources: X-linked recessive.

***X linked: hemizygous mutation in males, monoallelic mutations in females may cause disease (may be less severe, later onset than males)***: A variant in this gene can cause the

disease in males as they have one X-chromosome allele. A variant on one allele of this gene may also cause the disease in females, though the disease/phenotype may be less severe and may have a later-onset than is seen in males. X-linked inactivation and mosaicism in different tissues complicate whether a female presents with the disease, and can change over their lifetime. This term is the default setting used for X-linked genes, where it is not known definitively whether females require a variant on each allele of this gene in order to be affected. Mapped to the following commonly used terms from different sources: X-linked dominant, x-linked, X-LINKED, X-linked.

**MITOCHONDRIAL:** The gene is in the mitochondrial genome and variants within this can cause this disease, maternally inherited. Mapped to the following commonly used term from different sources: Mitochondrial.

**Unknown:** Mapped to the following commonly used terms from different sources: Unknown, NA, information not provided.

**Other - please specify in evaluation comments:** For example, if the mode of inheritance is digenic, please indicate this in the comments and which other gene is involved.

## Sources

The source of the gene-phenotype information is provided. The sources are summarised in Appendix A.

## Phenotypes

Phenotypes collected from the sources are provided where possible and include phenotypes and disease names together with the MIM identifier.

## OMIM

A link to the gene page on OMIM is provided to give reviewers quick access to gene-disease information.



## ClinVar Variants

A link to the gene page on ClinVar is provided for quick access to information regarding variants within the gene that are associated with different conditions.

## Penetrance

This is set as a default to "complete". Reviewers can provide information regarding the penetrance during their gene evaluations (Section 4.3).

## Publications

Publications that provide evidence linking this gene to this disorder, or provide evidence disputing a role for a gene in a disease.

## Mode of pathogenicity

For each gene in a gene panel in PanelApp, it is assumed that loss-of-function variants (see Appendix E) in this gene can cause the disease/phenotype unless an exception to this rule is known. In PanelApp, we are collecting information regarding exceptions to this rule.

## Sequence Ontology (SO) Terms and Descriptions

In PanelApp, we classify loss-of-function (high-impact) variants as those with the following [Sequence Ontology](#) (SO) terms:

SO ID	Name	Definition
SO:0001893	transcript_ablation	A feature ablation whereby the deleted region includes a transcript feature.
SO:0001574	splice_acceptor_variant	A splice variant that changes the 2 base region at the 3' end of an intron.
SO:0001575	splice_donor_variant	A splice variant that changes the 2 base region at the 5' end of an intron.
SO:0001587	stop_gained	A sequence variant whereby at least one base of a codon is changed, resulting in a premature stop codon, leading to a shortened transcript.
SO:0001589	frameshift_variant	A sequence variant which causes a disruption of the translational reading frame, because the number of

		nucleotides inserted or deleted is not a multiple of three.
SO:0001578	stop_lost	A sequence variant where at least one base of the terminator codon (stop) is changed, resulting in an elongated transcript.
SO:0001582	initiator_codon_variant	A codon variant that changes at least one base of the first codon of a transcript.

## History

A record of when the gene was added to the panel in PanelApp and additional key changes to information regarding the gene.

## Tags

Attached to a gene within a gene panel by a curator. Tags highlight useful information about a gene or gene variants that may affect gene ratings, or may be useful for future curation.

The [tag](#) is specific to a gene within a given disorder. The descriptions of key tags are:

PanelApp Tag	Tag description
nucleotide-repeat-expansion	For this phenotype, nucleotide-repeat-expansions can cause the disorder.
adult-onset	This relevant phenotype shows only adult onset
CNV	There are pathogenic copy-number-variants reported for this gene.
deletions	There are pathogenic deletion variants reported for this gene
dominant-negative	Gene2Phenotype lists dominant negative as the mutation consequence.
founder-effect	There is only a single variant that has been reported to have a founder effect in a particular population, or a shared haplotype has been observed. Genes with a founder-effect tag are rated Red as there is not currently enough evidence that other variants in the gene are disease causing
gene-duplication	There are pathogenic gene duplication variants reported for this gene.
missense	Only missense variants have been reported for this gene for this phenotype/disorder.

monogenic-polygenic:	Both monogenic associations and polygenic associations have been reported for this gene.
polygenic	Only associations in combination with other variants in other genes have been reported. Genes with a 'polygenic' tag are rated Red as monogenic variants are reported for the 100,000 Genomes interpretation pipeline
multifactorial	The genetic association is in combination with environmental/other factors. Note that these genes are <u>not</u> Green genes.
new-gene-name	The HGNC gene symbol has been updated compared to the gene symbol on PanelApp. These symbols will be updated in-line with Ensembl.
non-coding-known-pathogenic	There are non-coding pathogenic variants reported for this gene
treatable	There is a treatment that targets variants in this gene, or there are treatment options for this disorder based on a diagnosis from variants in this gene, or supplementation may prevent or alleviate symptoms.
mosaicism	Mosaicism has been reported
x-linked over dominance	Gene2Phenotype records dominant negative as the mutation consequence
promoter	Pathogenic variants have been reported in the gene promoter, or variations to promoter length have been associated with the phenotype.
structural-variant	Pathogenic structural rearrangements have been reported
sva	Pathogenic short interspersed nuclear element, variable number of tandem repeats, and Alu composite have been reported
pathogenic-synonymous	For genes with synonymous variants with proven pathogenicity
pharmacogenetics	Genes in which variants can affect drug response eg: variants in CYP2C8 are associated with cerivastatin-induced rhabdomyolysis.
y-chromosome	Gene is encoded by the Y-chromosome.

**Table 3. Description of tags attached to a gene within PanelApp.**

## Appendix F: Uses of PanelApp

### I am a Clinician or other Healthcare Professional...

You could use PanelApp to:

- View and interpret a panel that has been applied to your patient (Section 3)
- Look at the evidence for inclusion of a gene(s) in your patient report during a MDT (Sections 3.4 and 3.5)
- Review gene(s) on panel(s) for disease(s) matching your expertise (Section 4.3)
- Add diagnostic genes missing from a panel (Section 4.4)
- Add your publications as evidence for gene-disease relationships (Section 4.3)
- Suggest additional panels to be added that would be useful for research or the clinical community  
(contact [panelapp@genomicsengland.co.uk](mailto:panelapp@genomicsengland.co.uk))
- Provide input on whether gene panels should be combined/merged  
(contact [panelapp@genomicsengland.co.uk](mailto:panelapp@genomicsengland.co.uk))

### I am a Researcher...

You could use PanelApp to:

- Source data for hypothesis generation.
- Study gene-disease relationships for genome interpretation, pathway analysis and more.
- Use 'tagged' genes to investigate genes with interesting disease-causing mechanisms (Appendix E).
- Use **Red** and **Amber** genes as a source of genes needing further evidence/investigation within your disease of interest for certain diseases (Section 2.3).
- Review genes and/or panels you have expertise in to help genome interpretation (Section 4.3).
- Add novel genes to panels that you find within your research (Section 4.4)

- Add your publications as evidence for gene-disease relationships (Section 4.3)
- Suggest additional panels to be added that would be useful for research or the clinical community (contact [panelapp@genomicsengland.co.uk](mailto:panelapp@genomicsengland.co.uk))
- Provide input on whether gene panels should be combined/merged (contact [panelapp@genomicsengland.co.uk](mailto:panelapp@genomicsengland.co.uk))
- Query PanelApp data through WebServices (Section 3.9, and Appendix D).

### I am a Bioinformatician

You could use PanelApp to:

- Use panels for your exome/genome interpretation pipeline
- Query PanelApp data through WebServices (Section 3.9, and Appendix D).

## 9 Disclaimer

### **PanelApp Uses Exclusions of Liability**

PanelApp gene lists are provided by Genomics England in good faith, and for the benefit of the research community. The original gene lists have been supplied through commercial and academic providers, but have not been separately verified by Genomics England. Equally, expert reviewers and curators adding content and comments through PanelApp do so under their own responsibility and without verification by Genomics England. Users must themselves verify the accuracy and content any information (including in respect of ownership of any intellectual property rights) obtained through PanelApp in advance of its use for any purpose. Genomics England, any expert reviewers and curators hereby exclude any and all liability, including without limitation under any laws of contract, tort (including negligence) or statutory duty or otherwise, and do not accept any liability or responsibility for uses made of the PanelApp gene lists or comments by individual reviewers.

### **PanelApp Connections Exclusions of Liability**

Access to the PanelApp is not guaranteed. Genomics England accepts no liability and excludes all liability in respect of interruptions in accessing or inability to access the PanelApp gene lists at any time. Persons accessing PanelApp are responsible keep their anti-virus and security software up to date. Genomics England consequently accepts no liability for any loss or damage occurring as a result of any person using or connecting to or through PanelApp.

### **General Exclusion of Liability and Limitations on exclusions of Liability**

Genomics England shall not be responsible for any of the following losses to persons using or accessing PanelApp, howsoever incurred, whether in contract, tort (including negligence), breach of statutory duty or otherwise: indirect losses, consequential losses, loss of income or revenue, loss of profit, third party claims, loss of business, loss of data, loss of anticipated savings, or any loss of opportunity.

No provision of this disclaimer shall operate to limit or exclude liabilities which cannot by the applicable laws of England be so limited or excluded.

## 10 Acknowledgements

**PanelApp creator:** Antonio Rueda-Martin

**PanelApp Curators (past and present):** Ellen McDonagh, Sarah Leigh, Rebecca Foulger, Louise Daugherty, Olivia Niblock, Alice Gardham, Arianna Tucci, Helen Brittain, Eik Haraldsdóttir, Ellen Thomas, Richard Scott, Caroline Wright, Emma Baple, Damian Smedley, Chris Boustred, Kirsty McCaffrey, Chris Campbell, Maria Athanasopoulou.

**Software Developers:** Paul Hayes, Oleg Gerasimenko

**Other contributors to the PanelApp and PanelApp documentation:** Augusto Rendon, Katherine Smith, Clare Turnbull, Jo Whittaker, Mina Ryten, Tom Fowler and members of the V&F GeCIP Domain.

Acknowledgment of reviewer names and affiliations can be viewed for each individual gene panel on PanelApp.

*Thank you to all experts who have contributed gene lists during the development of rare disease eligibility statements and data models, or by submitting their own gene panels. These have been added to the gene panels on PanelApp where possible. Also thank you to all our reviewers and for all feedback that has aided the development of the PanelApp tool.*

## 11 Document History

The controlled copy of this document is maintained in the Genomics England internal document management system. Any copies of this document held outside of that system, in whatever format (for example, paper, email attachment), are considered to have passed out of control and should be checked for currency and validity. This document is uncontrolled when printed.

This document has not yet received final approval from Genomics England internal governance processes or NHS England and is therefore potentially subject to change.

### 5.1 Version History

Version	Date	Description
<b>3.0</b>	21/08/2015	Incorporation of feedback from Eik Haraldsdóttir, Richard Scott, Katherine Smith.
<b>3.1</b>	24/08/2015	Formatting and grammatical changes.
<b>3.2</b>	02/09/2015	Formatting and grammatical changes.
<b>3.3</b>	03/09/2015	Formatting and grammatical changes.
<b>3.4</b>	08/09/2015	Formatting and grammatical changes.
<b>3.5</b>	08/09/2015	Formatting and grammatical changes.
<b>4.0</b>	19/01/2016	Update of the Handbook to reflect changes to the PanelApp website and tools, and addition of a disclaimer.
<b>4.1</b>	19/01/2016	Incorporation of feedback from Tom Fowler.
<b>5.0</b>	05/09/2017	Update of the Handbook by Rebecca Foulger, Ellen McDonagh, and Genomics England curators to reflect current practices.
<b>5.1</b>	02.10.2017	Incorporation of feedback by Richard Scott and Helen Brittain
<b>5.2</b>	11.10.2017	Incorporation of PanelApp2 features and PanelApp2 URLs from Oleg Gerasimenko
<b>5.3</b>	31.10.2017	Formatting to finalise handbook
<b>5.4</b>	06.11.2017	Final check for release.
<b>5.5</b>	07.11.2017	Additional webservice queries added
<b>5.6</b>	10.11.2017	Additional updates with respect to PanelApp2 features, including new screen shot and connecting hyperlinks
<b>5.7</b>	14.11.2017	Correction of email address from <a href="mailto:panelapp@genomicsengland.ac.uk">panelapp@genomicsengland.ac.uk</a> to <a href="mailto:panelapp@genomicsengland.co.uk">panelapp@genomicsengland.co.uk</a>



## 5.2 Reviewers

This document must be reviewed by the following:

Name	Title	Version

## 5.3 Approvers

This document must be approved by the following:

Name	Responsibility	Date	Version

Work stream	Bioinformatics	Document Record ID Key	
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