A process for gaining consensus gene panels in the Genomic Medicine Service using PanelApp

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ACGS summer meeting 2019

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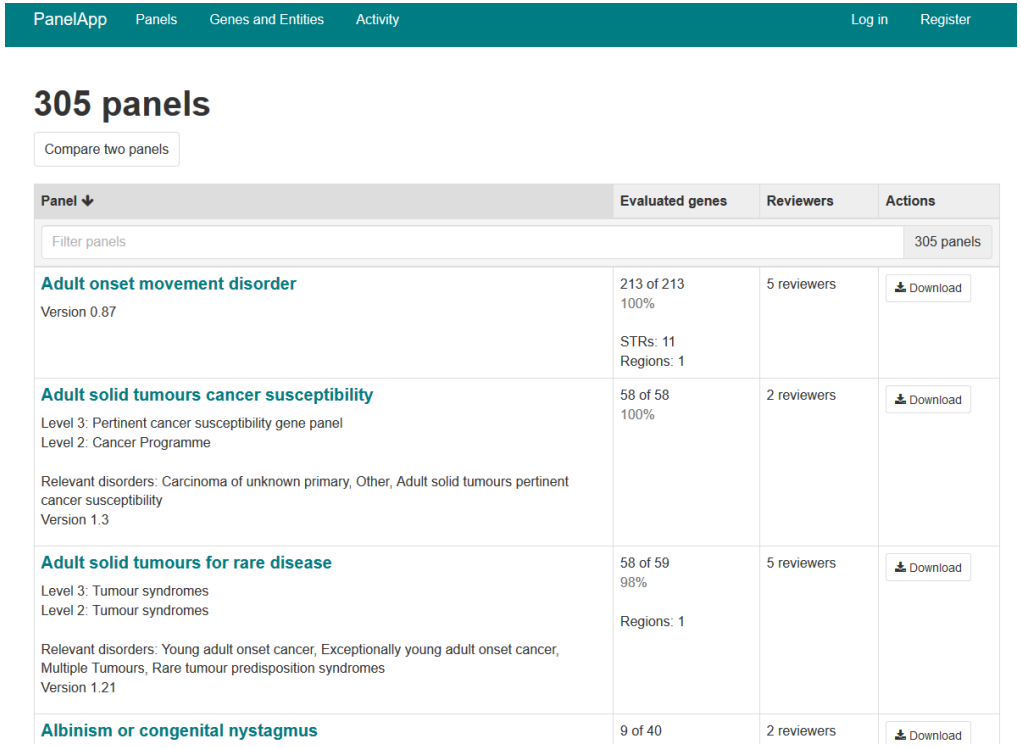
100,000 Genomes Project

- **108,447 whole genome sequences** of National Health Service (NHS) patients with Rare Diseases (and family members) or Cancer have been sequenced.

- Ongoing: **interpretation** of genomes and **return of primary findings** to Genomic Medicine Centres (GMCs), validation and feedback of results to patients.

PanelApp

https://panelapp.genomicsengland.co.uk/



- Crowdsourcing tool
- Knowledge base for scientific community to share virtual gene panels (gene lists)
- Publically available and can be viewed, queried and downloaded via the website or webservices.
- >550 registered reviewers worldwide
- Genes, CNVs and STRs

Enable open discussions in the wider scientific/clinical communities about gene panels and collaborative curation

Achieving consensus panels for NHS England Genomic Medicine Service (GMS) rare disease: PanelApp curators' perspective

NHS England and NHS Improvement

GMS National Genomic Test Directory

- The **National Genomic Test Directory (NGTD)** was established for the Genomic Medicine Service and **lists the tests** that will be **commissioned by the NHS**.
- Developed in collaboration with Genomics England and two expert groups; one for rare diseases and the other for cancers.
- The **NGTD for rare diseases builds on** the evaluation work undertaken by the **UK Genetic Testing Network**. It **combines national and international evaluation approaches, emerging evidence from research and the 100,000 Genomes Project and analysis of current NHS testing activity**.
- The NGTD for rare and inherited disease was consulted on throughout 2018 and published in March 2019.
- It is intended that the **NGTD will be updated on an annual basis**, although there is an expectation that within the first year to 18 months it will remain fairly stable.
- **Proposals to update the NGTD will be submitted to an NHS England Evaluation Panel** that will make recommendations on new tests to be added and changes to current testing.

Purpose of PanelApp in the NHS GMS

NHS GMS

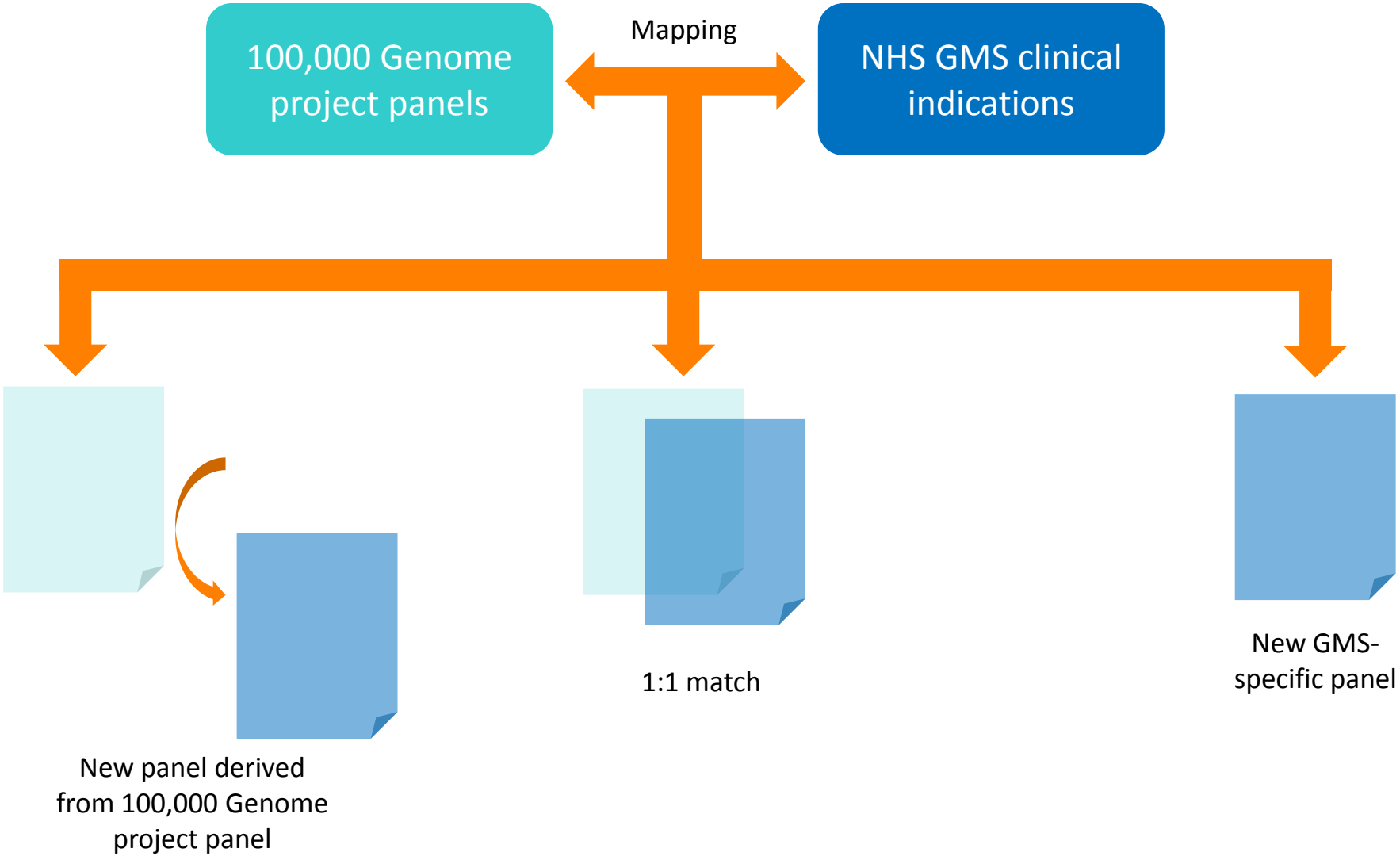
- 16 specialist groups of tests
  - Test working group (expert clinicians and clinical scientists from Genomic Laboratory Hubs, GLHs)
- ~150 disease panels
  - Virtual panels (WES and WGS)
  - 'Wet lab' panels

PanelApp

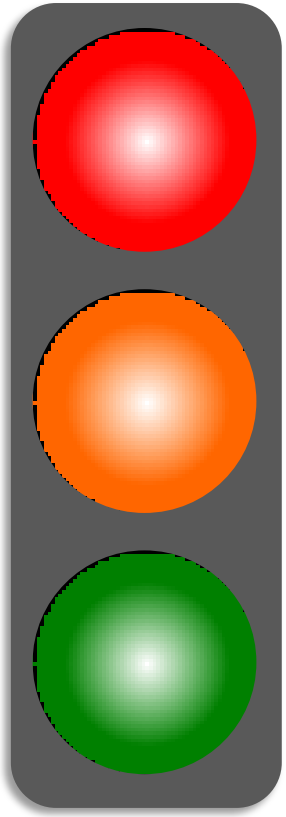
- Platform for GMS consensus panels
- Repository for evidence and details of panel composition
- Easily share and opens up dialogue about panel design and composition between clinicians and scientists

Specialist groups
Cardiology
Endocrinology
Eyes
Gastrohepatology
Haematology
Hearing
Immunology
Inherited cancer
Metabolic
Mitochondrial
Musculoskeletal
Neurology
Renal
Respiratory
Skin
NIPD

Rare Disease Panel Creation



Gene Rating



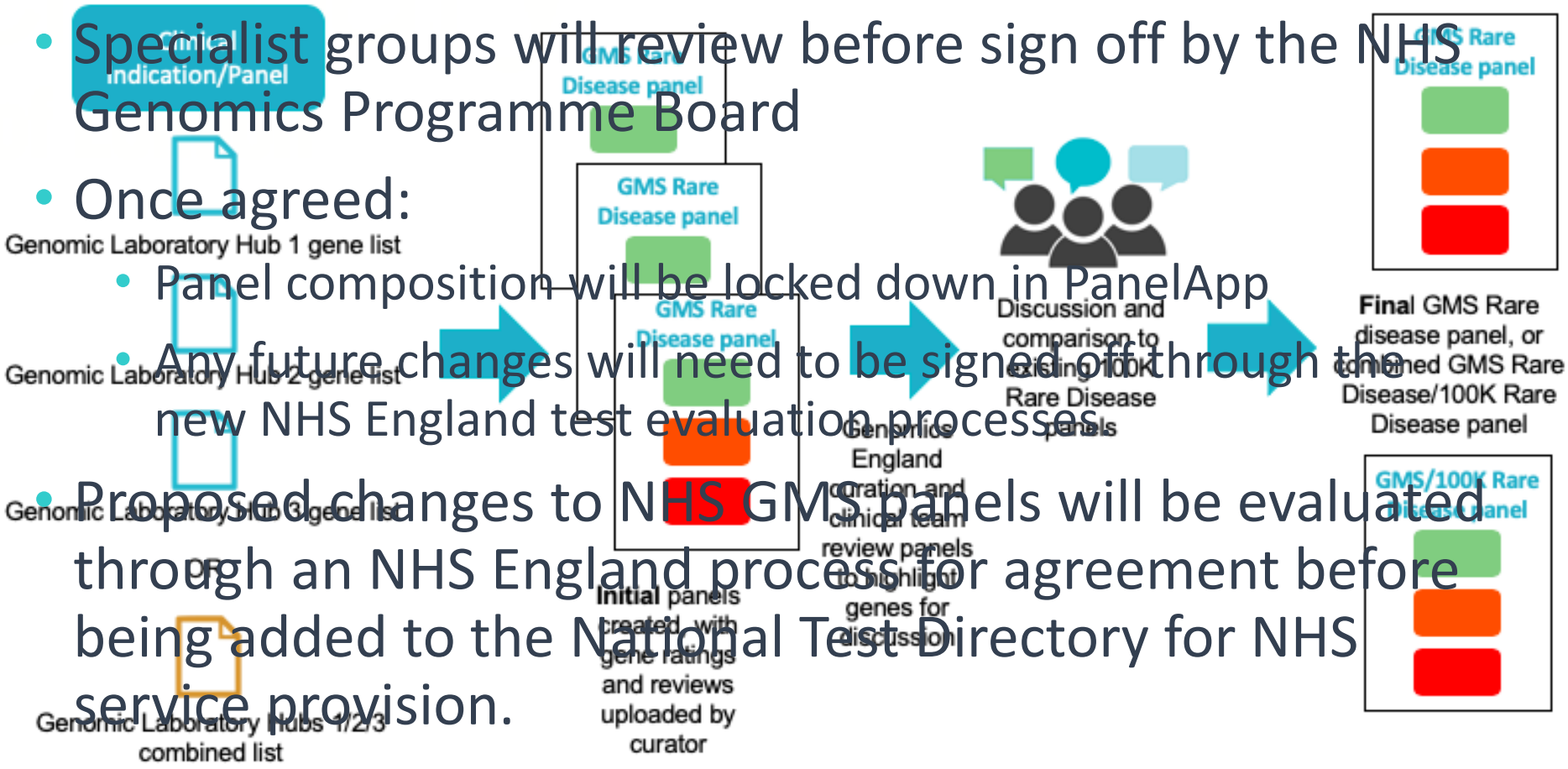
Not enough evidence → Should not be included

Moderate evidence → Could be included for service development purposes (not mandatory)

High level of evidence → Diagnostic grade gene

Workflow for reaching consensus

- Specialist groups will review before sign off by the NHS Genomics Programme Board
- Once agreed:
  - Panel composition will be locked down in PanelApp
  - Any future changes will need to be signed off through the new NHS England test evaluation processes.
- Proposed changes to NHS GMS panels will be evaluated through an NHS England process for agreement before being added to the National Test Directory for NHS service provision.



Thank you: Eleanor Williams & Anna de Burca

PanelApp Curation team

- Facilitate with the consensus process
- Ensure diagnostically relevant genes are included
  - Supported by high level of evidence based on submission of gene lists by specialist groups.
- Ensure all relevant details about the panels are recorded in PanelApp. For example:
  - Genes that are difficult to amplify/sequence
  - Genes that have only a single variant associated with disease
  - Disease-associated variants may only be in untranslated regions (promoter and UTRs)

Topics for discussion

Amber genes

Should these be included for testing? If so then:

- **Can these be promoted to green?**
- **Are there any new cases?**
- **Any additional evidence? (i.e. unpublished data)**

New genes that have been suggested

Genes that have conflicting reviews

Scope of the panels

Mode of inheritance

Members of relevant gene families

Post-discussions

- Changes that were agreed during the discussions are made:
  - Amber genes promoted to Green rating if sufficient evidence is available
  - Additional evidence provided by the specialist group added to the panel
  - New genes added
- Several calls may be required for some specialist groups

Congenital adrenal hypoplasia

Gene: CDKN1C

Green List (high evidence)

CDKN1C (cyclin dependent kinase inhibitor 1C)
EnsemblGeneIds (GRCh38): ENSG00000129757
EnsemblGeneIds (GRCh37): ENSG00000129757
OMIM: 600856, Gene2Phenotype
CDKN1C is in 17 panels

Reviews (4) | Details | History

4 reviews

Anna de Burca (Genomics England Curator)

> As discussed in the GMS Endocrinology Specialist Test Group webex call 28th Jan 2019: this gene presents a difficult target for NGS due to its GC-rich nature.
>
> **5 Mar 2019, 11:22 a.m.**

5 Mar 2019, 11:22 a.m.
Panel version: 1.7

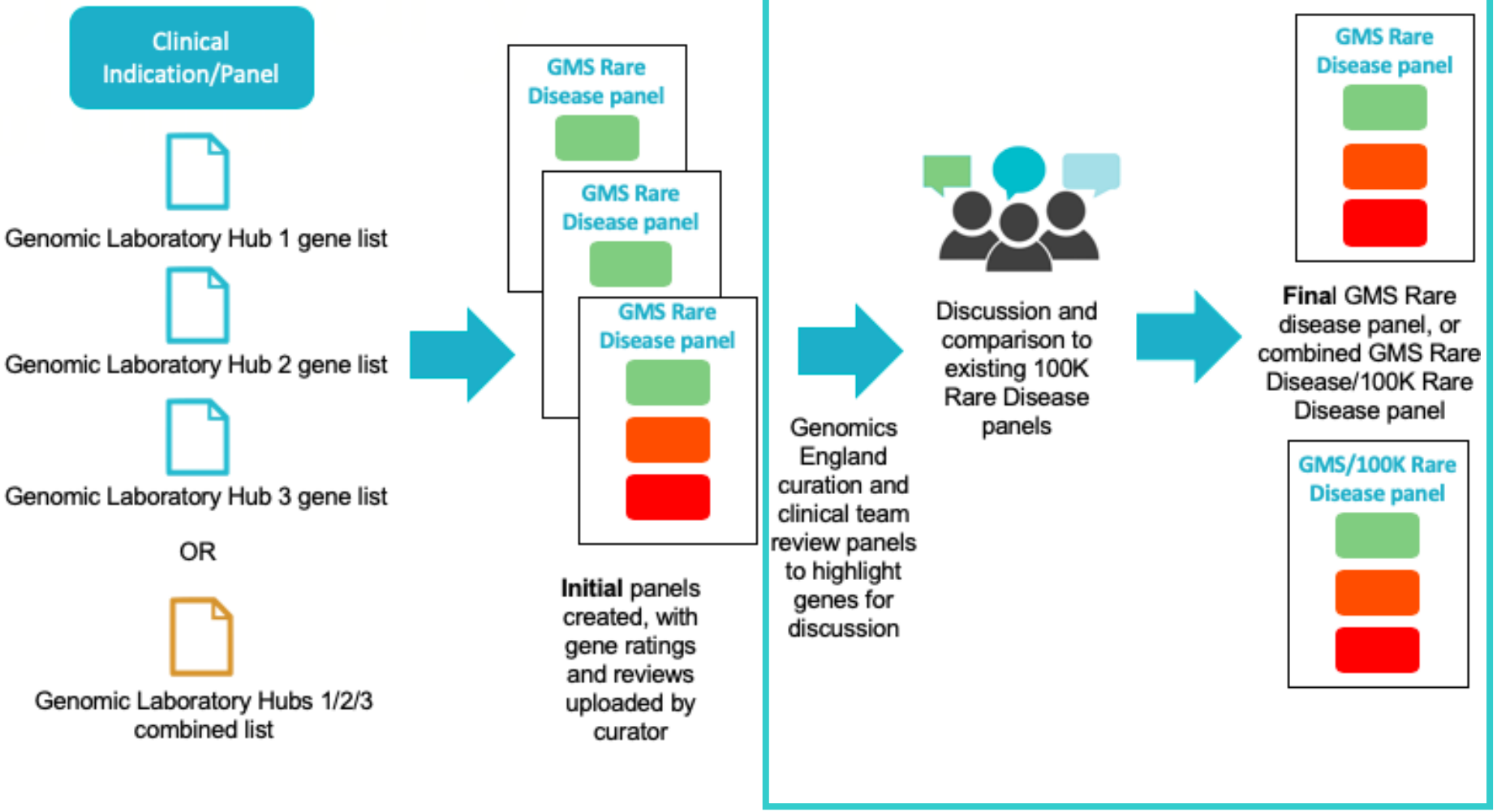
Ivone Leong (Genomics England Curator)

Green List (high evidence)

> Comment when marking as ready: As discussed in the GMS Gastrohepatology Specialist Test Group webex call 14th Jan 2019: The Specialist Test Group agreed that there is enough evidence to rate this gene green.
>
> **12 Mar 2019, 11:27 a.m.**

> Comment when marking as ready: Both OMIM and Gene2Phenotype confirm that ENPP1 is associated with autosomal recessive hypophosphataemic rickets (ARHR). One study (PMID: 20137773) describes 5 individuals with ARHR from 4 unrelated families. The study found 3 different ENPP1 variants. Another study (PMID: 20137772) reported on two brothers with ARHR who have homozygous ENPP1 variant.
>
> **28 Nov 2018, 2:35 p.m.**

Progress so far…



Challenges — Curators' perspective

- Formatting of gene lists before uploading to PanelApp
- Scheduling calls
- Preparation completed for discussions scheduled by NHS England
- Lots to discuss but too little time during the call
  - Large panels – prioritise which genes are most important for discussion
- Gene families
- Creation of panels to encompass wide clinical indications (creation of super panel functionality)
- Knock-on effect of changing a gene rating in GMS super panels

Benefits to PanelApp from GMS process

- Working more closely with the clinical community
- Updates to 100,000 Genome Project panels
- Increased PanelApp reviewers and users
- International collaborations
  - Other countries may want to adopt what we are doing
- Global consensus of gene panels

Acknowledgements

Participants & Partners of the 100,000 Genomes Project

Jane Deller, NHS England Genomics Unit
NHS Genomic Laboratory Hubs & GMS Specialist Group members
Anna de Burca, Genomics England Clinical Team

Reviewers, collaborators & users

PanelApp Developers: Antonio Rueda-Martin, **Oleg Gerasimenko**, Emanuil Ivanov, Paul Hayes

Head of Curation and Pharmacogenomics: Ellen McDonagh

PanelApp Curators: Sarah Leigh, Rebecca Foulger, Louise Daugherty, Eleanor Williams, Olivia Niblock, Helen Brittain.

Other contributers to PanelApp curation, creation, documentation, outreach: Arianna Tucci, Rachel Jones, Eik Haraldsdottir, Alice Gardham, Ellen Thomas, Richard Scott, Caroline Wright, Emma Baple, Damian Smedley, Chris Boustred, Kirsty McCaffrey, Chris Campbell, Augusto Rendon, Mark Caulfield, Katherine Smith, Clare Turnbull, Jo Whittaker, Mina Ryten, Tom Fowler, Andrew Devereau, Alona Sosinksy, Maria Athanasopoulou, Kristina Ibanez-Garikano, Dalia Kasperaviciute, Corey Johnson, James Carroll, Lisa Carr, Lisa Dinh, Verity Fryer, Freya Boardman-Pretty, James Carroll, Matthew Parker, Lara Hawkes, Genomics England Platform Team & Service Desk, Members of the E&I GeCIP Domain (Sian Ellard, Steve Abbs, Dominic McCullun, Helen Firth, William Newman),

Please sign up as a reviewer!

https://panelapp.genomicsengland.co.uk/

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@PanelAppTeam
#PanelApp