



Using the Research Environment for clinical diagnostic discovery

Emily Perry

Research Engagement Manager

13th January 2026



Data security

- This training session will include data from the GEL Research Environment
- As part of your IG training you have agreed to not distribute these data in any way
- If you are joining virtually, you are not allowed to:
 - Invite colleagues to watch this training with you
 - Take any screenshots or videos of the training
 - Share your webinar link (we will remove anyone who is here twice)

Questions



All your
microphones
are muted



Use the Zoom
Q&A to ask
questions



Upvote your
favourite
questions: if we
are short on
time we will
prioritise those
with the most
votes

Helpers



Mimoza Hoti
Clinical Research
Interface Lead



Susan Walker
Director of
Translational
Genomics



**Matthieu
Vizuete-Forster**
Bioinformatician -
Research Services

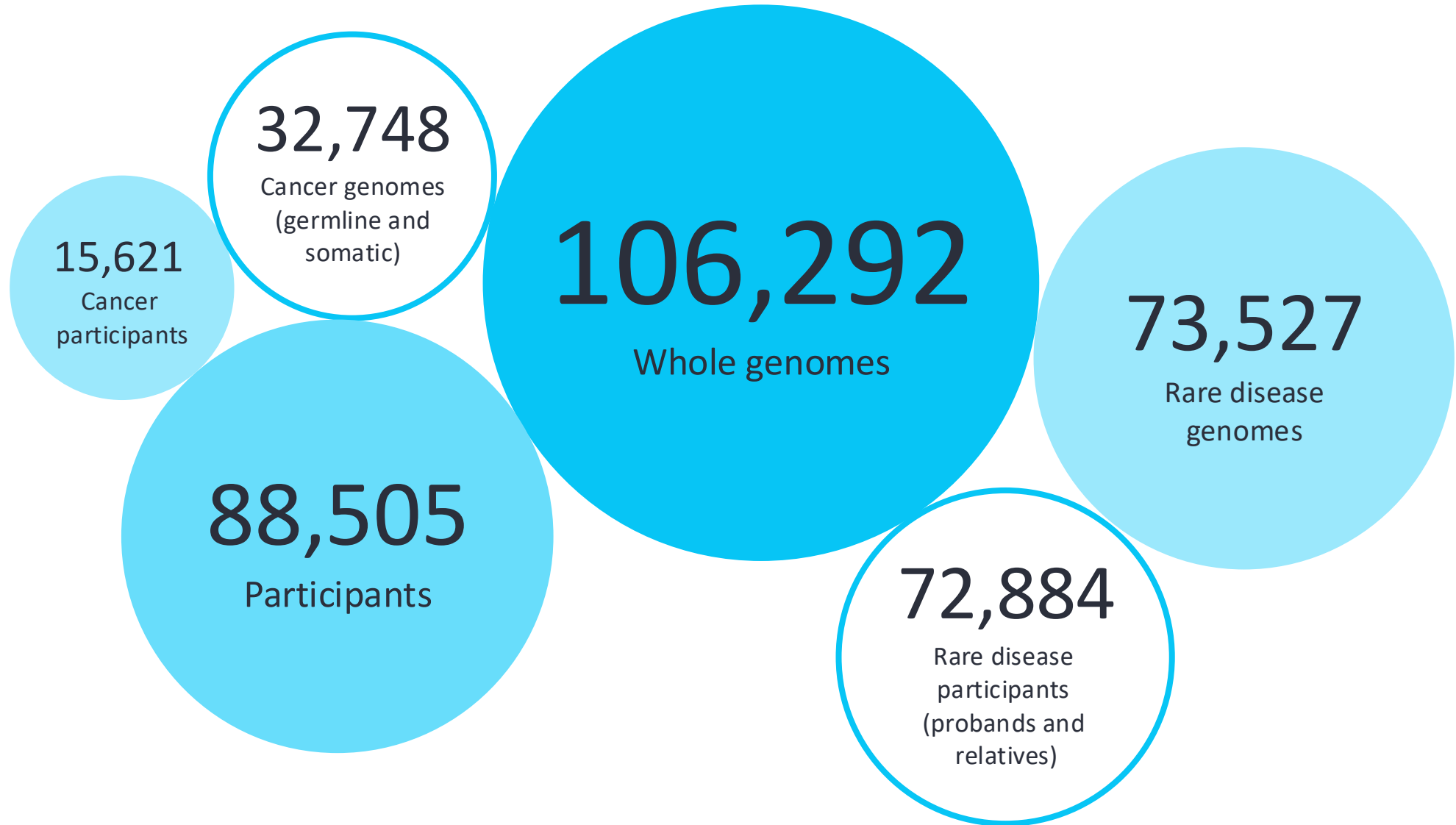
Agenda

- 1 Introduction and admin
- 2 GEL ingestion of rare disease participants
- 3 Identifying participants who need a diagnosis
- 4 Finding results of GEL analysis
- 5 Exploring variants in IVA
- 6 QC your diagnosis
- 7 Find and compare other participants with the same variant
- 8 Submit your diagnosis and/or contact clinicians
- 9 Help and questions

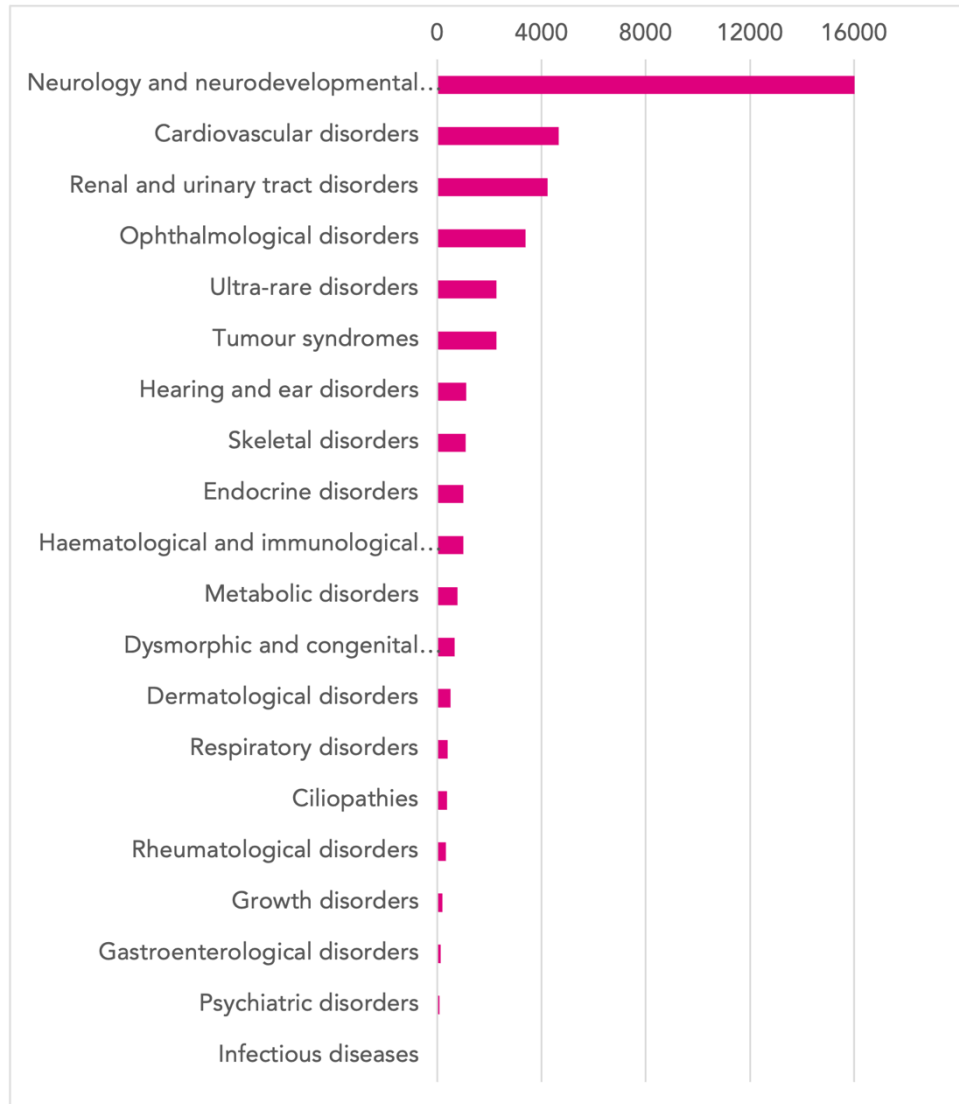


2. GEL ingestion of rare disease participants

100,000 Genomes Project



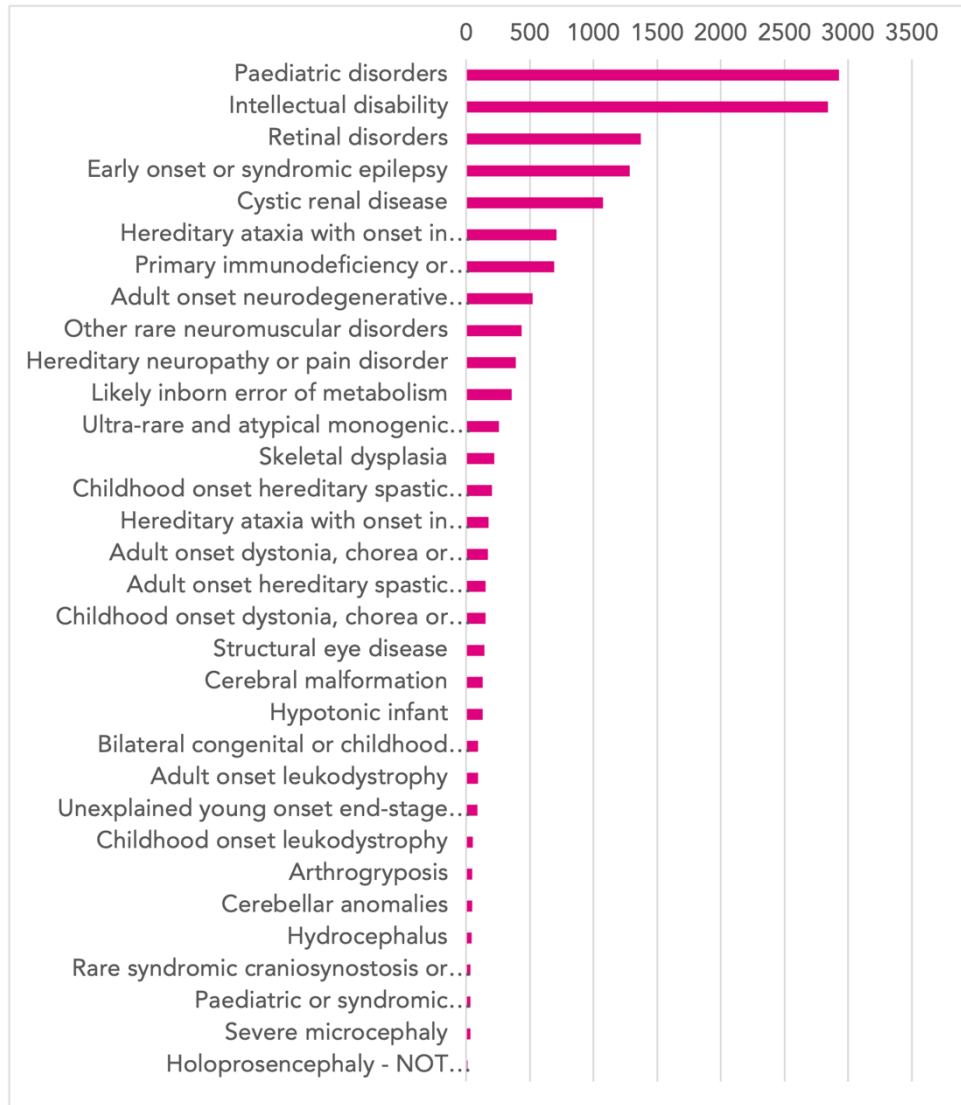
100,000 Genomes rare disease



NHS GMS



NHS GMS rare disease



100kGP

NHS GMS



Outcomes detail



Tiering, exomiser and panels



Phenotyping



Medical history



Participant Explorer



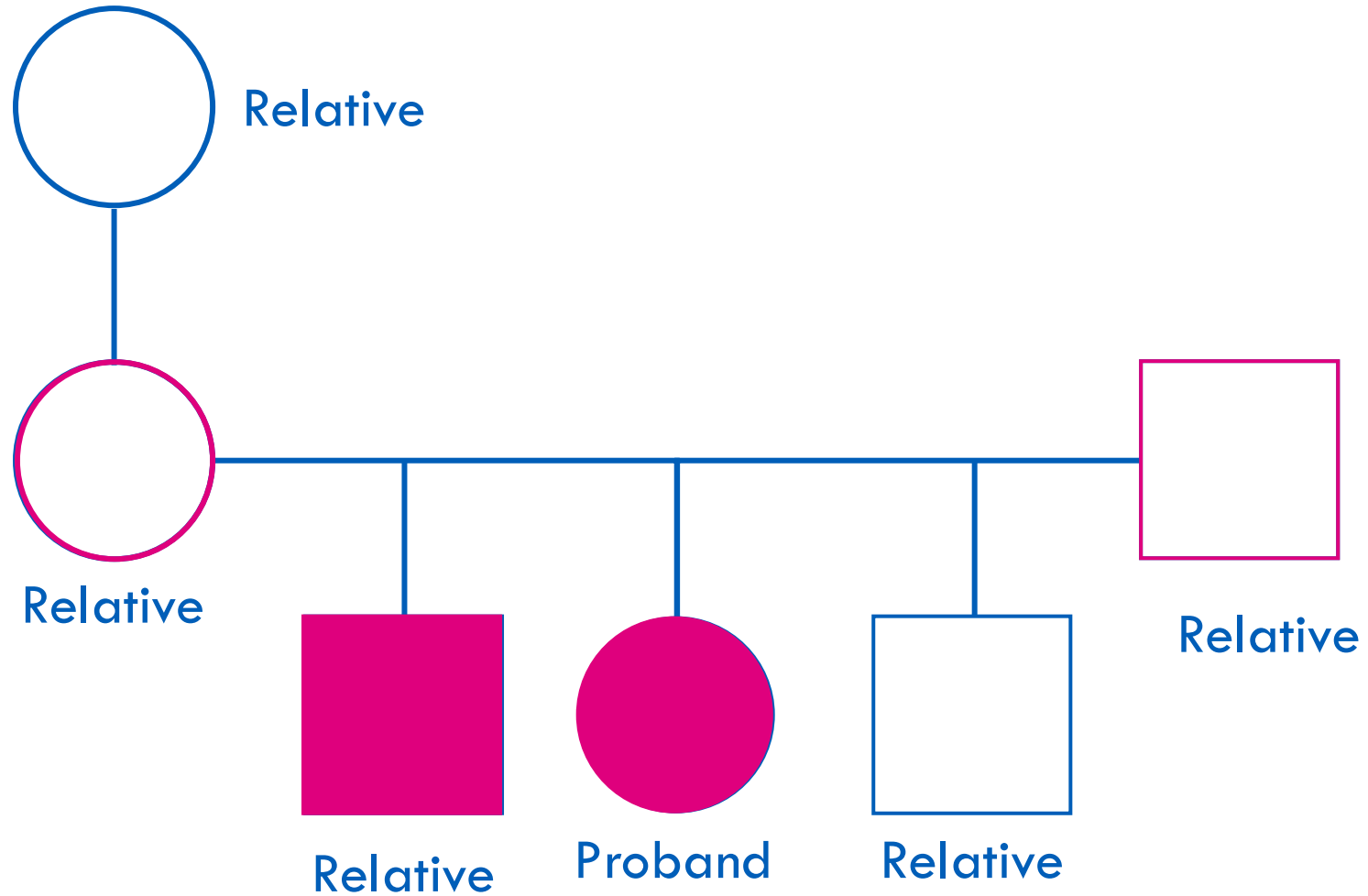
IVA



Genomes as BAMs and VCFs



Pedigrees



Genome
No genome

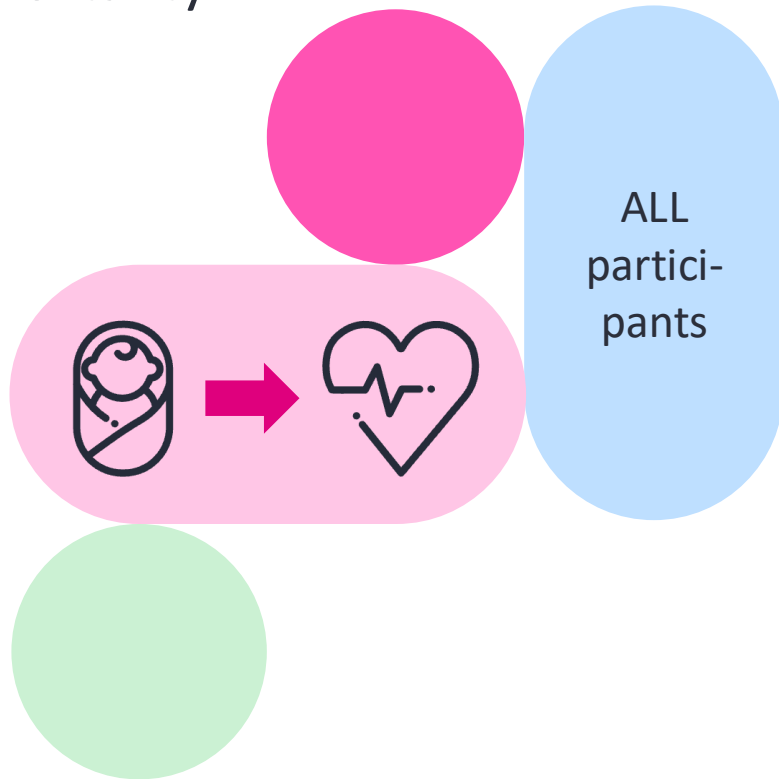
Rare disease phenotyping

- Disease classification
- HPO terms present/absent
- Measurements and observations (not universal)
 - general measurements
 - early childhood observations
 - details of imaging (but not results)
 - genetic tests
 - lab tests

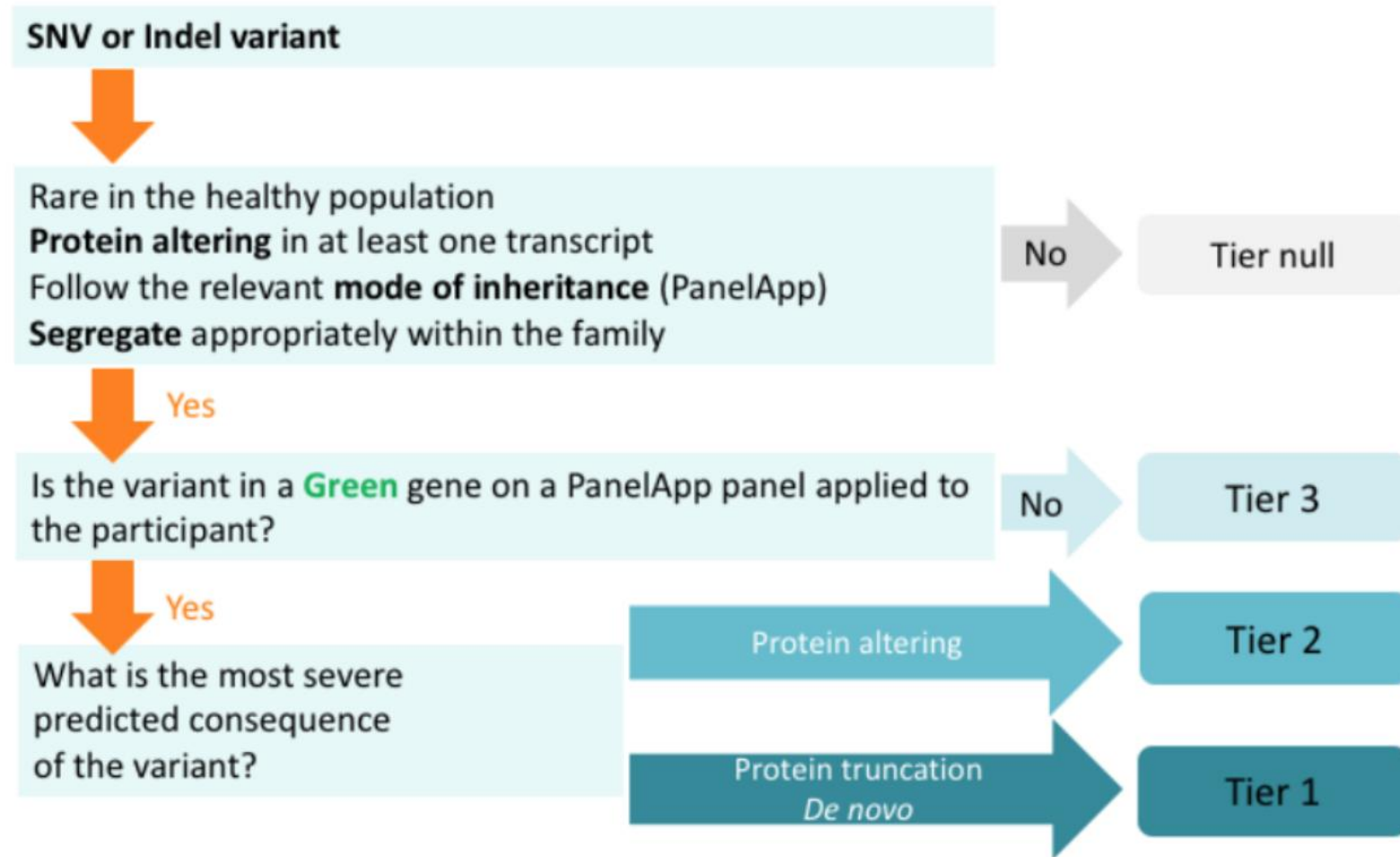


Medical history

- NHSE hospital episode statistics
- Mental health data
- Mortality



Rare disease tiering



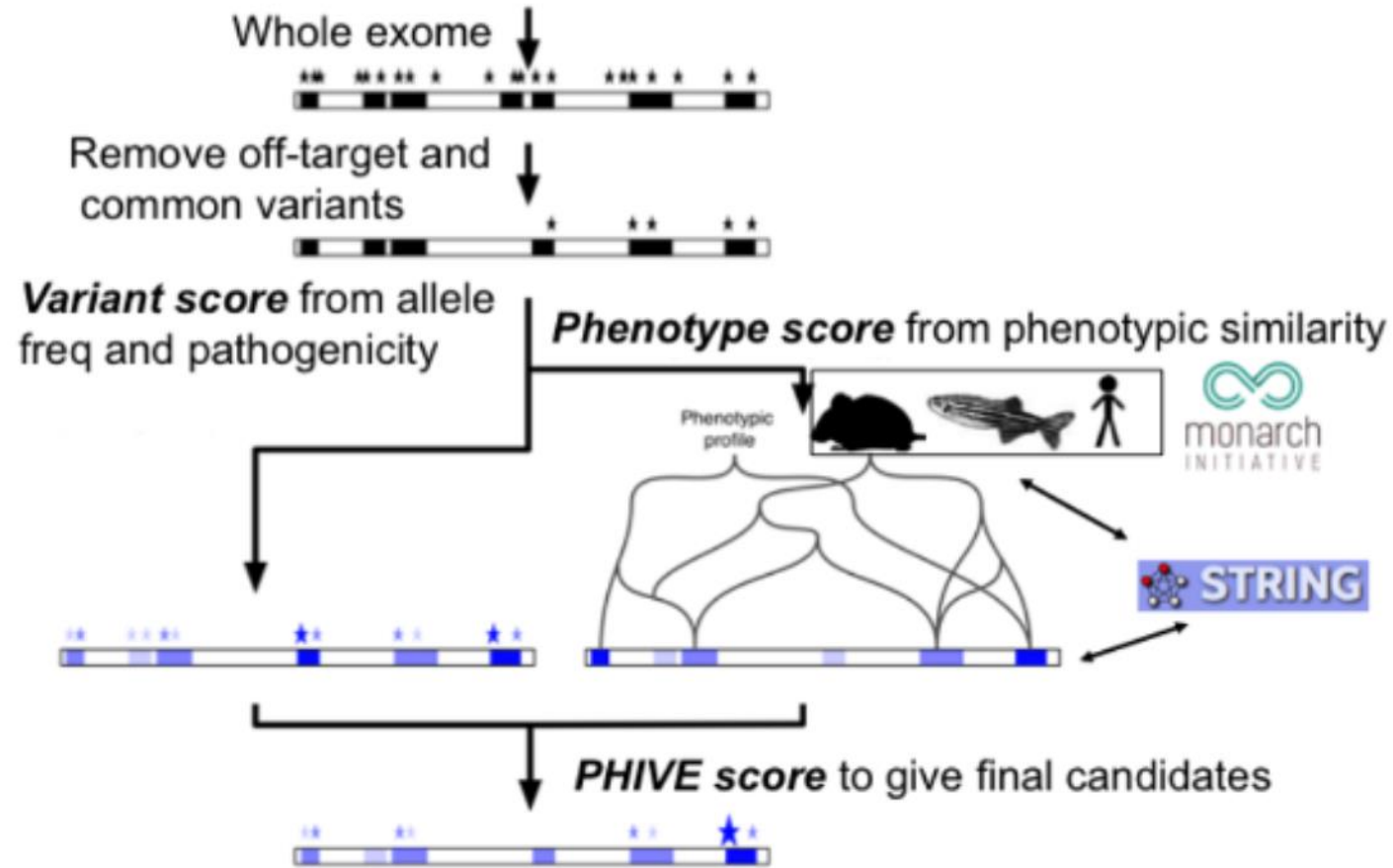
Rare disease tiering based on PanelApp genes

- Gene panels curated by clinicians/geneticists
- Genes rated as:
 - High evidence/diagnostic grade
 - Moderate evidence/ research grade
 - Insufficient evidence
- Includes mode of inheritance required
- Panel(s) chosen according to phenotypes
- Panel version at time of usage listed

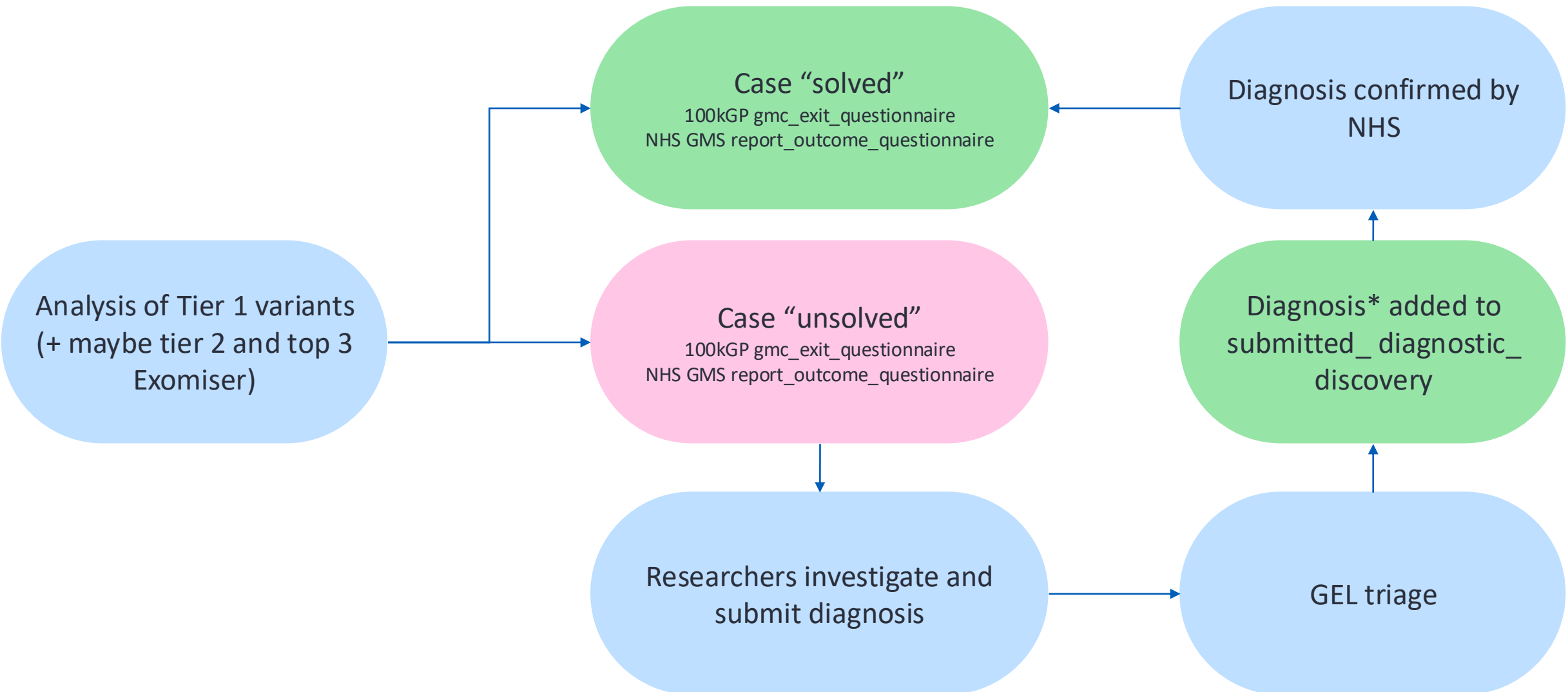
List ↑	Entity	Reviews	Mode of inheritance	Details
	Filter Entities			8 Entities
Green	ATP1A3	1 review 1 green	MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	Sources <ul style="list-style-type: none">• Expert Review• Expert Review Green Phenotypes <ul style="list-style-type: none">• 601338• 614820 Tags
Green	DFNB59	2 reviews 1 green	BIALLELIC, autosomal or pseudoautosomal	Sources <ul style="list-style-type: none">• Expert Review• Expert Review Green Phenotypes <ul style="list-style-type: none">• 610219 Tags <input type="text" value="new-gene-name"/>
Green	OPA1	2 reviews 1 green	MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	Sources <ul style="list-style-type: none">• Eligibility statement prior genetic testing• Expert Review Green Phenotypes <ul style="list-style-type: none">• Optic atrophy 1, OMIM:165500• Optic atrophy plus syndrome, OMIM:125250 Tags
Green	OTOF	1 review 1 green	BIALLELIC, autosomal or pseudoautosomal	Sources <ul style="list-style-type: none">• Expert Review Green• Radboud University Medical Center, Nijmegen Phenotypes <ul style="list-style-type: none">• 601071 Tags
Amber	DIAPH3	3 reviews 1 red	BOTH monoallelic and biallelic, autosomal or pseudoautosomal	Sources <ul style="list-style-type: none">• Expert Review Amber• Radboud University Medical Center, Nijmegen Phenotypes <ul style="list-style-type: none">• Auditory neuropathy, autosomal dominant, 1, 609129 Tags

Rare disease Exomiser

Exomiser

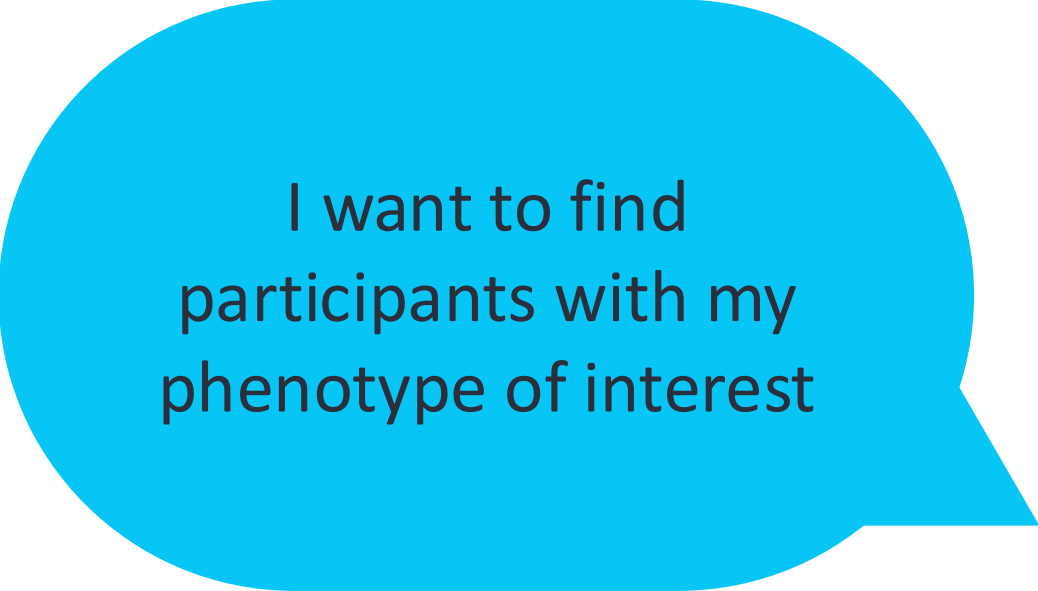


Solved cases

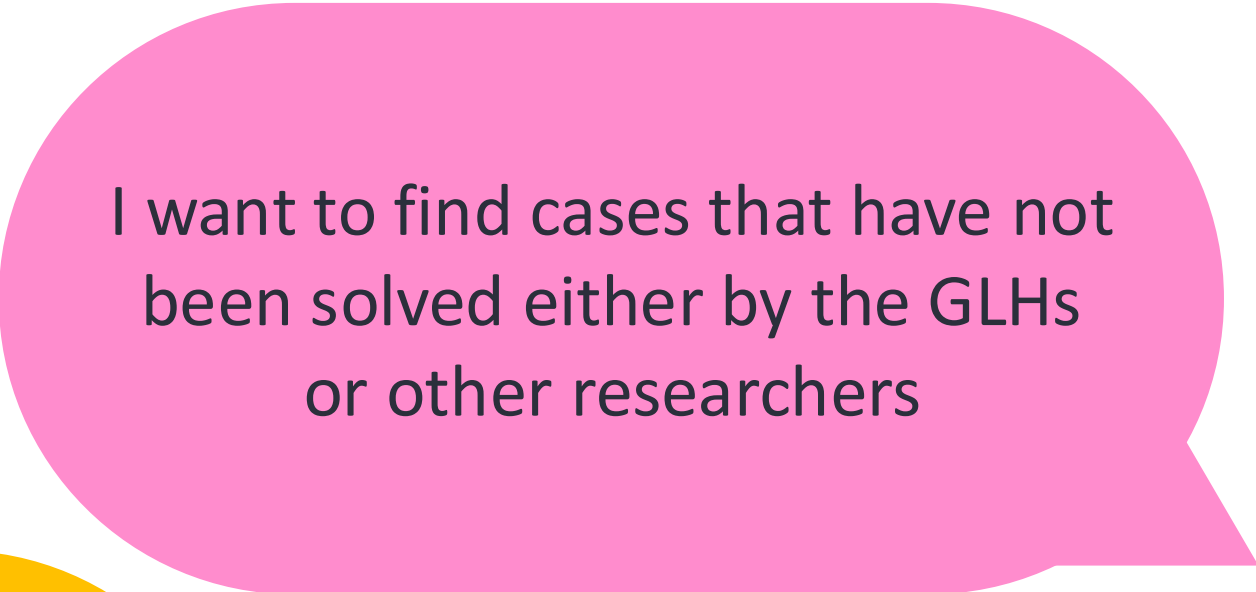


3. Identifying participants who need a diagnosis

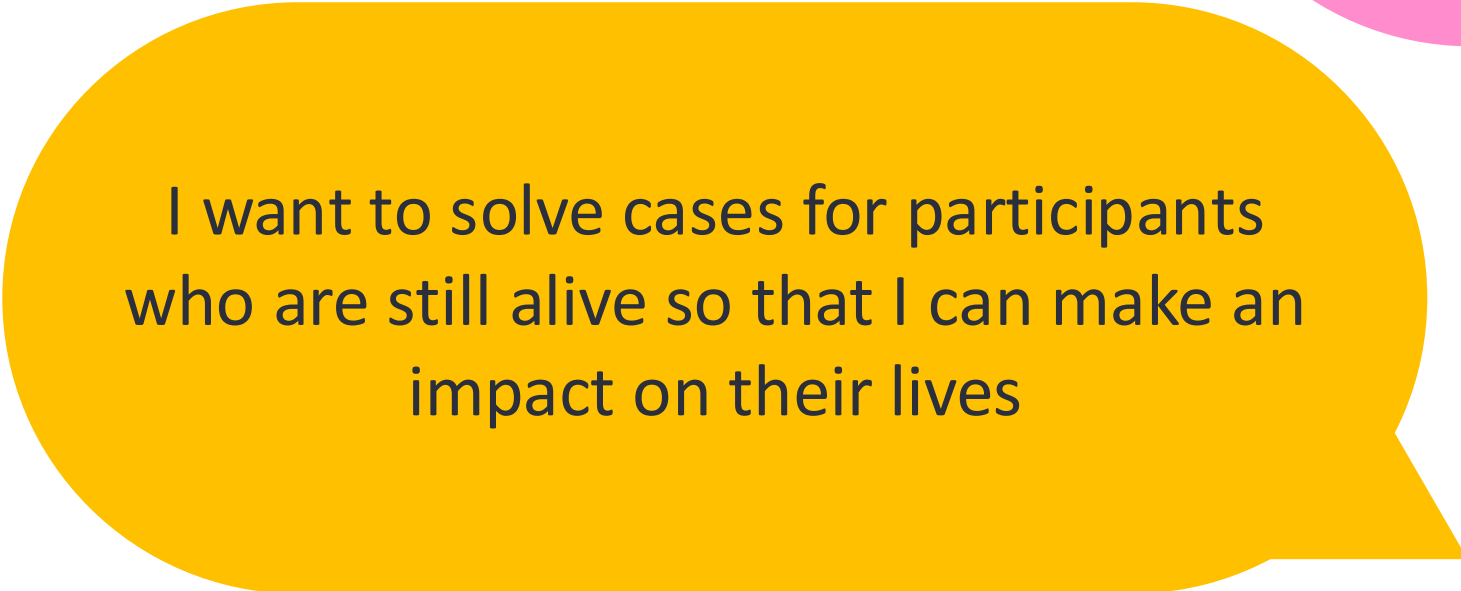




I want to find participants with my phenotype of interest



I want to find cases that have not been solved either by the GLHs or other researchers



I want to solve cases for participants who are still alive so that I can make an impact on their lives

Data tables



100kGP: participant_summary;
death_date
NHS GMS: mortality



100kGP: gmc_exit_questionnaire,
submitted_diagnostic_discovery
NHS_GMS:
report_outcome_questionnaire

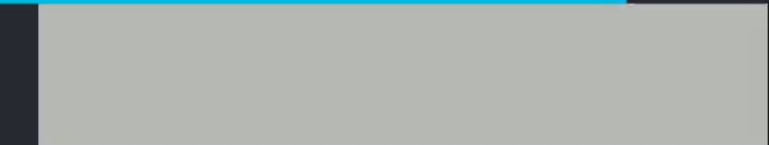
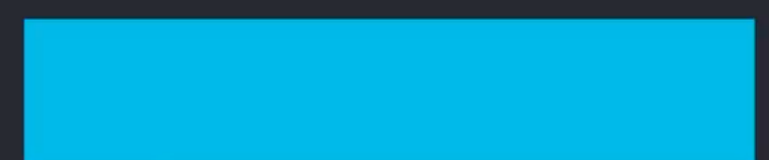


100kGP:
rare_disease_participant_disease,
rare_disease_participant_phenotype
NHS_GMS: referral, observation
Both: hes_ae, hes_apc, hes_op,
ecds; diag_all

LabKey demo

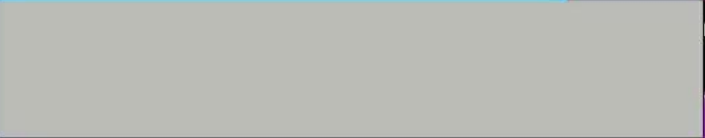
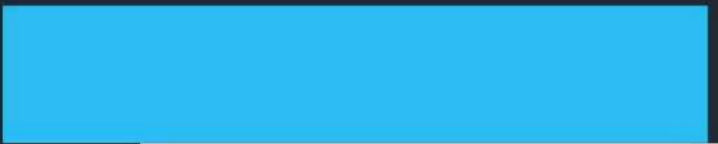


- Computer
- eperry's Home
- Link to emily
- Old Firefox Data
- Airlock
- CloudOS Academic
- CloudOS Discovery Forum
- CloudOS Internal
- Desktop.Rproj
- Document Viewer
- Emacs
- Ensembl
- Firefox
- Git GUI
- GVim
- IGV Browser
- IVA
- Labkey
- LibreOffice 7.6
- Open Targets
- Panel App
- Participant Explorer
- R
- RE Messages
- Research Environment Documentation
- Research Registry
- RStudio
- Terminal Emulator
- Text Editor
- Visual Studio Code
- Welcome Pack
- Trash



Participant Explorer demo

- Computer
- Emacs
- Participant Explorer
- xStata
- eperry's Home
- Ensembl
- R
- Link to emily
- Firefox
- RE Messages
- Old Firefox Data
- Git GUI
- Research Environment Documentation
- Airlock
- GVim
- Research Registry
- CloudOS Academic
- IGV Browser
- RStudio
- CloudOS Industry
- IVA
- Terminal Emulator
- CloudOS Internal
- Labkey
- Text Editor
- Desktop.Rproj
- LibreOffice 7.6
- Visual Studio Code
- Document Viewer
- Open Targets
- Welcome Pack
- Dremio
- Panel App
- Trash



4. Finding results of GEL analysis

I'm going to look at
untiered or Tier 3
variants only

Are there any Tier 1/2 or highly ranked
Exomiser variants with new evidence
that would cause me to reexamine
them?

Are the panels used the latest
version? Would other variants be
Tier 1/2 if we used the latest
panel?

Data tables



tiering_data
panels_applied
exomiser

LabKey demo

re.extge.co.uk/ovd/

Participant Explorer — Mozilla Firefox

https://research-participantexplorer.prod.aws.gel.ac

Genomics **Participant Explorer** Search Participants Code Systems

Search Criteria Result 13 Compare Participant Download

Participant #10 of 13

Participant Details	
Programme	Rare Diseases
Participant Type	Proband
Recruited Disease	Congenital hypothyroidism
Year of Birth	2014
Phenotypic Sex	Female
Ethnic Category	White: British
Consent Form	Child R5
Life Status	Alive
Family Case Solved	No
	N/A

Family Members for Proband 119002198			Medical Review	
Relationship to Proband	Sex	Affection Status	Participant ID	Pedigree Member ID
Proband	Female	Affected		
Father	Male	Unaffected		
Mother	Female	Unaffected		
Family Member	Male	Uncertain		
Family Member	Male	Uncertain		
Family Member	Female	Uncertain		
Family Member	Female	Uncertain		

Genome Sequence

5. Exploring variants in IVA

I want to recreate the tiering process with a more recent version of the panel.

Recent evidence makes me want to look at a particular gene.

I suspect a family member's affectation status is wrong and I want to look for variants found in them too

IVA Case Interpreter

Filter variants in proband by:

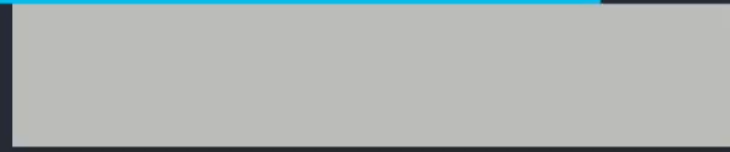
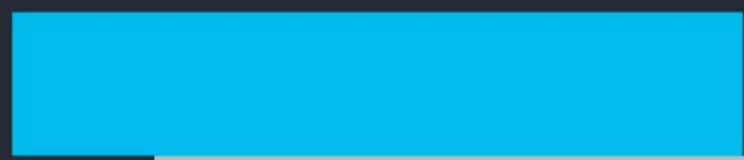
- Frequency
- Genes (including panels)
- Family genotypes
- Consequences
- Conservation



IVA demo



- Computer
- eperry's Home
- Link to emily
- Old Firefox Data
- Airlock
- CloudOS Academic
- CloudOS Discovery Forum
- CloudOS Internal
- Desktop.Rproj
- Document Viewer
- Emacs
- Ensembl
- Firefox
- Git GUI
- GVim
- igv
- IGV Browser
- IVA
- Labkey
- LibreOffice 7.6
- Open Targets
- Panel App
- Participant Explorer
- R
- RE Messages
- Research Environment Documentation
- Research Registry
- RStudio
- Terminal Emulator
- Text Editor
- Visual Studio Code
- Welcome Pack
- Trash



6. QC your diagnosis

A yellow speech bubble with a tail pointing towards the bottom right.

Is the variant I have
found real?

A pink speech bubble with a tail pointing towards the bottom right.

Are the family genotypes
for this variant correct?

Validate with IGV

View BAM files in IGV:

- Proband
- Relatives



IGV demo

Participant #10 of 13

Participant Details	
Programme	Rare Diseases
Participant Type	Proband
Recruited Disease	Congenital hypothyroidism
Year of Birth	2014
Phenotypic Sex	Female
Ethnic Category	White: British
Consent Form	Child R5
Life Status	Alive
Family Case Solved	No
	N/A

Family Members for Proband 1				
Relationship to Proband	Sex	Affection Status	Participant ID	Pedigree Member ID
Proband	Female	Affected		
Father	Male	Unaffected		
Mother	Female	Unaffected		
Family Member	Male	Uncertain		
Family Member	Male	Uncertain		
Family Member	Female	Uncertain		
Family Member	Female	Uncertain		

Rows per page: 10 1-7 of 7

Genome Sequence

Is there anything more to know about primary phenotypes, such as those that develop with age?

Is the variant linked to a secondary phenotype in the proband?

Do any relatives who share the variant have evidence of the phenotype, perhaps due to incomplete penetrance?

Participant Explorer

- View/compare medical histories



Participant Explorer demo

IGV

File Genomes View Tracks Regions Tools Help

Human hg38 local chr15 chr15:45,111,487-45,111,507 Go

8 tracks loaded chr15:45,111,498 211M of 309M

Frequency Types 9 populationFrequencyAlt 2

Columns Export Settings

	Clinical Info	Interpretation	
Frequencies	ClinVar	Cosmic	ACMG Prediction
	P	x	P PVS1, PP5, PM4
	P LP	x	P PVS1, PP5, PM4

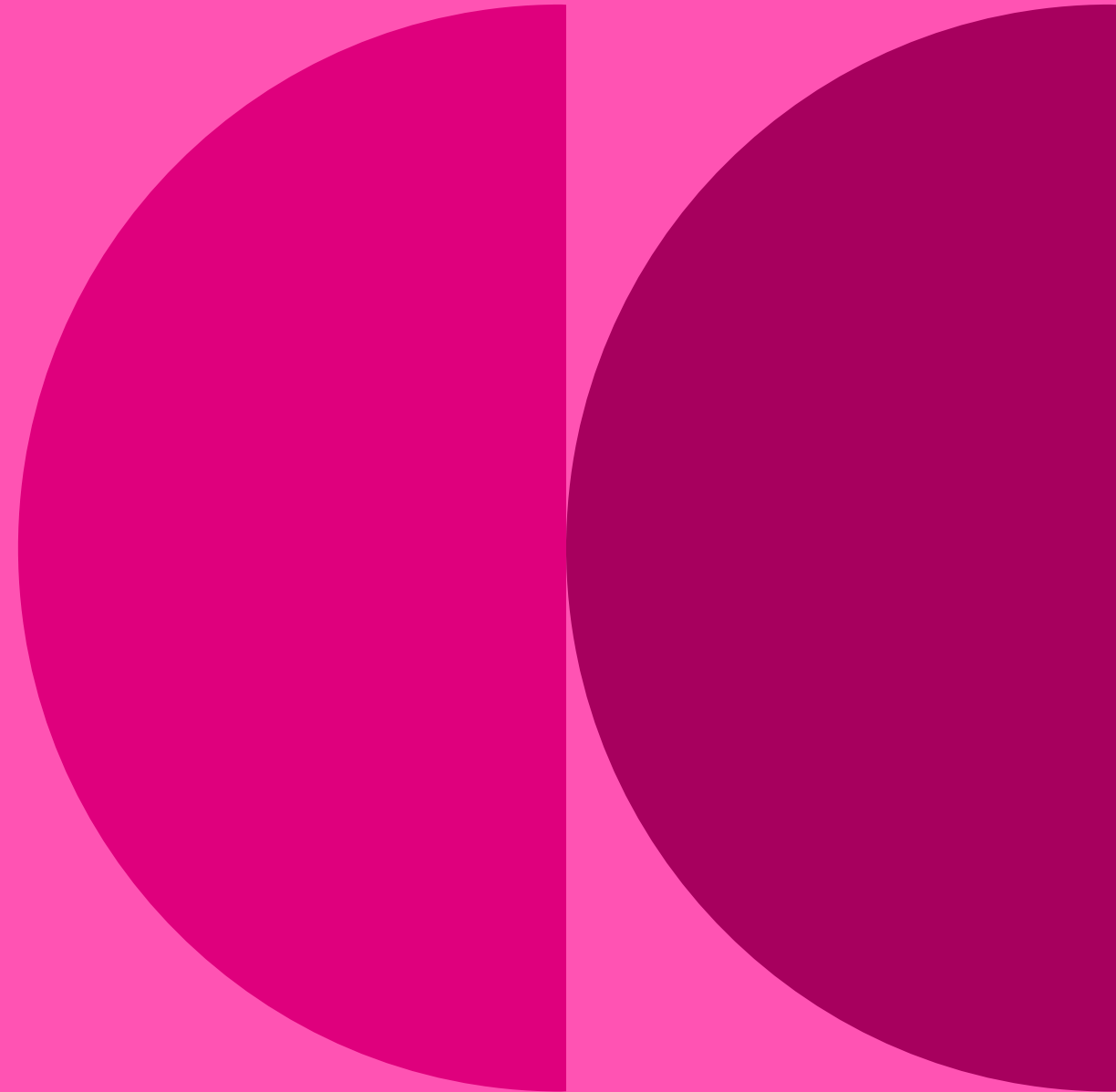
Review Edit ... Act

Gene	Gene ID	Transcript ID	Source	Biotype	Transcript Flag	Consequence Types (SO term)
+	DUOX2	ENSG00000140279	ENST00000389039	-	protein_coding	frameshift_variant (SO:0001589)
+	DUOX2	ENSG00000140279	ENST00000603300	-	protein_coding	frameshift_variant (SO:0001589)
+	DUOX2	ENSG00000140279	ENST00000558383	-	retained_intron	non_coding_transcript_exon_variant (SO:0001792)

Protein Variant Annotation

UniProt Accession	Position	Ref/Alt	Sift	Polyphen
-	201	GLY/GLY	-	-
-	201	GLY/GLY	-	-

7. Find and compare other participants with the same variant



Are there other participants
with the same variant

Do they share phenotypes
with our target participant?

Is there anything that
contradicts our findings?

Compare participants demo

re.extge.co.uk/ovd/

Participant Explorer — Mozilla Firefox

https://research-participantexplorer.prod.aws.gel.ac

Genomics **Participant Explorer** Search Participants Code Systems

Search Criteria **Result 3** Compare Participant Download

View by Participant Age Caution: Encounter dates are normalised by calculated Participant age and are indicative only

Included Data Categories: 6 included / 1 excluded

Participant Shared Codes Threshold: shared by at least 2

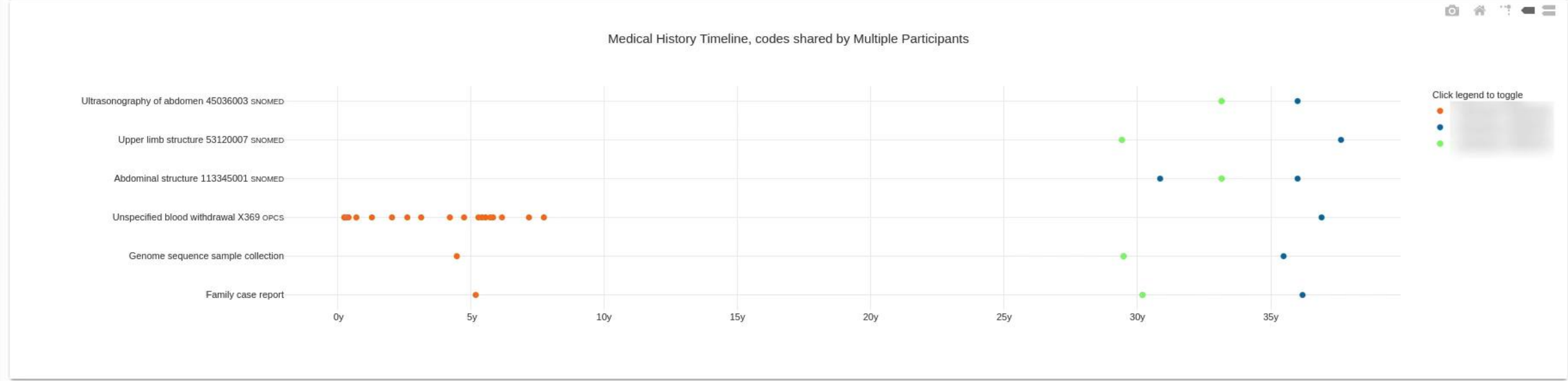
No Code Grouping: 0 1 2 3 4 5 Max Code Grouping: Show Subsumed Codes Alternate Palette

Text or Code Filter: text to filter by e.g. acute

Top Level Concepts: filter codes subsumed by

Browser may slow above 15k data points total: 229 visible filtered: 33

Download



**8. Submit your
diagnosis and/or
contact clinicians**

Form in Airlock



Contact clinical team



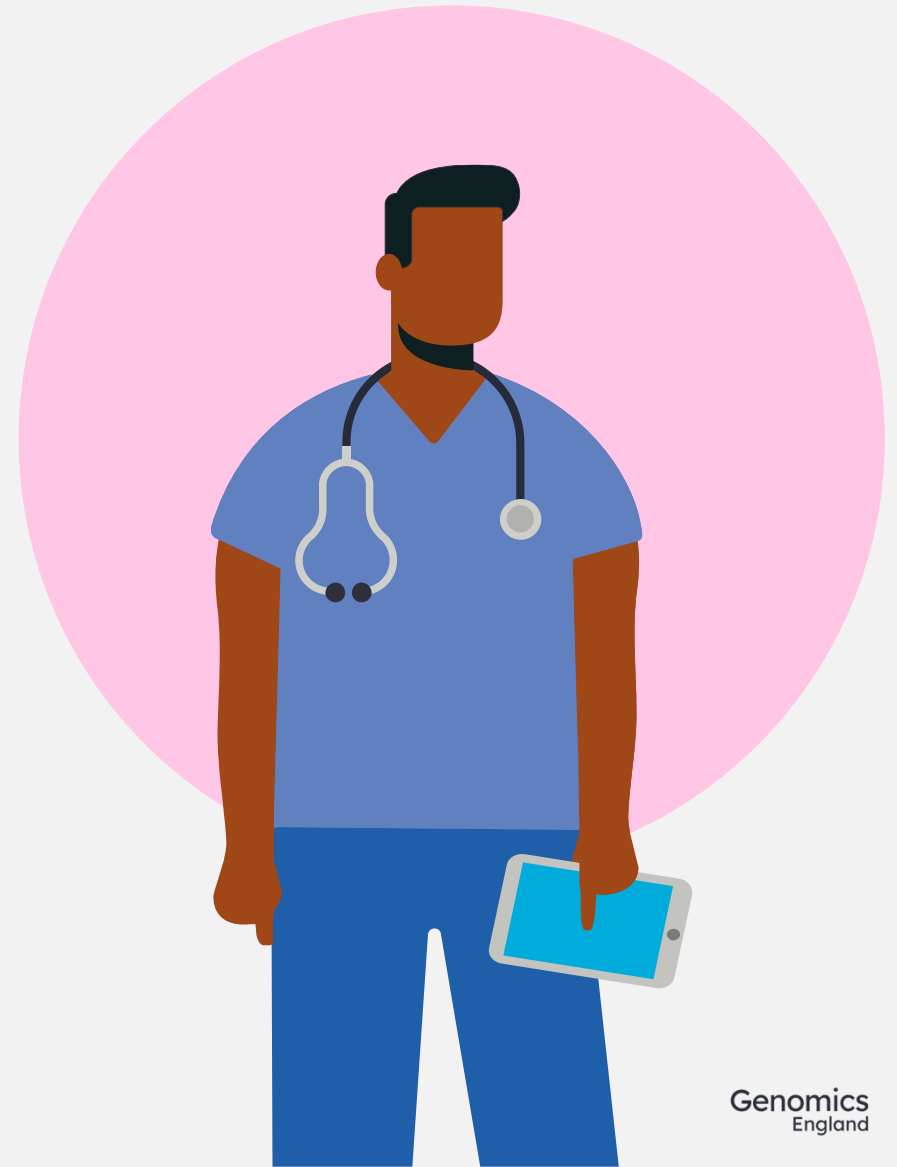
Report potential diagnosis



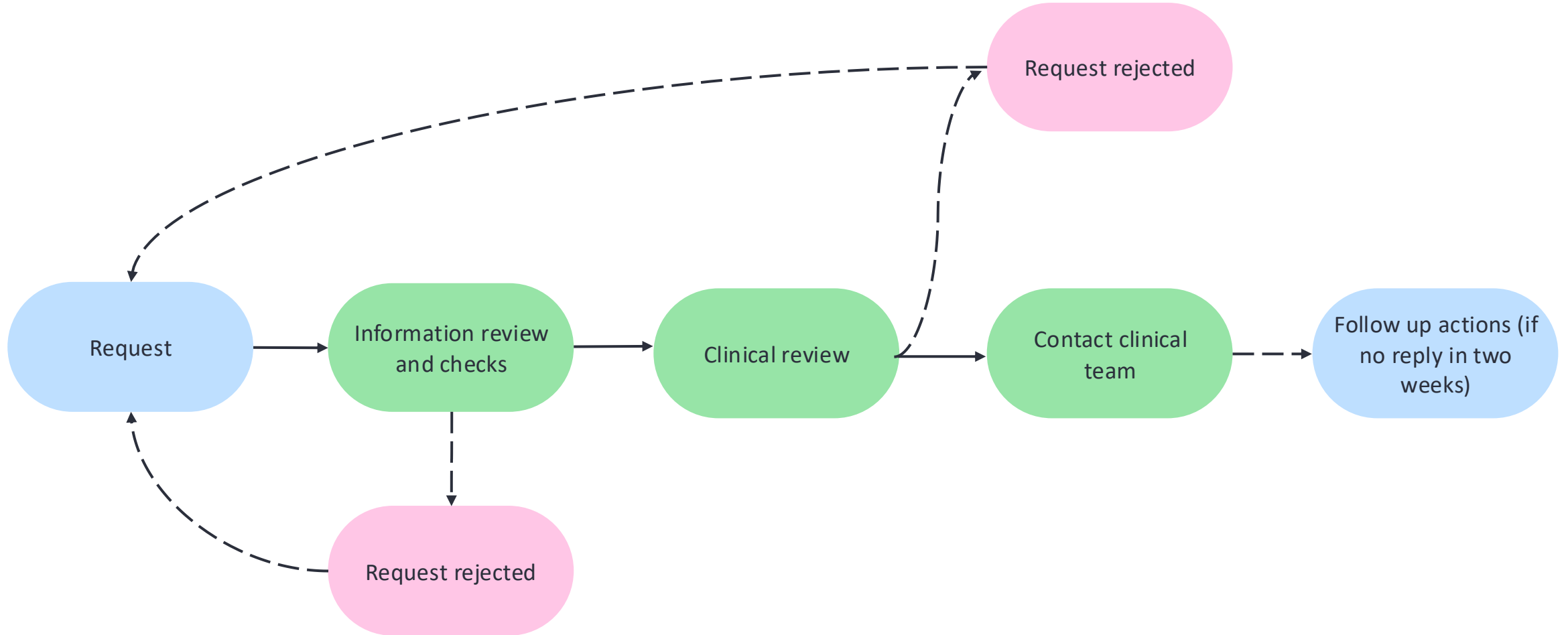
Clinical collaboration

Examples of collaboration include:

- Request for patient consent to publish paper
- Inviting a clinician as a co-author on a paper
- Request for further health information or clinical tests
- To discuss with the clinician a potential diagnostic variant
- To offer laboratory tests to investigate in more detail whether a particular variant is likely to be diagnostic or not



Clinical collaboration

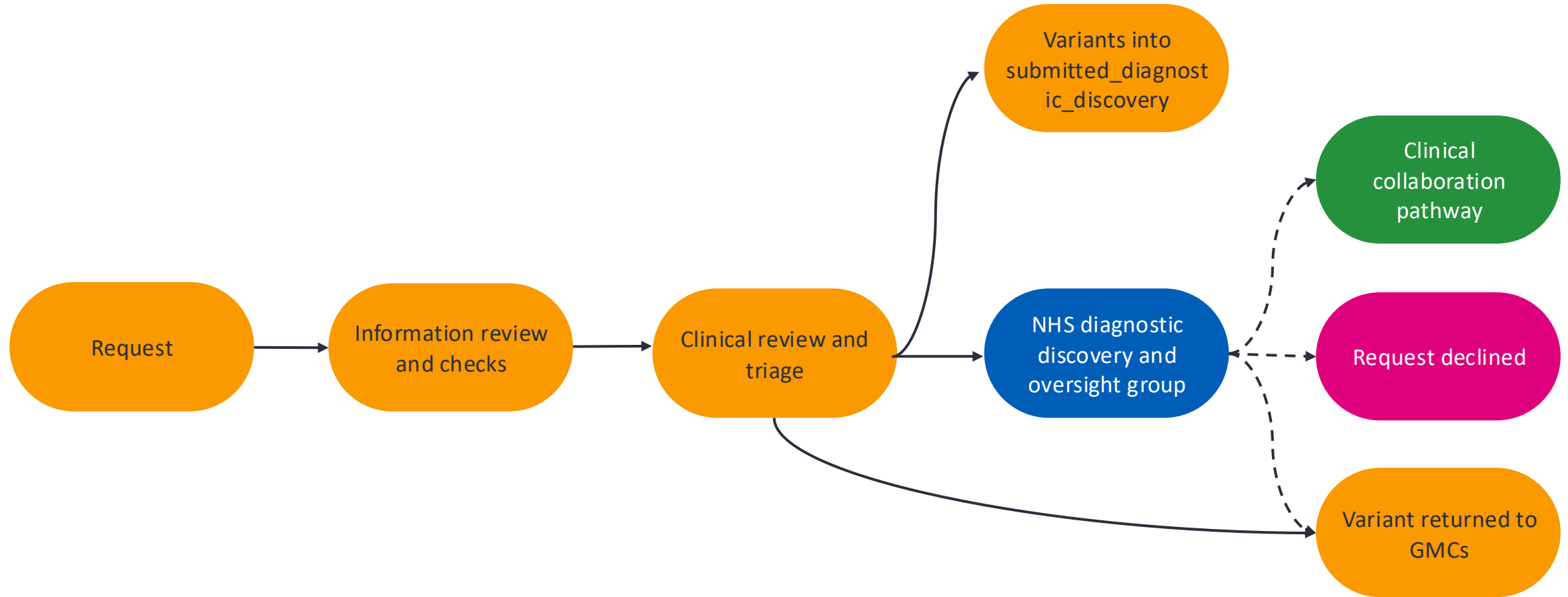


Diagnostic Discovery

- Diagnostic Discovery Oversight Group: clinicians and scientists from each Genomic Laboratory Hub (GLH), together with NHS England and Genomics England
- Checks de-identified variants nominated by researchers
- Provides assurance to the GLHs that the diagnoses being returned are of high quality and clinical relevance
- Variants approved by the group: returned to their corresponding GLH for assessment
- The group meets 1-2 monthly
- Separate pathway for rapid return of urgent variants



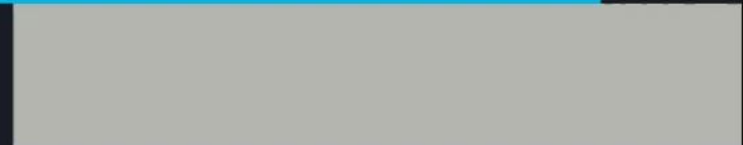
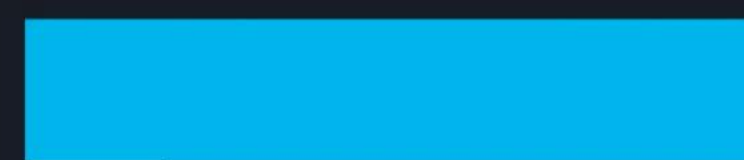
Diagnostic discovery



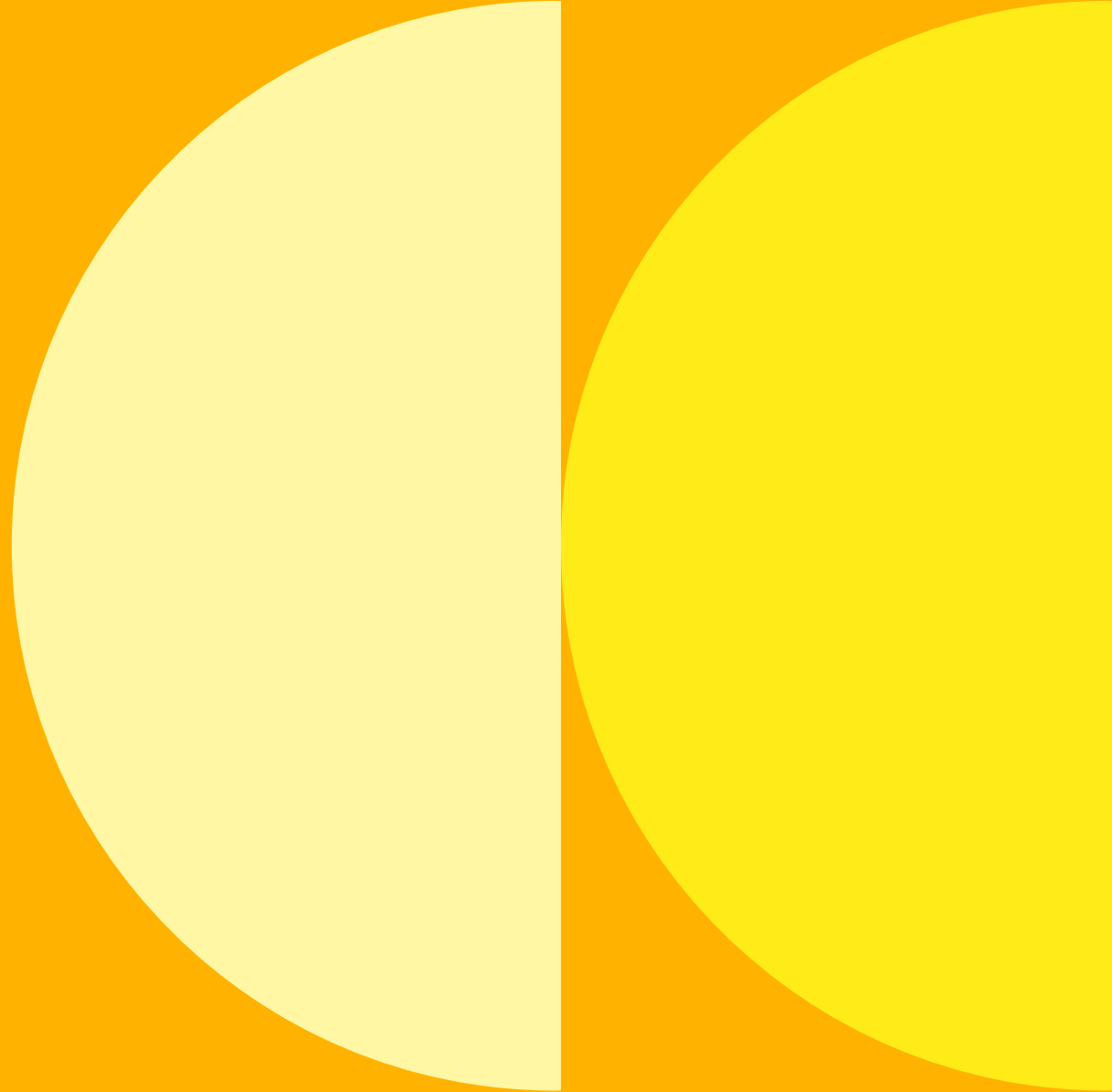
Form demo



- Computer
- Text Editor
- Airlock
- Research Environment Documentation
- Welcome Pack
- eperry's Home
- Data Discovery
- Participant Explorer
- report.tsv
- Trash
- Firefox
- Visual Studio Code
- Ensembl
- Document Viewer
- IGV Browser
- RE Messages
- IVA 2.0
- R
- Terminal Emulator
- Rocket Chat
- LibreOffice
- Panel App
- Research Registry
- GVim
- Labkey
- Git GUI
- RStudio
- Old Firefox Data
- Open Targets
- Emacs
- LibreOffice 7.6



9. Getting help and questions



Getting help



Check our documentation:
<https://re-docs.genomicsengland.co.uk/>
Click on the documentation icon in the environment



Contact our Service Desk:
<https://jiraservicedesk.extge.co.uk/plugins/servlet/desk>

Training sessions

3rd Tuesday every month

Introduction to the RE

20/1

17/2

17/3



Materials from
past training
all online

Training sessions

10/2

Importing tools and data to use in the Research Environment

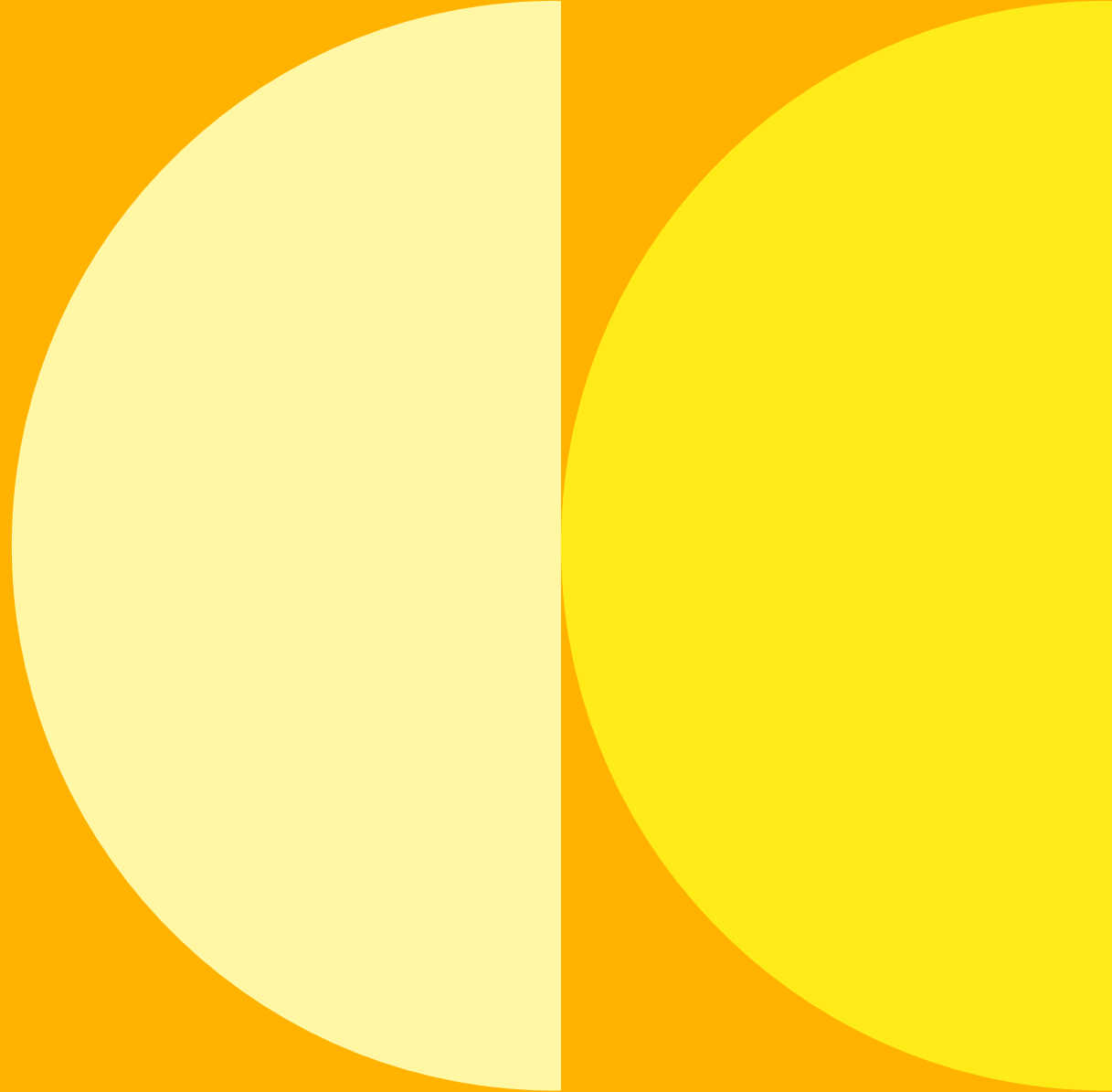
10/3

Working with the new aggregate VCFs – AggV3



Materials from
past training
all online

Feedback



Thank you

Visit: <https://re-docs.genomicsengland.co.uk/>