Using the Research Environment for clinical diagnostic discovery

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Research Engagement Manager

14th January 2025

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

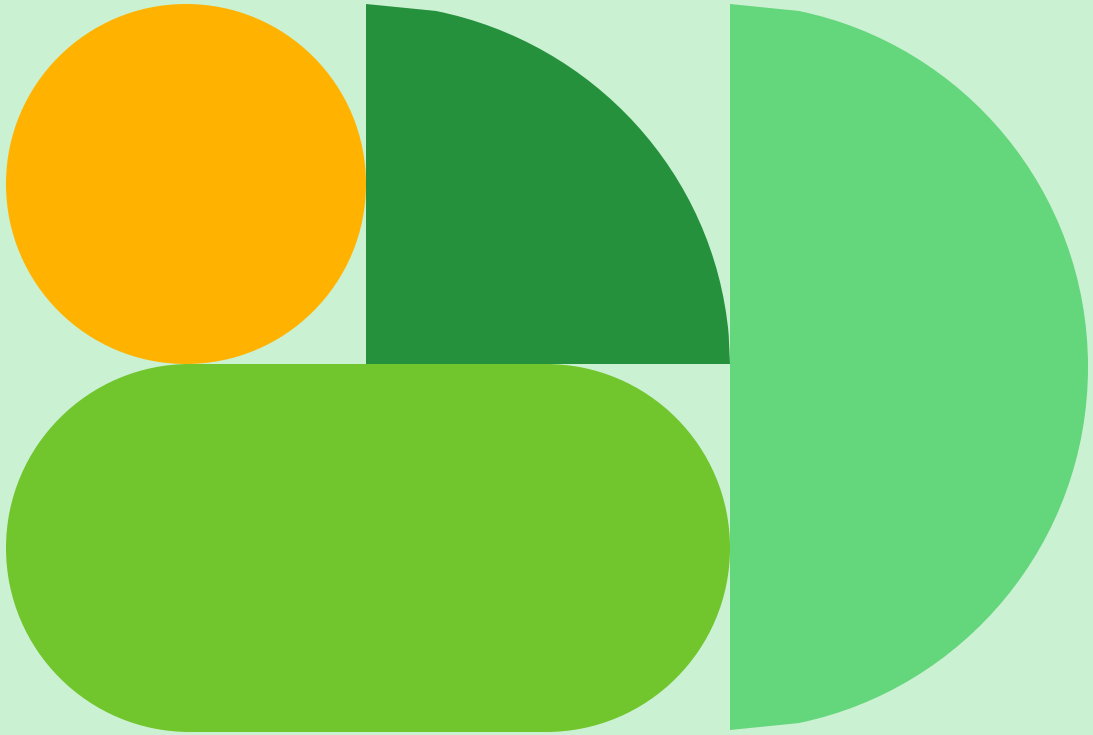
Helpers

Joanne Yang
Clinical Research Interface Coordinator

Susan Walker
Director of Translational Genomics

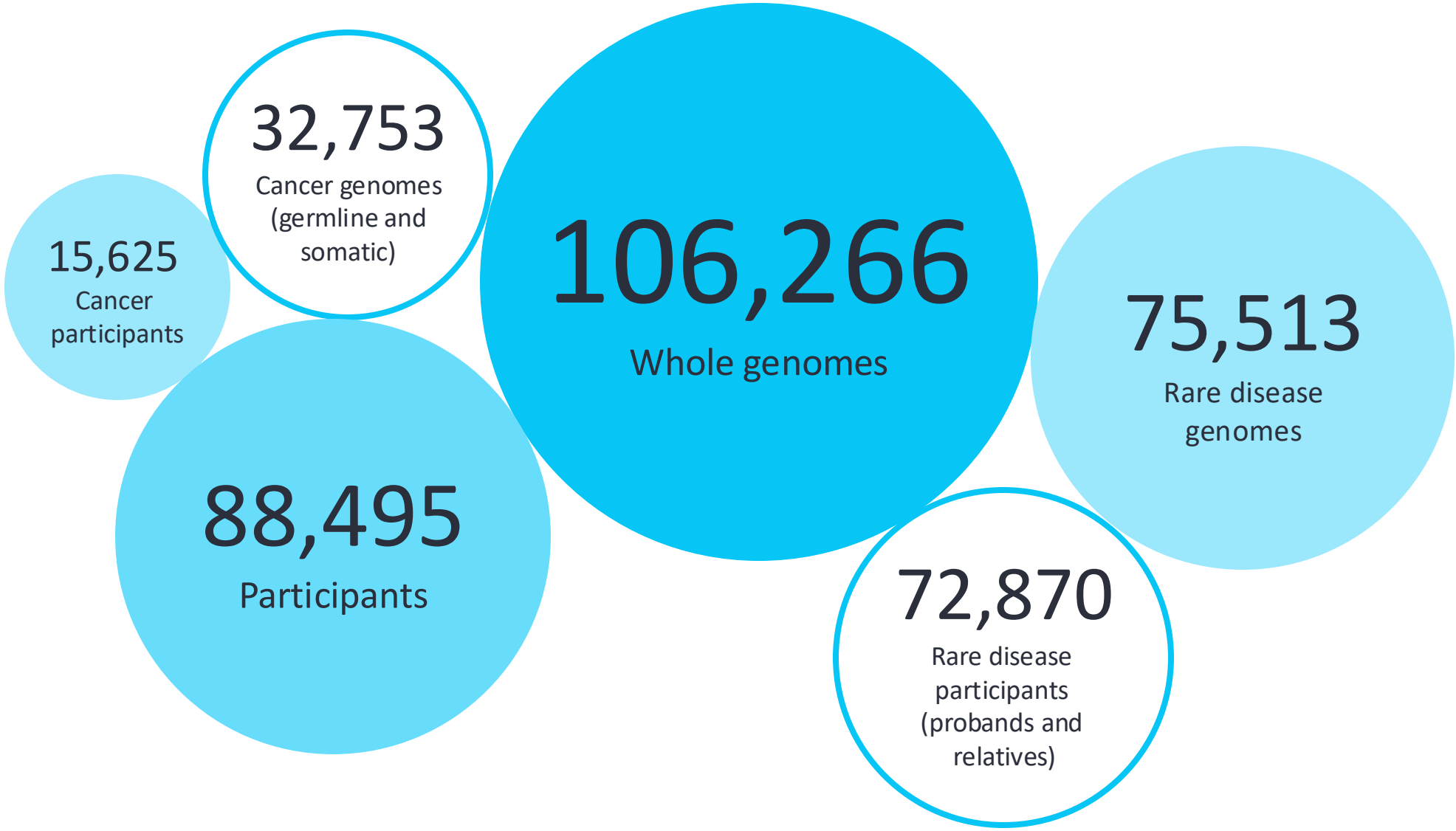
Agenda

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. Validate your diagnosis
7. Find and compare other participants with the same variant
8. Submit your diagnosis and/or contact clinicians
9. Help and questions



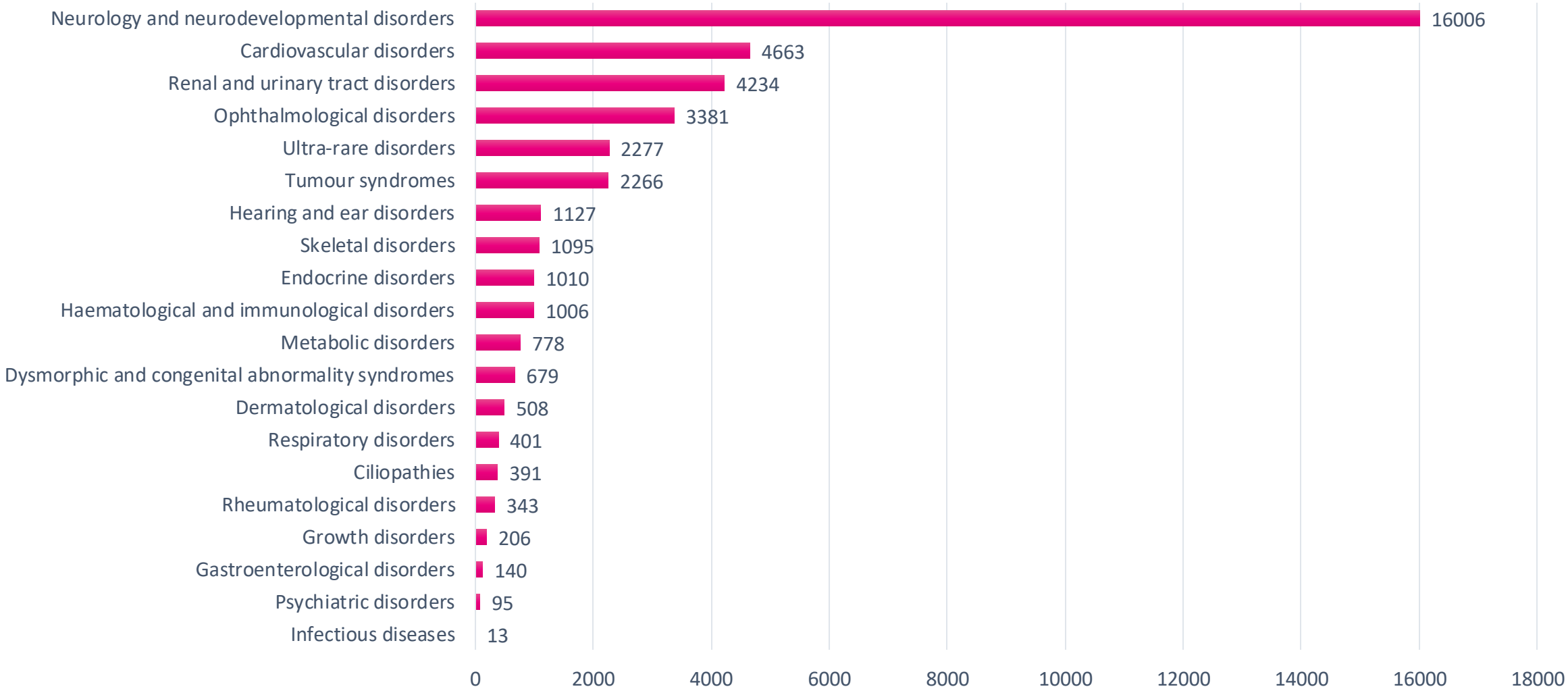
2. GEL ingestion of rare disease participants

100,000 Genomes Project



https://re-docs.genomicsengland.co.uk/release18/

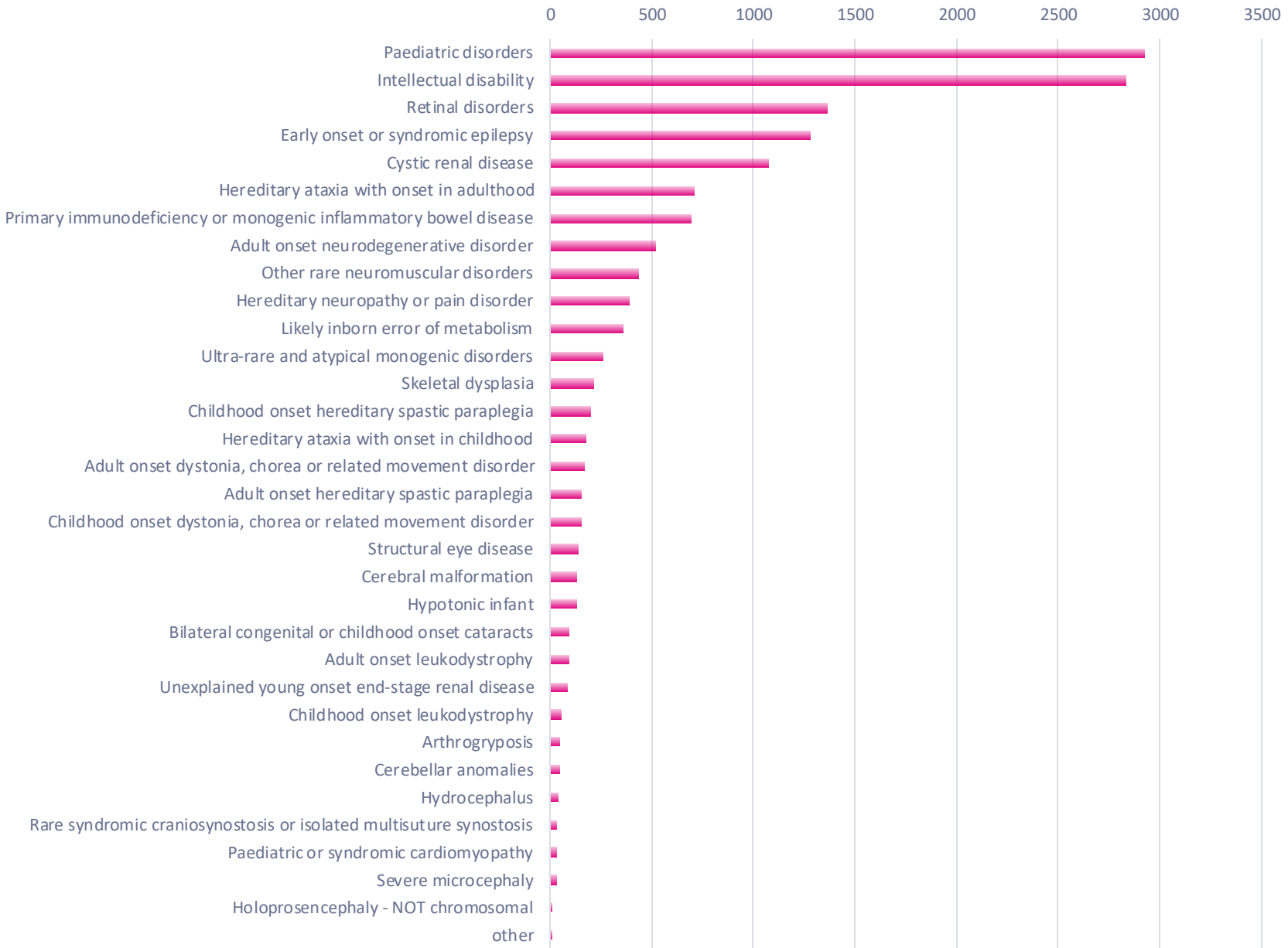
100,000 Genomes rare disease



NHS GMS

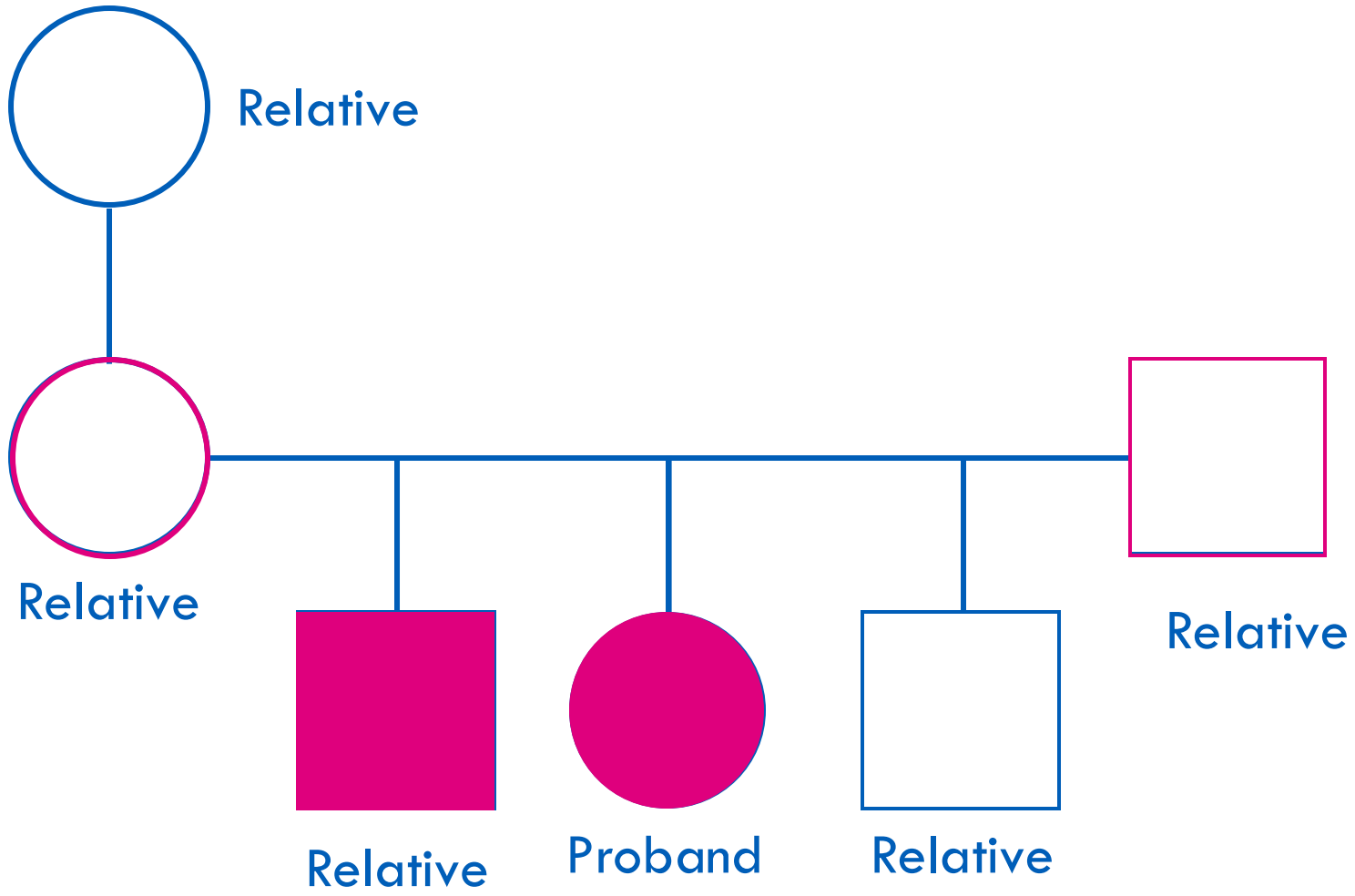
https://re-docs.genomicsengland.co.uk/gms_release3/

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

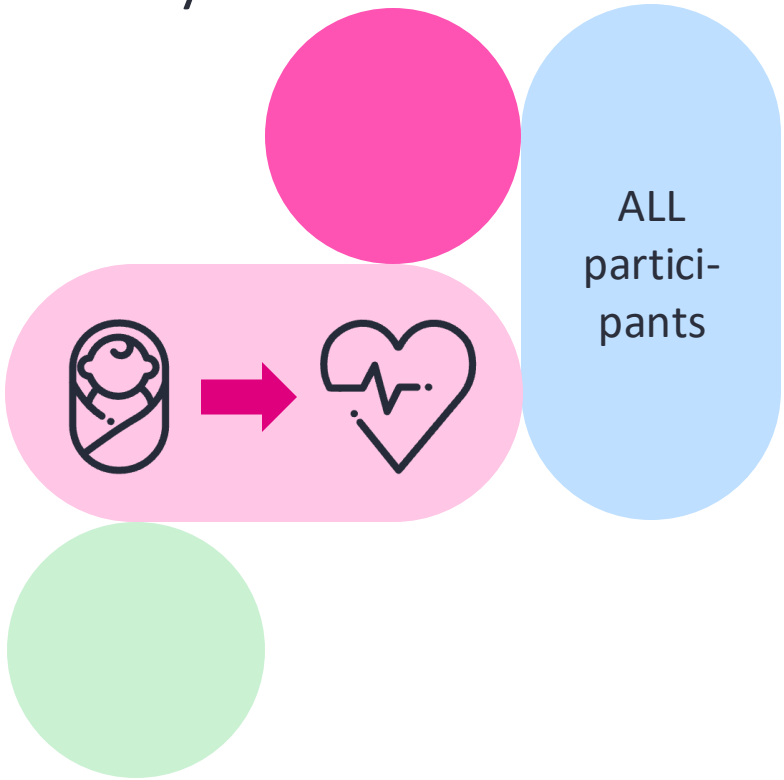
Rare disease phenotyping

- 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

https://re-docs.genomicsengland.co.uk/rare_disease_clinical/

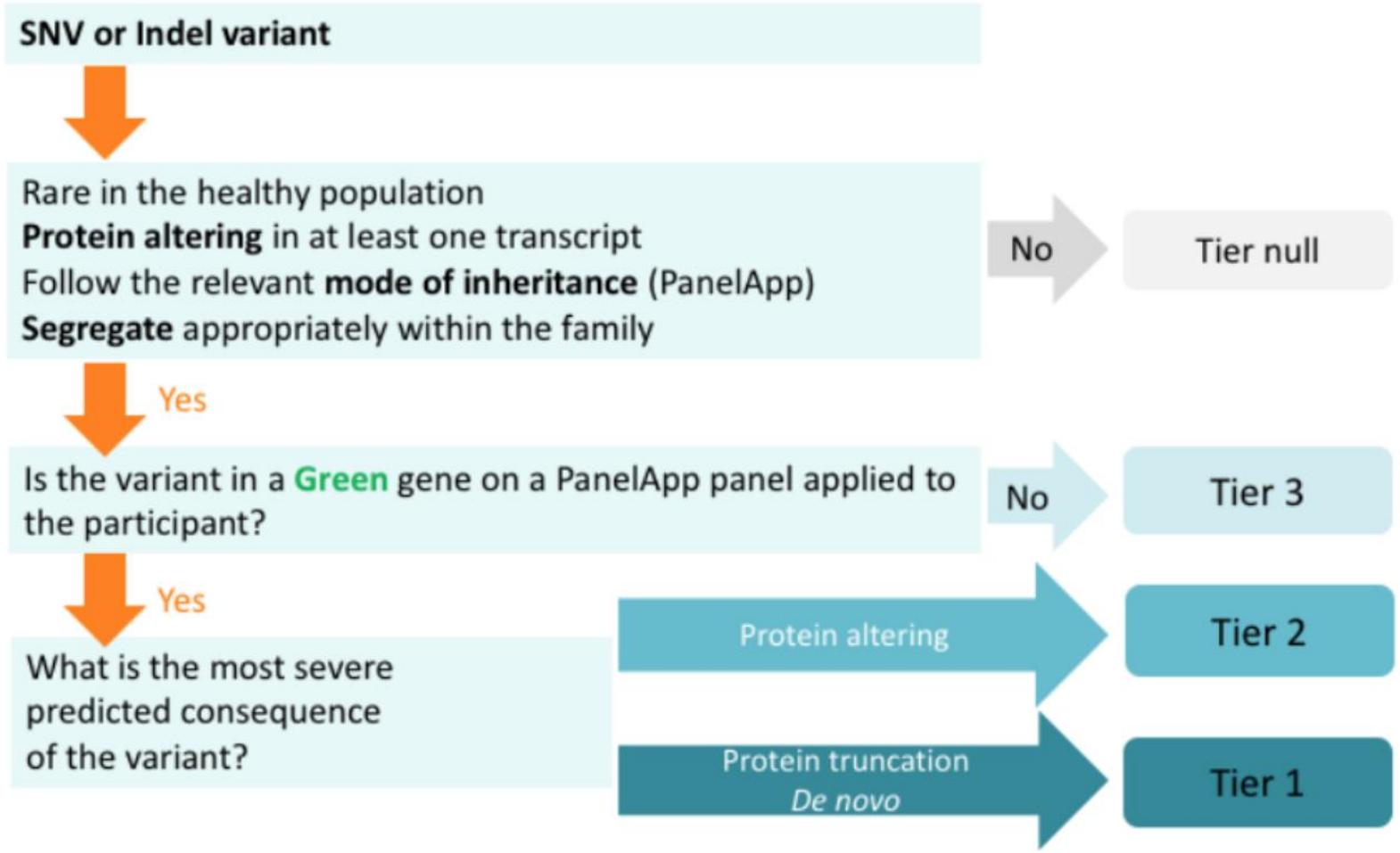
Medical history

- NHSE hospital episode statistics
- Mental health data
- Mortality



https://re-docs.genomicsengland.co.uk/general_clinical/

Rare disease tiering

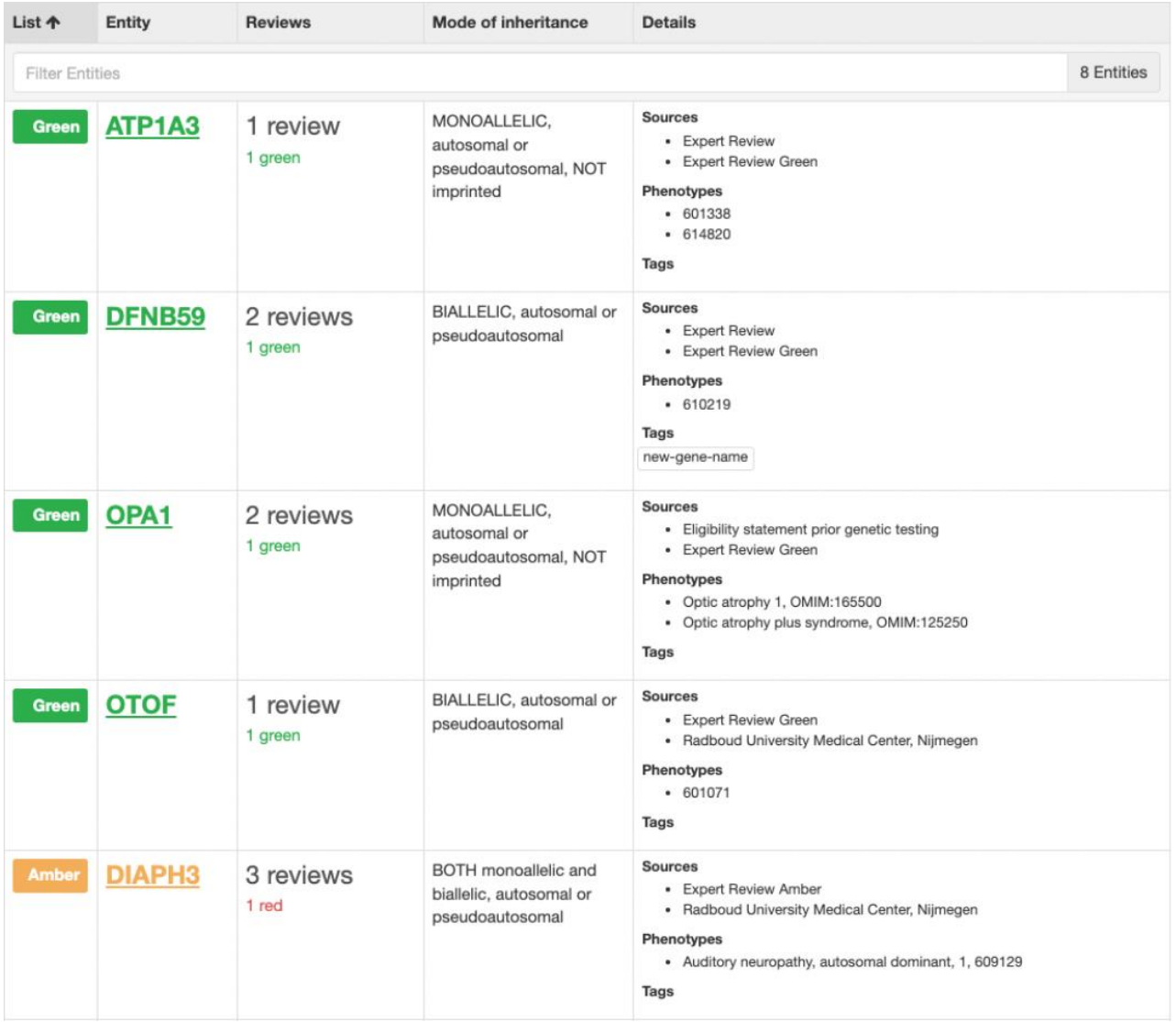


https://re-docs.genomicsengland.co.uk/tiering/

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

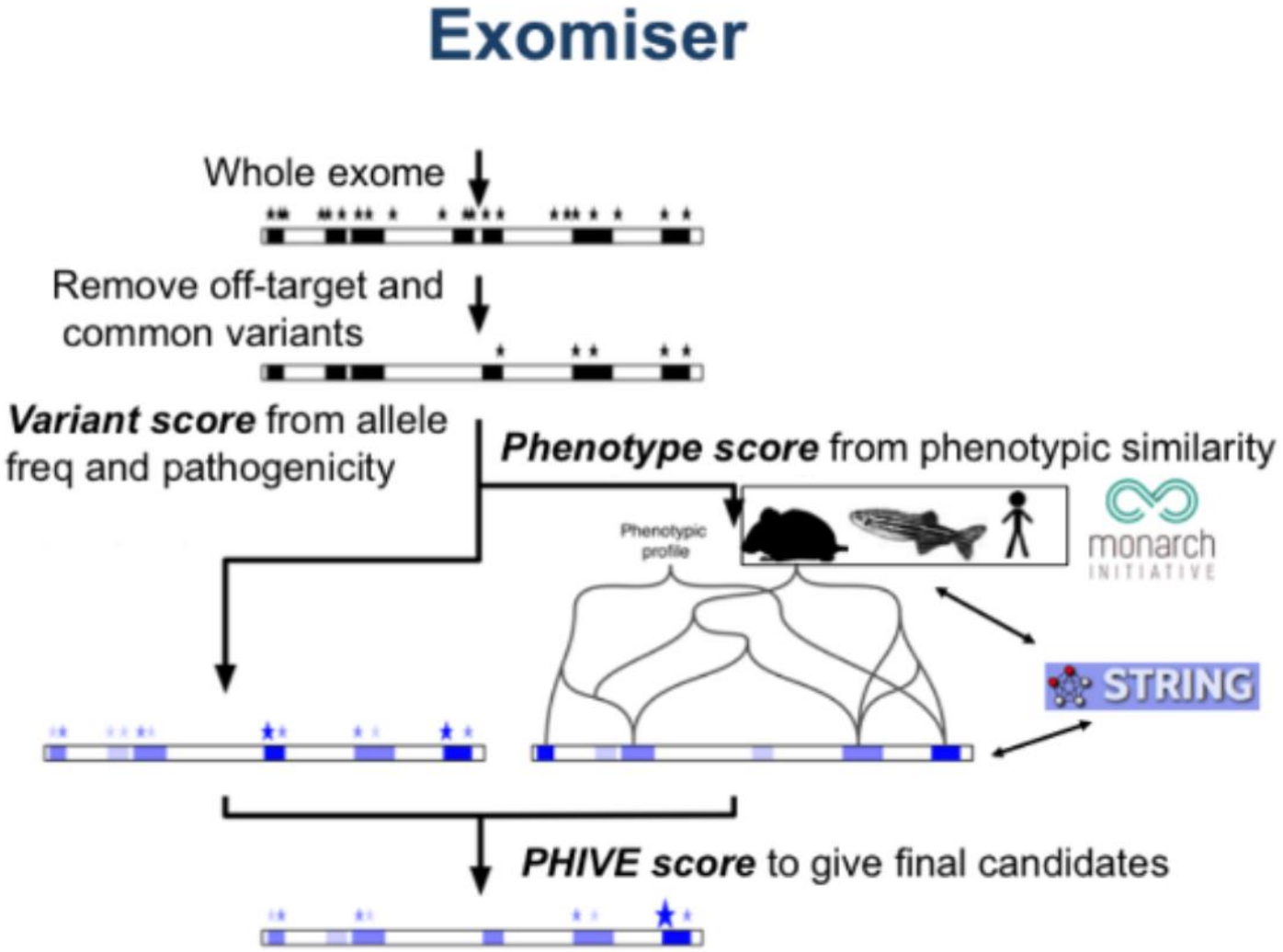
- Panel(s) chosen according to phenotypes
- Panel version at time of usage listed



List	Entity	Reviews	Mode of inheritance	Details
Filter Entities				8 Entities
Green	ATP1A3	1 review 1 green	MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	**Sources** • Expert Review • Expert Review Green **Phenotypes** • 601338 • 614820 **Tags**
Green	DFNB59	2 reviews 1 green	BIALLELIC, autosomal or pseudoautosomal	**Sources** • Expert Review • Expert Review Green **Phenotypes** • 610219 **Tags** new-gene-name
Green	OPA1	2 reviews 1 green	MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	**Sources** • Eligibility statement prior genetic testing • Expert Review Green **Phenotypes** • Optic atrophy 1, OMIM:165500 • Optic atrophy plus syndrome, OMIM:125250 **Tags**
Green	OTOF	1 review 1 green	BIALLELIC, autosomal or pseudoautosomal	**Sources** • Expert Review Green • Radboud University Medical Center, Nijmegen **Phenotypes** • 601071 **Tags**
Amber	DIAPH3	3 reviews 1 red	BOTH monoallelic and biallelic, autosomal or pseudoautosomal	**Sources** • Expert Review Amber • Radboud University Medical Center, Nijmegen **Phenotypes** • Auditory neuropathy, autosomal dominant, 1, 609129 **Tags**

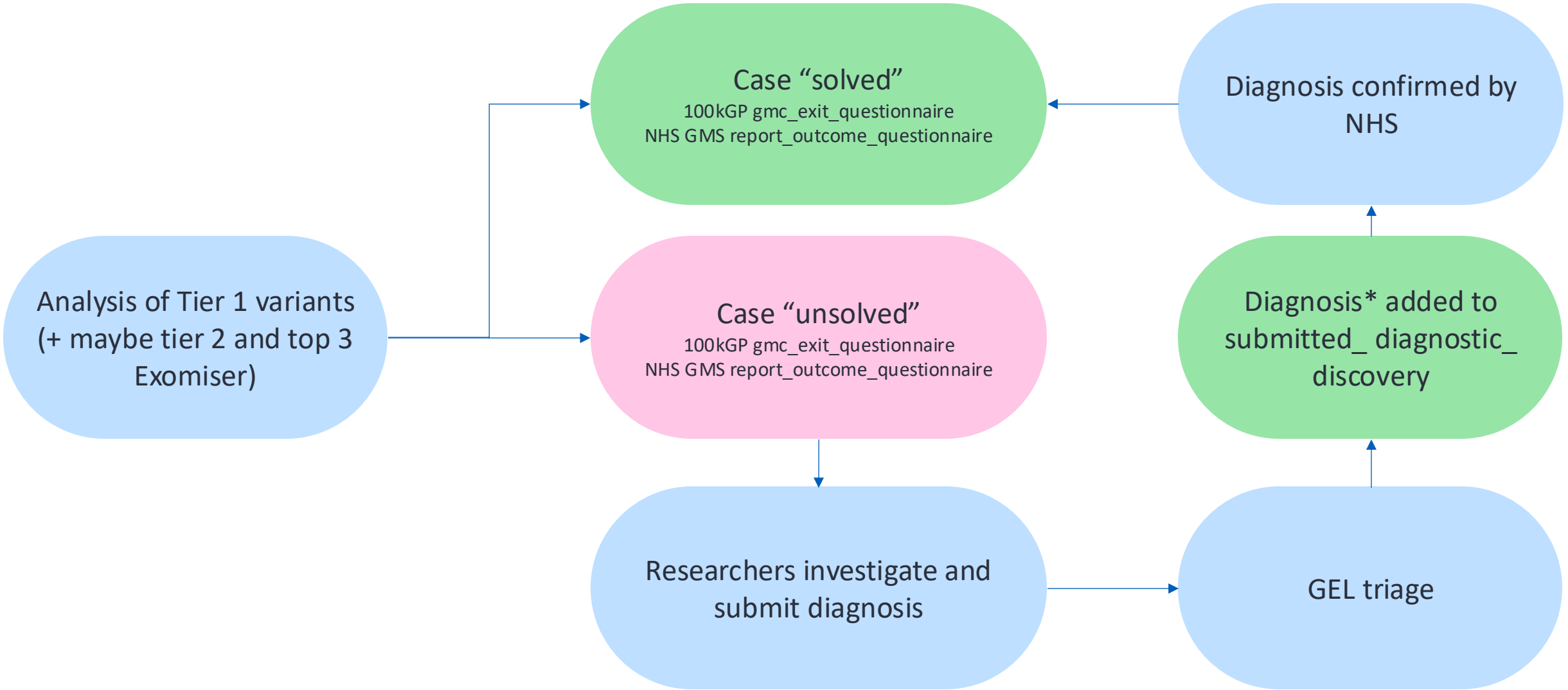
https://re-docs.genomicsengland.co.uk/panelapp/

Rare disease Exomiser



https://re-docs.genomicsengland.co.uk/exomiser/

Solved cases



https://re-docs.genomicsengland.co.uk/exit_questionnaire/

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

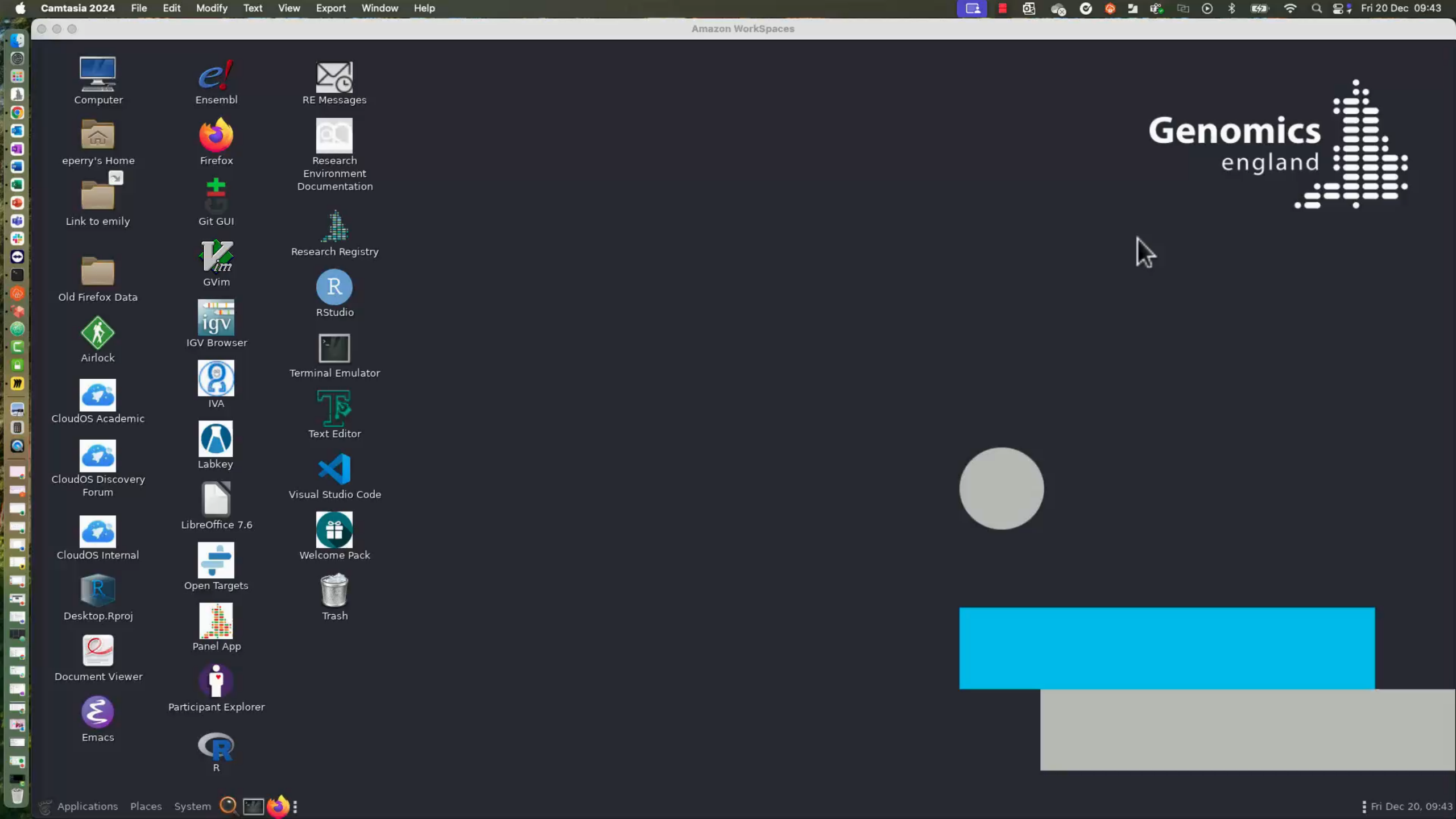
Data tables

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


Camtasia 2024
File
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Help
Fri 20 Dec 09:43
Amazon WorkSpaces
Computer
Ensembl
RE Messages
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Research Environment Documentation
Link to emily
Git GUI
Research Registry
GVim
Old Firefox Data
RStudio
IGV Browser
Airlock
Terminal Emulator
IVA
CloudOS Academic
Text Editor
Labkey
CloudOS Discovery Forum
Visual Studio Code
LibreOffice 7.6
CloudOS Internal
Welcome Pack
Open Targets
Desktop.Rproj
Trash
Panel App
Document Viewer
Participant Explorer
Emacs
R
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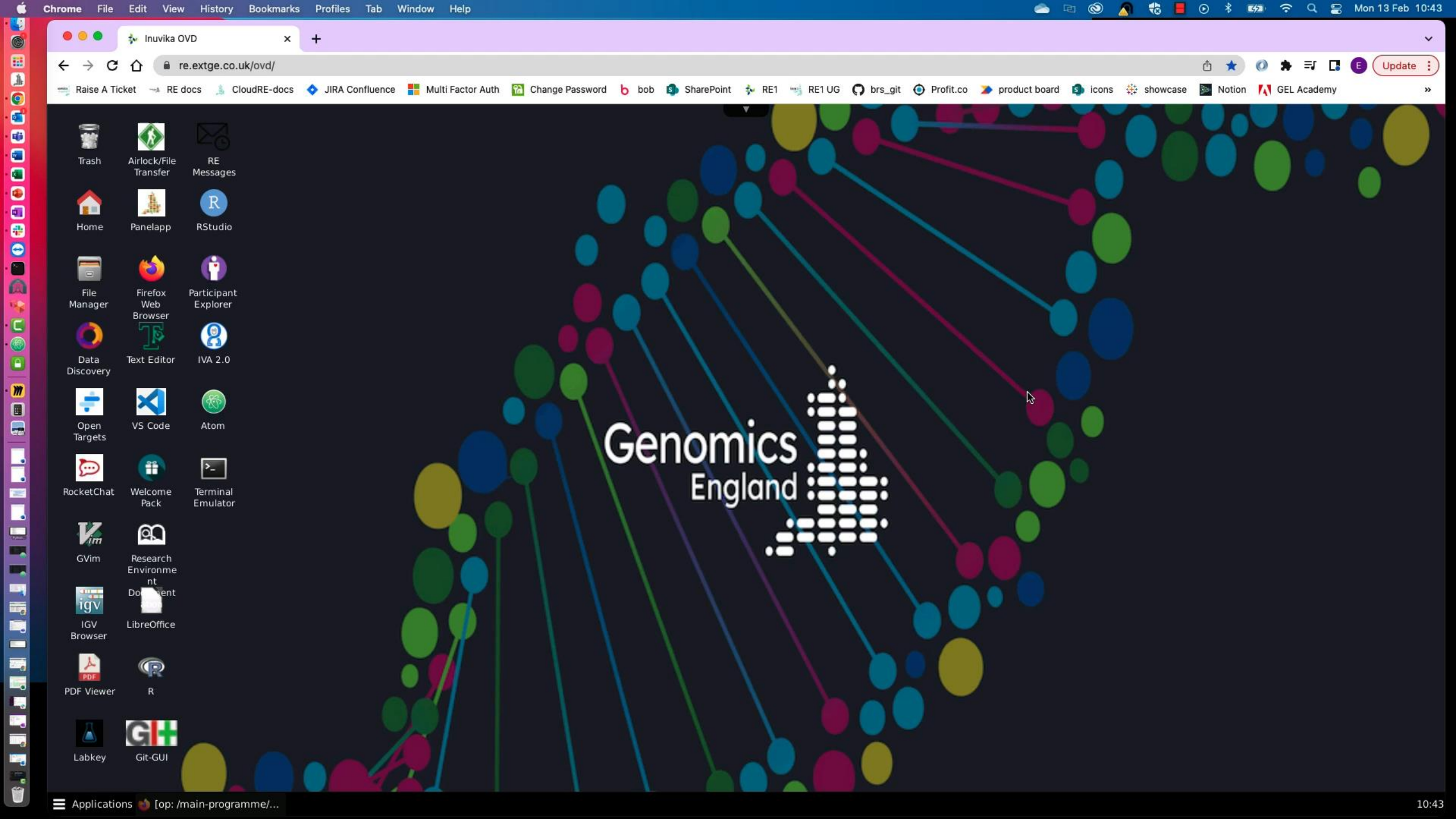
Applications
Places
System
Fri Dec 20, 09:43

Participant Explorer demo


Chrome File Edit View History Bookmarks Profiles Tab Window Help
Mon 13 Feb 10:43
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re.extge.co.uk/ovd/
Update
Raise A Ticket
RE docs
CloudRE-docs
JIRA Confluence
Multi Factor Auth
Change Password
bob
SharePoint
RE1
RE1 UG
brs_git
Profit.co
product board
icons
showcase
Notion
GEL Academy
Trash
Airlock/File Transfer
RE Messages
Home
Panelapp
RStudio
File Manager
Firefox Web Browser
Participant Explorer
Data Discovery
Text Editor
IVA 2.0
Open Targets
VS Code
Atom
RocketChat
Welcome Pack
Terminal Emulator
GVim
Research Environment
IGV Browser
LibreOffice
PDF Viewer
R
Labkey
Git-GUI
Genomics England
Applications
[op: /main-programme/...
10:43

4. Finding results of GEL analysis

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

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

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

Chrome File Edit View History Bookmarks Profiles Tab Window Help

Mon 13 Feb 10:50

Inuvika OVD

re.extge.co.uk/ovd/

Update

Raise A Ticket | RE docs | CloudRE-docs | JIRA Confluence | Multi Factor Auth | Change Password | bob | SharePoint | RE1 | RE1 UG | brs_git | Profit.co | product board | icons | showcase | Notion | GEL Academy

Participant Explorer — Mozilla Firefox

about:sessionrestore | Start Page: /main-pr | submitted_diagnost | op: /main-programn | rare_diseases_partic | rare_diseases_partic | key_columns: /main | gmc_exit_questionn | Participant Explorer

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

Genomics england

Participant Explorer

Search Participants | Code Systems

Search Criteria | Result 13 | Compare | Participant | Download

Participant [redacted]

#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
[redacted]	N/A

Family Members for Proband 119002198

Medical Review [redacted]

Relationship to Proband	Sex	Affection Status	Participant ID	Pedigree Member ID
Proband	Female	Affected	[redacted]	[redacted]
Father	Male	Unaffected	[redacted]	[redacted]
Mother	Female	Unaffected	[redacted]	[redacted]
Family Member	Male	Uncertain		[redacted]
Family Member	Male	Uncertain		[redacted]
Family Member	Female	Uncertain		[redacted]
Family Member	Female	Uncertain		[redacted]

Genome Sequence

Applications | Participant Explorer — ...

10:50

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

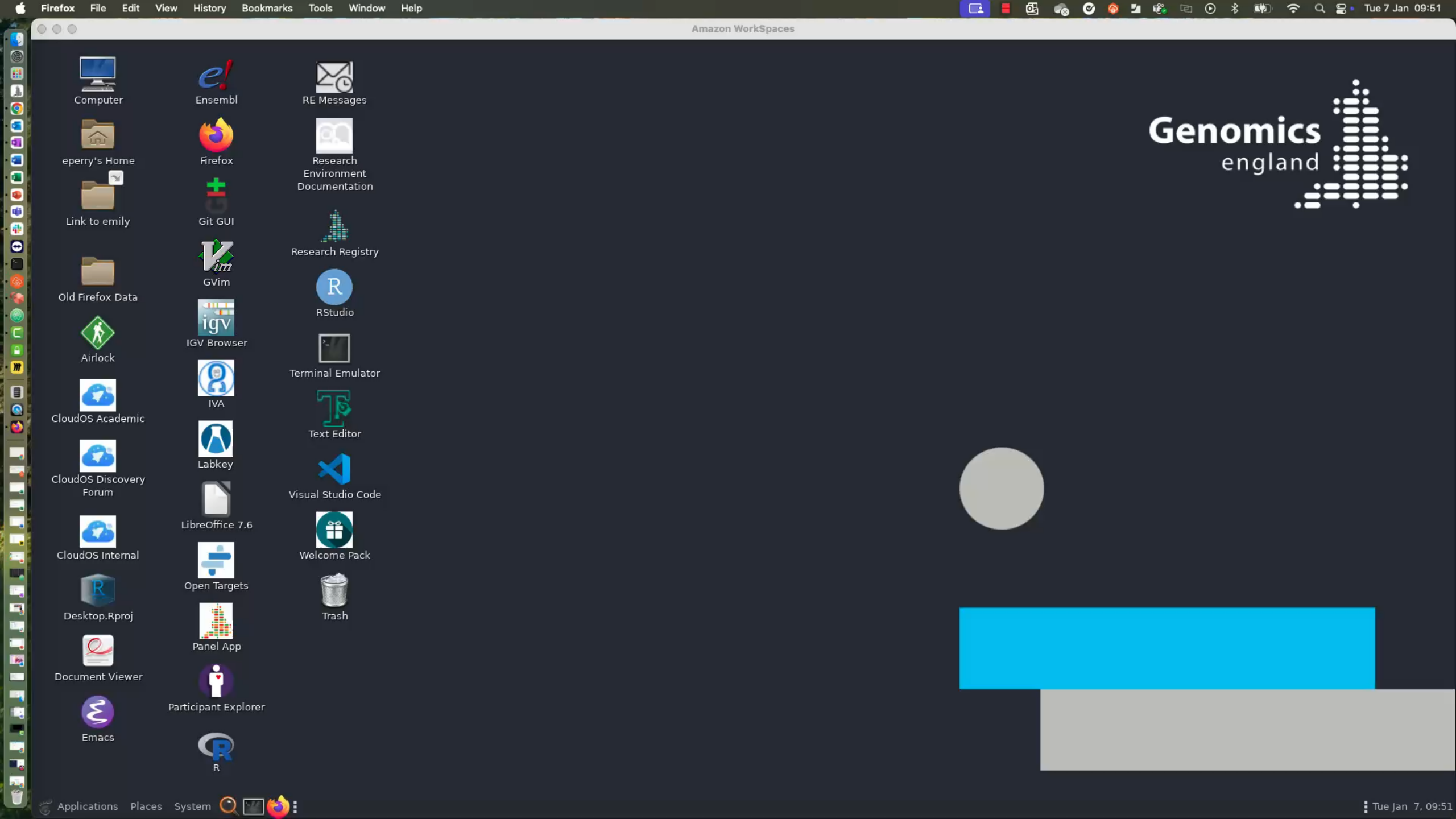
IVA Case Interpreter

Filter variants in proband by:

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

https://re-docs.genomicsengland.co.uk/iva/

IVA demo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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
Genomics england
Applications Places System
Tue Jan 7, 09:51

6. Validate your diagnosis

Is the variant I have found real?

Are the family genotypes for this variant correct?

Validate with IGV

View BAM files in IGV:

- Proband
- Relatives

https://re-docs.genomicsengland.co.uk/igv/

IGV demo

Chrome File Edit View History Bookmarks Profiles Tab Window Help

Mon 13 Feb 11:08

Inuvika OVD

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Update

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Participant Explorer — Mozilla Firefox

about:session | Start Page | panels_ap | exomiser: | tiering_dat | submitted_ | op: /main-p | rare_disea | rare_disea | key_colum | gmc_exit_c | Participa | Congenital hy | IVA v2.2.3 | rs5675003

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

Genomics england

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
[redacted]	N/A

Family Members for Proband 1

Relationship to Proband	Sex	Affection Status	Participant ID	Pedigree Member ID
Proband	Female	Affected	[redacted]	[redacted]
Father	Male	Unaffected	[redacted]	[redacted]
Mother	Female	Unaffected	[redacted]	[redacted]
Family Member	Male	Uncertain		[redacted]
Family Member	Male	Uncertain		[redacted]
Family Member	Female	Uncertain		[redacted]
Family Member	Female	Uncertain		[redacted]

Rows per page: 10 1-7 of 7

Genome Sequence

Applications | Participant Explorer — ... | IGV

11:08

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

https://re-docs.genomicsengland.co.uk/pxa/

Participant Explorer demo

Genomic Location

3:444-55555,1:1-100000

Gene	Gene ID	Transcript ID	Source	Biotype	Transcript Flag	Consequence Types (SO Term)	UniProt Accession	Position	Ref/Alt	Sift	Polyphen
DUOX2	ENSG00000140279	ENST00000389039	-	protein_coding	NA	frameshift_variant (SO:0001589)	-	201	GLY/GLY	-	-
DUOX2	ENSG00000140279	ENST00000603300	-	protein_coding	NA	frameshift_variant (SO:0001589)	-	201	GLY/GLY	-	-
DUOX2	ENSG00000140279	ENST00000558383	-	retained_intron	NA	non_coding_transcript_exon_variant (SO:0001792)	-	-	-	-	-

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

Chrome File Edit View History Bookmarks Profiles Tab Window Help

Mon 13 Feb 11:16

Inuvika OVD

re.extge.co.uk/ovd/

Update

Raise A Ticket | RE docs | CloudRE-docs | JIRA Confluence | Multi Factor Auth | Change Password | bob | SharePoint | RE1 | RE1 UG | brs_git | Profit.co | product board | icons | showcase | Notion | GEL Academy

Participant Explorer — Mozilla Firefox

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

Genomics england

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

Comparison help

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

Medical History Timeline, codes shared by Multiple Participants

Applications | Participant Explorer — ... | IGV

11:16

8. Submit your diagnosis and/or contact clinicians

Form in Airlock

- Contact clinical team
- Report potential diagnosis

https://re-docs.genomicsengland.co.uk/cli/

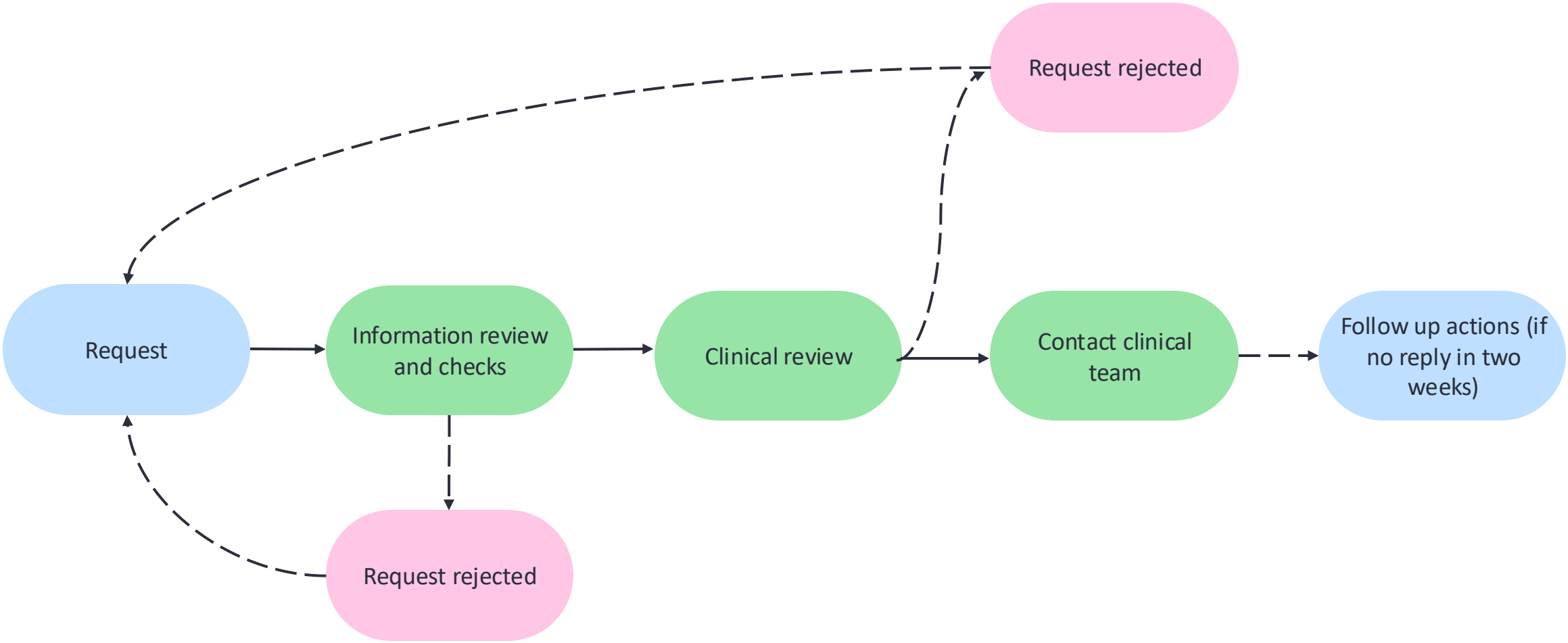
Clinical collaboration

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

https://re-docs.genomicsengland.co.uk/cli/

Clinical collaboration



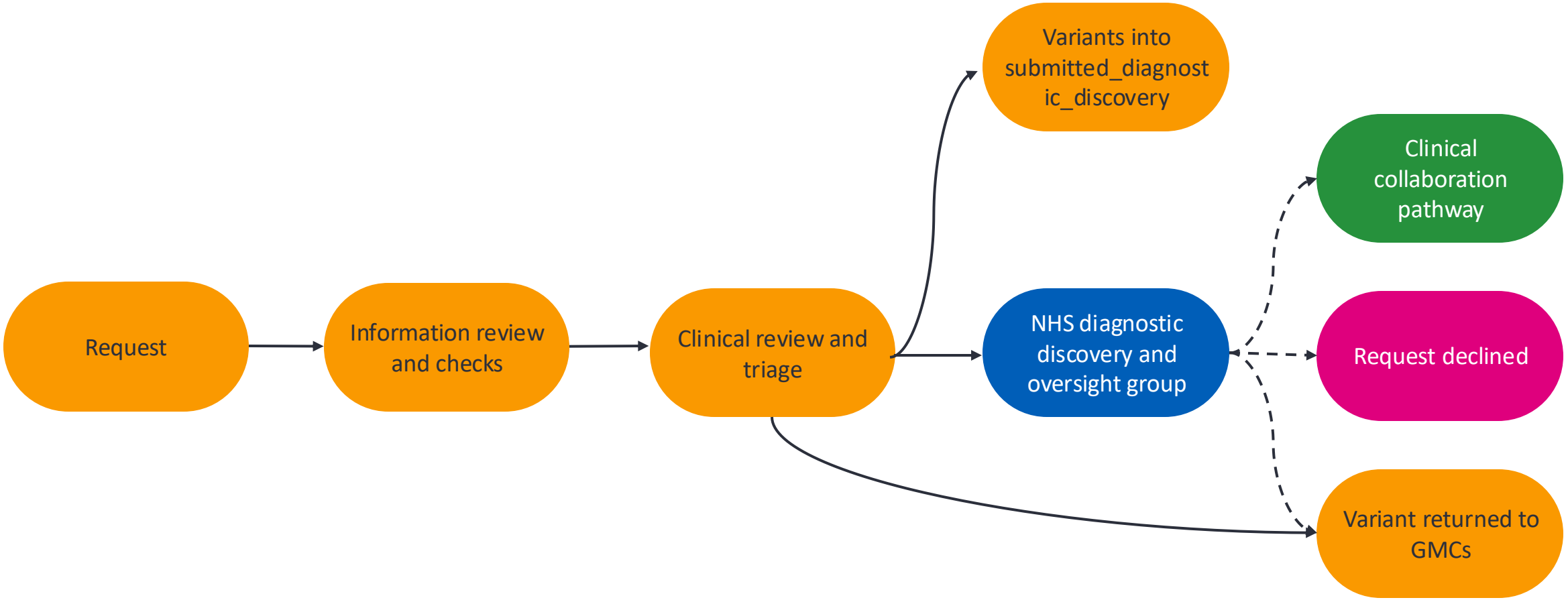
https://re-docs.genomicsengland.co.uk/cli/

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

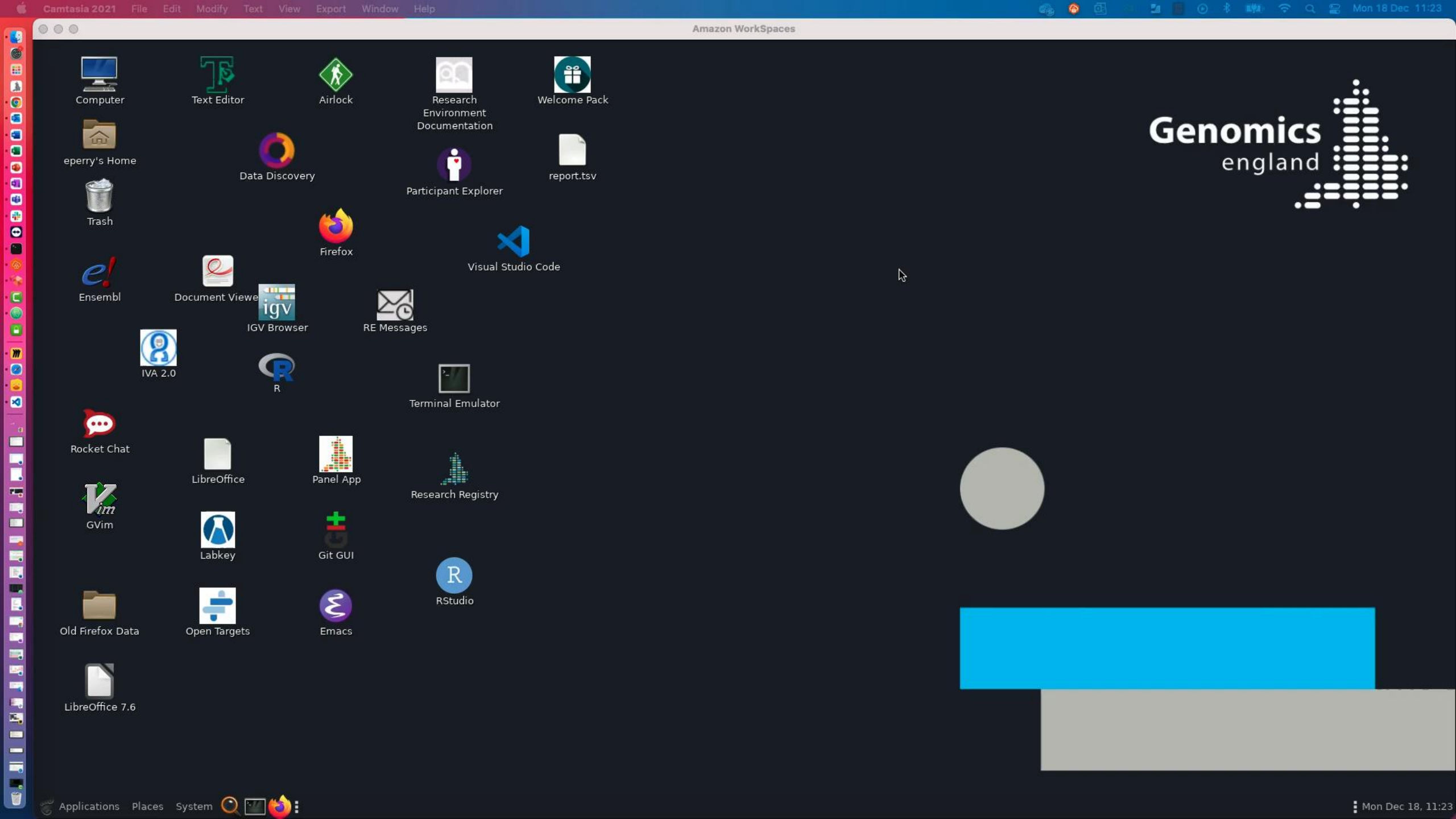
https://re-docs.genomicsengland.co.uk/cli/

Diagnostic discovery



https://re-docs.genomicsengland.co.uk/cli/

Form demo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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
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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

21/1 18/2 18/3

15/4 20/5 22/7

https://re-docs.genomicsengland.co.uk/upcoming/

Materials from past training all online

Training sessions

11/2	Importing data and tools to use in the RE
11/3	Working with R in the RE
8/4	Working with python in the RE
13/5	Building cancer cohorts and survival analysis
10/6	Building rare disease cohorts with matching controls
8/7	Finding participants based on genotypes

https://re-docs.genomicsengland.co.uk/upcoming/

Feedback

Thank you

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