

Plataforma RD-Cat: módulo de datos fenotípicos

Gemma Bullich Leslie Matalonga

Centre Nacional d'Anàlisi Genòmica, CNAG-CRG, Barcelona

Tècniques òmiques en el diagnòstic de malalties minoritàries,
16/11/2022



```
print $142
syntax error
tro@ns indelcalling]$ cp /scratch/COPY_temp/indelcalling/
tro@ns indelcalling]$ cp --help' for more information.
tro@ns indelcalling]$ cp /scratch/devel/fcastro/data/1000genomes/indelcalling/CEU* .
tro@ns indelcalling]$ cp /scratch/devel/fcastro/data/1000genomes/indelcalling/README* .
tro@ns indelcalling]$ ls RPO00031.2010_03.indels.genotypes.vcf.gz CEU.SRP000031.2010_03.indels.genotypes.vcf.gz.tbi CEU
tro@ns indelcalling]$ cp /scratch/devel/fcastro/data/1000genomes/indelcalling/CEU* .
tro@ns indelcalling]$ pwd /devel/fcastro/COPY_temp/indelcalling
tro@ns indelcalling]$ cd /scratch/
```

6, 123 0|0:123:123, 123 0|1:123:123, 123 0|1:49:52, 5
0:123:123, 123 0|0:123:123, 123 0|0:123:123, 123 0|0:
6, 123 0|0:123:123, 123 0|0:123:123, 123 0|0:52:123,
1:123:123, 123
6, 123 1|0:123:123, 123:56;0.0852854;21;19 0|0
6, 123 0|0:83:83, 123 0|1:43:123, 43 0|0:123:123
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, 51 0|0:43:43, 123 0|0:87:123, 87 0|0:114:123
0:37:37, 123 0|0:123:123, 123 0|0:123:123, 123 0|0
3, 123 1|0:123:123, 123
3, 123 0|0:123:123, 123:59;0.102882;5:3 0|0:113:123
0:123:123, 123 0|0:123:123, 123 0|0:76:105, 76 0|0
3, 123 0|0:76:76, 123 0|0:123:123, 123 0|0:123:123
0:123:123, 123 0|0:123:123, 123 1|0:123:123
3, 123 1|0:123:123, 123 0|1:106:123, 106
0:113:123, 113
0:123:1

Agenda

Día 1:

15:00 – 15:30: Introducción al proyecto iGenCO – Sergi Beltran (CNAG-CRG)

15:30 – 17:00: Plataforma RD-Cat: módulo de datos fenotípicos - teoría (30 min) + práctica (1h) –
Leslie Matalonga (CNAG-CRG) y Gemma Bullich (CNAG-CRG)

17:00 – 17:30: Coffee Break

17:30 – 19:00: Plataforma RD-Cat: módulo de datos genómicos - teoría (30 min) + práctica (1h) –
Gemma Bullich (CNAG-CRG) y Leslie Matalonga (CNAG-CRG)

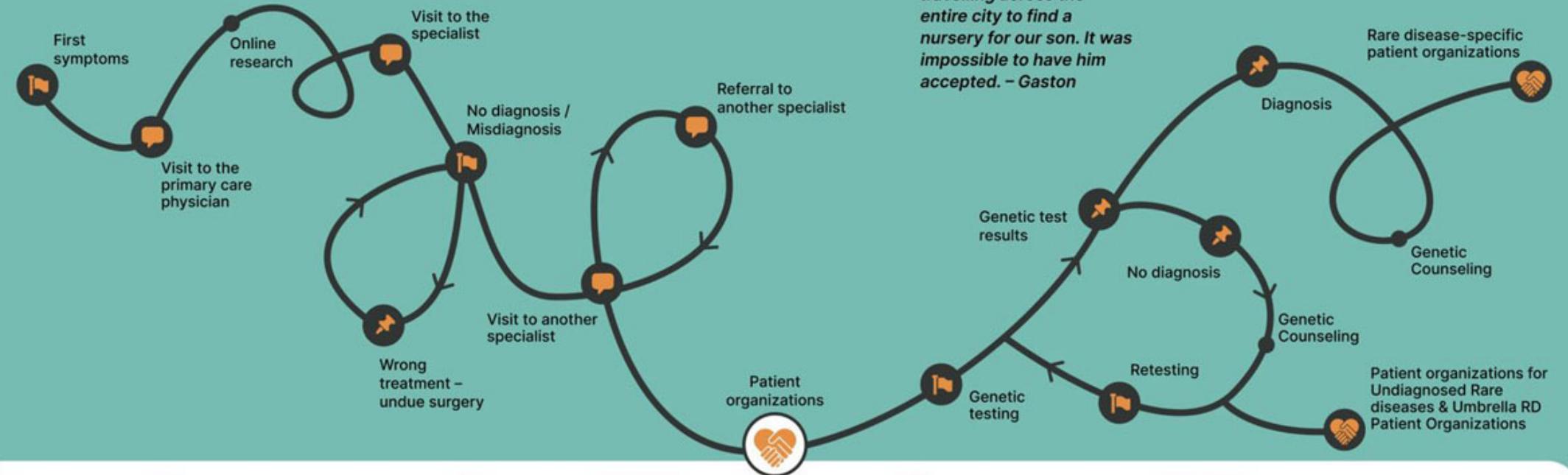
Diagnostic odyssey and unsolved patients with rare diseases

Patient Journey through diagnosis

“It's a waiting game, but you tell a mum to wait when she's waited 15 years. It's difficult. – Nuria

“People began to ask which side of the family it came from...It was a difficult time for us as parents. – Alexa

“A diagnosis may be bad news, it may be very bad news or it may be no news. But all of that's OK and there's help and support for whatever spectrum you end up on. – Peter



Solve*ORD*



EuroGentest



EUROGENTEST
Guidelines



GLOBAL COMMISSION
to End the Diagnostic Odyssey for Children with a Rare Disease



RARECONNECT.
ORG



WILHELM
FOUNDATION



ENSERIO
STUDY.
TIME TO
DIAGNOSIS



UNDIAGNOSED
PHOTO
PROJECT



feder



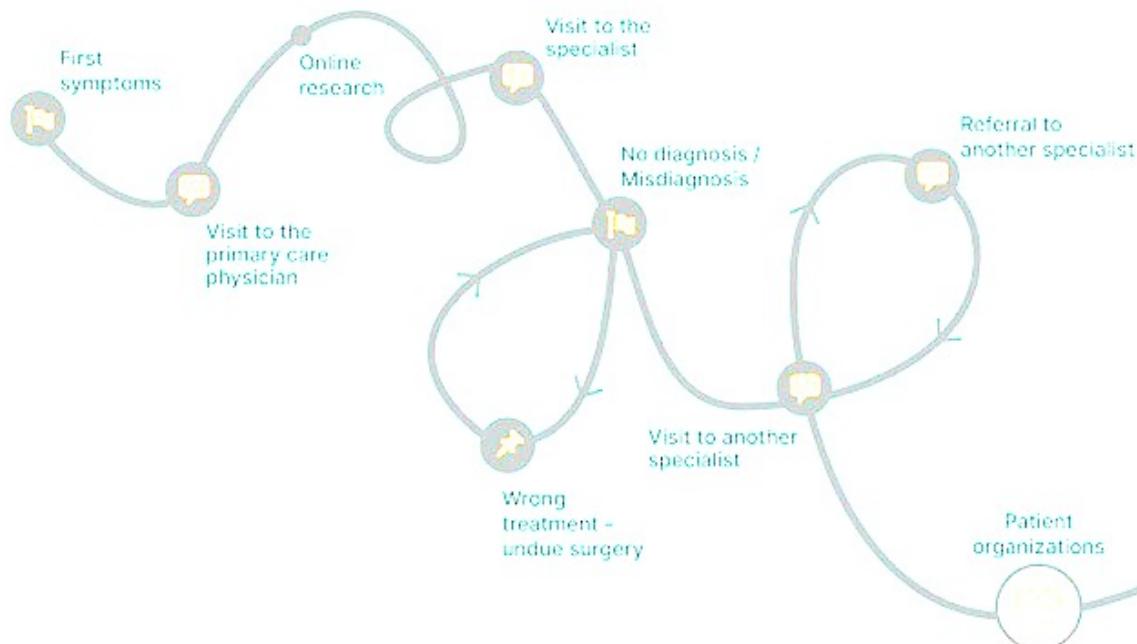
SWAN



UDNI

Diagnostic odyssey and unsolved patients with rare diseases

Patient Journey through diagnosis

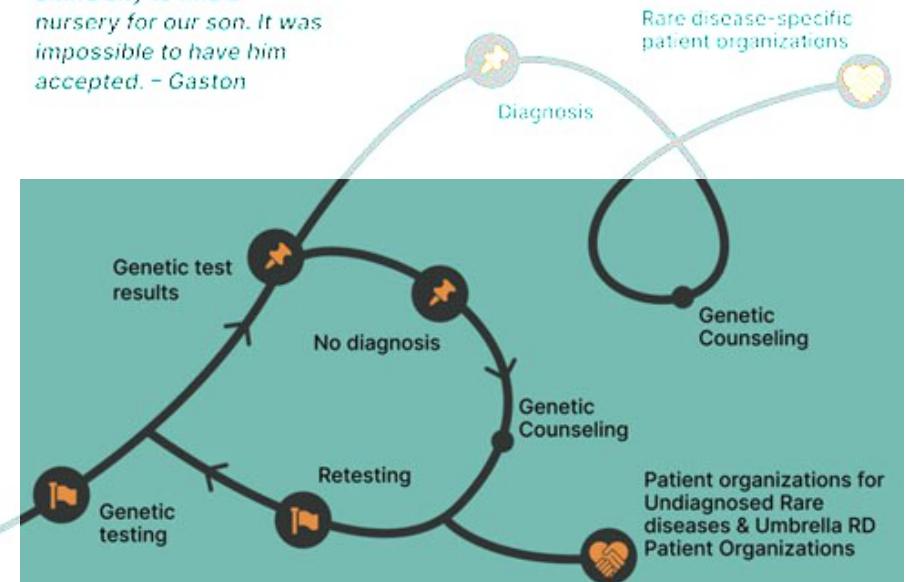


“It's a waiting game, but you tell a mum to wait when she's waited 15 years. It's difficult. – Nuria

“People began to ask which side of the family it came from...It was a difficult time for us as parents. – Alexa

“A diagnosis may be bad news, it may be very bad news or it may be no news. But all of that's OK and there's help and support for whatever spectrum you end up on. – Peter

“We went around, travelling across the entire city to find a nursery for our son. It was impossible to have him accepted. – Gaston



Unsolved after WES:

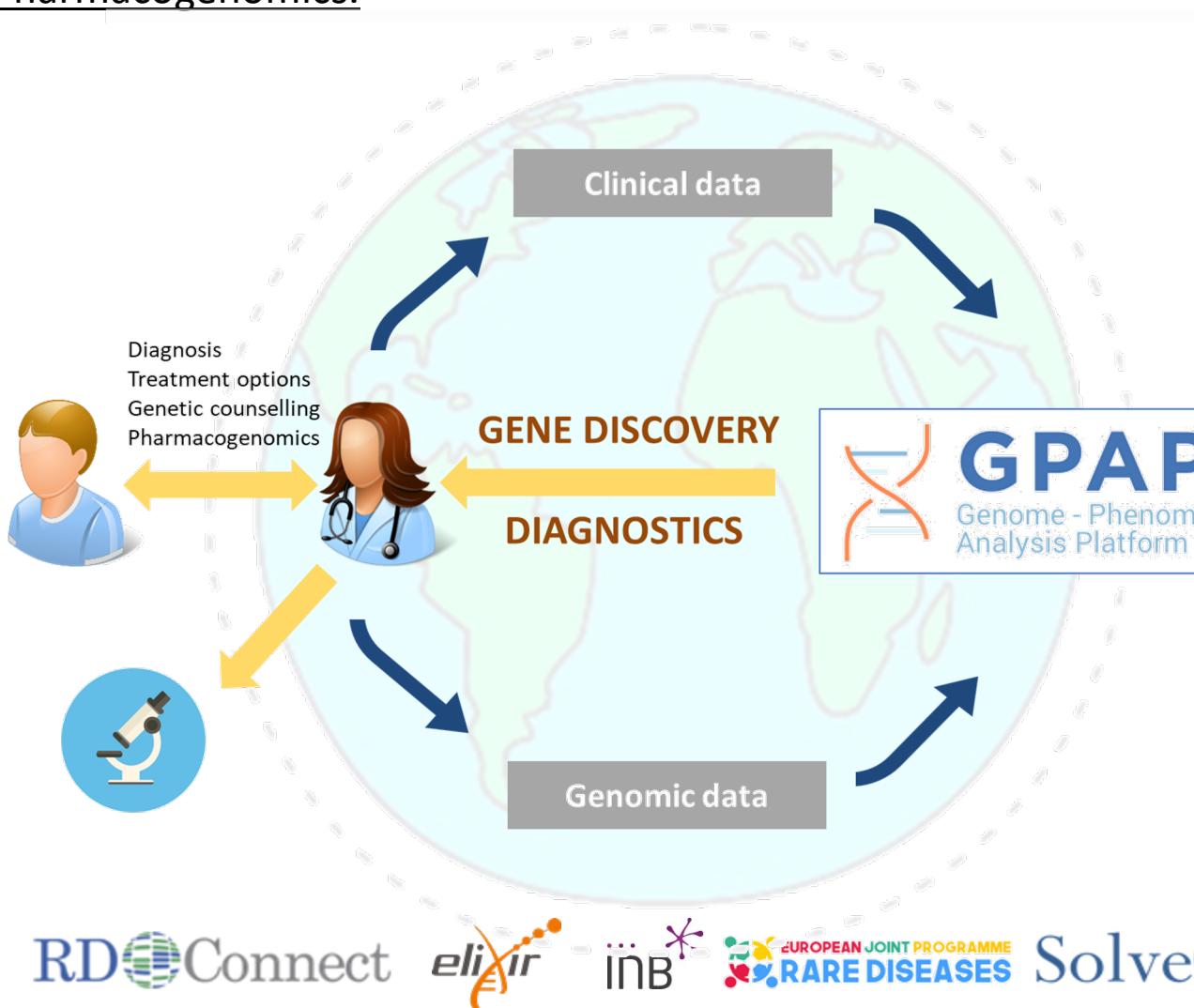
50 % of all patients with a rare disease will not have access to health care without a clear diagnosis

- 30 Millions patients in EU (15M unsolved)



GPAP: Genome-Phenome Analysis platform

The GPAP is an online system that facilitates **collation, sharing, analysis and interpretation of integrated genome-phenome datasets**. Mostly used for Rare Disease diagnosis and gene discovery, but may also be used for somatic cancer and Pharmacogenomics.

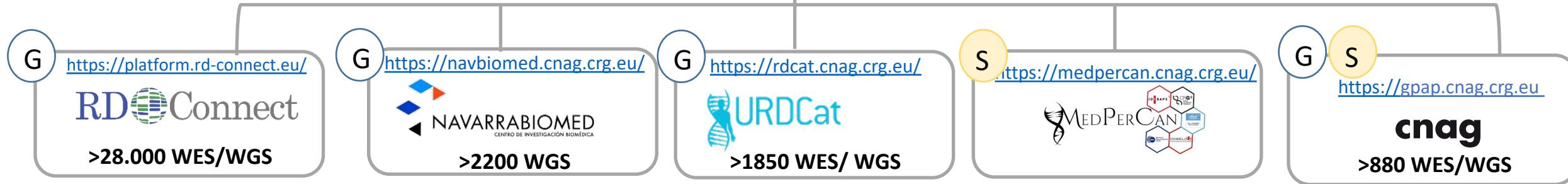


- Big data technologies (Elasticsearch and Apache spark)
- Scalable system (>31,000 WES/WGS held)
- Interoperable (FAIR): GA4GH standards
- Clinical ontologies and controlled vocabulary (HPO, OMIM, ORDO)
- Data is pseudonymised
- Secure data access (AAI)
- User activity logged
- GDPR compliant

GPAP instances



GPAP
Genome - Phenome
Analysis Platform



Solve
European Reference Networks
Reanalysis
>7000 negative cases
>1000 solved

246 consanguineous cases
Diagnostic yield 86%
8 novel disease causing genes

317 RD cases
Diagnostic yield 37% (8-95%)
10 novel candidate genes

NAGEN
PROYECTO GENOMA 1000 NAVARRA
NAGEN1000
NAGENPEDIATRICS
NAGENCOL
NAGENMX
Current diagnostic yield 15-52%

ciberer **La Marató**
Centro de Investigación Biomédica en Red
Enfermedades Raras

PERIS²⁰¹⁶
934 Neurological cases
Diagnostic yield 32.5%
Reanalysis 20.7%

PERIS²⁰¹⁶
236 hereditary cancer
108 Tumor/Normal
Tumor characterization

Agenda

- **Parte 1: Estandarización e integración de datos clínicos**
- Parte 2 (práctica):
 1. Entrada de datos clínicos de forma estandarizada
 2. Creación de cohortes en base a la información clínica

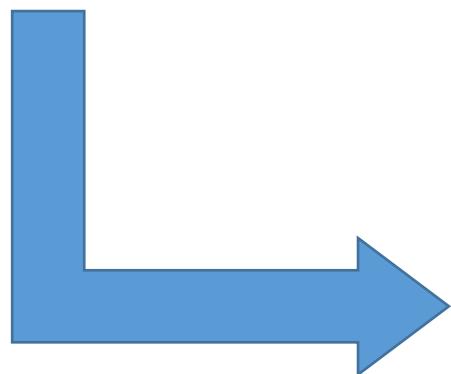
Need to gather all the phenotypic information

Diagnostic requires the collaboration of experts from different units, hospitals and countries

Video GA4GH: <https://www.youtube.com/watch?v=GLgB6mvVx5E&feature=youtu.be>

Need of standards, ontologies and tools to standardise and centralise the electronic health information across units, centres and countries:

- easily import-export / compare phenotypic data across databases and systems
- benefit from the use of software that helps to fasten the clinical and molecular diagnosis (HOOM, Phenomizer, Face2gene, Mendelian.co, etc)



Main Ontologies for rare genetic disorders:

- Orphanet Rare Disease Ontology (ORDO)
- Human Phenotype Ontology (HPO)
- Online Mendelian inheritance in Man (OMIM)

The Orphanet Rare Disease Ontology (ORDO) was jointly developed by Orphanet and the European Bioinformatics Institute (EMBL-EBI) to provide a **structured vocabulary for rare diseases**, capturing relationships between **diseases, genes and other relevant features, forming a useful resource for the computational analysis of rare diseases**.

In ORDO a clinical entity is either a group of rare disorders, a rare disorder or a subtype of disorder

› [Rare genetic disease](#) ORPHA:98053

└ [Rare genetic eye disease](#) ORPHA:101435

└ [Rare genetic disorder of the visual organs](#) ORPHA:522504

└ [Rare genetic disorder of the anterior segment of the eye](#) ORPHA:522538

└ [Genetic lens and zonula anomaly](#) ORPHA:183607

└ [Rare genetic disorder with lens opacification](#) ORPHA:522546

└ [Syndromic genetic cataract](#) ORPHA:522548

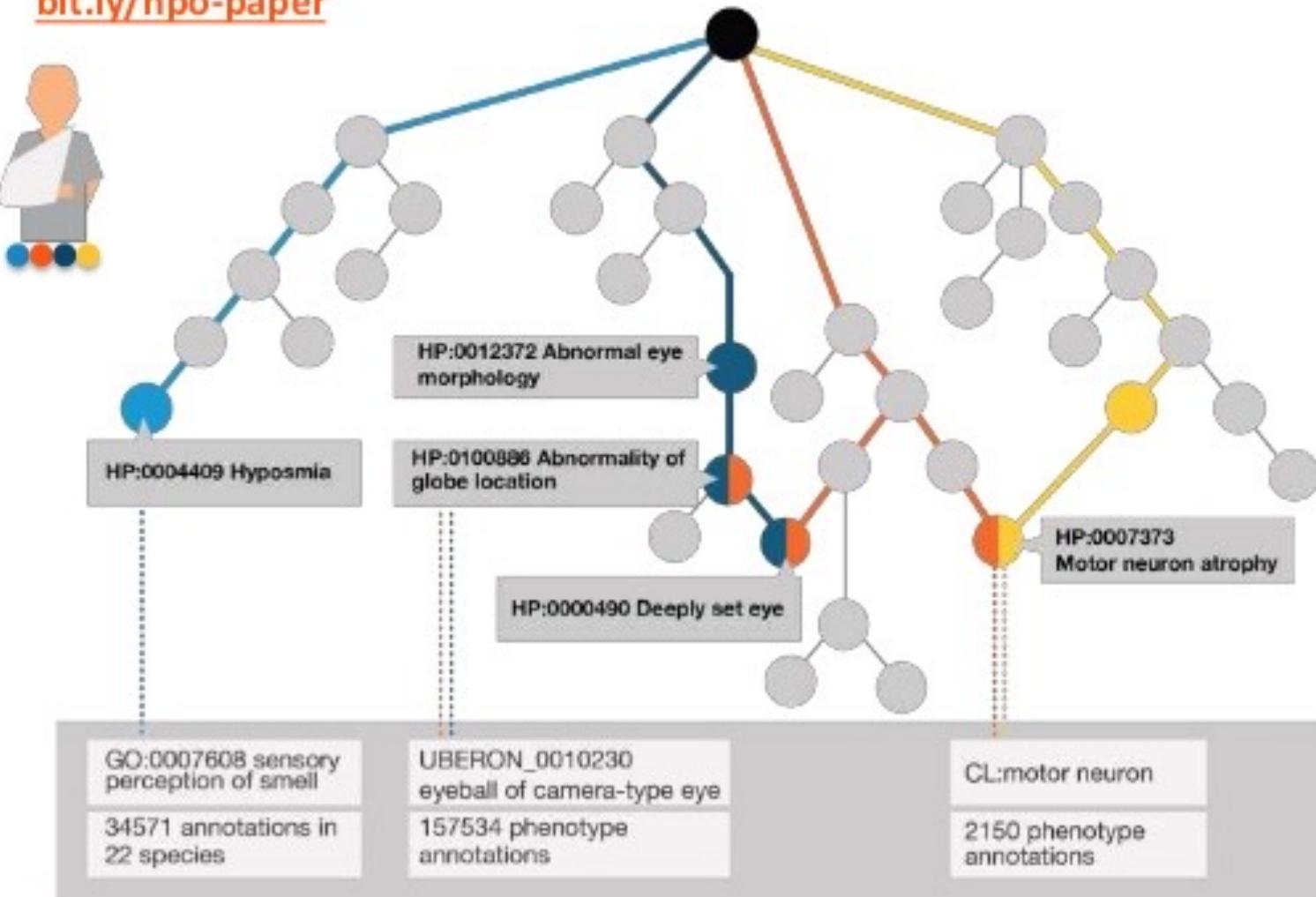
└ [Leber congenital amaurosis](#) ORPHA:65

Human Phenotype Ontology (HPO)

<https://hpo.jax.org/app/>

SYMPTOM LEVEL

bit.ly/hpo-paper



- Standardised vocabulary of phenotypic abnormalities
- Tree based classification – symptom granularity
- Developed using medical literature: Orphanet, OMIM and Decipher
- Terms are mapped with other ontologies (e.g. GO)
- Currently comprises more than 13,000 terms and over 156,000 annotations to hereditary diseases

Online Mendelian inheritance in Man (OMIM)

Online Catalog of Human Genes and Genetic Disorders. <https://omim.org/>

GENETIC LEVEL

OMIM is a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily.

Number of Entries in OMIM (Updated November 13th, 2022) :

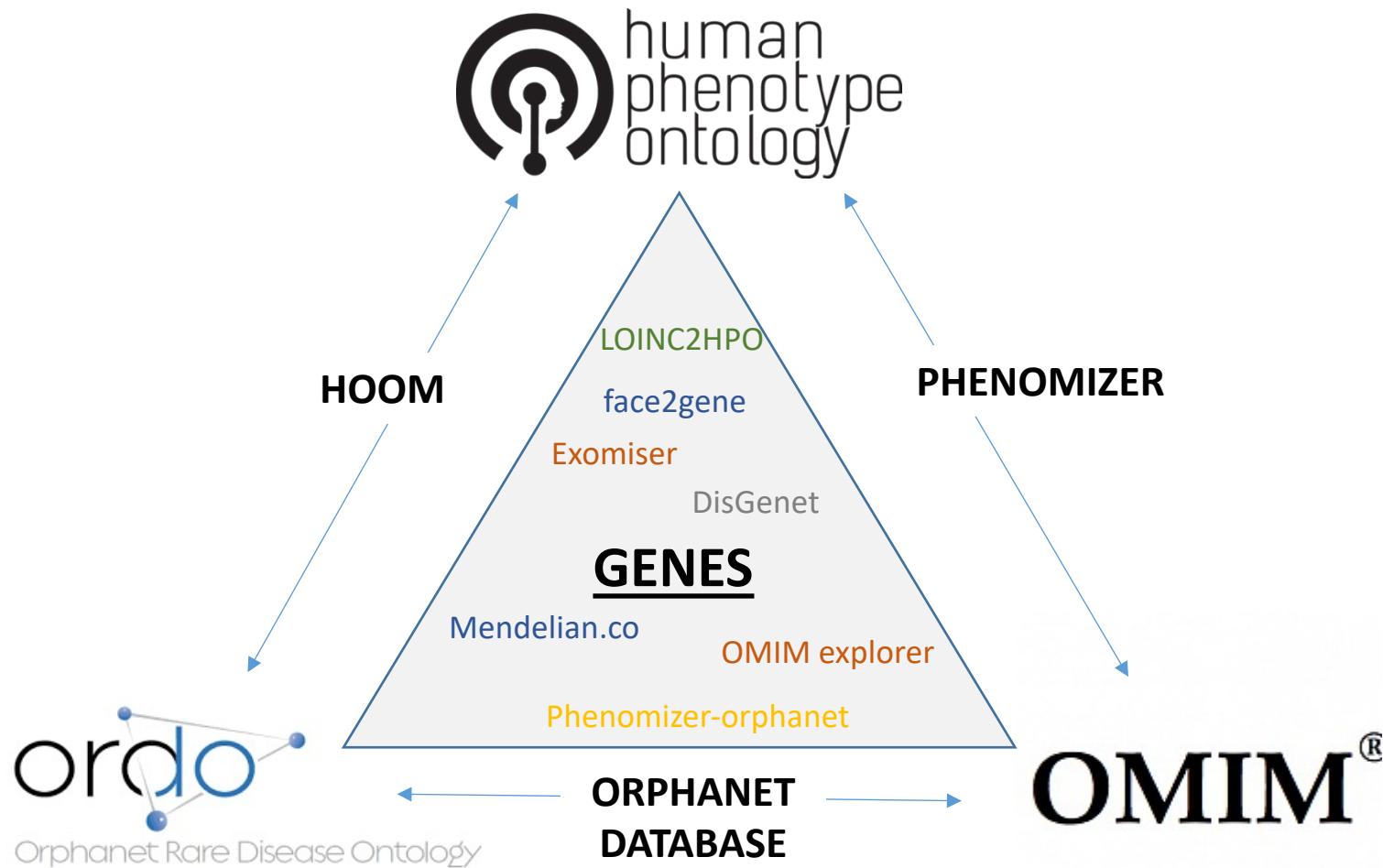
MIM Number Prefix	Autosomal	X Linked	Y Linked	Mitochondrial	Totals
Gene description *	16,028	758	51	37	16,874
Gene and phenotype, combined +	27	0	0	0	27
Phenotype description, molecular basis known #	6,100	370	5	34	6,509
Phenotype description or locus, molecular basis unknown %	1,394	112	4	0	1,510
Other, mainly phenotypes with suspected mendelian basis	1,645	102	3	0	1,750
Totals	25,194	1,342	63	71	26,670

Number of Entries in OMIM (Updated October 30th, 2019) :

MIM Number Prefix	Autosomal	X Linked	Y Linked	Mitochondrial	Totals
Gene description *	15,382	736	51	37	16,206
Gene and phenotype, combined +	37	0	0	0	37
Phenotype description, molecular basis known #	5,280	342	5	33	5,660

+900 since 2019!!

Main Ontologies for rare genetic disorders and tools associated



Disease similarity algorithms: phenomyzer

Menu. ▾ Support the Phenomizer. Help.

The Phenomizer

Features. Diseases. Ontology.

Enter feature... search. reset.

HPO id.	Feature.
HP:0010704	1-2 finger syndactyly
HP:0005767	1-2 toe complete cutaneous syndactyly
HP:0010711	1-2 toe syndactyly
HP:0010706	1-3 finger syndactyly
HP:0001459	1-3 toe syndactyly
HP:0010707	1-4 finger syndactyly
HP:0010712	1-4 toe syndactyly
HP:0006088	1-5 finger complete cutaneous syndactyly
HP:0010708	1-5 finger syndactyly
HP:0010713	1-5 toe syndactyly
HP:0030300	10 pairs of ribs
HP:0000878	11 pairs of ribs
HP:0030306	11 thoracic vertebrae
HP:0001233	2-3 finger syndactyly
HP:0005709	2-3 toe cutaneous syndactyly
HP:0004691	2-3 toe syndactyly
HP:0010709	2-4 finger syndactyly
HP:0005768	2-4 toe cutaneous syndactyly
HP:0010714	2-4 toe syndactyly
HP:0010692	2-5 finger syndactyly
HP:0010715	2-5 toe syndactyly
HP:0008083	2nd-5th toe middle phalangeal hypoplasia
HP:0011939	3-4 finger cutaneous syndactyly
HP:0006097	3-4 finger syndactyly
HP:0009779	3-4 toe syndactyly
HP:0010710	3-5 finger syndactyly
HP:0010716	3-5 toe syndactyly

Page 1 of 424 | Features 1 - 27 of 11442

Patient's Features. Diagnosis.

Algorithm: resnik (Unsymmetric). | 9 Features.

p-value.	Disease Id.	Disease name.	Genes.
0.2404	OMIM:100...	#100800 ACHONDROPLASIA; ACH	FGFR3 (2261)
0.2404	OMIM:616...	#616482 ACHONDROPLASIA, SEVERE, WITH DEVELOPMENTAL DELAY AND ACANTHOSIS NIGRICANS; SADD...	FGFR3 (2261)
0.2404	OMIM:612...	#612247 CROUZON SYNDROME WITH ACANTHOSIS NIGRICANS; CAN;;CROUZONODERMOSENKELT SYNDR...	FGFR3 (2261)
0.7491	OMIM:123...	#123500 CROUZON SYNDROME;;CRANIOFACIAL DYSOSTOSIS, TYPE I; CFD1;;CROUZON CRANIOFACIAL DY...	FGFR2 (2263)...
1.0000	OMIM:303...	#303600 COFFIN-LOWRY SYNDROME; CLS	RPS6KA3 (61...
1.0000	OMIM:182...	#182212 SHPRINTZEN-GOLDBERG CRANIOSYNOSTOSIS SYNDROME; SGS;;CRANIOSYNOSTOSIS WITH ARA...	SKI (6497), F...
1.0000	OMIM:218...	#218040 COSTELLO SYNDROME;;FACIOCUTANEOSENKELT SYNDROME;;FCS SYNDROMEMYOPATHY, CON...	HRAS (3265)
1.0000	OMIM:109...	#109400 BASAL CELL NEVUS SYNDROME; BCNS;;GORLIN SYNDROME;;GORLIN-GOLTZ SYNDROME;;NEVOI...	PTCH2 (8643)...
1.0000	OMIM:214...	#214800 CHARGE SYNDROME;;CHARGE ASSOCIATION--COLOBOMA, HEART ANOMALY, CHOANAL ATRESI...	CHD7 (55636)...
1.0000	ORPHANE...	MUCOPOLYSACCHARIDOSIS TYPE 1	
1.0000	OMIM:210...	#210253 VILLEFARESTDA SYNDROME--CHROMOSOME 9q34.2 DELETION SYNDROME--ON-SYNDROME--ON-SURT	EHMT1 / 70813)
1.0000	OMIM:268...	#268310 ROBINOW SYNDROME, AUTOSOMAL RECESSIVE; RRS;;COSTOVERTEBRAL SEGMENTATION DEFEC...	ROR2 (4920)
1.0000	ORPHANE...	MOVED TO	NOTCH2 (4853)
1.0000	OMIM:122...	#122470 CORNELIA DE LANGE SYNDROME 1; CDLS1;;CDL; CDLS;;TYPUS DEGENERATIVUS AMSTELODAME...	SMC1A (8243...)
1.0000	OMIM:217...	%217980 CORPUS CALLOSUM, AGENESIS OF, WITH FACIAL ANOMALIES AND ROBIN SEQUENCE;;TORIELLO...	
1.0000	OMIM:223...	%2223370 DUBowitz SYNDROME	NSUN2 (5488...)
1.0000	OMIM:602...	602613 SKELETAL DYSPLASIA AND PROGRESSIVE CENTRAL NERVOUS SYSTEM DEGENERATION,LETHAL	
1.0000	OMIM:607...	#607872 CHROMOSOME 1P36 DELETION SYNDROME;;MONOSOMY 1P36 SYNDROME	SKI (6497), K...

Page 1 of 268 | Improve Differential Diagnosis. Download Results.

SIMILARITY ALGORITHMS ARE TRAINED
TO PROPOSE POSSIBLE DIAGNOSES
UPON ORDO AND OMIM DISEASE
ANNOTATIONS

Phenotypic data module

DATA SUBMISSION DATA ANALYSIS DATA MANAGEMENT
GPAP RD Connect
GUIDELINES CONTACT WELCOME GUEST
GPAP Home / Data Submission / Phenotypic Data Submission

Welcome to the Phenotypic Submission App
Submit and share standardised phenotypic information of rare disease patients

Information
Individual Information Patient Consent Family Information Medical History Measurements Signs & Symptoms Genetic Testing Diagnosis Comments
Required Optional

➤ Measurements

Date of measurement (*The complete date has to be filled in) 27 / 04 / 2020
Age: 2 y and 1 m

Height (cm)
150
Height for age, birth to 36 months, boys
Age (months)
The CDC Growth Charts for US

Weight (Kg)
20
Weight for age, birth to 36 months, boys
Age (months)
The CDC Growth Charts for US

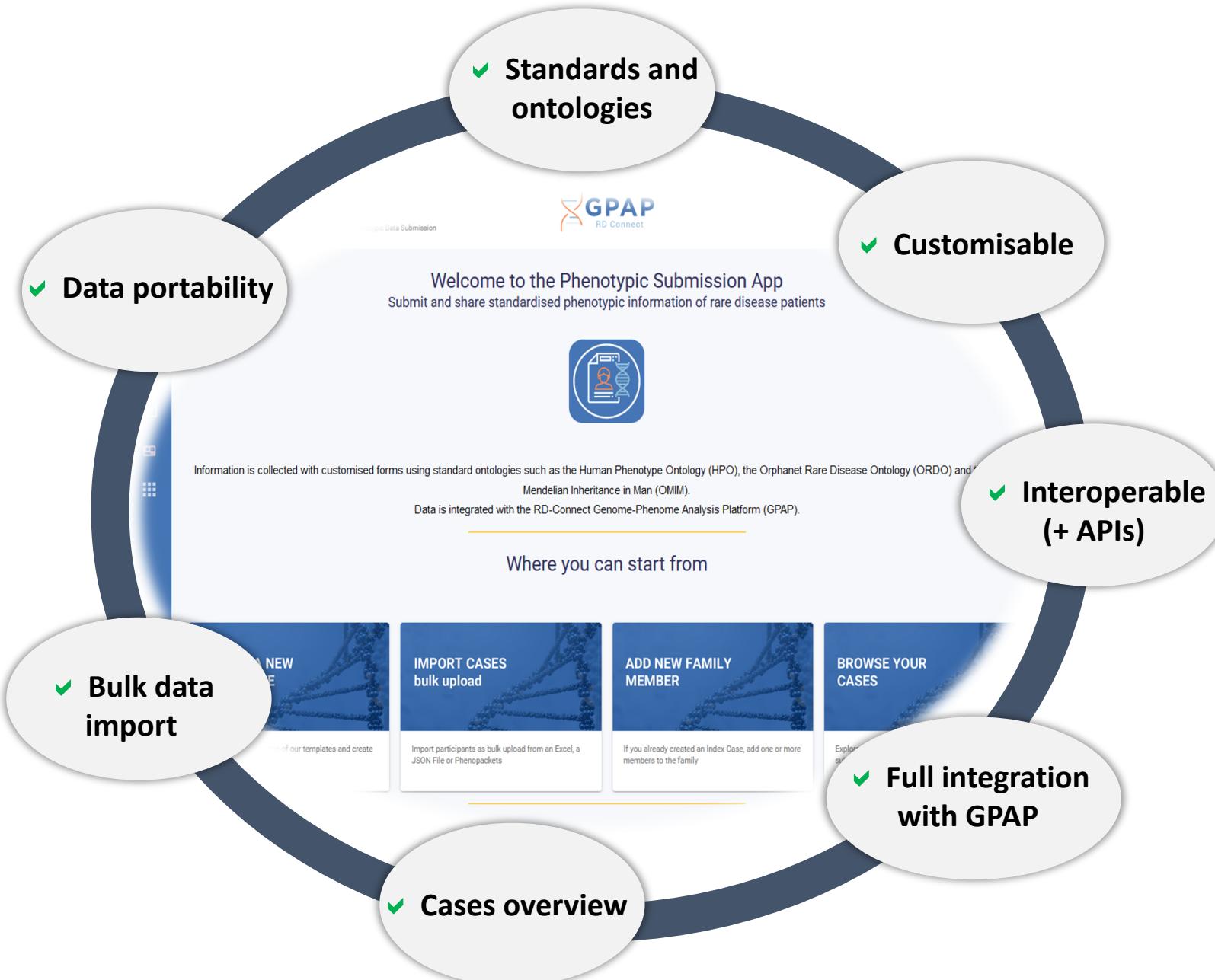
Head circumference (cm)

<https://platform.rd-connect.eu/>



user-friendly tool that enables collecting, sharing and exporting of standardised phenotypic information from rare disease patients

Phenotypic data module



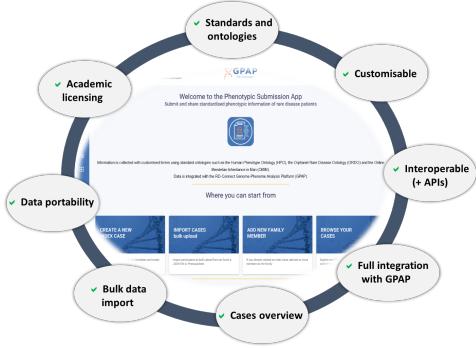


Data model based on GEL and mapped with ERNs

20 disease forms based on **Genomics England data model**
are already available to facilitate phenotypic data entry

- Cardiovascular disorders**
Disorders of the heart and blood vessels
ERN GUARD-HEART, VASCERN, ERN EURO-NMD, ERN ReCONNED, ERN LUNG
- Ciliopathies**
Abnormal formation or function of cilia
ERN LUNG, ERKNet, ERN EYE, ERNICA, ERN BOND
- Dermatological disorders**
Conditions that affect the integumentary system
ERN Skin, ERN ReCONNED
- Dysmorphic and congenital abnormality syndromes**
Congenital structural abnormalities
SELECTED
ERN eEUROGEN, ERN CRANIO, ERNICA, ERN ITHACA, ERN BOND, ERN-RND, MetabERN, Endo-ERN, ERKNet
- Endocrine disorders**
Disorders related to the endocrine glands of the body
Endo-ERN, MetabERN, ERN ITHACA
- Gastroenterological disorders**
Disorders that occur within the gastrointestinal tract
ERN RARE-LIVER, ERNICA

European Reference Networks are
mapped in collaboration with
Orphanet team



Data model based on GEL and mapped with ERNs

Tumour syndromes
Higher risk of certain types of cancer
ERN GENTURIS, ERN PaedCan, ERN EURACAN, Endo-ERN
SELECTED

Browse Categories

- + Breast and endocrine
- + GI tract
- + Muscle and nerve
- + Skin
- + Young onset tumour syndromes
- Multiple Primaries
 - + Breast carcinoma
 - + Neoplasm of the lung
 - Ovarian neoplasm
 - + Dysgerminoma
 - + Malignant ovarian granulosa tumor
 - + Ovarian sex cord-stromal tumor

Tumor Information

- Polyposis:

Adenomatous polyps	<input checked="" type="radio"/> none	<input type="radio"/> <10	<input type="radio"/> 10-20	<input type="radio"/> 20-50	<input type="radio"/> 50-100	<input type="radio"/> 100-1000	<input type="radio"/> >1000	<input type="radio"/> Not specified
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Serrated polyps	<input checked="" type="radio"/> none	<input type="radio"/> <10	<input type="radio"/> 10-20	<input type="radio"/> 20-50	<input type="radio"/> 50-100	<input type="radio"/> 100-1000	<input type="radio"/> >1000	<input type="radio"/> Not specified
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Hyperplastic polyps	<input checked="" type="radio"/> none	<input type="radio"/> <10	<input type="radio"/> 10-20	<input type="radio"/> 20-50	<input type="radio"/> 50-100	<input type="radio"/> 100-1000	<input type="radio"/> >1000	<input type="radio"/> Not specified
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Juvenile polyps:	<input checked="" type="radio"/> none	<input type="radio"/> <10	<input type="radio"/> 10-20	<input type="radio"/> 20-50	<input type="radio"/> 50-100	<input type="radio"/> 100-1000	<input type="radio"/> >1000	<input type="radio"/> Not specified
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- Tumor features:

Microsatellite instable	<input type="radio"/> Yes	<input type="radio"/> No	<input checked="" type="radio"/> Unknown
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Hypermutated	<input type="radio"/> Yes	<input type="radio"/> No	<input checked="" type="radio"/> Unknown
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- **Custom fields can be added to templates** to gather disease relevant information
- Relevant signs and symptoms displayed
 - Deep phenotyping
 - Differential diagnosis

Phenotypic data import



STEP 1
Choose a template
Select if to create an Index Case with the default template or a disease specific one



STEP 2
Create index case
Start by entering phenotypic information using templates or by bulk upload



STEP 3
Draw Family Pedigree
Enter family information through a pedigree drawing tool



STEP 4
Add family members information
Create entries for family members for which you would be submitting genomic data

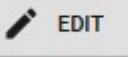
A. Case by case approach through the user interface

- Few cases
- Data NOT standard

B. Bulk import

- Data already available in a standardised format
- High number of cases

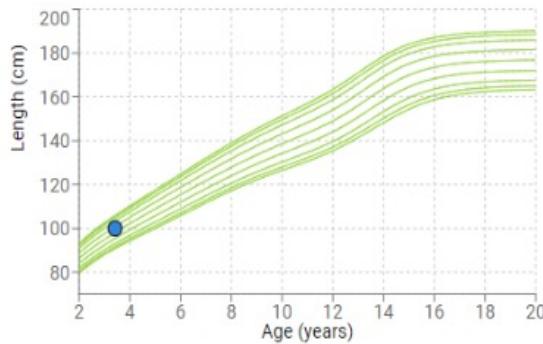
Excel file
JSON – PhenoTips
Phenopackets (ongoing)

PEDIGREE  EXPORT PDF

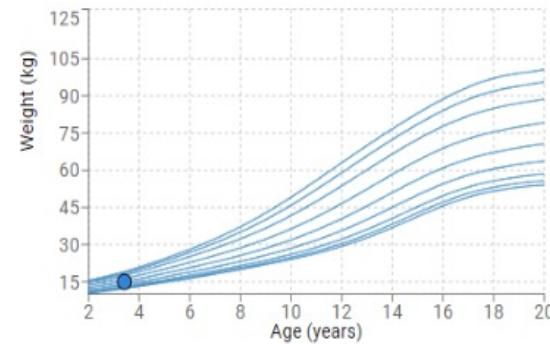
Individual Information
Patient Consent
Family Information
Medical History

Measurements

Height for age, 2 to 20 years, boys



Weight for age, 2 to 20 years, boys

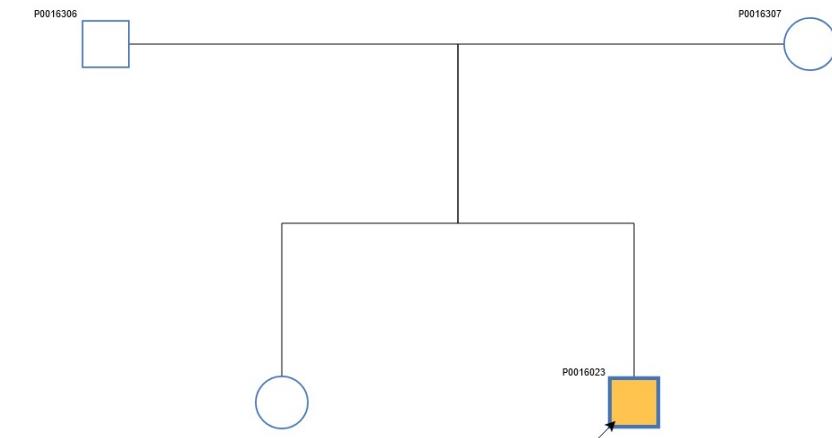


Symptoms

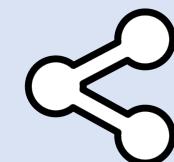
Genetic Testing

Diagnosis

Comments



GA4GH-Phenopackets
JSON



RD-Connect members

Data interoperability and portability

PEDIGREE EDIT PDF EXPORT PDF

Individual Information
Patient Consent
Family Information
Medical History

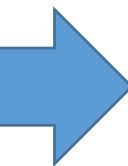
Measurements
Height for age, 2 to 20 years, boys

Length(cm) vs Age(years)

The CDC Growth Charts for US

Symptoms
Genetic Testing
Diagnosis
Comments

```
{
  "title": "FromPhenoTipsToPhenoPacket",
  "persons": [
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      "sex": "F"
    }
  ],
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              "label": "Neonatal onset"
            }
          ]
        },
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            "label": "MYASTHENIC SYNDROME, CONGENITAL, 6, PRESYNAPTIC"
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      }
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        "phenotype": {
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              "label": "Scapular winging"
            }
          ]
        }
      }
    ]
  ]
}
```



Global Alliance
for Genomics & Health



GA4GH-Phenopackets

Phenopacket format (PXD) enables
secure and standardised phenotypic
data portability

Overview of cases and export

♀♂ Sex

Unsolved

Affected status

Index cases

EXPORT TO TSV

PS ID	Local ID	Family ID	Index case	Affected status	Solved status	Sex	Consanguinity	ORDO	OMIM
P0958984		FAM0828574	Yes	Affected	Unsolved	M	Unknown		
P0007876		FAM0007717	Yes	Affected	Unsolved	M	Unknown		
P0012584		FAM0004961	Yes	Affected	Solved	F	Yes		
P0016023		FAM0006472	Yes	Affected	Unsolved	M	Unknown	Hereditary spasti...	
P0012505		FAM0004839	Yes	Affected	Solved	F	Unknown		
P0016166		FAM0006613	Yes	Affected	Unsolved	F	No	Hereditary spasti...	
P0002853		FAM0010069	Yes	Affected	Unsolved	F	Unknown		

Previous

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10 rows

Next

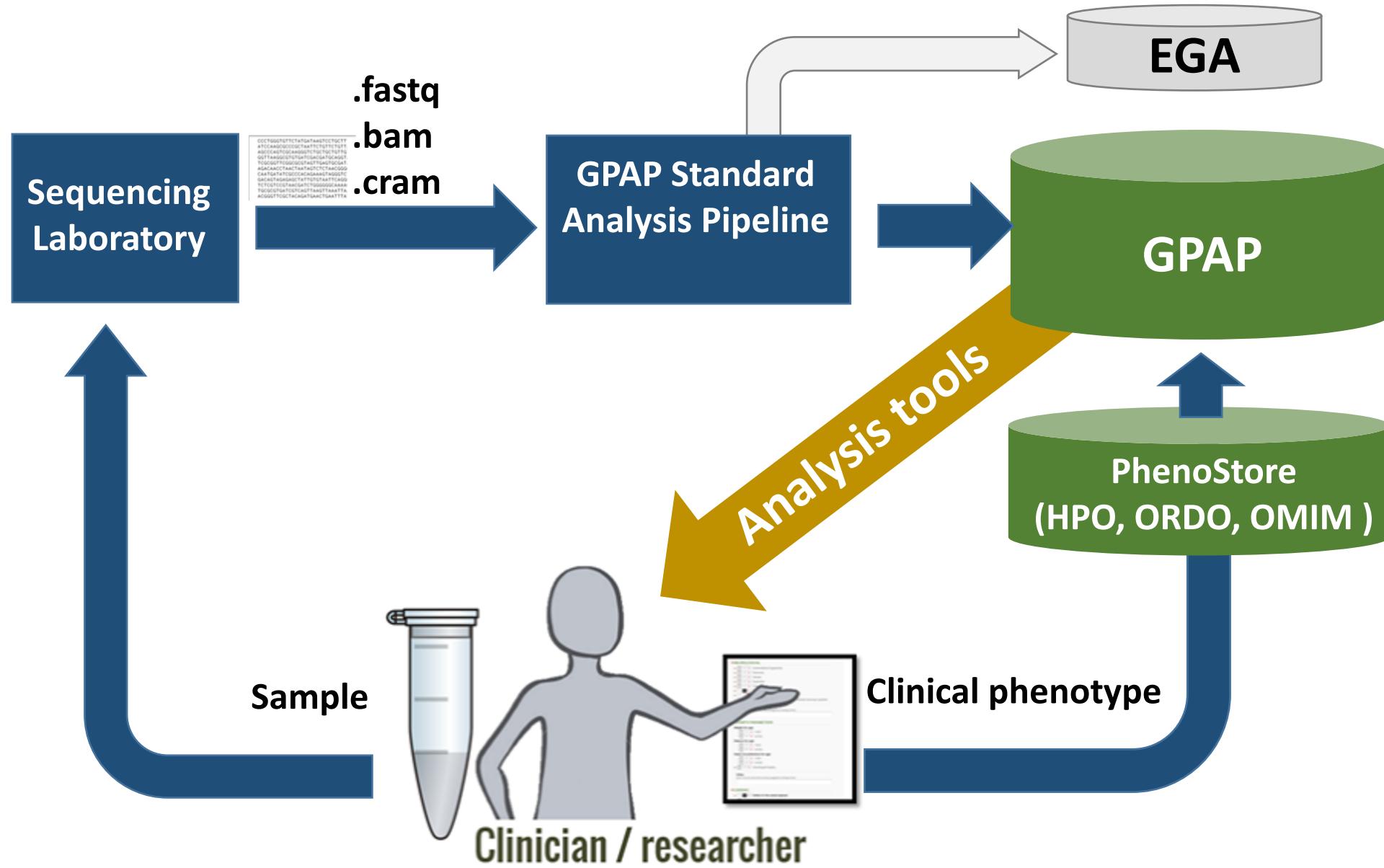
Browse, filter and export your data

CRG
Centre for Genomic Regulation

Centro Nacional de Análisis Genómico

centro nacional de análisis genómico

Genome-phenome data integration



RD-Connect GPAP: functionalities

platform.rd-connect.eu

- ✓ Standard filters and annotations for SNVs, InDels and CNVs (variant impact on protein, frequency in control populations, frequency within database, *in silico* predictors, gene, genomic position, etc.)
- ✓ Filter by genes of interest (predefined/custom lists, GEL's PanelApp, Mendelian.co, OMIM disease, HPO symptoms or Reactome)
- ✓ Phenotype driven strategy for variant prioritization (Exomiser)
- ✓ Filter by variants annotated in ClinVar database
- ✓ Filter to regions with observed long Runs of homozygosity (RoH)
- ✓ Direct link to multiple external resources (Ensembl, UCSC, gnomAD, HGMD, Human Splicing Finder, DiseaseCards, ALFA, etc.)
- ✓ TAG and share candidate variants using ACMG guidelines
- ✓ Search for variants in genes across all samples for which you have access in the system (embargo)
- ✓ Collaborative environment: share data and queries (DAC, security audit, GDPR compliant, user activity logged)
- ✓ Anonymized data discovery through Beacon and Matchmaker exchange

Human Phenotype ontology: genome-phenome data integration

^ SYMPTOMS (0)

First, extract or search for HPO terms below. When you made a selection, collect

Disgenet

GET HPOS FROM PARTICIPANTS

search for HPO terms

In the next step, you can extract genes from HPOs and add them to your queries

8 selected HPOs

HP:0001249, Intellectual disability	
HP:0001250, Seizures	
HP:0001263, Global developmental delay	
HP:0001942, Metabolic acidosis	
HP:0003201, Rhabdomyolysis	
HP:0003236, Elevated serum creatine phosphokinase	
HP:0004756, Ventricular tachycardia	
HP:0045045, Elevated plasma acylcarnitine levels	

Select Resource:

HPO ONTOLOGY

DISGENET

Select Method:

union of genes in this section is applied

APPLY INTERSECTION OF GENES



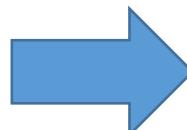
You included the genes in your query. You made an union between the HPO genes

RESET HPO GENE LIST

ADD GENES TO QUERY

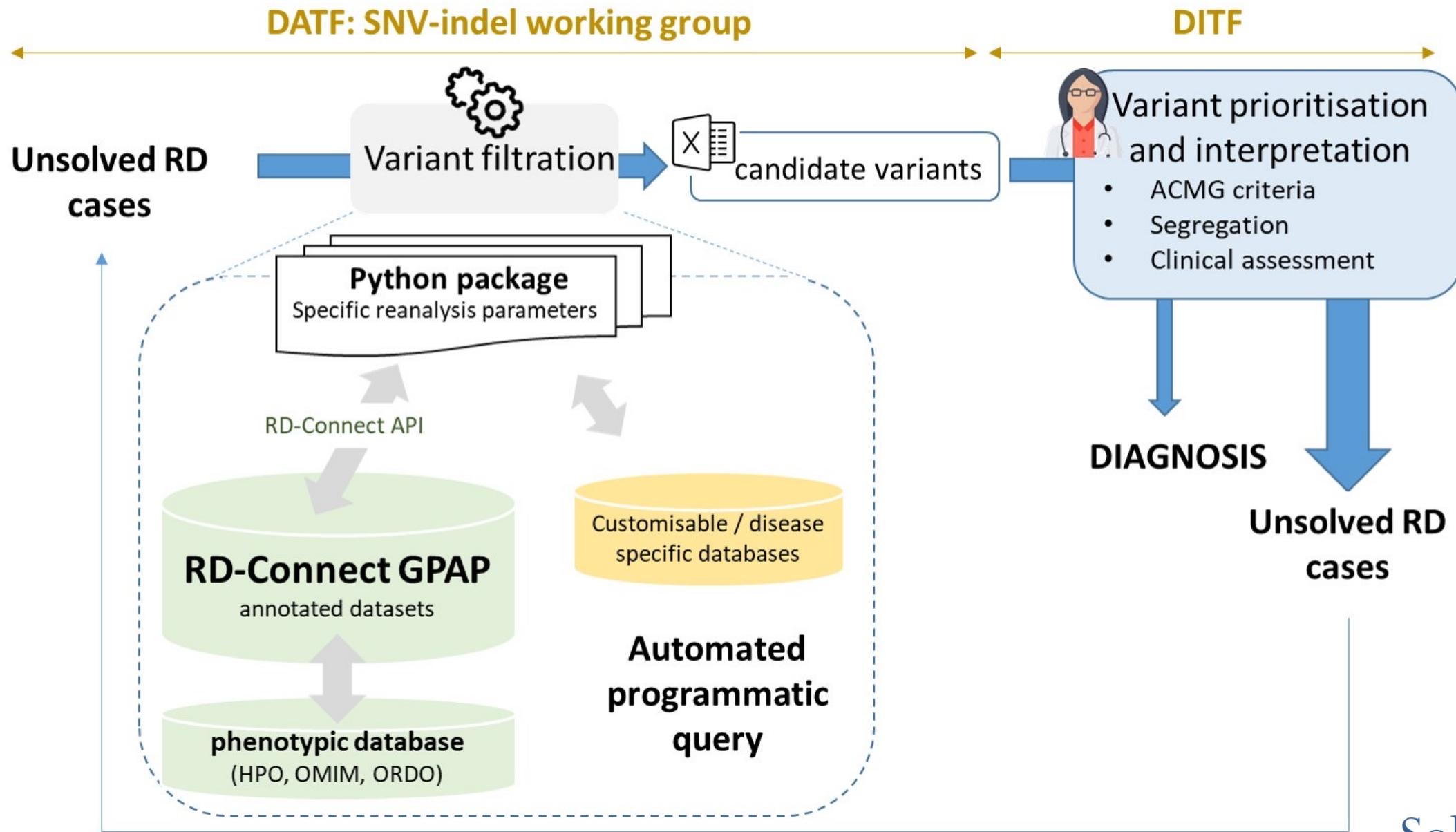
Current Selected Genes (n=2880)

AAAS, AARS1, AASS, ABAT, ABCA2, ABCA4, ABCA5, ABCA7, ABCB7, ABCC6, ABCC8, ABCC9, ABCD1, ABCD4, ABHD5, ABL1, ACAD8, ACAD9, ACADM, ACADS, ACADSB, ACADVL, ACAT1, ACAT2, ACD, ACER3, ACO2, ACOX1, ACOX2, ACP5, ACSF3, ACSL4, ACTA1, ACTA2, ACTB, ACTC1, ACTG1, ACTL6A, ACTL6B, ACTN2, ACVR1, ACVRL1, ACY1, ADA2, ADAM22, ADAMTS10, ADAMTS3, ADAMTS2, ADAR, ADARB1, ADAT3, ADCY3, ADCY5, ADD3, ADGRG1, ADGRV1, ADH5, ADK, ADNP, ADORA2A, ADPRS, ADRA2B, ADSL, ADSS1, AEBP1, AFF2, AFF3, AFF4, AFG3L2, AGA, AGBL5, AGGF1, AGL, AGO2, AGPAT2, AGRN, AGTPBP1, AGTR2, AGXT, AHCY, AHDC1, AH1, AHR, AHSG, AIFM1, AIM1P1, AIM2P, AIP, AIP1L, AKAP9, AKT1, AKT2, AKT3, ALAD, ALB, ALDH18A1, ALDH3A2, ALDH4A1, ALDH5A1, ALDH6A1, ALDH7A1, ALDOA, ALDOB, ALG1, ALG11, ALG12, ALG13, ALG14, ALG2, ALG3, ALG6, ALG8, ALG9, ALKBH8, ALMS1, ALOX12B, ALOXE3, ALPL, ALS2, ALX1, ALX3, ALX4, AMACR, AMER1, AMMECR1, AMPD1, AMPD2, AMPD3, AMT, ANAPC1, ANAPC7, ANGPTL6, ANK1, ANK2, ANK3, ANKH, ANKLE2, ANKRD1, ANKRD11, ANKRD17, ANO10, ANO5, ANOS1, ANTXR1, ANTXR2, ANXA11, AP1B1, AP1G1, AP1S1, AP1S2, AP2M1, AP3B1, AP3B2, AP3D1, AP4B1, AP4E1, AP4M1, AP4S1, AP5Z1, APC, APC2, APOE, APP, APR, AQP2, AR, ARCN1, ARF1, ARGEF2, ARG1, ARHGAP31, ARHGDI, ARHGEF18, ARHGEF2, ARHGEF6, ARHGEF9, ARID1A, ARID1B, ARID2, ARL13B, ARL2BP, ARL3, ARL6, ARL6IP1, ARL6IP6, ARMC9, ARNT2, ARSA, ARSB, ARSI, ARSL, ARV1, ARVCF, ARX, ASAHI, ASCC1, ASCL1, ASH1L, ASL, ASNS, ASPA, ASPM, ASS1, ASXL1, ASXL2, ASXL3, ATAD1, ATAD3A, ATCAY, ATG5, ATG7, ATIC, ATL1, ATM, ATN1, ATP10A, ATP13A2, ATP1A1, ATP1A2, ATP1A3, ATP2A2, ATP2B3, ATP5F1A, ATP5F1D, ATP5F1E, ATP6AP1, ATP6AP2, ATP6V0A2, ATP6V0A4, ATP6V1A, ATP6V1B1, ATP6V1B2, ATP6V1E1, ATP7A, ATP7B, ATP8A2, ATP8A3, ATP10D, ATP10Y, ATYN10, ATYN17, AUL1, AUTS2, AVBD2



Gene list used to filter your genomic data

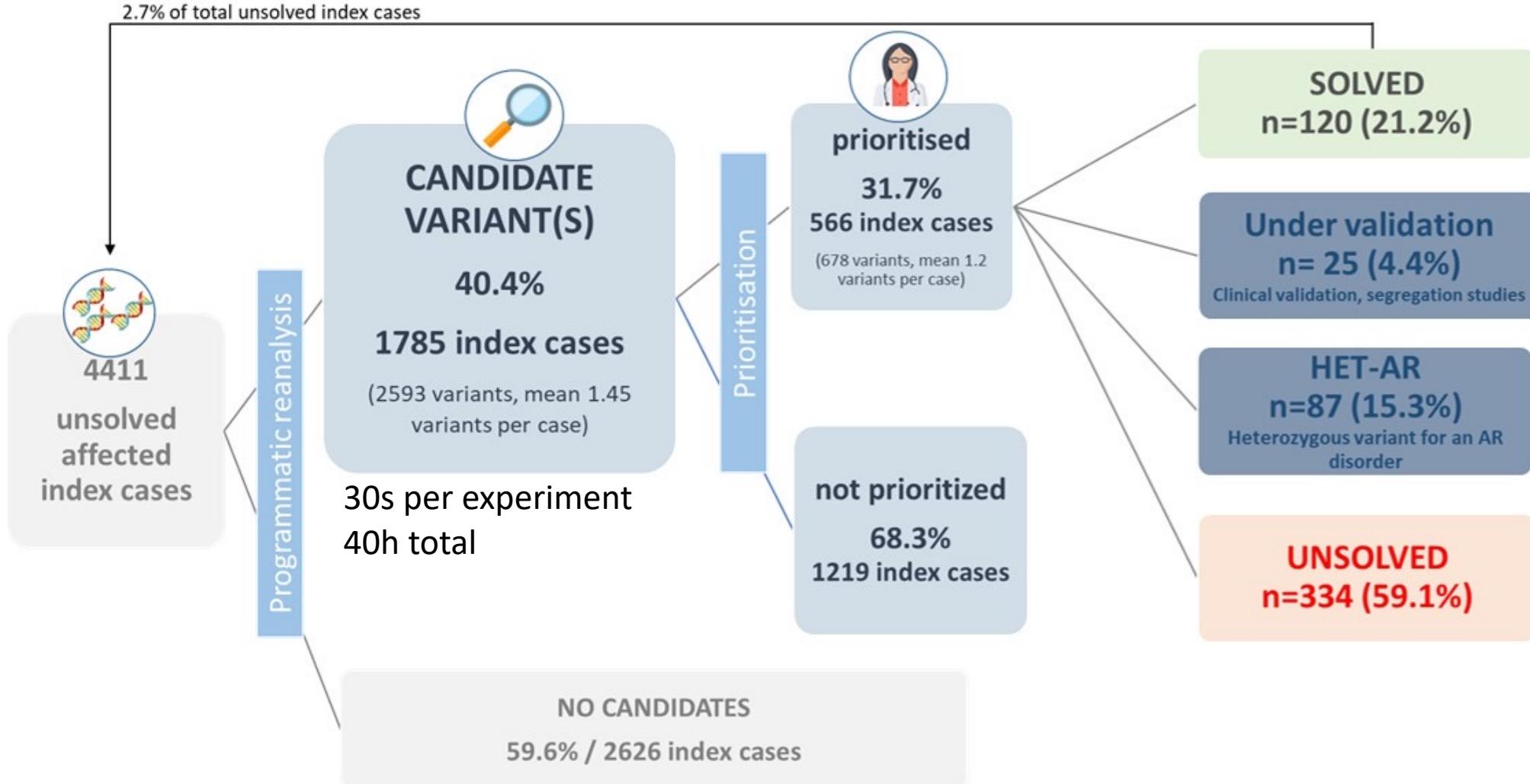
Human Phenotype ontology: genome-phenome data integration





“Low-hanging fruit”

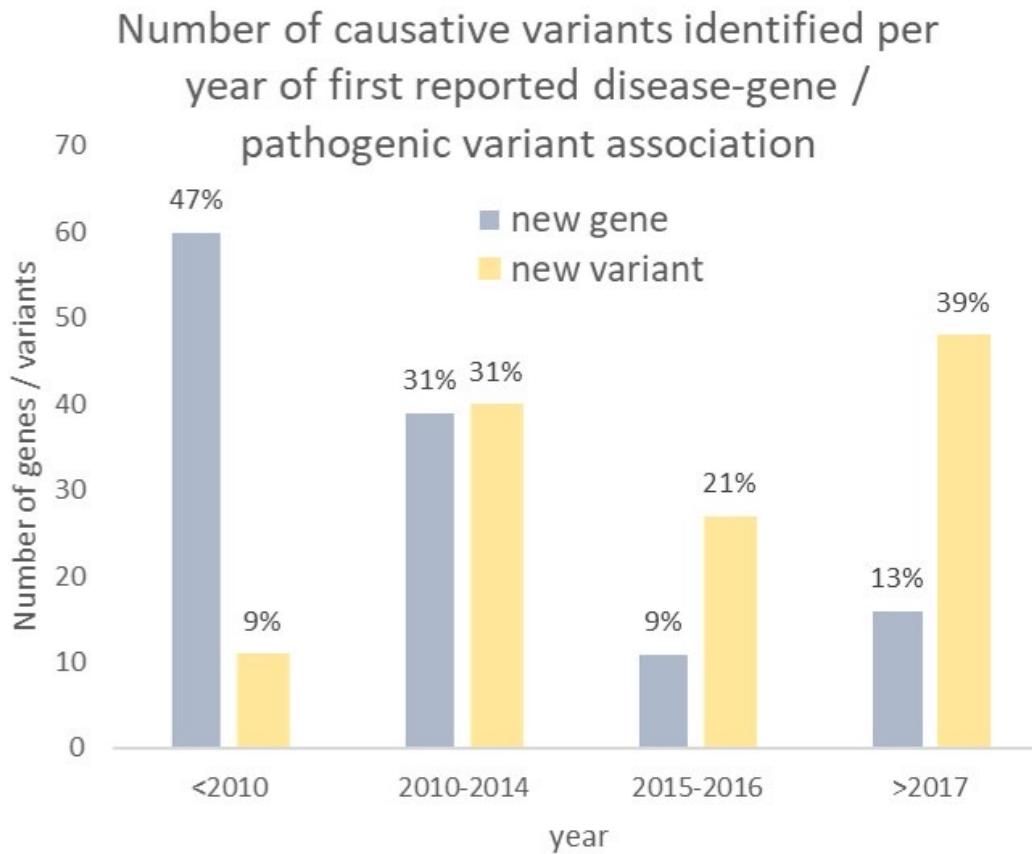
Known pathogenic variants in known disease-associated genes
SNV-indel WG and DITF members





“Low-hanging fruit”

Known pathogenic variants in known disease-associated genes
SNV-indel WG and DITF members

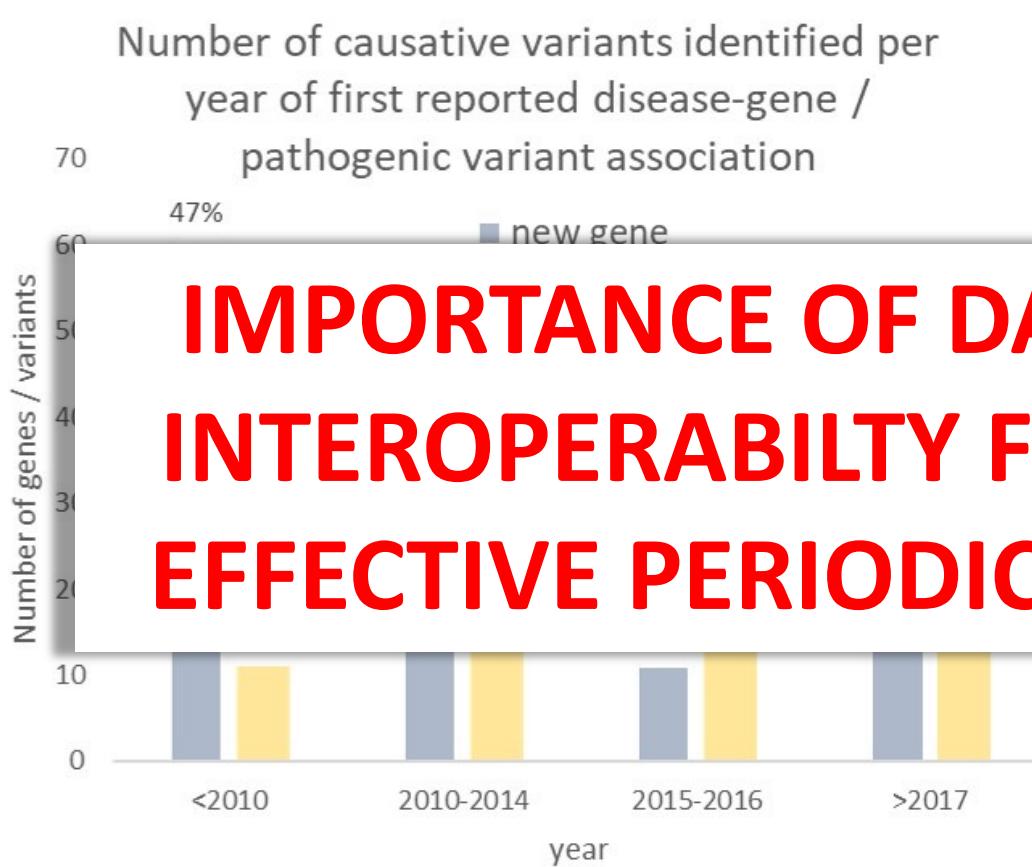


- **New disease-causing genes:**
 - 13% of the newly identified causative variants were in genes not associated with disease in the 2 years prior to reanalysis (described since 2017)
 - 22% since 2015
- **Updated variant classification:**
 - 39% were variants not reported as (likely) pathogenic for similar clinical manifestations at that time.
 - 60% since 2015
- **New bioinformatic pipeline**



“Low-hanging fruit”

Known pathogenic variants in known disease-associated genes
SNV-indel WG and DITF members



- **New disease-causing genes:**
 - 13% of the newly identified causative variants were in genes not associated with disease in the 2 years prior to reanalysis (described since 2017)

IMPORTANCE OF DATA STANDARISATION AND INTEROPERABILITY FOR A SCALABLE AND COST-EFFECTIVE PERIODIC AUTOMATED RE-ANALYSIS

- **New bioinformatic pipeline**

EXOMISER – variant prioritisation tool

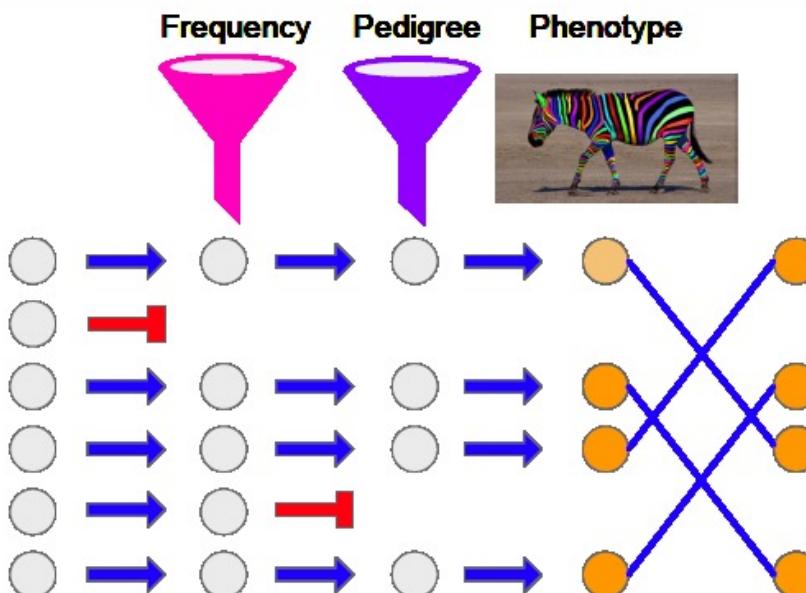
Slides kindly provided by Peter Robinson and Daniel Danis (JAX)

Gene Prioritization

- Bioinformatic/statistical ranking of lists of genes
- Leads to decision about which genes to follow up
- and which genes to leave out owing to lack of time/resources
- Result: A ranked list of candidates

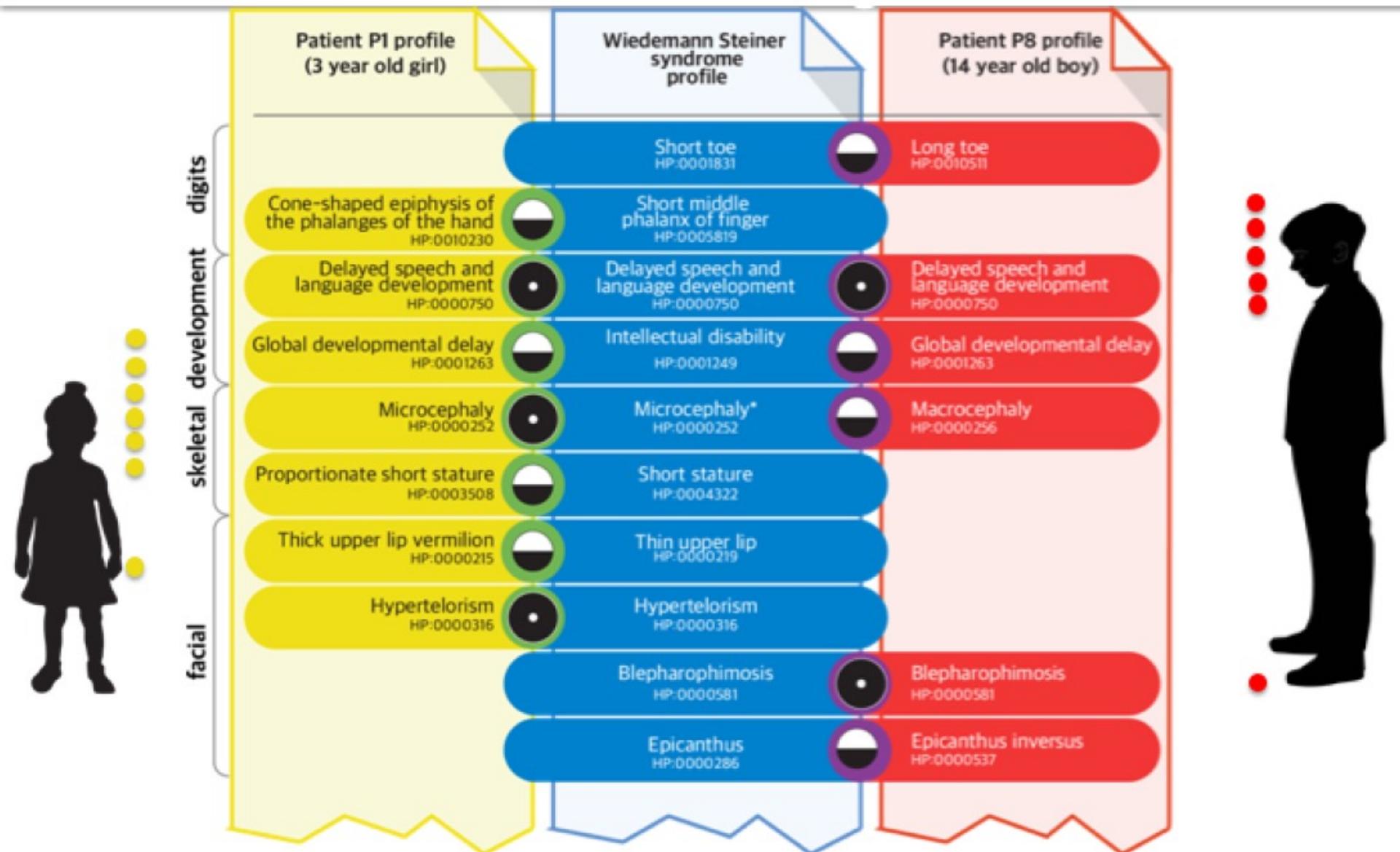
Moreau Y, Tranchevent LC (2012) *Nat Rev Genet* 13:523–36.

- Filter out common variants
- Filter out variants/genes that do not cosegregate
- Assess phenotypic relevance
- Re-rank candidates



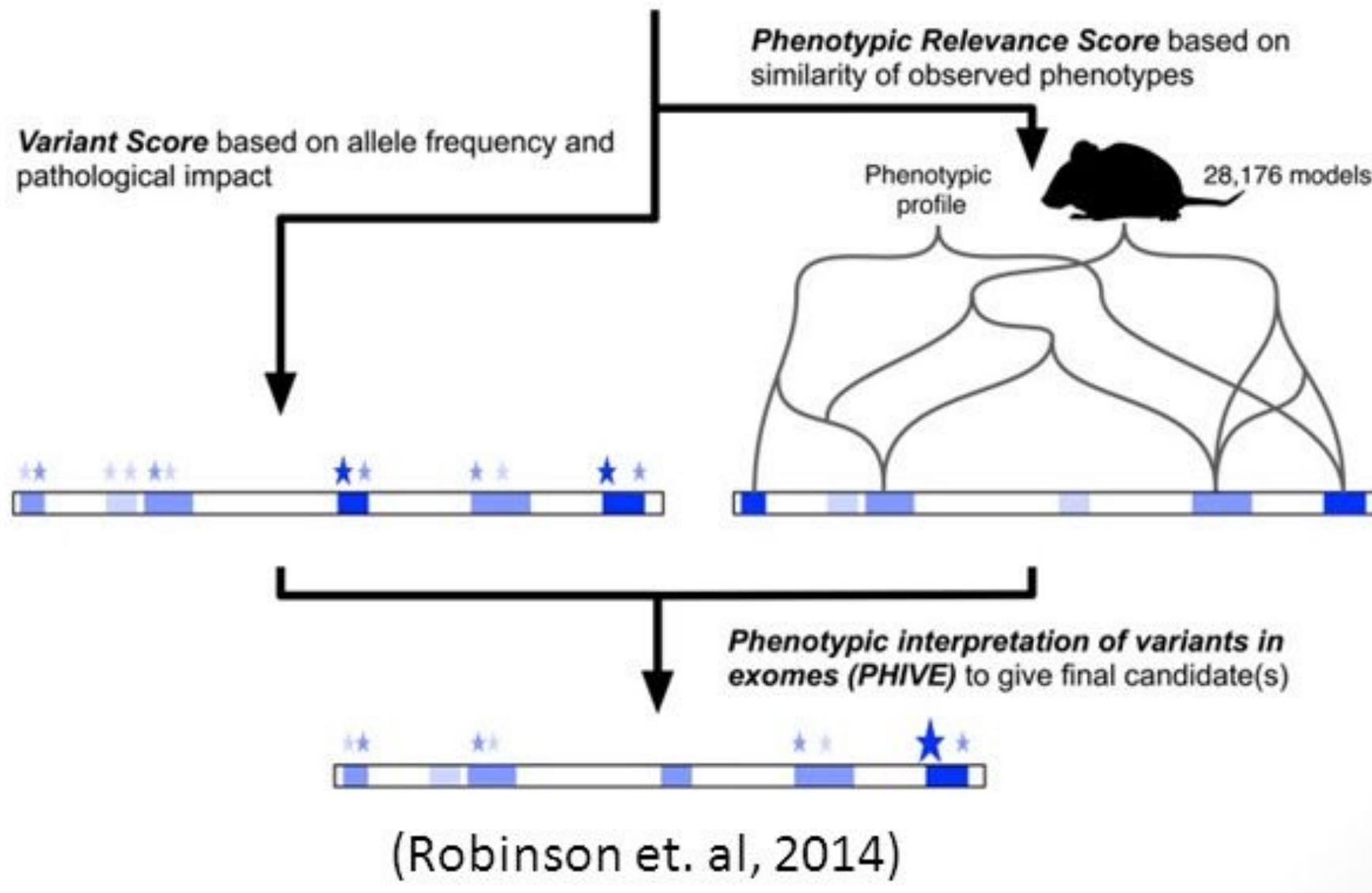
EXOMISER – variant prioritisation tool

Slides kindly provided by Peter Robinson and Daniel Danis (JAX)



EXOMISER – variant prioritisation tool

Use Exomiser (IRDiRC recognised resource) to prioritise variants according to patient's HPO terms



Exomiser: results section

Use Exomiser (IRDiRC recognised resource) to prioritise variants according to patient's HPO terms

Exomiser: Filter and prioritise likely causative variants



The Exomiser plugin is able to identify disease-causing variants from whole-exome (Exomiser) or whole-genome sequencing data (Genomiser).

***For GPAP performance reasons, Exomiser can only be run with 1000 variants or less.

HPO term(s)

Search for HPO terms –

Mitochondrial respiratory chain defects X Intellectual disability X

Seizures X Global developmental delay X Metabolic acidosis X

Rhabdomyolysis X Elevated serum creatine phosphokinase X

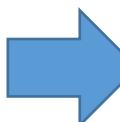
Ventricular tachycardia X Elevated plasma acylcarnitine levels X

Inheritance model

Autosomal dominant ▼

Choose Prioritiser

PhenIX (compare phenotypes against human only) ▼



PROM1 Exomiser Score: **0.605**

Phenotype matches:
PhenIX semantic similarity score: 2.61 (p-value: 0.002410)

Known diseases:
OMIM:603786 Stargardt disease 4 - autosomal dominant
OMIM:608051 Macular dystrophy, retinal, 2 - autosomal dominant
OMIM:612095 Retinitis pigmentosa 41 - autosomal recessive
OMIM:612657 Cone-rod dystrophy 12 - autosomal dominant
ORPHA:1872 Cone Rod Dystrophy
ORPHA:791 Retinitis Pigmentosa
ORPHA:827 Stargardt Disease

Top ranked variants:
SPLICING chr4:g.16037357C>T [0/1] rs777673930 (variation viewer)
Variant score: 0.898 CONTRIBUTING VARIANT

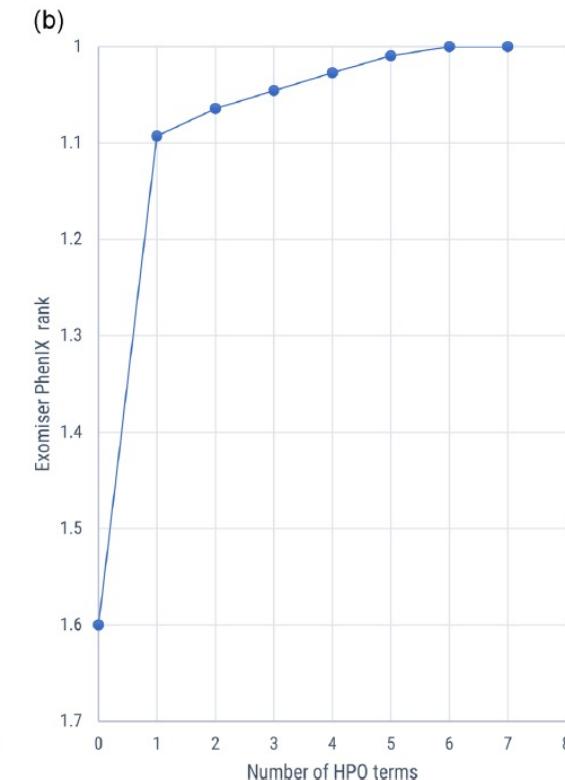
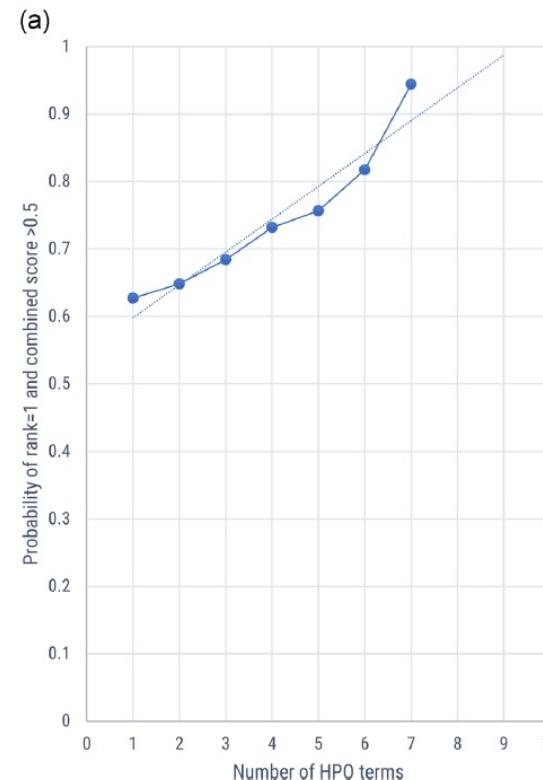
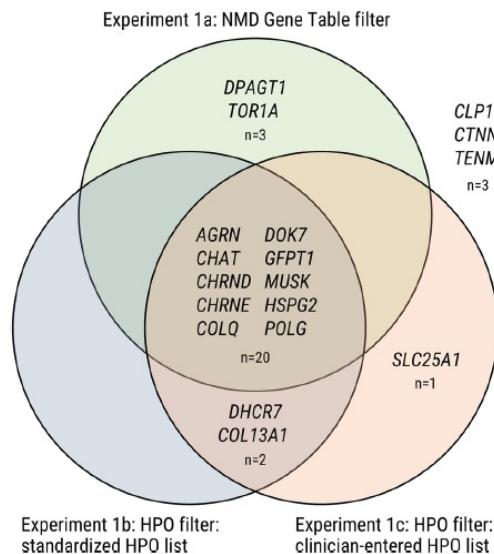
Transcripts:
PROM1:uc003goo.2:c.303+1G>A:p.?
PROM1:uc003gor.2:c.303+1G>A:p.?
PROM1:uc003got.2:c.303+1G>A:p.?
PROM1:uc003gop.2:c.277-2225G>A:p.(=)
PROM1:uc003goq.3:c.277-2225G>A:p.(=)
PROM1:uc003gos.2:c.277-2225G>A:p.(=)
PROM1:uc003gou.2:c.277-2225G>A:p.(=)
PROM1:uc010iec.1:c.-63-2225G>A:p.(=)

Increasing phenotypic annotation improves the diagnostic rate of exome sequencing in a rare neuromuscular disorder

Rachel Thompson ✉, Anastasios Papakonstantinou Ntalis, Sergi Beltran, Ana Töpf, Eduardo de Paula Estephan, Kiran Polavarapu, Peter A. C. 't Hoen, Paolo Missier, Hanns Lochmüller

First published: 23 June 2019 | <https://doi.org/10.1002/humu.23792> | Citations: 2

cohort of 29 patients with congenital myasthenic syndromes



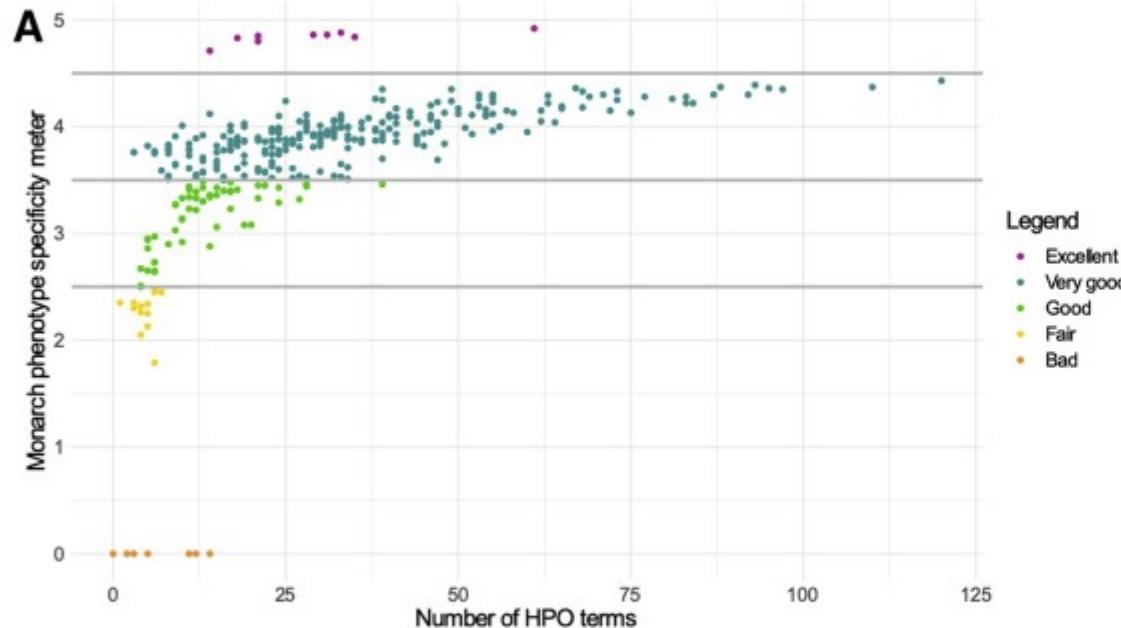
increasing phenotypic annotation improved prioritization of the causative variant, from **62% ranked first on variant alone to 90% with seven HPO annotations.**

We conclude that any HPO-based phenotypic annotation aids variant discovery and that annotation with **over five terms is recommended in our context.**

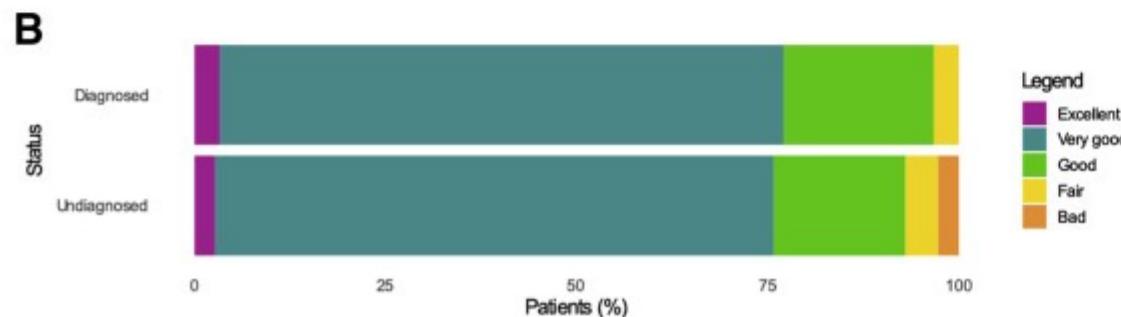
Systematic Collaborative Reanalysis of Genomic Data Improves Diagnostic Yield in Neurologic Rare Diseases

Gemma Bullich • Leslie Matalonga • Montserrat Pujadas • ... Luis A. Pérez-Jurado • Sergi Beltran  

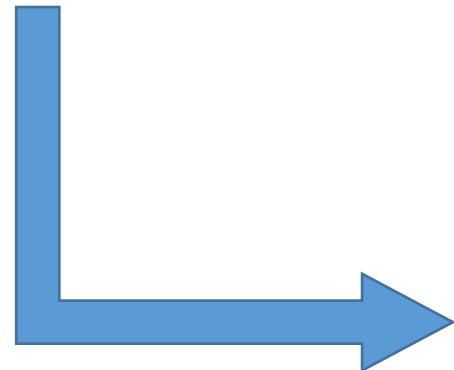
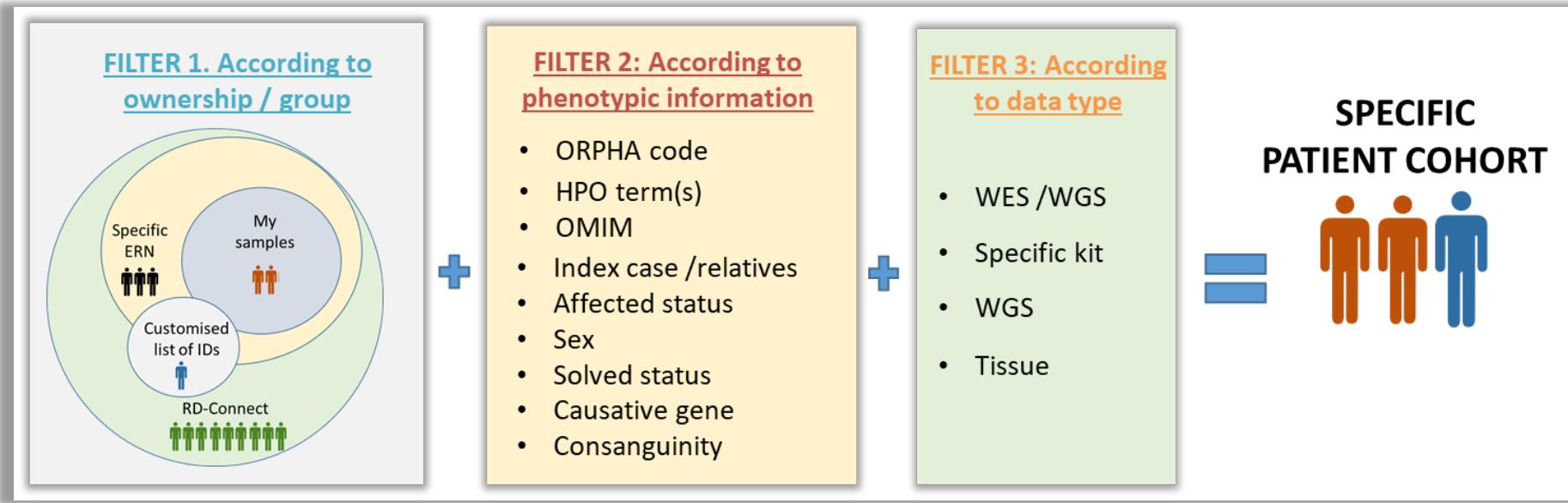
Undiagnosed Rare Disease Program of Catalonia (URD-Cat) Consortium • Show all authors



A slightly better phenotype quality was observed in diagnosed patients, with 96.7% of them classified as having excellent, very good, or good phenotype quality compared with 93.0% of undiagnosed patients falling into those categories. However, these results are not statistically significant ($P = 0.3863$).



Cohort creation for downstream genomic analysis and gene discovery



Cohort Selected
Cohort selected: Index cases

Cohorts ready for analysis

C

Index cases (15 experiments)

Additional features of interest for data analysis and interpretation

Matchmaker Exchange

Genomic discovery through the exchange of phenotypic & genotypic profiles



Question: Do you have a patient with similar phenotype and genotype as mine?

Data discovery

Question: Do you have a patient with similar phenotype and genotype as mine?

PhenoTips ID (E000040)

P0000128

Target Endpoint

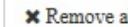
RD-Connect -> RD-Connect

Mode of Inheritance Sporadic

Age of Onset Neonatal onset

Candidate gene(s)

CHRND

 Remove all

Add gene(s)

e.g.:BRCA1

HPO term(s) +

Ptosis, Ophthalmoparesis, Dysphagia, Respiratory insufficiency, Respiratory failure, obsolete Respiratory difficulties, Generalized muscle weakness, EMG: decremental response of compound muscle action potential to repetitive nerve stimulation, Abnormality of muscle morphology



Matches found: 16

Score (0 to 1), is based on a gene-match and a phenotypic similarity which is calculated using the: UI score

Contact	Patient	Score	Submitter	Phenotype	Genes
	P0004537	0.72	RD-Connect Matchmaker Exchange	Muscle fiber atrophy, Abnormality of muscle morphology, Chewing difficulties, Abnormality of muscle fibers, Episodic flaccid weakness, Proximal muscle weakness, Type 2 muscle fiber atrophy, EMG: decre...	CHRND
	P0004552	0.70	RD-Connect Matchmaker Exchange	Fatigable weakness, EMG: decremental response of compound muscle action potential to repetitive nerve stimulation, Ptosis ...	CHRND

Matchmaker Exchange Statistics (last updated September 2020)

MME Node	Patients/Cases Total	Patients/Cases In MME	Unique Genes
DECIPHER (UK)	80,000	35,092	6,965
GeneMatcher (USA)	46,939	46,419	12,058
IRUD (Japan)	3,578	62	55
MyGene2 (USA)	2,521	1,239	1,059
PatientMatcher (Sweden)	4,190	10	13
PhenomeCentral (Canada)	10,816	7,223	2,449
RD-Connect GPAP (Europe)	11,418	2,606	54
seqr (USA)	7,628	924	968

Matchmaker Exchange Gene Discoveries

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Agenda

- Parte 1: Estandarización e integración de datos clínicos
- Parte 2 (práctica):
 1. Entrada de datos clínicos de forma estandarizada
 2. Creación de cohortes en base a la información clínica

<https://playground.rd-connect.eu/phenostore/>

User: test_full

Password: 1234





DESCRIPCIÓN DEL CASO

Sospecha clínica: miopatía congénita

grupo de enfermedades que se caracteriza clínicamente por hipotonía y debilidad muscular

Fecha nacimiento: 19 febrero 2014 (Barcelona, España)

Antecedentes familiares: Primer hijo de pareja no consanguinea. No otros parientes afectos.

Descripción del caso: Varón que presenta hipotonía al nacer. Actualmente tiene 5 años y presenta debilidad muscular leve en la parte superior de las piernas y caderas, hipotonía facial. Su madre reportó movimientos fetales reducidos.

Caminaba a los 15 meses pero a los 5 años no podía saltar. Era lento para correr en comparación con sus compañeros y fue descrito como torpe con una tendencia a caerse con frecuencia. También se presentó con anomalías esqueléticas que implican la curvatura de la columna vertebral. Sin deterioro cognitivo.

Medidas: 12-06-2019: 15kg, 1m

Pruebas previas: SANGER *RYR1* descartado, no se han identificado variantes patogénicas

Consentimiento: consentimiento para compartición de datos en entorno de investigación. El probando no quiere ser informado de hallazgos secundarios



<https://adc.bmjjournals.org/content/88/12/1051>



DESCRIPCIÓN DEL CASO

Sospecha clínica: miopatía congénita

grupo de enfermedades que se caracteriza clínicamente por hipotonía y debilidad muscular

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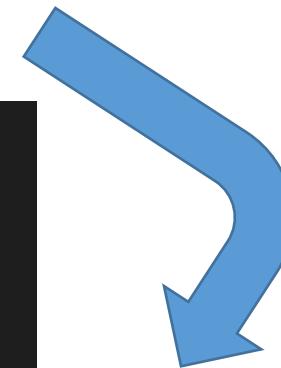
<https://adc.bmjjournals.org/content/88/12/1051>



<https://playground.rd-connect.eu/phenostore/#/summary/P0928505>

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2    "id": "P0928505",
3    "subject": {
4      "id": "P0928505",
5      "alternateIds": [
6        "Test_LM"
7      ],
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9      "vitalStatus": {
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11      },
12      "sex": "MALE"
13    },
14    "phenotypicFeatures": [
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21      {
22        "type": {
23          "id": "HP:0007340",
24          "label": "Lower limb muscle weakness"
25        }
26      },
27      {
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30          "label": "Neonatal hypotonia"
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36          "label": "Decreased fetal movement"
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51    ]
52  }
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53  ],
54  "interpretations": [
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59        "disease": {
60          "id": "NA",
61          "label": "NA"
62        }
63      },
64      "genomicInterpretations": [
65        {
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67          "interpretationStatus": "REJECTED",
68          "gene": {
69            "valueId": "HGNC:10483",
70            "symbol": "RYR1"
71          }
72        }
73      ]
74    },
75    {
76      "term": {
77        "id": "Orphanet:97245",
78        "label": "Congenital myopathy"
79      }
80    }
81  ]
82 }
```



Phenopacket



Detailed phenotypic records using standards and ontologies

- Update records
- Share record with other clinicians who can view and/or edit
- Export your data to other systems

Limitations:

- Not all the information is always HPO encoded
- Retrospective approach: loose clinical information
- Loose clinical subjectivity-interpretation



Computer READABLE!

Differential diagnosis using available tools (Monarch scoring system)

Use the information to filter and prioritise genomic data

Create cohorts

<https://playground.rd-connect.eu/cohortapp/>

User: test_full

Password: 1234





Data analysis: S. Beltran, R. Tonda, J.R. Trotta, G. Parra, J. Morata, S. Laurie, L. Matalonga, G. Bullich, D. Piscia, A. Papakonstantinou, D. Picó, M. Fernández, A. Corvo, C. Hernández, I. Paramonov, L. Zalatnai

Production Bioinformatics: M. Ingham, J. Camps, E. Casals, C. Frias

Collaborators from around the world

GPAP users and tester

European Reference Networks members



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la INDUSTRIA y la SOCIEDAD

