Using HPO in genomic medicin

VEP course 2019

Jeroen van Reeuwijk
Researcher Translational Genomics

Human Genetics Nijmegen
Radboudumc

Lecture objectives & outline

Objectives

- Next-generation phenotyping: Human Phenotype Ontology
- HPO tools for variant/disease gene prioritization

Outline

Part 1: Introduction to HPO

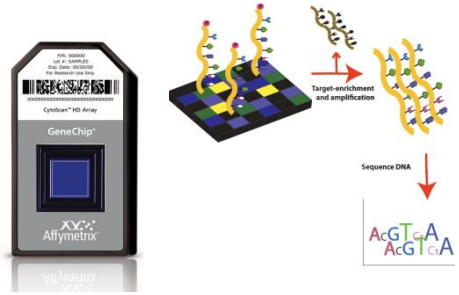
- Use of phenotypic information in clinical genetics
- Standardized phenotyping using HPO
- HPO structure

Part 2: Applications using HPO

- Capturing patient clinical data in HPO format
- Using HPO-profiles in variant-disease interpretation
- Phenotype matching tools
- Outlook

Use of phenotypic information

- Pre-genetic testing:
  - differential diagnosis
  - choice of genetic testing: single gene, genepanel(s), exome/genome, SNP array



- Post-genetic testing:
  - genotype-phenotype correlation
  - candidate disease gene/variants analysis
    - disease processes and biochemical pathways
    - clinically similar patients
    - animal disease models

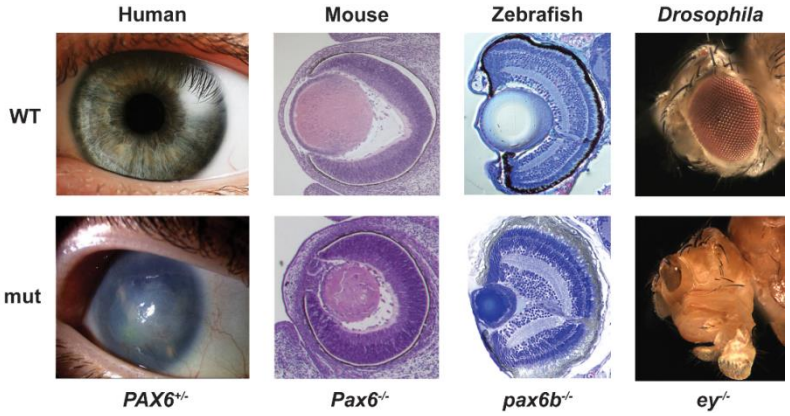


Figure 1 of Washington et al. PLoS Biol 7(11): e1000247

Use of phenotypic information

in exome/genome diagnostics:

Variant Effect Predictions

+

Clinical symptoms

➔ Clinical molecular diagnosis

Computational use of phenotypic info

Computable data:

- Standardized terminology
- Relationship between terms

➔ “Next-generation phenotyping”

Human Phenotype Ontology: HPO

Am J Hum Genet. 2008 Nov;83(5):610-5. doi: 10.1016/j.ajhg.2008.09.017. Epub 2008 Oct 23.

The Human Phenotype Ontology: a tool for annotating and analyzing human hereditary disease.

Robinson PN[1], Köhler S, Bauer S, Seelow D, Horn D, Mundlos S.

Peter Robinson
& Sebastian Köhler

- Standardized clinical terminology
- Ontology data model: entities, attributes and relations

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D1018–D1027 Nucleic Acids Research, 2019, Vol. 47, Database issue Published online 22 November 2018
doi: 10.1093/nar/gky1105

Expansion of the Human Phenotype Ontology (HPO) knowledge base and resources

HPO Today: the standard for electronic clinical phenotyping in medical genetics

- Standardized clinical terminology for ~14.000 clinical features
- Annotation of 7000+ disorders with HPO terms
- Algorithms for diagnostics & translational research

Part of monarch INITIATIVE

Global Alliance for Genomics & Health

Collaborate. Innovate. Accelerate.

International recognition core resource

IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Standardized phenotyping using HPO

Table 1. A selection of public-facing clinical databases using HPO to annotate patient data for disease-gene discovery projects

Name	URL
PhenomeCentral	phenomecentral.org
DDD (Deciphering Developmental Disorders)	www.ddduk.org
DECIPHER (DatabasE of genomiC varIation and Phenotype in Humans using Ensembl Resources)	decipher.sanger.ac.uk
ECARUCA (European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations)	http://umcecaruca01.extern.umcn.nl:8080/ecaruca/ecaruca.jsp
The 100 000 Genomes Project	https://www.genomicsengland.co.uk/
Geno2MP (Exome sequencing data linked to phenotypic information from a wide variety of Mendelian gene discovery projects)	http://geno2mp.gs.washington.edu
NIH UDP (Undiagnosed Diseases Program)	available via phenomecentral.org
NIH UDN (Undiagnosed Diseases Network)	available via phenomecentral.org
HDG (Human Disease Gene Website series)	www.humandiseasegenes.com
Phenopolis (An open platform for harmonization and analysis of sequencing and phenotype data)	https://phenopolis.github.io
GenomeConnect (Patient portal developed by ClinGen (67)	www.genomeconnect.org
FORGE Canada & Care4Rare Consortium	available via phenomecentral.org
RD-Connect	platform.rd-connect.eu
Genesis	thegenesisprojectfoundation.org

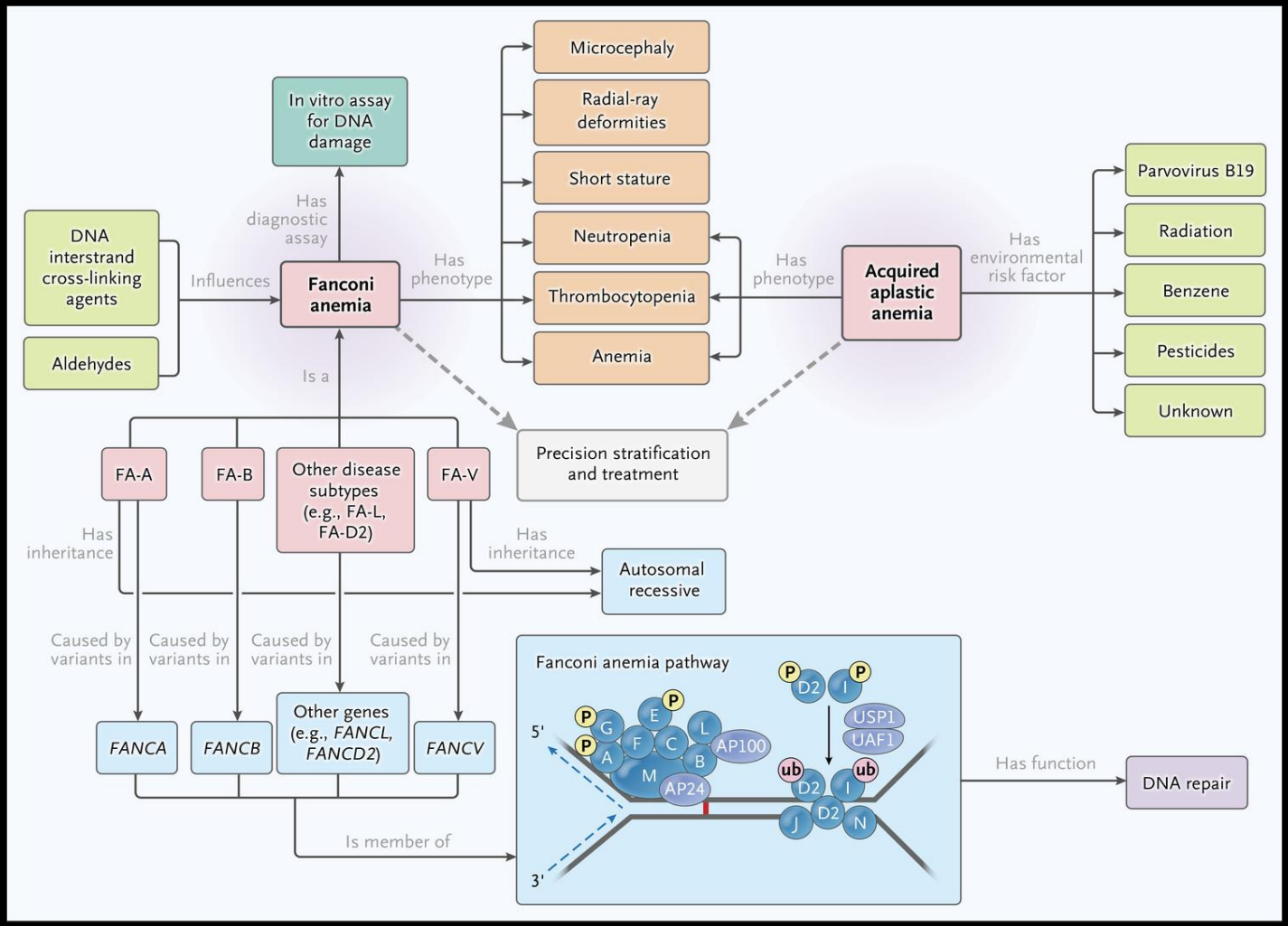
Köhler et al. AJHG 2017

Standardized phenotyping using HPO

Commercial software for variant interpretation such as

- FDNA: Face2Gene
- Cartagenia BENCH
- GEPADO – Software Solutions for Genetics – GmbH
- BioDiscovery's NxClinical
- Diploid: Diagnosing rare diseases: Moon
- Centogene
- SimulConsult
- Fabric Genomics
- Qiagen
- Congenica

Ontology-Driven Representation of Fanconi Anemia and Acquired Aplastic Anemia.



MA Haendel et al. N Engl J Med 2018;379:1452-1462.

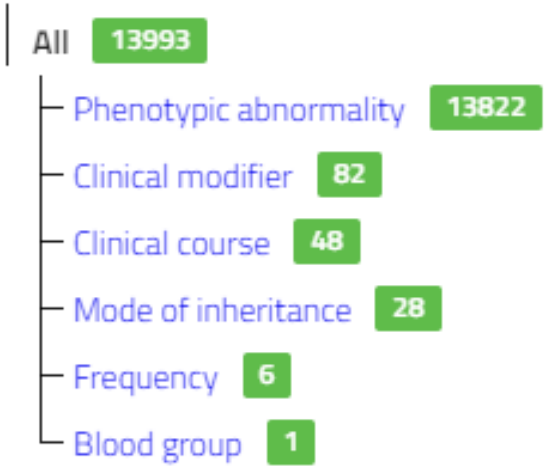
The NEW ENGLAND JOURNAL of MEDICINE

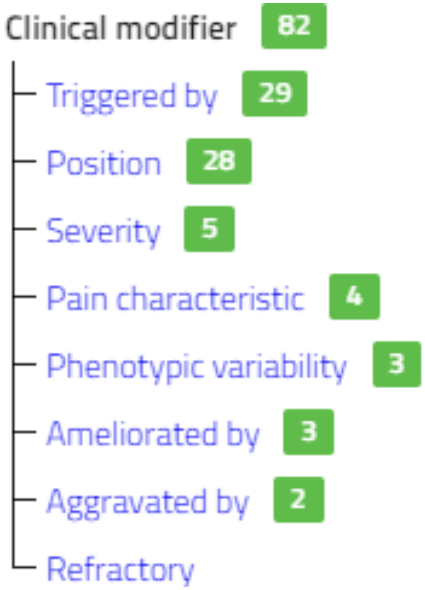
HPO: structure & ontologies

- HPO structure
  - Terms (~14.000)
  - Term relationship (subclass of ..)

<u>Intellectual disability</u>
Primary ID: HP:0001249
Synonyms: mental retardation, …
Textual definition: Subnormal intellectual functioning …
…defined as an IQ score below 70.

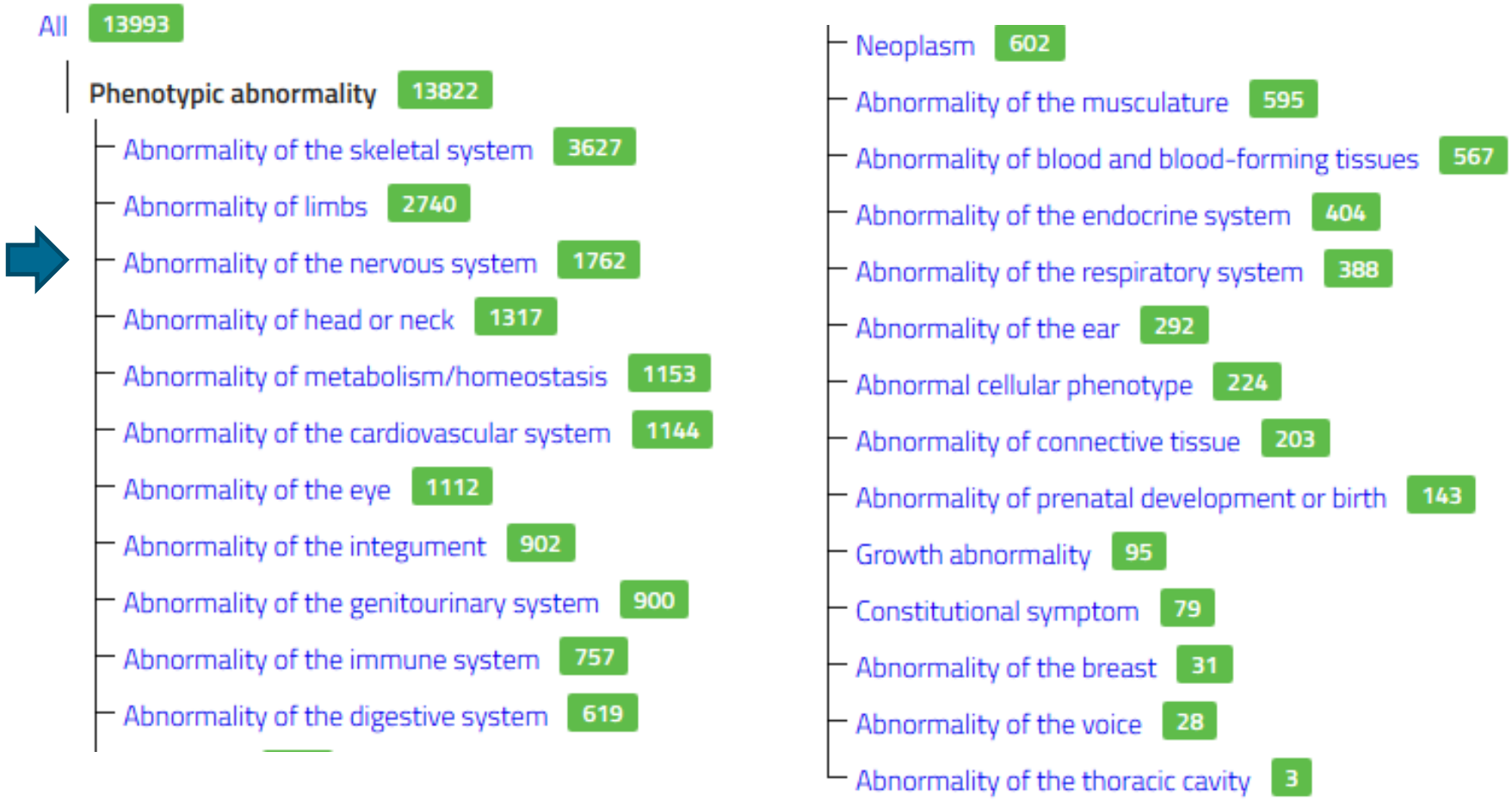
- HPO subontologies:





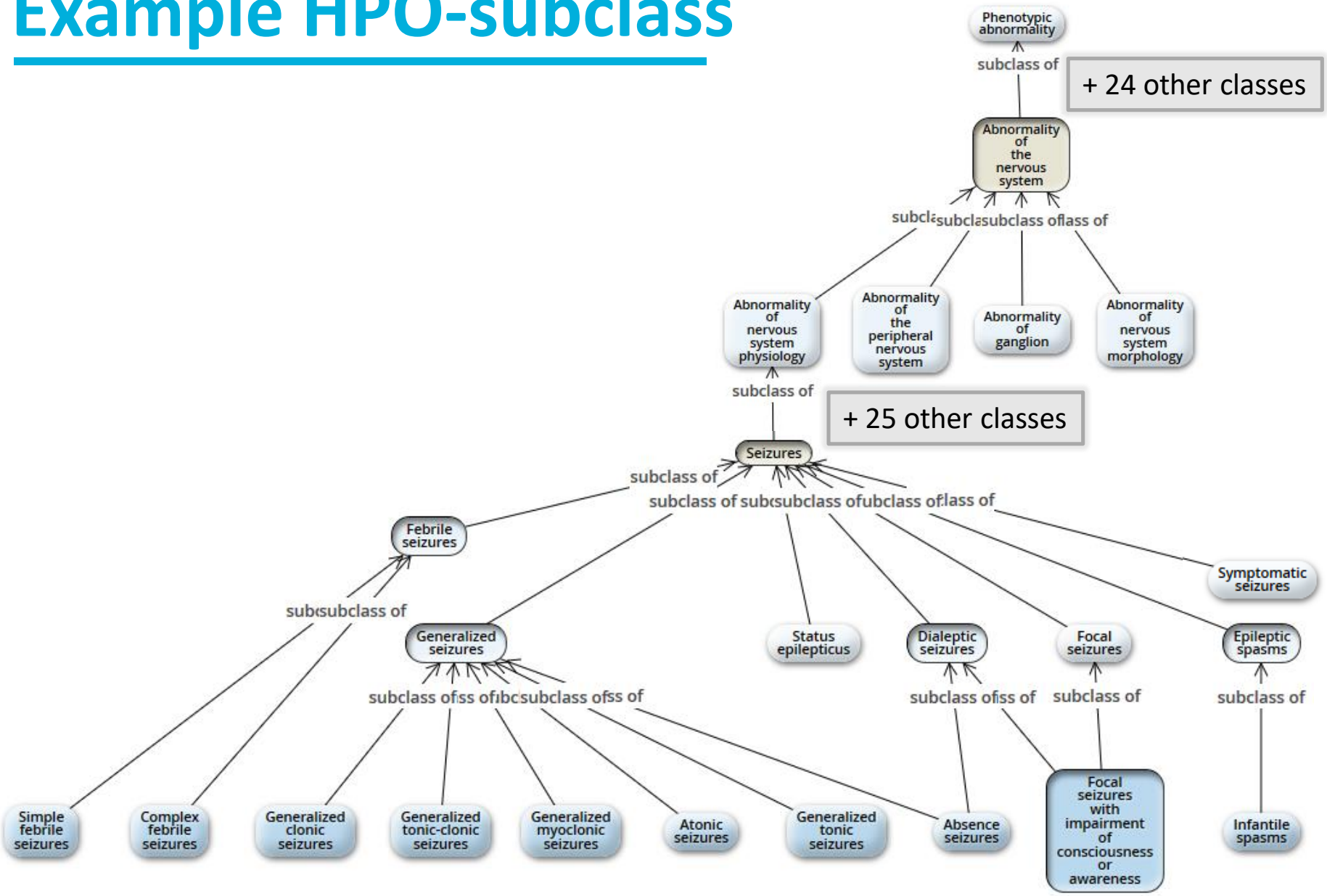
HPO-browser: <u>https://hpo.jax.org/app/</u>

HPO-subontology Phenotypic abnorm.



HPO-browser: https://hpo.jax.org/app/

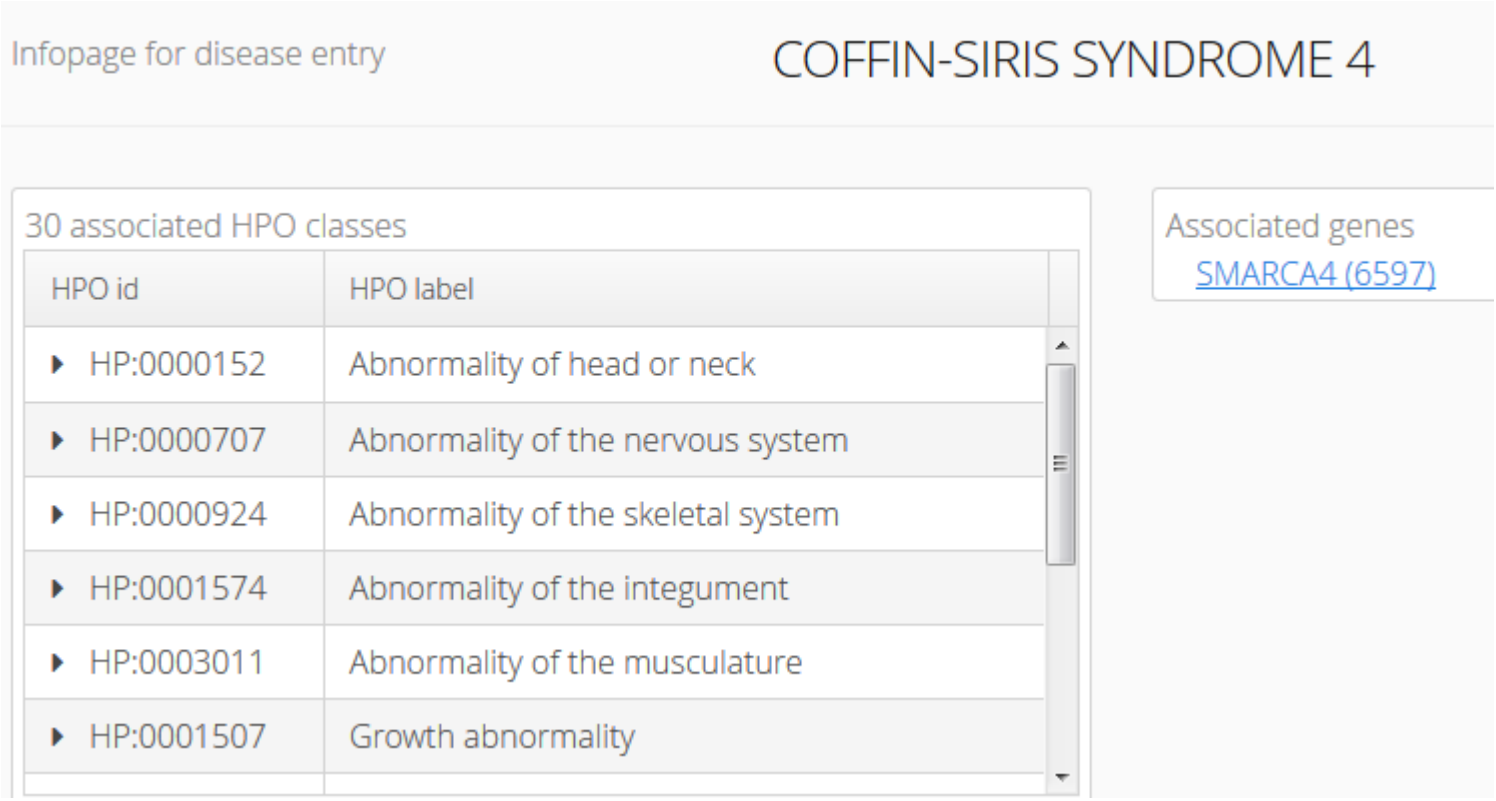
Example HPO-subclass



HPO-browser: http://compbio.charite.de/hpoweb/showterm?id=HP:0000118

HPO-annotation disorders

Manual by HPO-team (mainly OMIM) example:



Infopage for disease entry

COFFIN-SIRIS SYNDROME 4

30 associated HPO classes

HPO id	HPO label
HP:0000152	Abnormality of head or neck
HP:0000707	Abnormality of the nervous system
HP:0000924	Abnormality of the skeletal system
HP:0001574	Abnormality of the integument
HP:0003011	Abnormality of the musculature
HP:0001507	Growth abnormality

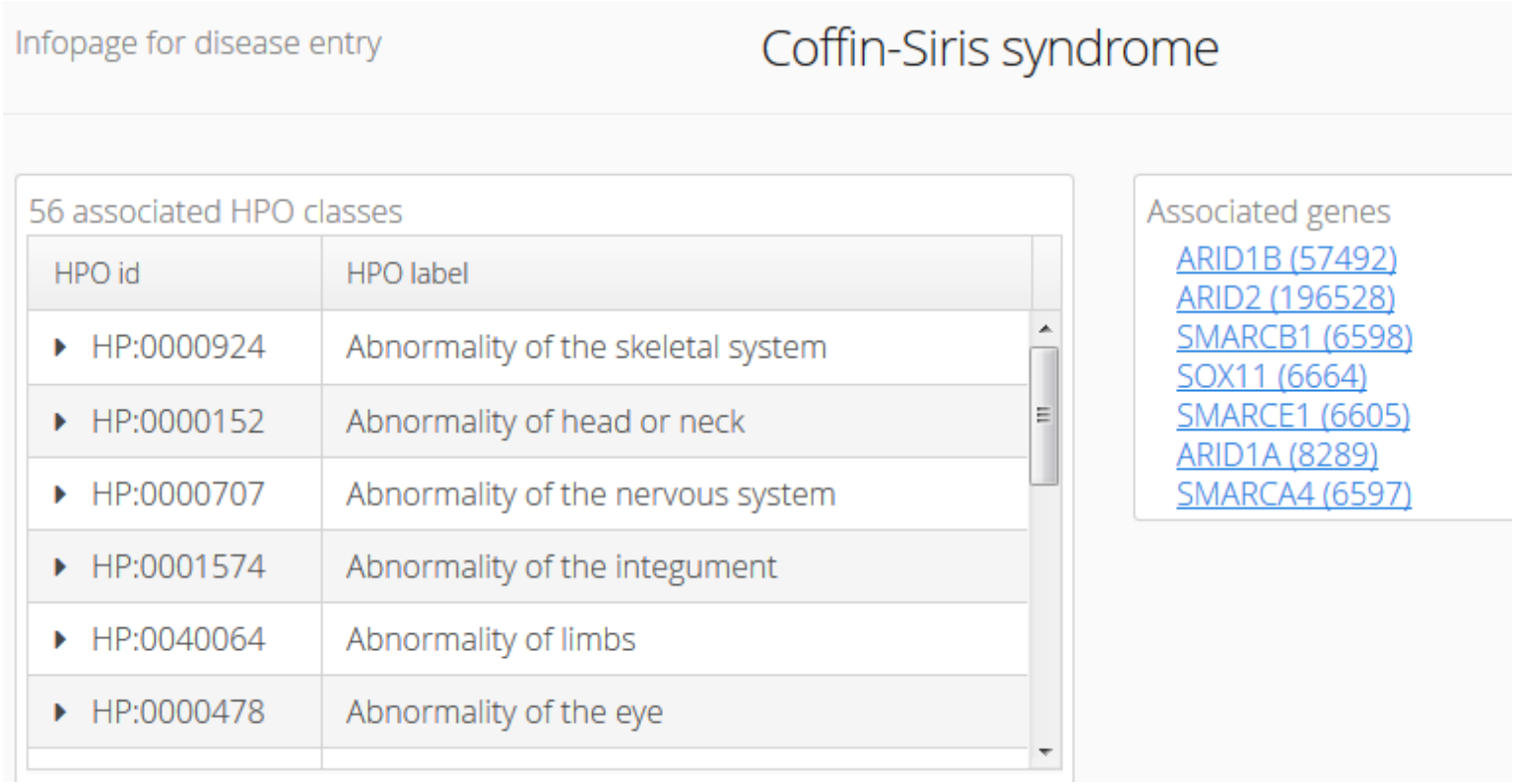
Associated genes

SMARCA4 (6597)

HPO-browser: http://compbio.charite.de/hpoweb/showterm?id=HP:0000118

HPO-annotation disorders

Manual & semi-automated (OMIM, Orphanet, DECIPHER) example:



➔difference in number of HPO associated with gene
OMIM: disease subtypes ➔ more specific; Orphanet: more inclusive

HPO-browser: http://compbio.charite.de/hpoweb/showterm?id=HP:0000118

HPO-annotation of genes

- Gene annotation files:
  - Source: OMIM, Orphanet or All
  - Frequent (present >50% patients) or all frequencies
  - Most specific HPO or including all “ancestors”

- Gene ←→ Disorder(s) ←→ HPO-term(s)

  - SMARCA4 → COFFIN-SIRIS SYNDROME 4 (OMIM)→ 30 most specific HPO terms

  - 1220 Genes ← 1382 Disorders (OMIM) ← Intellectual disability (incl. more specific “descendants” terms)

Summary part 1

- Importance of clinical information in genetic testing
- The HPO project provides a great computable resource for clinical features that characterize diseases and associated genes

Part 2: Applications using HPO

- Capturing patient clinical data in HPO format
- Using HPO-profiles in variant-disease interpretation
- Phenotype matching tools
- Outlook

Capturing phenotypic information

- (Electronic) Patient Dossier:
  - No standardised terminology
  - Unstructured text
  - At different locations
  - Limited access

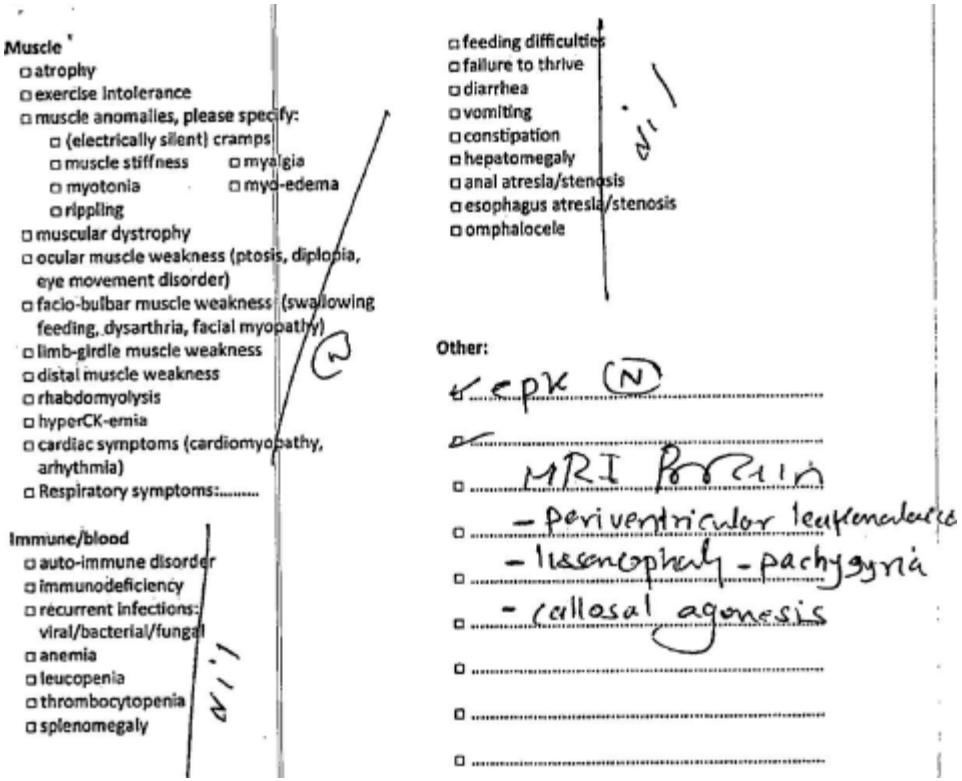
Reden van verwijzing: verstandelijke beperking
Gaarne onderzoek voor ivm mentale retardatie eci. M
Locatie:

Aanwezig: en beide ouders
Medische voorgeschiedenis
- aangeboren heupluxatie/dysplasie
- blindheid (hoge myopie)
- verstandelijke bepeking
- refluxoesophagitis
- kyphose/scoliose

Anamnese
Hulpvraag: diagnose ook voor de andere kinderen
Graviditeit en partus: ongecompliceerd. Apgar 9/10.
Congenitale afwijkingen: heupluxatie/dysplasie
Neonatale periode: geen voedingsproblemen; bij drie maanden
veel oorontstekingen en ook na de tweede vaccinatie had zij ee
Psychomotore ontwikkeling: de ontwikkeling is traag verlopen.
herkent de dagelijkse patronen. Structuur is sowieso belangrijk
Overige tractusanamnese: ziet slecht. De visus is -13 dpt (via
Psychosociaal: woont bij haar ouders. Ze gaat naar de
Versleten linker heup. Obstipatie.

Capturing phenotypic information

(Electronic) Request form genome diagnostics Radboudumc



Muscle
- atrophy
- exercise intolerance
- muscle anomalies, please specify:
  - (electrically silent) cramps
  - muscle stiffness
  - myalgia
  - myotonia
  - myo-edema
  - rippling
- muscular dystrophy
- ocular muscle weakness (ptosis, diplopia, eye movement disorder)
- facio-bulbar muscle weakness (swallowing feeding, dysarthria, facial myopathy)
- limb-girdle muscle weakness
- distal muscle weakness
- rhabdomyolysis
- hyperCK-emia
- cardiac symptoms (cardiomyopathy, arrhythmia)
- Respiratory symptoms:.....

Immune/blood
- auto-immune disorder
- immunodeficiency
- recurrent infections: viral/bacterial/fungal
- anemia
- leucopenia
- thrombocytopenia
- splenomegaly

- feeding difficulties
- failure to thrive
- diarrhea
- vomiting
- constipation
- hepatomegaly
- anal atresia/stenosis
- esophagus atresia/stenosis
- omphalocele

Other:
- CPK (N)
- MRI Brain
- periventricular leukomalacia
- lissencephaly - pachygyria
- callosal agenesis

Clinical relevant information

Feel free to fill out the blank field with all the clinical information you want to share. Or use the standard checkboxes below.

Cancer

Digestive tract and liver

Ear

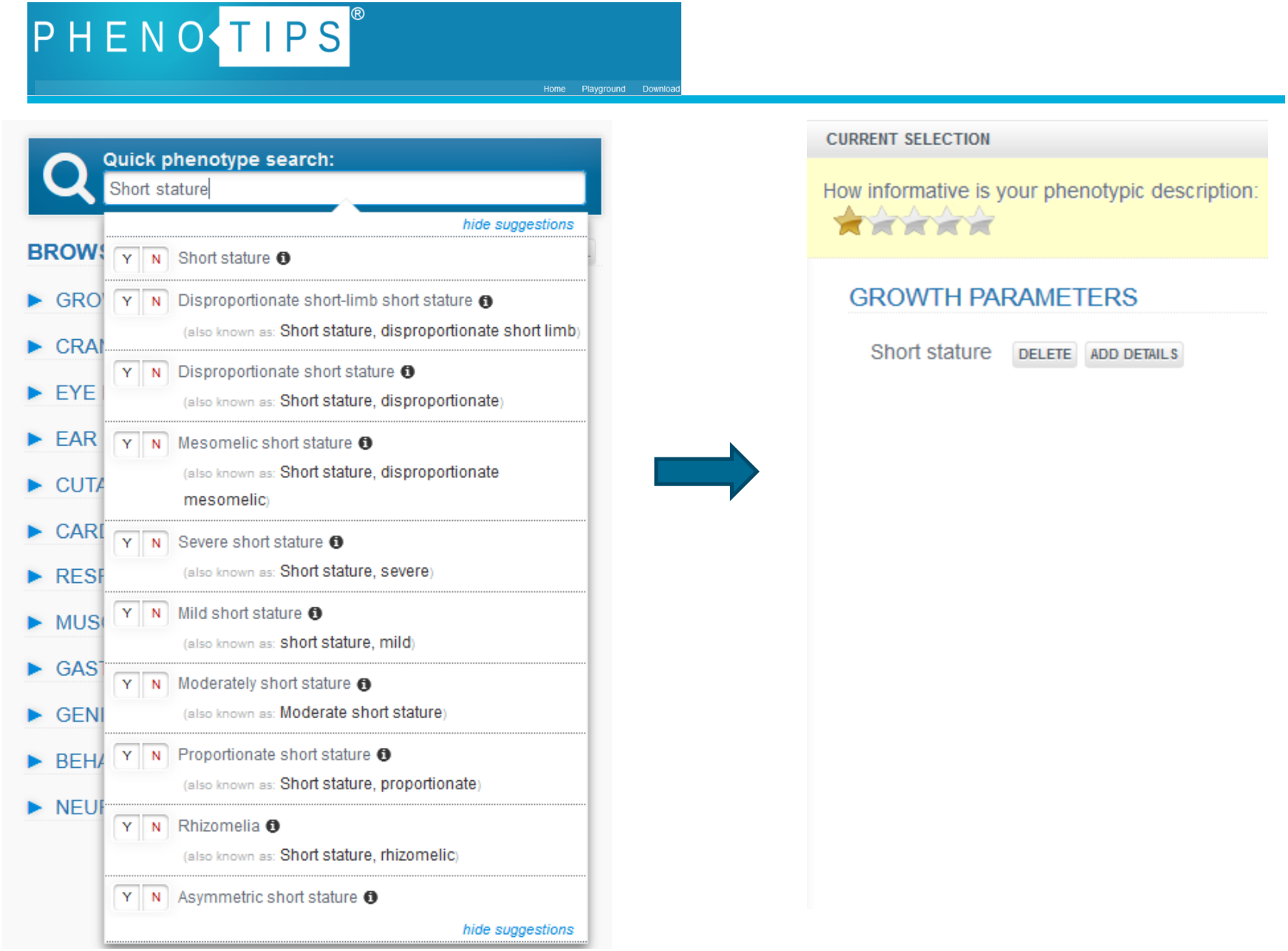
Eye

- retinal dystrophy
- achromatopsia
- congenital stationary night blindness
- cataract
- anophthalmia
- microphthalmia
- coloboma
- hypertelorism
- ptosis
- nystagmus

Clinical Registry tool using HPO

Open source software: phenotype/genotype collection tool

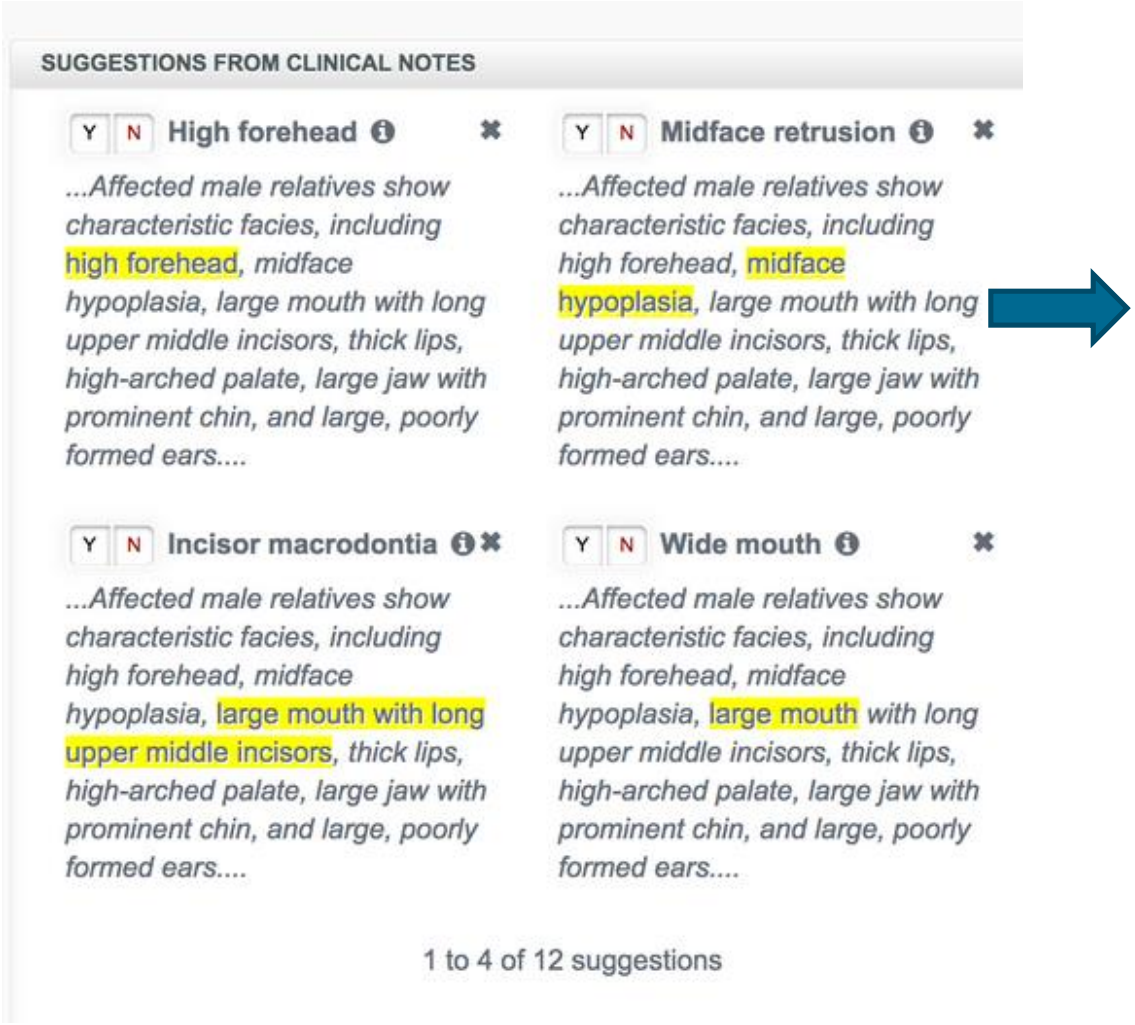
- Intuitive interface for HPO phenotyping
- HPO suggestions for Differential Diagnosis / Deep phenotyping
- HPO-mining of clinical notes by concept recognition algorithms
- Suggestions on matching OMIM disorders
- Operational at CARE for RARE (Canada), Sanford Health (USA)
- Commercial support by Gene42

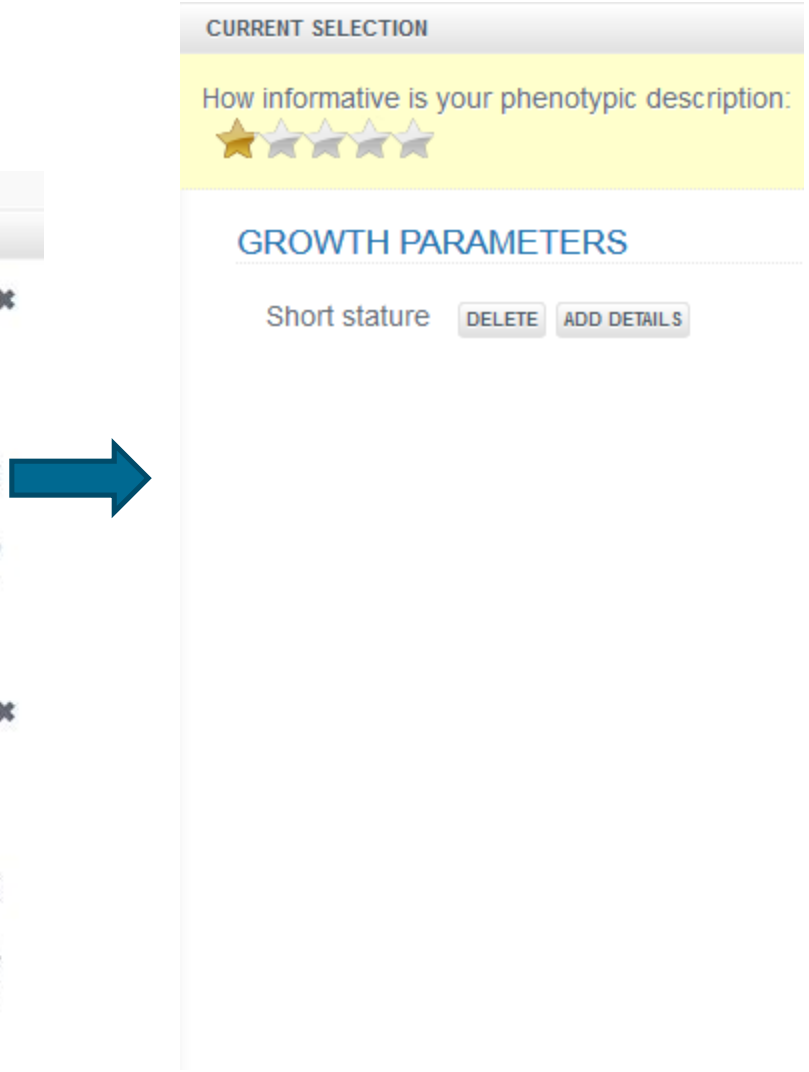

PHENOTIPS®
Home
Playground
Download
Quick phenotype search:
Short stature
hide suggestions
Y N Short stature
Y N Disproportionate short-limb short stature
(also known as: Short stature, disproportionate short limb)
Y N Disproportionate short stature
(also known as: Short stature, disproportionate)
Y N Mesomelic short stature
(also known as: Short stature, disproportionate mesomelic)
Y N Severe short stature
(also known as: Short stature, severe)
Y N Mild short stature
(also known as: short stature, mild)
Y N Moderately short stature
(also known as: Moderate short stature)
Y N Proportionate short stature
(also known as: Short stature, proportionate)
Y N Rhizomelia
(also known as: Short stature, rhizomelic)
Y N Asymmetric short stature
hide suggestions
CURRENT SELECTION
How informative is your phenotypic description:
GROWTH PARAMETERS
Short stature
DELETE
ADD DETAILS

PHENOTIPS®

Home Playground Download

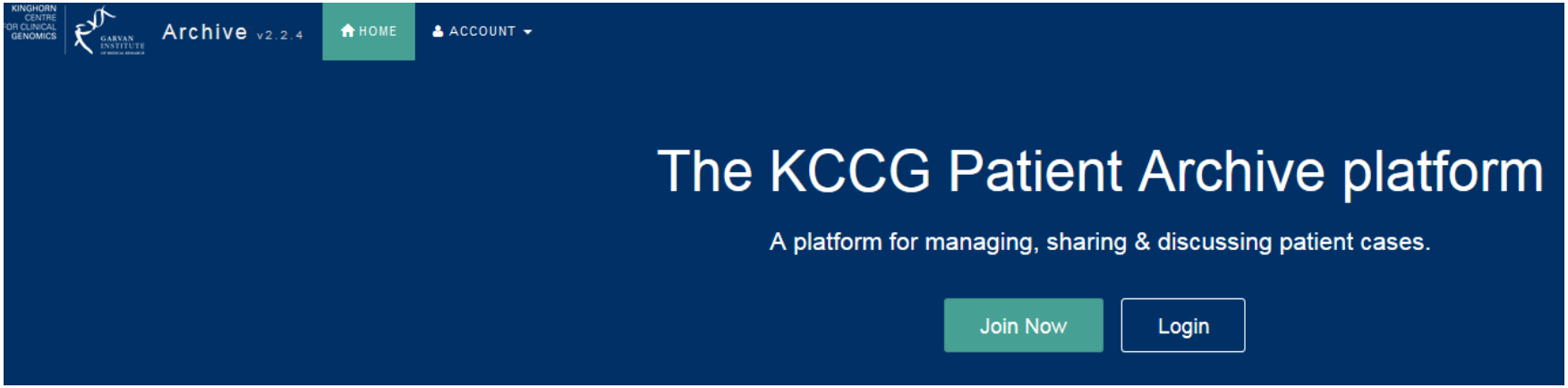
HPO-mining of clinical notes






PHENOTIPS®
Home Playground Download
How informative is your phenotypic description:
What's this?
GROWTH PARAMETERS
Short stature DELETE ADD DETAILS
CRANIOFACIAL
Coarse facial features DELETE ADD DETAILS
Long eyelashes DELETE ADD DETAILS
Sparse scalp hair DELETE ADD DETAILS
EYE DEFECTS
Visual impairment DELETE EDIT DETAILS CLEAR DETAILS
No additional information.
EAR DEFECTS
Hearing impairment DELETE ADD DETAILS
CARDIOVASCULAR
Malformation of the heart and great vessels DELETE ADD DETAILS
MUSCULOSKELETAL
Aplasia/Hypoplasia of the distal phalanges of the hand DELETE ADD DETAILS
YOU MAY WANT TO INVESTIGATE...
Phenotypes that are likely to help improve differential diagnosis
Y N Partial agenesis of the corpus callosum
Y N Facial hypertrichosis
Y N Intussusception
Y N Gastric ulcer
Y N Aplasia/Hypoplasia of the patella
Y N Hypoplastic fifth fingernail
How informative is your phenotypic description:
What's this?
CUTANEOUS
Hypoplastic fifth fingernail DELETE ADD DETAILS
Facial hypertrichosis DELETE ADD DETAILS
CARDIOVASCULAR
Malformation of the heart and great vessels DELETE
ADD DETAILS

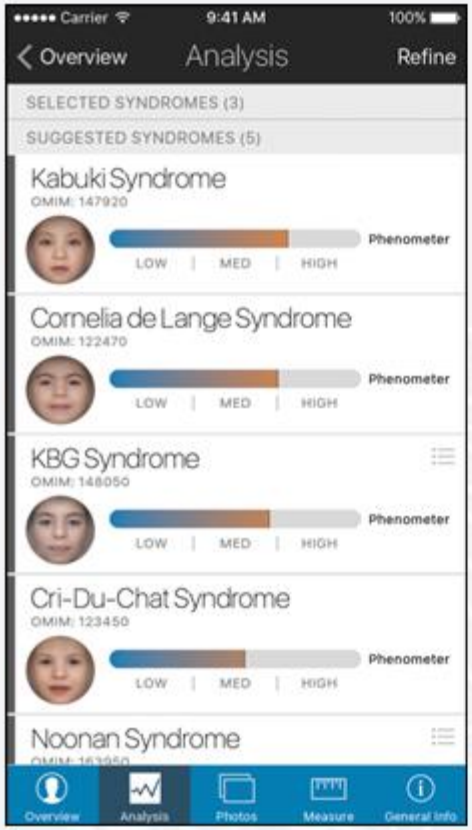
Clinical Registry using HPO



- Patient Archive (HPO-centric patient phenotyping)
  - Intuitive interface for HPO phenotyping
  - HPO-mining of clinical notes by concept recognition algorithms
  - Operational at
    - UDP, The University of Western Australia (UWA)
    - IRUD, Japan

HPO in Facial Phenotyping

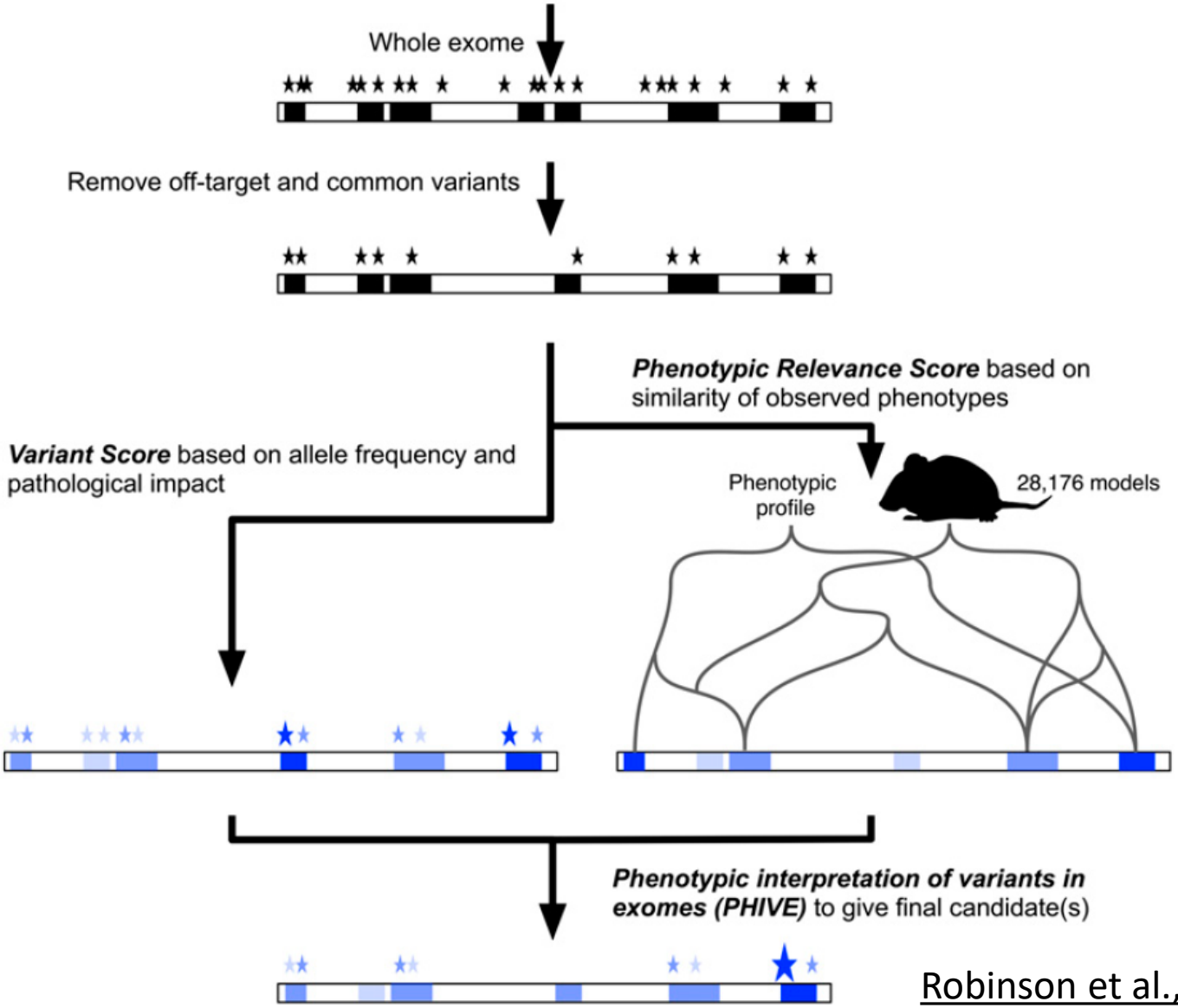
Create a case by uploading an image or photographing your patient.



Review a prioritized list of suggested syndromes.

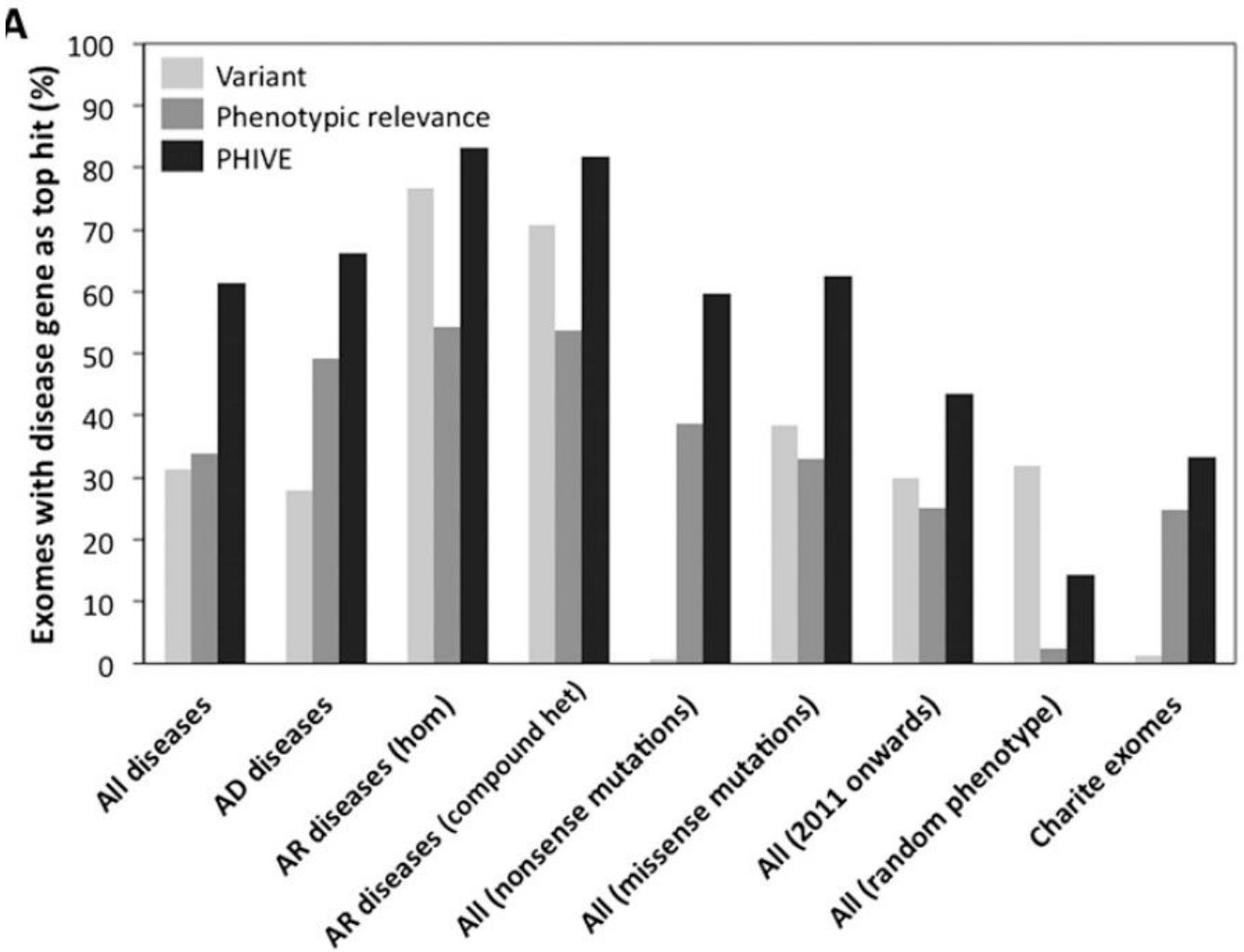
FACE2GENE
Smart Phenotyping. Better Genetics.

Phenotypic interpretation of variants



Robinson et al., Genom Res 2014

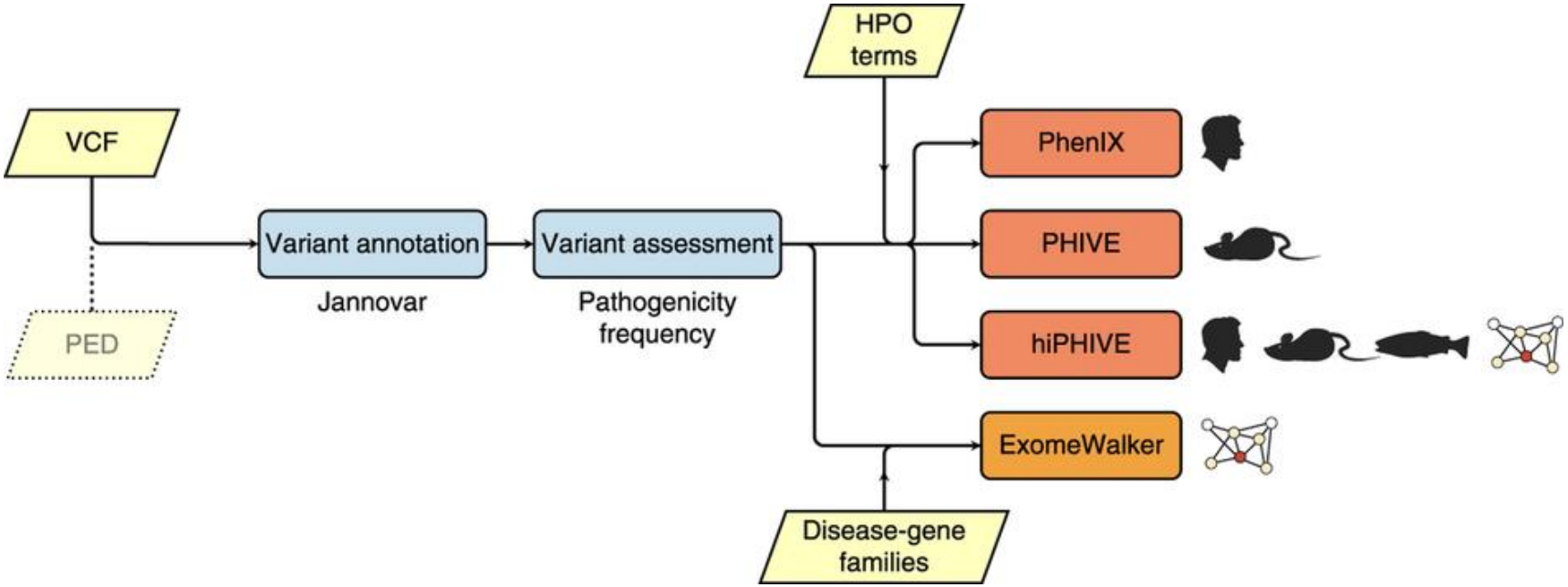
Phenotypic interpretation of variants



Robinson et al., Genom Res 2014

Exomiser

Automated phenotypic interpretation of variants in Exomes



Smedley et al., Nat Prot. 2014

Exomiser

Benchmarking of Exomiser on simulated exomes with HGMD* variants

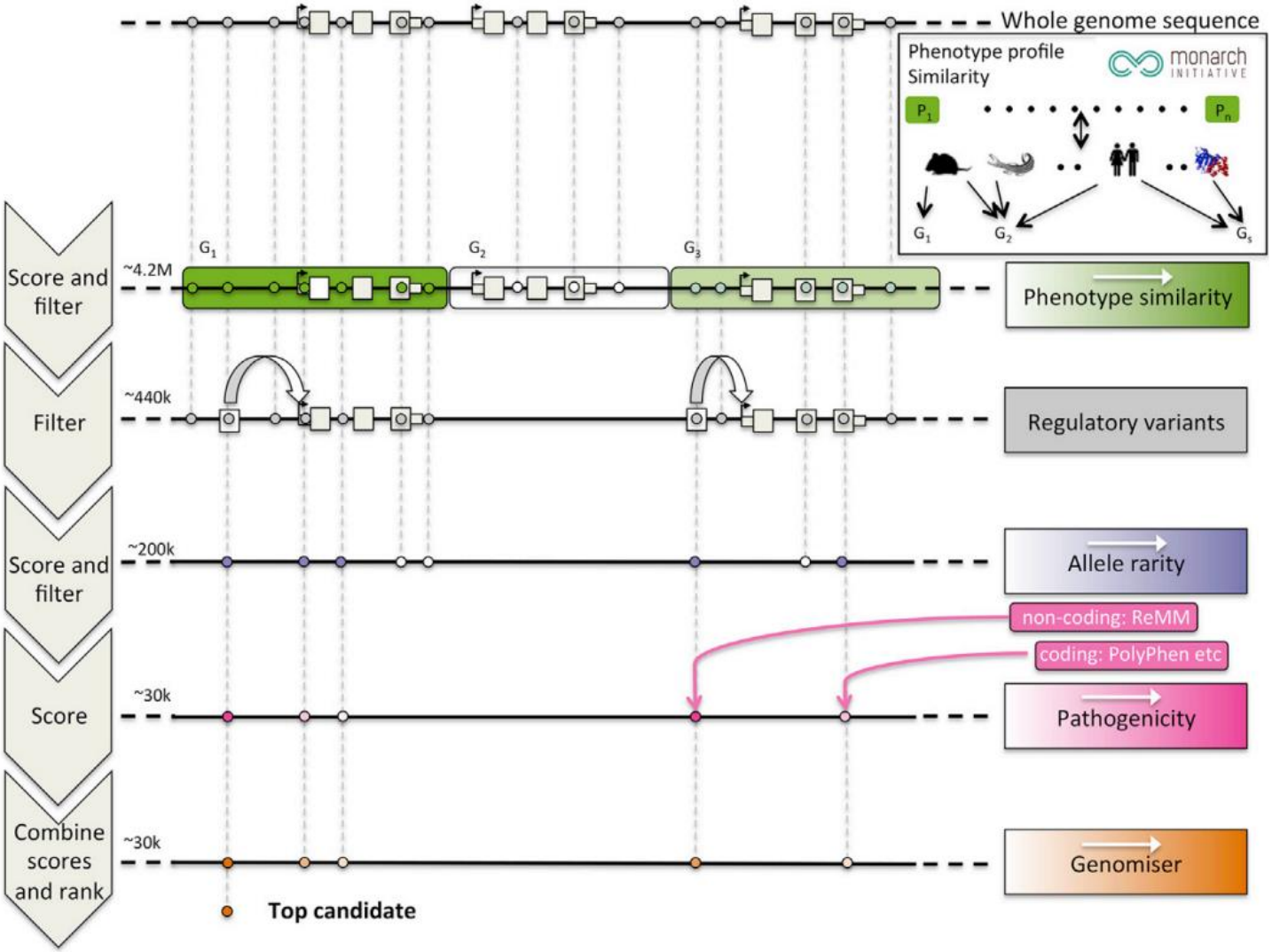
		1000 Genomes and ESP frequency data		
		Unknown inheritance[a]	Autosomal dominant[b]	Autosomal recessive[c]
Known	Full phenotype	96.8	97.1	97.1
	Imperfect phenotype	94.0	94.3	96.0
Novel	Full phenotype	73.6	78.8	86.6
	Imperfect phenotype	61.4	68.1	78.8

% of exomes with top-ranked variant

*HGMD: Human Gene Mutation Database
ESP: US Exome Sequencing Project collaboration

Bone et al., Genet Med 2015

Genomiser: also non-coding



https://hpo.jax.org/app/tools/genomiser

HPO driven variant interpretation

Integrated in commercial software:

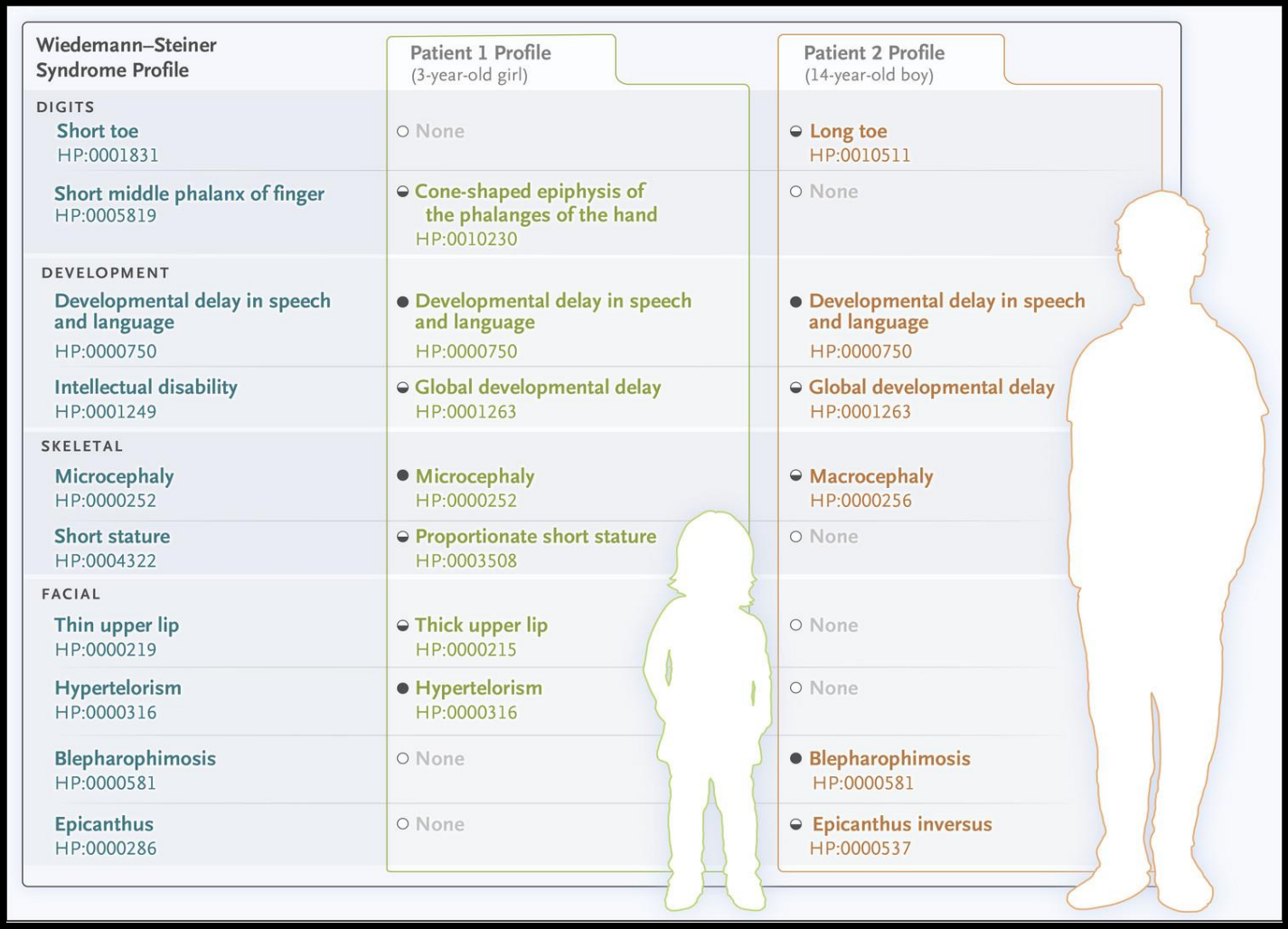
- FDNA: Face2Gene.
- Cartagenia BENCH
- GEPADO – Software Solutions for Genetics – GmbH
- BioDiscovery's NxClinical
- Diploid: Diagnosing rare diseases: Moon
- Centogene
- SimulConsult
- Fabric Genomics
- Qiagen
- Congenica

Phenotype matching tools

Matching of unrelated cases for rare disorders worldwide

- Disease gene identification
- Disease prognosis

“Fuzzy” Matching of Phenotypic Profiles.



Wiedemann–Steiner Syndrome Profile	Patient 1 Profile (3-year-old girl)	Patient 2 Profile (14-year-old boy)
DIGITS		
Short toe HP:0001831	○ None	◒ Long toe HP:0010511
Short middle phalanx of finger HP:0005819	◒ Cone-shaped epiphysis of the phalanges of the hand HP:0010230	○ None
DEVELOPMENT		
Developmental delay in speech and language HP:0000750	● Developmental delay in speech and language HP:0000750	● Developmental delay in speech and language HP:0000750
Intellectual disability HP:0001249	◒ Global developmental delay HP:0001263	◒ Global developmental delay HP:0001263
SKELETAL		
Microcephaly HP:0000252	● Microcephaly HP:0000252	◒ Macrocephaly HP:0000256
Short stature HP:0004322	◒ Proportionate short stature HP:0003508	○ None
FACIAL		
Thin upper lip HP:0000219	◒ Thick upper lip HP:0000215	○ None
Hypertelorism HP:0000316	● Hypertelorism HP:0000316	○ None
Blepharophimosis HP:0000581	○ None	● Blepharophimosis HP:0000581
Epicanthus HP:0000286	○ None	◒ Epicanthus inversus HP:0000537

MA Haendel et al. N Engl J Med 2018;379:1452-1462.

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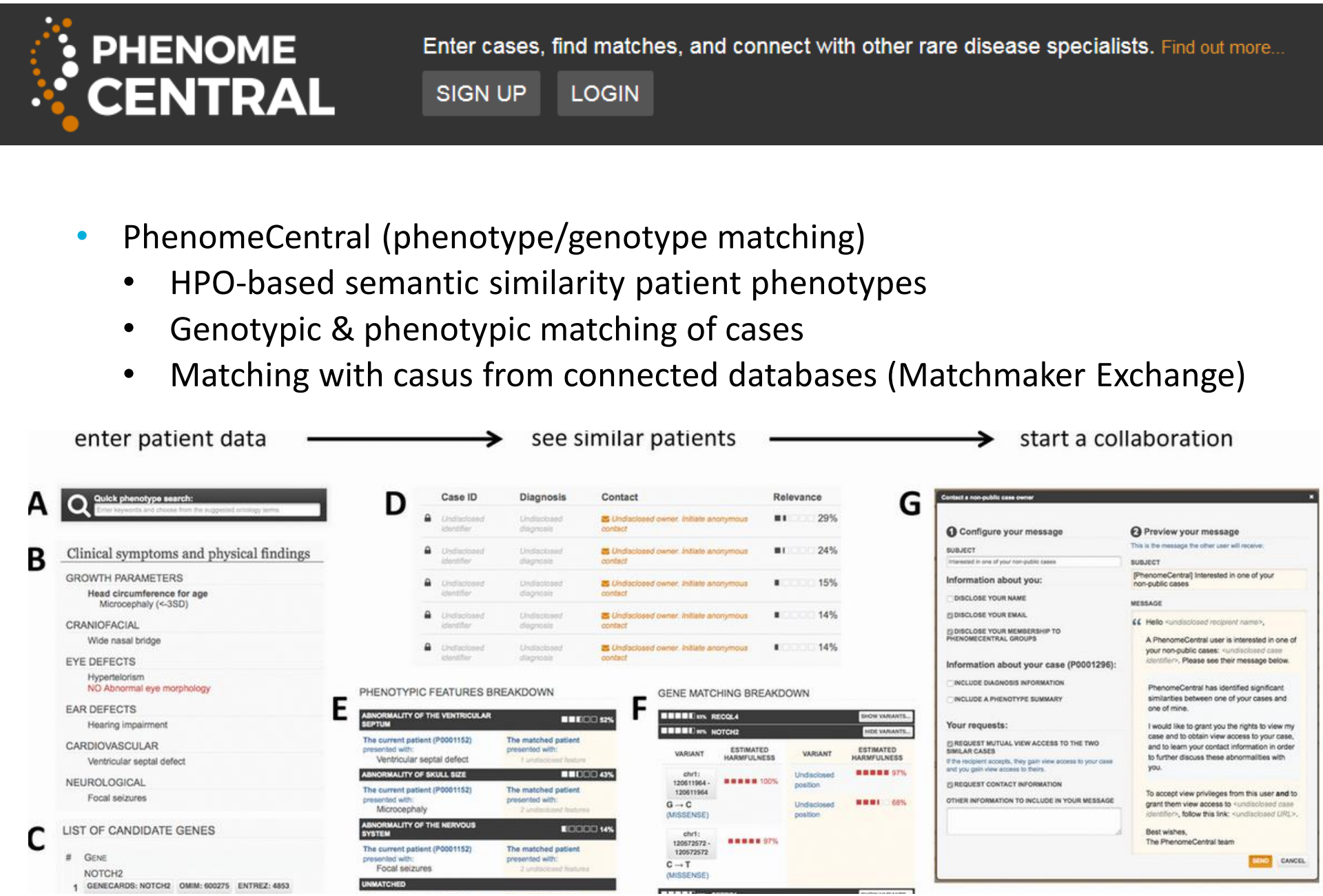
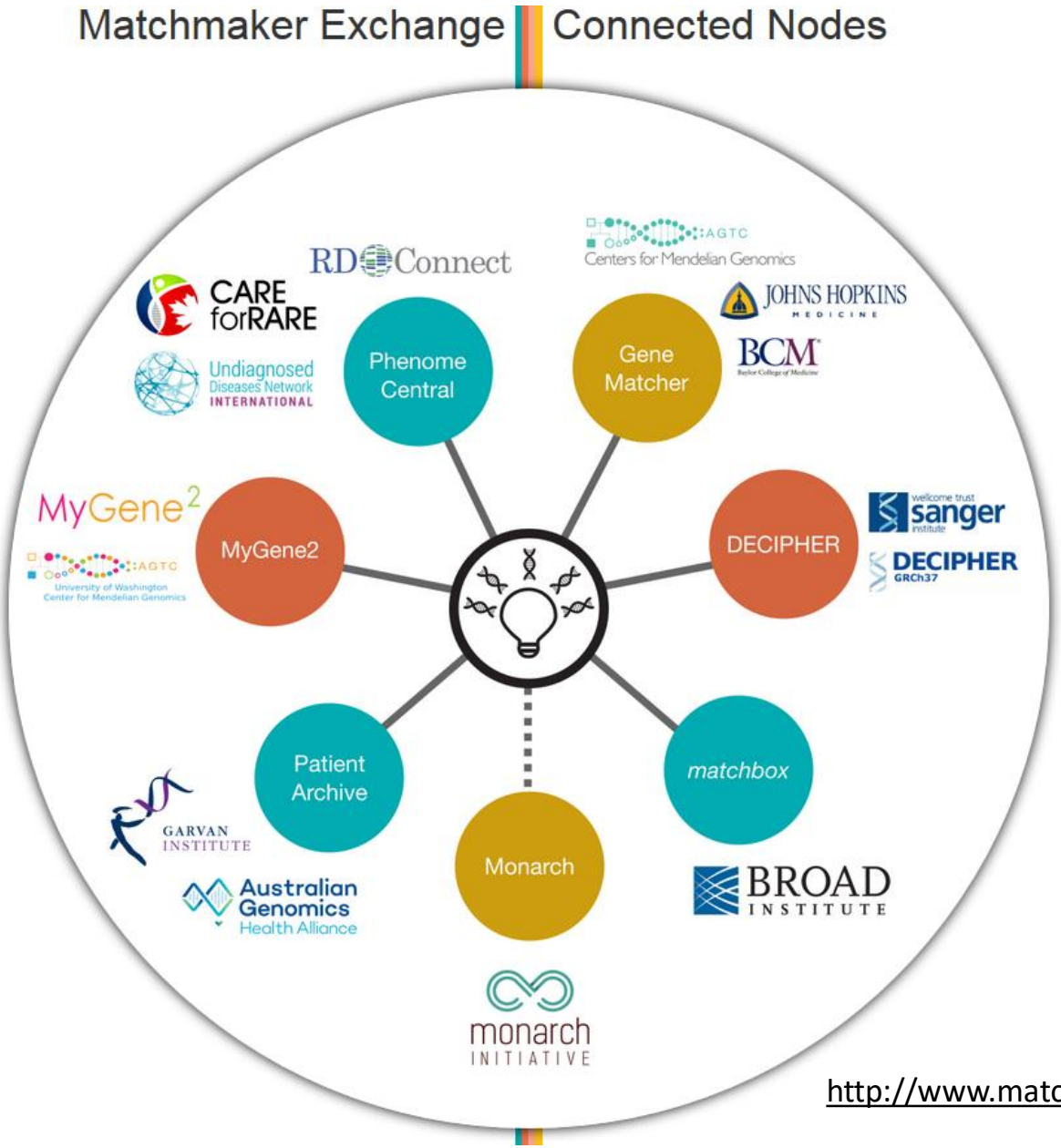


https://www.phenomecentral.org/

Clinical Pheno/Genotype Matching



http://www.matchmakerexchange.org/

Summary

Conclusion:

Structured phenotype data of patients and model organisms improves the diagnostic efficiency and prioritization of exome variants associated with known and new disorders

Critical points:

- HPO-annotation updates for disorders/genes
- completeness of coverage phenotypes by HPO-terms
- HPO-translation to other languages for use in hospital patient registries

Outlook

Integration of HPO in hospital clinical registry / diagnostic applications

HPO integrated in genome diagnostics

- HPO-based genepanels
- HPO-based genetic test selection
- HPO-based prioritization of exomic/genomic variants

HPO in genome research

- HPO-based candidate disease gene prioritization
- Cohort selection

Questions?


"My parents died. Their parents died. Their parents died... it runs in the family."

References

HPO project/browser/tools: https://hpo.jax.org/app/
HPO 2018 paper: https://www.ncbi.nlm.nih.gov/pubmed/30476213
HPO-browser (old): http://compbio.charite.de/hpoweb/showterm?id=HP:0000118

Contribute to HPO annotation:

- https://phenotate.org/
- https://hpo.jax.org/app/tools/workbench

Phenotype data integration: https://monarchinitiative.org/