ヒト疾患における異常な臨床表現型を記述する Human Phenotype Ontology

2019年12月17日

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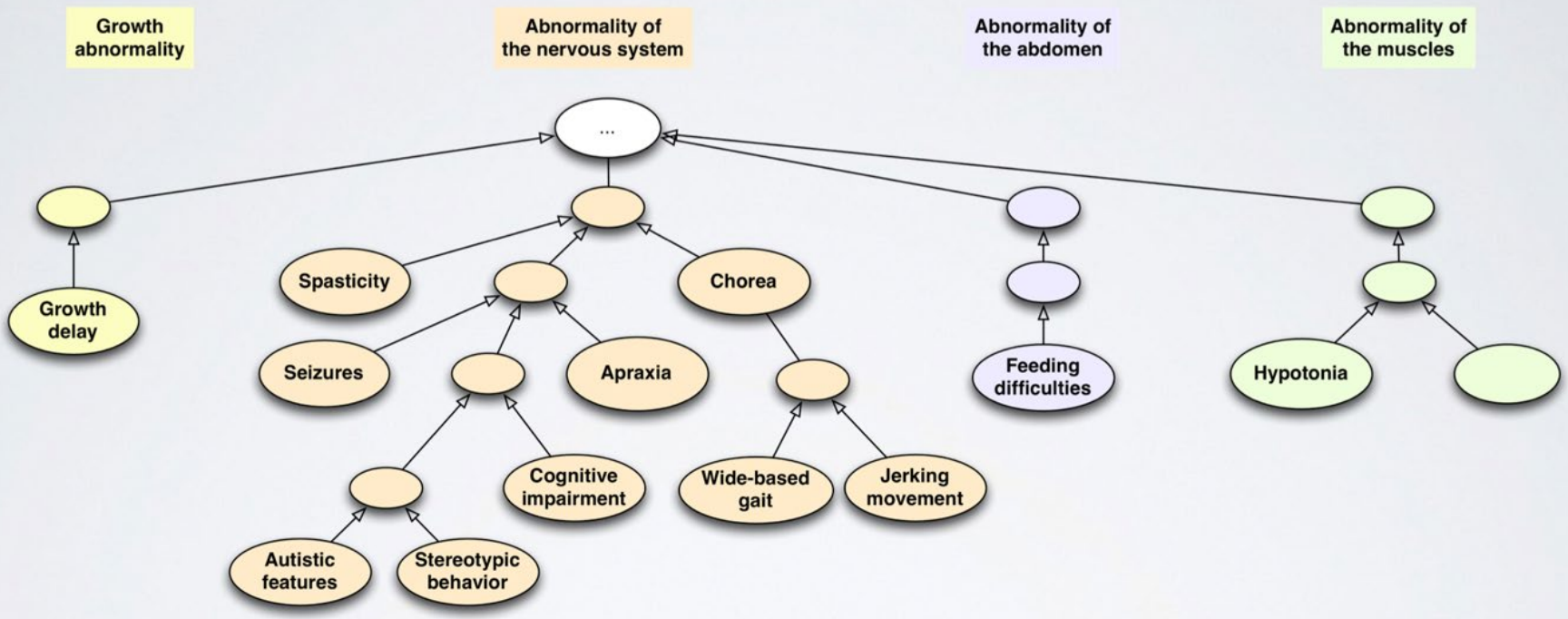
Human Phenotype Ontology (HPO)

Human Phenotype Ontology (HPO) はヒト疾患における表現型を記述する統制語彙・オントロジー



13,000 terms
156,000 annotations

Marfan Syndrome [MIM:154700]

Arachnodactyly [HP:0001166]

Ectopia lentis [HP:0001083]

HPOの主な構造

NUMBER OF CLASSES:	16232
NUMBER OF INDIVIDUALS:	0
NUMBER OF PROPERTIES:	0
MAXIMUM DEPTH:	15
MAXIMUM NUMBER OF CHILDREN:	33
AVERAGE NUMBER OF CHILDREN:	3
CLASSES WITH A SINGLE CHILD:	1056
CLASSES WITH MORE THAN 25 CHILDREN:	22
CLASSES WITH NO DEFINITION:	6683

- **臨床的修飾**
- **頻度**
- **遺伝様式**
- **死亡/加齢**
- **表現型異常**

の大分類の構造

- All
  - Clinical modifier
    - Aggravated by
    - Ameliorated by
    - Onset
    - Pace of progression
    - Pain characteristic
    - Phenotypic variability
    - Position
    - Severity
    - Temporal pattern
    - Triggered by
  - Frequency
    - Excluded
    - Frequent
    - Obligate
    - Occasional
    - Very frequent
    - Very rare
  - Mode of inheritance
    - Autosomal dominant inheritance
    - Autosomal recessive inheritance
    - Contiguous gene syndrome
    - Familial predisposition
    - Genetic anticipation
    - Gonosomal inheritance
    - Heterogeneous
    - Mitochondrial inheritance
    - Multifactorial inheritance
    - Somatic mutation
    - Sporadic
  - Mortality/Aging
    - Age of death
      - Death in adolescence
      - Death in childhood
      - Death in early adulthood
      - Death in infancy
      - Neonatal death
      - Stillbirth
      - Sudden death
  - Phenotypic abnormality
    - Abnormal cellular phenotype
    - Abnormal test result
    - Abnormality of blood and blood-forming tissues
    - Abnormality of connective tissue
    - Abnormality of head or neck
    - Abnormality of limbs
    - Abnormality of metabolism/homeostasis
    - Abnormality of prenatal development or birth
    - Abnormality of the breast
    - Abnormality of the cardiovascular system
    - Abnormality of the digestive system
    - Abnormality of the ear
    - Abnormality of the endocrine system
    - Abnormality of the eye
    - Abnormality of the genitourinary system
    - Abnormality of the immune system
    - Abnormality of the integument
    - Abnormality of the musculature
    - Abnormality of the nervous system
    - Abnormality of the respiratory system
    - Abnormality of the skeletal system
    - Abnormality of the thoracic cavity
    - Abnormality of the voice
    - Constitutional symptom
    - Growth abnormality
    - Neoplasm

- Phenotypic abnormality
  - Abnormal cellular phenotype
  - Abnormality of blood and blood-forming tissues
  - Abnormality of connective tissue
  - Abnormality of head or neck
  - Abnormality of limbs
  - Abnormality of metabolism/homeostasis
  - Abnormality of prenatal development or birth
  - Abnormality of the breast
  - Abnormality of the cardiovascular system
    - Abnormal cardiac test
    - Abnormal cardiovascular system physiology
    - Abnormality of cardiovascular system morphology
    - Abnormality of the fetal cardiovascular system
    - Abnormality of the vasculature
      - Abnormal vascular morphology
      - Abnormal vascular physiology
      - Abnormality of gastrointestinal vasculature
      - Abnormality of head blood vessel
        - Abnormality of infraorbital artery
      - Abnormality of neck blood vessel
      - Abnormality of the cerebral vasculature
      - Abnormality of the hepatic vasculature
      - Abnormality of the lymphatic system
      - Abnormality of the pulmonary vasculature
      - Abnormality of the vasculature of the eye
      - Vascular neoplasm
      - Vascular skin abnormality
        - Angioedema
        - Angiokeratoma
        - Cutis marmorata
        - Erythema
        - Non-pruritic urticaria
        - Prominent superficial blood vessels
        - Subcutaneous hemorrhage
        - **Telangiectasia** 毛細血管拡張症
          - Diffuse telangiectasia
          - Mucosal telangiectasiae
          - Nail bed telangiectasia
          - Retinal telangiectasia
          - Telangiectasia macularis eruptiva perstans
          - Telangiectasia of the skin
        - Urticaria
        - Vasculitis in the skin

- Phenotypic abnormality
  - Abnormal cellular phenotype
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  - Abnormality of the eye
  - Abnormality of the genitourinary system
  - Abnormality of the immune system
  - Abnormality of the integument
  - Abnormality of the musculature
  - Abnormality of the nervous system
    - Abnormality of ganglion
    - Abnormality of nervous system morphology
    - Abnormality of nervous system physiology
      - Abnormal cranial nerve physiology
      - Abnormal hypothalamus physiology
      - Abnormal nervous system electrophysiology
      - Abnormal synaptic transmission
      - Abnormality of central motor function
      - Abnormality of central sensory function
      - Abnormality of higher mental function
      - Abnormality of intracranial pressure
      - Abnormality of movement
      - Abnormality of pineal physiology
      - Abnormality of taste sensation
      - Abnormality of the sense of smell
      - Behavioral abnormality
      - Brain imaging abnormality
        - Bulbar palsy
        - Bulbar signs
        - Cataplexy
      - Dysphagia
        - Easy fatigability
      - Encephalopathy
      - Headache 頭痛
        - Hypocalcemic tetany
        - Lhermitte's sign
      - Neurodevelopmental abnormality
      - Pseudobulbar signs
      - **Seizures** 発作

Can we help machines understand phenotype terms?

Human phenotype

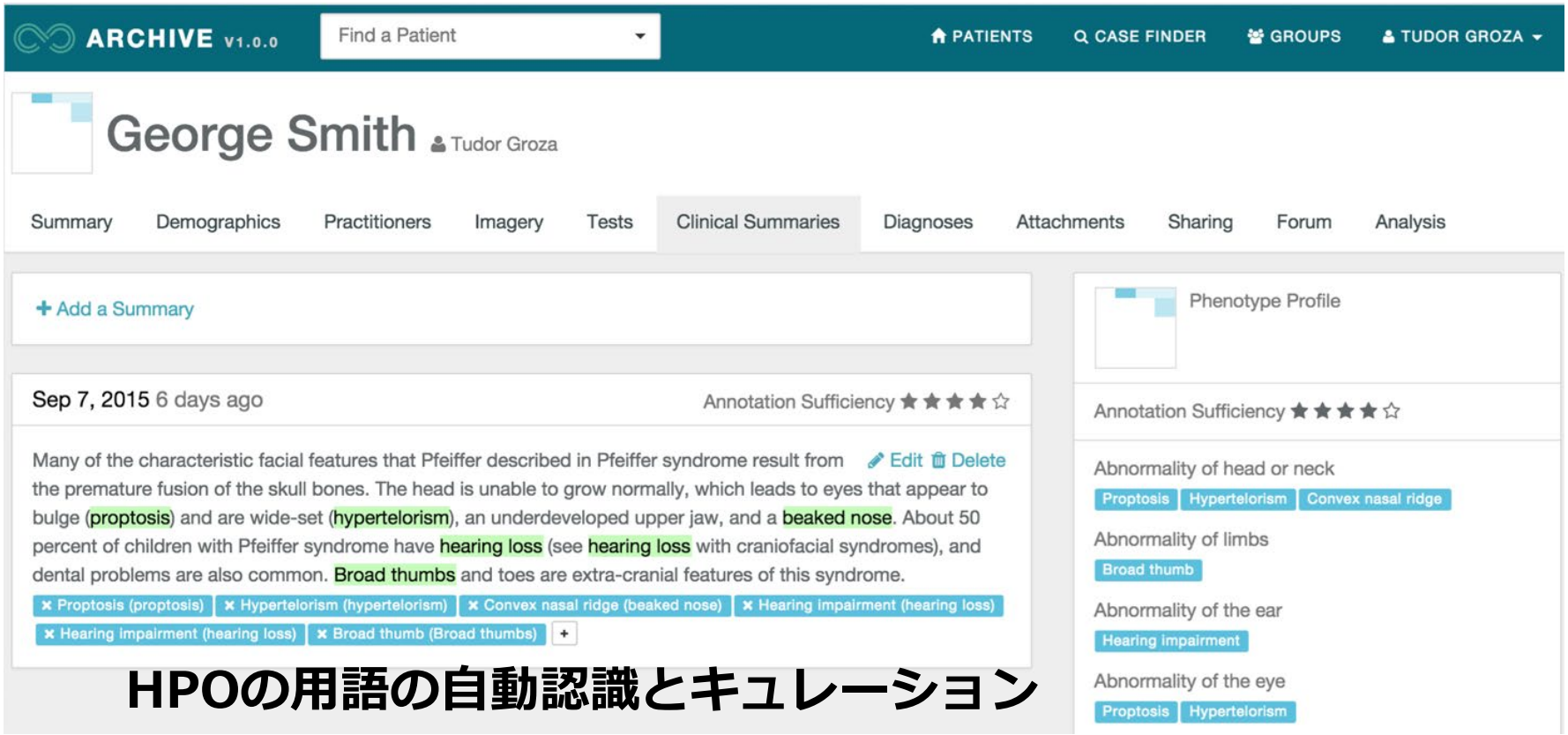
"Palmoplantar hyperkeratosis"

I have absolutely no idea what that means

Courtesy of Mellisa Haendel

診療テキストからのHPOによる表現型の抽出

希少疾患や未診断疾患では、診療テキストの自然言語処理によるフェノタイピングがなされている。Human Phenotype Ontology (HPO) に収載された用語を認識して、表現型を抽出する

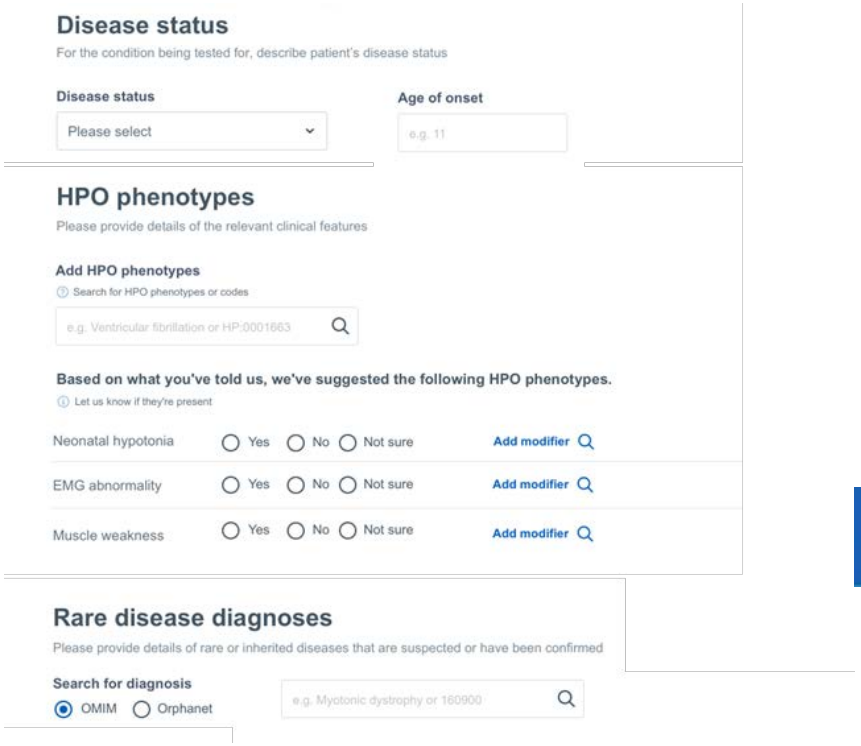


HPOの用語の自動認識とキュレーション

HPOの日本へのローカライゼーションを進めており、これにより日本語の診療テキストからのフェノタイピングが可能になる

テンプレートによるHPOによる表現型の入力
Genomics England

Phenotype capture



Genomics England

NHS England Genomic Medicine Service

テンプレートによるHPOによる表現型の入力
Australian Genomics

Phenotype capture

Acute Care: HPO terms in REDCap
(via Ontoserver and REDCap Ontology Module)

Australian Genomics Health Alliance

Principal phenotypic features	Coarse facial features HPO terms	HP:0000280
Principal phenotypic features	Sparse hair HPO terms	HP:0008070
Principal phenotypic features	Hypertrichosis HPO terms	HP:0000998
Principal phenotypic features	Aplasia/Hypoplasia of ... HPO terms	HP:0008386
Principal phenotypic features	Dysplastic corpus callo... HPO terms	HP:0006989
Principal phenotypic features	HPO terms	

他統制語彙・オントロジーとのマッピング

185の他オントロジーへのマッピング

マッピングするオントロジー名	マッピング数
Bone Dysplasia Ontology	26,453
Online Mendelian Inheritance in Man	3,608
Suggested Ontology for Pharmacogenomics	2,633
Robert Hoehndorf Version of MeSH	2,318
Human Disease Ontology	2,154
SNOMED CT	1,804
Medical Dictionary for Regulatory Activities	1,720
Cell Culture Ontology	1,596
Experimental Factor Ontology	1,596
International Classification of Primary Care - 2 PLUS	1,536
International Classification of Diseases, Version 10 - Clinical Modification	1,365
Read Codes, Clinical Terms Version 3 (CTV3)	1,205
National Cancer Institute Thesaurus	1,188
Fanconi Anemia Ontology	1,039
Cigarette Smoke Exposure Ontology	915
Logical Observation Identifier Names and Codes	807
MedlinePlus Health Topics	798
Medical Subject Headings	789
Neuroscience Information Framework (NIF) Standard Ontology	765
Mammalian Phenotype Ontology	709
Systematized Nomenclature of Medicine, International Version	694
Natural Products Ontology	615
Common Terminology Criteria for Adverse Events	612
Galen Ontology	509
Resource of Asian Primary Immunodeficiency Diseases (RAPID) Phenotype Ontology	456
Mouse Pathology Ontology	423
Human Dermatological Disease Ontology	396
Computer Retrieval of Information on Scientific Projects Thesaurus	389
Orphanet Rare Disease Ontology	371
Radiology Lexicon	369
Coding Symbols for a Thesaurus of Adverse Reaction Terms	368
International Classification of Diseases, Version 9 - Clinical Modification	358
Cell Line Ontology	336
World Health Organization (WHO) Adverse Reaction Terminology	334
International Classification of Diseases, Version 10	327
Clinical Signs and Symptoms Ontology	291
BioMedBridges Diabetes Ontology	254
Pediatric Terminology	239
Neuroscience Information Framework (NIF) Dysfunction Ontology	219

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The Human Phenotype Ontology in 2017

Sebastian Köhler[1,*], Nicole A. Vasilevsky[2], Mark Engelstad[2], Erin Foster[2], Julie McMurry[2], Ségolène Aymé[3], Gareth Baynam[4,5], Susan M. Bello[6], Cornelius F. Boerkoel[7], Kym M. Boycott[8], Michael Brudno[9], Orion J. Buske[9], Patrick F. Chinnery[10,11], Valentina Cipriani[12,13], Laureen E. Connell[14], Hugh J.S. Dawkins[15], Laura E. DeMare[14], Andrew D. Devereau[16], Bert B.A. de Vries[17], Helen V. Firth[18], Kathleen Freson[19], Daniel Greene[20,21], Ada Hamosh[22], Ingo Helbig[23,24], Courtney Hum[25], Johanna A. Jähn[24], Roger James[11,21], Roland Krause[26], Stanley J. F. Laulederkind[27], Hanns Lochmüller[28], Gholson J. Lyon[29], Soichi Ogishima[30], Annie Olry[31], Willem H. Ouwehand[20], Nikolas Pontikos[12,13], Ana Rath[31], Franz Schaefer[32], Richard H. Scott[16], Michael Segal[33], Panagiotis I. Sergouniotis[34], Richard Sever[14], Cynthia L. Smith[6], Volker Straub[28], Rachel Thompson[28], Catherine Turner[28], Ernest Turro[20,21], Marijcke W.M. Veltman[11], Tom Vulliamy[35], Jing Yu[36], Julie von Ziegenweidt[20], Andreas Zankl[37,38], Stephan Züchner[39], Tomasz Zemojtel[1], Julius O.B. Jacobsen[16], Tudor Groza[40,41], Damian Smedley[16], Christopher J. Mungall[42], Melissa Haendel[2] and Peter N. Robinson[43,44,*]

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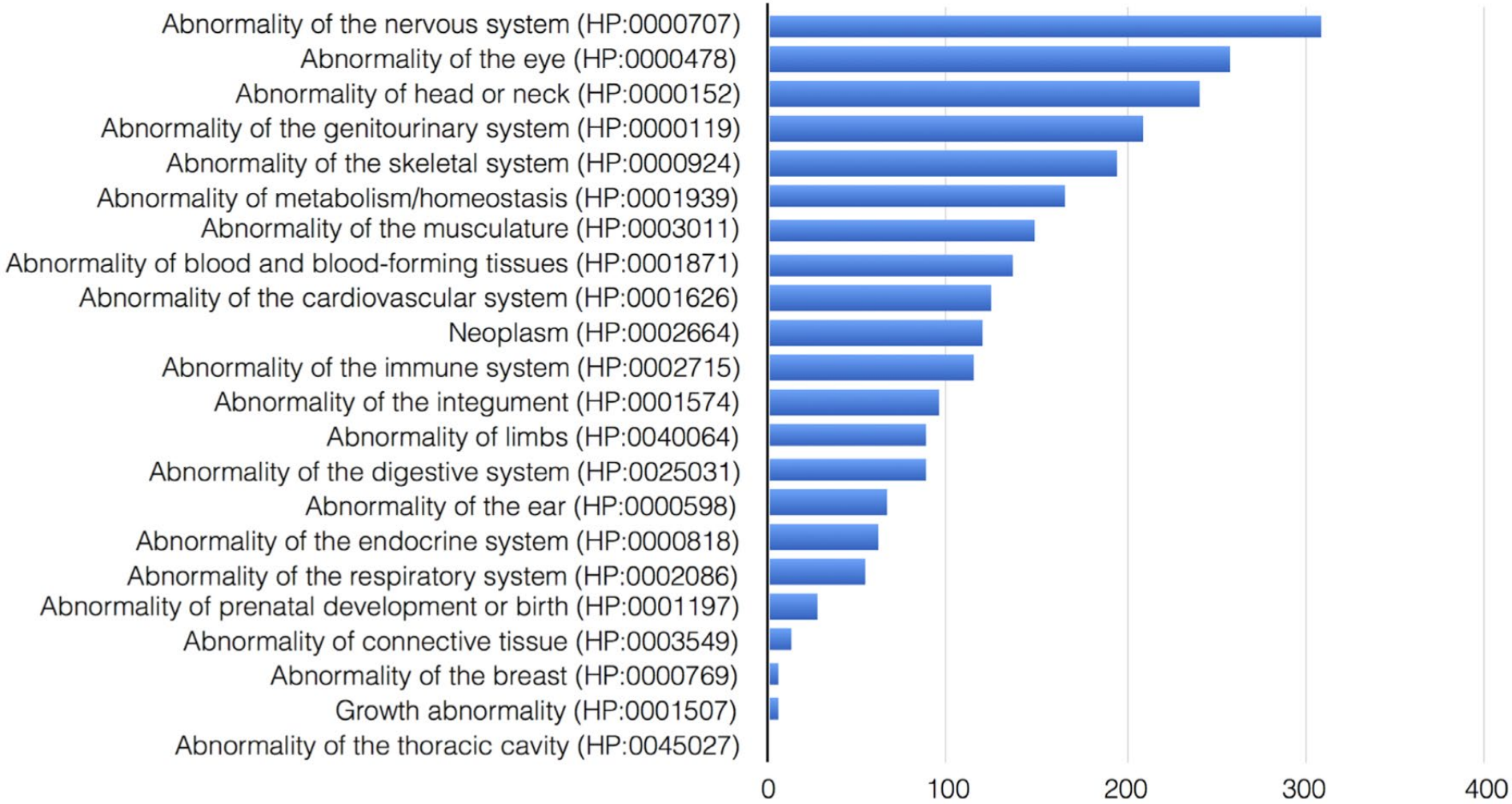
HPOの用語の追加・拡大

1,725の用語を追加・拡大、123,724の希少疾患のアノテーション、132,620の多因子疾患のアノテーション



Köhler S, et al. (2017) The Human Phenotype Ontology in 2017. Nucleic Acids Res. 45(D1):D865-D876.

疾患関連遺伝子の探索で広く利用されるHPO

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 S, et al. (2017) The Human Phenotype Ontology in 2017. Nucleic Acids Res. 45(D1):D865-D876.

HPOを利用したツール、アプリケーション

Phenotype-driven differential diagnosis
- Phenomizer
- BOQA
- FACE2GENE
- Phenolyzer

Phenotype-driven exome/genome analysis
- Exomiser
- PhenIX
- Phevor
- PhenoVar
- eXtasy
- OMIMExplorer
- Phen-Gen
- Geno2MP
- Genomiser
- SimReg
- ontologySimilarity

Functional and network analysis
- TopGene/ToppFunn
- WebGestalt
- SUPERFAMILY
- GREAT
- Random walk on heterogeneous network
- PANDA
- PREDICT

Clinical data management and analysis
- Phenotips
- Patient Archive
- GENESIS (GEM.app)

Cross-species phenotype analysis
- PhenoDigm
- MouseFinder
- Monarch
- PhenomeNet
- UberPheno
- MORPHIN
- PhenogramViz

Phenotype knowledge resources and databases
- Orphanet
- MalaCards
- NIH genetic testing registry
- OMIM
- dcGO
- ClinVar
- GeneSetDB
- MSeqDR
- DIDA (digenic diseases database)
- Genetic and Rare Diseases (GARD) Information Center

Visualization
- PhenoStacks
- PhenoBlocks
- DECIPHER (phenogram)
- phenogrid
- ontologyPlot

Köhler S, et al. (2017) The Human Phenotype Ontology in 2017. Nucleic Acids Res. 45(D1):D865-D876.

Phenopackets

patients.pxf

header

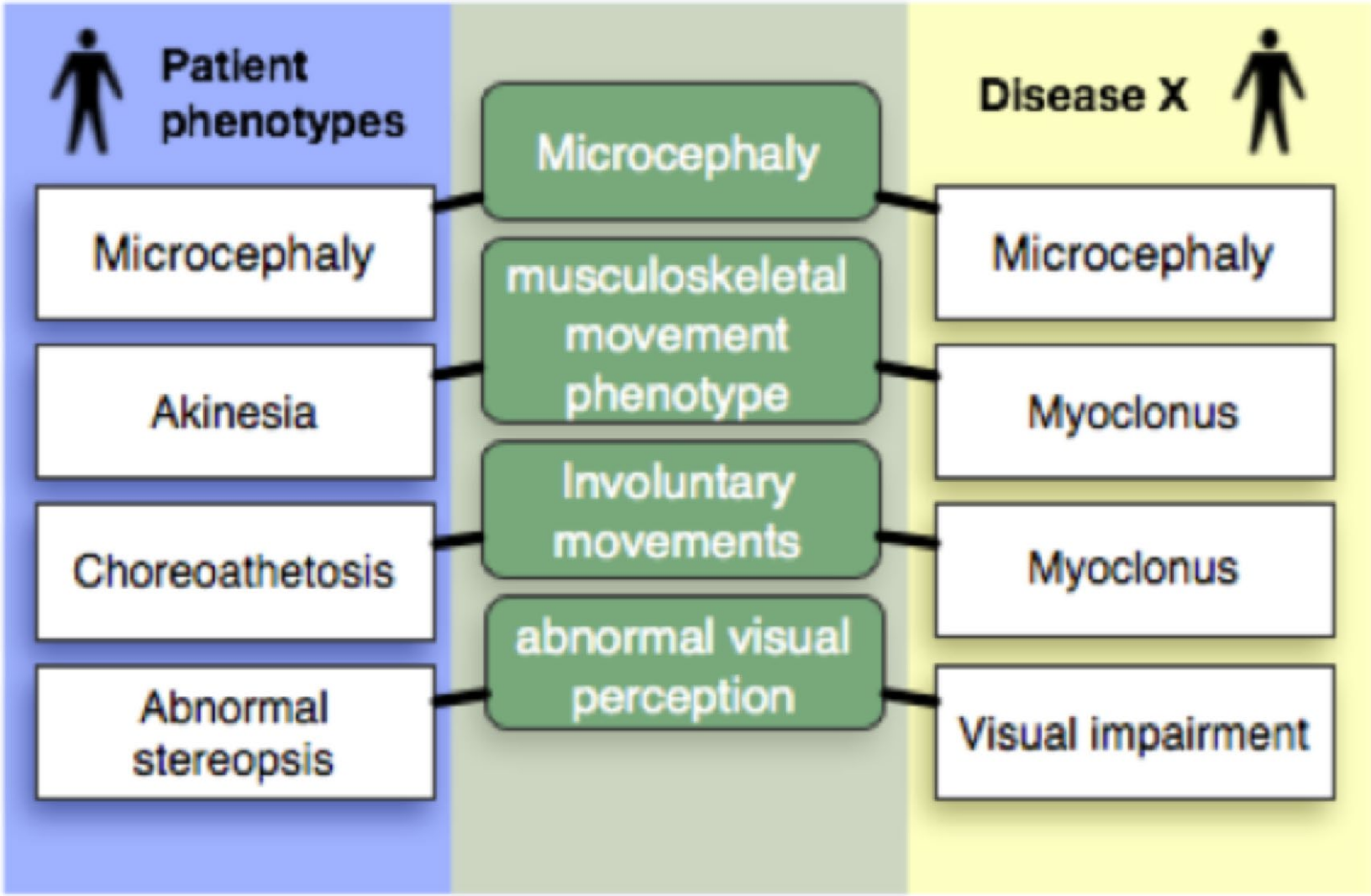
entities

assocs

```
persons:
 - id: „#1“
   label: Mickey Mouse
   date_of_birth: 1928-01-01
   sex: M
 - id: „#2“
   label: Goofy
   sex: M
```

```
phenotype_profile:
 - entity: “#1”
   phenotype:
     types:
       - id: HP:0100024
         label: conspicuously happy disposition
     onset:
       types:
         - id: HP:0011463
           label: Childhood onset
     description: “welcomes strangers with open arms”
 - entity: “#1”
   phenotype:
     types:
       - id: MP:0001284
         label: absent vibrissae
 - entity: “#2”
   phenotype:
     types:
       - id: HP:0100024
         label: conspicuously happy disposition
```

HPOによる表現型の類似度の評価



GA4GHによる国際的なハーモナイゼーションへの取り組み

COMMON WORKFLOW LANGUAGE

ClinGen
Clinical Genome Resource

CIViC
CLINICAL INTERPRETATIONS OF VARIANTS IN CANCER

Global Alliance
for Genomics & Health

Collaborate. Innovate. Accelerate.

50ケ国の500超の機関が参加する
ゲノム医療・医学の促進を目指す対話の場

monarch INITIATIVE

human phenotype ontology

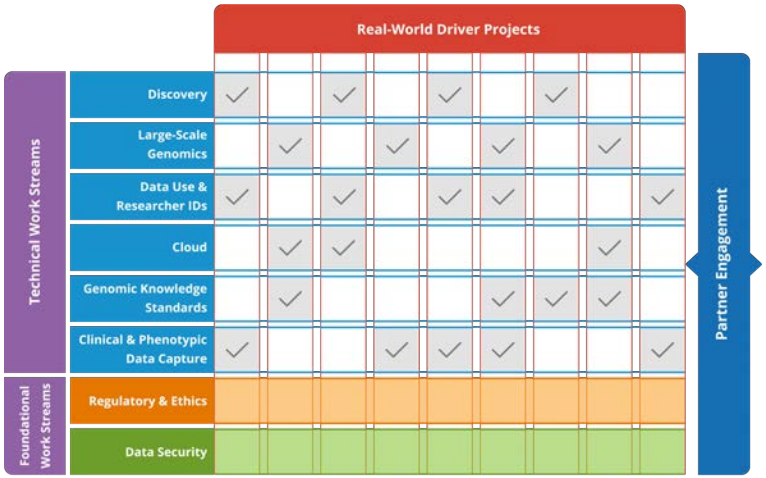
PHENOTIPS®

Roadmap & Leadership Roles

Global Alliance for Genomics & Health alth

GA4GH Driver Projects **are real-world** genomic **data** initiatives that help guide our development efforts and pilot our tools. Stakeholders around the globe advocate, mandate, implement, and use our **frameworks** and standards in their local contexts.

GA4GH Foundational and Technical Work Streams develop standards and tools that are designed to overcome technical and regulatory hurdles to international genomic data-sharing.



The GA4GH Partner Engagement initiative facilitates two-way dialogue with the international community, including national initiatives, major health care centres, and patient advocacy groups.

Clinical & Phenotypic Data Capture Work Stream

AMED-GA4GH

国立研究開発法人 日本医療研究開発機構
Japan Agency for Medical Research and Development

Global Alliance for Genomics & Health
Collaborate. Innovate. Accelerate.

GEM Japan workshop

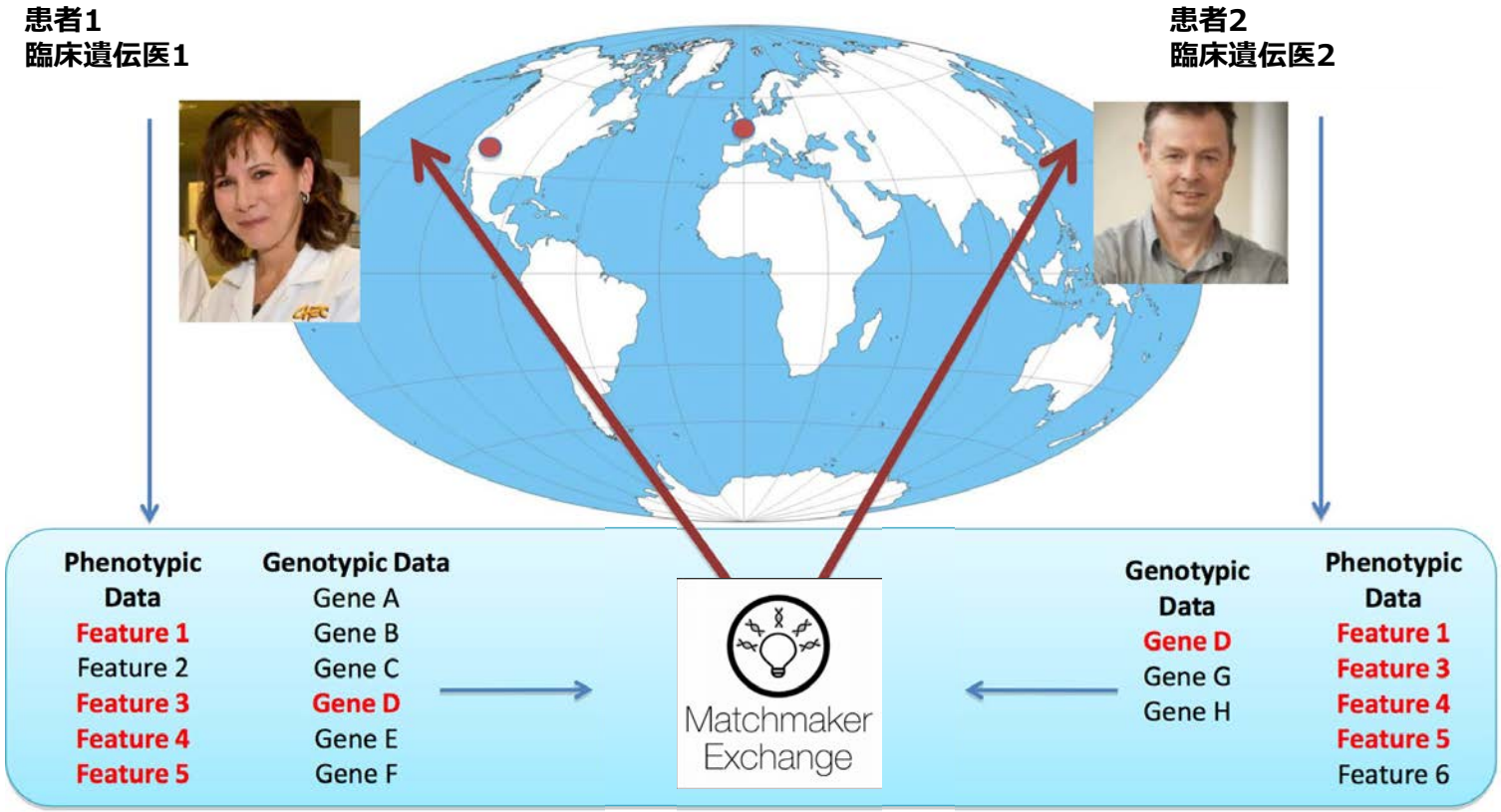
March 18 – 21, 2019 in Sendai

| ToMMo, Tohoku Univ | Sendai Akiu |

Data Sharing for Promotion of Genome Based Medicine

Genomic Knowledge Standards / Clinical & Phenotypic Data Capturing / Cloud / Data Use & Researcher Identities

GA4GHの国際的なハーモナイゼーションと日本の対応について議論



HPOによる記述

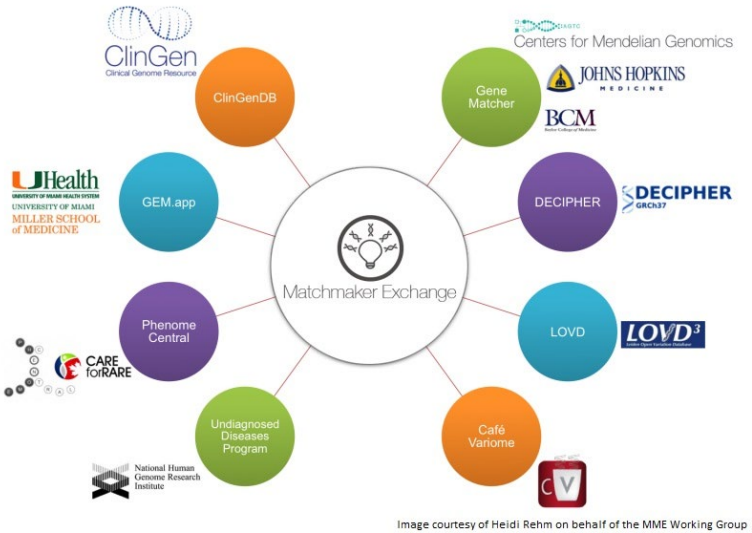


Image courtesy of Heidi Rehm on behalf of the MME Working Group

MatchMaker Exchangeによる臨床試験・治験支援

MatchMaker Exchange API

データ種	属性	データ例	概要	データ型
Patient	id	“F0000011”	Unique, persistent patient identifier	String
	label	“174 170258”	Human-readable identifier, no personally identifiable information	String
	species	“NCBITaxon:9606”	NCBI taxon identifier	String
	sex	“FEMALE”	Genetic sex (“FEMALE”, “MALE”, “OTHER”)	String
	ageOfOnset	**“HP:0003623”**	Age interval at onset of the majority of the symptoms (HPO term identifier)	String
	inheritanceMode	**“HP:0000006”**	Mode of inheritance (HPO term identifier)	String
Disorder	id	“MIM:136140”	OMIM or ORDO identifier	String
Feature	id	**“HP:0004322”**	HPO term identifier	String
GenomicFeature	zygosity	“1”	Allelic dosage (1: hetero, 2: homo)	Number
Gene	id	“SRCAP”	Gene symbol, Ensembl gene ID, or Entrez gene ID	String
Variant	assembly	“GRCh37”	Reference assembly identifier	String
	referenceName	“16”	Chromosome	String
	start	“30748691”	Start position (0-based)	Number
	end	“30748692”	End position (0-based, exclusive)	Number
	referenceBases	“C”	VCF-style reference allele of at least one base	String
	alternateBases	“T”	VCF-style alternate allele of at least one base	String
GenomicFeatureType	id	“SO:0001587”	SO term identifier	String
	label	“STOPGAIN”	Human-readable description	String

(Human Mutation, July 2015)

http://www.irdirc.org/wp-content/uploads/2015/04/humu22850.pdf

MatchMaker Exchangeにおける類似度計算手法

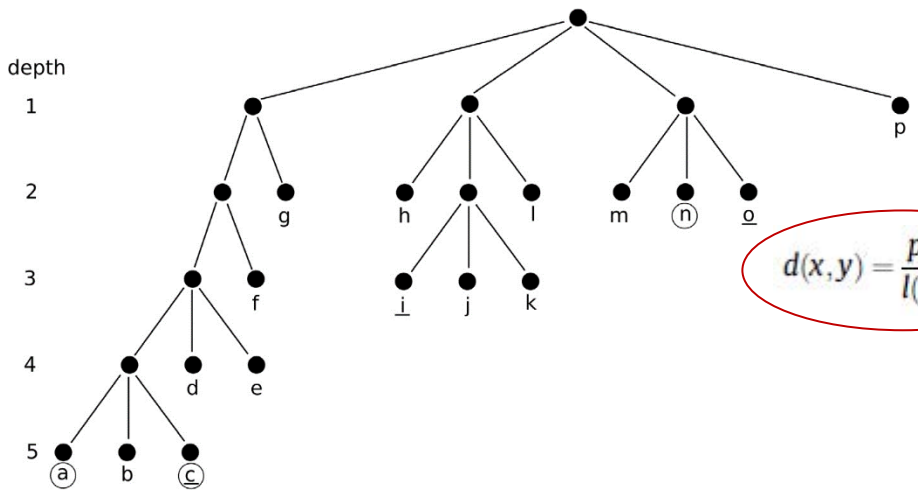
- **既存の類似度計算13手法を検証比較し、PhenoDigmを推奨**
- PhenoDigm, simGICが同程度の高い精度(top1:69%,top5:90%)
- PhenoDigmはsimGICよりノイズに強くロバスト
  - ✓ PhenoDigm top1:11%,top5:29%
  - ✓ simGIC top1:3%,top5:9%
- ただし、PhenoDigmの処理時間はsimGICの17.64倍

  1000 termに対する類似度計算実行時間はsimGICが34秒、PhenoDigmが10分

Measure	Versions	Definition	Reference
Resnik	avg, max	$Resnik(a,b) = max_{t \in g^a \cap g^b} IC(t)$	see the review by (Pesquita et al., 2009)
Lin	avg, max	$Lin(a,b) = \frac{2 * Resnik(a,b)}{IC(a) + IC(b)}$	
JC	avg, max	$JC(a,b) = \frac{1}{IC(a) + IC(b) - 2 * Resnik(a,b) + 1}$	
Jaccard	avg, max	$Jaccard(a,b) = \frac{\lvert g^a \cap g^b \rvert}{\lvert g^a \cup g^b \rvert}$	
UI		$UI(P,Q) = \frac{\lvert g^P \cap g^Q \rvert}{\lvert g^P \cup g^Q \rvert}$	
PhenoDigm	avg, max, combined	$PhenoDigm(P,Q) =$ see reference	(Smedley et al., 2013)
simGIC		$sim_{GIC}(P,Q) = \frac{\sum_{t \in g^P \cap g^Q} IC(t)}{\sum_{t \in g^P \cup g^Q} IC(t)}$	(Pesquita et al., 2007)

Buske OJ, et al. (2015) PhenomeCentral: a portal for phenotypic and genotypic matchmaking of patients with rare genetic diseases. Hum Mutat. 36(10):931-40.

HPOによる表現型の類似度の算出



患者A :a,c,n
患者B :c,i,o

$$d(x,y) = \frac{p_{\min}(x,y)}{l(x)+l(y)},$$

$$d(\mathrm{a,c}) = \frac{2}{5+5} = \frac{1}{5}; \quad d(\mathrm{a,i}) = \frac{8}{5+3} = 1; \quad d(\mathrm{a,o}) = \frac{7}{2+5} = 1;$$

$$d(\mathrm{n,c}) = \frac{7}{2+5} = 1; \quad d(\mathrm{n,i}) = \frac{5}{2+3} = 1; \quad d(\mathrm{n,o}) = \frac{2}{2+2} = \frac{1}{2};$$

$$d(\mathrm{i,c}) = \frac{8}{5+3} = 1; \quad d(\mathrm{o,c}) = \frac{7}{2+5} = 1.$$

	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p
S_1	✓		✓											✓		
S_2			✓						✓						✓	
Jaccard contribution	1		0						1					1	1	
Hierarchical contribution	$\frac{11}{15}$		0						1					$\frac{5}{6}$	$\frac{5}{6}$	

$$\underbrace{\frac{1}{3}(d(\mathrm{a,c}) + d(\mathrm{a,i}) + d(\mathrm{a,o}))}_{x=\mathrm{a}} + \underbrace{\frac{1}{3}(d(\mathrm{n,c}) + d(\mathrm{n,i}) + d(\mathrm{n,o}))}_{x=\mathrm{n}}$$
$$+ \underbrace{\frac{1}{3}(d(\mathrm{i,a}) + d(\mathrm{i,c}) + d(\mathrm{i,n}))}_{y=\mathrm{i}} + \underbrace{\frac{1}{3}(d(\mathrm{o,a}) + d(\mathrm{o,c}) + d(\mathrm{o,n}))}_{y=\mathrm{o}},$$

$$d_H(X,Y) = \frac{1}{|X \cup Y|}\left(\sum_{x \in X \setminus Y} \frac{1}{|Y|} \sum_{y \in Y} d(x,y) + \sum_{y \in Y \setminus X} \frac{1}{|X|} \sum_{x \in X} d(y,x)\right).$$

$$d_H(S_1,S_2) = \frac{1}{5}\left(\frac{11}{15} + 0 + 1 + \frac{5}{6} + \frac{5}{6}\right) = \frac{17}{25} = 0.68.$$

Girardi D et al. (2016) Using concept hierarchies to improve calculation of patient similarity. J Biomed Inform. 63:66-73.

未診断疾患のクリニカルシーケンスによる診断

1. 次世代シーケンサによる変異解析

SNP　300万

2. フィルタリング

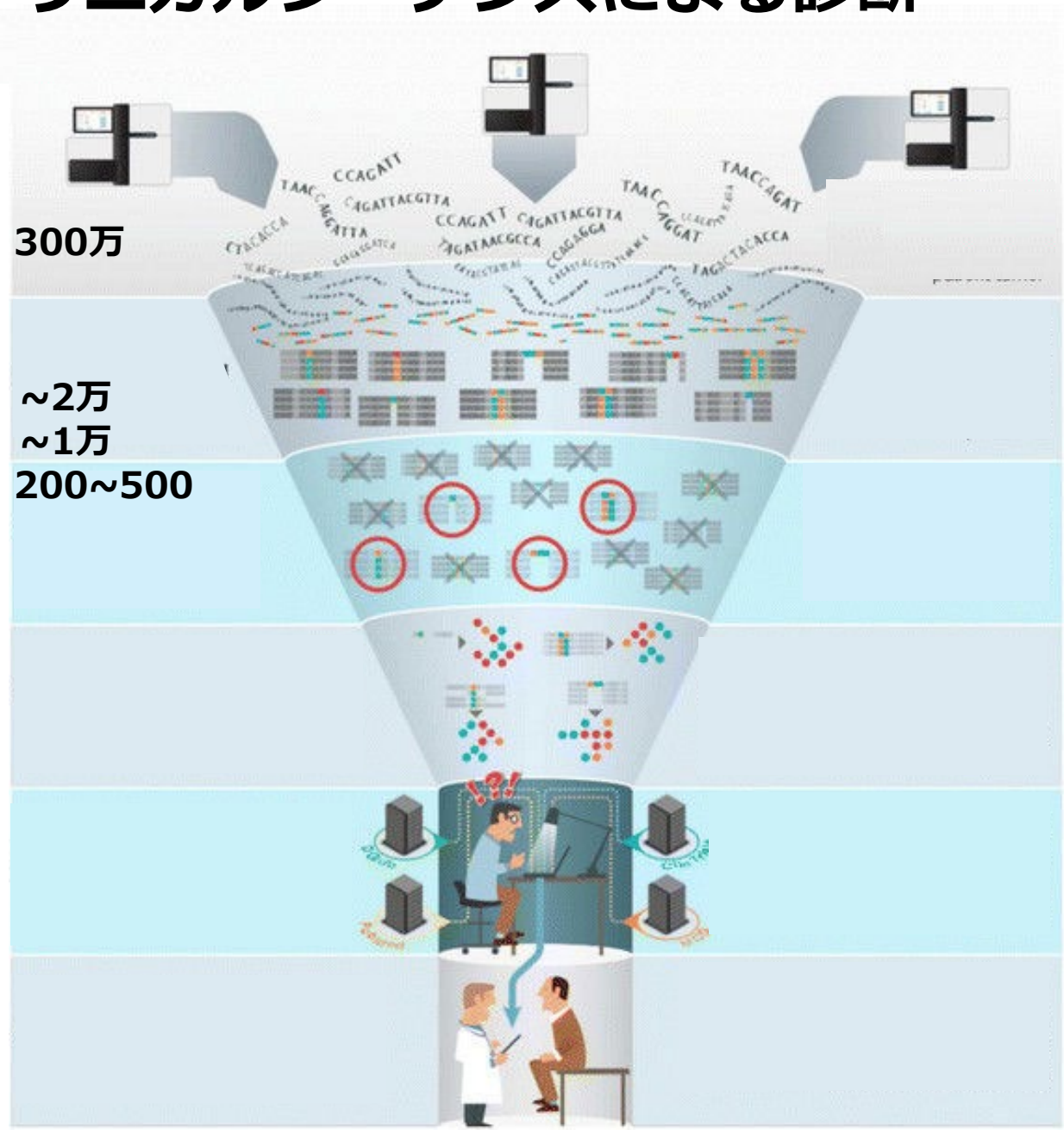
コード領域　~2万
非同義置換　~1万
新規SNP　200~500

3. 変異への注釈付け

4. 解釈・レポート作成

専門医、遺伝カウンセラーのチームが治療方針を決定

5. 変異にあわせた診断・治療



HPOの表現型からの罹患疾患の推測

疾患とHPOの表現型の関連性のデータを利用した罹患疾患の推測

Orphamizer http://compbio.charite.de/phenomizer_orphanet/

可能性のある罹患疾患のランキング

Menu. Support the Orphamizer. Help. The Orphamizer

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:0030927	1-minute APGAR score of 0
HP:0030928	1-minute APGAR score of 1
HP:0030929	1-minute APGAR score of 2
HP:0030930	1-minute APGAR score of 3
HP:0030931	1-minute APGAR score of 4
HP:0030932	1-minute APGAR score of 5
HP:0030933	1-minute APGAR score of 6
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

Page 1 of 447 Features 1 - 27 of 12067

Patient's Features. Diagnosis.

Algorithm: BOQA 5 Features.

Probability.	Disease Id.	Disease name.	Genes.
0.9299	ORPHA:31...	Infantile convulsions and choreoathetosis	SCN8A, PRRT2
0.0634	ORPHA:28	Vitamin B12-responsive methylmalonic acidemia	
0.0019	ORPHA:66...	Cutaneous mastocytosis	
0.0018	ORPHA:774	Hereditary hemorrhagic telangiectasia	SMAD4, ACV...
0.0005	ORPHA:98...	Ichthyosis associated with a cornified cell envelope and epidermal lipid metabolism anomaly	
0.0004	ORPHA:85...	Microphthalmia-ankyloblepharon-intellectual disability syndrome	
0.0003	ORPHA:343	Hyperimmunoglobulinemia D with periodic fever	MVK
0.0003	ORPHA:3090	Congenital pulmonary venous return anomaly	
0.0003	ORPHA:79...	Seizures-intellectual disability due to hydroxylysinuria syndrome	
0.0002	ORPHA:98...	Secondary polycythemia	
0.0001	ORPHA:14...	Short stature due to primary acid-labile subunit deficiency	IGFALS
0.0001	ORPHA:19...	EAST syndrome	KCNJ10
0.0001	ORPHA:2798	Pachygyria-intellectual disability-epilepsy syndrome	
0.0001	ORPHA:454	Acquired ichthyosis	
0.0001	ORPHA:91...	Pituitary deficiency due to empty sella turcica syndrome	
0.0001	ORPHA:511	Maple syrup urine disease	
0.0000	ORPHA:36...	Adiposis dolorosa	
0.0000	ORPHA:25...	Distal 7q11.23 microdeletion syndrome	
0.0000	ORPHA:49...	Achromatopsia	PDE6H, PDE...
0.0000	ORPHA:27...	L1 syndrome	
0.0000	ORPHA:31...	Ebola hemorrhagic fever	
0.0000	ORPHA:26...	17q12 microduplication syndrome	
0.0000	ORPHA:1193	Atkin-Flaitz syndrome	
0.0000	ORPHA:86...	Hereditary palmoplantar keratoderma, Gamborg-Nielsen type	
0.0000	ORPHA:702	Pelizaeus-Merzbacher disease	
0.0000	ORPHA:33...	Mercury poisoning	
0.0000	ORPHA:17...	Adult intestinal botulism	

Page 1 of 87 Improve Differential Diagnosis. Download Results.

Orphamizer http://compbio.charite.de/phenomizer_orphanet/

疾患とHPOの表現型の関連性

OMIM, Orphanet, DECIPHERに登録された疾患とHPOの表現型の関連性が利用可能

DECIPHER	1	WOLF-HIRSCHHORN SYNDROME	HP:0000252	DECIPHER:1	IEA	O	2013.05.29	HPO:skoehler	
DECIPHER	1	WOLF-HIRSCHHORN SYNDROME	HP:0001249	DECIPHER:1	IEA	O	2013.05.29	HPO:skoehler	
DECIPHER	1	WOLF-HIRSCHHORN SYNDROME	HP:0001250	DECIPHER:1	IEA	O	2013.05.29	HPO:skoehler	
DECIPHER	1	WOLF-HIRSCHHORN SYNDROME	HP:0001252	DECIPHER:1	IEA	O	2013.05.29	HPO:skoehler	
DECIPHER	1	WOLF-HIRSCHHORN SYNDROME	HP:0001518	DECIPHER:1	IEA	O	2013.05.29	HPO:skoehler	
…									
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000006		IEA	I	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000098	OMIM:154700	TAS	O	2012.04.24	HPO:probinson	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000189	OMIM:154700	IEA	O	2013.08.18	HPO:skoehler	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000218		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000268		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000272		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000275	OMIM:154700	TAS	O	2012.05.01	HPO:probinson	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000276	OMIM:154700	TAS	O	2012.05.01	HPO:probinson	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000278		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000347		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000490		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000494		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000501	OMIM:154700	IEA	O	2013.01.22	HPO:skoehler	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000518	OMIM:154700	PCS	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000541		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000545		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000565	OMIM:154700	IEA	rare	O	2015.07.26	HPO:skoehler
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000577	OMIM:154700	IEA	rare	O	2015.07.26	HPO:skoehler
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000678		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000767		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0000768		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0001002		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0001065		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0001083		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0001166		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0001371		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0001382		IEA	O	2012.04.24	HPO:curators	
OMIM	154700	#154700 MARFAN SYNDROME;MARFAN SYNDROME, TYPE I; MFS1	HP:0001548	OMIM:154700	IEA	O	2013.01.22	HPO:skoehler	
…									
OMIM	100100	ABDOMINAL MUSCLES, ABSENCE OF, WITH URINARY TRACT ABNORMALITY ANDCRYPTORCHIDISM	HP:0000003	ORPHANET:2970	TAS	typical			
…									

ただし、登録対象の症例報告にすべての表現型が報告されているとは限らない

症例報告には新奇の表現型が報告される

日本語へのローカライズ

AMED臨床ゲノム情報統合データベース整備事業
1次 小崎班・2次 小崎班

human phenotype ontology

- エキスパート、自然言語処理によるローカライズを実施
- 95%程度完了
- AMED GEM Japan ワークショップにおいてローカライズの検討

AMEDの他の希少疾患の研究開発事業での利用

- 未診断疾患イニシアチブIRUD

IRUD 未診断疾患イニシアチブ
Initiative on Rare and Undiagnosed Diseases

- AMED難治性疾患実用化研究事業
  難病プラットホーム RADDR-J

RADDAR-J
難病プラットフォーム
Rare Disease Data Registry of Japan

Human Phenotype Ontology, now with 6,200 plain language synonyms for patients, families, and non-experts

Apert's syndrome		
	Plain language	**Medical term**
	Webbed toes	Syndactyly
	Deformity due to premature fusing of skull bones	Cranio-synostosis
	Wide-set eyes	Ocular hypertelorism

@HP_ontology

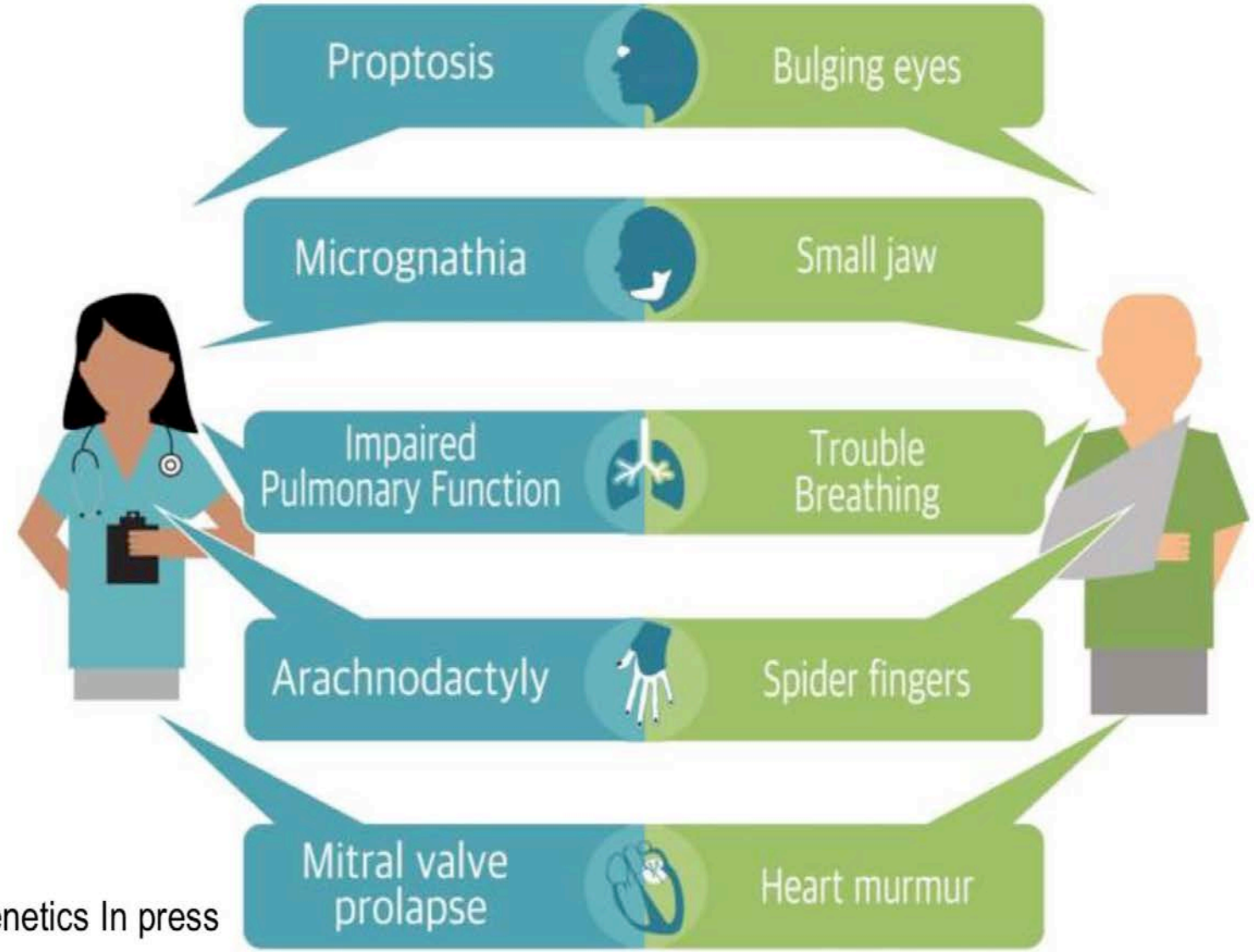
www.human-phenotype-ontology.org

Courtesy of Mellisa Hendel

Patients should be empowered to help.

Courtesy of Mellisa Hendel

Example Lay-Synonyms



Nature Genetics In press
doi:10.5281/zenodo.1168737

Courtesy of Mellisa Hendel

Layperson disease coverage

- 4,555 terms in the HPO are annotated with at least one lay person synonym (35.4% coverage)
- 7,607 number of lay person synonyms total
- 60% of all disease annotations (73,932 of 122,120) are referring to HPO terms with lay translations

Courtesy of Mellisa Hendel

Layperson-HPO driven phenotyping tool

PHENOTYPR

CONTACT US

P H E N O T Y P R

Patient Provided Phenotyping

Let's get started

WHAT IS PHENOTYPR?

Phenotypr is an educational tool for parents and families who believe they may have a child with a genetic intellectual disorder. Using

WHAT IS HPO?

The Human Phenotype Ontology (HPO) aims to provide a standardized vocabulary of phenotypic abnormalities

WHY USE HPO?

Knowing the HPO mapping of your child can provide your clinicians access to quality, structured phenotyping data. Providing this

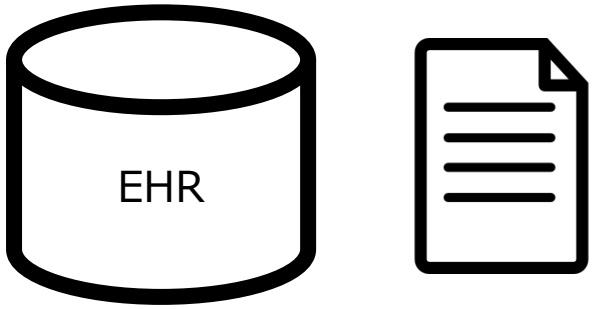
pcori

https://www.pcori.org/research-results/2017/realization-standard-care-rare-diseases-using-patient-engaged-phenotyping

Courtesy of Mellisa Hendel

診療情報に基づく表現型の取得と ゲノム医療研究開発への利活用

希少疾患



診療テキスト

多因子疾患

診療データ

病名 (Dx)
投薬 (Rx)
検査結果

画像情報

表現型の取得
(phenotype capture)

病型分類
(phenotyping)

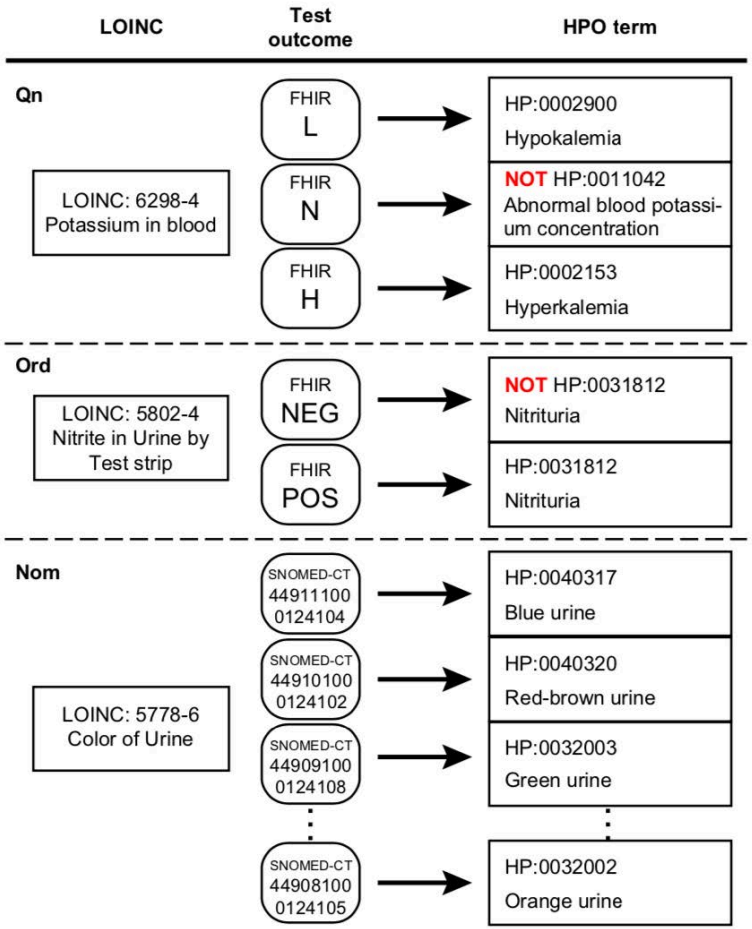
表現型

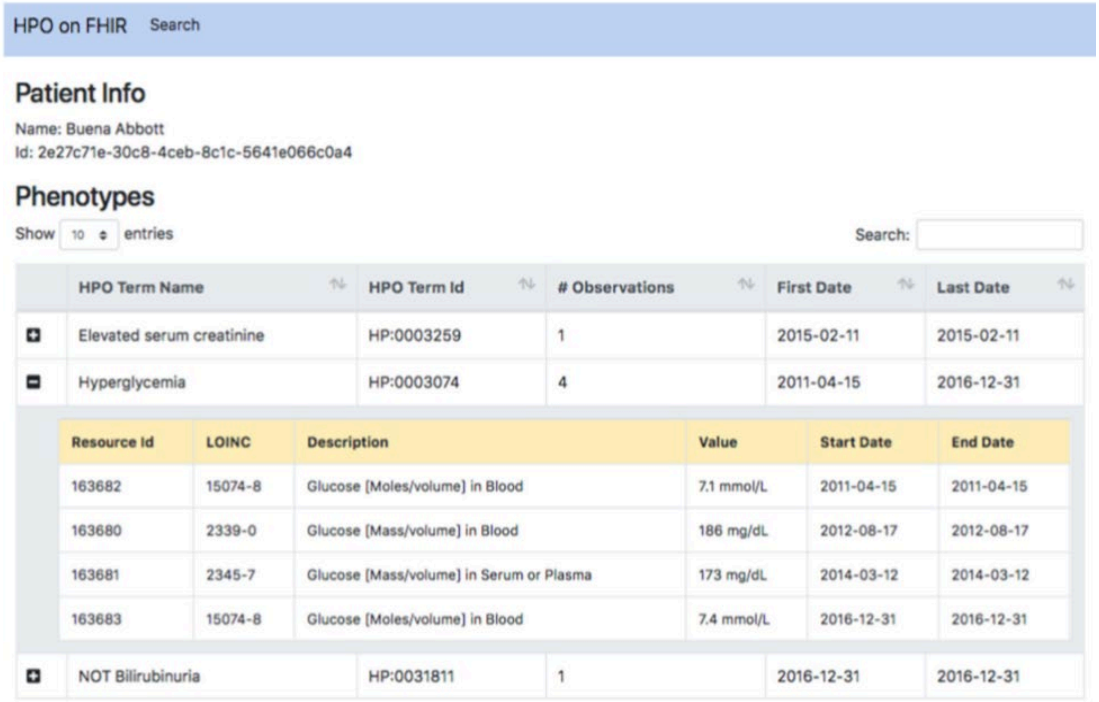
human phenotype ontology

ICD-10

ゲノム医療 研究開発

HL7 FHIRによるHPOへのマッピング





HL7 FHIRによりSNOMED-CTによりコードされた検査のアウトカムをHPOの臨床表現型にマッピング

AMED臨床ゲノム情報統合データベース整備事業
1次 小崎班・2次 小崎班開発事業での利用

ご静聴ありがとうございました

Monarch Initiative

Peter Robinson
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