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Detailed Clinical Phenotyping in Precision Medicine

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Aims

To confer basic knowledge of the description of physical characteristics of patients

To describe the current state of systems for defining, categorizing and capture of these characteristics

To explain the problems faced when implementing a clinically usable data capture system and to provide a working

Introduction

Which data of phenotyping to rely on?

How to capture and store clinical data?

How to enable contextual assignments, categorization and analytic evaluation of the data

How to use the data to answer clinically decisive questions for achieving optimal outcomes?

What is a phenotype? – Peter Robinson, Charité, Berlin

- At least five definitions of phenotype in use in the biology literature
- The collection of observable traits of an organism, comprising its morphology, its physiology at the level of the cell, the organ, and the body, and its behaviour, comprising even characteristics such as the gene expression profiles in response to environmental cues

Robinson P Human Mutation 2012;33:778

Phenotype for purely clinical purposes

- Collection of traits elicited from the health history and physical findings of a given patient

Precision medicine

- Using the comprehensive phenotype and all available, validated medical knowledge to tailor patient care with the aim of achieving an optimal outcome

Systems for Clinical Phenotyping

Clinical data from diagnostic classification systems of diseases

Standardized nomenclature systems

- SNOMED
- ICD (International Classification of Diseases)
- ICF (International Classification of Functioning)

DECIPHER (DatabasE of genomiC varlation and Phenotype in Humans using Ensembl Resources)

Human Phenotype Ontology (HPO)

Background

Many patients suffering from Rare Disease harbour genomic variants (sequence variants or copy number variants) that by disrupting normal gene expression lead to disease. However, many variants are novel or extremely rare, making clinical interpretation problematic and genotype-phenotype correlations uncertain. Identification of patients sharing variants in a given gene and having phenotypic features in common leads to greater certainty in the pathogenic nature of the gene and enables to the role of novel genes in development and disease to be defined. Furthermore, analysis of the type of genomic variant and of its consequence (eg. Loss of function or gain of function) enables insight into the mechanism of disease and potential therapeutic targets.

DECIPHER Project Proposal

DECIPHER

DECIPHER (DatabasE of genomiC varIation and Phenotype in Humans using Ensembl Resources) is an interactive web-based database which incorporates a suite of tools designed to aid the interpretation of genomic variants.

DECIPHER enhances clinical diagnosis by retrieving information from a variety of bioinformatics resources relevant to the variant found in the patient. The patient's variant is displayed in the context of both normal variation and pathogenic variation reported at that locus thereby facilitating interpretation.

The DECIPHER Community

Contributing to the DECIPHER database is an international community of academic departments of clinical genetics and rare disease genomics now numbering more than 270 centres and having uploaded more than 36,000 cases. Each contributing centre has a nominated rare disease clinician or clinical geneticist who is responsible for overseeing data entry and membership for their centre. DECIPHER enables a flexible approach to data-sharing. Each centre maintains control of its own patient data (which are password protected within the centre's own DECIPHER project) until consent is given to share the data with chosen parties in a collaborative group or to allow anonymous genomic and phenotypic data to become freely viewable within Ensembl and other genome browsers (see below). Once data are shared, consortium members are able to gain access to the patient report and contact each other to discuss patients of mutual interest.

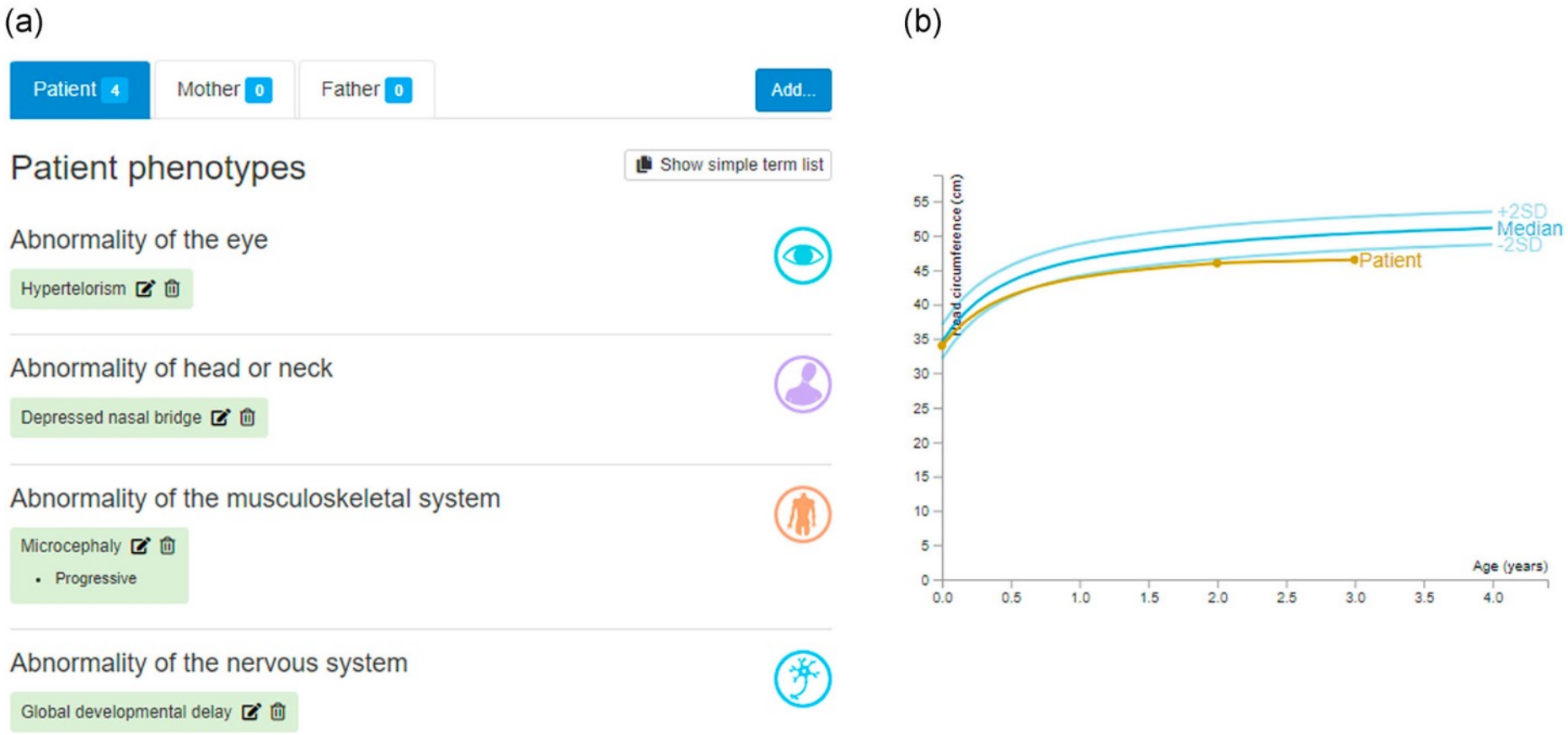
Public Data Access

With patient consent, positional genomic information together with a brief description of the associated phenotype becomes viewable without password protection, for example, via the DECIPHER track in Ensembl. This is of benefit not only to clinicians advising patients with similar findings but also to researchers working on specific phenotypes, Rare Diseases, drug targets or the role of genes in health and development.

DECIPHER (**D**atabas**E** of genomi**C** var**I**ation and **P**henotype in **H**umans using **E**nsembl **R**esources)

- Interactive web-based database which incorporates a suite of tools designed to aid the interpretation of genomic variants
- DECIPHER **enhances clinical diagnosis by retrieving information from a variety of bioinformatics resources relevant to the variant found in the patient**
- Patient's variant displayed in the context of both normal variation and pathogenic variation reported at that locus, thereby facilitating interpretation

https://www.deciphergenomics.org



(a) DECIPHER enables the deposition of phenotypes using HPO terms. (b) DECIPHER supports the deposition of developmental milestones and anthropometric measurements, for example, occipitofrontal (head) circumference

Foreman J Human Mutation 2022;43:682-697

DECIPHER GRCh38 About Browse DDD (UK) Search DECIPHER

Phenotypic abnormality in open-access patients in DECIPHER

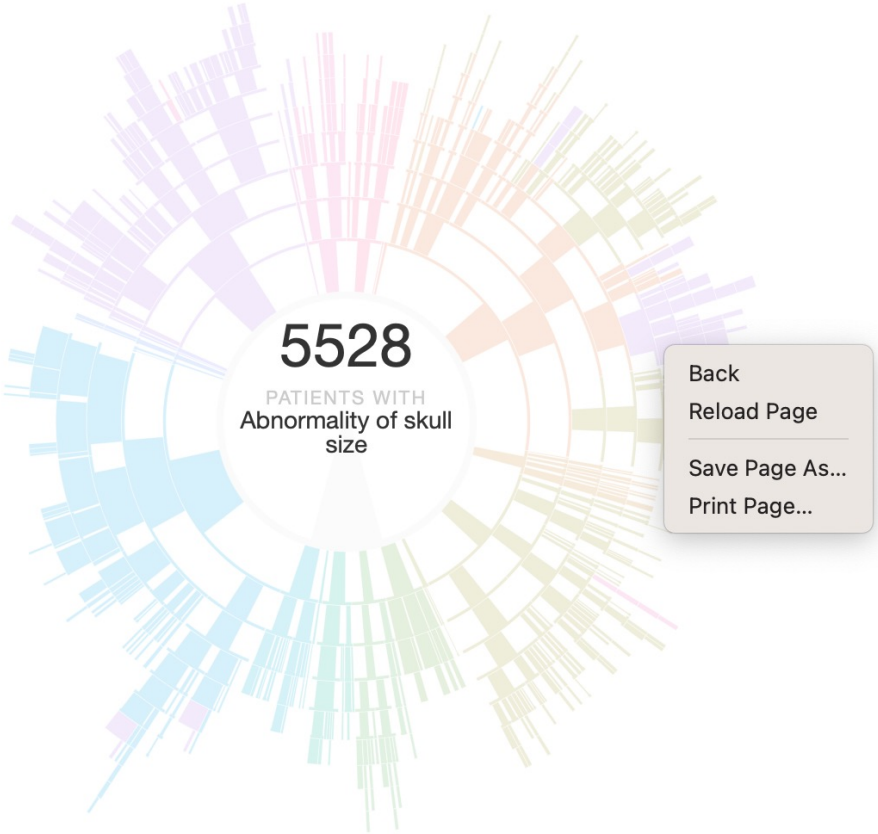
Hide redundant paths | Simple view | About

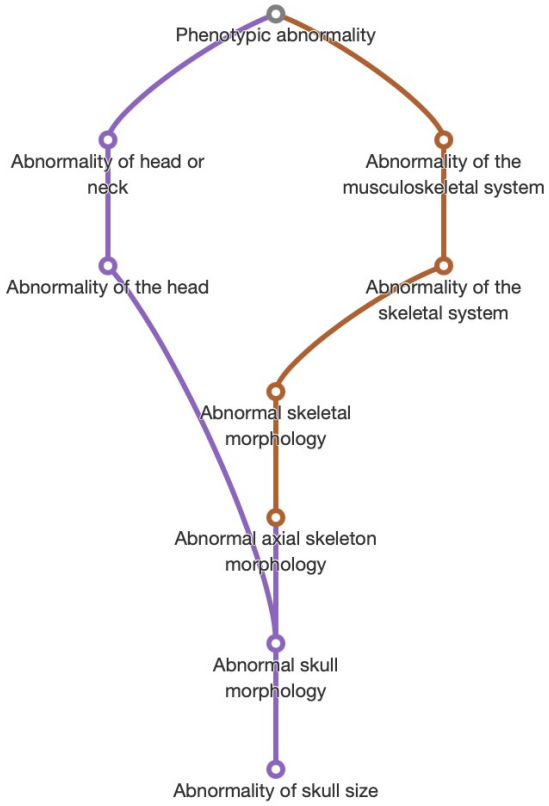
- Abnormality of the cardiovascular system
- Abnormality of blood and blood-forming tissues
- Abnormality of the endocrine system
- Abnormality of the musculoskeletal system
- Abnormality of the digestive system
- Abnormality of limbs
- Abnormality of prenatal development or birth
- Growth abnormality
- Abnormality of the genitourinary system
- Abnormality of the ear
- Abnormality of metabolism/homeostasis
- Abnormal cellular phenotype
- Abnormality of the eye
- Abnormality of the nervous system
- Neoplasm
- Constitutional symptom
- Abnormality of the immune system
- Abnormality of the voice
- Abnormality of the respiratory system
- Abnormality of head or neck
- Abnormality of the breast
- Abnormality of the integument

DECIPHER GRCh38 About Browse DDD (UK) Search DECIPHER Hel

Phenotypic abnormality in open-access patients in DECIPHER

Hide redundant paths | Simple view | About





Search results for "HP:0010978" (Refine Search)

Patients 1417 | CNV syndromes 1 | DDD research variants 0 | Genes 0

Results | Browser

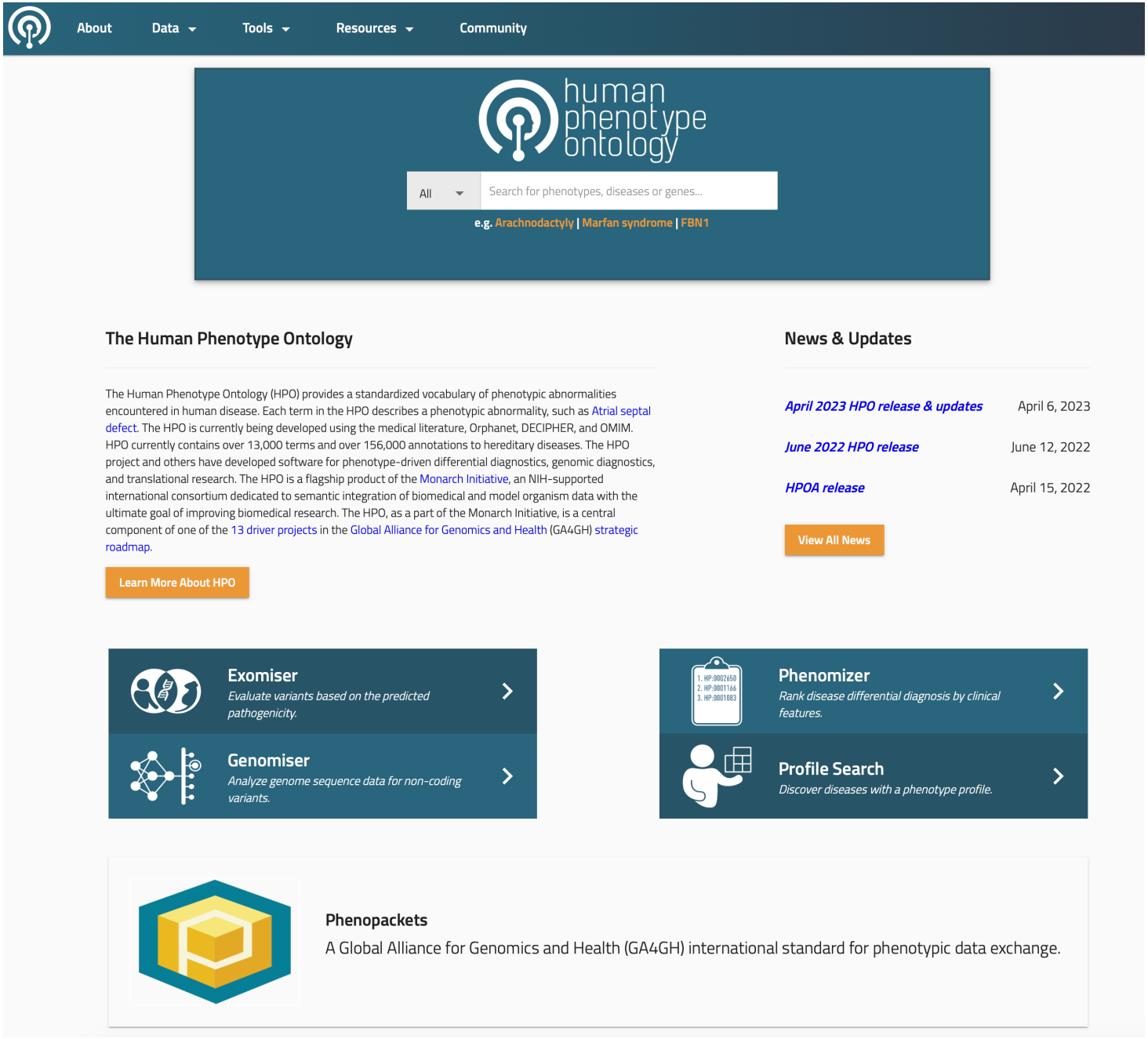
Patients: 11 to 20 of 1417

Filter...

DECIPHER Patient ID	Sex	Phenotype(s)	Variants	Contact
1375	46XY	Accessory oral frenulum, Alveolar ridge overgrowth, Delayed cranial suture closure, Diastasis recti, Feeding difficulties in infancy, Frontal bossing, Generalized hirsutism, High palate, Hoarse voice, Hyperactivity, Hypotonia, Intellectual disability, Low-set ears, Midface retrusion, Pes planus, Recurrent infections, Ridged cranial sutures, Strabismus	1	
1593	46XX	Abnormal heart morphology, Abnormal pinna morphology, Abnormality of the tarsal bones, Abnormality of the upper respiratory tract, Blepharophimosis, Blue sclerae, Feeding difficulties in infancy, Hypertelorism, Hypotonia, Intellectual disability, Microcephaly, Micrognathia, Patent ductus arteriosus, Recurrent infections, Seizure, Short stature, Single transverse palmar crease, Sleep disturbance, Wide nasal bridge	4	
1721	Other	Atopic dermatitis, Ichthyosis	3	
1925	46XY	Abnormal pinna morphology, Dolichocephaly, Exaggerated cupid's bow, Hypermetropia, Intellectual disability, Posteriorly rotated ears, Recurrent infections	1	
1993	Other	Cleft of alveolar ridge of maxilla, Constipation, Hypoglycemia, Lipodystrophy, Recurrent infections, Small nail, Sparse hair	2	
1995	Other	Abnormal hair pattern, Abnormality of the forehead, Arachnodactyly, Constipation, Multiple renal cysts, Recurrent infections, Tapered finger	3	
2068	46XX	Atopic dermatitis, Clinodactyly of the 5th finger, Delayed speech and language development, Fine hair, Intellectual disability, Microcephaly, Prominent nose, Short hallux, Short nail, Short palm, Short thumb, Tetralogy of Fallot, Tooth malposition	3	
2069	46XX	Atopic dermatitis, Autism, Behavioral abnormality, Bilateral tonic-clonic seizure, Brachycephaly, Constipation, Delayed speech and language development, Echolalia, Hypertelorism, Intellectual disability, Low anterior hairline, Strabismus, Widely spaced teeth	1	
2126	46XX	Abnormality of the periorbital region, Ataxia, Constipation, Delayed speech and language development, Intellectual disability, Microcephaly, Recurrent infections, Recurrent urinary tract infections, Short stature, Stridor	2	
2154	46XX	Abnormal dental enamel morphology, Atopic dermatitis, Bulbous nose, Congenital diaphragmatic hernia, Feeding difficulties in infancy, Hypermetropia, Hypotonia, Intellectual disability, Macrotia, Microcephaly, Scoliosis, Small for gestational age, Thin upper lip vermilion	1	

10

Previous 1 2 3 4 5 ... 142 Next



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

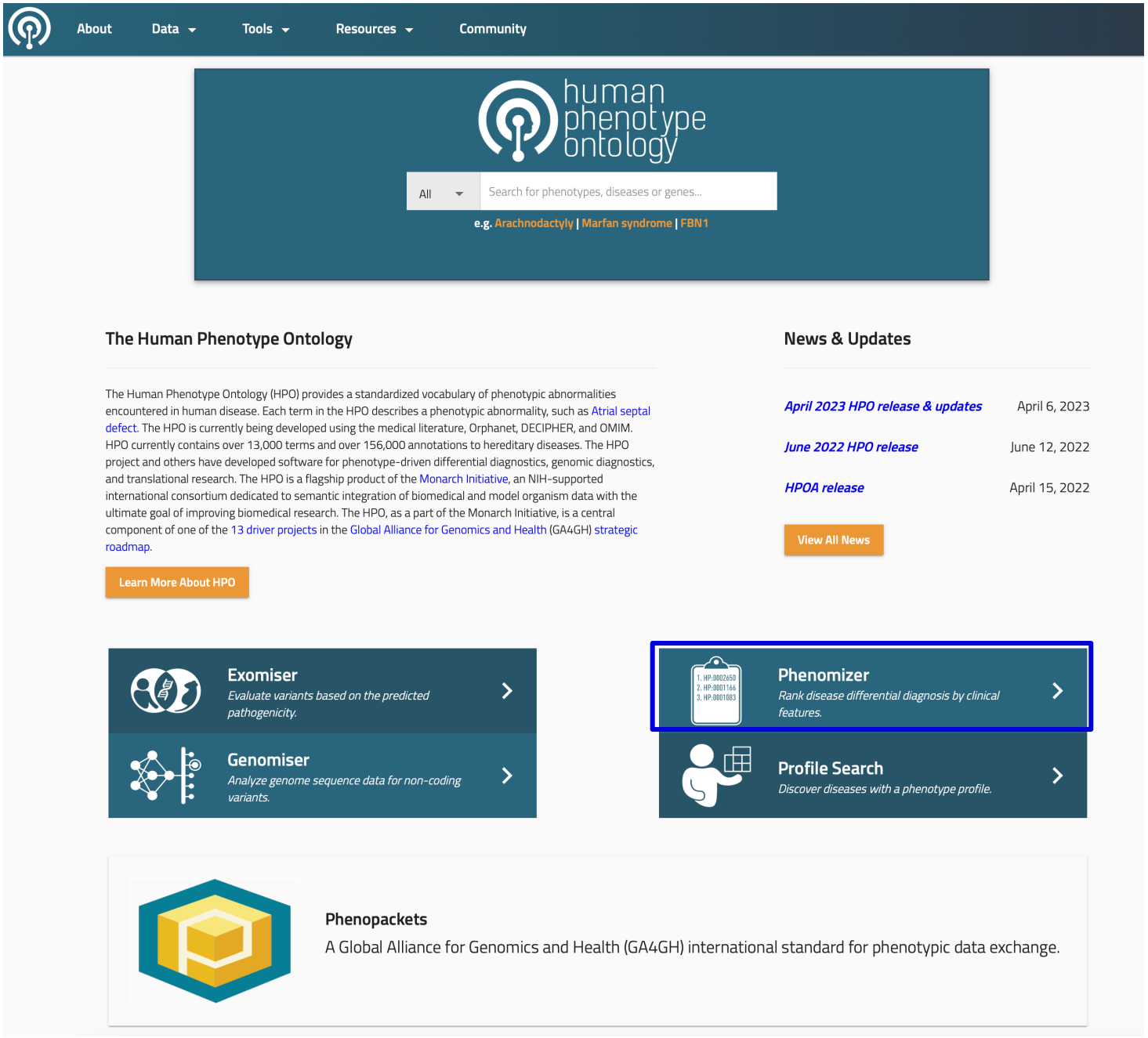
Human phenotype ontology

Standardized vocabulary of phenotypic abnormalities in human disease

In development using

- Medical literature
- Orphanet (https://www.orpha.net/consor/cgi-bin/index.php)
- DECIPHER (https://www.deciphergenomics.org)
- OMIM (Online Mendelian Inheritance in Man; https://www.omim.org)

HPO currently contains over 13,000 terms and over 156,000 annotations to hereditary diseases

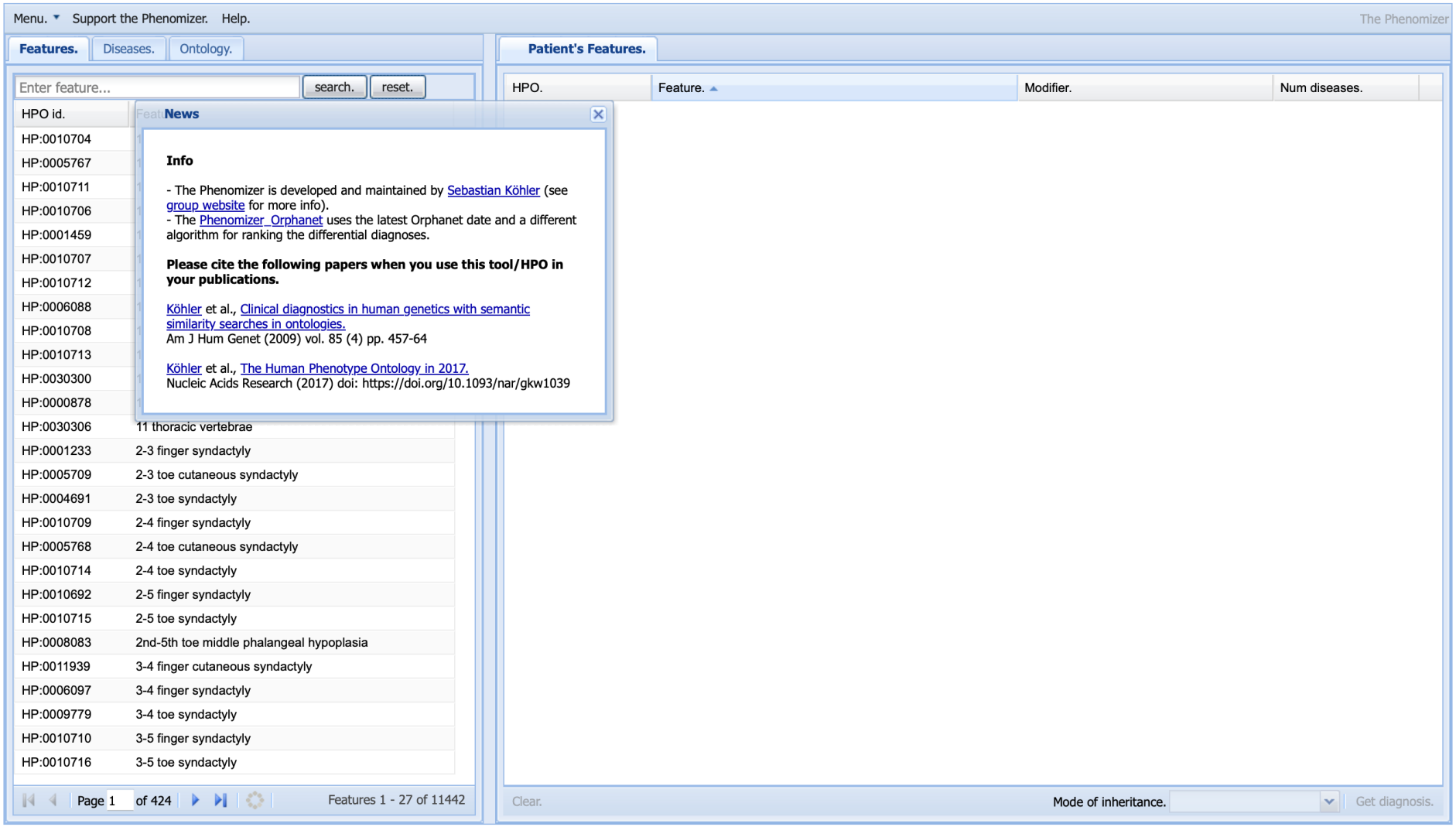


https://hpo.jax.org/app/

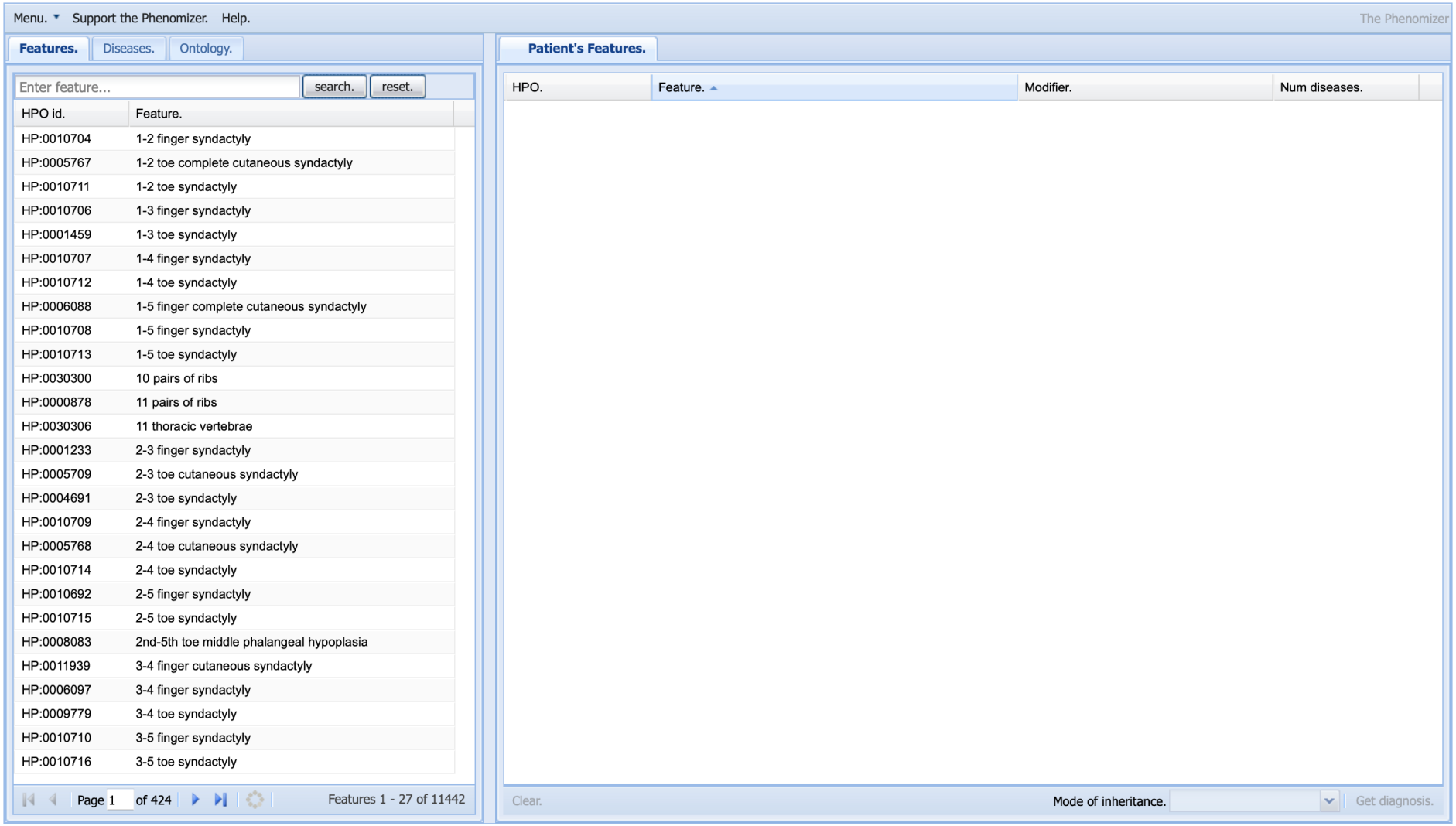
Phenomizer

April 2023

- 11’442 features
- 8’057 diseases



https://compbio.charite.de/phenomizer/



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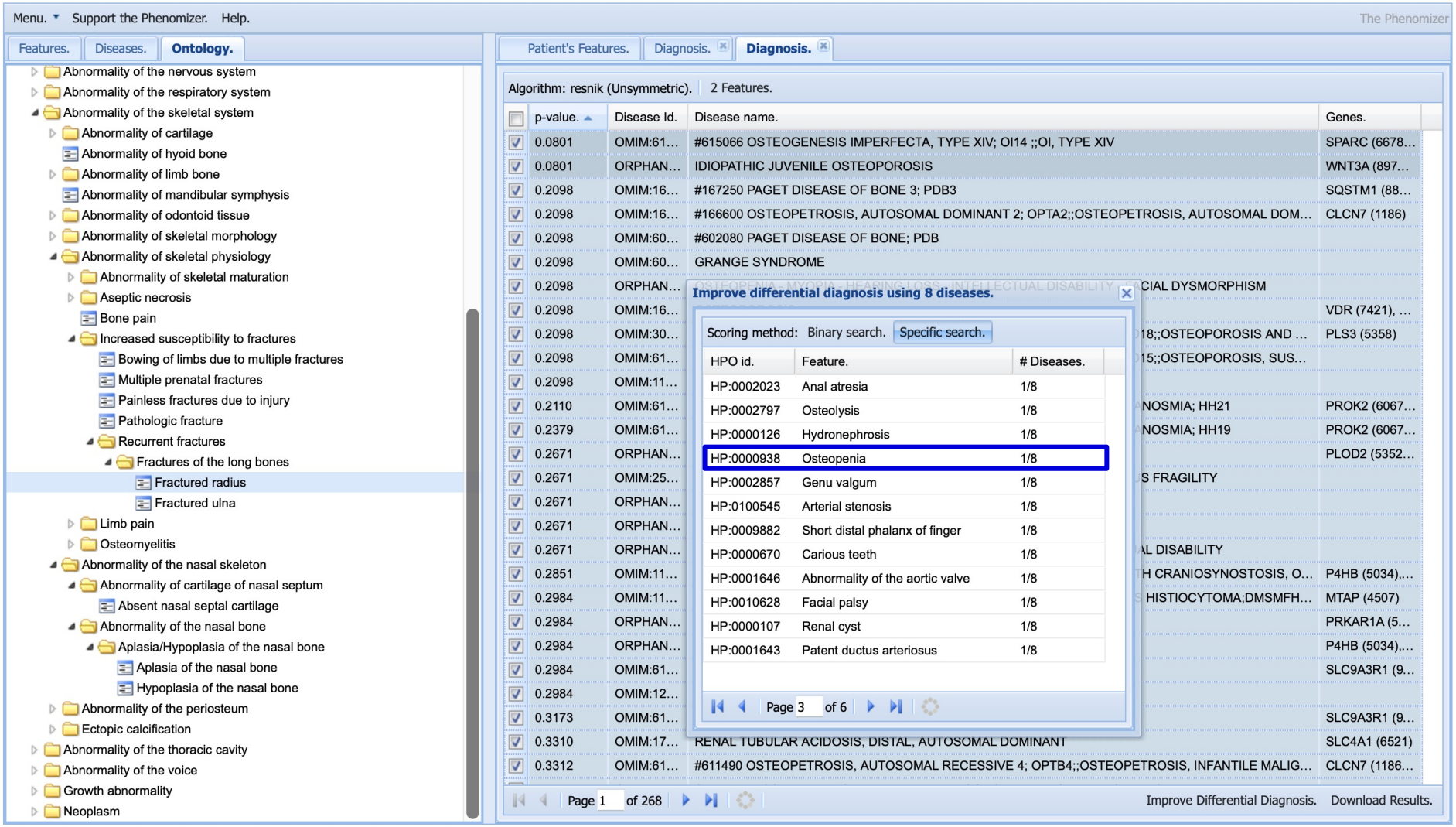

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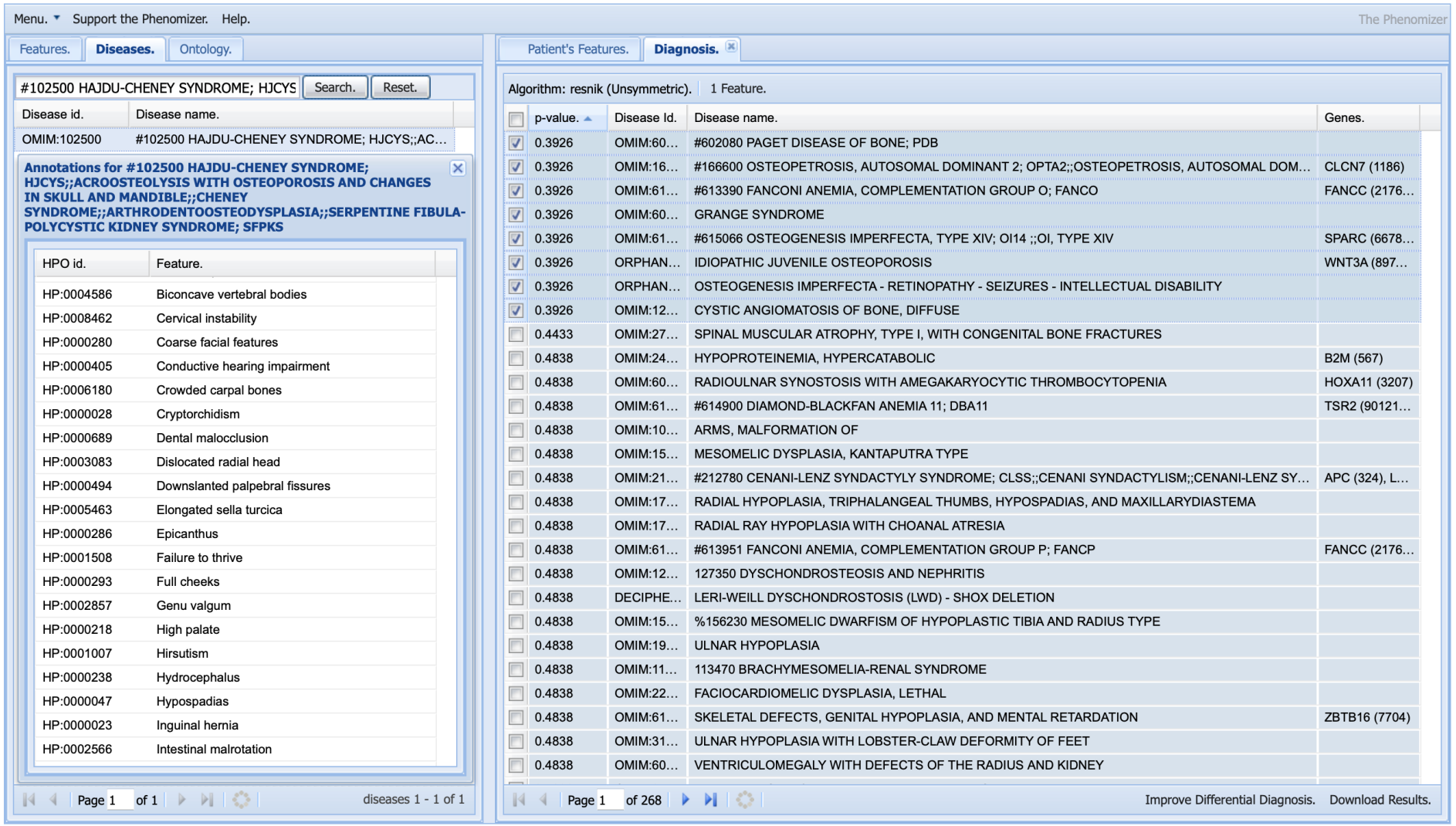


https://compbio.charite.de/phenomizer/

Impediments to use in clinical medicine

Documentation of health history and physical findings

- Insufficient resolution
- No system for documentation or reporting

Features mostly related to genetic defects

Incomplete ontology due to

- Lacking resolution
- Binary and specific search aids insufficient
- Omission of standard diagnostic attributes

Multiple time points not possible

Curation centralized

Changes require extensive resources

Language restricted to English

Data capture for clinical medicine

How to capture and store clinical data?

How to enable contextual assignments, categorization and analytic evaluation of the data

How to operationalize our data to ask and answer decisive questions about outcomes?

Prerequisites

1. Unrestricted ability to migrate
   - Data (-base)
   - Programmes/ algorithms
2. No proprietary storage system
3. Full addressability of data at blinding speed (search engine technology)

Concept

To provide a **comprehensive basis for digital diagnostics**:

- **Structured data entry** (SDE) **tool** to capture clinical data as discrete items/features with references to defined properties, anatomic location and time
- Application of advanced IT tools to consolidate and analyse data from different sources to enable evaluation of large cohorts

To enable **seamless integration of existing genomic and imaging data of large cohorts of patients** with all other **modalities*** in an easy to use clinical decision support system (CDSS):

- By directly targeting the data stream of high-throughput, allelic level resolution whole genome sequencing (WGS)
- By examining the prospect for image analysis in addition to routinely collected (unstructured) data in clinical care
- By aggregating data to obtain data-driven diagnostic and prognostic information to support precise and fast clinical decision making and personalised medicine

Documentation of a health history and physical findings

Efficient and reliable electronic capture

Time-stamped, discrete data objects and their attributes

Incorporated real-time report generator

Multiple language data entry and report

Data storage system provides basis for broad analysis and inter-actability of data with other storage

The user interface is accessible in two roles, a consumer role (CR) and an administrator role (AR); designated domain experts get access in AR

In AR the domain expert has access to backend subsystems that permit

- To create, modify and delete fields
- To set field-properties, such as the type (text field, checkbox, radio-button, etc.)
- To position
- To create new forms

Content and phrasing of the report generator can be defined in AR

Clinicians use the CR to create new content of existing forms, alter content, search for content, and generate reports

Captured content is processed in a semantically cohesive format by real-time report generation with the intention to spare physician and allied health care personnel resources

Anamnese | Untersuch | Prozedere

- Allgemein
- Haut und Nägel
- Kopf und Hals
- Lymphknoten
- Thorax
- Kreislauf
- Abdomen
- Neurostatus
- Bewegungsapparat

Allgemeinzustand

- (•) gut
- ( ) pathologisch

[ ] Details

Bewusstsein

- ( ) normal
- (•) pathologisch
  - ( ) somnolent
  - ( ) soporös
  - (•) auf Schmerzreiz reagierend
  - ( ) bewusstlos

Glasgow Coma Scale

Eye Opening Response

- ( ) Spontaneous, open with blinking at baseline
- (•) Opens to verbal command, speech, or shout
- ( ) Opens to pain, not applied to face
- ( ) None

Verbal Response

- ( ) Oriented

Customization via Module

Entry via:

Login > **Domain Routine** > **Customise my Modules** > click on **Master** of choice, file builds

To edit:

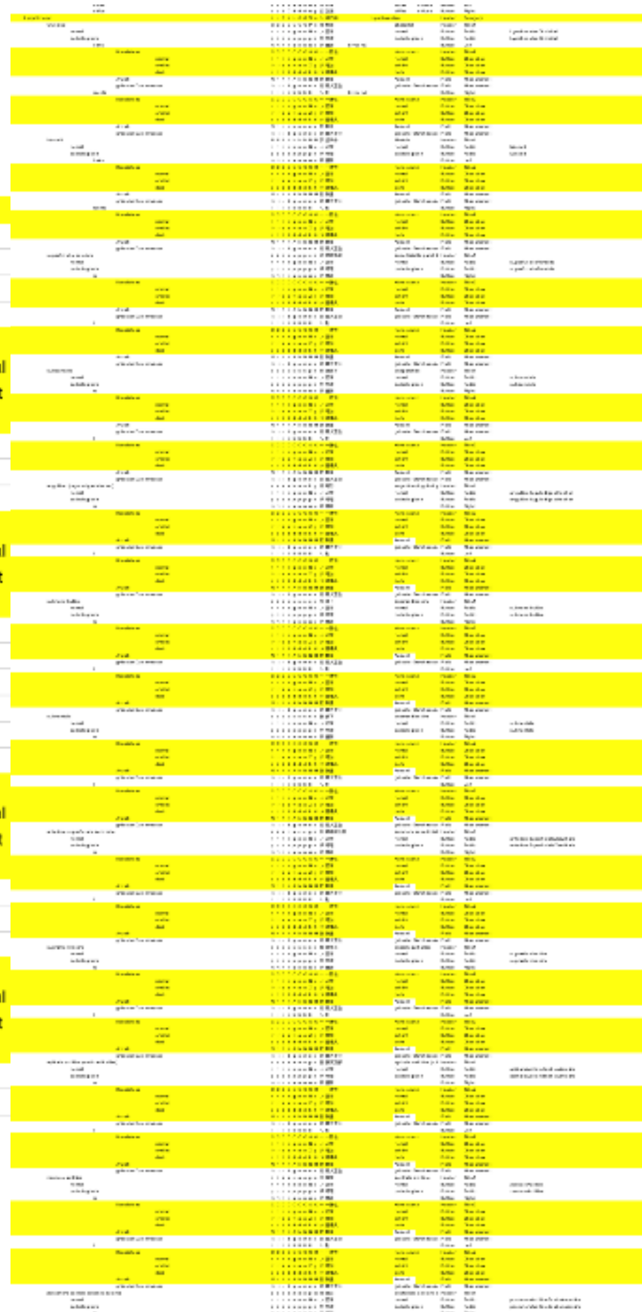
Scroll to element of choice > click on line of interest > click on **pencil icon** > click on **Edit**

Change items available

Use **Save**, **Preview** and **Discard** as appropriate

To save changes to existing module, click **Save**

Lymphknoten				
	Okzipital			
		normal		
		pathologisch		
			links	
				Konsistenz
				normal
				erhöht
				derb
				Anzahl
				grösster Durchmesser
			rechts	
				Konsistenz
				normal
				erhöht
				derb
				Anzahl
				grösster Durchmesser
	Mastoid			
		normal		
		pathologisch		
			links	
				Konsistenz
				normal
				erhöht
				derb
				Anzahl
				grösster Durchmesser
			rechts	
				Konsistenz
				normal
				erhöht
				derb
				Anzahl
				grösster Durchmesser



	Lymphknoten		Header	Category
		Okzipital	Header	Title1
		normal	Button	Radio
		pathologisch	Button	Radio
vor re?			Button	Left
		Konsistenz	Header	Title2
		normal	Button	Checkbox
		erhöht	Button	Checkbox
		derb	Button	Checkbox
		Anzahl	Field	Measurement
		grösster Durchmesse	Field	Measurement
vor re?			Button	Right
		Konsistenz	Header	Title2
		normal	Button	Checkbox
		erhöht	Button	Checkbox
		derb	Button	Checkbox
		Anzahl	Field	Measurement
		grösster Durchmesse	Field	Measurement
		Mastoid	Header	Title1
		normal	Button	Radio
		pathologisch	Button	Radio
			Button	Left
		Konsistenz	Header	Title2
		normal	Button	Checkbox
		erhöht	Button	Checkbox
		derb	Button	Checkbox
		Anzahl	Field	Measurement
		grösster Durchmesse	Field	Measurement
			Button	Right
		Konsistenz	Header	Title2
		normal	Button	Checkbox
		erhöht	Button	Checkbox
		derb	Button	Checkbox
		Anzahl	Field	Measurement
		grösster Durchmesse	Field	Measurement

Customization via Table

Entry via:

Login > **Domain Routine** > **Customize my Modules** > click on field > choose table* for new version or new module

*For new version or module rename table before upload

For Upload:

Click on field + > Choose File > fill in new **Module Name** > **Submit > Back Button**

When count complete, module ready for use

Beispiel Glasgow Coma Scale (GCS)

Glasgow Coma Scale			Gl	Gl	Éc	Sc	Gl	Es	Es	Sh	Ш	グ	格拉斯哥昏迷量表	Glasgow Coma Scale		Header	Title1		
	Eye Opening Response		Ey	Ey	Rc	Ri	Oı	Rı	Rı	Rı	Or	開	睁眼反应		Eye Openi	Header	Title2		
		Spontaneous, open with blinking at baseline	Sp	Sp	Sp	Sp	Sp	Es	Es	Sp	Cı	自	自发的，开放的，基线上有闪烁的现象		Spontaneo	Button	Radio		GCSEye
		Opens to verbal command, speech, or shout	Oı	Oı	S'	Si	Oı	Se	Al	Ol	Or	口	开启口头命令、讲话或喊话。		Opens to v	Button	Radio		GCSEye
		Opens to pain, not applied to face	Oı	Oı	S'	Si	Oı	Se	Al	Ol	Or	痛	开启疼痛，不应用于面部		Opens to p	Button	Radio		GCSEye
		None	Nı	Nı	Au	Nı	Gı	Ni	Nı	Br	Hı	な	无		None	Button	Radio		GCSEye
	Verbal Response		Ve	Ve	Rı	Ri	M	Rı	Rı	Rı	Yı	口	口头回应		Verbal Re:	Header	Title2		
		Oriented	Oı	Oı	Oı	Oı	Gı	Oı	Oı	Zc	Oı	オ	面向		Oriented	Button	Radio		GCSVerbal
		Confused conversation, but able to answer questions	Cı	Cı	Cı	Cı	Ve	Cı	Cı	Zc	Cl	会	谈话混乱，但能回答问题		Confused	Button	Radio		GCSVerbal
		Inappropriate responses, words discernible	In	In	Rı	Ri	Oı	Rı	Rı	Ni	Hı	不	反应不当，言语可辨。		Inappropri	Button	Radio		GCSVerbal
		Incomprehensible speech	In	In	Uı	Di	Oı	Di	Di	Ni	He	不	难以理解的语言		Incompreh	Button	Radio		GCSVerbal
		None	Nı	Nı	Au	Nı	Gı	Ni	Nı	Br	Hı	な	无		None	Button	Radio		GCSVerbal
	Motor Response		M	M	Rı	Ri	M	Rı	Rı	Rı	pe	モ	电机反应		Motor Res	Header	Title2		
		Obeys commands for movement	Ol	Ol	Ol	Ol	Gı	Ol	Ol	W	Пı	移	服从运动指令		Obeys con	Button	Radio		GCSMotor
		Purposeful movement to painful stimulus	Pı	Pı	Uı	M	Dı	M	M	Cı	Щı	痛	对疼痛刺激有目的的运动		Purposefu	Button	Radio		GCSMotor
		Withdraws from pain	W	W	Se	Ri	Oı	Se	Rı	W	Cı	痛	从痛苦中退出		Withdraws	Button	Radio		GCSMotor
		Abnormal (spastic) flexion, decorticate posture	Ab	Ab	Fl	Fl	Al	Fl	Fl	Ni	Hı	異	异常（痉挛性）屈曲、颓废姿势		Abnormal	Button	Radio		GCSMotor
		Extensor (rigid) response, decerebrate posture	Ex	Ex	Rı	Ri	Ex	Rı	Rı	Rı	Pε	伸	外展(刚性)反应，去脊柱的姿势		Extensor (r	Button	Radio		GCSMotor
		None	Nı	Nı	Au	Nı	Gı	Ni	Nı	Br	Hı	な	无		None	Button	Radio		GCSMotor
	GCS Score		Gl	Gl	Sc	Pı	Gı	Pı	Pc	W	6a	Gl	GCS分数	GCS Score	GCS Score	Field	Measurement		

Elemente aufgelistet, Berechnung hinterlegt

Im Bericht GCS Score

Auflistung der Art von Feldern

Verschiedene Sprachen hinterlegt

- Allgemein
- Haut und Nägel
- Kopf und Hals
- Lymphknoten
- Thorax
- Kreislauf
- Abdomen
- Neurostatus
- Bewegungsapparat

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Diagnoseraster für degenerative Wirbelsäulenerkrankungen

Zerviko-								
	vertebrales Syndrom							
	zephales Syndrom							
	spondylogenes Syndrom							
		bei/mit						
			Fehlhaltung/Fehlform					
				Lordosierung/ Kopfprotraktion				
				Streckhaltung				
				Kyphosierung				
				Schiefhals/Torticollis				
					rechts			
					links			
				Beckegeradstand				
				Beckentiefstand				
					rechts	cm		
					links	cm		
				Skoliose				
					lumbale			
						links-konvexe		
						rechts-konvexe		
					thorakale			
						links-konvexe		
						rechts-konvexe		
					thorakolumbale			
						links-konvexe		
						rechts-konvexe		
					kompensiert			
						Lot	rechts	cm
							links	cm
				Schultertiefstand				
					rechts	cm		
					links	cm		
			muskulärer Dysbalance					
				insuffiziente segmentale Stabilisation				
					ventral			
					dorsal			
			Tendpomyosen					

Implications of structured data entry

For patients
- Improved and personalized diagnostics
- Access to own data possible
- Structured follow-up data for outcome assessment and quality control

For physicians
- Documentation with discrete, time-stamped data points is available real-time and is paired with reporting,
- Fully addressable and analyzable data for quality control and research
- More face time with patients
- Analysis for individual care, quality control and research

For health professionals
- Structured data entry tailored for disease, as for physicians
- Suggestions for structured diagnosis

For technology
- Data from diverse sources for improved diagnosis, outcome measurement, research
- Option to expand to any other disease

For my institution
- Data to drive process organization and optimization for increased quality and cost savings

Summary

Phenotyping systems for physical characteristics available for research purposes

Not operational for clinical routine not given

- Insufficient resolution
- No system for clinical documentation or reporting
- Limited sequential input
- Adaptations resource-intensive
- Limited language editions

Structured data entry with enabled domain implemented adaptations technically feasible for embedding in a given system

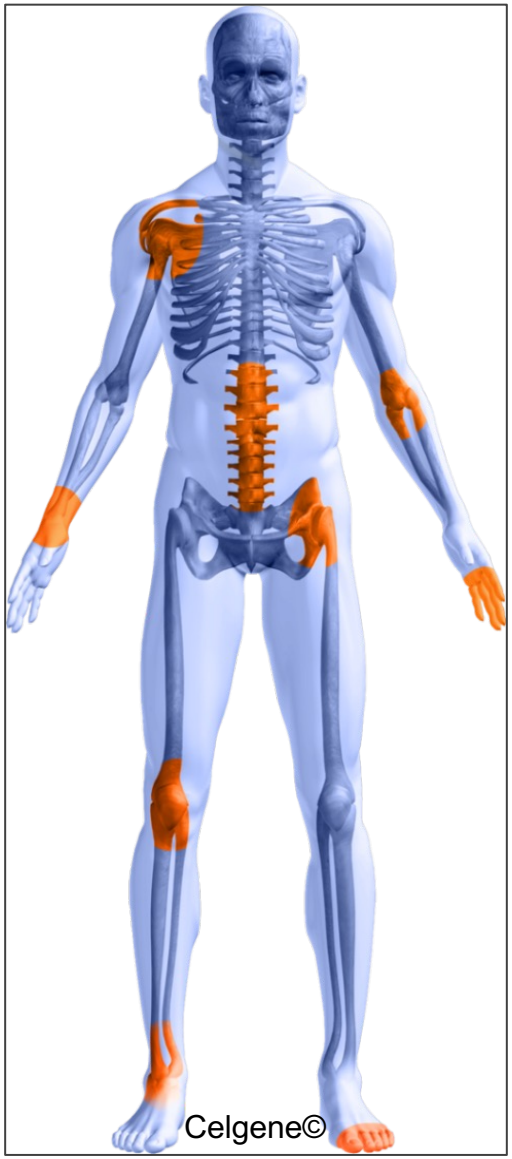
What next?

Avatar for medical purposes

Structured data entry
- Health history
- Physical findings

Apparative diagnostics
- Physiologic
- functional

Molecular diagnostics
- Genetics
- Epigenetics
- Other



Routine laboratory
- General
- Specialized

Imaging
- Radiation based
- Ultrasound
- MRI, others
- combined

Response to therapy
- Efficacy, Effectiveness
- Undesired effects