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Supplemental information

The Medical Action Ontology: A tool for annotating and analyzing treatments and clinical management of human disease

Leigh C. Carmody, Michael A. Gargano, Sabrina Toro, Nicole A. Vasilevsky, Margaret P. Adam, Hannah Blau, Lauren E. Chan, David Gomez-Andres, Rita Horvath, Megan L. Kraus, Markus S. Ladewig, David Lewis-Smith, Hanns Lochmüller, Nicolas A. Matentzoglu, Monica C. Munoz-Torres, Catharina Schuetz, Berthold Seitz, Morgan N. Similuk, Teresa N. Sparks, Timmy Strauss, Emilia M. Swietlik, Rachel Thompson, Xingmin Aaron Zhang, Christopher J. Mungall, Melissa A. Haendel, and Peter N. Robinson

MAxO term	OMIM:609192	OMIM:312870	OMIM:236200	OMIM:154700	OMIM:617168	OMIM:131300	HPO terms
clinical assessment [MAXO:0000487]	+	+	+	+	+	+	Total of 44 HPO terms. Submucous cleft lip [HP:0009101]; Disproportionate tall stature [HP:0001519]; Cryptorchidism [HP:0000028]; Lower limb pain [HP:0012514]; Limitation of joint mobility [HP:0001376] ...
chest radiograph procedure [MAXO:0010356]	+	+	+	+	+	+	Scoliosis [HP:0002650]; Kyphoscoliosis [HP:0002751]; Cervical ribs [HP:0000891]; Short ribs [HP:0000773]
echocardiography [MAXO:0010203]	+	+	+	+	+	-	Total of 19 HPO terms. Mitral annular calcification [HP:0005136]; Cardiomyopathy [HP:0001638]; Tricuspid regurgitation [HP:0005180]; Pulmonic stenosis [HP:0001642]; Total anomalous pulmonary venous return [HP:0005160] ...
slit-lamp examination [MAXO:0000973]	+	-	+	+	-	-	Total of 6 HPO terms. Blue sclerae [HP:0000592]; Ectopia lentis [HP:0001083]; Lens subluxation [HP:0001132]; Microspherophakia [HP:0030961]; Astigmatism [HP:0000483] ...
MRI of the spinal cord [MAXO:0035014]	-	-	-	+	+	-	2 Dural ectasia [HP:0100775]
bone marrow examination [MAXO:0000753]	-	-	-	-	-	+	Bone marrow hypocellularity [HP:0005528]

Table S1: **Application of MAxO diagnostic annotations for supporting differential diagnosis, related to Figure 3**. In this example, six hereditary diseases characterized by *Tall stature* (HP:0000098) are analyzed to identify MAxO terms that represent phenotypic abnormalities (HPO terms) that are found in each disease: OMIM:617168 Aortic aneurysm, familial thoracic 10; OMIM:131300 - Camurati-Engelmann disease; OMIM:236200 - Homocystinuria due to cystathionine beta-synthase deficiency; OMIM:609192 - Loeys-Dietz syndrome 1; OMIM:154700 - Marfan syndrome; and OMIM:312870 - Simpson-Golabi-Behmel syndrome, type 1. For instance, Marfan syndrome is characterized by *Scoliosis* [HP:0002650], which in turn can be diagnosed by *chest radiograph procedure* [MAXO:0010356]. Some of the diagnostic examinations provide information about multiple HPO terms that may help differentiate between multiple diseases; for instance, the same chest radiograph would provide information about Scoliosis [HP:0002650]; Kyphoscoliosis [HP:0002751]; Cervical ribs [HP:0000891]; Short ribs [HP:0000773] and thereby potentially provide information relevant to the diagnosis of five of the six diseases. On the other hand, a bone marrow biopsy would characterize at most one disease and the absence of this finding would not differentiate between the other five diseases (which do not have bone marrow abnormalities). Thus, MAxO diagnostic annotations may be useful in planning diagnostic procedures in the course of differential diagnosis.

MAxO Term	Relation	HPO term	citation
(A)			
enzyme replacement or supplementation therapy (MAXO:0000933)	TREATS	Urinary glycosaminoglycan excretion (HP:0003541)	PMID:29478819
allogeneic hematopoietic stem cell transplantation (MAXO:0001479)	TREATS	Urinary glycosaminoglycan excretion HP:0003541	
(B)			
dietary phytanic acid intake avoidance (MAXO:0010119)	TREATS	Elevated circulating phytanic acid concentration HP:0010571	PMID:20301527
dietary phytanic acid intake avoidance (MAXO:0010119)	TREATS	Ichthyosis (HP:0008064)	PMID:20301527
(C)			
implantable cardioverter-defibrillator placement (MAXO:0000474)	PREVENTS	Ventricular arrhythmia (HP:0004308)	PMID:26320108
antiarrythmic agent therapy (MAXO:0000185)	PREVENTS	Ventricular arrhythmia (HP:0004308)	PMID:29084731
avoid excessive exercise (MAXO:0000802)	PREVENTS	Ventricular arrhythmia (HP:0004308)	PMID:31078652

Table S2: **Application of MAxO therapeutic annotations for supporting clinical management, related to Table 3**. A typical envisaged use case for MAxO annotations is to look up relevant literature about the clinical management of a rare disease following diagnosis of the disease by next-generation sequencing (NGS). In our experience, it is not uncommon that NGS analysis leads to the diagnosis of a disease for which special expertise is not available on site. Clinicians can use MAxO annotations to find relevant literature to plan initial management and refer to specialists if indicated. Three examples are shown: **(A)** MAxO annotations for Mucopolysaccharidosis Type VII; **(B)** MAxO Annotations for Refsum Disease (MONDO:0009958); and **(C)** MAxO Annotations for Arrhythmogenic Right Ventricular Dysplasia, Familial, 9 (MONDO:0012180).