Supplementary Material

Design and Implementation

Data: nPerm = Number of monte carlo permutations
AE = All unique classes in O that appear in E
Result: testDist = Sorted list of calculated test statistics, length = nPerm + 1
pValue = Calculated empirical p-value
for *n in nPerm* **do**
  $\text{ET}_j = |E|$
  for *p in E* **do**
    $\text{ET}_{jp} = random\_sample(AE, length(E_p))$
  end
  $\text{testDist}_n = calculate\_inclusion\_and\_exclusion(ET)$
end
testDist = rank(testDist);
r = length(testStat $\geq$ testDist);
pValue = $\frac{r+1}{nPerm+1}$;
return pValue;

Algorithm 1: Algorithm for generating p-values for inclusion and exclusion scores through permutation.

Use Case: Pulmonary Embolism

Table 1: Multivariable Klarigi results for pneumonia and pulmonary embolism considered without control. Resnik IC was used, with other parameters set to default.

pneumonia (552 members)	**Inclusion**	**IC**
Dyspnea (HP:0002094)	0.89	0.83
Abnormal breath sound (HP:0030829)	0.81	0.8
Cough (HP:0012735)	0.78	0.87
Abnormal systemic blood pressure (HP:0030972)	0.76	0.76
Chest pain (HP:0100749)	0.64	0.95
Increased blood pressure (HP:0032263)	0.64	0.83
Hypertension (HP:0000822)	0.64	0.89
Abnormality of temperature regulation (HP:0004370)	0.63	0.77
Fever (HP:0001945)	0.62	0.83
Crackles (HP:0030830)	0.62	0.92
Overall	*99.28*	-

pulmonary embolism (233 members)	**Inclusion**	**IC**
Dyspnea (HP:0002094)	0.9	0.83
Chest pain (HP:0100749)	0.78	0.95
Abnormal systemic blood pressure (HP:0030972)	0.75	0.76
Increased blood pressure (HP:0032263)	0.66	0.83
Hypertension (HP:0000822)	0.65	0.89
Abnormal breath sound (HP:0030829)	0.6	0.8
Cough (HP:0012735)	0.51	0.87
Crackles (HP:0030830)	0.49	0.92
Abnormal heart valve physiology (HP:0031653)	0.48	0.8
Abnormality of temperature regulation (HP:0004370)	0.47	0.77
Nausea and vomiting (HP:0002017)	0.47	0.89
Fever (HP:0001945)	0.45	0.83
Abnormal pericardium morphology (HP:0001697)	0.45	0.76
Pericardial effusion (HP:0001698)	0.45	0.92
Abnormal pleura morphology (HP:0002103)	0.44	0.74
Abnormal atrioventricular valve physiology (HP:0031650)	0.43	0.87
Abnormal aortic valve physiology (HP:0031652)	0.43	0.92
Nausea (HP:0002018)	0.42	1.0
Chills (HP:0025143)	0.42	1.0
Abnormal thrombosis (HP:0001977)	0.41	0.75
Aortic regurgitation (HP:0001659)	0.39	1.0
Mitral regurgitation (HP:0001653)	0.39	1.0
Abnormal mitral valve physiology (HP:0031481)	0.39	0.92
Diarrhea (HP:0002014)	0.39	0.8
Vomiting (HP:0002013)	0.38	0.92
Constipation (HP:0002019)	0.38	0.95
Venous thrombosis (HP:0004936)	0.37	0.83
Hypotension (HP:0002615)	0.35	0.87
Dermatological manifestations of systemic disorders (HP:0001005)	0.35	0.84
Abdominal pain (HP:0002027)	0.35	0.84
Abnormal cell morphology (HP:0025461)	0.34	0.73
Abnormal myeloid cell morphology (HP:0020047)	0.34	0.92
Pleural effusion (HP:0002202)	0.34	0.89
Atelectasis (HP:0100750)	0.33	0.95
Deep venous thrombosis (HP:0002625)	0.33	1.0
Hyperlipidemia (HP:0003077)	0.33	0.95
Cyanosis (HP:0000961)	0.32	0.92
Abnormal erythroid lineage cell morphology (HP:0012130)	0.3	0.92
Abnormality of body weight (HP:0004323)	0.3	0.73
Tachycardia (HP:0001649)	0.3	0.74
Impairment in personality functioning (HP:0031466)	0.3	0.72
Overall	*100.0*	-

Table 2: All univariate scores for pulmonary embolism, derived by Klarigi with default parameters, using Resnik IC.

Class	**Power**	**Inclusivity**	**Exclusivity**	**Specificity**
Abnormal thrombosis (HP:0001977)	0.37	0.41	0.35	0.75

Table 2 – continued from previous page

Class	Power	Inclusivity	Exclusivity	Specificity
Venous thrombosis (HP:0004936)	0.35	0.37	0.34	0.83
Deep venous thrombosis (HP:0002625)	0.33	0.33	0.34	1.0
Abnormality of coagulation (HP:0001928)	0.22	0.15	0.41	0.61
Hypercoagulability (HP:0100724)	0.19	0.11	0.7	1.0
Lower limb pain (HP:0012514)	0.18	0.14	0.26	0.89
Limb pain (HP:0009763)	0.18	0.14	0.25	0.84
Pleuritic chest pain (HP:0033771)	0.17	0.15	0.22	1.0
Increased body weight (HP:0004324)	0.17	0.15	0.19	0.84
Sinus tachycardia (HP:0011703)	0.17	0.25	0.13	1.0
Obesity (HP:0001513)	0.15	0.13	0.17	0.87
Abnormality of skin adnexa physiology (HP:0025276)	0.12	0.12	0.13	0.83
Hyperhidrosis (HP:0000975)	0.12	0.12	0.13	0.95
Hypohidrosis or hyperhidrosis (HP:0007550)	0.12	0.12	0.13	0.92
Abnormal exteroceptive sensation (HP:0033747)	0.12	0.09	0.16	0.8
Somatic sensory dysfunction (HP:0003474)	0.12	0.09	0.16	0.75
Syncope (HP:0001279)	0.12	0.09	0.16	0.89
Thromboembolism (HP:0001907)	0.12	0.07	0.4	0.89
Hiatus hernia (HP:0002036)	0.11	0.08	0.18	1.0
Hypoesthesia (HP:0033748)	0.11	0.08	0.16	1.0

Table 3: All univariate scores for pneumonia, derived by Klarigi with default parameters, using Resnik IC.

Class	Power	Inclusivity	Exclusivity	Specificity
Renal insufficiency (HP:0000083)	0.22	0.39	0.15	0.84
Airway obstruction (HP:0006536)	0.2	0.34	0.14	0.87
Atrial fibrillation (HP:0005110)	0.2	0.27	0.15	0.95
Respiratory insufficiency (HP:0002093)	0.2	0.24	0.17	0.81
Chronic pulmonary obstruction (HP:0006510)	0.2	0.33	0.14	1.0
Respiratory distress (HP:0002098)	0.2	0.37	0.13	0.92
Congestive heart failure (HP:0001635)	0.2	0.32	0.14	0.95
Aspiration (HP:0002835)	0.19	0.29	0.15	1.0
Respiratory failure (HP:0002878)	0.19	0.22	0.17	1.0
Productive cough (HP:0031245)	0.19	0.17	0.22	1.0
Chronic kidney disease (HP:0012622)	0.18	0.17	0.21	0.87
Atrial arrhythmia (HP:0001692)	0.18	0.29	0.13	0.83
Rhonchi (HP:0030831)	0.18	0.27	0.13	1.0
Stage 5 chronic kidney disease (HP:0003774)	0.17	0.13	0.24	1.0
Confusion (HP:0001289)	0.17	0.18	0.15	1.0
Abnormality of the upper respiratory tract (HP:0002087)	0.16	0.16	0.17	0.61
Sepsis (HP:0100806)	0.16	0.17	0.15	1.0
Respiratory tract infection (HP:0011947)	0.15	0.13	0.18	0.73
Abnormality of the pharynx (HP:0000600)	0.15	0.12	0.19	0.74
Pharyngalgia (HP:0033050)	0.14	0.11	0.18	1.0
Abnormal pharynx physiology (HP:0033152)	0.14	0.11	0.18	1.0
Nonproductive cough (HP:0031246)	0.13	0.09	0.22	1.0
Abnormal tracheobronchial morphology (HP:0005607)	0.13	0.11	0.16	0.67
Delirium (HP:0031258)	0.12	0.1	0.17	1.0
Abnormal bronchus morphology (HP:0025426)	0.12	0.1	0.16	0.72
Malaise (HP:0033834)	0.12	0.08	0.23	1.0
Hepatitis (HP:0012115)	0.11	0.09	0.14	0.81
Abnormality of the abdominal wall (HP:0004298)	0.1	0.08	0.16	0.73

Table 3 – continued from previous page

Class	Power	Inclusivity	Exclusivity	Specificity
Abnormal pulmonary interstitial morphology (HP:0006530)	0.1	0.07	0.17	0.65

Table 4: Enrichment results for pneumonia and pulmonary embolism

	Binomial			Fisher		
Pulmonary embolism	zscore	OR	p	zscore	OR	p
Abnormal thrombosis (HP:0001977)	9.72	1	1.4e-11	9.72	1	1.5e-18
Abnormality of coagulation (HP:0001928)	6.18	1.44	0.0014	6.18	1.44	2.1e-06
Hypercoagulability (HP:0100724)				4.65	1.09	0.00062
	Binomial			Fisher		
Pneumonia	zscore	OR	p	zscore	OR	p
Cough (HP:0012735)	7.49	1.26	0.0088	7.49	1.26	1.4e-10
Abnormal breath sound (HP:0030829)				5.94	2.78	3.9e-06
Respiratory distress (HP:0002098)				5.48	0.206	7.9e-06
Airway obstruction (HP:0006536)				5.41	1.7	1e-05
Congestive heart failure (HP:0001635)				5.1	0.258	6.3e-05
Renal insufficiency (HP:0000083)				4.98	4.35	0.002
Aspiration (HP:0002835)				4.94	0.975	0.00014
Respiratory insufficiency (HP:0002093)				4.92	3.31	0.00011
Abnormal renal physiology (HP:0012211)				4.1	1.01	0.043
Supraventricular arrhythmia (HP:0005115)				3.8	0.721	0.046
Productive cough (HP:0031245)				3.71	3.72	0.038
Malaise (HP:0033834)				3.61	0	0.042

Use Case: Phenopackets

Table 5: All univariate scores for IHPRF3 (OMIM:616900).

Class	r-score	Inclusivity	Exclusivity	IC
Severe muscular hypotonia (HP:0006829)	0.8	0.68	0.95	1.0
Developmental regression (HP:0002376)	0.63	0.58	0.68	1.0
Severe global developmental delay (HP:0011344)	0.5	0.42	0.62	1.0
Abnormality of upper lip vermillion (HP:0011339)	0.46	0.47	0.45	0.83
Respiratory insufficiency (HP:0002093)	0.42	0.42	0.42	0.81
Reduced tendon reflexes (HP:0001315)	0.42	0.53	0.35	0.82
Small basal ganglia (HP:0012697)	0.41	0.26	0.95	1.0
Exaggerated cupid's bow (HP:0002263)	0.41	0.26	0.95	1.0
Macroglossia (HP:0000158)	0.39	0.26	0.78	0.95
Areflexia (HP:0001284)	0.39	0.32	0.5	0.89
Abnormality of the basal ganglia (HP:0002134)	0.38	0.26	0.66	0.69
Profound global developmental delay (HP:0012736)	0.36	0.26	0.58	1.0
Prominent nasal bridge (HP:0000426)	0.36	0.26	0.58	1.0
Skeletal muscle hypertrophy (HP:0003712)	0.35	0.26	0.51	0.78
Sloping forehead (HP:0000340)	0.34	0.21	0.95	1.0
Aplasia/Hypoplasia of the cerebellar vermis (HP:0006817)	0.33	0.26	0.45	0.87
Highly arched eyebrow (HP:0002553)	0.33	0.26	0.45	1.0
Cerebellar vermis hypoplasia (HP:0001320)	0.33	0.26	0.45	0.95
Tented upper lip vermilion (HP:0010804)	0.31	0.21	0.62	1.0
Coarse facial features (HP:0000280)	0.29	0.26	0.34	1.0
Small forehead (HP:0000350)	0.29	0.26	0.34	1.0
Narrow forehead (HP:0000341)	0.29	0.26	0.34	1.0

Table 5 – continued from previous page

Class	r-score	Inclusivity	Exclusivity	IC
Aplasia/Hypoplasia of the corpus callosum (HP:0007370)	0.29	0.37	0.24	0.95
Aplasia/Hypoplasia of the cerebral white matter (HP:0012429)	0.29	0.37	0.24	0.95
EEG abnormality (HP:0002353)	0.29	0.32	0.27	0.58
Hypoplasia of the corpus callosum (HP:0002079)	0.29	0.32	0.27	1.0
Abnormality of muscle size (HP:0030236)	0.29	0.32	0.27	0.63
Cerebral white matter hypoplasia (HP:0012430)	0.29	0.32	0.27	1.0
Brachycephaly (HP:0000248)	0.29	0.21	0.45	0.95
Absent speech (HP:0001344)	0.28	0.37	0.23	1.0
Abnormality of the cerebellar vermis (HP:0002334)	0.27	0.26	0.28	0.8
Diffuse cerebellar atrophy (HP:0100275)	0.27	0.16	0.95	1.0
Global brain atrophy (HP:0002283)	0.27	0.16	0.95	1.0
Abnormality of central nervous system electrophysiology (HP:0030178)	0.27	0.32	0.24	0.56
Global developmental delay (HP:0001263)	0.26	0.95	0.15	0.89
Open mouth (HP:0000194)	0.26	0.16	0.7	1.0
Diffuse cerebral atrophy (HP:0002506)	0.26	0.16	0.7	1.0
Seizures (HP:0001250)	0.26	0.79	0.15	0.62
Visual impairment (HP:0000505)	0.25	0.21	0.31	0.87
Shallow orbits (HP:0000586)	0.25	0.16	0.55	1.0
Abnormality of bony orbit of skull (HP:3000030)	0.25	0.16	0.55	0.95
Partial agenesis of the corpus callosum (HP:0001338)	0.25	0.16	0.55	1.0
Abnormality of the corpus callosum (HP:0001273)	0.25	0.37	0.18	0.83
Abnormality of upper lip (HP:0000177)	0.24	0.47	0.16	0.69
Cerebellar malformation (HP:0002438)	0.24	0.26	0.23	0.74
Muscular hypotonia (HP:0001252)	0.24	0.95	0.14	0.8
Abnormality of the periorbital region (HP:0000606)	0.24	0.53	0.15	0.65
Deeply set eye (HP:0000490)	0.24	0.32	0.19	1.0
Abnormal tongue morphology (HP:0030809)	0.24	0.26	0.21	0.69
Abnormality of the tongue (HP:0000157)	0.24	0.26	0.21	0.65
Cerebral atrophy (HP:0002059)	0.23	0.21	0.26	0.82
Abnormality of the lip (HP:0000159)	0.23	0.53	0.15	0.62
Focal seizures (HP:0007359)	0.22	0.16	0.38	0.69
Agenesis of corpus callosum (HP:0001274)	0.22	0.16	0.38	1.0
Osteoporosis (HP:0000939)	0.22	0.16	0.38	0.92
Atrophy/Degeneration affecting the cerebrum (HP:0007369)	0.22	0.21	0.24	0.78
Ventriculomegaly (HP:0002119)	0.22	0.32	0.16	0.81
Generalized seizures (HP:0002197)	0.21	0.21	0.22	0.77
Abnormality of the external nose (HP:0010938)	0.21	0.42	0.14	0.67
Abnormality of the cerebral white matter (HP:0002500)	0.21	0.37	0.14	0.68
Abnormal nervous system electrophysiology (HP:0001311)	0.2	0.32	0.15	0.56
Abnormality of the forehead (HP:0000290)	0.2	0.53	0.13	0.7

Table 6: Enrichment results for IHPRF3 (OMIM:616900)

	Binomial			Fisher		
	zscore	OR	p	zscore	OR	p
Abnormality of upper lip vermillion (HP:0011339)	9	4.14	4.7e-07	3.86	Inf	0.015
Respiratory insufficiency (HP:0002093)	8.17	1.99	5.8e-06	3.96	1.99	0.015
Severe muscular hypotonia (HP:0006829)	7.98	Inf	2e-07	7.98	Inf	3.3e-10
Developmental regression (HP:0002376)	7.76	0	1.5e-06	7.76	0	3.2e-07
Muscular hypotonia (HP:0001252)	7.23	0	4.4e-10			
Cerebellar vermis hypoplasia (HP:0001320)	6.64	24.9	0.00091			
Aplasia/Hypoplasia of the cerebellar vermis (HP:0006817)	6.64	24.9	0.00091			
Reduced tendon reflexes (HP:0001315)	6.23	14.7	8.2e-05	6.23	14.7	0.00017
Abnormal muscle tone (HP:0003808)	6.07	0	4.4e-08			
EEG abnormality (HP:0002353)	5.47	0	0.0031			
Abnormality of the cerebellar vermis (HP:0002334)	5.16	0.879	0.0089			
Abnormality of muscle physiology (HP:0011804)	5.14	0.172	2e-06			
Abnormality of central nervous system electrophysiology (HP:0030178)	5.12	0	0.0059			
Visual impairment (HP:0000505)	4.86	13.3	0.023			
Abnormality of the corpus callosum (HP:0001273)	4.82	0	0.0069			
Seizures (HP:0001250)	4.69	0	0.00037	4.69	0	0.0014
Abnormality of the musculature (HP:0003011)	4.5	24.7	3.2e-05	4.5	24.7	0.00046
Abnormality of the tongue (HP:0000157)	4.39	12.3	0.033			
Abnormal tongue morphology (HP:0030809)	4.39	0	0.033			
Severe global developmental delay (HP:0011344)	4.28	44.8	0.032	4.28	44.8	0.026
Functional respiratory abnormality (HP:0002795)	4.21	0	0.018			
Abnormality of the cerebral white matter (HP:0002500)	4.2	6.68	0.025			
Ventriculomegaly (HP:0002119)	4.16	0	0.036			
Absent speech (HP:0001344)	3.51	11.8	0.034			
Abnormality of the head (HP:0000234)	3.47	Inf	0.0024			
Abnormality of muscle size (HP:0030236)	3.45	0	0.026			
Abnormality of head or neck (HP:0000152)	3.39	1.87	0.0035	3.39	1.87	0.038
Aplasia/Hypoplasia of the corpus callosum (HP:0007370)	3.22	0.344	0.038			
Neurodevelopmental abnormality (HP:0012759)	3.11	0	0			
Abnormality of the nervous system (HP:0000707)	2.93	0	0			
Neurodevelopmental delay (HP:0012758)	2.29	0	0			
Abnormality of nervous system physiology (HP:0012638)	1.6	Inf	0			

Table 7: HPO database phenotype annotations for IHPRF3 (OMIM:616900)

Term ID	Label
HP:0002465	Poor speech
HP:0010945	Fetal pyelectasis
HP:0001298	Encephalopathy
HP:0001250	Seizure
HP:0001265	Hyporeflexia
HP:0001263	Global developmental delay
HP:0002553	Highly arched eyebrow
HP:0002518	Abnormal periventricular white matter morphology
HP:0000007	Autosomal recessive inheritance
HP:0001320	Cerebellar vermis hypoplasia
HP:0002650	Scoliosis
HP:0001321	Cerebellar hypoplasia
HP:0000158	Macroglossia
HP:0002093	Respiratory insufficiency
HP:0002079	Hypoplasia of the corpus callosum
HP:0002059	Cerebral atrophy
HP:0002119	Ventriculomegaly
HP:0002263	Exaggerated cupid's bow
HP:0100704	Cerebral visual impairment
HP:0002376	Developmental regression
HP:0010804	Tented upper lip vermilion
HP:0006829	Severe muscular hypotonia
HP:0012697	Small basal ganglia
HP:0006989	Dysplastic corpus callosum
HP:0006970	Periventricular leukomalacia
HP:0012736	Profound global developmental delay
HP:0000750	Delayed speech and language development
HP:0012708	Reduced brain N-acetyl aspartate level by MRS
HP:0011471	Gastrostomy tube feeding in infancy
HP:0000286	Epicanthus
HP:0000280	Coarse facial features
HP:0000256	Macrocephaly
HP:0000212	Gingival overgrowth
HP:0001562	Oligohydramnios
HP:0001558	Decreased fetal movement
HP:0001500	Broad finger
HP:0000341	Narrow forehead
HP:0000340	Sloping forehead
HP:0012471	Thick vermilion border
HP:0000490	Deeply set eye
HP:0000463	Anteverted nares
HP:0012444	Brain atrophy
HP:0000414	Bulbous nose
HP:0000426	Prominent nasal bridge
HP:0001837	Broad toe
HP:0012510	Extra-axial cerebrospinal fluid accumulation

Table 8: Multivariable Klarigi results for the 19 patients with IHPRF3 described in the phenopackets dataset, grouped by the publication they are described in.

Chong 2016 (5 members)	**r-score**	**Inclusion**	**Exclusion**	**IC**
Profound global developmental delay (HP:0012736)	0.85	1.0	0.74	1.0
Prominent nasal bridge (HP:0000426)	0.85	1.0	0.74	1.0
Abnormality of the nasal alae (HP:0000429)	0.85	1.0	0.74	0.82
Abnormality of the nares (HP:0005288)	0.85	1.0	0.74	0.82
Feeding difficulties (HP:0011968)	0.85	1.0	0.74	0.83
Exaggerated cupid's bow (HP:0002263)	0.85	1.0	0.74	1.0
Cerebellar vermis hypoplasia (HP:0001320)	0.85	1.0	0.74	0.95
Small forehead (HP:0000350)	0.85	1.0	0.74	1.0
Small basal ganglia (HP:0012697)	0.85	1.0	0.74	1.0
Narrow forehead (HP:0000341)	0.85	1.0	0.74	1.0
Anteverted nares (HP:0000463)	0.85	1.0	0.74	0.95
Aplasia/Hypoplasia of the cerebellar vermis (HP:0006817)	0.85	1.0	0.74	0.87
Abnormality of the cerebellar vermis (HP:0002334)	0.85	1.0	0.74	0.8
Cerebellar malformation (HP:0002438)	0.85	1.0	0.74	0.74
Highly arched eyebrow (HP:0002553)	0.85	1.0	0.74	1.0
Overall	-	*100.0*	-	-
Zapata-Aldana 2019 (2 members)	**r-score**	**Inclusion**	**Exclusion**	**IC**
Impaired social interactions (HP:0000735)	0.94	1.0	0.89	0.87
Poor eye contact (HP:0000817)	0.94	1.0	0.89	1.0
Respiratory failure (HP:0002878)	0.94	1.0	0.89	1.0
Abnormal social behavior (HP:0012433)	0.94	1.0	0.89	0.81
Long philtrum (HP:0000343)	0.94	1.0	0.89	1.0
Abnormality of the philtrum (HP:0000288)	0.94	1.0	0.89	0.79
Overall	-	*100.0*	-	-
Bhoj 2016 (10 members)	**r-score**	**Inclusion**	**Exclusion**	**IC**
Cognitive impairment (HP:0100543)	0.6	0.8	0.47	0.77
Intellectual disability (HP:0001249)	0.6	0.8	0.47	0.85
Severe global developmental delay (HP:0011344)	0.47	0.7	0.35	1.0
Overall	-	*100.0*	-	-
Guerreiro 2016 (2 members)	**r-score**	**Inclusion**	**Exclusion**	**IC**
Early onset of sexual maturation (HP:0100000)	0.94	1.0	0.89	0.83
Overlapping toe (HP:0001845)	0.94	1.0	0.89	1.0
Deep palmar crease (HP:0006191)	0.94	1.0	0.89	1.0
Single transverse palmar crease (HP:0000954)	0.94	1.0	0.89	1.0
Abnormal dermatoglyphics (HP:0007477)	0.94	1.0	0.89	0.72
Precocious puberty (HP:0000826)	0.94	1.0	0.89	0.85
Infantile muscular hypotonia (HP:0008947)	0.94	1.0	0.89	1.0
Abnormality of the palmar creases (HP:0010490)	0.94	1.0	0.89	0.82
Abnormal palmar dermatoglyphics (HP:0001018)	0.94	1.0	0.89	0.74
Overall	-	*100.0*	-	-