Walkthrough of IEMbase

When users open the application interface, the starting page presents a disclaimer. Upon agreeing to the disclaimer, users are directed to the main page, which presents a search form and the following three buttons: Browse, Search, and Mini-Expert (Figure S1). In the search form - which is also accessible by the Search button - users can type in disorder, gene, biomarker, or symptom names to look up information on a particular disorder.

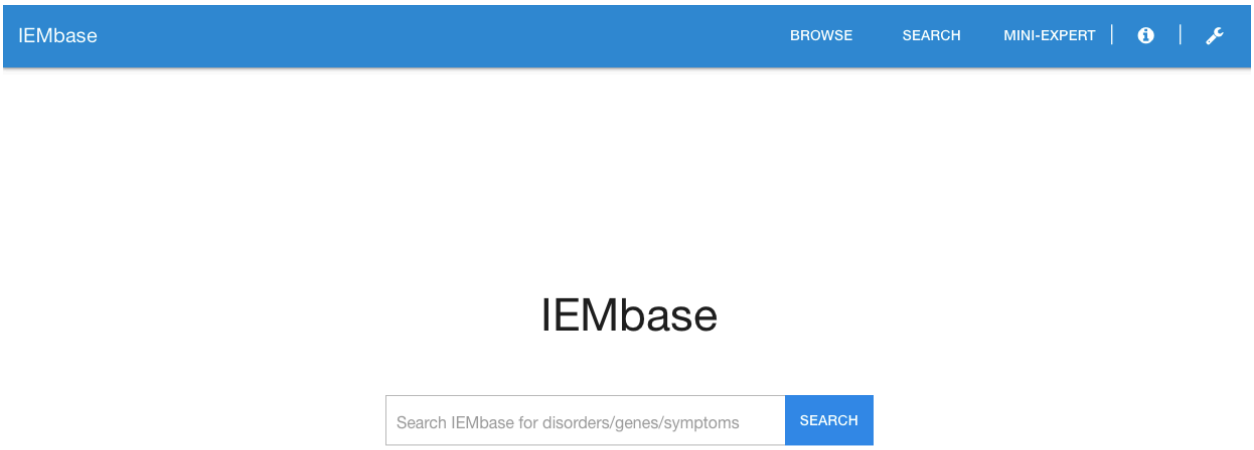

Figure S1. Screenshot of main page

The Browse button directs to a page with a full catalog of IEMs that are currently curated on IEMbase (Figure S2). The catalog is represented as a tree, where each branch represents a disease classification used by the IEM community. Users can hide or expand the branches of the tree as they browse, and they can look up detailed information on each disorder by clicking on the disorder name (Figure S3). In addition, users can search for a particular disorder by its name using the search form located above the catalog.

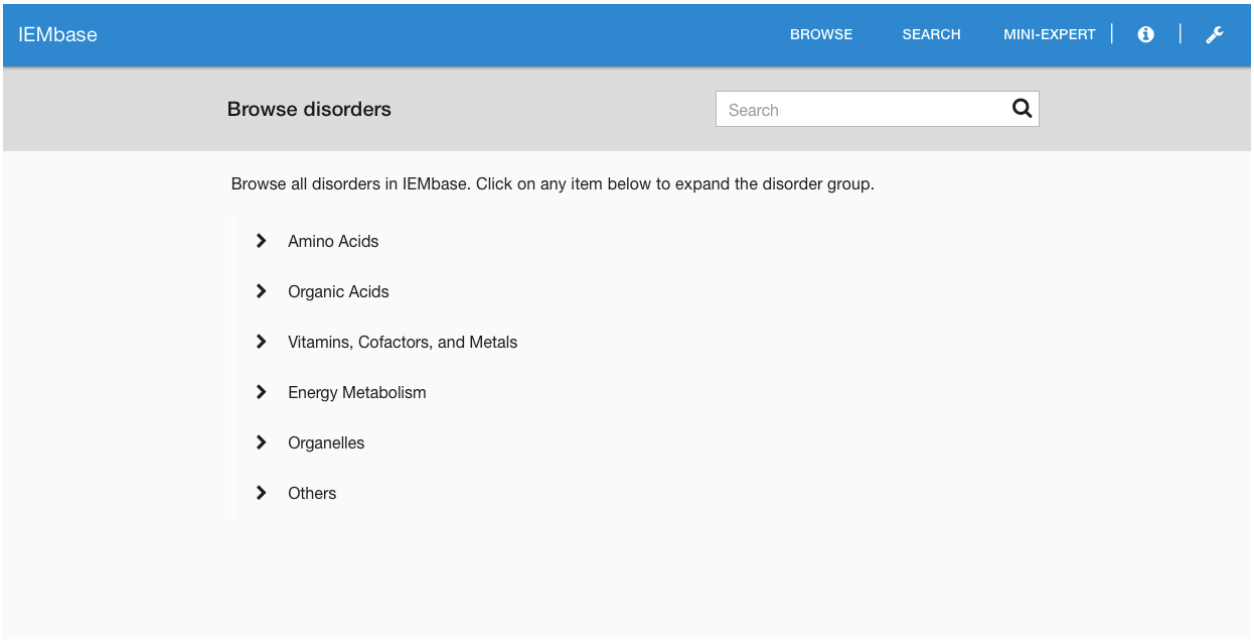

Figure S2. Screenshot of Browse page

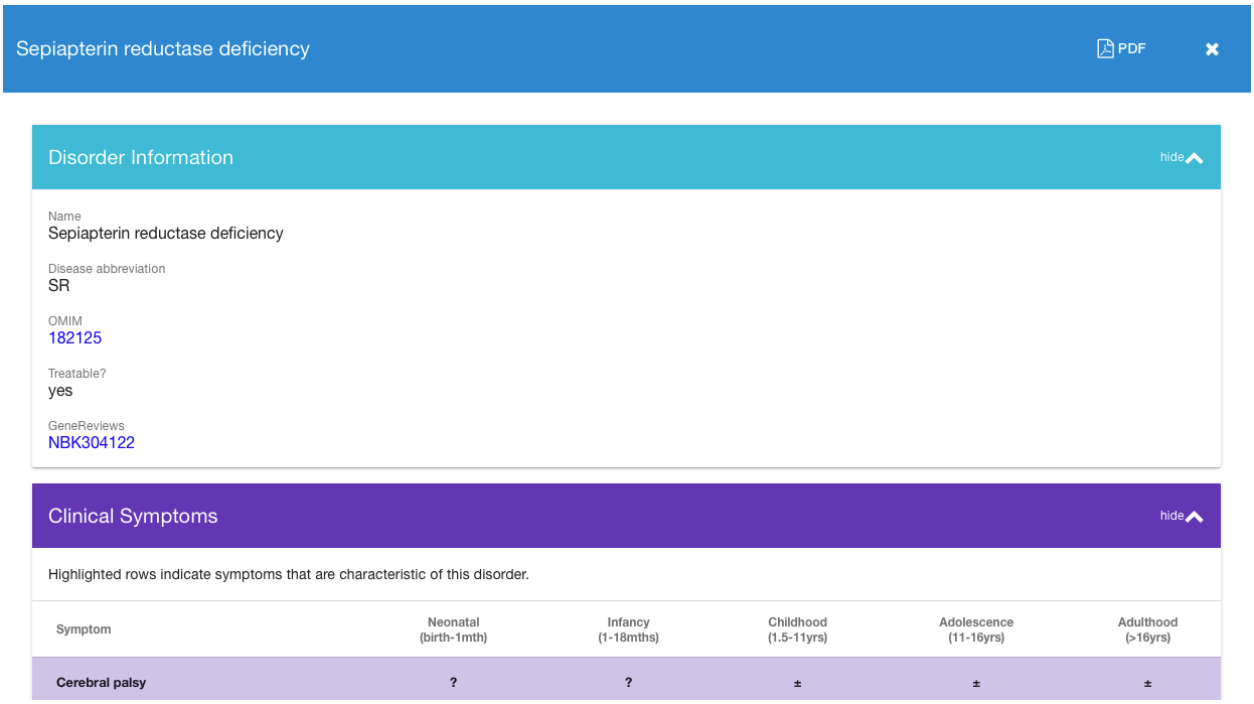

Figure S3. Screenshot of Disorder Information page

Upon selecting the Mini-Expert option, users are directed to a page with the Input Profile form (Figure S4). In this form, users are asked to enter a list of biochemical and clinical phenotypes using a search bar.

For biochemical entries, the system asks to specify relative levels as low, normal, or high. As the phenotypes are added, they will appear in the list below the search bar.

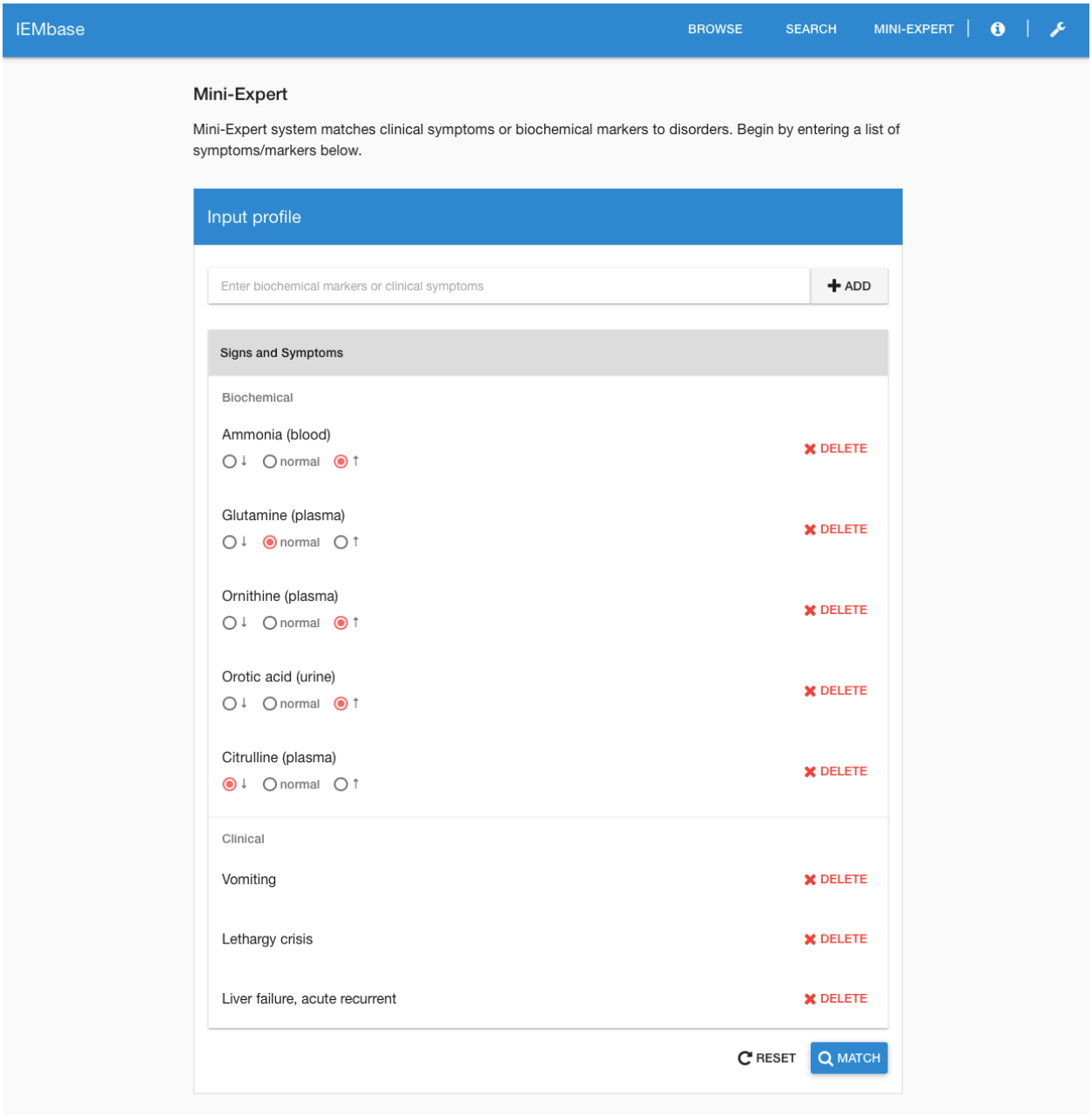

Figure S4. Screenshot of Mini-Expert Query page

Upon submitting the phenotype list, the system returns a list of matching IEMs in the Results section, which is located below the Mini-Expert Query section (Figure S5). In the Results section, users can look up the details of each disorder in the list, build a differential diagnosis chart, or build a gene panel.

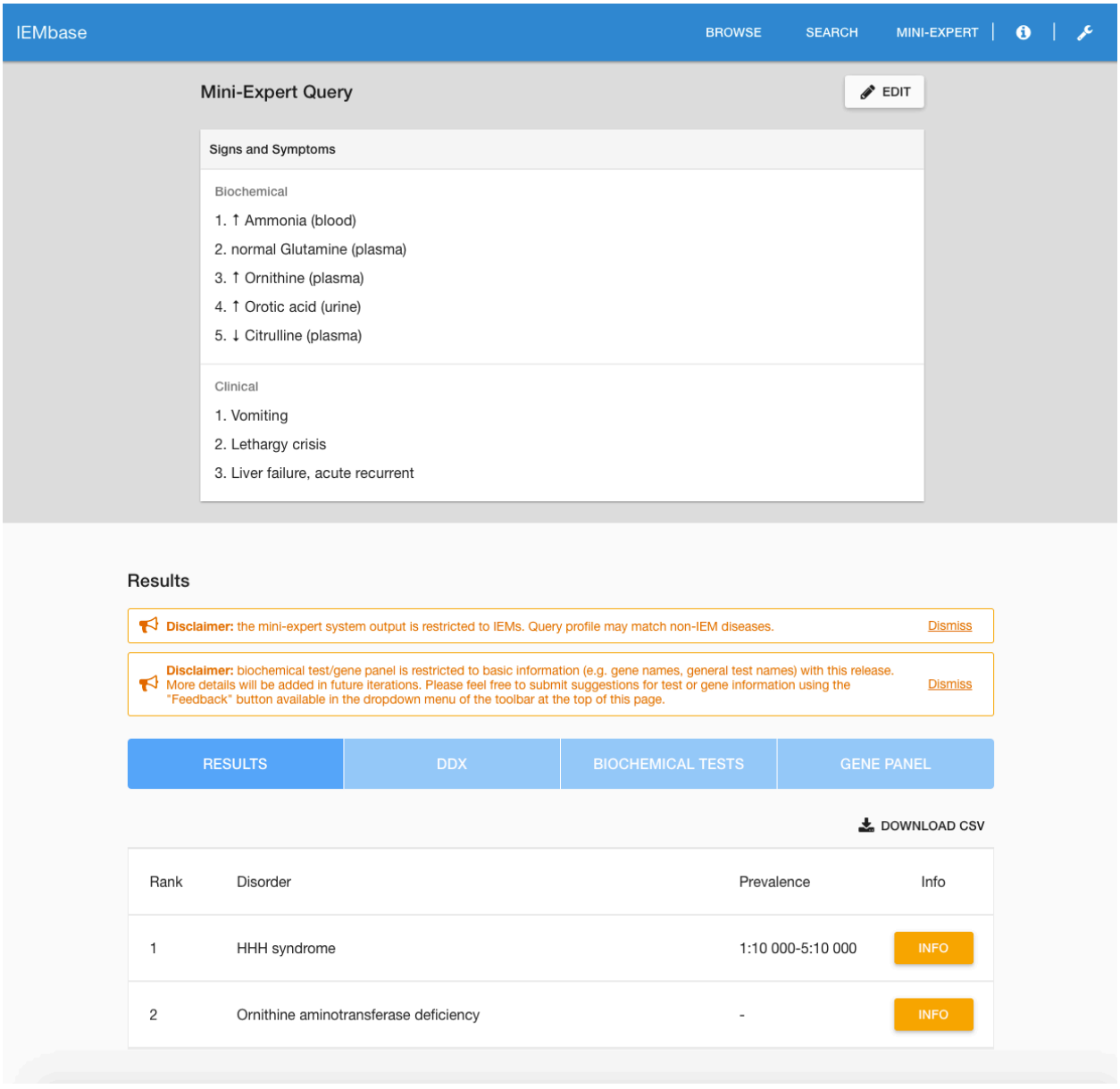

Figure S5. Screenshot of Mini-Expert Results page

The DDx button in the Results section leads to a page where users can select multiple candidate disorders (Figure S6) and generate a differential diagnosis chart based on their selection (Figure S7). Similarly, the

Gene Panel button and Biochemical Test button in the Results section direct to respective pages where users can select multiple disorders and generate a gene panel or a biochemical test panel based on their selection (Figure S8, S9).

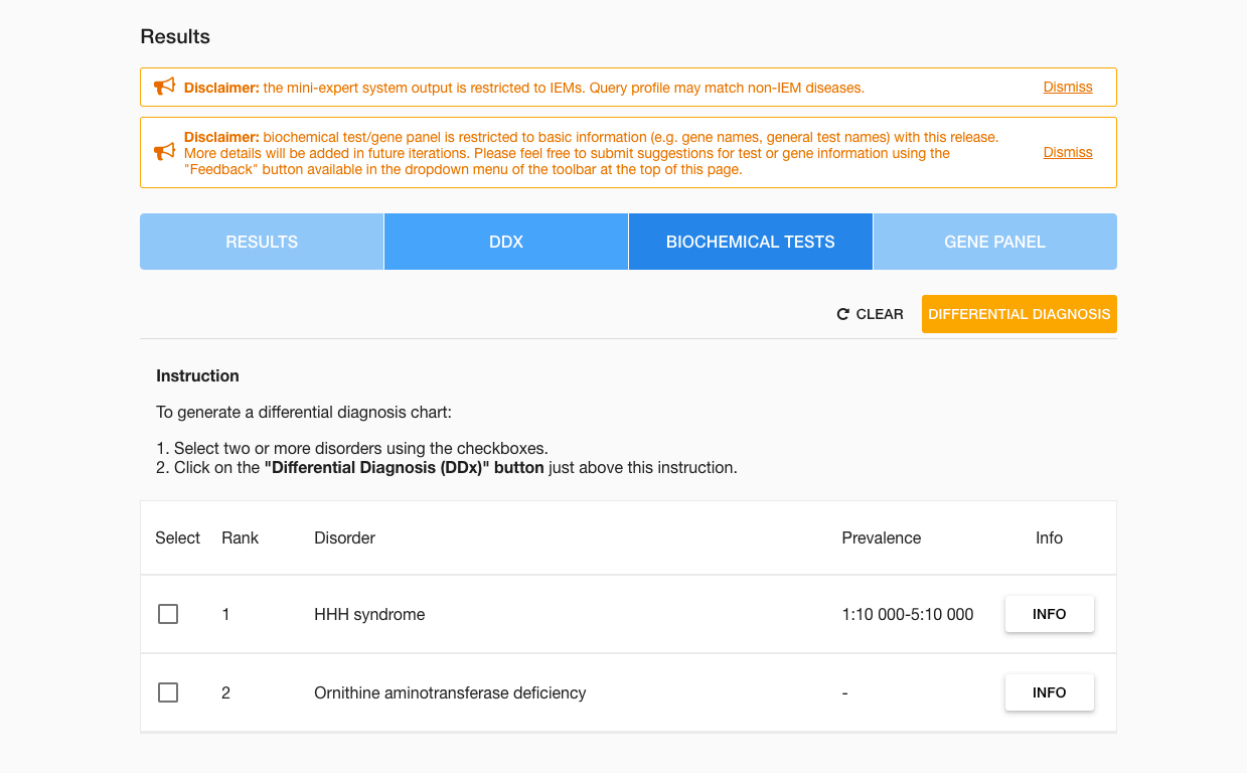

Figure S6. Screenshot of Mini-Expert DDx (Differential Diagnosis) selection page

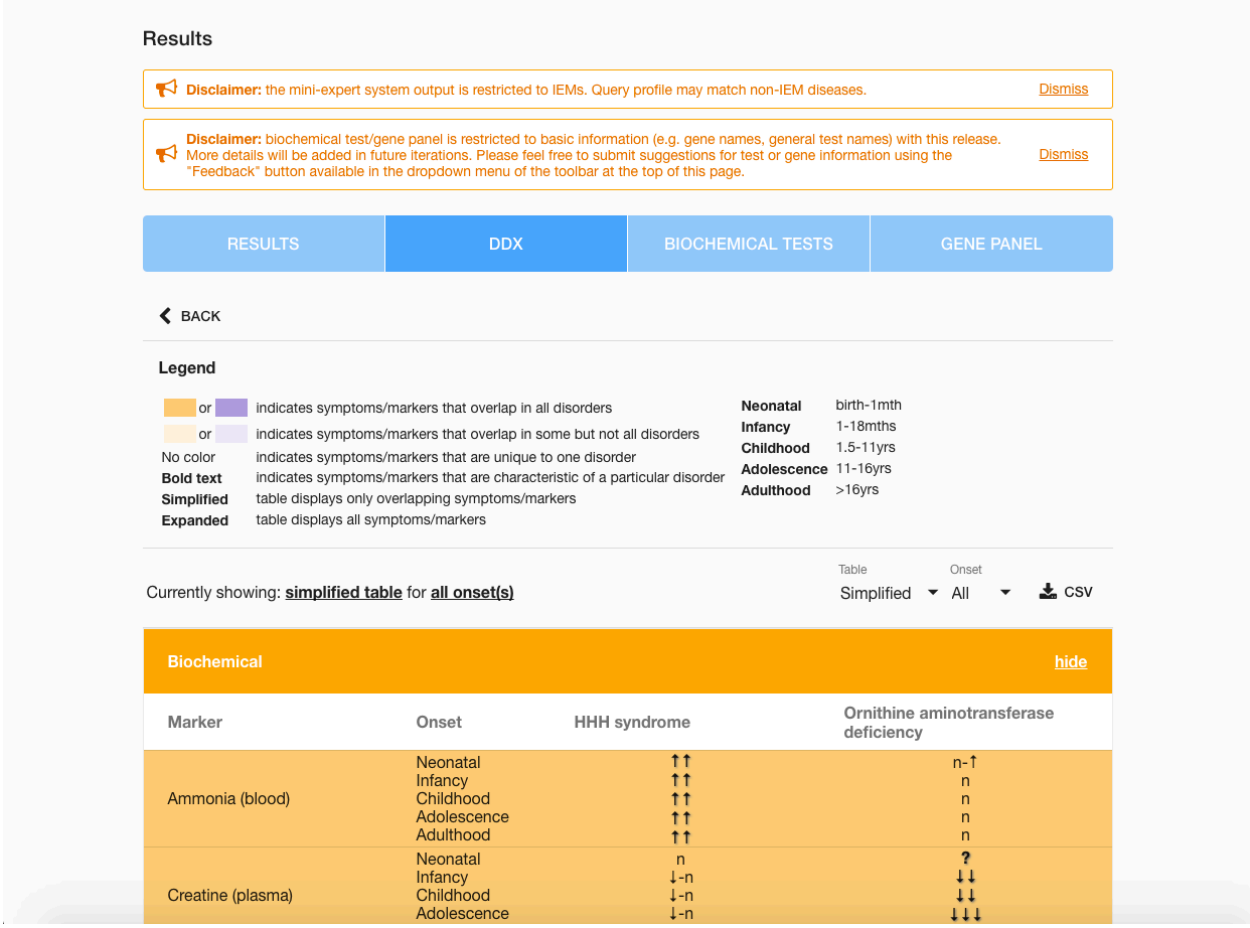

Figure S7. Screenshot of Mini-Expert DDx (Differential Diagnosis) result page

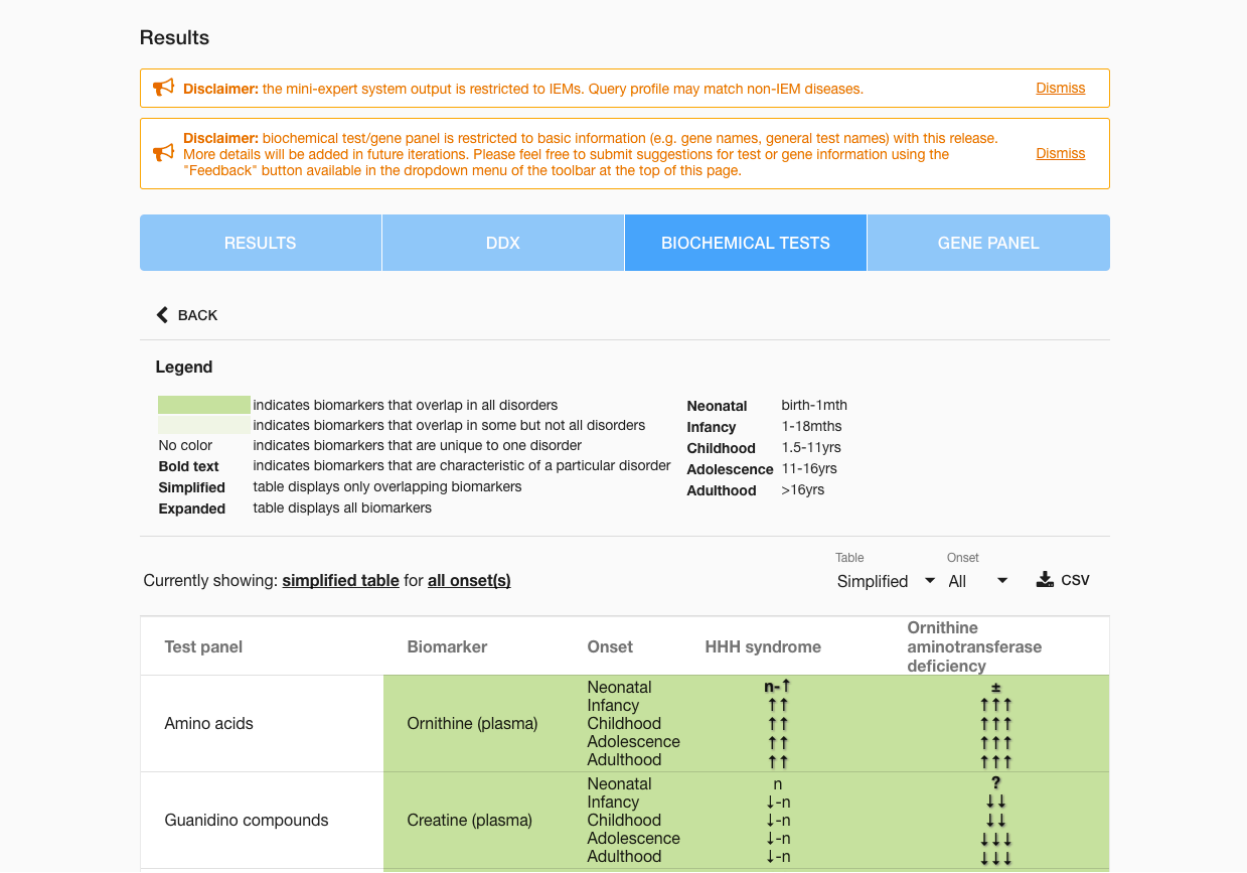

Figure S8. Screenshot of Mini-Expert Biochemical Tests page

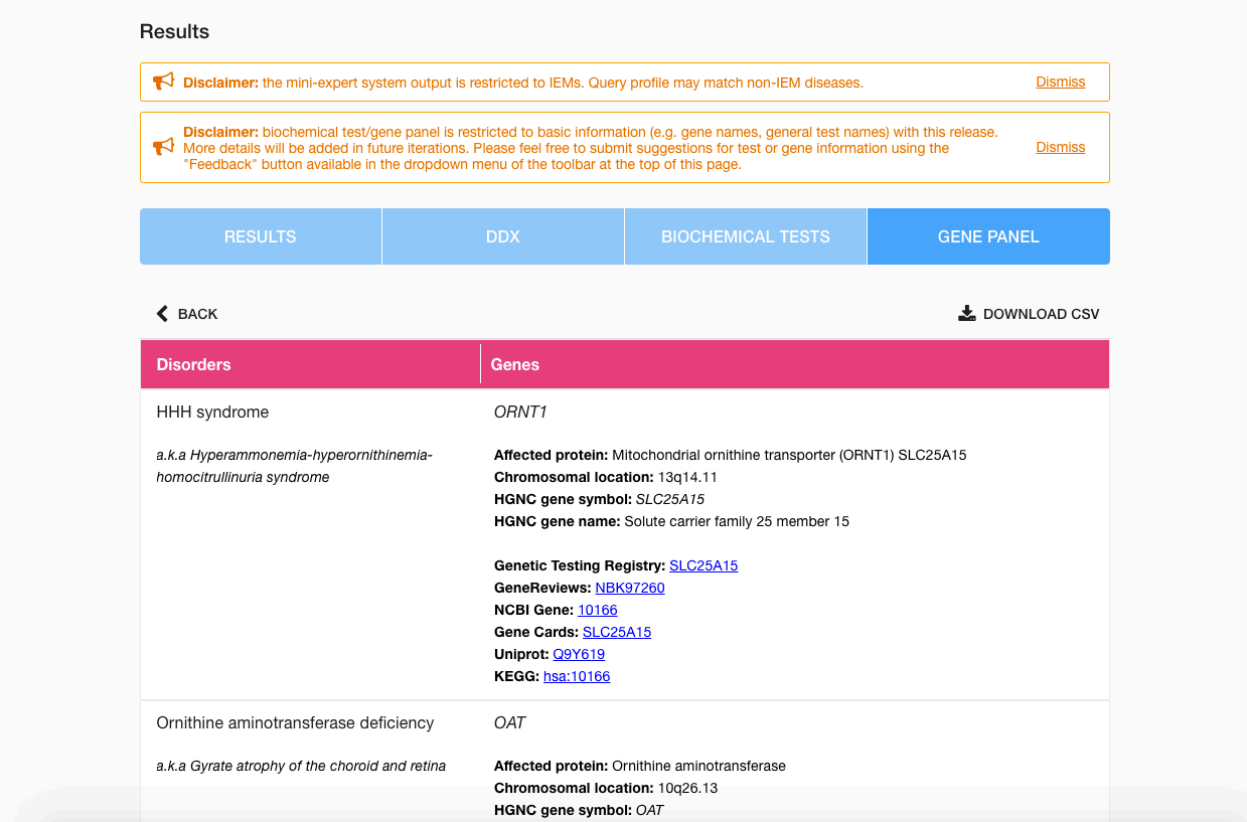

Figure S9. Screenshot of Mini-Expert Gene Panel page

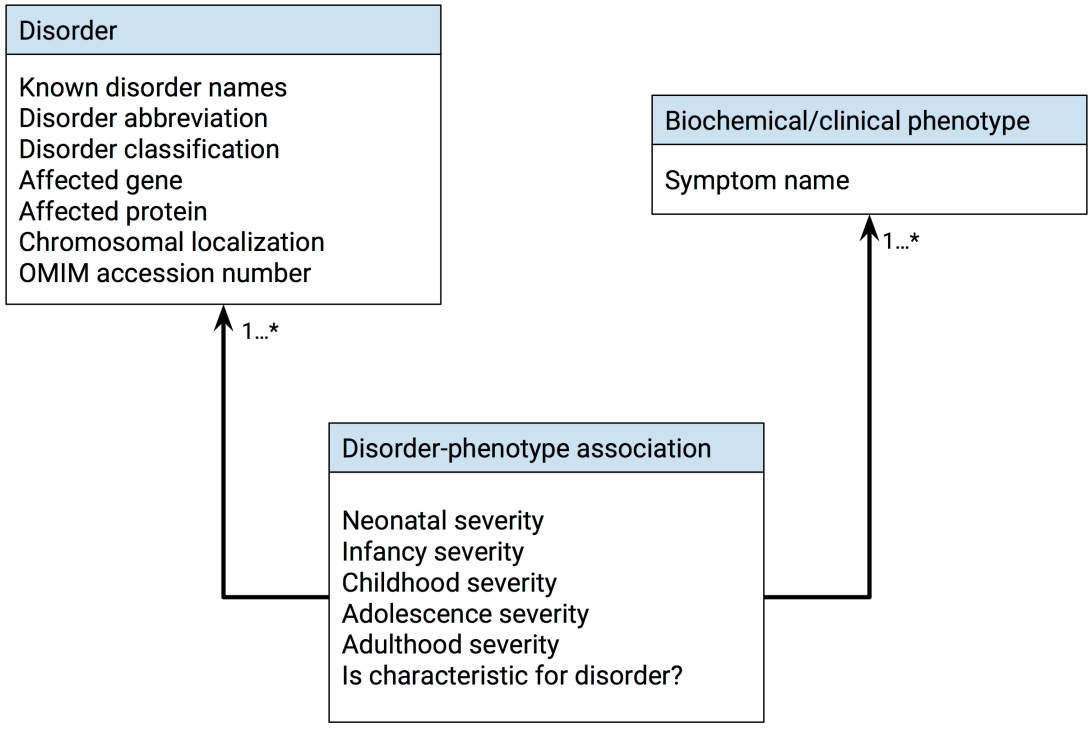

Figure S10. Knowledgebase schema

The knowledgebase consisted of three tables which were extracted from the nascent disease database. Each table represented different data types: disorders, biochemical/clinical phenotypes, and associations between disorders and phenotypes.

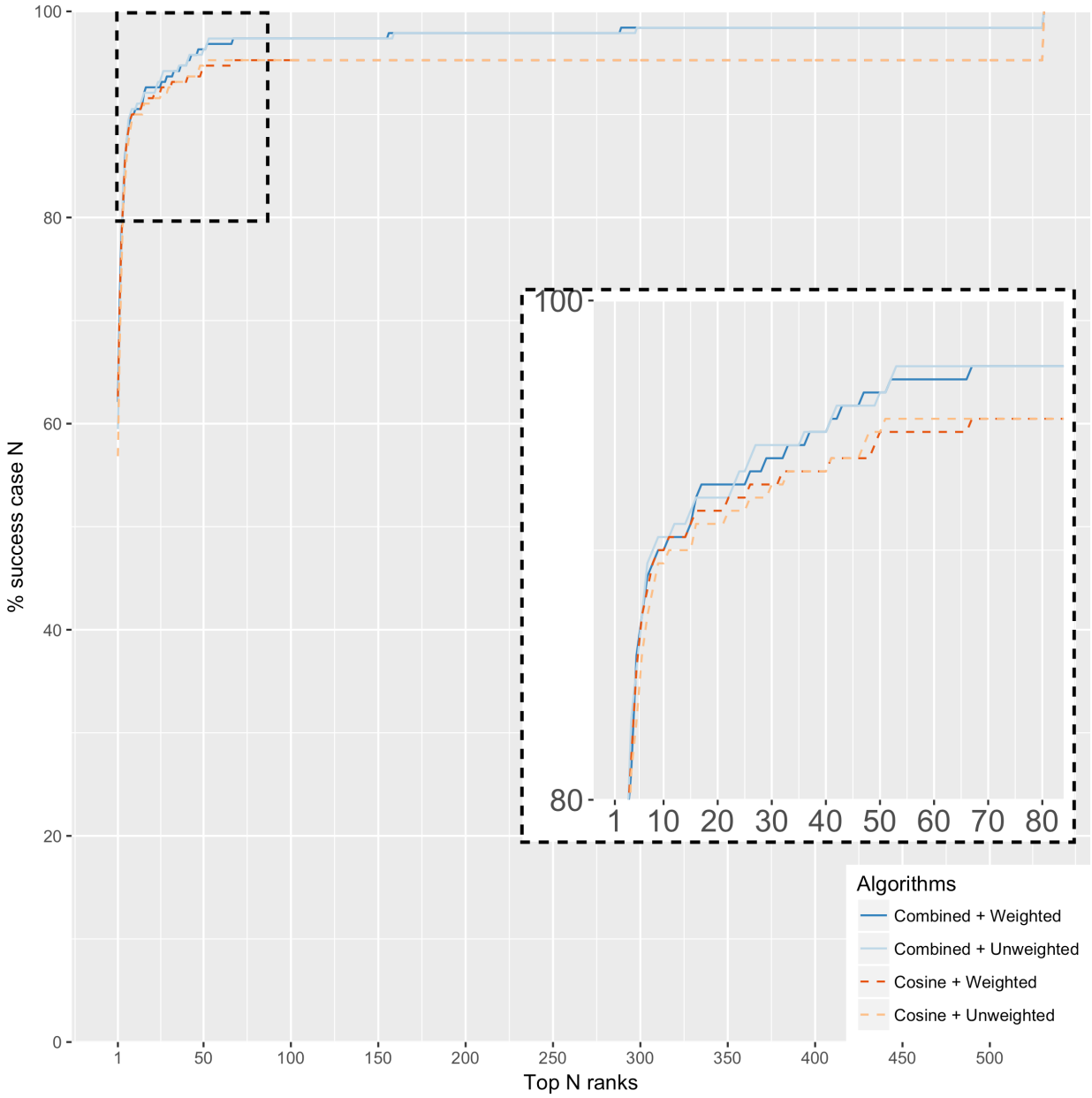

Figure S11. Mini-expert system performance evaluation results

The performance of IEMbase's mini-expert algorithm (Combined + Weighted) was compared to three other algorithms: combined cosine similarity and semantic similarity without weights (Combined +

Unweighted), cosine similarity only with weights (Cosine + Weighted), and cosine similarity only without weights (Cosine + Unweighted). There was no significant performance difference between the mini-expert system and other algorithms ($p = 0.66$ in Mini-expert vs Combined + Unweighted, $p = 1.0$ in Mini-expert vs Cosine + Weighted, $p = 0.30$ in Mini-expert vs Cosine + Unweighted; Mann-Whitney-U). Black dotted boxes show a section of the plot between the top one candidate disorder and the top 80 candidate disorders.

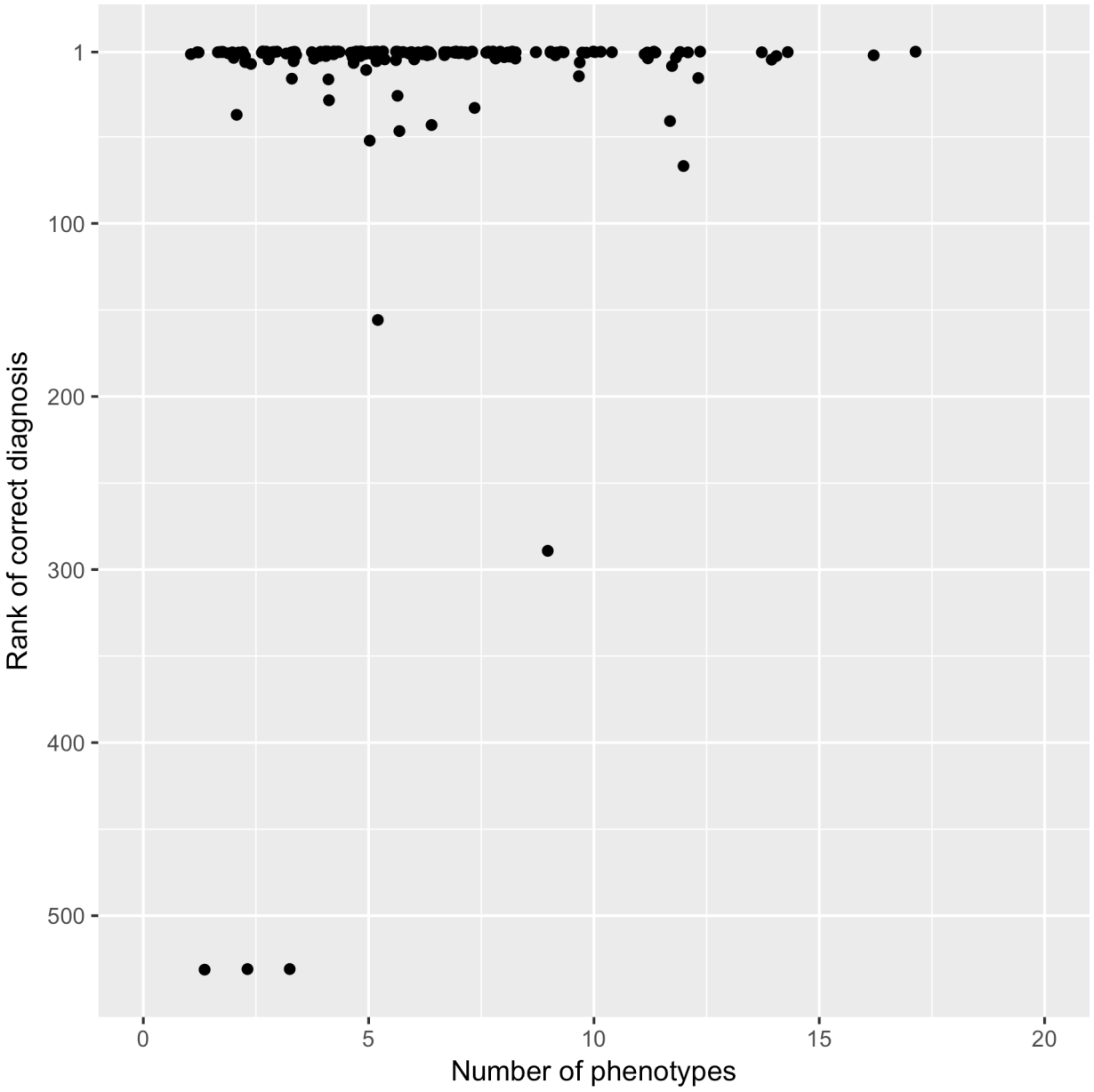

Figure S12. Scatterplot of rank of correct diagnosis against number of phenotypes specified

Rank of correct diagnosis did not correlate with number of phenotypes specified for each case ($p = 0.69$; Spearman's rank correlation test).

Table S1. Case study query

Biochemical markers
1. ↑ Ammonia (blood)
2. Normal Glutamine (plasma)
3. ↑ Ornithine (plasma)
4. ↑ Orotic acid (urine)
5. ↓ Citrulline (plasma)
Clinical symptoms
1. Vomiting
2. Lethargy crisis
3. Liver failure, acute recurrent

Table S2. Overview of disorders (n=117) investigated within the validation of 190 cases

Diagnosis	Number of cases with diagnosis	Rank of actual diagnosis*
Glutaric aciduria type I	6	1, 2, 3
HHH syndrome	4	1
Tyrosinaemia type I	4	1, 2, 29
Succinic semialdehyde dehydrogenase deficiency	4	1
Fructose-1,6-bisphosphatase deficiency	4	1, 5, 15
Molybdenum cofactor deficiency A	4	1, 2, 3
Guanidinoacetate methyltransferase deficiency	3	1
Smith-Lemli-Opitz syndrome	3	1
S-adenosylhomocysteine hydrolase deficiency	3	1
Cystathionine beta-synthase deficiency	3	1, 7, 9
Suphite oxidase deficiency	3	1, 6
Nonketotic hyperglycinaemia	3	1
6-Pyruvoyl-tetrahydropterin synthase deficiency	3	1
Prolidase deficiency	3	1, 5, 7
Ornithine aminotransferase deficiency	3	1
Propionic acidemia	3	1, 3, 5
Methylenetetrahydrofolate reductase deficiency	3	1
Carnitine palmitoyltransferase 1 deficiency	3	1, 2, **
Glycerol kinase deficiency, isolated	3	2, 3
Aromatic L-amino acid decarboxylase deficiency	2	1
Ornithine transcarbamylase deficiency	2	1
Citrullinemia type I	2	1
Argininemia	2	1
Canavan disease	2	1
Fumarase deficiency	2	1
Citrullinemia type II	2	1, 289
Tyrosinaemia type II	2	1
Alkaptonuria	2	1
Hurler, Scheie disease	2	1
Refsum disease (classic, adult)	2	1, 47
Hyperprolinaemia type II	2	1
Galactosaemia	2	1, 41
Glycogen storage disease type III	2	1, 52
Lysinuric protein intolerance	2	1, 3

Maple syrup urine disease	2	1
Congenital hypophosphatasia	2	1
Methylmalonic acidemia	2	1
Alpha-amino adipic semialdehyde (AASA) dehydrogenase deficiency	2	1
Sepiapterin reductase deficiency	2	1
Biotinidase deficiency	2	1, 43
Arginine:glycine amidinotransferase deficiency	2	2
Metachromatic leukodystrophy-like disorder due to saposin B deficiency	2	2, 3
Galactokinase deficiency	2	2, 4
Multiple acyl-CoA dehydrogenase deficiency	2	3, 17
Adenosylcobalamin and methylcobalamin synthesis defect - cblC	2	5, 11
Niemann-Pick disease type C1	2	6, 16
Maternally Inherited Mitochondrial Dystonia	1	**
2-Methylbutyrylglycinuria	1	**
Adenylosuccinate lyase deficiency	1	1
Hypoxanthine guanine phosphoribosyltransferase deficiency	1	1
Argininosuccinic aciduria	1	1
3-Hydroxy-3-methylglutaryl-CoA synthase deficiency	1	1
Isolated deficiency of long-chain 3-hydroxyacyl-CoA dehydrogenase	1	1
Sterol 27-hydroxylase deficiency	1	1
Transaldolase deficiency	1	1
Ribose-5-phosphate isomerase deficiency	1	1
Acrodermatitis enteropathica	1	1
Trimethylaminuria	1	1
Gamma-glutamylcysteine synthetase deficiency	1	1
Hawkinsinuria	1	1
Pyruvate dehydrogenase complex deficiency E3	1	1
Hunter disease	1	1
Morquio A disease	1	1
Fucosidosis	1	1
Salla disease	1	1
Dihydropyrimidinase deficiency	1	1
3-Hydroxy-3-methylglutaryl-CoA lyase deficiency	1	1
Tay-Sachs disease	1	1
Farber disease	1	1
GTP cyclohydrolase I deficiency	1	1
Lysosomal acid lipase deficiency	1	1
Phosphoglycerate dehydrogenase deficiency	1	1
Hydroxyprolinemia	1	1

Glutamate formimino transferase deficiency	1	1
Hereditary fructose intolerance	1	1
Cystinuria	1	1
Glucose transporter-1 deficiency	1	1
Glycogen storage disease type I a	1	1
Glycogen storage disease type I non-a	1	1
Hartnup disorder	1	1
Isovaleric acidemia	1	1
Folate receptor alpha deficiency	1	1
Carnitine transporter deficiency	1	1
Thiamine-responsive megaloblastic anemia syndrome (SLC19A2)	1	1
Primary hyperoxaluria type I	1	1
Tyrosine hydroxylase deficiency	1	1
L-2-hydroxyglutaric aciduria	1	2
D-2-hydroxyglutaric aciduria type I	1	2
Pyruvate dehydrogenase complex deficiency E3 X	1	2
Mitochondrial trifunctional protein deficiency	1	2
Phosphoribosyl pyrophosphate synthetase 1 superactivity	1	2
Xanthine dehydrogenase deficiency	1	2
Hyperprolinemia type I	1	2
3-Hydroxy-3-methyl glutaric aciduria	1	2
2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency	1	2
Zellweger spectrum disorders	1	3
Multiple sulfatase deficiency	1	3
Adenosine kinase deficiency	1	3
Hyperinsulinism of infancy	1	3
Pyruvate dehydrogenase complex deficiency E1a	1	4
Medium - chain acyl CoA dehydrogenase deficiency	1	4
Methylacetoacetyl-CoA thiolase deficiency	1	4
Transcobalamin deficiency	1	4
GM1-gangliosidosis	1	5
Krabbe disease	1	5
Adenosylcobalamin and methylcobalamin synthesis defect - cblD-MMA/HC	1	5
ATP synthase deficiency	1	5
Methylglutaconic aciduria type IV	1	5
3-Methylcrotonylglycinuria	1	6
MEGDEL Syndrome	1	7
Carnitine palmitoyltransferase 2 deficiency	1	8
Dopa-responsive dystonia	1	16

Methylcobalamin synthesis defect - cblD-HC	1	26
X-linked adrenoleukodystrophy and adrenomyeloneuropathy	1	33
Tangier disease (ABCA1)	1	37
Mitochondrial Depletion Syndrome 4A	1	67
Carbamoyl phosphate synthetase I deficiency	1	156

Cases have been selected to validate the mini-expert system using a diverse range of disorders. The selected cases cover approximately 22% of the 530 disorders in IEMbase. In the "Rank of actual diagnosis" column, multiple ranks are recorded as some cases ranked differently than one another.

* Disorders ranked over 20 are described in detail in Table S3.

** Disorder was ranked out.

Table S3. Overview of cases whose diagnoses ranked out of the top 20

Rank	Diagnosis	Comment	User specified biomarkers	User specified clinical symptoms
Ranked out	2-Methylbutyrylglycinuria	"C5 2-Methylbutyrylcarnitin" should be high, not "C4 Butyrylcarnitine", in 2-Methylbutyrylglycinuria.	↑ C4 Butyrylcarnitine (blood)	No entry
Ranked out	Carnitine palmitoyltransferase 1 deficiency	"C18:2-Acylcarnitine (dried blood spot)" should be low in carnitine palmitoyltransferase 1 deficiency.	↑ C18:2-acylcarnitine (dried blood spot) ↑ Carnitine, free (dried blood spot)	No entry
Ranked out	Maternally Inherited Mitochondrial Dystonia	There are no biomarkers specified in the database or in the literature for this disease.	↑ C16 Hexadecanoylcarnitine ↑ Carnitine, free (dried blood spot) ↑ C2 Acetylcarnitine	No entry
26	Methylcobalamin synthesis defect - cblD-HC	"Methylmalonic acid (plasma)" should be normal in cblD-HC. Megaloblastic anemia is one of the characteristic features. Different cobalamin defects within top 5.	↑ Homocysteine, total (plasma) ↑ Methylmalonic acid (urine)	Nystagmus Intellectual disability Diminished visual activity Heart Failure
29	Tyrosinaemia type I	The validator did not provide any essential biomarkers for this case.	No entry	Hepatosplenomegaly Growth retardation Renal Fanconi Syndrome Osteopenia
33	X-linked adrenoleukodystrophy and adrenomyeloneuropathy	Duplicate entries in the system caused incorrect matching of "Very long-chain fatty acids (0)", which was entered by the user. In the latest database, duplicate entries are merged to "Very-long-chain fatty acids (plasma)"	↑ Very long-chain fatty acids (O) normal Phytanic acid (plasma) normal Pristanic acid (plasma) ↑ C26:0 fatty acid (plasma)	Developmental regression Adrenal insufficiency White matter abnormalities (MRI)
37	Tangier disease (ABCA1)	"LDL cholesterol" was missing from the description of Tangier disease in the database. The latest database includes the biomarker and the system ranks Tangier disease at rank	↓ LDL cholesterol (plasma)	Splenomegaly

		#5 after the correction.		
41	Galactosaemia	The validator may have entered in "↑ Prothrombin time" to indicate "↓ Coagulation factors (plasma)".	↓ Hemoglobin (blood) ↑ Transaminase (plasma) ↑ Bilirubin, total/direct (plasma) ↑ Prothrombin time	Fontanel enlarged Brain edema (MRI) Cataract Ascites Anemia, hemolytic Hepatomegaly Liver failure Hyperbilirubinemia, prolonged conjugated
43	Biotinidase deficiency	"↑ 3-Hydroxyisovaleric acid (urine)" was missing from the description of biotinidase deficiency in the database. The latest database includes the biomarker in the description, and biotinidase deficiency ranks at #1 for this case after the correction.	↑ Lactate (plasma) ↑ 3-Hydroxyisovaleric acid (urine)	Loss of hair Epilepsy Developmental delay Blindness
47	Refsum disease (classic, adult)	"↑ Pipecolic acid (serum)" was missing from the description of Refsum disease in the database. The latest version includes the biomarker, and Refsum disease ranks at #5 for this case after the correction.	↑ Pipecolic acid (serum)	Deafness, sensorineural Developmental delay Retinopathy Facial dysmorphism Hypotonia
52	Glycogen storage disease type III	The system does not recognize the relationship between "Transaminase (plasma)" and other enzymes specified in the description of this disease. In a future development cycle, the system will be able to make the recognition using a synonyms table.	↑ Transaminase (plasma) ↑ Creatine kinase (plasma)	Hepatomegaly Hypoglycemia, episodic Motor developmental delay

67	Mitochondrial Depletion Syndrome 4A	Only "↑ Lactate (plasma)" is associated with Mitochondrial Depletion Syndrome 4A in the database. The listed biomarkers may not be specific enough for the system to make a match.	↑ Protein (CSF) ↓ 5-Methyl-THF (CSF) ↑ Neopterin (CSF) ↑ Lactate (MRS)	Epilepsy +/- encephalopathy Developmental delay Regression, psychomotor Developmental regression Seizures, Intractable Seizures, myoclonic MR Spectroscopy brain Cerebral atrophy (MRI)
156	Carbamoyl phosphate synthetase I deficiency	The validator likely entered carbamoyl phosphate synthase I instead of carnitine palmitoyltransferase 1 deficiency as the final diagnosis - which would therefore rank at #1.	↑ Carnitine, free normal Dicarboxylic acids (urine) ↓ Long-chain acylcarnitine (DBS)	Hepatopathy Renal tubular acidosis
289	Citrullinemia type II	Biomarkers and clinical presentation are not specific enough for the system to match to a disorder	↑ Ketone, during hypoglycemia normal Lactate (plasma) normal Acylcarnitine, all (plasma) ↑ Beta-hydroxybutyrate (urine) ↑ Acetoacetate (urine) ↓ Amino acids (urine)	Hypoglycemia, episodic Abdominal pain Short stature

Table S4. Mini-expert system performance using only biochemical/clinical queries

	Biochemical only	Clinical only
MRR	0.70	0.29
% success at 1	60	19
% success at 5	83	38
% success at 10	89	49
% success at 20	91	55

Mean reciprocal rank (MRR) measures how close the correct match is to the top rank on average. It ranges from 0 to 1 and values close to 1 indicate that correct matches appear closer to the top on average. % success at N = % of cases with correct diagnoses within top N ranks. Cases with only biochemical phenotypes or only clinical phenotypes were removed from the set (n=172).