Supporting Online Materials

Supporting Online Materials Table 1:

Categories	Characteristics	Scoring method	Description
Clinical Impact of Phenotype	**Age of onset:**	Prenatal, 0-2, 3-7, 8-13, 14-18, 19-30, 31-50, 50+	Age or age range during which phenotype presents and/or begins to have impact on individual's health
	Severity with treatment	Scored on a Likert scale, ranged 1 to 5, low to high	Phenotypic severity after treatment (if available), considering impact on day to day life and longterm morbidity and risk
	Severity without treatment	Scored on a Likert scale, ranged 1 to 5, low to high	Phenotypic severity before or without any treatment, considering impact on day to day life and longterm morbidity and risk
	Reproductive issues:	No impact	Possible reproductive considerations resulting from phenotype
		Physical or medical problem(s) directly affecting reproduction	
		Decreased reproductive fitness based on lifespan issues	
		Decreased reproductive fitness based on physical or mental disability	
Clinical Actionability	**Efficacy**	Scored on a Likert scale, ranged 1 to 5, low to high	How effective are available treatments and interventions, how much can these interventions alleviate or prevent symptoms/presentations of the condition
	Invasiveness/ Challenge	Scored on a Likert scale, ranged 1 to 5, low to high	How physically invasive are available interventions, how much risk is involved, how challenging might these interventions be (physically, emotionally, socially, etc.)
	Frequency/ Duration	Scored on a Likert scale, ranged 1 to 5, low to high	How often must an affected individual undertake treatments and interventions or engage in management behaviors
	Medical benefit of presymptomatic knowledge	Scored on a Likert scale, ranged 1 to 3, low to high	If available, how beneficial are presymptomatic interventions, including screening and monitoring, prophylactics measures, etc.
	Medical harm of presymptomatic knowledge	Scored on a Likert scale, ranged 1 to 3, low to high	If available, how potentially harmful are presymptomatic interventions, including screening and monitoring, prophylactics measures, etc.
	Comments	Standardized list of intervention types	Details concerning presymptomatic medical interventions
Association Validity	**Relative Risk**	Scored on a Likert scale, ranged 1 to 4, low to high	If available, what is the relative risk (or odds ratio) value for the association
	Validity	Scored on a Likert scale, ranged 1 to 3, low to high	How strong is the reported association, how likely is it that the variant is causative or a risk factor for the listed phenotype
	Validity comments	Free text field	Details concerning the validity score, including study factors and association data that contributed to validity score

Supporting Online Materials Figure 1: The complete criteria used by the consensus group of expert by genetic counselors to annotate each sampled variant.

Supporting Online Materials Table 2: Annotation scores for the 160 reviewed variants. Each row includes the phenotype of the reviewed variant, in addition to the severity of associated phenotype with and without treatment, as well as the validity of each phenotype-variant association.

Phenotype	Severity without treatment	Severity with treatment	Change in Severity	Validity
22q11.2 deletion	4	3	1	Low
22q11.2 deletion syndrome (VCFS)	4	3	1	Moderate
Acute intermittent porphyria	3	3	0	Low
AD Spastic paraplegia	4	4	0	Low
Agammaglobulinemia (XL)	4	3	1	Low
Age of natural menopause	2	1	1	Unknown
Alexander disease	4	4	0	High
Alport syndrome (XL)	5	Variable	Variable	Low
Altered nAChR function	Unknown	Unknown	Unknown	Low
Androgen sensitivity in prostate cancer cells as a result of somatic mutation	Unknown	Unknown	Unknown	Low
Aniridia	3	2	1	High
Aniridia	3	2	1	Low
Aniridia	3	2	1	Low
Aplastic anemia	Variable	3	Variable	Low
AR Polycystic kidney and hepatic disease	4	3	1	Low
Association with myocardial infarction*	4	4	0	Low
Ataxia telangiectasia	4	4	0	High
Autosomal recessive deafness	1	1	0	High
Autosomal recessive osteopetrosis	5	4	1	Moderate
Bardet-Biedl syndrome	3	3	0	Low
Beckwith-Wiedemann syndrome	4	3	1	Moderate
Benign recurrent intrahepatic cholestasis	3	3	0	Low
Beta thalassemia - Hb Korea	2	2	0	Low
Bethlem myopathy	3	3	0	High
Bifid nose, renal agenesis, and anorectal malformation syndrome (BNAR)	Variable	Unknown	Unknown	High

Catecholaminergic polymorphic ventricular tachycardia	4	3	1	Low
Central Core disease	Variable	Variable	Variable	High
Cerebral cavernous malformation type1	3	3	0	High
Cerebral cavernous malformations	3	3	0	Unknown
Charcot-Marie-Tooth disease 4C	4	4	0	Low
Charcot-Marie-Tooth disease 4h	4	4	0	Moderate
Charcot-Marie-Tooth disease type 1b	4	4	0	Moderate
Chronic granulomatosis disease (AR)	4	3	1	Moderate
Colorectal cancer (NOS?)	Unknown	Unknown	Unknown	Unknown
Complement C7 deficiency	3	3	0	Unknown
Complement C7 deficiency	3	3	0	High
Congenital hypothyroidism	2	1	1	Low
Congenital lipoid adrenal hyperplasia	5	1	4	High
Coronary artery disease	4	4	0	Moderate
Currarino syndrome	5	2	3	High
Cystic fibrosis	4	4	0	Moderate
Cystic fibrosis	4	4	0	Low
Cystic fibrosis	4	4	0	High
Cystinuria	3	2	1	Low
Duchenne muscular dystrophy	5	5	0	Low
Dystophic epidermolysis bullosa	5	5	0	High
Early onset sarcoidosis	3	3	0	Moderate
Ectodermal dysplasia	4	3	1	Low
Ectopia lentis	2	2	0	Low
Emery Dreifuss muscular dystrophy	4	4	0	High
Enchanced S Cone syndrome	2	2	0	Moderate
Epidermolysis bullosa simplex (Dowling-Meara type)	4	3	1	Unknown
Erythrokeratodermia variabilis	2	2	0	Moderate
Fabry disease	5	4	1	Low

Factor XI deficiency (Hemophilia C)	3	3	0	High
Familial adenomatous polyposis	5	3	2	Moderate
Familial adenomatous polyposis	5	3	2	Low
Familial adenomatous polyposis	5	3	2	Low
Familial intrahepatic cholestasis	5	4	1	Low
FAP (attenuated)	4	2	2	Low
FAP (attenuated)	4	2	2	High
Gastric cancer susceptibility	5	4	1	Low
Gitelman syndrome	1	1	0	Low
Glioma	Variable	Variable	Variable	Low
Glucose transporter 1 deficiency syndrome	4	4	0	Moderate
Glucose-6-phosphate dehydrogenase deficiency	3	3	0	Low
Glucosephosphate isomerase deficiency	3	3	0	Moderate
H-antigen deficiency (Bombay)	1	1	0	Moderate
Harlequin Ichthyosis	5	4	1	Moderate
Harlequin ichthyosis (AR)	5	4	1	Moderate
Hemoglobin Tacoma	1	1	0	High
Hereditary angioedema	3	3	0	Moderate
Hereditary angioedema	3	3	0	Low
Hereditary Breast and Ovarian Cancer syndrome	5	3	2	High
Hereditary Breast and Ovarian Cancer syndrome	5	3	2	High
Hereditary Breast and Ovarian Cancer syndrome	5	3	2	Low
Hereditary Breast and Ovarian Cancer syndrome	5	3	2	Moderate
Hereditary hemorrhagic telangiectasia	3	3	0	High
Hereditary Hemorrhagic Telangiectasia	3	3	0	High
Hereditary Spastic Paraplegia	4	3	1	Moderate
Hirschsprung disease	4	2	2	Moderate

Hirschsprung disease	4	2	2	Low
HLA-B null allele	1	1	0	Moderate
HNPCC	5	4	1	Low
Homocystinura cblD type	4	3	1	Moderate
Hypercholesterolemia	Variable	3	Variable	Low
Hypercholesterolemia	Variable	3	Variable	Low
Hypercholesterolemia	Variable	3	Variable	High
Hypertension (essential)	3	2	1	Low
Hypoprothrombinemia	3	3	0	Moderate
Incomplete congenital stationary night blindness (type 2)	1	1	0	Low
Increased risk for type II diabetes	4	2	2	High
Juvenile intestinal polyposis	4	3	1	Low
Limb Girdle muscular dystrophy type 2a	3	3	0	Low
Long QT syndrome	4	2	2	Low
Macular corneal dystrophy type 1	3	3	0	Low
Marfan syndrome	4	4	0	Low
Marinesco-Sjogren syndrome	4	4	0	High
Maturity onset diabetes of the young (MODY) type II	Variable	1	Variable	Low
Maturity onset diabetes of the young (MODY) type III	Variable	1	Variable	High
Modifier of risk for obesity	3	1	2	Low
Molybdenum cofactor deficiency	5	Unknown	Unknown	Unknown
MPS II - Hunter syndrome	Variable	Variable	Variable	Low
Mucolipidosis type 2 (I-cell diease)	5	5	0	High
Multiple endocrine neoplasia type 1	4	3	1	Low
Multiple epiphyseal dysplasia	3	3	0	Low
Nemaline myopathy	Variable	Variable	Variable	High
Nephrogenic diabetes insipidus	4	2	2	Low
Nephropathic cystinosis	5	4	1	High

Neurofibromatosis type 1 (NF1)	Variable	Variable	Variable	High
Neurofibromatosis type 1 (NF1)	Variable	Variable	Variable	Moderate
Nevoid basal cell carcinoma	5	3	2	Moderate
Niemann-Pick disease type A	5	5	0	High
Niemann-Pick type C	5	5	0	Moderate
Nocturnal asthma	3	2	1	High
Oculocutaneous albinism type 1A	2	1	1	Unknown
Oculocutaneous albinism, type 1A	2	1	1	Unknown
Oral white sponge nevus	1	1	0	Moderate
Ornithine transcarbamylase deficiency	5	2	3	Low
Osteogenesis imperfecta	4	4	0	Moderate
Osteoporosis	3	2	1	Moderate
PKU (phenylketonuria)	5	1	4	High
Polycystic kidney disease 2	5	4	1	Moderate
Polycystic kidney disease type 1 (AD)	4	3	1	Moderate
Polymorphic ventricular tachycardia	4	3	1	Moderate
Primary congenital glaucoma	4	2	2	Moderate
Primary open-angle glaucoma	3	1	2	Low
Progressive external ophthalmoplegia	Variable	Variable	Variable	Moderate
Properdin deficiency	4	1	3	Moderate
Protein S deficiency	3	2	1	Low
Protoporphyria	3	3	0	Unknown
Pulmonary hyptertension	Unknown	Unknown	Unknown	Low
Renal glucosuria	1	1	0	Low
Retinitis Pigmentosa - autosomal dominant	2	2	0	Low
Retinol deficiency	2	Unknown	Unknown	Moderate
Retinoschisis	2	2	0	Moderate
Rett syndrome	5	5	0	Moderate
Rett syndrome	5	5	0	Low
Rett syndrome	5	5	0	High

Salla disease	5	5	0	High
Shprintzen-Goldberg syndrome (or related disorders)	4	4	0	Moderate
Slow channel myasthenic syndrome	3	3	0	High
Spherocytosis	Variable	Variable	Variable	Low
Spondyloepiphyseal dysplasia	3	3	0	High
Stargardt disease	2	2	0	Unknown
Susceptibility to TB	3	3	0	Moderate
Tropical pancreatitis	3	3	0	Moderate
Tuberous sclerosis	4	4	0	Moderate
Tuberous sclerosis	4	4	0	Unknown
Tuberous sclerosis	4	4	0	Moderate
Tyrosinemia type 1	5	2	3	High
Ullrich congenital muscular dystrophy	4	4	0	Low
Variegate porphyria	Variable	3	Variable	Low
Von Hippel-Lindau	4	4	0	Low
Walker Warburg syndrome	5	5	0	Moderate
Wilson disease	4	2	2	Moderate
Wilson disease	4	2	2	Moderate
Xeroderma pigmentosum (variant type)	5	4	1	Moderate
XL lymphoproliferative syndrome	5	4	1	Moderate
XL SCID (severe combined immunodeficiency)	5	2	3	Moderate