



## Review article

## Expanded carrier screening: A current perspective

Enrica Mastantuoni<sup>a</sup>, Gabriele Saccone<sup>a,\*</sup>, Huda B. Al-Kouatly<sup>b</sup>, Mariano Paternoster<sup>c</sup>, Pietro D'Alessandro<sup>a</sup>, Bruno Arduino<sup>a</sup>, Luigi Carbone<sup>a</sup>, Giuseppina Esposito<sup>a</sup>, Antonio Raffone<sup>a</sup>, Valentino De Vivo<sup>a</sup>, Giuseppe Maria Maruotti<sup>a</sup>, Vincenzo Berghella<sup>b</sup>, Fulvio Zullo<sup>a</sup>

<sup>a</sup> Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy

<sup>b</sup> Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA

<sup>c</sup> Department of Advanced Biomedical Sciences, School of Medicine, University of Naples Federico II, Naples, Italy



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## ABSTRACT

Prenatal carrier screening has expanded to include a large number of genes offered to all couples considering pregnancy or with an ongoing pregnancy. Expanded carrier screening refers to identification of carriers of single-gene disorders outside of traditional screening guidelines. Expanded carrier screening panels include numerous autosomal recessive and X-linked genetic conditions, including those with a very low carrier frequency, as well as those with mild or incompletely penetrant phenotype. Therefore, the clinical utility of these panels is still subject of debate. Priority should be given to carrier screening panels that include a comprehensive set of severe childhood-onset disorders. Psychosocial support and genetic counseling should be available prior to screening and for the return of positive results. Systems are needed to reduce the risk of misinterpreting results. Finally, attention should be paid on the impact of expanded carrier screening on health care organizations and burden of cost.

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### Background on carrier screening

Carrier screening is defined as a genetic study aimed at discovering the presence of carriers for autosomal recessive or X-

linked recessive disorders in a not at *a priori* risk population, based on the personal and family genetic disease history [1].

Nowadays we count more than 2000 recessive disorders among autosomal and X-linked [2–5]. Recessive disorders affect at least 25 in 10,000 children and 1 in 100 couples are carriers, with a risk of 25% of having a child affected with an autosomal recessive genetic condition [1,5,6]. Currently, carrier screening is becoming a standard practice for individuals with a positive family history of a recessive disease [7].

\* Corresponding author.

E-mail address: [gabriele.saccone.1990@gmail.com](mailto:gabriele.saccone.1990@gmail.com) (G. Saccone).

We can identify two different time intervals where carrier screening can be offered to individuals or couples: preconception screening before pregnancy, and prenatal during pregnancy. Although the prenatal screening is at present the one most performed, the preconceptional screening seems to be a better alternative to allow the parents conscious reproductive choices [7]. Newborn screening must be distinguished from carrier screening. The aim of newborn screening is to detect diseases for early treatment by testing directly the newborn. Carrier screening may allow the neonates to obtain medical care earlier than newborn screening. Carrier screening alone, however, without newborn screening would miss many affected neonates [8].

One of the major discussions about carrier screening is to whom it should be offered. It can be offered to individuals, usually the woman, or couples, especially when a maternal or paternal mutation is identified. Moreover, populations with different risks for heterozygous carrier frequency can be examined: low risk populations in which the test can be part of a general screening program or high risk populations because of positive family history or being a member of a particular ethnic group [2,7,9,10].

In 2013, the American College of Medical Genetics and Genomics (ACMG) published a position statement on carrier screening.<sup>11</sup> For a disorder to be included in carrier screening, ACMG set the following criteria: the at-risk patients and their partners identified would consider having a prenatal diagnosis; when adult-onset disorders are included in the screening panels, patients must provide consent to screening for these conditions; the causative gene(s), mutations and mutation frequencies should be known in the population being tested so that residual risk in those who test negative can be assessed; there must be a strong clinical association between mutation(s) and the severity of the disorder and compliance with ACMG quality control and proficiency testing. Genetic counseling before testing should be available and post-test genetic counseling for those with positive results is recommended. ACMG discourages including as many disorders as possible, not only because it could be not appropriated belonging to a criteria, but also because it could be unpractical for a provider to discuss each clinical condition included in a multidisease carrier screening panel [11]. Other societies such as, ACOG, the National Society of Genetics Counselors and the Society of Maternal-Fetal Medicine (SMFM) agree with ACMG criteria and recommendations [12].

In 2017, the ACOG's Committee Opinion, Carrier Screening in the Age of Genomic Medicine, defined similar criteria and recommendations for clinicians to evaluate predefined commercial expanded carrier panels and to determine their appropriateness [13].

- Expanded carrier screening is an acceptable strategy for pre-pregnancy and prenatal screening
- Counseling should be offered;
- Patients should be counseled regarding residual risk with negative result;
- The reproductive partner of a woman found to be a carrier for a specific condition should be offered screening. If carriers for the same mutation are identified before pregnancy, genetic counseling is encouraged to discuss and maximize reproductive options (donor gametes, preimplantation genetic diagnosis, prenatal diagnosis);
- Given the high variability of genetic panels currently on the market, the disorders selected for inclusion should meet several of the following consensus-determined criteria: have a carrier frequency of 1 in 100 or greater, have a well-defined phenotype, have a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life. Additionally, screened conditions should be able to be diagnosed prenatally and may afford opportunities for antenatal intervention to improve perinatal

outcomes, changes to delivery management to optimize newborn and infant outcomes, and education of the parents about special care needs after birth. Carrier screening panels should not include conditions primarily associated with a disease of adult onset.

Nowadays, carrier screening has expanded to include a larger number of genes offered to all couples considering pregnancy or with an ongoing pregnancy. Benefits of including too many conditions in expanded panels must be weighed against harms in order to limit the psychological consequences of anxiety, stigmatization and confusion, financial expense, and clinician time and optimize the utility of the screening [14–16].

Stevens et al. established more specific criteria for inclusion of genetic conditions on expanded panels and analyzed several commercially available screening panels to evaluate if they are in line with the committee opinion [14]. On average, 73% of conditions on expanded carrier screening panels they analyzed did not match the criteria recommended by ACMG and ACOG. Terhaar et al. found that with a panel of 218 diseases, the likelihood of identifying a carrier can be as high as 36% [15].

### New generation expanded carrier screening

In the age of genomic medicine, the interest in the carrier screening is growing as the genetic tests are becoming widely available and their costs are much more affordable. In the past, carrier screening has evaluated a relatively small group of mutations selected based on two main characteristics: high frequency in specific populations and severe morbidity and mortality. Currently, commercial laboratories offer test panels that screen for four to over 1700 diseases, which are not selected based on racial or ethnic background. The majority of conditions are autosomal-recessive, but some may be X-linked or autosomal-dominant single gene disorders. The rationale for expanded carrier screening is that the majority of carrier individuals have no family history of the genetic condition(s) they carry, or are not aware of their full ancestry or true ethnicity. Table 1 shows one of the preconceptional expanded carrier screening panels available on the market, including more than 700 conditions. These expanded panels include also some conditions that result in only mild to moderate health complications (e.g. factor V Leiden), have significant variations in or poorly defined phenotype (e.g. fragile X) or have onset in adulthood (e.g. BRCA1/2). The frequency of some conditions is unknown in the general population, rendering calculation of residual risk after a positive test inconclusive. Including these type of conditions in a screening panel is in direct conflict with the accepted clinical criteria for screening programs [4,6,12]. Moreover, identifying variants of uncertain clinical significance, may create patient anxiety despite counselling, which will complex and time-consuming with the inclusion of large set of disorders on the expanded screening panel. Therefore, the clinical utility of these expanded panels is still subject to debate.

### Diseases screened

In 1968, Wilson and Jungner outlined the principles for using a screening test for early disease detection [4]. These principles are still used by the World Health Organization and are still valid to justify a screening program. For reproductive screening, the aim is not of early diagnosis but to facilitate reproductive decision making.

One of the biggest challenges in the development of expanded carrier screening is to identify the appropriate criteria to uniform the test and to reduce the huge variability in current commercially available panels. The European Society of Human Genetics

**Table 1**  
Example of one of the preconceptional expanded carrier screening panel available on the market.

	Disease Name	PhenOMIM	Gene
1	17-alpha-hydroxylase/17,20-lyase deficiency	202110	CYP17A1
2	17-beta-hydroxysteroid dehydrogenase X deficiency	300438	HSD17B10
3	3-beta-hydroxysteroid dehydrogenase, type II, deficiency	201810	HSD3B2
4	3-hydroxy-3-methylglutaric aciduria	246450	HMGCL
5	3-methylglutaconic aciduria type 1	250950	AUH
6	3-methylglutaconic aciduria type 3	258501	OPA3
7	46XY sex reversal 3	612965	NR5A1
8	4-hydroxybutyric aciduria	271980	ALDH5A1
9	Aarskog-Scott syndrome	305400	FGD1
10	ABCD syndrome	600501	EDNRB
11	Achalasia-addisonianism-alacrimia syndrome	231550	AAAS
12	Achondrogenesis type 1B	600972	SLC26A2
13	Acyl-CoA dehydrogenase 9 deficiency	611126	ACAD9
14	Adrenal hyperplasia, congenital, due to 11-beta-hydroxylase deficiency	202010	CYP11B1
15	Adrenal insufficiency, congenital, with 46XY sex reversal, partial or complete	613743	CYP11A1
16	Adrenocortical insufficiency	612965	NR5A1
17	Adrenoleukodystrophy	300100	ABCD1
18	Adult neuronal ceroid lipofuscinosis	256730	PPT1
19	Adult neuronal ceroid lipofuscinosis 10	610127	CTSD
20	Adult neuronal ceroid lipofuscinosis 4A	204300	CLN6
21	Aicardi-Goutières syndrome	225750	TREX1
22	Aicardi-Goutières syndrome 2	610181	RNASEH2B
23	Aicardi-Goutières syndrome 3	610329	RNASEH2C
24	Aicardi-Goutières syndrome 4	610333	RNASEH2A
25	Aicardi-Goutières syndrome 5	612952	SAMHD1
26	Aldosteronism, glucocorticoid-remediable	103900	CYP11B1
27	Allan-Herndon-Dudley syndrome	300523	SLC16A2
28	Alpers syndrome	203700	POLG
29	Alpha-methylacyl-CoA Racemase deficiency	614307	AMACR
30	Alph A-T halassemia	604131	HBA1
31	Alph A-T halassemia myelodysplasia syndrome, somatic	300448	ATRX
32	Alph A-T halassemia/mental retardation syndrome	301040	ATRX
33	Alport syndrome	301050	COL4A5
34	Alport syndrome autosomal recessive (gene COL4A3)	203780	COL4A3
35	Alport syndrome autosomal recessive (gene COL4A4)	203780	COL4A4
36	Alström syndrome	203800	ALMS1
37	Amish infantile epilepsy syndrome	609056	ST3GAL5
38	Amyotrophic lateral sclerosis 2, juvenile	205100	ALS2
39	Anauxetic dysplasia	607095	RMRP
40	Angelman syndrome	105830	UBE3A
41	Antenatal Bartter syndrome	241200	KCNJ1
42	Antenatal Bartter syndrome type 1	601678	SLC12A1
43	Antley-Bixler syndrome with genital anomalies and disordered steroidogenesis	201750	POR
44	Aplasia/hypoplasia of limbs and pelvis	276820	WNT7A
45	Aplastic anemia	609135	NBN
46	Apparent mineralocorticoid excess	218030	HSD11B2
47	Argininosuccinic aciduria	207900	ASL
48	Aromatic L-amino acid decarboxylase deficiency	608643	DDC
49	Arthrogryposis - renal dysfunction - cholestasis	208085	VPS33B
50	Arthrogryposis, renal dysfunction, and cholestasis 2	613404	VIPAR
51	Ataxia - oculomotor apraxia type 1	208920	APTX
52	Ataxia with vitamin E deficiency	277460	TTPA
53	Ataxi A-T elangiectasia	208900	ATM
54	Atelosteogenesis type II	256050	SLC26A2
55	Autism, susceptibility to, X-linked 5	300847	RPL10
56	Autoimmune lymphoproliferative syndrome, type IA	601859	FAS
57	Autoimmune lymphoproliferative syndrome, type IB	601859	FASLG
58	Autoimmune lymphoproliferative syndrome, type II	603909	CASP10
59	Autoimmune polyendocrinopathy syndrome, type I, with or without reversible metaphyseal dysplasia	240300	AIRE
60	Autosomal dominant Charcot-Marie-Tooth disease type 2K	607831	GDAP1
61	Autosomal recessive ataxia due to ubiquinone deficiency	612016	ADCK3
62	Autosomal recessive Charcot-Marie-Tooth disease with hoarseness	607706	GDAP1
63	Autosomal recessive distal spinal muscular atrophy type 4	611067	PLEKHG5
64	Autosomal recessive dopa-responsive dystonia	605407	TH
65	Autosomal recessive hypophosphatemic rickets 1	241520	DMP1
66	Autosomal recessive hypophosphatemic rickets 2	613312	ENPP1
67	Autosomal recessive intermediate Charcot-Marie-Tooth disease type A	608340	GDAP1
68	Autosomal recessive limb-girdle muscular dystrophy type 2I	607155	FKRP
69	Autosomal recessive limb-girdle muscular dystrophy type 2M	611588	FKTN
70	Autosomal recessive limb-girdle muscular dystrophy type C	613157	POMGNT1
71	Autosomal recessive limb-girdle muscular dystrophy type C	609308	POMT1
72	Autosomal recessive limb-girdle muscular dystrophy type C	613158	POMT2
73	Autosomal recessive malignant osteopetrosis 1	259700	TCIRG1
74	Autosomal recessive malignant osteopetrosis 4	611490	CLCN7

Table 1 (Continued)

Disease Name	PhenOMIM	Gene	
75	Autosomal recessive nonsyndromic sensorineural deafness type DFNB12	601386	CDH23
76	Autosomal recessive nonsyndromic sensorineural deafness type DFNB18	602092	USH1C
77	Autosomal recessive nonsyndromic sensorineural deafness type DFNB1A (gene GJB2)	220290	GJB2
78	Autosomal recessive nonsyndromic sensorineural deafness type DFNB2	600060	MYO7A
79	Autosomal recessive polycystic kidney disease	263200	PKHD1
80	Autosomal recessive progressive external ophthalmoplegia	258450	POLG
81	Autosomal recessive spastic ataxia of Charlevoix-Saguenay	270550	SACS
82	Autosomal recessive spondylocostal dysostosis 1	277300	DLL3
83	Bannayan-Riley-Ruvalcaba syndrome	153480	PTEN
84	Barth syndrome	302060	TAZ
85	Becker muscular dystrophy	300376	DMD
86	Beckwith-Wiedemann syndrome	130650	NSD1
87	Bet A-T halassemia	613985	HBB
88	Bethlem myopathy	158810	COL6A1
89	Bethlem myopathy	158810	COL6A2
90	Bethlem myopathy	158810	COL6A3
91	Bifunctional enzyme deficiency	261515	HSD17B4
92	Biotinidase deficiency	253260	BTD
93	Björnstad syndrome	262000	BCS1L
94	Bloom syndrome	210900	BLM
95	Brachytelephalangic chondrodysplasia punctata	302950	ARSE
96	Brittle cornea syndrome	229200	ZNF469
97	Caffey disease	114000	COL1A1
98	Canavan disease	271900	ASPA
99	Carbamoylphosphate synthetase deficiency	237300	CPS1
100	Cardioencephalomyopathy, fatal infantile, due to cytochrome c oxidase deficiency 1	604377	SCO2
101	Cardioencephalomyopathy, fatal infantile, due to cytochrome c oxidase deficiency 2	615119	COX15
102	Carnitine deficiency, systemic primary	212140	SLC22A5
103	Carnitine palmitoyl transferase 1A deficiency	255120	CPT1A
104	Carnitine palmitoyl transferase II deficiency, infantile form	600649	CPT2
105	Carnitine palmitoyl transferase II deficiency, neonatal form	608836	CPT2
106	Carnitine-acylcarnitine translocase deficiency	212138	SLC25A20
107	Carpenter syndrome	201000	RAB23
108	Cartilage-hair hypoplasia	250250	RMRP
109	Cataract - intellectual deficit - hypogonadism	212720	RAB3GAP2
110	Cataract 40, X-linked	302200	NHS
111	Cerebellar ataxia - intellectual deficit - dysequilibrium syndrome	224050	VLDR
112	Cerebral dysgenesis-neuropathy-ichthyosis-palmoplantar keratoderma syndrome	609528	SNAP29
113	Cerebrotendinous xanthomatosis	213700	CYP27A1
114	Charcot-Marie-Tooth disease axonal type 2B1	605588	LMNA
115	Charcot-Marie-Tooth disease type 4A	214400	GDAP1
116	Charcot-Marie-Tooth disease type 4E	605253	EGR2
117	Charcot-Marie-Tooth disease type 4F	614895	PRX
118	Charcot-Marie-Tooth disease type 4H	609311	FGD4
119	Charcot-Marie-Tooth disease, type 1A	118220	PMP22
120	Charcot-Marie-Tooth disease, type 1B	118200	MPZ
121	Charcot-Marie-Tooth disease, type 1E	118300	PMP22
122	Charcot-Marie-Tooth disease, type 2I	607677	MPZ
123	Charcot-Marie-Tooth disease, type 2J	607736	MPZ
124	Chediak-Higashi syndrome	214500	LYST
125	Chilblain lupus 2	614415	SAMHD1
126	Childhood-onset hypophosphatasia	241510	ALPL
127	Cholestasis, benign recurrent intrahepatic	243300	ATP8B1
128	Cholestasis, benign recurrent intrahepatic, 2	605479	ABCB11
129	Cholestasis, intrahepatic, of pregnancy, 1	147480	ATP8B1
130	Cholestasis, intrahepatic, of pregnancy, 3	614972	ABCB4
131	Cholestasis, progressive familial intrahepatic 1	211600	ATP8B1
132	Cholestasis, progressive familial intrahepatic 2	601847	ABCB11
133	Cholestasis, progressive familial intrahepatic 3	602347	ABCB4
134	Chondrodysplasia, Blomstrand type	215045	PTH1R
135	Citrullinemia type I	215700	ASS1
136	Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency	201910	CYP21A2
137	Classic galactosemia	230400	GALT
138	Classic maple syrup urine disease	248600	DBT
139	Classical homocystinuria	236200	CBS
140	COACH syndrome	216360	TMEM67
141	Cockayne syndrome type A	216400	ERCC8
142	Cockayne syndrome type B	133540	ERCC6
143	Coenzyme Q10 deficiency, primary, 5	614654	COQ9
144	Coffin-Lowry syndrome	303600	RPS6KA3
145	COFS syndrome 1	214150	ERCC6
146	Cohen Syndrome type 1	216550	VPS13B
147	Cold-induced sweating syndrome	272430	CRLF1
148	Combined immunodeficiency with skin granulomas	233650	RAG1
149	Combined immunodeficiency with skin granulomas	233650	RAG2
150	Combined oxidative phosphorylation defect type 2	610498	MRPS16
151	Combined oxidative phosphorylation defect type 5	611719	MRPS22

Table 1 (Continued)

Disease Name	PhenOMIM	Gene	
152	Combined oxidative phosphorylation deficiency 4	610678	TUFM
153	Combined pituitary hormone deficiencies, genetic forms	182230	HESX1
154	Combined pituitary hormone deficiencies, genetic forms	613038	POU1F1
155	Combined pituitary hormone deficiencies, genetic forms	262600	PROP1
156	Combined pituitary hormone deficiency with spine abnormalities	221750	LHX3
157	Complete androgen insensitivity syndrome	300068	AR
158	Complex I, mitochondrial respiratory chain, deficiency of	252010	NDUFS6
159	Congenital bile acid synthesis defect type 4	214950	AMACR
160	Congenital disorder of glycosylation type 1a	212065	PMM2
161	Congenital disorder of glycosylation type 1b	602579	MPI
162	Congenital disorder of glycosylation type 1e	608799	DPM1
163	Congenital disorder of glycosylation type 1j	608093	DPAGT1
164	Congenital disorder of glycosylation type 2a	212066	MGAT2
165	Congenital disorder of glycosylation type 2c	266265	SLC35C1
166	Congenital disorder of glycosylation type 2d	607091	B4GALT1
167	Congenital disorder of glycosylation type 2f	603585	SLC35A1
168	Congenital disorder of glycosylation type 1c	603147	ALG6
169	Congenital disorder of glycosylation type 1k	608540	ALG1
170	Congenital disorder of glycosylation, type 1d	601110	ALG3
171	Congenital disorder of glycosylation, type 1f	609180	MPDU1
172	Congenital disorder of glycosylation, type 1g	607143	ALG12
173	Congenital disorder of glycosylation, type 1h	608104	ALG8
174	Congenital disorder of glycosylation, type 1i	607906	ALG2
175	Congenital disorder of glycosylation, type 1lb	606056	MOGS
176	Congenital disorder of glycosylation, type 1le	608779	COG7
177	Congenital disorder of glycosylation, type 1lg	611209	COG1
178	Congenital disorder of glycosylation, type 1lh	611182	COG8
179	Congenital disorder of glycosylation, type 1l	608776	ALG9
180	Congenital disorder of glycosylation, type 1m	610768	DOLK
181	Congenital disorder of glycosylation, type 1n	612015	RFT1
182	Congenital disorder of glycosylation, type 1q	612379	SRD5A3
183	Congenital fibrinogen deficiency (gene FGA)	202400	FGA
184	Congenital heart defects, nonsyndromic, 1, X-linked	306955	ZIC3
185	Congenital hereditary endothelial dystrophy type II	217700	SLC4A11
186	Congenital lipoid adrenal hyperplasia	201710	STAR
187	Congenital malabsorptive diarrhea due to paucity of enteroendocrine cells	610370	NEUROG3
188	Congenital muscular dystrophy type 1A	607855	LAMA2
189	Congenital muscular dystrophy type 1D	608840	LARGE
190	Congenital muscular dystrophy type 4B	613152	FKTN
191	Congenital muscular dystrophy type 5B	606612	FKRP
192	Congenital muscular dystrophy with cerebellar involvement	613151	POMGNT1
193	Congenital muscular dystrophy with cerebellar involvement	613155	POMT1
194	Congenital muscular dystrophy with cerebellar involvement	613156	POMT2
195	Corneal dystrophy - perceptive deafness	217400	SLC4A11
196	Corpus callosum agenesis - neuropathy	218000	SLC12A6
197	Corpus callosum hypoplasia-retardation-adducted thumbs-spasticity- hydrocephalus syndrome	307000	L1CAM
198	Cowden syndrome 1	158350	PTEN
199	Craniofrontonasal dysplasia	304110	EFNB1
200	Cutis laxa, autosomal dominant 2	614434	FBLN5
201	Cutis laxa, autosomal recessive, type IA	219100	FBLN5
202	Cutis laxa, autosomal recessive, type IB	614437	EFEMP2
203	Cutis laxa, autosomal recessive, type IIA	219200	ATP6V0A2
204	Cystic fibrosis; mucoviscidosis	219700	CFTR
205	Cystinosis	219800	CTNS
206	Deafness - encephaloneuropathy - obesity - valvulopathy	614651	PDSS1
207	Dejerine-Sottas disease	145900	MPZ
208	Dejerine-Sottas disease	145900	PMP22
209	Dent disease	300009	CLCN5
210	Dent disease 2	300555	OCRL
211	Desmoterolosis	602398	DHCR24
212	Diabetes mellitus, noninsulin-dependent	125853	ABCC8
213	Diabetes mellitus, permanent neonatal	606176	ABCC8
214	Diabetes mellitus, transient neonatal 2	610374	ABCC8
215	Diastrophic dwarfism	222600	SLC26A2
216	Dihydropyrimidine dehydrogenase deficiency	274270	DPYD
217	Dilated cardiomyopathy with ataxia	610198	DNAJC19
218	Donnai-Barrow syndrome	222448	LRP2
219	Duchenne muscular dystrophy	310200	DMD
220	Dyskeratosis congenita X-linked	305000	DKC1
221	Dystrophic epidermolysis bullosa pruriginosa	604129	COL7A1
222	Early infantile epileptic encephalopathy	308350	ARX
223	Early infantile epileptic encephalopathy	609304	SLC25A22
224	Ectodermal dysplasia 1, hypohidrotic, X-linked	305100	EDA
225	Ectodermal dysplasia, hypohidrotic, with immune deficiency	300291	IKBK
226	Ectodermal, dysplasia, anhidrotic, lymphedema and immunodeficiency	300301	IKBK
227	Ehlers-Danlos syndrome type 6	225400	PLOD1
228	Ehlers-Danlos syndrome, cardiac valvular type	225320	COL1A2

Table 1 (Continued)

Disease Name	PhenOMIM	Gene	
229	Ehlers–Danlos syndrome, type I	130000	COL1A1
230	Ehlers–Danlos syndrome, type VIIA	130060	COL1A1
231	Eiken syndrome	600002	PTH1R
232	Ellis–van Creveld syndrome	225500	EVC2
233	Ellis–van Creveld syndrome	225500	EVC
234	Encephalopathy due to prosaposin deficiency	611721	PSAP
235	Epidermolysis bullosa simplex with muscular dystrophy	226670	PLEC
236	Epidermolysis bullosa simplex with pyloric atresia	612138	PLEC
237	Epilepsy, progressive myoclonic 2A (Lafora)	254780	EPM2A
238	Epilepsy, progressive myoclonic 2B (Lafora)	254780	NHLRC1
239	Epilepsy, pyridoxine-dependent	266100	ALDH7A1
240	Epileptic encephalopathy, early infantile, 15	615006	ST3GAL3
241	Epileptic encephalopathy, early infantile, 2	300672	CDKL5
242	Epileptic encephalopathy, early infantile, 8	300607	ARHGFB9
243	Epileptic encephalopathy, early infantile, 9	300088	PCDH19
244	Escobar syndrome	265000	CHRN3
245	Ethylmalonic encephalopathy	602473	ETHE1
246	Exudative vitreoretinopathy 2, X-linked	305390	NDP
247	Fabry disease	301500	GLA
248	Failure of tooth eruption, primary	125350	PTH1R
249	Familial dysautonomia	223900	IKBKAP
250	Familial hypomagnesemia - hypercalciuria - nephrocalcinosis - severe ocular involvement	248190	CLDN19
251	Familial Mediterranean fever	249100	MEFV
252	Fanconi anemia complementation group C	227645	FANCC
253	Fatal infantile lactic acidosis with methylmalonic aciduria	245400	SUCLG1
254	Fatal mitochondrial disease due to combined oxidative phosphorylation deficiency 3	610505	TSFM
255	Favism	134700	G6PD
256	Fertile eunuch syndrome	228300	GNRHR
257	Fetal akinesia deformation sequence	208150	RAPSN
258	Fetal akinesia deformation sequence	208150	DOK7
259	Fetal Gaucher disease	608013	GBA
260	FG syndrome 4	300422	CASK
261	Fibular hypoplasia or aplasia - femoral bowing - oligodactyly	228930	WNT7A
262	Fraser syndrome (gene FRAS1)	219000	FRAS1
263	Fraser syndrome (gene FRAS2)	219000	FREM2
264	Free sialic acid storage disease, infantile form	269920	SLC17A5
265	French-Canadian type Leigh syndrome	220111	LRPPRC
266	Fucosidosis	230000	FUCA1
267	Fukuyama congenital muscular dystrophy	253800	FKTN
268	Fumaric aciduria	606812	FH
269	Galactokinase deficiency with cataracts	230200	GALK1
270	Gallbladder disease 1	600803	ABC4
271	Gaucher disease type 2	230900	GBA
272	Gaucher disease type 3	231000	GBA
273	Gaucher disease type 3C	231005	GBA
274	Geleophysic dysplasia 1	231050	ADAMTSL2
275	Generalized junctional epidermolysis bullosa, non-Herlitz type	226650	COL17A1
276	Glutaric acidemia type 2 (gene ETFA)	231680	ETFPA
277	Glutaric acidemia type 2 (gene ETFB)	231680	ETFB
278	Glutaric acidemia type 2 (gene ETFDH)	231680	ETFDH
279	Glutaryl-CoA dehydrogenase deficiency	231670	GCDH
280	Glutathione synthetase deficiency with 5-oxoprolinuria	266130	GSS
281	Glycine encephalopathy	605899	AMT
282	Glycine encephalopathy	605899	GCSH
283	Glycine encephalopathy	605899	GLDC
284	Glycogen storage disease due to acid maltase deficiency	232300	GAA
285	Glycogen storage disease due to glucose-6-phosphatase deficiency type 1a	232200	G6PC
286	Glycogen storage disease due to glucose-6-phosphatase deficiency type b	232220	SLC37A4
287	Glycogen storage disease due to glucose-6-phosphatase deficiency type c	232240	SLC37A4
288	Glycogen storage disease due to glycogen branching enzyme deficiency, childhood combined hepatic and myopathic form	232500	GBE1
289	Glycogen storage disease due to glycogen debranching enzyme deficiency	232400	AGL
290	Glycogen storage disease due to muscle glycogen phosphorylase deficiency	232600	PYGM
291	GM1 gangliosidosis type 1	230500	GLB1
292	GM1 gangliosidosis type 2	230600	GLB1
293	GM1 gangliosidosis type 3	230650	GLB1
294	GRACILE syndrome	603358	BCS1L
295	Greenberg dysplasia	215140	LBR
296	Griscelli disease type 1	214450	MYO5A
297	Griscelli disease type 2	607624	RAB27A
298	Guanidinoacetate methyltransferase deficiency	612736	GAMT
299	Hemochromatosis, type 2A	602390	HFE2
300	Hemolytic anemia due to G6PD deficiency	300908	G6PD
301	Hemolytic anemia due to red cell pyruvate kinase deficiency	266200	PKLR
302	Hemophagocytic lymphohistiocytosis, familial, 2	603553	PRF1
303	Hemophagocytic lymphohistiocytosis, familial, 3	608898	UNC13D
304	Hemophagocytic lymphohistiocytosis, familial, 4	603552	STX11

Table 1 (Continued)

Disease Name	PhenOMIM	Gene	
305	Hemophagocytic lymphohistiocytosis, familial, 5	613101	STXBP2
306	Hemophilia A	306700	F8
307	Hemophilia B	306900	F9
308	Hepatic venoocclusive disease with immunodeficiency	235550	SP110
309	Hepatoencephalopathy due to combined oxidative phosphorylation deficiency type 1	609060	GFM1
310	Hereditary fructose intolerance	229600	ALDOB
311	Hereditary sensory and autonomic neuropathy type 4	256800	NTRK1
312	Hermansky-Pudlak syndrome 2	608233	AP3B1
313	Hermansky-pudlak syndrome 9	614171	PLDN
314	Heterotaxy, visceral, 1, X-linked	306955	ZIC3
315	Histidinemia	235800	HAMP
316	Holocarboxylase synthetase deficiency	253270	HLCS
317	Hoyeraal-Hreidarsson syndrome	300240	DKC1
318	Hyaline fibromatosis syndrome	228600	ANTXR2
319	Hyperammonemia due to N-acetylglutamate synthetase deficiency	237310	NAGS
320	Hyper-IgE recurrent infection syndrome, autosomal recessive	243700	DOCK8
321	Hyperinsulinemic hypoglycemia, familial, 1	256450	ABCC8
322	Hyperornithinemia-hyperammonemia-homocitrullinuria	238970	SLC25A15
323	Hypoglycemia of infancy, leucine-sensitive	240800	ABCC8
324	Hypogonadotropic hypogonadism 7 without anosmia	146110	GNRHR
325	Hypomyelination - congenital cataract	610532	FAM126A
326	Hypoparathyroidism - intellectual deficit - dysmorphism syndrome	241410	TBCE
327	Hypophosphatemic rickets	300554	CLCN5
328	Ichthyosis follicularis - alopecia - photophobia	308205	MBTPS2
329	Ichthyosis, autosomal recessive 4B (harlequin)	242500	ABCA12
330	Ichthyosis, congenital, autosomal recessive 1	242300	TGM1
331	Ichthyosis, congenital, autosomal recessive 4A	601277	ABCA12
332	Ichthyosis, leukocyte vacuoles, alopecia, and sclerosing cholangitis 607626		CLDN1
333	Immunodeficiency 10	612783	STIM1
334	Immunodeficiency 17, CD3 gamma deficient	615607	CD3G
335	Immunodeficiency 18, SCID variant	615615	CD3E
336	Immunodeficiency 19	615617	CD3D
337	Immunodeficiency 27A, mycobacteriosis, AR	209950	IFNGR1
338	Immunodeficiency 28, mycobacteriosis	614889	IFNGR2
339	Immunodeficiency 29, mycobacteriosis	614890	IL12B
340	Immunodeficiency 30	614891	IL12RB1
341	Immunodeficiency 31A, mycobacteriosis, autosomal dominant	614892	STAT1
342	Immunodeficiency 31B, mycobacterial and viral infections, autosomal recessive	613796	STAT1
343	Immunodeficiency 31C, autosomal dominant	614162	STAT1
344	Immunodeficiency 33	300636	IKBKG
345	Immunodeficiency 35	611521	TYK2
346	Immunodeficiency 9	612782	ORAI1
347	Immunodeficiency, common variable, 1	607594	ICOS
348	Immunodeficiency, common variable, 3	613493	CD19
349	Immunodeficiency-centromeric instability-facial anomalies syndrome 1	242860	DNMT3B
350	Immunodysregulation, polyendocrinopathy, and enteropathy, X-linked	304790	FOXP3
351	Incontinentia pigmenti, type II	308300	IKBKG
352	Infantile bilateral striatal necrosis	271930	NUP62
353	Infantile hypophosphatasia	241500	ALPL
354	Infantile neuroaxonal dystrophy 2A	256600	PLA2G6
355	Infantile neuroaxonal dystrophy 2B	610217	PLA2G6
356	Infantile onset spinocerebellar ataxia	271245	C10orf2
357	Interleukin 1 receptor antagonist deficiency	612852	IL1RN
358	Isolated CoQ-cytochrome C reductase deficiency	124000	BCSL1
359	Isolated growth hormone deficiency type III	307200	BTK
360	Isolated thyroid-stimulating hormone deficiency	275100	TSHB
361	Isovaleric acidemia	243500	IVD
362	Jeune syndrome	611263	IFT80
363	Johanson-Blizzard syndrome	243800	UBR1
364	Joubert syndrome 4	609583	NPHP1
365	Joubert syndrome 6	610688	TMEM67
366	Joubert syndrome with hepatic defect	216360	RPGRIP1L
367	Joubert syndrome with ocular defect	608629	AHI1
368	Joubert syndrome with oculorenal defect 5	610188	CEP290
369	Junctional epidermolysis bullosa - pyloric atresia	226730	ITGA6
370	Junctional epidermolysis bullosa with piloric atresia	226730	ITGB4
371	Junctional epidermolysis bullosa, Herlitz type (gene LAMA3)	226700	LAMA3
372	Junctional epidermolysis bullosa, Herlitz type (gene LAMB3)	226700	LAMA3
373	Junctional epidermolysis bullosa, Herlitz type (gene LAMC2)	226700	LAMC2
374	Junctional epidermolysis bullosa, non-Herlitz type	226650	ITGB4
375	Junctional epidermolysis bullosa, non-Herlitz type (gene LAMA3)	226650	LAMA3
376	Junctional epidermolysis bullosa, non-Herlitz type (gene LAMB3)	226650	LAMB3
377	Junctional epidermolysis bullosa, non-Herlitz type (gene LAMC2)	226650	LAMC2
378	Juvenile neuronal ceroid lipofuscinosis 3	204200	CLN3
379	Kahrizi syndrome	612713	SRD5A3
380	Kelley-Seegmiller syndrome	300323	HPRT1
381	Kennedy disease	313200	AR

Table 1 (Continued)

Disease Name	PhenOMIM	Gene	
382	Ketoacidosis due to beta-ketothiolase deficiency	203750	ACAT1
383	Krabbe disease	245200	GALC
384	Krabbe disease	611722	PSAP
385	Lacticacidemia due to PDX1 deficiency	245349	PDHX
386	Late infantile neuronal ceroid lipofuscinosis	610951	MFS08
387	Late infantile neuronal ceroid lipofuscinosis 5	256731	CLN5
388	Late infantile neuronal ceroid lipofuscinosis 6	601780	CLN6
389	Late infantile neuronal ceroid lipofuscinosis 8	600143	CLN8
390	Lathosterolosis	607330	SC5DL
391	Leigh syndrome	256000	BCS1L
392	Leigh syndrome	256000	DLD
393	Leigh syndrome	256000	NDUFAF2
394	Leigh syndrome	256000	NDUFS4
395	Leigh syndrome	256000	NDUFS7
396	Leigh syndrome due to cytochrome c oxidase deficiency	256000	COX15
397	Leigh syndrome due to mitochondrial complex I deficiency	256000	NDUFS3
398	Leigh syndrome due to mitochondrial complex I deficiency	256000	NDUFS8
399	Leigh syndrome due to mitochondrial COX4 deficiency	256000	COX10
400	Leigh syndrome with nephrotic syndrome	607426	COQ2
401	Leigh syndrome with nephrotic syndrome	614652	PDSS2
402	Leigh syndrome, due to COX deficiency	256000	SURF1
403	Leigh syndrome, X-linked	308930	PDHA1
404	Leprechaunism	246200	INSR
405	Lesch-Nyhan syndrome	300322	HPRT1
406	Lethal acantholytic epidermolysis bullosa	609638	DSP
407	Lethal ataxia with deafness and optic atrophy	301835	PRPS1
408	Lethal congenital contractural syndrome 2	607598	ERBB3
409	Lethal congenital contracture syndrome type 1	253310	GLE1
410	Lethal osteosclerotic bone dysplasia	259775	FAM20C
411	Lethal restrictive dermopathy	275210	LMNA
412	Lethal restrictive dermopathy	275210	ZMPSTE24
413	Leukocyte adhesion deficiency, type III	612840	FERMT3
414	Leydig cell adenoma, somatic, with precocious puberty	176410	LHCGR
415	Leydig cell hypoplasia with hypergonadotropic hypogonadism	238320	LHCGR
416	Leydig cell hypoplasia with pseudohermaphroditism	238320	LHCGR
417	Lhermitte-Duclos syndrome	158350	PTEN
418	Limb girdle dystrophy with epidermolysis bullosa simplex	613723	PLEC
419	Lissencephaly 3	611603	TUBA1A
420	Lissencephaly syndrome, Norman-Roberts type	257320	RELN
421	Lissencephaly, X-linked	300067	DCX
422	Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency	609016	HADH
423	Luteinizing hormone resistance, female	238320	LHCGR
424	Lymphoproliferative syndrome, X-linked, 2	300635	XIAP
425	Macrocephaly/autism syndrome	605309	PTEN
426	Macroglobulinemia, Waldenstrom	153600	MYD88
427	Macular degeneration, age-related, 3	608895	FBN5
428	Mandibuloacral dysplasia with type A lipodystrophy	248370	LMNA
429	Mandibuloacral dysplasia with type B lipodystrophy	608612	ZMPSTE24
430	Mannosidosis, alpha-, types I and II	248500	MAN2B1
431	Maple syrup urine disease	248600	DLD
432	Maple syrup urine disease (gene BCKDHA)	248600	BCKDHA
433	Maple syrup urine disease (gene BCKDHB)	248600	BCKDHB
434	Marinesco-Sjögren syndrome	248800	SIL1
435	Masa syndrome	303350	L1CAM
436	Meckel syndrome type 1	249000	MKS1
437	Meckel syndrome, type 5	611561	RPGRIP1L
438	Medium chain acyl-CoA dehydrogenase deficiency	201450	ACADM
439	Megalencephalic leukoencephalopathy with subcortical cysts	604004	MLC1
440	Menkes disease	309400	ATP7A
441	Mental retardation and microcephaly with pontine and cerebellar hypoplasia	300749	CASK
442	Mental retardation, autosomal recessive 1	249500	PRSS12
443	Mental retardation, autosomal recessive 12	611090	ST3GAL3
444	Mental retardation, autosomal recessive 13	613192	TRAPP9
445	Mental retardation, autosomal recessive 5	611091	NSUN2
446	Mental retardation, autosomal recessive, 6	611092	GRIK2
447	Mental retardation, with or without nystagmus	300422	CASK
448	Mental retardation, X-linked	300495	NLGN4X
449	Mental retardation, X-linked 19	300844	RPS6KA3
450	Mental retardation, X-linked 21/34	300143	ILTRAPL1
451	Mental retardation, X-linked 30/47	300558	PAK3
452	Mental retardation, X-linked 41	300849	GDI1
453	Mental retardation, X-linked 46	300436	ARHGEP6
454	Mental retardation, X-linked 63	300387	ACSL4
455	Mental retardation, X-linked 72	300271	RAB39B
456	Mental retardation, X-linked 9	309549	FTSJ1
457	Mental retardation, X-linked 90	300850	DLG3
458	Mental retardation, X-linked 93	300659	BRWD3



Table 1 (Continued)

	Disease Name	PhenOMIM	Gene
459	Mental retardation, X-linked 96	300802	SYP
460	Mental retardation, X-linked 97	300803	ZNF711
461	Mental retardation, X-linked syndromic 16	305400	FGD1
462	Mental retardation, X-linked syndromic 5	304340	AP1S2
463	Mental retardation, X-linked syndromic, Christianson type	300243	SLC9A6
464	Mental retardation, X-linked syndromic, Nascimento-type	300860	UBE2A
465	Mental retardation, X-linked syndromic, Raymond type	300799	ZDHHC9
466	Mental retardation, X-linked syndromic, Turner type	300706	HUWE1
467	Mental retardation, X-linked, FRAXE type	309548	AF2
468	Mental retardation, X-linked, Snyder-Robinson type	309583	SMS
469	Mental retardation, X-linked, syndromic 14	300676	UPF3B
470	Mental retardation, X-linked, syndromic 15 (Cabezas type)	300354	CUL4B
471	Mental retardation, X-linked, syndromic, Claes-Jensen type	300534	KDM5C
472	Mental retardation, X-linked, with cerebellar hypoplasia and distinctive facial appearance	300486	OPHN1
473	Mental retardation, X-linked, with isolated growth hormone deficiency	300123	SOX3
474	Mental retardation-hypotonic facies syndrome, X-linked	309580	ATRX
475	Metachromatic leukodystrophy	250100	ARSA
476	Metachromatic leukodystrophy	249900	PSAP
477	Metaphyseal chondrodysplasia, Murk Jansen type	156400	PTH1R
478	Metaphyseal dysplasia without hypotrichosis	250460	RMRP
479	Methylmalonic acidemia with homocystinuria, type cblC	277400	MMACHC
480	Methylmalonic acidemia with homocystinuria, type cblD	277410	MMACHC
481	Mevalonic aciduria	610377	MVK
482	Micro syndrome	600118	RAB3GAP1
483	Microphthalmia, syndromic 2	300166	BACOR
484	Mitochondrial complex I deficiency	252010	NDUFA1
485	Mitochondrial complex I deficiency	252010	NDUFAF2
486	Mitochondrial complex I deficiency	252010	NDUFAF4
487	Mitochondrial complex I deficiency	252010	NDUFS3
488	Mitochondrial complex I deficiency	252010	NDUFS4
489	Mitochondrial complex I deficiency	252010	NDUFV1
490	Mitochondrial complex IV deficiency	220110	COX10
491	Mitochondrial complex IV deficiency	220110	COX6B1
492	Mitochondrial complex IV deficiency	220110	FASTKD2
493	Mitochondrial complex IV deficiency		SCO1
494	Mitochondrial DNA depletion syndrome 1 (MNGIE type)	603041	TYMP
495	Mitochondrial DNA depletion syndrome 5 (encephalomyopathic with or without methylmalonic aciduria)	612073	SUCLA2
496	Mitochondrial DNA depletion syndrome 8A (encephalomyopathic type with renal tubulopathy)	612075	RRM2B
497	Mitochondrial DNA depletion syndrome 8B (MNGIE type)	612075	RRM2B
498	Mitochondrial DNA depletion syndrome, hepatocerebral form due to DGUOK deficiency 3	251880	DGUOK
499	Mitochondrial DNA depletion syndrome, myopathic form	609560	TK2
500	Mitochondrial neurogastrointestinal encephalomyopathy	613662	POLG
501	Mitochondrial respiratory chain complex III deficiency	124000	UQCRCB
502	Mitochondrial respiratory chain complex III deficiency	124000	UQCRCQ
503	Mitochondrial trifunctional protein deficiency	609015	HADHA
504	Mitochondrial trifunctional protein deficiency	609015	HADHB
505	Mohr-Tranebjaerg syndrome	304700	TMM8A
506	Mowat-Wilson syndrome	235730	ZEB2
507	Mucopolipidosis type 2	252500	GNPTAB
508	Mucopolipidosis type 3	252600	GNPTAB
509	Mucopolipidosis type 4	252650	MCOLN1
510	Mucopolysaccharidosis 1h	607014	IDUA
511	Mucopolysaccharidosis 1h/s	607015	IDUA
512	Mucopolysaccharidosis 1s	607016	IDUA
513	Mucopolysaccharidosis type 2	309900	IDS
514	Mucopolysaccharidosis type 3A (Sanfilippo syndrome type A)	252900	SGSH
515	Mucopolysaccharidosis type 4B	253010	GLB1
516	Mucopolysaccharidosis type 6	253200	ARSB
517	Mucopolysaccharidosis type 7	253220	GUSB
518	Mucopolysaccharidosis type IIIB (Sanfilippo B)	252920	NAGLU
519	MULIBREY nanism	253250	TRIM37
520	Multiple epiphyseal dysplasia type 4	226900	SLC26A2
521	Multiple pterygium syndrome, lethal type	253290	CHRNA1
522	Multiple pterygium syndrome, lethal type	253290	CHRNA1
523	Multiple pterygium syndrome, lethal type	253290	CHRNA1
524	Muscle-eye-brain disease	613153	FKRP
525	Muscle-eye-brain disease	613154	LARGE
526	Myasthenia gravis, neonatal transient	100730	CHRNA1
527	Myasthenia, limb-girdle, familial	254300	DOK7
528	Myasthenic syndrome, fast-channel congenital	608930	CHRNA1
529	Myasthenic syndrome, fast-channel congenital	608930	CHRNA1
530	Myasthenic syndrome, slow-channel congenital	601462	CHRNA1
531	Myasthenic syndrome, slow-channel congenital	601462	CHRNA1

Table 1 (Continued)

	Disease Name	PhenOMIM	Gene
532	Myopathy, tubular aggregate, 1	160565	STIM1
533	Myopathy, tubular aggregate, 2	615883	ORAI1
534	Nance-Horan syndrome	302350	NHS
535	Navajo neurohepatopathy	256810	MPV17
536	Nemaline myopathy 2	256030	NEB
537	Neonatal adrenoleukodystrophy (gene PEX12)	266510	PEX12
538	Neonatal adrenoleukodystrophy (gene PEX26)	614873	PEX26
539	Neonatal adrenoleukodystrophy (gene PEX5)	202370	PEX5
540	Nephrolithiasis, type 1	310468	CLCN5
541	Nephronophthisis 2, infantile	602088	INVS
542	Nephrotic syndrome, tupe 3	610725	PLCE1
543	Nephrotic syndrome, type 1	256300	NPHS1
544	Nephrotic syndrome, type 2	600995	NPHS2
545	Nephrotic syndrome, type 5, with or without ocular abnormalities	614199	LAMB2
546	Neurodegeneration due to 3-hydroxyisobutyryl-CoA hydrolase deficiency	250620	HIBCH
547	Neurodegeneration due to cerebral folate transport deficiency	613068	FOLR1
548	Neuronal ceroid lipofuscinosis 2	204500	TPP1
549	Neuropathy, congenital hypomyelinating	605253	MPZ
550	Neutropenia, severe congenital 3, autosomal recessive	610738	HAX1
551	Niemann-Pick disease type A	257200	SMPD1
552	Niemann-Pick disease type B	607616	SMPD1
553	Niemann-Pick disease type C1	257220	NPC1
554	Niemann-Pick disease type C2	607625	NPC2
555	Nijmegen breakage syndrome	251260	NBN
556	Norrie disease	310600	NDP
557	ntal retardation, autosomal recessive 7	611093	TUSC3
558	Occipital horn syndrome	304150	ATP7A
559	Oculocerebrorenal syndrome	309000	OCRL
560	Omenn syndrome	603554	DCLRE1C
561	Omenn syndrome (gene RAG1)	603554	RAG1
562	Omenn syndrome (gene RAG2)	603554	RAG2
563	Opitz GBBB syndrome, type I	300000	MID1
564	Ornithine transcarbamylase deficiency	311250	OTC
565	Osteogenesis imperfecta type 8	610915	LEPRE1
566	Osteogenesis imperfecta type VII	610682	CRTAP
567	Osteogenesis imperfecta, type I	166200	COL1A1
568	Osteogenesis imperfecta, type II	166210	COL1A1
569	Osteogenesis imperfecta, type III	259420	COL1A1
570	Osteogenesis imperfecta, type IV	166220	COL1A1
571	Osteopetrosis with renal tubular acidosis	259730	CA2
572	Osteopetrosis, autosomal recessive 5	259720	OSTM1
573	Paget disease, juvenile	239000	TNFRSF11B
574	Panhypopituitarism, X-linked	312000	SOX3
575	Pantothenate kinase-associated neurodegeneration	234200	PANK2
576	Partial androgen insensitivity syndrome	312300	AR
577	Pelizaeus-Merzbacher-like due to GJC2 mutation	608804	GJC2
578	Peroxisomal acyl-CoA oxidase deficiency	264470	ACOX1
579	Peroxisome biogenesis disorder 11A (Zellweger)	614883	PEX13
580	Peroxisome biogenesis disorder 11B	614885	PEX13
581	Peroxisome biogenesis disorder 6A (Zellweger)	614870	PEX10
582	Peroxisome biogenesis disorder 6B	614871	PEX10
583	Perrault syndrome	233400	HSD17B4
584	Phenylketonuria	261600	PAH
585	Pierson syndrome	609049	LAMB2
586	Pitt-Hopkins syndrome	610954	TCF4
587	Plasminogen deficiency type 1	217090	PLG
588	Pontocerebellar hypoplasia type 2A	277470	TSEN54
589	Pontocerebellar hypoplasia type 4	225753	TSEN54
590	Porphyria, congenital erythropoietic	263700	UROS
591	Precocious puberty, male	176410	LHCGR
592	Primary lateral sclerosis, juvenile	606353	ALS2
593	Progressive epilepsy - intellectual deficit, Finnish type	610003	CLN8
594	Properdin deficiency, X-linked	312060	CFP
595	Propionic acidemia (gene PCCA)	606054	PCCA
596	Propionic acidemia (gene PCCB)	606054	PCCB
597	CLCN5		
598	Proximal spinal muscular atrophy type 1	253300	SMN1
599	Proximal spinal muscular atrophy type 2	253550	SMN1
600	Proximal spinal muscular atrophy type 3	253400	SMN1
601	Proximal spinal muscular atrophy type 4	271150	SMN1
602	Pseudohermaphroditism, male, with gynecomastia	264300	HSD17B3
603	Pseudohypoadosteronism type 1, autosomal recessive (gene SCNN1A)	264350	SCNN1A
604	Pseudohypoadosteronism type 1, autosomal recessive (gene SCNN1B)	264350	SCNN1B
605	Pseudohypoadosteronism type 1, autosomal recessive (gene SCNN1G)	264350	SCNN1G
606	Pseudovaginal perineoscrotal hypospadias	264600	SRD5A2
607	Pycnodysostosis	265800	CTSK
608	Pyogenic bacterial infections, recurrent, due to MYD88 deficiency	612260	MYD88

Table 1 (Continued)

Disease Name	PhenOMIM	Gene	
609	Pyridoxal phosphate-responsive seizures	610090	PNPO
610	Pyruvate carboxylase deficiency	266150	PC
611	Pyruvate dehydrogenase phosphatase deficiency	608782	PDP1
612	Renal-hepatic-pancreatic dysplasia	208540	NPHP3
613	Renpenning syndrome	309500	PQBP1
614	Rett syndrome, congenital variant	613454	FOXG1
615	Rhizomelic chondrodysplasia punctata type 1	215100	PEX7
616	Rhizomelic chondrodysplasia punctata type 3	600121	AGPS
617	Rigid spine syndrome	602771	SEPN1
618	Roberts syndrome	269000	ESCO2
619	Roussy-Levy syndrome	180800	MPZ
620	Roussy-Levy syndrome	180800	PMP22
621	Sandhoff disease	268800	HEXB
622	Sanfilippo syndrome type C	252930	HGSNAT
623	Schneckenbecken dysplasia	269250	SLC35D1
624	Schwartz-Jampel syndrome	255800	HSPG2
625	Seckel syndrome	210600	ATR
626	Senior-Loken syndrome	610189	CEP290
627	Senior-Loken syndrome	606996	NPHP4
628	Senior-Loken syndrome 1	266900	NPHP3
629	Senior-Loken syndrome 5	609254	IQCB1
630	Sensory ataxic neuropathy - dysarthria - ophthalmoparesis	607459	POLG
631	Severe combined immunodeficiency due to adenosine deaminase deficiency	102700	ADA
632	Severe combined immunodeficiency due to complete RAG1/2 deficiency	601457	RAG1
633	Severe combined immunodeficiency due to complete RAG1/2 deficiency	601457	RAG2
634	Severe combined immunodeficiency due to DCLRE1C deficiency	602450	DCLRE1C
635	Severe combined immunodeficiency with microcephaly, growth retardation, and sensitivity to ionizing radiation	611291	NHEJ1
636	Severe combined immunodeficiency with sensitivity to ionizing radiation	602450	LIG4
637	Severe generalized recessive dystrophic epidermolysis bullosa	226600	COL7A1
638	Severe neonatal-onset encephalopathy with microcephaly	300673	MECP2
639	Severe T-cell immunodeficiency - congenital alopecia - nail dystrophy	601705	FOXP1
640	Short-rib thoracic dysplasia 3 with or without polydactyly	613091	DYNC2H1
641	Shwachman-Diamond syndrome	260400	SBS1
642	Sialidosis, type I	256550	NEU1
643	Sialidosis, type II	256550	NEU1
644	Sickle cell anemia	603903	HBB
645	Simpson-Golabi-Behmel syndrome type 2	300209	OFD1
646	Simpson-Golabi-Behmel syndrome, type 1	312870	GPC3
647	Síndrome de Dursun	612541	G6PC3
648	Sjogren-Larsson syndrome	270200	ALDH3A2
649	Smith-Lemli-Opitz syndrome	270400	DHCR7
650	Sotos syndrome 1	117550	NSD1
651	Spastic paralysis, infantile onset ascending	607225	ALS2
652	Spastic paraplegia type 2, X-linked	312920	PLP1
653	Spinal muscular atrophy with respiratory distress	604320	IGHMBP2
654	Stocco dos Santos X-linked mental retardation syndrome	300434	SHROOM4
655	Stormorken syndrome	185070	STIM1
656	Stüve-Wiedemann syndrome	601559	LIFR
657	Subcortical laminar heteropia, X-linked	300067	DCX
658	Succinyl CoA:3-oxoacid CoA transferase deficiency	245050	OXCT1
659	Sudden infant death with dysgenesis of the testes syndrome	608800	TSPYL1
660	Sulfite oxidase deficiency due to molybdenum cofactor deficiency type A (gene MOCS1)	252150	MOCS1
661	Sulfite oxidase deficiency due to molybdenum cofactor deficiency type A (gene MOCS2)	252150	MOCS2
662	Sulfocysteinuria	272300	SUOX
663	Surfactant metabolism dysfunction, pulmonary, 1	265120	SFTPB
664	Surfactant metabolism dysfunction, pulmonary, 2	610913	SFTPC
665	Surfactant metabolism dysfunction, pulmonary, 3	610921	ABCA3
666	Syndromic microphthalmia type 9	601186	STRA6
667	Tay-Sachs disease	272800	HEXA
668	T-B+ severe combined immunodeficiency due to gamma chain deficiency	300400	IL2RG
669	T-B+ severe combined immunodeficiency due to JAK3 deficiency	600802	JAK3
670	T-B+ severe combined immunodeficiency, X-linked	312863	IL2RG
671	Tetra-amelia, autosomal recessive	273395	WNT3
672	Thrombocythemia 2	601977	MPL
673	Thrombocytopenia, congenital amegakaryocytic	604498	MPL
674	Thrombotic thrombocytopenic purpura, familial	274150	ADAMTS13
675	Tooth agenesis, selective, X-linked 1	313500	EDA
676	Trichothiodystrophy, complementation group A	601675	GTF2H5
677	Tyrosinemia type 1	276700	FAH
678	Tyrosinemia type 2	276600	TAT
679	Tyrosinemia type 3	276710	HPD
680	Ullrich congenital muscular dystrophy	254090	COL6A1
681	Ullrich congenital muscular dystrophy	254090	COL6A2
682	Ullrich congenital muscular dystrophy	254090	COL6A3
683	Unverricht-Lundborg disease	254800	CSTB
684	Usher syndrome type 1	276900	MYO7A
685	Usher syndrome type 1C	276904	USH1C

**Table 1** (Continued)

Disease Name	PhenOMIM	Gene	
686	Usher syndrome type 1G	606943	<i>USH1G</i>
687	Usher syndrome type 2A	276901	<i>USH2A</i>
688	Usher syndrome type 2C	605472	<i>GPR98</i>
689	Usher syndrome type 3A	276902	<i>CLRN1</i>
690	Very long chain acyl-CoA dehydrogenase deficiency	201475	<i>ACADVL</i>
691	Vitamin B12-responsive methylmalonic acidemia type cblA	251100	<i>MMAA</i>
692	Vitamin B12-responsive methylmalonic acidemia type cblB	251110	<i>MMAB</i>
693	Vitamin B12-unresponsive methylmalonic acidemia type mut-	251000	<i>MUT</i>
694	Vitamin D-dependent rickets type 2A	277440	<i>VDR</i>
695	Vitamin D-dependent rickets, type 1	264700	<i>CYP27B1</i>
696	Waardenburg-Shah syndrome 4A	277580	<i>EDNRB</i>
697	Waardenburg-Shah syndrome 4B	613265	<i>EDN3</i>
698	Walker-Warburg syndrome (gene POMGNT1)	253280	<i>POMGNT1</i>
699	Walker-Warburg syndrome (gene POMT1)	236670	<i>POMT1</i>
700	Walker-Warburg syndrome (gene POMT2)	613150	<i>POMT2</i>
701	Weyers acrofacial dysostosis	193530	<i>EVC</i>
702	Wilson disease	277900	<i>ATP7B</i>
703	Wiskott-Aldrich syndrome	301000	<i>WAS</i>
704	Wolcott-Rallison syndrome	226980	<i>EIF2AK3</i>
705	Wrinkly skin syndrome	278250	<i>ATP6V0A2</i>
706	Xeroderma pigmentosum complementation group A	278700	<i>XPA</i>
707	Xeroderma pigmentosum complementation group E	278740	<i>DDB2</i>
708	Xeroderma pigmentosum, group C	278720	<i>XPC</i>
709	Xeroderma pigmentosum/Cockayne syndrome complex complementation group B	610651	<i>ERCC3</i>
710	Xeroderma pigmentosum/Cockayne syndrome complex complementation group D	278730	<i>ERCC2</i>
711	Xeroderma pigmentosum/Cockayne syndrome complex complementation group F	278760	<i>ERCC4</i>
712	Xeroderma pigmentosum/Cockayne syndrome complex complementation group G	278780	<i>ERCC5</i>
713	X-linked agammaglobulinemia	300755	<i>BTK</i>
714	X-linked centronuclear myopathy	310400	<i>MTM1</i>
715	X-linked Charcot-Marie-Tooth disease type 5	311070	<i>PRPS1</i>
716	X-linked creatine transporter deficiency	300352	<i>SLC6A8</i>
717	X-linked distal spinal muscular atrophy	300489	<i>ATP7A</i>
718	X-linked hyper-IgM syndrome	308230	<i>CD40LG</i>
719	X-linked intellectual deficit with marfanoid habitus	309520	<i>MED12</i>
720	X-linked lymphoproliferative disease	308240	<i>SH2D1A</i>
721	Odontonychodermal dysplasia	257980	<i>WNT10A</i>
722	X-linked spinal muscular atrophy type 2	301830	<i>UBA1</i>
723	Zellweger syndrome 1A	214100	<i>PEX1</i>
724	Zellweger syndrome 7A	614872	<i>PEX26</i>

analysed the mutations screened by different laboratories, 74–210 mutations, and only 29 were found in common [17]. This poor method uniformity doesn't allow expanded carrier screening be a recommended test by clinicians.

Lazarin et al. based a classification algorithm on four tiers of severity: profound, severe, moderate and mild. The disease characteristics chosen were: life span, intellectual disability, impaired mobility, physical malformations and dysmorphic features, sensory impairment, immunodeficiency/cancer, mental illness, reduced fertility, available treatment, and expressivity [18]. In this background, variants of uncertain significance and non pathogenic mutations increase the complexity in choosing the appropriate panel and counselling of patients.

In 2017, the ACOG published a committee opinion about common genetic conditions for which carrier screening is recommended: [19]

- Spinal Muscular Atrophy. This screening should be offered to all women during preconceptional or prenatal period, and to patients with a family history of SMA.
- Cystic Fibrosis. This screening should be offered to all women during preconceptional or prenatal period. Today about two thousand mutations of the CFTR gene are known and the complete analysis of the gene is not recommended for routine screening.
- Hemoglobinopathies. A complete blood count with red blood cells indices should be offered to all women during and before pregnancy, also to diagnose their risk of anemia. If a low mean

corpuscular volume results, a hemoglobin electrophoresis would also be indicated, especially in some at risk populations: African, Mediterranean, Middle Easten, Southeast Asia or West Indian descendants.

- Fragile X Syndrome. This screening should be offered to all women during preconception and prenatal period, if a family history or suggestive intellectual disorders occur. If a woman has unexplained ovarian insufficiency or high levels of FSH before the age of 40, an FMR1 premutation could be present and the screening should be recommended. Prenatal diagnosis for fragile X syndrome should be offered to known carriers of premutation or full mutation.
- Tay-Sachs Disease. This screening should be offered to all women during preconception and prenatal period, if either member of a couple belongs to some particular ethnicity, such as Ashkenazi Jewish, French-Canadian or Cajun, or if there is a suggestive family history.
- Expanded carrier screening does not replace the above risk-based screening recommendations

#### Analytic and clinical validity and utility

Analytic validity of a genetic test defines its ability to accurately and reliably measure the genotype of interest. Current commercial providers use mostly microarray-based genetic tests covering the most frequent sequence variants in selected genes. Alternatively, whole genes, and not only selected sequence variants can be sequenced by next-generation sequencing (NGS) [7].

Clinical validity of a genetic test defines its ability to detect or predict the associated disorder, including carrier status. It is currently difficult to assess the clinical validity of screening panels due to various confounding factors. Many genes are characterized by numerous variants, not all of them are pathogenic, equally associated with severe phenotype and not all of them are necessarily reported in commercially available panels [7].

As to clinical utility, a genetic test is designed to provide clinical practice with a valid support to improve patient outcomes. In this case, the aim of preconception carrier screening is to facilitate reproductive choices and autonomy of couples. Options for future parents include preimplantation genetic diagnosis, prenatal diagnosis, using donor sperms or oocytes, adoption, or accepting the risk of conceiving an affected child [20,21].

Expanded carrier screening may also support prenatal diagnosis with early management of genetic disorders [20–22]. For example screening for ornithine transcarbamylase deficiency, a rare and potentially fatal disorder in a male neonate, could improve the prognosis [22]. This will also help the parents to better approach the pregnancy and be ready for psychosocial consequences of having a child with a genetic condition.

Another aspect of the expanded carrier screening is the clinical implication on the carrier patient. The screening may reveal genetic conditions that may predispose the carrier to increased morbidity and mortality. Carriers of ataxia telangiectasia have a major risk of breast cancer [23] and heterozygous variants of glucocerebrosidase gene is linked to Parkinson's disease [24].

Attention should be also paid to the impact of expanded carrier screening on the health care organizations and burden of cost. Lynch et al. found that the median time for results disclosure is about 64 min, ranging from 5 to 229 min with preparation work being the most time-consuming activity. [25] Carrier screening requires significant increases in genetic counseling time, and new resources to reduce preparation work or develop other strategies such as the creation of new models to deliver this type of service are needed. [25]

### Expanded carrier screening and Noninvasive prenatal diagnosis

Sequencing of cell-free DNA in maternal plasma has enabled definitive noninvasive prenatal diagnosis for monogenic disorders and also for pregnancies with unexpected fetal anomalies. The current standard for testing for Mendelian disorders is gene panels and that is available for many ultrasound abnormalities like holoprosencephaly, congenital heart disease, skeletal dysplasia, and others. Most Mendelian disorders however, are associated with normal prenatal ultrasound findings. Future developments may be toward noninvasive prenatal diagnosis with fetal whole exome or whole genome sequencing. This has been performed on limited disorders so far and to generalize it to diagnose the large number of Mendelian disorders on the expanded carrier screening panels is premature for now [26]. In fact, this highlights even more the importance of clear guidelines for expanded carrier screening panels.

### Ethical issues

The introduction of expanded carrier screening raises many concerns about complex decisions, including preimplantation genetic diagnosis, prenatal diagnosis, and pregnancy management and may impact the psychological well-being, perceptions of health, and feelings of discrimination or stigmatization with social consequences. Studies have also demonstrated increased distress levels among carriers [10]. Already pregnancy is a very high emotional state where expanded carrier screening is only one aspect of many evaluations that the pregnant patient has to deal

with. Therefore, careful appraisal of the advantages and disadvantages for universal screening before conception is necessary. Obtaining consent has been considered much more challenging as the carrier screening panels expand [7]. Women may also have a legitimate interest in not knowing their genetic make up to avoid serious psychological consequences.

### Conclusion

Expanded carrier screening aims to identify couples who have an increased risk of having an affected child in order to facilitate informed reproductive decision making. New genetic testing technologies enable the expansion of screening to multiple conditions including those with very low carrier frequency, and those with mild or incompletely penetrant phenotypes. Priority should be given to carrier screening panels that include a comprehensive set of severe childhood-onset disorders. Panels should have high clinical validity and clinical utility. Psychosocial support and genetic counseling should be available prior to screening and for the return of positive results. Systems are needed to reduce the risk of misinterpreting results. Finally, attention should be paid on the impact of expanded carrier screening on health care organization and burden of cost.

### Conflicts of interest

The authors report no conflict of interest

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