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Human Medicines Research and Development Support

This document was valid from 16 December 2014 to 9 January 2018. It is no longer valid.

Examples of prevalence sources previously considered in orphan medicinal product designation procedures

Further to the publication of the Relevant sources for orphan disease prevalence data (EMA/452415/2012), the Agency has decided to provide additional sources that have previously been considered by the Committee of Orphan Medicinal Products (COMP) for a number of ophthalmological, metabolic and neuromuscular conditions. This document is a non-exhaustive list of epidemiological references with the aim to facilitate the justification of the prevalence criterion when the sponsors are applying for orphan medicinal product designations.

It is stressed that as per Regulation (EC) No.141/2000, it is the sponsors' responsibility to establish that the prevalence criterion is met. This document does not substitute the responsibility of the sponsor to provide an original, up to date and adequate epidemiological analysis in the relevant section of the application, in order to demonstrate to the COMP that the prevalence of the disease in the European Union at the time of application is below the accepted threshold: 5 in 10 000 people.

For more information with regards to the establishment of the prevalence, guidance is provided in the Points to consider on the calculation and reporting on the prevalence of a condition for orphan designation (COMP/436/01).

If you have any queries or comments with regards to the table of prevalent sources provided, please contact us at orphandrugs@ema.europa.eu.

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Number	Designated Condition	Prevalence (per 10 000 in the EU, as per the latest designation)	Sources for calculation of prevalence at time of orphan designation
1	Macular telangiectasia type 2	<2.3	(1) Aung KZ, Wickremasinghe SS, *et al*. The prevalence estimates of macular telangiectasia type 2: the Melbourne Collaborative Cohort Study. *Retina.* 2010; 30(3):473-8 (2) Klein R, Blodi BA *et al*. The prevalence of macular telangiectasia type 2 in the Beaver Dam eye study. *Am J Ophthalmol*. 2010; 150(1):55-62
2	Friedreich ataxia	<0.7	(1) Pandolfo M. Friedreich ataxia: The clinical picture. *J Neurol.* 2009; 1 (Supp 1):3-8 (2) Arnulf H. Koeppen. Friedreich's ataxia: Pathology, pathogenesis, and molecular genetics. *J Neurol Sci*. 2011; 15: 303(1-2):1–12 (3) Delatycki MB, Williamson R, Forrest SM. Friedrich ataxia: an overview. *J Med Genet*. 2000; 37:1–8 (4) Schulz JB, Boesch S, Burk K, Durr A, Giunti P, *et al*. Diagnosis and treatment of Friedreich ataxia: a European perspective. *Nat Rev Neurol*. 2009; 5:222-234 (5) http://www.ninds.nih.gov/ (National Institute of Neurological Disorders and Stroke) (6) http://www.inserm.fr (French National Institute of Health and Medical Research)
3	Retinitis Pigmentosa	<3.7	(1) Haim M. The epidemiology of retinitis in Denmark. *Acta Ophthalmol Scand Suppl.* 2002; 80 (Supplement s233):1–34 (2) Chizzolini M, Galan A, *et al.* Epidemiologic Practice in Retinitis Pigmentosa: From

			Phenotyping to Biobanking. *Curr Genomics*, 2011; 12:260-266 (3) Puech B, Kostrubiec B, *et al* Epidemiology and prevalence of hereditary retinal dystrophies in the Northern France. *J Fr Ophtalmol*. 1991; 14 (3):153-64 (4) Ammann F, *et al*. Genetic and epidemiological investigations on pigmentary degeneration of the retina and allied disorders in Switzerland. *J Neurol Sci*. 1965; 2:183-196 (5) Grøndahl J, *et al.* Estimation of prognosis and prevalence of retinitis pigmentosa and Usher syndrome in Norway. *Clin Genet.* 1987; 31(4):255-64 (6) Bundey S and Crews SJ. A study of retinitis pigmentosa in the city of Birmingham. *J Med Genet*. 1986; 23(2):188 (7) Peterlin B, Canki-Klain N, *et al*. Prevalence of retinitis pigmentosa in Slovenia. *Clin Genet*. 1992; 42(3):122-3 (8) Nájera C, Millán JM, *et al*. Epidemiology of retinitis pigmentosa in the Valencian community (Spain). *Genet Epidemiol*. 1995; 12(1):37-46 (9) Spanish Retinal Dystrophies Research Network - http://www.esretnet.org
4	Non-infectious uveitis	<4.8	(1) Baarsma GS. The epidemiology and genetics of endogenous uveitis: a review. *Curr Eye Res.* 1992; Suppl:1-9 (2) Saari KM, Päivönsalo-Hietanen T. Epidemiology of endogenous uveitis in south-western Finland. *Acta Ophthalmol Scand*. 1995; 73(4):345-9 (3) Päivönsalo-Hietanen T, Tuominen J, Saari KM. Uveitis in children: Population based study in Finland. *Acta Ophthalmol. Scand.* 2000; *78:84–88*

			(4) Päivönsalo-Hietanen, T *et al*. Incidence and prevalence of different uveitis entities in Finland. *Acta Ophthalmol Scand*. 1997; 75(1):76-81 (5) Vadot E. Epidemiology of intermediate uveitis: a prospective study in Savoy. *Dev Ophthalmol*. 1992; 23:33-4 (6) Mercanti A, Parolini B, *et al*. Epidemiology of endogenous uveitis in north-eastern Italy. Analysis of 655 new cases. *Ophthalmol. Scand*. 2001*:*79: 64–68 (7) Tran VT, *et al*. Epidemiological characteristics of uveitis in Switzerland. *Int Ophthalmo*l. 1994-1995; 18(5):293-8 (8) Thean LH, Thompson J, Rosenthal AR. A uveitis register at the Leicester Royal Infirmary. *Ophthalmic Epidemiol*. 1996; 3(3):151-8 (9) Williams GJ, Brannan S, *et al.* The prevalence of sight-threatening uveitis in Scotland. *Br J Ophthalmol*. 2007; 91(1):33-6 (10) Heiligenhaus A, *et al*. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. *Rheumatology*. 2007; 46(6):1015-9 (11) Talin Barisani-Asenbauer *et al*. Uveitis- a rare disease often associated with systemic diseases and infections- a systematic review of 2619 patients *Orphanet Journal of Rare Diseases.* 2012; 7:57
5	Duchenne muscular dystrophy	<0.8	(1) Norwood FL, Harling C, Chinnery PF, Eagle M, Bushby K, Straub V. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. *Brain.* 2009; 132(Pt 11):3175–3186 (2) Mah JK, Korngut L, Dykeman J, Day L, Pringsheim T, Jette N. A systematic review and meta-analysis on the epidemiology of Duchenne and Becker muscular dystrophy.

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			study. *Clin. Pediat.* 2010; 49(2):177-179 (12) Duchenne muscular dystrophy 3rd Ed Oxford University Press, New York. 2003
6	Growth-hormone deficiency	4	(1) Thomas M, Massa G, Craen M, de Zegher F, Bourguignon J P, Heinrichs C, De Schepper J, Du Caju M, Thiry-Counson G and Maes M. Prevalence and demographic features of childhood growth hormone deficiency in Belgium during the period 1986–2001. *Eur J Endocrinol.* 2004; 151: 67–72 (2) Stochholm K, Gravholt CH, Laursen T, Jørgensen JO, Laurberg P, Andersen M, Kristensen LO, Feldt-Rasmussen U, Christiansen JS, Frydenberg M and Green A. Incidence of GH deficiency – a nationwide study. *Eur J Endocrinol.* 2006; 155:61–71 (3) Lindsay R, Feldkamp M, Harris D, Robertson J, and Rallison, M. Utah Growth Study: Growth standards and the prevalence of growth hormone deficiency. *J Pediatr*. 1994; 125:29-35 (4) Regal M, Páramo C, Sierra JM, Garcia-Mayor RV. Prevalence and incidence of hypopituitarism in an adult Caucasian population in northwestern Spain. *Clin Endocrinol.* 2001; 55:735-40 (5) Stochholm K, Gravholt CH, Laursen T, Laurberg P, Andersen M, Kristensen LO, Feldt-Rasmussen U, Christiansen JS, Frydenberg M and Green A. Mortality and GH deficiency: a nationwide study. *Eur J Endocrinol.* 2007; 157:9–18 (6) Vimpani GV, Vimpani AF, Lidgard GP, Cameron EHD, Farquhar JW. Prevalence of severe growth hormone deficiency. *Br Med J*. 1977; 2(6084): 427–430 (7) Hilken J. UK audit of childhood growth hormone prescription, 1998. *Arch Dis Child*. 2001; 84(5):387-9 (8) National Institute for Health and Care Excellence - http://www.nice.org.uk/guidance/ta188/chapter/2-clinical-need-and-

			(published May 2010)
7	Long-chain 3-Hydroxyacyl-CoA Dehydrogenase (LCHAD) Deficiency	0.17	(1) Korenke GC, Marquardt I, Motz R, Voges A, Wanders RJA, Steuerwald U, Sander J. Long-chain hydroxyacyl-CoA dehydrogenase deficiency-LCHAD defect. Two-year follow-up of two patients. *Monatsschrift fur Kinderheilkunde*. 2005;153(7):657-663 (2) Lindner M, Hoffmann GF, Matern D. Newborn screening for disorders of fatty-acid oxidation: experience and recommendations from an expert meeting. *J Inherit Metab Dis.* 2010; 33(5):521-6 (3) McHugh DM, Cameron CA, Abdenur JE *et al*. Clinical validation of cutoff target ranges in newborn screening of metabolic disorders by tandem mass spectrometry: a worldwide collaborative project. *Genet Med*. 2011; 13(3):230-54 (4) Schulze A, Lindner M, Kohlmüller D, Olgemolle K, Mayatepek E, Hoffmann GF. Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: results outcome, and implications. *Pediatrics* 2003; 111:1399-406 (5) Sykut-Cegielska J, Gradowska W, Piekutowska-Abramczuk D, Andresen BS, Olsen RK, Ołtarzewski M, Pronicki M, *et al*. Urgent metabolic service improves survival in long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency detected by symptomatic identification and pilot newborn screening. *J Inherit Metab Dis.* 2011; 34(1):185-95 (6) Tyni T, Pihko H. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. *Acta Paediatr*. 1999; 88(3):237-45. (7) Vilarinho L, Rocha H, Sousa C, Marcão A, Fonseca H, Bogas M, Osório RV. Four years of expanded newborn screening in Portugal with tandem mass spectrometry. *J Inherit Metab Dis*. 2010; 33 (Suppl 3):S133-8 (8) Kasper DC, Ratschmann R, Metz TF, Mechtler TP, Möslinger D, Konstantopoulou V, Item CB, Pollak A, Herkner KR. The National Austrian Newborn Screening Program - Eight

			years' experience with mass spectrometry. Past, present, and future goals. *Wien Klin Wochenschr*. 2010 Oct 15
8	Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency	0.32	(1) Boneh A, Andresen BS, Gregersen N, Ibrahim M, Tzanakos N, Peters H, Yaplito-Lee J, Pitt JJ. VLCAD deficiency: Pitfalls in newborn screening and confirmation of diagnosis by mutation analysis. *Mol Genet Metab*. 2006; 88(2):166-70 (2) Lindner M, Hoffmann GF, Matern D. Newborn screening for disorders of fatty-acid oxidation: experience and recommendations from an expert meeting. *J Inherit Metab Dis.* 2010; 33(5):521-6 (3) McHugh DM, Cameron CA, Abdenur JE *et al*. Clinical validation of cut off target ranges in newborn screening of metabolic disorders by tandem mass spectrometry: a worldwide collaborative project. *Genet Med.* 2011; 13(3):230-54 (4) Schulze A, Lindner M, Kohlmüller D, Olgemolle K, Mayatepek E, Hoffmann GF. Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: results outcome, and implications. *Pediatrics* 2003; 111:1399-406 (5) Spiekerkoetter U, Sun B, Zytkovicz T, Wanders R, Strauss AW, Wendel U. MS/MS-based newborn and family screening detects asymptomatic patients with very-long-chain acyl-CoA dehydrogenase deficiency. *J Pediatr*. 2003;143(3):335-42 (6) Spiekerkoetter U, Haussmann U, Mueller M, ter Veld F, Stehn M, Santer R, Lukacs Z. Tandem mass spectrometry screening for very long-chain acyl-CoA dehydrogenase deficiency: the value of second-tier enzyme testing. *J Pediatr*. 2010; 157(4):668-73 (7) Vilarinho L, Rocha H, Sousa C, Marcão A, Fonseca H, Bogas M, Osório RV. Four years of expanded newborn screening in Portugal with tandem mass spectrometry. *J Inherit Metab Dis.* 2010; 33: 3(3 Suppl):133-138

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9	Mucopolysaccharidosis type IIIB (Sanfilippo B syndrome)	0.009	(1) Poorthuis BJ, Wevers RA, Kleijer WJ, Groener JE, de Jong JG, van Weely S, *et al*. The frequency of lysosomal storage diseases in The Netherlands. *Hum Genet*. 1999;105(1-2):151-6 (2) Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. *JAMA*. 1999; 281(3):249-54 (3) Baehner F, Schmiedeskamp C, Krummenauer F, Miebach E, Bajbouj M, Whybra C, *et al*. Cumulative incidence rates of the mucopolysaccharidoses in Germany. *J Inherit Metab Dis*. 2005; 28(6):1011-7 (4) Malm G, Lund AM, Månsson JE, Heiberg A. Mucopolysaccharidoses in the Scandinavian countries: incidence and prevalence. *Acta Paediatr*. 2008; 97(11):1577-81 (5) Héron B, Mikaeloff Y, Froissart R, Caridade G, Maire I, *et al*. Incidence and natural history of mucopolysaccharidosis type III in France and comparison with United Kingdom and Greece. *Am J Med Genet A*. 2011; 155A(1):58-68 (6) Poupetová H, Ledvinová J, Berná L, Dvoráková L, Kozich V, Elleder M. The birth prevalence of lysosomal storage disorders in the Czech Republic: comparison with data in different populations. *J Inherit Metab Dis*. 2010; 33(4):387-96

10	Spinal Muscular atrophy	0.2	(1) Norwood FL, Harling C, *et al*. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. *Brain.* 2009; 132(Pt 11):3175-86 (2) Hughes MI, Hicks EM, *et al*. The prevalence of inherited neuromuscular disease in Northern Ireland. *Neuromuscul Disord.* 1996; 6(1):69-73 (3) Spiegler AW, Hausmanowa-Pertrusewicz I, *et al*. Population data on acute infantile and chronic childhood spinal muscular atrophy in Warsaw. *Hum Genet*. 1990; 85(2):211-4 (4) Jedrzejowska M, Milewski M, *et al*. Incidence of spinal muscular atrophy in Poland--more frequent than predicted? *Neuroepidemiology.* 2010; 34(3):152-7 (5) Ludvigsson P, Olafsson E, *et al*. Spinal muscular atrophy. Incidence in Iceland. *Neuroepidemiology.* 1999; 18(5):265-9 (6) Kvasnicova M, J. Stykova, *et al*. Incidence of spinal muscular atrophy and Duchenne's muscular dystrophy in the juvenile population of central Slovakia. *Bratisl Lek Listy.* 1994; 95(2):78-82 (7) Mostacciuolo M L, Danieli GA, *et al*. Epidemiology of spinal muscular atrophies in a sample of the Italian population. *Neuroepidemiology.* 1992; 11(1):34-8 (8) D'Amico A, Mercuri E, Tiziano FD and Bertini E. Spinal Muscular Atrophy. *Orphanet Journal of Rare Diseases.* 2011, 6:71
11	Wilson's disease	0.6	(1) Chappuis P, Callebert J, Quignon V, Woimant F, Laplanche JL. Late neurological presentations of Wilson disease patients in French population and identification of 8 novel mutations in the ATP7B gene. *J Trace Elem Med Biol*. 2007; 21(1):37-42 (2) Møller LB, Horn N, Jeppesen TD, Vissing J, Wibrand F, Jennum P, Ott P. Clinical presentation and mutations in Danish patients with Wilson disease. *Eur J Hum Genet*.

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12	X-linked juvenile retinoschisis (XLRS)	0.4	(1) Forsius H, Krause U, Helve J, Vuopala V, Mustonen E, Vainio-Mattila B, Fellman J, Eriksson AW. Visual acuity in 183 cases of X-chromosomal retinoschisis. *Can J Ophthalmol.* 1973; 8:385-93 (2) Rudanko SL, Flage T, Hansen E, Rosenberg T, Viggosson G, Riise R. Visual impairment in Nordic children. V. X-linked juvenile retinoschisis. *Acta Ophthalmol. (Copenh)* 1993; 71:586-9 (3) Puech B, Kostrubiec B, Hache JC, Francois P. Epidemiology and prevalence of hereditary retinal dystrophies in the Northern France. *J Fr Ophtalmol.* 1991; 14:153-64 (4) De La Chapelle A, Alitalo T, Forsius H. X-linked juvenile retinoschisis. In: Wright AF, Jay B, eds. Molecular genetics of inherited eye diseases. Switzerland: Harwood Academic Publishers; 1994:339-57
13	Achromatopsia caused by mutations in the *CNGB3* gene	0.15	(1) Judd DB. Facts of color-blindness. *J Opt Soc Amer*. 1943; 33: 294-307 (2) Sharpe LT A. Stockman, et al. (1999). Opsin genes, cone photopigments, color vision, and color blindness: rod monochromacy. In: Color Vision: from Genes to Perception. K. Gegenfurtner and L. T. Sharpe. Cambridge University Press:48-51 (3) Sharpe, L. T. and K. Nordby (1990). Total colour-blindness: an introduction. In: Night Vision: Basic, Clinical and Applied Aspects. R. F. Hess, L. T. Sharpe and K. Nordby. Cambridge, Cambridge University Press:253-289

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14	Leber's hereditary optic neuropathy	<1	(1) Man PYW, *et al*. The Epidemiology of Leber Hereditary Optic Neuropathy in the North East of England *Am J Hum Genet.* 2003; 72:333 – 339 (2) Spruijt L, *et al*. Influence of mutation type on clinical expression of Leber hereditary optic neuropathy. *Am J Ophthalmol.* 2006; 141:676–682 (3) Mackey DA. The epidemiology of Leber hereditary optic neuropathy in Australia. *Clin Neuroscience.* 1994; 2:162–164 (4) Jančić J, Dejanović I, Samardžić J *et al*. Leber hereditary optic neuropathy in the population of Serbia. *Eur J Paediatr Neurol*. 2014; 18(3):354-359
15	Ataxia Telangiectasia	0.1	Registries: (1) Ataxia-Telangiectasia patient registry - contributes to the ESID Database; Klinikum der Johann Wolfgang Goethe - Universität Frankfurt; Pädiatrische Pneumologie, Allergologie und Mukoviszidose (Germany) (2) Registro Italiano per l'Atassia Teleangiectasia; A.O. S. Andrea; Servizio di Genetica Medica (Italy) (3) CoF-AT study: a French cohort on ataxia-telangiectasia (France)
16	Leber’s congenital amaurosis	<1	(1) Puech B, Kostrubiec B, Hache JC, Francois P. Epidemiology and prevalence of hereditary retinal dystrophies in the Northern France. *J Fr Ophtalmol*. 1991; 14(3):153-64 (2) Stone EM. Leber congenital amaurosis - a model for efficient genetic testing of heterogeneous disorders: LXIV Edward Jackson Memorial Lecture. *Am J Ophthalmol*. 2007; 144(6):791-811 (3) Koenekoop RK. An overview of Leber congenital amaurosis: a model to understand

			human retinal development. *Surv Ophthalmol.* 2004; 49(4):379-398 (4) Hanein S, Perrault I, Gerber S, Tanguy G, Barbet F, Ducroq D, *et al*. Leber congenital amaurosis: comprehensive survey of the genetic heterogeneity, refinement of the clinical definition, and genotype-phenotype correlations as a strategy for molecular diagnosis. *Hum Mutat.* 2004; 23(4):306-17 (5) Hanein S, Perrault I, Gerber S, Tanguy G, Rozet JM, and Kaplan J. Leber congenital amaurosis: survey of the genetic heterogeneity, refinement of the clinical definition and phenotype-genotype correlations as a strategy for molecular diagnosis. Clinical and molecular survey in LCA. *Adv Exp Med Biol.* 2006; 572:15-20 (6) Simonelli F, Ziviello C, Testa F, Rossi S, Fazzi E, Bianchi PE, Fossarello M, Signorini S, *et al*. Clinical and molecular genetics of Leber's congenital amaurosis: a multicenter study of Italian patients. *Invest Ophthalmol Vis Sci.* 2007; 48(9):4284-90 (7) Foundation for Retinal Research - http://www.tfrr.org/index.php/en/about-lca/228-nike-free-run-2-0-id-odio-vestibulum
17	Huntington's disease	1	(1) Harper PS. The epidemiology of Huntington's disease. *Hum Genet*. 1992; 89:365-76 (2) Pringsheim T, Wiltshire K, Day L, *et al*. The Incidence and Prevalence of Huntington's Disease: A Systematic Review and Meta-analysis. *Move Disord.* 2012; 27:1083-1091 (3) Palo J, Somer H, Ikonen E, et al. Low Prevalence of Huntington's Disease in Finland. *Lancet.* 1987; II:805-806 (4) Frontali M, Malspina P, Rossi C, et al. Epidemiological and Linkage Studies on Huntington's Disease in Italy. *Hum Genet.* 1990; 85:165-170 (5) Ramos-Arroyo MA, Moreno S, Valiente A. Incidence and Mutation Rates of Huntington's Disease in Spain: Experience of 9 Years of Direct Genetic Testing. *J Neurol*

			Neurosurg Psychiatry. 2005; 76:337-342 (6) Mattsson B. Huntington's Chorea in Sweden. *Acta Psychiatrica Scandinavica, Supplementum.* 1974; 225:211-220 (7) Simpson SA, Johnston AW. The prevalence of patterns of care of Huntington's chorea in Grampian. *British J of Psych.* 1989;155:799-804 (8) Quarrell OWJ, Tyler A, Jones MP, et al. Population Studies of Huntington's Disease in Wales. *Clin Genet.* 1988; 33:189-195 (9) Evans SJ, Douglas I, Rawlins MD, Wexler NS, Tabrizi SJ, Smeeth L. Prevalence of adult Huntington's disease in the UK based on diagnoses recorded in general practice records. *J Neurol Neurosurg Psychiatry*. 2013; 84(10):1156-60 (10) Panas M, Karadima G, Vassos E, Kalfakis N, Kladi A, Christodoulou K, Vassilopoulos D. Huntington's disease in Greece: the experience of 14 years. *Clin Genet*. 2011; 80(6):586-90 (11) European Huntington's Disease Network (EHDN) - www.euro-hd.net
18	Myasthenia gravis	<2	(1) Sardu C, Cocco E, Mereu A, Massa R, Cuccu A, Marrosu MG, Contu P. Population based study of 12 autoimmune diseases in Sardinia, Italy: prevalence and comorbidity. *PLoS One*. 2012; 7(3):e32487 (2) Montomoli C, Citterio A, Piccolo G, Cioccale R, Ferretti VV, Fratti C, Bergamaschi R, Cosi VE. Epidemiology and geographical variation of myasthenia gravis in the province of Pavia, Italy. *Neuroepidemiology*. 2012; 38(2):100-5 (3) Andersen JB, Engeland A, Owe JF, Gilhus NE. Myasthenia gravis requiring pyridostigmine treatment in a national population cohort. *Eur J Neurol*. 2010; 17(12):1445-50

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19	Stargardt's disease	1.5	(1) Turut P and Puech B. Heredity in Stargardt disease and fundus flavimaculatus. *Ophtalmologie.* 1989; 3(3):187-192 (2) Puech B, Kostrubiec B, Hache JC, and Francois P. Epidemiology and prevalence of hereditary retinal dystrophies in the Northern France. *J Fr Ophtalmol.* 1991; *14*(3):153-164 (3) Blacharski PA, 1988. Fundus flavimaculatus. In *Retinal dystrophies and degenerations*. New York: Raven Press, pp. 135–159
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60	Pyridoxamine 5'-phosphate oxidase deficiency	<0.02	(1) Plecko B, *et al.* Pyridoxine responsiveness in novel mutations of the PNPO gene. *Neurology.* 2014; 82(16):1425–1433 (2) Mills PB., *et al*. Epilepsy due to PNPO mutations: genotype, environment and treatment affect presentation and outcome. *Brain.* 2014; 137(Pt 5):1350-60 (3) Mills PB, Footitt EJ, Clayton PT. Chapter 156.1: Vitamin B6 metabolism and inborn errors. Book: “The online metabolic and molecular bases of inherited disease”, Valle D, Beaudet AL, Vogelstein B, Kinzler KW, Antonarakis SE, Ballabio A, *et al*. 2012

List of useful websites/ databases

1) http://epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&language=en&pcode=tps00001&tableSelection=1&footnotes=yes&labeling=labels&plugin=1 - EUROSTAT, provides accurate demographic figures

2) http://www.orpha.net/consor/cgi-bin/index.php
and http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf - updated in May 2014, database of rare diseases as provided by Orphanet- Euoropean based

3) http://www.ncbi.nlm.nih.gov/omim - OMIM database for human genes and genetic diseases developed by the NCBI

4) http://rarediseases.info.nih.gov- genetic and rare diseases information centre as provided by the National Institute of Health (NIH) a US national agency

5) http://globocan.iarc.fr - database providing the prevalence, incidence and mortality of major cancers, as compiled by the International Agency for Research on Cancer (IARC)

6) https://www.healthonnet.org - Health On the Net Foundation developed by physicians and professors, researchers and senior representatives of the World Health Organisation (WHO), International Telecommunication Union (ITU), the European Laboratory for Particle Physics (CERN), the European Commission, the National Library of Medicine, and the G7-Global Healthcare Applications Project. It is aimed at providing reliable online health information

7) http://ghr.nlm.nih.gov/condition - service of the US National Library of Medicine, part of the National Institutes of Health, providing information about genetic diseases

8) http://ommbid.mhmedical.com - online resource for genetic and metabolic disorders

9) http://www.ninds.nih.gov - information provided about neurological disorders by the National Institute of Neurological Disorders and Stroke, part of NIH

10) https://www.imbio.de/stable/php/ramedis/htdocs/eng/index.php - RAMEDIS, a database for rare metabolic diseases

11) https://www.rarediseases.org - information about rare diseases as provided by the National Organization for Rare Disorders (NORD), US organisation

12) http://www.socialstyrelsen.se/rarediseases - database for rare diseases produced by medical specialists and patients as provided by the Swedish National Board of Health and Welfare

13) http://www.inserm.fr - French National Institute of Health and Medical Research

14) http://www.enerca.org - European Network for Rare and Congenital Anaemias

15) http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm - EU Register of Designated Orphan Medicianl Products

16) http://www.europac-org.eu - European Registry of Pancreatitis and Familial Pancreatic Cancer (EUROPAC)

17) http://www.hscic.gov.uk/hes - Hospital Episode Statistics. HES is a records based system that covers all NHS trusts in England, including acute hospitals, primary care trusts and mental health trusts, containing details of all admissions, outpatient appointments and A&E attendances at NHS hospitals in England.

18) http://www.rarecare.eu/ - Surveillance of rare cancers in Europe