ORIGINAL ARTICLE

List of rare diseases in Bulgaria

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Abstract

Defining and setting a rare disease inventory is a fundamental part of rare disease policy. This tool is of a paramount importance, as it greatly affects the knowledge and awareness of rare diseases not only among health care practitioners, but among all rare disease stakeholders. An official list of rare diseases is particularly beneficial now in the context of the European reference networks for rare diseases, generating added value at both international and local levels.

In this publication, we demonstrate and analyse the establishment of the List of rare diseases in Bulgaria. The Bulgarian experience is a result of a decade-long international collaboration within EU bodies like the Rare Diseases Task Force and the EU Committee of Experts on Rare Diseases, as well as participation in major EU projects, such as RD-Portal (Orphanet), EUROPLAN, EPIRARE, BURQOL-RD, RARE-Bestpractices and RD-Action. Bulgarian rare disease stakeholders applied a transparent, proactive methodology when defining and setting the list. This is a substantial prerequisite for the successful implementation of all ongoing rare disease activities in the country. The described approach could be easily adapted and used in other countries.

Key words

Rare diseases, health policy, centres of expertise, registries, list of rare diseases.

Introduction

Ministerial Ordinance no. 16 on the designation of centres of expertise and on the establishment of a national registry for rare diseases was formally adopted in 2014 in Bulgaria [1]. This document was a result of the input from a working group, consisting of health authorities, clinicians and patient representatives. It legally defined the terms and conditions for designation of local health care providers as centres of expertise for rare diseases, as well as the procedures for establishment of a national rare disease registry. A Commission on Rare Diseases was set up and mandated to monitor and evaluate the implementation of these policies, including the definition of an official list of rare diseases in Bulgaria [1, 2].

The List of rare diseases in Bulgaria is approved and amended by the Minister of Health upon a recommendation by the Commission on Rare Diseases. Apart from the obvious aim to create an inventory for rare diseases, the overall objective of the list is to integrate medical and social approaches to rare disease patients and their families in Bulgaria. This formal catalogue is expected to improve the awareness of and increase the visibility of rare disorders at all levels of the Bulgarian health system. The list is envisaged to greatly influence all rare disease activities in the country. In particular, the National registry of rare diseases, the centres of expertise and reference networks will be defined and operating based on the rare disorders, included in the list [2, 3]. To this date, Italy is the only other country in the EU with an official list of rare diseases, set back in 2001 [4, 5]. In this context, the Bulgarian experience on establishing such a rare disease inventory is important from both methodological and political points of view.

Aim

This publication aims to critically analyze the officially approved List of rare diseases in Bulgaria, its scope and prospects.

Material and methods

We performed a critical analysis on Ministerial Orders RD-01-277 of 27 November 2015 and RD-01-92 of 30 March 2016 that set and supplemented the List of rare diseases in Bulgaria [6,7]. We systematically reviewed the public records of the Commission on Rare Diseases meetings from 2015 and 2016, thus collecting additional information on the list definition, especially the concerns of the Commission when discussing and adopting a recommendation on specific disorders [8]. Search in Medline/PubMed was conducted to identify similar health policies on rare diseases in other EU Member States for comparative analysis.

Results and discussion

Mechanisms for adoption and amendment of the List of rare diseases

The mechanisms for adoption and amendment of the Bulgarian List of rare diseases are regulated by Ordinance no. 16. Any rare disease stakeholder is allowed to submit a disease dossier. The Commission on Rare Diseases formally evaluates it and adopts a recommendation to the Minister of Health, who makes a final decision by issuing an order to amend the list. It is very important to underline that the list is supplemented on a case by case basis. The initially approved version of the list is not closed for modifications [1,2].

A disease dossier must present standardised information, including definition and synonyms, disease classification, epidemiological data, diagnostic criteria, treatment and follow-up protocols, prevention activities if available, proposals for patient access schemes, description of specific local experience and expertise. It is mandatory to present Bulgarian epidemiological data for the condition in question. Once approved for inclusion, this dossier is made publicly available from an open access electronic database [1, 2, 8]. This is a substantial prerequisite for high-quality, equable health care for rare disease patients within the different centres of expertise across the country [9,10].

When included in the list, the conditions are classified according to International Classification of Diseases, 10th revision (ICD-10). In case of a lack of an individual ICD-10 code, the Orphanet code system is applied [11]. Nevertheless, Commission members and local stakeholders have detected some problems using the Orpha codes. For example, non-rare disorders have been assigned an Orpha code [8].

The initial version of the list, recommended by the Commission on Rare Diseases, was approved by the Minister of Health in November 2015 (Ministerial Order RD-01-277). The Commission's proposal was based on the List of conditions, whose outpatient medicinal treatment is reimbursed by the National Health Insurance Fund (NHIF) [12]. This decision was motivated by the presumption that the list should be built upon those conditions, for which there is already established health care infrastructure in the country [13]. Available and accessible medicinal therapy is essential to enhance rare disease health care [14]. The Commission extracted from that list all conditions, which meet the legal definition for a rare disease – prevalence of no more than 5 in 10,000 people. This task was not easy, since local epidemiogical data for rare diseases are virtually missing. There are national disease-specific registries for a very small number of rare conditions [15]. The Orphanet database was generally consulted to determine, if a specific disorder is rare or not [16]. Orphanet was preferred as a decision-making tool over other scientific databases, since it is explicitly mentioned in the EU Cross-Border Health Care Directive [17].

During these initial activities, the Commission gave opportunities for local rare disease stakeholders to take part in the definition of the list. A general call for submission of rare disease dossiers was announced on the websites of the Ministry of Health and NHIF. The Commission sent letters to medical societies and patient umbrella organisations as well. The annual National Conference for Rare Diseases and Orphan Drugs in 2015 provided an additional platform for broad dissemination and consensus building.

Nosological scope of the List of rare diseases

The official List of rare diseases was promulgated by Ministerial Order RD-01-277 in November 2015. This catalogue originally contained 116 rare disorders, listed by ICD-10 code. Ministerial Order RD-01-92 of 30 March 2016 added 18 more rare nosologies to the list (Table 1). By October 2016, 19 more conditions were recommended for inclusion to the List by the Commission and are pending final approval by the Minister of Health [8].

Rare diseases of the blood and blood-forming organs and certain rare disorders, involving the immune mechanism, make more than a half of the list's content (n = 57; 43%). Rare endocrine, nutritional and metabolic conditions (n = 30; 22%) and rare congenital malformations, deformations and chromosomal abnormalities (n = 26; 19%) significantly contributed as well (Figure 1).

The structure of the List of rare diseases in Bulgaria is a logical result of the nature of rare diseases in general. The vast majority of these disorders have a genetic or unknown etiology and predominantly affect infants and children [18, 19]. Furthermore, the content of the list was influenced by the availability and accessibility of orphan therapies. Orphan drug research and development experienced a huge progress in the last decade [20]. New orphan

Table 1. List of rare diseases in Bulgaria by 30 March 2016

No.	ICD-10 code*	Rare disease
1	D55.0	Anaemia due to glucose-6-phosphate dehydrogenase [G6PD] deficiency
2	D56.1/ORPHA231214	Thalassaemia major
3	D56.1/ORPHA231222	Thalassaemia intermedia
4	D58.0/ORPHA822	Minkowski-Chauffard syndrome
5	D59.5	Paroxysmal nocturnal haemoglobinuria [Marchiafava-Micheli]
6	D61.0/ORPHA124	Blackfan-Diamond syndrome
7	D61.0/ORPHA84	Fanconi anaemia
8	D64.4	Congenital dyserythropoietic anaemia
9	D66	Hereditary factor VIII deficiency
10	D67	Hereditary factor IX deficiency
11	D68.0	Von Willebrand disease
12	D68.1/ORPHA329	Hereditary factor XI deficiency
13	D68.2	Hereditary deficiency of other clotting factors
14	D68.2/ORPHA325	Deficiency of factor: II [prothrombin]
15	D68.2/ORPHA326	Deficiency of factor: V [labile]
16	D68.2/ORPHA327	Deficiency of factor: VII [stable]
17	D68.2/ORPHA328	Deficiency of factor: X [Stuart-Prower]
18	D68.2/ORPHA330	Deficiency of factor: XII [Hageman]
19	D68.2/ORPHA331	Deficiency of factor: XIII [fibrin-stabilizing]
20	D68.2/ORPHA335	Deficiency of factor: I [fibrinogen]
21	D69.3	Idiopathic thrombocytopenic purpura
22	D80.0	Hereditary hypogammaglobulinaemia
23	D80.1	Nonfamilial hypogammaglobulinaemia
24	D80.2	Selective deficiency of immunoglobulin A [IgA]
25	D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
26	D80.4	Selective deficiency of immunoglobulin M [IgM]
27	D80.5	Immunodeficiency with increased immunoglobulin M [IgM]
28	D80.6	Antibody deficiency with near-normal immunoglobulins or with hyperimmuno-globulinaemia
29	D80.7	Transient hypogammaglobulinaemia of infancy
30	D80.8	Other immunodeficiencies with predominantly antibody defects
31	D80.9	Immunodeficiency with predominantly antibody defects, unspecified
32	D81.0	Severe combined immunodeficiency [SCID] with reticular dysgenesis
33	D81.1	Severe combined immunodeficiency [SCID] with low T- and B-cell numbers

Continues →

Table 1. Continued

No.	ICD-10 code*	Rare disease
34	D81.2	Severe combined immunodeficiency [SCID] with low or normal B-cell numbers
35	D81.3	Adenosine deaminase [ADA] deficiency
36	D81.4	Nezelof syndrome
37	D81.5	Purine nucleoside phosphorylase [PNP] deficiency
38	D81.6	Major histocompatibility complex class I deficiency
39	D81.7	Major histocompatibility complex class II deficiency
40	D81.8	Other combined immunodeficiencies
41	D81.9	Combined immunodeficiency, unspecified
42	D82.0	Wiskott-Aldrich syndrome
43	D82.1	Di George syndrome
44	D82.2	Immunodeficiency with short-limbed stature
45	D82.3	Immunodeficiency following hereditary defective response to Epstein-Barr virus
46	D82.4	Hyperimmunoglobulin E [IgE] syndrome
47	D82.8	Immunodeficiency associated with other specified major defects
48	D82.9	Immunodeficiency associated with major defect, unspecified
49	D83.0	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
50	D83.1	Common variable immunodeficiency with predominant immunoregulatory T-cell disorders
51	D83.2	Common variable immunodeficiency with autoantibodies to B- or T-cells
52	D83.8	Other common variable immunodeficiencies
53	D83.9	Common variable immunodeficiency, unspecified
54	D84.0	Lymphocyte function antigen-1 [LFA-1] defect
55	D84.1	Defects in the complement system
56	D84.8	Other specified immunodeficiencies
57	D84.9	Immunodeficiency, unspecified
58	E20.0	Idiopathic hypoparathyroidism
59	E22.0	Acromegaly and pituitary gigantism
60	E22.1	Hyperprolactinaemia
61	E22.8	Other hyperfunction of pituitary gland
62	E23.0	Hypopituitarism
63	E23.2	Diabetes insipidus
64	E24.0	Pituitary-dependent Cushing disease
65	E27.1	Primary adrenocortical insufficiency
66	E70.0	Classical phenylketonuria

Continues →

Table 1. Continued

No.	ICD-10 code*	Rare disease
67	E72.2	Disorders of urea cycle metabolism
68	E74.0	Glycogen storage disease
69	E75.2/ORPHA324	Disease: Fabry (-Anderson)
70	E75.2/ORPHA355	Disease: Gaucher
71	E75.2/ORPHA646	Disease: Niemann-Pick
72	E76.1	Mucopolysaccharidosis, type II
73	E76.2	Other mucopolysaccharidoses
74	E80.0/ORPHA79273	Hereditary coproporphyria
75	E80.0/ORPHA79276	Acute intermittent porphyria
76	E80.0/ORPHA79277	Congenital erythropoietic porphyria
77	E80.0/ORPHA79278	Autosomal erythropoietic protoporphyria
78	E80.0/ORPHA79473	Porphyria variegata
79	E80.1	Porphyria cutanea tarda
80	E80.2	Other porphyria
81	E83.0	Disorders of copper metabolism
82	E83.1	Disorders of iron metabolism
83	E83.3	Disorders of phosphorus metabolism and phosphatases
84	E84.0	Cystic fibrosis with pulmonary manifestations
85	E84.1	Cystic fibrosis with intestinal manifestations
86	E84.8	Cystic fibrosis with other manifestations
87	E85.1	Neuropathic heredofamilial amyloidosis
88	G71.0	Muscular dystrophy
89	G71.1	Myotonic disorders
90	G95.0	Syringomyelia and syringobulbia
91	I27.0	Primary pulmonary hypertension
92	J84.1/ORPHA2032	Idiopathic pulmonary fibrosis
93	K50.0	Crohn disease of small intestine
94	M05.0	Felty syndrome
95	M08.0	Juvenile rheumatoid arthritis
96	M08.1	Juvenile ankylosing spondylitis
97	M08.2	Juvenile arthritis with systemic onset
98	M08.3	Juvenile polyarthritis (seronegative)
99	M08.4	Pauciarticular juvenile arthritis
100	M30.0	Polyarteritis nodosa
101	M31.3	Wegener granulomatosis
102	M32.1	Systemic lupus erythematosus with organ or system involvement
103	M32.8	Other forms of systemic lupus erythematosus
104	M33.0	Juvenile dermatomyositis
105	M33.1	Other dermatomyositis
106	M33.2	Polymyositis

Continues →

Table 1. Continued

No.	ICD-10 code*	Rare disease
107	M34.0	Progressive systemic sclerosis
108	M34.1	CR(E)ST syndrome
109	Q21.2	Atrioventricular septal defect
110	Q21.8	Other congenital malformations of cardiac septa
111	Q07.0	Arnold-Chiari syndrome
112	Q20.0	Common arterial trunk
113	Q20.1	Double outlet right ventricle
114	Q20.3	Discordant ventriculoarterial connection
115	Q20.4	Double inlet ventricle
116	Q21.0	Ventricular septal defect
117	Q21.4	Aortopulmonary septal defect
118	Q22.6	Hypoplastic right heart syndrome
119	Q23.0	Congenital stenosis of aortic valve
120	Q25.0	Patent ductus arteriosus
121	Q25.1	Coarctation of aorta
122	Q25.5	Atresia of pulmonary artery
123	Q26.2	Total anomalous pulmonary venous connection
124	Q26.3	Partial anomalous pulmonary venous connection
125	Q81.0	Epidermolysis bullosa simplex
126	Q81.1	Epidermolysis bullosa letalis
127	Q81.2	Epidermolysis bullosa dystrophica
128	Q87.1	Congenital malformation syndromes predominantly associated with short stature
129	Q96.0	Karyotype 45, X
130	Q96.1	Karyotype 46, X iso (Xq)
131	Q96.2	Karyotype 46, X with abnormal sex chromosome, except iso (Xq)
132	Q96.3	Mosaicism, 45, X/46, XX or XY
133	Q96.4	Mosaicism, 45, X/other cell line(s) with abnormal sex chromosome
134	Q96.8	Other variants of Turner syndrome

*ORPHA code is given in cases of no ICD-10 code or an ICD-10 code for a group of disorders.

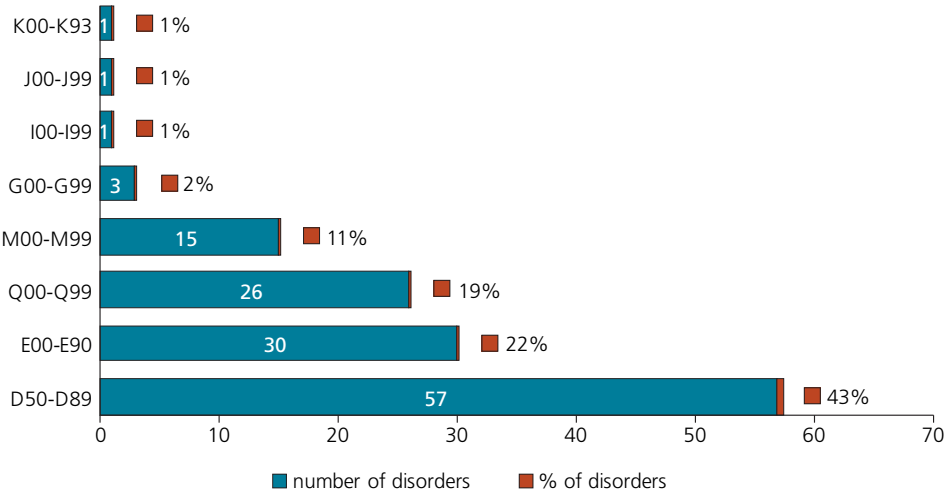

Figure 1. List of rare diseases in Bulgaria by 30 March 2016 by ICD-10 classes.

therapies also mean increased awareness of the indicated rare conditions [21]. Finally, local hematology and medical genetics societies in Bulgaria have been extremely active in rare disease policy making, ensuring effective engagement of these medical professionals in rare diseases.

Examining the public meeting records of the Commission on Rare Diseases showed that only two disorders were rejected for an inclusion [8]. Systemic lupus erythematosus and hidradenitis suppurativa dossiers were negatively assessed because of prevalence exceeding the conventional rare disease threshold. No local epidemiological data were presented in both cases. A Commission decision is currently pending on the dossier of ovarian cancer (ORPHA code 213500). Due to the lack of formal definition of rare cancers, the Commission decided to make a consultation with Bulgarian health authorities and medical societies. Rare diseases and rare cancers do share a lot of commonalities [22, 23]. Having in mind, however, the prospects of the personalised and precise medicine, especially the possibility to fragmentise common cancer nosologies into rare subtypes [24], the Commission considered to explore this issue in depth before making a final recommendation. This decision will set an important precedent in any way with potential significant impact on the national health system.

Conclusion

Defining and setting a rare disease inventory is a fundamental part of rare disease policy. This tool is of a paramount importance, as it greatly affects the knowledge and awareness of rare diseases not only among health care practitioners, but among all rare disease stakeholders. An official list of rare diseases is particularly beneficial now in the context of the European reference networks for rare diseases, generating added value at both international and local levels. We demonstrated and analysed the establishment of the List of rare diseases in Bulgaria. This experience is a result of a decade-long international collaboration within EU bodies like the Rare Diseases Task Force and the EU Committee of Experts on Rare Diseases, as well as participation in major EU projects, such as RD-Portal (Orphanet), EUROPLAN, EPIRARE, BURQOL-RD, RARE-Bestpractices and RD-Action. Bulgarian rare disease stakeholders applied a transparent, proactive methodology when defining and setting the list. This is a substantial prerequisite for the successful implementation of all ongoing rare disease activities in the country. The described approach could be easily adapted and used in other countries.

References

1. Ministry of Health. Ordinance no. 16 of 30 July 2014 on the terms and conditions for registration of rare diseases and on the centres of expertise and reference networks for rare diseases. State Gazette 67 of 12 August 2014. https://www.mh.government.bg/media/filer_public/2015/04/16/naredba16-ot-30-07-2014g-registrirane-redki-zaboliavania.pdf Last accessed on 29 November 2016.
2. Hristova E, Iskrov G, Stefanov R. New horizons for centres of expertise for rare diseases in Bulgaria. Rare Dis Orphan Drugs 2014;1(4):116-20.
3. Montserrat Moliner A, Waligóra J. The European Union policy in the field of rare diseases. Public Health Genomics 2013;16(6):268-77.
4. Ministry of Health. [Regulation of the establishment of the national network for rare diseases and exemption from participation in the costs related to health services, in accordance with art. 5, paragraph 1, letter b of Legislative Decree no. 124/98.] [in Italian]. http://www.iss.it/binary/ccmr/cont/20040614_DGR570.pdf
5. Rodwell C, Aymé S (Eds). Report on the State of the Art of Rare Disease Activities in Europe, July 2014. http://www.eucerd.eu/upload/file/Reports/2014ReportStateofArtRDActivitiesV.pdf Last accessed on 29 November 2016.

6. Ministry of Health. Order RD-01-277 of 25 November 2015. http://ncphp.government.bg/files/komisia_rare_diseases/Zapoved_SpisakRB.pdf Last accessed on 29 November 2016.
7. Ministry of Health. Order RD-01-92 of 30 March 2016. http://ncphp.government.bg/files/komisia_rare_diseases/Zapoved_dopalvane_spisakRB.pdf Last accessed on 29 November 2016.
8. National Centre of Public Health and Analyses. Commission on Rare Diseases. http://ncpha.government.bg/index.php?option=com_content&view=article&id=1317:zasedania&catid=355&Itemid=637&lang=bg Last accessed on 29 November 2016.
9. Taruscio D, Vittozzi L, Choquet R, Heimdal K, Iskrov G, Kodra Y, Landais P, Posada M, Stefanov R, Steinmueller C, Swinnen E. National registries of rare diseases in Europe: an overview of the current situation and experiences. Public Health Genomics 2015;18(1):20-5.
10. Ferrelli RM, De Santis M, Gentile AE, Taruscio D. Exploring the usability of EUCERD core indicators for rare diseases. Ann Ist Super Sanità 2015;51(4):342-5.
11. List of rare diseases and synonyms listed in alphabetical order. Orphanet Report Series, Rare Diseases collection, March 2016. http://www.orpha.net/orphacom/cahiers/docs/GB/List_of_rare_diseases_in_alphabetical_order.pdf Last accessed on 29 November 2016.
12. Ministry of Health. Ordinance no. 38 of 16 November 2004 establishing the list of conditions whose outpatient medicinal treatment, medical devices and special nutrition are fully or partially paid by the National Health Insurance Fund. State Gazette 106 of 3 December 2004. http://www.mh.government.bg/media/filer_public/2015/04/17/naredba38-ot-16-11-2004g-zaplashtane-lekarstva.pdf Last accessed on 29 November 2016.
13. Iskrov G, Jessop E, Miteva-Katrandzhieva T, Stefanov R. Budget impact of rare diseases: proposal for a theoretical framework based on evidence from Bulgaria. Georgian Medical News 2015;242:46-53.
14. Logviss K, Krievins D, Purvina S. Impact of orphan drugs on Latvian budget. Orphanet J Rare Dis 2016;11(1):59.
15. Miteva-Katrandzhieva T, Iskrov G, Stefanov R, Naumova E, Guergueltcheva V, Savov A. Overview of epidemiological rare diseases registries in Bulgaria. Rare Dis Orphan Drugs 2016;3(1):11-5.
16. Prevalence of rare diseases: bibliographic data. Orphanet Report Series, Rare Diseases collection, March 2016, Number 1: Diseases listed in alphabetical order. http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_diseases.pdf Last accessed on 29 November 2016.
17. Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare. Official Journal of the European Union L 88/45, 4 April 2011.
18. Gainotti S, Turner C, Woods S, Kole A, McCormack P, Lochmüller H, Riess O, Straub V, Posada M, Taruscio D, Mascalzoni D. Improving the informed consent process in international collaborative rare disease research: effective consent for effective research. Eur J Hum Genet 2016;24:1248-54.
19. Kodra Y, Kondili LA, Ferraroni A, Serra MA, Caretto F, Ricci MA, Taruscio D. Parent training education program: a pilot study, involving families of children with Prader-Willi syndrome. Ann Ist Super Sanita 2016;52(3):428-33.
20. Polizzi A, Balsamo A, Bal MO, Taruscio D. Rare diseases research and practice. Endocr Dev 2014;27:234-56.
21. Kanters TA, Steenhoek A, Hakkaart L. Orphan drugs expenditure in the Netherlands in the period 2006-2012. Orphanet J Rare Dis 2014;9:154.
22. Sandrucci S, Gatta G, Trama A, Dei Tos AP, Casali PG. Specialized teams or specialist networks for rare cancers? Eur J Surg Oncol 2015;41(9):1115-7.
23. Mallone S, De Angelis R, van der Zwan JM, Trama A, Siesling S, Gatta G, Capocaccia R, RARECARE WG. Methodological aspects of estimating rare cancer prevalence in Europe: the experience of the RARECARE project. Cancer Epidemiol 2013;37(6):850-6.
24. Vozikis A, Cooper DN, Mitropoulou C, Kambouris ME, Brand A, Dolzan V, Fortina P, Innocenti F, Lee MT, Leyens L, Macek M Jr, Al-Mulla F, Prainsack B, Squassina A, Taruscio D, van Schaik RH, Vayena E, Williams MS, Patrinos GP. Test pricing and reimbursement in genomic medicine: towards a general strategy. Public Health Genomics 2016; Sep 28 [Epub ahead of print].