RESEARCH

Demographics, in-hospital analysis, and prevalence of 33 rare diseases with effective treatment in Shanghai

Xiaoshu Cai†, Georgi Z. Genchev1,2,3,4†, Ping He5, Hui Lu1,2,3 and Guangjun Yu1*

Abstract

Background: Rare diseases are ailments which impose a heavy burden on individual patients and global society as a whole. The rare disease management landscape is not a smooth one—a rare disease is quite often hard to diagnose, treat, and investigate. In China, the country’s rapid economic rise and development has brought an increased focus on rare diseases. At present, there is a growing focus placed on the importance and public health priority of rare diseases and on improving awareness, definitions, and treatments.

Methods: In this work we utilized clinical data from the Shanghai HIE System to characterize the status of 33 rare diseases with effective treatment in Shanghai for the time period of 2013–2016.

Results and conclusion: First, we describe the total number of patients, year-to-year change in new patients with diagnosis in one of the target diseases and the distribution of gender and age for the top six (by patient number) diseases of the set of 33 rare diseases. Second, we describe the hospitalization burden in terms of in-hospital ratio, length of stay, and medical expenses during hospitalization. Finally, rare disease period prevalence is calculated for the rare diseases set.

Keywords: Rare disease, Orphan disease, Health care policy, Shanghai, China, Epidemiology, Rare disease prevalence

Background

Rare diseases: a global public health burden and challenges

Rare diseases are ailments which impose a heavy burden on individual patients and society as a whole [1]. Quite often, the total number of patients suffering from a specific rare disease is only a few tens or hundreds of people, however, rare diseases, considered holistically, are not so rare after all—in the United States, around 30 million Americans are afflicted with one of the ~ 7000 such diseases. There is no universally accepted definition what constitutes a rare disease [2]. The United States Orphan Drug Act of 1983 defines rare diseases as those that affect fewer than 200,000 individuals; the European Union defines them as diseases that affect less than 5 in 10,000 individuals, whereas the World Health Organization (WHO) defines rare diseases as those with prevalence in the range of 0.65–1‰.

Most rare diseases are of genetic etiology, and effective treatments exist for only a few of them [3]. The rare disease management landscape is not a smooth one—a rare disease is quite often hard to diagnose, treat, and investigate. For individual suffering from a rare disease the journey from symptoms, to diagnosis, and to treatment is arduous and difficult one. Firstly, receiving an accurate diagnosis may be a long-drawn process driven by the lack testing modalities and existing knowledge and...
information due to the rarity of the condition. Having overcome the hurdle of accurate diagnosis, the patient may face the obstacle of lack of treatment, or if the treatment is not included in a government established health insurance scheme—a financially ruinous self-funded cost of treatment [4]. From governance and health care perspective, while certain regions are well-advanced in many aspects of rare diseases management, in many others there is a lack of comprehensive policy, or a national rare disease plan and legislative framework that is specifically aimed to address the complex web of issues surrounding rare diseases is still in development or yet to be fully implemented [5].

Focus on China
China, as the most populous country in the world, offers its own unique perspectives. China’s rapid economic rise and development has also brought an increased focus on rare diseases. At present, there is a growing importance placed on the management of rare diseases and their inclusion as a public health priority. A current push is in place for improving awareness, definitions, and treatments, and there is a rise in current interest to search for a comprehensive healthcare policy solutions and research. In a recent development, in the last decade medical treatments for certain rare diseases such as Pompeii disease, Gaucher’s disease and others have been included as covered treatment in Shanghai and other locations, however rare diseases continue to impose a significant economic burden on Chinese society and individuals [6, 7].

While expert consensus indicates that a rare disease could be defined as one with incidence of < 1 in 500,000 [8], a formal legislative definition of rare disease is not yet fully developed [9] and alternative approaches such as rare disease lists in lieu of prevalence-based definitions have recently emerged [10]. The first local list of rare diseases was released by the Shanghai Health and Family Planning Commission, the list titled “List of Major Rare Diseases in Shanghai” [11] consists of 56 rare diseases with effective treatment (Shanghai List). In 2016, the National Rare Disease Registry of China was implemented. Furthermore, representing a major milestone, in 2018, China’s First National Rare Disease List (National List) was promulgated by the following five national governmental bodies: the Ministry of Science and Technology, the State Drug Administration, the Ministry of Industry and Information Technology, the National Health Commission, and the State Administration of Traditional Chinese Medicine [12]. The National List includes 121 diseases; prioritizing diseases that are characterized with higher prevalence and burden, and that are highly treatable. The creation of these lists has improved awareness and has the potential to lead to further improvements of the treatment and management of rare diseases in China.

Focus of this study
In our previous work [4], we examined the specifics of the economic burden and described the direct medical costs related to rare diseases in Shanghai. Herein we take a holistic view and focus on rare disease epidemiology in Shanghai. We present epidemiological characterization of a subset of 33 diseases of the Shanghai rare disease list computed from the patient records across local hospitals. Additionally, we focus on the 6 most-common rare diseases of this subset of 33 diseases for further stratification; we show in-hospital expenses and duration of hospitalization. Finally, a period prevalence is calculated for the rare diseases set. Our study’s goal is to contribute to addressing the gap in rare disease knowledge in China; our work is amongst the few that present epidemiology information and report prevalence information regarding rare diseases in China.

Materials and methods

Data source
The data sources for the analysis presented in this work were the Health Information System (HIE) [13] of Shanghai and the Shanghai List of rare diseases. The Health Information Exchange (HIE) system of Shanghai, established by Shanghai Hospital Development Center in 2010, integrates medical records from 38 tertiary hospitals, 6 district hospitals and 40 community health centers in Shanghai. The HIE receives a constant stream of new patient medical data and its data contents are constantly expanded; at the time of our data sourcing the HIE system contained information on over 61 million patients with over 210 million visit records, 16 million prescriptions, 9.9 million case notes, and 230 million laboratory results. The HIE systems serves as a foundational element utilized in hospital management activities such as analytics and business operation. In-hospital quality assurance and patient management activities can also be performed utilizing data sourced from the HIE as well as health-related and biomedical research.

Data extraction and processing

Disease list subset
First, we mapped the Shanghai list diseases to standard ICD10 codes from the International Statistical Classification of Disease and Related Health Problems 10th Shanghai Revision. 22 diseases did not have a corresponding ICD10 code and no information could be identified in the HIE, therefore we were able to source patient information for 34 diseases from the Shanghai List. One disease:
hypophosphatemic rickets (ICD CODE: E83.308) had no patient records, thus the set of diseases we considered contained 33 diseases.

**Rare disease patient data**

We obtained HIE rare disease medical record data consisting of patient demographic information, patient records (in- and outpatients), prescription information, medical practitioner advice, diagnosis, biomedical indicators, radiology records, and discharge records. Each patient had a major diagnosis and several secondary diagnoses entered in the HIE. Patients with either major or secondary diagnosis were included in our target population. For hemophilia we combined all subtypes:

- Hemophilia (ICD = D66.x02)
- Hemophilia A (ICD = D66.x01)
- Hemophilia B (ICD = D67.x01)
- Hemophilia C (ICD = D68.101)

From the medical records, we sourced a dataset containing the following data-points: patient medical record number, gender, date of birth, consultation date, diagnosis—disease name and ICD10 code, and organization code. For the inpatients we had also hospital admission date, hospital discharge date, and total hospitalization expenses.

To ensure that the privacy and confidentiality of the patients, personally-identifying information was removed before receiving the data. The data was entered into a MySQL database and queried with the database management programs DbVisualizer (DbVis Software AB, Stockholm, Sweden) and by the SQL database query language.

**Epidemiological Analysis**

**Number of patients, age, gender, outpatient and inpatient proportions, and year-to-year change**

Total number of patients per disease per year, age, gender distribution, proportions of inpatients and outpatients were calculated for the 33 diseases for the period January 2013 to December 2016. The total number of patients per disease is a summation of inpatients and outpatients, with duplicate records removed. Patients who have more than one medical record were counted only once, on the basis of the first time of presentation for the year. Age and gender were calculated by summation from the dataset. Age was considered as of the date of first hospital presentation for the year. Inpatient and outpatient proportions were also calculated by grouping from the dataset. The year-to-year change in patient numbers per disease was calculated for each on the 4 years (January 2013 – December 2016).

**Length of stay and hospitalization expenses**

We calculated the average length of hospital stay per disease, in hospital expenses, utilizing inpatient records. Of the 33 target rare diseases, 24 diseases had patients with in-hospital records. We averaged the length of stay in hospitalization by the patient numbers for each disease and the time period of four years. The hospitalization expenses were summed and then averaged by number of patients for each disease.

**Period prevalence**

The period prevalence of the rare diseases was calculated utilizing the following equation:

\[
\text{Prevalence} = \frac{\text{number of patients with Shanghai hukou in the dataset}}{\text{average number of population with Shanghai hukou (2013 – 2016)}}
\]

The denominator was set to 14,409,750 people which is the average number of individuals which were registered residents of Shanghai i.e. individuals who possess a Shanghai residence permit (hukou, 户口) for the years 2013–2016. Data was sourced from the Shanghai Municipal Statistics Bureau retrieved from: [http://tjj.sh.gov.cn/tjnj/nj17.htm?d1=2017tjnj/C0201.htm](http://tjj.sh.gov.cn/tjnj/nj17.htm?d1=2017tjnj/C0201.htm).

**Results and discussion**

In this work we utilized clinical data from the Shanghai HIE System to characterize of the status of rare diseases in Shanghai. First, we describe the total number of patients, year-to-year change in new patients and the distribution of gender and age for the top six (by patient number) diseases. Second, we described the hospitalization burden in terms of in-hospital ratio, length of stay and medical expenses during hospitalization. Finally, rare disease period prevalence is calculated. The motivation for our work is to present a China focused analysis and a period snapshot of the status of rare diseases in Shanghai. Our work utilizes a data-set that is Chinese sourced, an approach motivated by the potential differences that exist between China and other countries. Our work helps address a knowledge need and gives insights that are pertinent within the domain of China's health system.

**Total number of rare disease patients for the period 2013–2016 in Shanghai hospitals**

For the period 2013–2016, we identified a total of 16,933 patients diagnosed with a disease from the Shanghai List subset of 33 rare diseases in Shanghai hospitals. Within
the subset of 33 diseases, severe Congenital Neutropenia was the most prevalent disease. Patients numbers for six diseases exceeded one thousand (Fig. 1a), six other diseases had patient numbers in the range of 100 to 1000 (Fig. 1b). The remaining 21 diseases had number of patients fewer than 100, and 10 diseases were shown as especially rare in Shanghai with fewer than 20 patients counted during the investigation period of 2013–2016 (Fig. 1c).
Year-to-year patient numbers change
To gain a better understanding of the patient variation year by year, we calculated the number of new patients (patients who had a diagnosis recorded for them for the target disease for the first time that year) per year for the six top (by total patient number) diseases. Severe congenital neutropenia and congenital hyperinsulinemic hypoglycemia showed an apparent increasing trend year by year (Fig. 2a, b), hemophilia showed a decreasing trend (Fig. 2c), and hepatolenticular degeneration, idiopathic pulmonary arterial hypertension, and congenital adrenal hyperplasia showed a variable trend for this four-year period (Fig. 2d–f).

Age and gender
The distribution of patients by age (Fig. 3) indicates that the majority of the 33 rare diseases of the Shanghai list have patients of young age. For example, in the top six diseases, severe congenital neutropenia and idiopathic pulmonary arterial hypertension showed 33.1% and 26.7% of patients were under 5, respectively. Considering the typical age of onset of the top 6 rare diseases we observed that diseases with early onset such as severe congenital neutropenia show age distribution of diagnosis also skewed towards the early age. One notable difference is seen in Idiopathic pulmonary arterial hypertension which has onset during all ages, whereas it appears to be diagnosed predominantly at early age in the hospitals in the Shanghai HIE network.

The four of top six (by patient numbers) diseases from the Shanghai list have similar numbers of both male and female patients (Fig. 4) which illustrates that there is no evidence of gender bias in rare disease diagnosis in Shanghai hospitals. Amongst the top six rare diseases, two show an imbalanced gender ratio. The male to female ratio of Hemophilia (an X-linked recessive disorder) is 5.92:1 and the male to female ratio of congenital hyperinsulinemic hypoglycemia is 1:2.82. This finding provides further support to the notion of the potential role of X-linkage in the etiology of congenital hyperinsulinemic hypoglycemia [14, 15].

In-hospital analysis: hospitalization proportion
There is a notable difference in the numbers of inpatients and outpatients across the 33 rare diseases. Generally, outpatients accounted for a greater proportion in a majority of diseases. In two rare diseases, Diamond-Blackfan anemia and Wiscott–Aldrich syndrome, the

Fig. 2 Year-to-year patient numbers change. Year-to-year change in new patients is shown for the six top (by patient numbers) diseases from the Shanghai list. Each red bar depicts the number of new patients each year, (i.e. the number of patients who had a diagnosis for the target disease recorded for them for the first time in that year)
Fig. 3  Age distribution of the top six (by patient numbers) diseases. Age axis intervals are equal to 5 years. The age value is taken at the time when the patient had a diagnosis for one of the rare diseases recorded for them for the first time in the HIE system.

Fig. 4  Gender distribution of the top six (by patient number) diseases
number of inpatients greatly outnumbers the number of outpatients. In a few other cases, the proportions of inpatients and outpatients were nearly equal (Fig. 5).

In-hospital analysis: average length of stay and hospitalization expenses of hospitalization

The majority of the 33 rare diseases had an average length of stay in hospitalization of fewer than 30 days per person every year (calculated over all 4 years) (Fig. 6a). However, the average length of stay for patients diagnosed with Severe Congenital Neutropenia (a disease that is characterized with periods of potentially life-threatening infections [16] that require hospitalization) was 222 days per person in one year (averaged over the 4-year time period). 75.3% of the 33 rare diseases had an average hospitalization stays of more than 10 days. Patients diagnosed with rare disease incurred significant economic burden, and hospitalization expenses ranging from under 5000 CNY to 60,000 CNY – (averaged over the 4-year time period) (Fig. 6b). The top 2 most costly diseases were Wiscoff–Aldrich syndrome and Fancomy anemia with expenses exceeding 50,000 CNY.

Prevalence calculation

We calculated the period prevalence of rare diseases in Shanghai (Table 1). The 3 most prevalent diseases from the subset of 33 diseases of the Shanghai list were severe congenital neutropenia, congenital hyperinsulinemic hypoglycemia, and hemophilia. The least prevalent disease was primary carnitine deficiency. The prevalence calculation population is the set of people with Shanghai household registration (hukou, 户口), and the set of diagnosed patients with Shanghai hukou (户口), (n = 14,409,750, averaged over the 4-year time period).

Evidence-based prevalence metrics calculations inform health policy and also serve as establishing or updating existing rare-disease definition by establishing a population threshold [17]. The lack of available rare disease epidemiology data in China has fostered the development of other proposed approaches—such as the Shanghai List or other orphan drug economics-focused methods [18] and in general such prevalence calculations in the Chinese context have been scarce. The prevalence results presented in this work are one of the few available epidemiology data based calculations focused on one of China’s first-tier cities and can serve as a landmark evidence in rare disease research and policy development.

Summary and conclusion

Increasing knowledge and awareness of rare diseases for health care providers and the general public, ongoing work on developing new treatments and ensuring drug access, and fostering governmental policy implementation are some of the key aspects that will help drive the successful management of rare diseases.
Fig. 6  In-hospital analysis: average length of hospitalization and expenses for a 24 rare diseases subset of the Shanghai List.  

A  Average length of hospitalization-value shown is the length of stay per person per year for each disease (in days).

B  Average hospitalization expenses per person for each disease (in Chinese yuan CNY)
Table 1  Period prevalence (2013–2016) of 33 rare diseases in Shanghai residents

| Rank | Disease name                                      | ICD code         | ORPHA code | In National list | Number of patients (Shanghai hukou,户口) | Prevalence Period prevalence 1 in 1,000,000 (10⁻⁶) | Period prevalence 1 in 100,000 (10⁻⁵) |
|------|--------------------------------------------------|------------------|------------|------------------|------------------------------------------|--------------------------------------------------|----------------------------------------|
| 1    | Severe congenital neutropenia [19]               | D70.x00          | 42,738     | Yes              | 3703                                     | 2.57E−04                                            | 257                                    | 25.7                                   |
| 2    | Congenital hyperinsulinemic hypoglycemia [20]    | E16.103          | 657        | Yes              | 3337                                     | 2.32E−04                                            | 232                                    | 23.2                                   |
| 3    | Hemophilia [21]                                  | D66.x01 D66.x02 D67.x01 | 448        | Yes              | 931                                      | 6.46E−05                                            | 64.6                                   | 6.46                                   |
| 4    | Idiopathic pulmonary arterial hypertension [22]  | I27.000          | 422        | Yes              | 900                                      | 6.25E−05                                            | 62.5                                   | 6.25                                   |
| 5    | Hepatolenticular degeneration [23]               | E83.001          | 905        | Yes              | 531                                      | 3.69E−05                                            | 36.9                                   | 3.69                                   |
| 6    | Gaucher’s disease [24]                           | E75.201          | 355        | Yes              | 323                                      | 2.24E−05                                            | 22.4                                   | 0.224                                  |
| 7    | Glycogen storage diseases [25]                   | E74.000          | 79,201     | Yes              | 218                                      | 1.51E−05                                            | 15.1                                   | 1.51                                   |
| 8    | Congenital adrenal hyperplasia [26]              | E25.004          | 418        | Yes              | 196                                      | 1.36E−05                                            | 13.6                                   | 1.36                                   |
| 9    | Hereditary epidermolysis bullosa [27]            | Q81.900          | 79,361     | Yes              | 85                                       | 5.90E−06                                            | 5.9                                    | 0.59                                   |
| 10   | Maple syrup urine disease [28]                   | E71.001          | 511        | Yes              | 57                                       | 3.96E−06                                            | 3.96                                   | 0.396                                  |
| 11   | Osteogenesis imperfecta [29]                     | Q78.000          | 666        | Yes              | 54                                       | 3.75E−06                                            | 3.75                                   | 0.375                                  |
| 12   | Prader–Willi syndrome [30]                       | Q87.106          | 739        | Yes              | 33                                       | 2.29E−06                                            | 2.29                                   | 0.229                                  |
| 13   | Diamond–Blackfan anemia [31]                     | D61.001          | 124        | Yes              | 28                                       | 1.94E−06                                            | 1.94                                   | 0.194                                  |
| 14   | Fabry disease [32]                               | E75.205          | 324        | Yes              | 17                                       | 1.18E−06                                            | 1.18                                   | 0.118                                  |
| 15   | Niemann–Pick disease [33, 34]                    | E75.203 77,292(A); 77,293(B);646(C) | 33         | Yes              | 17                                       | 1.18E−06                                            | 1.18                                   | 0.118                                  |
| 16   | Fanconi anemia [35]                              | E72.002          | 84         | Yes              | 16                                       | 1.11E−06                                            | 1.11                                   | 0.111                                  |
| 17   | Phenylketonuria [36]                             | E70.000          | 716        | Yes              | 14                                       | 9.72E−07                                            | 0.972                                  | 0.0972                                 |
| 18   | Methylmalonic acidemia [37]                      | E71.102          | 293,355    | Yes              | 8                                        | 5.55E−07                                            | 0.555                                  | 0.0555                                 |
| 19   | Laron syndrome [38]                              | E34.304          | 633        | Yes              | 7                                        | 4.86E−07                                            | 0.486                                  | 4.86                                   |
| 20   | X-linked lymphoproliferative disease [39]        | D82.301          | 2442       | Yes              | 5                                        | 3.47E−07                                            | 0.347                                  | 0.0347                                 |
| 21   | Atypical hemolytic uremic syndrome [40]          | D59.301          | 2134       | Yes              | 4                                        | 2.78E−07                                            | 0.278                                  | 0.0278                                 |
| 22   | Propionic academia [41]                          | E71.101          | 35         | Yes              | 4                                        | 2.78E−07                                            | 0.278                                  | 0.0278                                 |
| 23   | Wiskott–Aldrich syndrome [42]                    | D82.000          | 906        | Yes              | 4                                        | 2.78E−07                                            | 0.278                                  | 0.0278                                 |
| 24   | Hypophosphatasia [43]                            | E83.306          | 436        | Yes              | 3                                        | 2.08E−07                                            | 0.208                                  | 0.0208                                 |
In this work the status of rare diseases in Shanghai, China is characterized. Total number of patients, year-to-year change in new patients and the distribution of gender and age for the top six (by patient number) diseases, together with the hospitalization burden in terms of in-hospital ratio, length of stay, and medical expenses during hospitalization are described. A rare disease period prevalence calculation for 33 rare diseases in Shanghai is presented. The work covers the period 2013–2016 and it is the authors’ goal to provide a 7-year update publication at a future date.

Acknowledgements
Not applicable.

Authors’ contributions
XC, GG, HL, and GY designed the study. XC collected and processed the data. XC and GG implemented the analysis. XC, GG, HL, and GY wrote and revised the manuscript. All authors read and approved the final manuscript.

Funding
This study was supported by National Key R&D Program of China Grant 2018YFC0910500, the Science and Technology Commission of Shanghai Municipality (STCSM) Grants 17DZ2251200, 19495810400, the Shanghai Municipal Commission of Health and Family Planning Grant 2018ZHYL0223, the Medical Conversion Cross-Fund of Shanghai Jiao Tong University grant ZH2018QNA30, and the Neil Shen’s SJTU Medical Research Fund.

Availability of data and materials
Not applicable.

Declarations
Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Center for Biomedical Informatics, Shanghai Children’s Hospital, Shanghai, China. 2 SJTU-Yale Joint Center for Biostatistics and Data Science, Shanghai Jiao Tong University, Shanghai, China. 3 Department of Bioinformatics and Biostatistics, Shanghai Jiao Tong University, Shanghai, China. 4 Bulgarian Institute for Genomics and Precision Medicine, Sofia, Bulgaria. 5 Shanghai Hospital Development Center, Shanghai, China.

Received: 12 October 2020   Accepted: 20 April 2021
Published online: 08 June 2021

References
1. Schey C, Milanova T, Hutchings A. Estimating the budget impact of orphan medicines in Europe: 2010–2020. Orphanet J Rare Dis. 2011;6:62.
2. Melnikova I. Rare diseases and orphan drugs. Nat Rev Drug Discov. 2012;11(4):267–8. https://doi.org/10.1038/nrd3654.
3. Luzzatto L, Hollak CEM, Cox TM, Schieppati A, Licht C, Kääriäinen H, et al. Rare diseases and effective treatments: are we delivering? Lancet. 2015;385(9970):750–2.
4. Cai X, Yang H, Genchev GZ, Lu H, Yu G. Analysis of economic burden and its associated factors of twenty-three rare diseases in Shanghai. Orphanet J Rare Dis. 2019;14(1):233. https://doi.org/10.1186/s13023-019-1168-4.
5. Dharssi S, Wong-Rieger D, Harold M, Terry S. Review of 11 national policies for rare diseases in the context of key patient needs. Orphanet J Rare Dis. 2017;12(1):63. https://doi.org/10.1186/s13023-017-0618-0.
6. Xin XX, Guan XD, Shi LW. Catastrophic expenditure and impoverishment of patients affected by 7 rare diseases in China. Orphanet J Rare Dis. 2016;11(1):74. https://doi.org/10.1186/s13023-016-0454-2.
7. Gong S, Wang Y, Pan X, Zhang L, Huang R, Chen X, et al. The availability and affordability of orphan drugs for rare diseases in China. Orphanet J Rare Dis. 2016;11(1):20. https://doi.org/10.1186/s13023-016-0392-4.
8. Song P, Gao J, Inagaki Y, Kokudo N, Tang W. Rare diseases, orphan drugs, and their regulation in Asia: current status and future perspectives. Intractable Rare Dis Res. 2012;1(1):3–9. https://doi.org/10.5352/irdr.2012.v1.3.

9. Gao J, Song P, Tang W. Rare disease patient in China anticipate the sunlight of legislation. Drug Discov Ther. 2017;3(3):126–8.

10. Planning SMCoHaF. Notice on issuance of The List of Major Rare Diseases of congenital hypoglycemia disorders. JAMA Dermatol. 2016;152(11):1231–8. https://doi.org/10.1001/jamadermatol.2016.10526.

11. He J, Kang Q, Hu J, Song P, Jin C. China has officially released its first national list of rare diseases. Intractable Rare Dis Res. 2018;7(2):145–7. https://doi.org/10.5352/irdr.2018.01056.

12. He J, Kang Q, Hu J, Song P, Jin C. China has officially released its first national list of rare diseases. Intractable Rare Dis Res. 2018;7(2):145–7. https://doi.org/10.5352/irdr.2018.01056.

13. Guangjun Y, Wenbin C, Li Z, Bates DW, Jianlei G, Hui L, editors. Implementation of a city-wide Health Information Exchange solution in the largest metropolitan region in China. In: 2016 IEEE international conference on bioinformatics and biomedicine (BIBM); 2016. 15–18 Dec. 2016.

14. Stanley CA. Perspective on the genetics and diagnosis of congenital hypersplenism disorders. J Clin Endocrinol Metab. 2016;101(5):815–26. https://doi.org/10.1210/jc.2015-3651.

15. De Leon DD, Stanley CA. Congenital hypoglycemia disorders: new aspects of etiology, diagnosis, treatment and outcomes: highlights of the proceedings of the congenital hyperinsulinism disorders symposium, Philadelphia, April 2016. Pediatr Diabetes. 2017;18(1):3–9. https://doi.org/10.1111/pedi.12453.

16. Donadiu E, Bennefaute O, Beauapain B, Mahlaoui N, Chantelot CB. Congenital neutropenia: diagnosis, molecular bases and patient management. Orphanet J Rare Dis. 2017;12:1. https://doi.org/10.1186/s13023-016-0205-7.

17. Zhou X, Cui Y, Han J. Methylmalonic acidemia: current status and research priorities. Intractable Rare Dis Res. 2018;7(2):73–8. https://doi.org/10.5352/irdr.2018.01026.

18. Schuchman EH, Wasserstein MP. Types A and B Niemann-Pick disease. J Blood Med. 2010;1:183–95. https://doi.org/10.2147/JBM.S6885.

19._BINDER G, Begemann M, Eggermann T, Kannenberg K. Silver-Russell syndrome (SRS). Orphanet J Rare Dis. 2015;10:28. https://doi.org/10.1186/s13023-015-0241-x.

20. Wolf B, Heard GS, Weissbecker KA, McVoy JR, Grier RE, Leshner RT. Biotinidase deficiency: initial clinical features and rapid diagnosis. Ann Neurol. 1985;18(5):614–7. https://doi.org/10.1002/ana.410180517.

21. Neurological disorders—clinical spectrum and frequency of different types. J Coll Phys Surg Pak. 2017;27(12):703–10. https://doi.org/10.14103/jcppsp.2017.12007.

22. Dobbyns WB, Goldstein NP, Gordon H. Clinical spectrum of Wilson's disease. Orphanet J Rare Dis. 2012;7:55–66. https://doi.org/10.1186/1750-1172-7-55.

23. Mehta A. Epidemiology and natural history of Gaucher's disease. Eur J Intern Med. 2006;17(Suppl 5):S5–S13. https://doi.org/10.1016/j.ejim.2006.07.005.

24. Ozen H. Glycogen storage diseases: new perspectives. World J Gastroenterol. 2007;13(18):2541–3. https://doi.org/10.3748/wjg.v13.i18.2541.

25. Merck DP, Bornstein SR. Congenital adrenal hyperplasia. Lancet. 2005;365(9477):2125–36. https://doi.org/10.1016/S0140-6736(05)66736-0.

26. Fine JD. Epidemiology of inherited Epidermolysis Bullosa based on incidence and prevalence estimates from the National Epidermolysis Bullosa Registry. JAMA Dermatol. 2016;152(11):1231–8. https://doi.org/10.1001/jamadermatol.2016.2473.

27. Blackburn PR, Gass JM, Vairo FPE, Farnham KM, Atwal HK, Macklin S, et al. Maple syrup urine disease: mechanisms and management. Appl Clin Genet. 2010;3:57–66. https://doi.org/10.2147/ACG.S12962.

28. Martin E, Shapiro JR. Osteogenesis imperfecta imperfecta: epidemiology and pathophysiology. Curr Osteoporos Rep. 2007;5(3):91–7. https://doi.org/10.1007/s11914-007-0023-2.

29. Martin E, Shapiro JR. Osteogenesis imperfecta imperfecta: epidemiology and pathophysiology. Curr Osteoporos Rep. 2007;5(3):91–7. https://doi.org/10.1007/s11914-007-0023-2.