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Using the Gaucher Earlier Diagnosis Consensus (GED-C) Delphi Score in a Real-World Dataset

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Abstract: Early and accurate diagnosis of Gaucher disease, a rare, autosomal recessive condition characterized by hepatosplenomegaly, thrombocytopenia, and anemia, is essential to facilitate earlier decision-making and prevent unnecessary tests and procedures. However, diagnosis can be challenging for non-specialists, owing to a wide variability in age, severity of disease, and types of clinical manifestation. The Gaucher Earlier Diagnosis Consensus (GED-C) scoring system was developed by a panel of 22 expert physicians using Delphi methodology on the signs and covariables considered important for diagnosing Gaucher disease. This study aimed to use the scoring system in a real-world dataset. We applied the GED-C scoring system to 265 confirmed cases of Gaucher disease identified in the Maccabi Health Services (MHS) database from 1998 to 2022. Overall Delphi scores were calculated using features applicable to type 1 Gaucher disease. Based on all available patient data up to one year after diagnosis, the median (interquartile range (IQR)) Delphi score was 8.0 (5.5–11.5), with patients reporting up to 15 variables each. A score of 9.5 (6.5–12.5) was determined for 205 patients diagnosed from 2000 to 2022. The overall GED-C score was highly dependent on the extraction of all relevant data. The number of features collected in the MHS database was fewer than those required to achieve a high score on the GED-C score.

Keywords: Gaucher disease; early diagnosis; machine learning; real-world data

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1. Introduction

Gaucher disease is a rare, autosomal recessive disorder characterized by the deficiency of the lysosomal enzyme β-glucocerebrosidase (GBA), caused by pathogenic variation in the *GBA1* gene [1]. The resultant accumulation of glucosylceramide in macrophages throughout the body leads to the onset of multisystemic disease manifestations that range in type and severity [1]. Disease manifestations are considered to occur along a phenotypic continuum: ranging from the milder type 1 Gaucher disease, typically involving enlargement of the spleen and liver and the presence of thrombocytopenia, anemia, and bone abnormalities; through type 3, characterized by the presence of neurologic symptoms; to type 2, the most severe, characterized by severe neurologic symptoms and early onset, often resulting in death in early childhood [1,2].

Systemic manifestations can be improved with the timely administration of enzyme replacement therapy or substrate reduction therapy [3–7]. Conversely, delayed initiation of therapy through late diagnosis can lead to irreversible bone disease, severe growth retardation, and a high risk of bleeding. In rare cases, a misdiagnosis can be life-threatening [8–10]. However, the diagnosis of Gaucher disease can be challenging, especially for non-specialists, owing to wide variability in age at presentation, severity, and type of clinical manifestation,

and the presence of non-specific features [10]. This is further compounded by a lack of awareness—among both patients and physicians—of the early signs and symptoms of the disease [8–10]. As a result, many patients face significant delays in obtaining a diagnosis. Indeed, in a survey of 212 patients with Gaucher disease, one in six were diagnosed more than 7 years after first consulting a doctor [10], and in a separate study, only 20% of physicians considered Gaucher disease when presented with a patient showing typical features of the disease [8]. There is, therefore, a clear need to improve the rate at which a diagnosis can be made for patients with Gaucher disease.

The Gaucher Earlier Diagnosis Consensus (GED-C) scoring system was developed by a panel of 22 expert physicians using Delphi methodology on the signs and covariables considered to be important for the diagnosis of Gaucher disease [11]. However, the predictive value of the GED-C scoring system remains to be validated in a real-world population, and no attempt to develop a scoring system for searching for undiagnosed patients with Gaucher disease in real-world, large-scale clinical data has been conducted to date.

The objective of this study was to evaluate the GED-C scoring system within a cohort of confirmed patients with Gaucher disease using real-world data.

2. Methods

2.1. Data Source

The study utilized electronic health records from the Maccabi Healthcare Service (MHS), which is the second largest health maintenance organization in Israel. The MHS includes 3 million health records from 25% of the Israeli population. Clinical records have been fully computerized since 1998 and are fully integrated with automated central laboratory, digitized imaging, and pharmacy purchase data. In addition, the MHS is associated with a biobank of samples collected from consenting donors among MHS participants.

2.2. Population

The electronic database of the MHS was scanned for patients diagnosed with MHS's diagnosis code for Gaucher disease (Y71156). The International Classification of Diseases version 9 (ICD-9) code 272.7 was not used for patient identification as it is non-specific for Gaucher disease. A liberal definition of Gaucher disease was utilized, with the intention of minimizing the risk of missing patients. MHS records for identified cases were screened for evidence of a specific Gaucher disease treatment prescription or prior authorization, such as enzyme replacement therapy (ERT) or substrate reduction therapy (SRT) medications. For those without evidence for Gaucher disease treatment, patient records were screened for notes indicating Gaucher disease. Potential cases with a diagnosis code for Gaucher disease who met any of the following criteria were excluded:

a. Patient has been recognized as "Gaucher carrier";
b. Where notes indicated a patient had been tested for Gaucher disease and was found negative);
c. No confirmation of diagnosis of Gaucher disease or disease-specific treatment in medical records, including physicians' notes, hospital discharges, etc.

All eligible cases with a confirmed diagnosis of Gaucher disease in the MHS database were included in the study. The study design was approved by MHS IRB- 0013-21-ASMC.

2.3. Use of the GED-C Scoring System

The GED-C scoring system (Table 1) was applied to confirmed cases of Gaucher disease for each item relevant to type 1 Gaucher disease that was possible to be extracted from MHS (maximum 18 items, maximum score 22). Data on each of the GED-C items were extracted for each patient from electronic health records of the MHS, including demographics, diagnosis codes (ICD-9), laboratory values, imaging reports, MHS osteoporosis register, weights and heights, and free-text notes from patient visits. Visit notes were searched for the following terms: splenomegaly, hepatomegaly, gallbladder stones, fatigue, bone pain, bleeding, and growth retardation. Data were extracted from the first record available

until one year after diagnosis of Gaucher disease. The one-year post-diagnosis cut-off was chosen to allow maximal capture of features on completion of relevant confirmatory testing for Gaucher disease. Items for GED-C scores were extracted as quantitative values where possible. The number of individuals with scores for each type 1 Gaucher disease-specific item on the GED-C scoring system was calculated based on two scenarios: with or without inclusion of free-text analysis of patient visit records.

Table 1. The GED-C scoring system.

	Weighting	Clinical Sign or Covariable		Application to MHS
Major signs and covariables	3 points	Splenomegaly (≥3× normal)	✓	Multiple of normal not applied
		Disturbed oculomotor function (slow horizontal saccades with unimpaired vision)		Not applicable to type 1 Gaucher disease
	2 points	Thrombocytopenia, mild or moderate (platelet count, 50–150 × 10^9/L)	✓	
		Bone issues, including pain, crises, avascular necrosis, and fractures	✓	
		Family history of Gaucher disease		
		Anemia, mild or moderate (hemoglobin, 95–140 g/L)	✓	
		Hyperferritinemia, mild or moderate (serum ferritin, 300–1000 µg/L)	✓	
		Jewish ancestry	✓	
		Disturbed motor function (impairment of primary motor development)		Not applicable to type 1 Gaucher disease
		Hepatomegaly, mild or moderate (≤3× normal)	✓	Multiple of normal not applied. Combined with severe hepatomegaly (2 points)
		Myoclonus epilepsy		Not applicable to type 1 Gaucher disease
		Kyphosis		Not applicable to type 1 Gaucher disease
		Gammopathy–monoclonal or polyclonal	✓	
	1 point	Anemia, severe (hemoglobin, <9.5 g/dL)	✓	
		Hyperferritinemia, severe (serum ferritin, >1000 µg/L)	✓	
		Hepatomegaly, severe (>3× normal)	✓	Multiple of normal not applied. Combined with mild/moderate hepatomegaly (2 points)
		Thrombocytopenia, severe (platelet count, <50 × 10^9/L)	✓	
Minor signs and covariables	0.5 points	Gallstones	✓	
		Bleeding, bruising, or coagulopathy	✓	
		Leukopenia	✓	
		Cognitive deficit		Not applicable to type 1 Gaucher disease
		Low bone mineral density	✓	
		Growth retardation including low body weight	✓	
		Asthenia	✓	Combined with fatigue
		Cardiac calcification		Not applicable to type 1 Gaucher disease
		Dyslipidemia	✓	
		Elevated angiotensin-converting enzyme levels	✓	Elevated angiotensin-converting enzyme
		Fatigue	✓	Combined with asthenia
		Pulmonary infiltrates		Not applicable to type 1 Gaucher disease
		Age ≤ 18 years	✓	
		Family history of Parkinson disease	✓	
		Blood relative who died of fetal hydrops and/or with diagnosis of neonatal sepsis of uncertain etiology		Not applicable to type 1 Gaucher disease
Max score			**22**	

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Pty Ltd. on behalf of Royal Australasian College of Physicians. GED-C = Gaucher Early Diagnosis Consensus; MHS = Maccabi Health Services.

To compute the GED-C score, the weight of each feature was set according to the published score (Table 1) [11]. For laboratory data, the maximum or minimum levels (as appropriate) were considered. Dichotomous variables were coded as 'yes' or 'no'. Evaluation of multiples of normal in spleen and liver size was not feasible; "splenomegaly" received a score of 3 irrespective of size, and "hepatomegaly" was scored as 2 points. Growth retardation based on height, weight, and body mass index (BMI) measures was defined as equal to or less than the 10th percentile for age as defined by the clinical growth charts of the Center for Disease Control and Prevention [12]. For men (≥20 years of age), the 10th percentile for height, weight, and BMI was 167.5 cm, 58 kg, and 22.4, respectively. For women (≥20 years of age), the 10th percentile for height, weight, and BMI was 156.9 cm, 48 kg, and 21.4, respectively [12]. Asthenia and fatigue were scored by one item as in Hebrew both descriptions use the same word. No ICD-9 code was available for family history of Gaucher disease.

2.4. Statistical Analyses

Results were reported using summary descriptive statistics: median (range) for continuous variables, and absolute and relative frequencies for nominal data. Data computation and statistical analyses were performed using R programming, version 1.4.1103, packages dplyr, stringr, tidiverse, lubridate, and ggplot2.

3. Results

A total of 346 potential cases of Gaucher diseases were identified from the MHS database. Of these, 265 were confirmed as Gaucher disease, either with a documented receipt of ERT or SRT with the Israeli Ministry of Health or confirmed by chart review (Table 2). Of the 81 cases excluded from further analyses, 11 were evaluated for Gaucher disease but were excluded based on normal bone marrow and/or genotyping as determined by the physicians seeing the patients in the clinic, 33 were determined to be asymptomatic carriers, and 37 were excluded owing to inconclusive data, i.e., lack of documented receipt of ERT or SRT and lack of free-text physician notes indicating Gaucher disease (Figure 1).

Table 2. Characteristics of 265 cases with confirmed Gaucher disease.

	Total (N = 265)
Male, n (%)	130 (49.1)
Median (range, IQR) age at first documentation, y	31 (0–88, 30.5–61.0)
Age category at first documentation, n (%)	
<2	24 (9.1)
2–9	23 (8.7)
10–18	27 (10.7)
19–29	48 (18.1)
30–39	59 (22.3)
40–49	29 (10.9)
50–59	29 (10.9)
60–69	13 (4.9)
>70	13 (4.9)
Dispensed ERT or SRT, n (%)	153 (58)

ERT = enzyme replacement therapy; IQR = interquartile range; SRT = substrate reduction therapy.

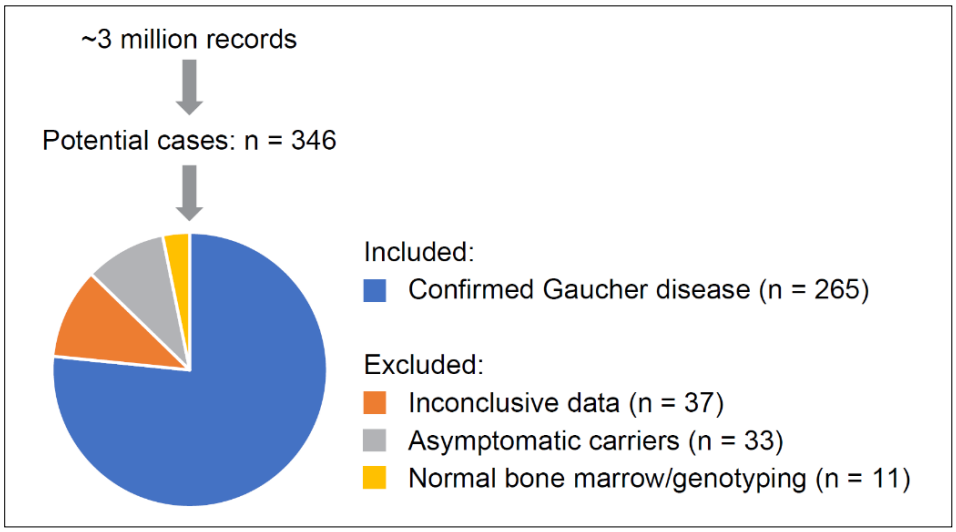


Figure 1. Patient inclusion.

The number of individuals with each non-laboratory item of the GED-C scoring system specific to type 1 Gaucher disease was determined based on ICD-9 coding plus laboratory data only, and all data sources (ICD-9 coding data plus data from clinical notes, osteoporosis register, and growth percentiles; Table 3). Laboratory items were recorded as the percentage of positive cases from the number of tests completed (Table 4). Based on clinical diagnoses, the most frequently occurring features were bone issues (56.6%), mild to moderate anemia (83.1%), splenomegaly (50.9%), and mild to moderate thrombocytopenia (60.4%).

Table 3. Application of the GED-C scoring system to patients with confirmed Gaucher disease: non-laboratory items.

Weighting	Parameter	ICD-9 Coding + Lab Data Onlyn (%)	ICD-9 + All Data Sources * n (%)
3 points	Splenomegaly **	65 (24.5)	135 (50.9)
2 points	Bone issues	95 (35.8)	150 (56.6)
	Hepatomegaly **	23 (8.7)	52 (19.6)
	Jewish ancestry	–	257 (97.0)
0.5 points	Gallstones	18 (6.8)	28 (10.6)
	Bleeding	27 (10.2)	69 (26.0)
	Low bone marrow density	24 (9.1)	64 (24.2)
	Growth retardation	13 (4.9)	124 (48.6) ***
	Fatigue	28 (10.6)	85 (32.1)
	Family history of PD	0	0
	Age at diagnosis <18 years	–	50 (18.9)

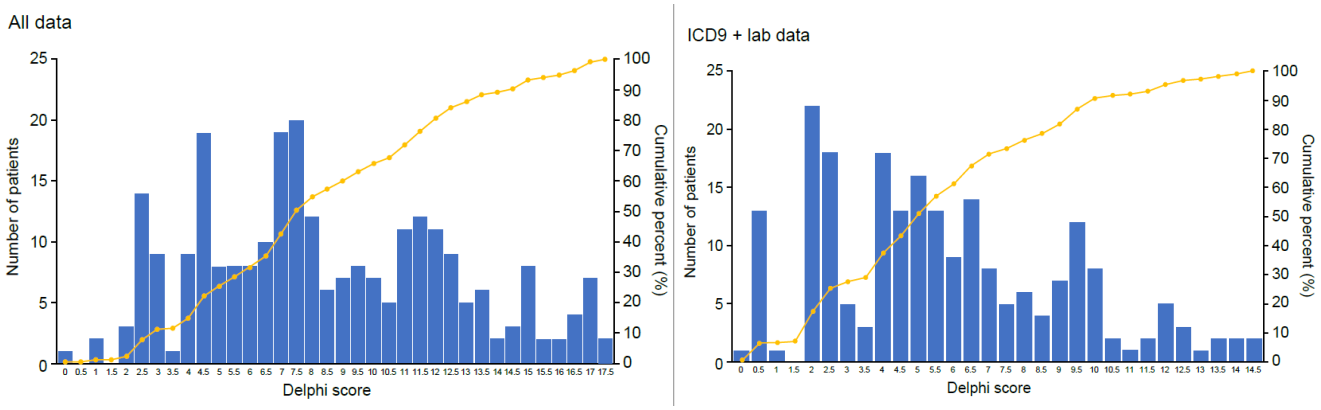
GED-C = Gaucher Early Diagnosis Consensus; ICD-9 = International Classification of Diseases, Ninth Revision; PD = Parkinson disease. * Other data sources include: visit notes, osteoporosis register, ancestry register, and growth (weight and height) percentiles; ** Because evaluation of multiples of normal in spleen and liver size was not feasible, diagnosis of splenomegaly, irrespective of size, received a score of 3. Hepatomegaly was scored 2; *** Height and weight measurements were available for 255 patients.

Table 4. Application of the GED-C scoring system to patients with confirmed Gaucher disease: laboratory-based items.

Weighting	Parameter	Measure	n/N * (%)
2 points	Thrombocytopenia	Platelet count: 50–150 $\times$ 10^9/L	107/177 (60.4)
	Anemia	Hemoglobin: 9.5–14 g/L	147/177 (83.1)
	Hyperferritinemia	Ferritin: 300–1000 ng/mL	45/108 (41.6)
	Gammopathy **	>normal range	29/71 (40.8)
1 point	Thrombocytopenia	Platelet count: <50 $\times$ 10^9/L	11/177 (6.2)
	Anemia	Hemoglobin: <9.5 g/L	16/177 (9.0)
	Hyperferritinemia	Ferritin: >1000 ng/mL	8/108 (7.4)
0.5 points	Leukopenia	<normal range	26/177 (14.7)
	Dyslipidemia	HDL cholesterol: <35 mg/dL	81/132 (61.4)
	Elevated ACE	>normal range	12/15 (80.0)

ACE = angiotensin converting enzyme; GED-C = Gaucher Early Diagnosis Consensus. * Number of tests carried out; ** Any type of immunoglobulin (IgG, IgM, IgA, IgE).

Overall Delphi summary scores for each cohort were calculated. Based on all data sources, the median Delphi score available for 264 patients was 8.0 (range 0–17.5, IQR 5.5–11.5; mean 8.6 points), including up to 15 variables per individual (median (IQR) 8.0 (5–10); mean (SD) 7.5 (3.2)) (Figure 2a). One patient with Gaucher disease had score of 0 based on two variables. A lower Delphi score of 5.0 (0–14, IQR: 2.5–8.0) across 11 variables (mean: 5.7 points) was calculated when only ICD-9 coding plus laboratory data were considered (Figure 2b). Of these, one patient had a zero score. As older data tend to include fewer parameters, we calculated the Delphi score from all sources for 205 patients diagnosed from 2000; a higher mean Delphi score of 9.5 (range 2–17.5, IQR 6.5–12.5) was determined, with a mean of 9.5. A similar calculation for ICD-9 and laboratory data only resulted in a median Delphi score of 5.5 (0–14, IQR: 4–8.4).



(**a**) (**b**)

Figure 2. Frequency and cumulative frequency of the GED-C scores of all data sources, and ICD-9 coding plus laboratory data. (**a**) All data; (**b**) ICD9 + lab data. GED-C = Gaucher Earlier Diagnosis Consensus; ICD-9 = International Classification of Diseases, Ninth Revision.

4. Discussion

In this study, we evaluated classifiers from the GED-C scoring system using real-world data for a cohort of 265 patients with confirmed Gaucher disease, identified from the MHS database in Israel. The number of Gaucher disease cases identified was close to the predicted population size and considered an appropriately sized sample for this analysis. The use of the Gaucher disease-specific MHS diagnosis code for initial screening of the MHS database may have resulted in the detection of more cases than would have been possible using ICD-9 272.7 alone; however, it is important to note that not all cases with

administrative codes for Gaucher disease in patient records were confirmed as cases, most notably owing to inaccurate diagnosis coding by treating physicians.

For this cohort, we computed a median Delphi score of 8.0 for type I Gaucher disease, ranging from 0 to 17.5, with a mean score of 8.6, based on all available data sources. However, interpretation of these findings should take into consideration the lower number of features included in this analysis, amounting to a maximum total GED-C score of 22 points from a maximum of 18 features, compared with 35.5 points from 28 features for the full GED-C scoring system, and a maximum of 24.5 points available from 20 features relevant to type 1 Gaucher disease [11]. In this study, patients reported data for up to 15 features each, with a median 8.0 features per patient, with missing data on additional features further limiting the maximum possible score.

A higher median score of 13 (range: 6–18.5) was obtained in a validation study of the GED-C scoring system in five patients with type 1 Gaucher disease from Finland, based on 28–29 variables per patient [13]. In this study, when information on hepatomegaly severity was unavailable, patients with hepatomegaly were assigned 2 points, and this assignation was applied to our study for consistency. From these data, the authors suggested that individuals with scores ≥ 4 (from the full GEC-D points complement) may be indicative of Gaucher disease [13]. The small number of patients and the clinical setting in which these five patients were evaluated allowed for capture of more detailed data than is possible from a database analysis, which may result in inflated overall scores.

To control for the number of features, a validation study including 25 patients from the UK calculated the overall score as a function of the number of features evaluated. This method resulted in a mean score of 1.08 for patients with Gaucher disease, compared with 0.58 for individuals without Gaucher disease [14]. Application of this method to findings from this study resulted in a slightly higher mean score of 1.15. Nonetheless, low scores for some patients in this study highlight the possibility that patients with low disease severity, with fewer features and low scores, may be missed by the scoring system.

The potential for missing data to result in lower scores is illustrated clearly in the present study by (a) the lower GED-C score obtained when only data from ICD-9 codes and laboratory values were utilized vs. all available data, and (b) the higher scores obtained when considering diagnoses made after the year 2000, after which time patient records are typically more complete. These findings underscore the potential for missed opportunities to diagnose when all relevant information is not gathered or considered.

A total of 28 patients had a GED-C score of ≤ 1, including one patient who scored zero, despite being confirmed as Gaucher disease cases. Furthermore, using all data, 30 of 260 (11.5%) patients had a score of ≤ 3.5 (Figure 2a), and when using only the ICD9 + lab data, 63 of 216 (29.2%) patients had a score of ≤ 3.5 (Figure 2b). Although scores lower than the suggested 4-point cut-off could be considered based on the smaller number of features evaluated [13], these patients may be missed on general application of the scoring system. It is possible that the GED-C scoring system may not work well for screening of Gaucher disease in the real-world setting, where missing data are very common. Alternatively, the actual scores assigned by the experts to each GED-C variable may need to be reconsidered.

A limitation of this study is that the GED-C scoring system was applied to patients with Gaucher disease identified from the database and not to patients suspected to have Gaucher based on the required variables in the algorithm. Furthermore, the lack of features for scoring the patients in this study further limits the ability to define a maximum GED-C score to prompt physicians to test for Gaucher disease. Therefore, the next part of this study, the design for which has been presented previously [15], will involve the development of algorithm classifiers using the results presented here. The cohort of positive Gaucher disease cases will each be matched with up to 13 control patients with no evidence of Gaucher disease, with 5-fold cross-validation used to evaluate the performance of classifiers. The best model will be applied to the MHS database to search for patients with suspected Gaucher disease for refinement of the predictive algorithm. The process of algorithm development will improve our understanding of Gaucher disease based on the relative

importance of features for Gaucher disease prediction. These tools, which may be applied in other countries where electronic records are available, can have a positive impact on patient care and quality of life, as well as healthcare costs, and may lead to changes in the approach for diagnosing rare diseases.

5. Conclusions

In conclusion, we found the overall GED-C score to be highly dependent on the availability and extraction of all relevant data for each individual tested, with missing data potentially resulting in lower scores. In patients with Gaucher disease identified in the Maccabi Health Services database, the number of features collected to make the diagnosis was fewer than those required to achieve a high score on the GED-C score.

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Institutional Review Board Statement: This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the Maccabi Research Committee (Approved [18 August 2020]: Ethics number 0081-20-MHS).

Informed Consent Statement: Patient consent was waived due to the use of aggregated, anonymized data.

Data Availability Statement: The de-identified dataset supporting this analysis may be available from the corresponding author on reasonable request.

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