APPENDICES S1–S9

Appendix S1. GED-C Delphi process round 1 questionnaire

1. The need for consensus in early Gaucher disease

Thank you for agreeing to participate in this modified Delphi initiative. All the information that you provide will be anonymous. The questions on this page are additional to the consensus initiative, and will provide us with general information about your experiences in the clinical management of patients with Gaucher disease. The last question will determine which parts of the survey you will be asked to complete.

To save your answers, click 'Next'. You can return to this page and change your answers at any time until you submit your questionnaire. If you want to leave the survey without submitting your answers, click 'Next', then 'Exit this survey' (button at the top of each page). Please do not use the 'back' button in your Internet browser.

1.1 Please provide some general information about your experience of treating patients with Gaucher disease.

Your main medical specialty
Years treating patients with Gaucher disease
Number of patients with Gaucher disease in your practice
Type of practice (e.g. private clinic, public hospital)

1.2 In your experience, what are the greatest barriers to diagnosis in patients with early Gaucher disease? For example, factors could be clinical, logistical or socioeconomic. There is no text limit, so please provide as much explanation as you think is necessary.

1.3 The aim of this initiative is to agree criteria that are likely to be indicative of early type 1 or type 3 Gaucher disease. Assuming that the initiative achieves this goal, what difference could it make to clinical practice?

1.4 Please choose an option from the drop-down menu that best describes your experience of managing patients with Gaucher disease.

- I have experience of type 1 Gaucher disease only
- I have experience of type 3 Gaucher disease only
- I have experience of both type 1 and type 3 Gaucher disease

2. Early type 1 Gaucher disease

In this section, we would like you to think about the clinical signs and co-variables that would make you consider a diagnosis of early type 1 Gaucher disease. 'Early' disease is defined as the time before symptoms impact significantly on a patient's quality of life.

Please answer the questions based both on your clinical experience and on your broader knowledge of Gaucher disease.

2.1 The following unexplained signs may be present in patients with early type 1 Gaucher disease:

Splenomegaly
Thrombocytopenia
Elevated ferritin levels
Bleeding
Anemia
Bone fractures
Growth retardation

Please specify which other unexplained signs may be present in patients with early type 1 Gaucher disease.

The next seven questions aim to determine whether two of these unexplained signs are more likely to indicate early type 1 Gaucher disease than one unexplained sign.

For example, you may think that the combination of bleeding and anemia is more likely to indicate early type 1 Gaucher disease than bleeding only.

2.2 Compared with unexplained splenomegaly only, would co-presentation of another of the signs listed above increase your suspicion of early type 1 Gaucher disease? [Yes/No]
If you answered 'Yes', please specify which sign(s).

2.3 Compared with unexplained thrombocytopenia only, would co-presentation of another of the signs listed above increase your suspicion of early type 1 Gaucher disease? [Yes/No]
If you answered 'Yes', please specify which sign(s).

2.4 Compared with unexplained elevated ferritin levels only, would co-presentation of another of the signs listed above increase your suspicion of early type 1 Gaucher disease? [Yes/No]
If you answered 'Yes', please specify which sign(s).

2.5 Compared with unexplained bleeding only, would co-presentation of another of the signs listed above increase your suspicion of early type 1 Gaucher disease? [Yes/No]
If you answered 'Yes', please specify which sign(s).

2.6 Compared with unexplained anemia only, would co-presentation of another of the signs listed above increase your suspicion of early type 1 Gaucher disease? [Yes/No]
If you answered 'Yes', please specify which sign(s).

2.7 Compared with unexplained bone fractures only, would co-presentation of another of the signs listed above increase your suspicion of early type 1 Gaucher disease? [Yes/No]
If you answered 'Yes', please specify which sign(s).

2.8 Compared with unexplained growth retardation only, would co-presentation of another of the signs listed above increase your suspicion of early type 1 Gaucher disease? [Yes/No]
If you answered 'Yes', please specify which sign(s).

The last three questions in this section explore how co-variables and additional signs may influence diagnosis.

2.9 The following co-variables may be important when considering a diagnosis of early type 1 Gaucher disease:

Ashkenazi Jewish ancestry
A family member with Gaucher disease
Age ≤18 years
Age >18 years

Please specify which other co-variables may be important to consider in early type 1 Gaucher disease.

2.10 For each of the unexplained signs below, please indicate which co-variables would increase your suspicion of early type 1 Gaucher disease.
For example, you may think that patients aged less than 18 years with bone fractures are more likely to have early type 1 Gaucher disease than patients in the general population with bone fractures.
You may select more than one answer in each row.

Unexplained sign	*Co-variable*				
	Ashkenazi Jewish ancestry	A family member with Gaucher disease	Age ≤18 years	Age >18 years	None of these co-variables
Splenomegaly					
Thrombocytopenia					
Elevated ferritin levels					
Bleeding					
Anemia					
Bone fractures					
Growth retardation					

2.11 If a patient has two unexplained signs that are potentially indicative of early type 1 Gaucher disease, would the presence of either of the following additional factors make the diagnosis more likely? [Yes/No]

Another sign

A co-variable

Please explain your answer.

3. Early type 3 Gaucher disease

In this section, we would like you to think about the clinical signs and co-variables that would make you consider a diagnosis of early type 3 Gaucher disease. 'Early' disease is defined as the time before symptoms impact significantly on a patient's quality of life.

Please answer the questions based both on your clinical experience and on your broader knowledge of Gaucher disease.

3.1 The following unexplained signs may be present in patients with early type 3 Gaucher disease:

Splenomegaly
Thrombocytopenia
Elevated ferritin levels
Bleeding
Anemia
Bone fractures
Growth retardation
Oculomotor apraxia

Please specify which other unexplained signs may be present in patients with early type 3 Gaucher disease.

The next eight questions aim to determine whether two of these unexplained signs are more likely to indicate early type 3 Gaucher disease than one unexplained sign.

For example, you may think that the combination of bleeding and anemia is more likely to indicate early type 3 Gaucher disease than bleeding only.

3.2 Compared with unexplained splenomegaly only, would co-presentation of another of the signs listed above increase your suspicion of early type 3 Gaucher disease? [Yes/No]
If you answered 'Yes', please specify which sign(s).

3.3 Compared with unexplained thrombocytopenia only, would co-presentation of another of the signs listed above increase your suspicion of early type 3 Gaucher disease? [Yes/No]
If you answered 'Yes', please specify which sign(s).

3.4 Compared with unexplained elevated ferritin levels only, would co-presentation of another of the signs listed above increase your suspicion of early type 3 Gaucher disease? [Yes/No]
If you answered 'Yes', please specify which sign(s).

3.5 Compared with unexplained bleeding only, would co-presentation of another of the signs listed above increase your suspicion of early type 3 Gaucher disease? [Yes/No]
If you answered 'Yes', please specify which sign(s).

3.6 Compared with unexplained anemia only, would co-presentation of another of the signs listed above increase your suspicion of early type 3 Gaucher disease? [Yes/No]
If you answered 'Yes', please specify which sign(s).

3.7 Compared with unexplained bone fractures only, would co-presentation of another of the signs listed above increase your suspicion of early type 3 Gaucher disease? [Yes/No]
If you answered 'Yes', please specify which sign(s).

3.8 Compared with unexplained growth retardation only, would co-presentation of another of the signs listed above increase your suspicion of early type 3 Gaucher disease? [Yes/No]
If you answered 'Yes', please specify which sign(s).

3.9 Compared with unexplained oculomotor apraxia only, would co-presentation of another of the signs listed above increase your suspicion of early type 3 Gaucher disease? [Yes/No]
If you answered 'Yes', please specify which sign(s).

The last three questions in this section explore how co-variables and additional signs may influence diagnosis.

3.10 The following co-variables may be important when considering a diagnosis of early type 3 Gaucher disease:

Ashkenazi Jewish ancestry
A family member with Gaucher disease
Age ≤18 years
Age >18 years

Please specify which other co-variables may be important to consider in early type 3 Gaucher disease.

3.11 For each of the unexplained signs below, please indicate which co-variables would increase your suspicion of early type 3 Gaucher disease.
For example, you may think that patients aged less than 18 years with bone fractures are more likely to have early type 3 Gaucher disease than patients in the general population with bone fractures.
You may select more than one answer in each row.

Unexplained sign	*Co-variable*				
	Ashkenazi Jewish ancestry	A family member with Gaucher disease	Age ≤18 years	Age >18 years	None of these co-variables
Splenomegaly					
Thrombocytopenia					
Elevated ferritin levels					
Bleeding					
Anemia					
Bone fractures					
Growth retardation					
Oculomotor apraxia					

3.12 If a patient has two unexplained signs that are potentially indicative of early type 3 Gaucher disease, would the presence of either of the following additional factors make the diagnosis more likely? [Yes/No]

Another sign

A co-variable

Please explain your answer.

Appendix S2. GED-C Delphi process round 2 questionnaire

Aim of the initiative

Thank you again for participating in this initiative. You were asked to provide a substantial amount of information in Round 1, but please be assured that Round 2 is simpler and will not take as much of your time.

Our goal is to develop a weighted diagnostic scoring system based on different signs and co-variables that might be present in patients with early Gaucher disease. Similar approaches have been used, for example, in hematology (the 4Ts score for heparin-induced thrombocytopenia) and in rheumatology (the ACR/EULAR [American College of Rheumatology/ European League Against Rheumatism] classification of rheumatoid arthritis).

In Round 1, you provided information about the signs and co-variables that may be important in early Gaucher disease. In Round 2, you will be asked to give an importance score for each of the signs and co-variables nominated in Round 1. The mean importance score for each parameter will then be calculated from the responses of all Round 2 participants, and used to give that parameter a weighting. As in Round 1, you will be asked to provide information based on your experience of types 1 and 3 Gaucher disease.

Please click 'Next' to save your answers. If you use the same computer in the same location, you can return to any page and change your answers at any time until you submit your questionnaire. If you want to leave the survey without submitting your answers, click 'Next', then 'Exit this survey' (button at the top of each page). Please do not use the 'back' button in your Internet browser.

1. Please choose the option from the drop-down menu that describes your experience of managing patients with Gaucher disease. **Please select the same option that you chose in Round 1.**

- I have experience of type 1 Gaucher disease only
- I have experience of type 3 Gaucher disease only
- I have experience of both type 1 and type 3 Gaucher disease

Early type 1 Gaucher disease

For each of the clinical signs and co-variables listed below, we would like you to indicate their level of importance when considering a diagnosis of early type 1 Gaucher disease. 'Early' disease is defined as the time before symptoms impact significantly on a patient's quality of life.

Please answer the questions based both on your clinical experience and on your broader knowledge of Gaucher disease.

2. Please indicate the importance of each of the following **gastroenterological signs** when considering a diagnosis of early type 1 Gaucher disease.

	Not important	Slightly important	Important	Very important	Extremely important
Elevated bilirubin levels					
Gallstones					
Hepatomegaly					
Splenomegaly					

3. Please indicate the importance of each of the following **hematological signs** when considering a diagnosis of early type 1 Gaucher disease.

	Not important	Slightly important	Important	Very important	Extremely important
Anemia					
Bleeding, bruising or coagulopathy					
Gammopathy – monoclonal or polyclonal					
Leukopenia					
Thrombocytopenia					

4. Please indicate the importance of each of the following **orthopedic signs** when considering a diagnosis of early type 1 Gaucher disease.

	Not important	Slightly important	Important	Very important	Extremely important
Bone issues, including pain, crises, avascular necrosis and fractures					
Low bone mineral density					

5. Please indicate the importance of each of the following **pediatric signs** when considering a diagnosis of early type 1 Gaucher disease.

	Not important	Slightly important	Important	Very important	Extremely important
Growth retardation, including low body weight					
Neonatal cholestasis					

6. Please indicate the importance of each of the following **general signs** when considering a diagnosis of early type 1 Gaucher disease.

	Not important	Slightly important	Important	Very important	Extremely important
Asthenia					
Dyslipidemia					
Fatigue					
Elevated angiotensin-converting enzyme levels					
Elevated ferritin levels					

7. Please indicate the importance of each of the following **co-variables** when considering a diagnosis of early type 1 Gaucher disease.

	Not important	Slightly important	Important	Very important	Extremely important
Jewish ancestry					
Family history of Gaucher disease					
Family history of Parkinson disease					

8. If there are any other signs or co-variables that you think should be considered in early type 1 Gaucher disease, please list them here.

Early type 3 Gaucher disease

For each of the clinical signs and co-variables listed below, we would like you to indicate their level of importance when considering a diagnosis of early type 3 Gaucher disease. 'Early' disease is defined as the time before symptoms impact significantly on a patient's quality of life.

Please answer the questions based both on your clinical experience and on your broader knowledge of Gaucher disease.

9. Please indicate the importance of each of the following **gastroenterological signs** when considering a diagnosis of early type 3 Gaucher disease.

	Not important	Slightly important	Important	Very important	Extremely important
Hepatomegaly					
Splenomegaly					

10. Please indicate the importance of each of the following **hematological signs** when considering a diagnosis of early type 3 Gaucher disease.

	Not important	Slightly important	Important	Very important	Extremely important
Anemia					
Bleeding, bruising or coagulopathy					
Gammopathy – monoclonal or polyclonal					
Thrombocytopenia					

11. Please indicate the importance of each of the following **orthopedic signs** when considering a diagnosis of early type 3 Gaucher disease.

	Not important	Slightly important	Important	Very important	Extremely important
Bone pain, including fractures					
Kyphosis					

12. Please indicate the importance of each of the following **pediatric signs** when considering a diagnosis of early type 3 Gaucher disease.

	Not important	Slightly important	Important	Very important	Extremely important
Growth retardation, including low body weight					

13. Please indicate the importance of each of the following **neurological signs** when considering a diagnosis of early type 3 Gaucher disease.

	Not important	Slightly important	Important	Very important	Extremely important
Cognitive deficit					
Disturbed motor function					
Myoclonus epilepsy					
Disturbed oculomotor function					

14. Please indicate the importance of each of the following **general signs** when considering a diagnosis of early type 3 Gaucher disease.

	Not important	Slightly important	Important	Very important	Extremely important
Cardiovascular calcification					
Fatigue					
Elevated angiotensin-converting enzyme levels					
Elevated ferritin levels					
Pulmonary infiltrates					

15. Please indicate the importance of each of the following **co-variables** when considering a diagnosis of early type 3 Gaucher disease.

	Not important	Slightly important	Important	Very important	Extremely important
Jewish ancestry					
Family history of Gaucher disease					
Family history of Parkinson disease					
Blood relative who died of fetal hydrops and/or with diagnosis of neonatal sepsis of uncertain etiology					
Age ≤18 years					

16. If there are any other signs or co-variables that you think should be considered in early type 3 Gaucher disease, please list them here.

Barriers to diagnosis and the impact of this initiative

In Round 1, you were asked to describe the main barriers to the diagnosis of early Gaucher disease and also to suggest what the impact of this consensus initiative might be on clinical practice. Several themes emerged and we would like to understand the importance of each.

17. Please indicate the importance of each of the following barriers to the diagnosis of early Gaucher disease.

	Not important	Slightly important	Important	Very important	Extremely important
Owing to its rarity, there is a lack of awareness of Gaucher disease among HCPs					
Early signs can be mild and may be overlooked					
Some early signs do not seem specific to Gaucher disease, and their clinical presentation can be variable or heterogeneous					
Gaucher disease is not normally considered as a differential diagnosis					
Early signs are under-recognized as characteristic of possible Gaucher disease					
Access to diagnostic tests is poor in some countries and in some socioeconomic situations					
Geographic dispersion or socioeconomic division of families can reduce awareness of a family history of Gaucher disease					
Use of enzymatic diagnostic tests may be limited by cost or logistical barriers or by an HCP's unwillingness to request them					
Lack of a diagnostic algorithm					

18. Please indicate the importance of each of the following reasons regarding the difference this consensus initiative could make to clinical practice.

	Not important	Slightly important	Important	Very important	Extremely important
Patients could be diagnosed earlier in the disease course, and monitored and managed appropriately to improve long-term outcomes and quality of life					
Earlier diagnosis would help to reduce serious or irreversible late-onset complications, and comorbidities of the disease could be avoided or managed appropriately					
HCPs' awareness of the disease might improve, and its inclusion as a differential diagnosis might avoid unnecessary invasive diagnostic procedures					
With earlier diagnosis, patients could be followed up from an earlier stage of disease, leading to a better understanding of disease phenotypes and progression					
Earlier diagnosis would allow family planning and genetic counselling to be offered earlier					
Goals for diagnosis would be clearer					
More rapid diagnosis would facilitate earlier decision-making to support patients					
It might lead to wider use and availability of diagnostic testing					

Appendix S3. GED-C Delphi process round 3 questionnaire

Aim of the initiative

Thank you for your continued participation in this initiative. As described in Round 2, our goal is to develop a weighted diagnostic scoring system based on different signs and co-variables that might be present in patients with early Gaucher disease.

Based on the level of importance you assigned to each sign and co-variable in Round 2, we have classified these factors as major or minor. In Round 3, we would like to find out how strongly you agree or disagree with this classification. This information should allow us to reach consensus about which diagnostic factors are important in early Gaucher disease and therefore to build an initial diagnostic point-scoring system.

We would also like you to provide some additional information relating to some of these factors and to indicate how strongly you agree or disagree with statements relating to barriers to diagnosis and to the potential impact of this initiative.

Please click 'Next' to save your answers. If you use the same computer in the same location, you can return to any page and change your answers at any time until you submit your questionnaire. If you want to leave the survey without submitting your answers, click 'Next', then 'Exit this survey' (button at the top of each page). Please do not use the 'back' button in your Internet browser.

1. Please choose the option from the drop-down menu that describes your experience of managing patients with Gaucher disease. **Please select the same option that you chose in Round 1.**

- I have experience of type 1 Gaucher disease only
- I have experience of type 3 Gaucher disease only
- I have experience of both type 1 and type 3 Gaucher disease

Early type 1 Gaucher disease

Based on the importance ratings the panel provided in Round 2, the signs or co-variables identified as relevant in early type 1 Gaucher disease have been categorized as major or minor. The first question in this section will establish your level of agreement with this classification and will help us to reach a consensus.

As in previous rounds, please answer the questions based both on your clinical experience and on your broader knowledge of Gaucher disease. 'Early' disease is defined as the time before symptoms impact significantly on a patient's quality of life.

2. In Round 2, more than 75% of the panel rated the following signs and co-variables as 'important', 'very important' or 'extremely important' in early type 1 Gaucher disease. It is therefore proposed that each of these should be classified as a major sign or co-variable.

For each factor, please indicate how strongly you agree or disagree with its classification as **major**.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Anemia					
Bleeding, bruising or coagulopathy					
Bone issues, including pain, crises, avascular necrosis and fractures					
Elevated ferritin levels					
Family history of Gaucher disease					
Gammopathy – monoclonal or polyclonal					
Hepatomegaly					
Jewish ancestry					
Splenomegaly					
Thrombocytopenia					

3. Based on the panel's responses in Round 2, we have classified the following as minor signs or co-variables in early type 1 Gaucher disease.

Asthenia

Dyslipidemia

Elevated angiotensin-converting enzyme levels

Elevated bilirubin levels

Fatigue

Family history of Parkinson disease

Gallstones

Growth retardation, including low body weight

Leukopenia

Low bone mineral density

Neonatal cholestasis

If you have any comments about this classification, please add them here.

The next five questions ask you to consider whether specified levels of some of these major signs are consistent with a diagnosis of Gaucher disease, or make this diagnosis unlikely. You may check more than one box if you think more than one range is relevant. If you think that none of the proposed ranges apply, please check 'A different range' and provide the values that you think are most relevant in the comment box.

4. **Anemia** in early type 1 Gaucher disease.

	Mild (Hb >115–140 g/L)	Moderate (Hb = 95–115g/L)	Severe (Hb <95 g/L)	A different range
Consistent with early Gaucher disease				
Unlikely to be Gaucher disease				

If you think a different Hb range is relevant, please specify the range here (in g/L):

5. **Elevated levels of ferritin** in early type 1 Gaucher disease.

	Mild (ferritin = 300–600 µg/L)	Moderate (ferritin >600–1000 µg/L)	Severe (ferritin >1000 µg/L)	A different range
Consistent with early Gaucher disease				
Unlikely to be Gaucher disease				

If you think a different ferritin range is relevant, please specify the range here (in µg/L):

6. **Hepatomegaly** in early type 1 Gaucher disease.

	Mild (1.5–2 x enlarged)	Moderate (>2–3 x enlarged)	Severe (>3 x enlarged)	A different range
Consistent with early Gaucher disease				
Unlikely to be Gaucher disease				

If you think a different range of liver enlargement is relevant, please specify the range here:

7. **Splenomegaly** in early type 1 Gaucher disease.

	Mild (3–5 x enlarged)	Moderate (>5–9 x enlarged)	Severe (>9 x enlarged)	A different range
Consistent with early Gaucher disease				
Unlikely to be Gaucher disease				

If you think a different range of spleen enlargement is relevant, please specify the range here:

8. **Thrombocytopenia** in early type 1 Gaucher disease.

	Mild (platelet count, >100–150 x 10^9/L)	Moderate (platelet count, 50–100 x 10^9/L)	Severe (platelet count, <50 x 10^9/L)	A different range
Consistent with early Gaucher disease				
Unlikely to be Gaucher disease				

If you think a different platelet range is relevant, please specify the range here:

9. In Round 1 you were asked to estimate the total number of patients with Gaucher disease in your practice. Please estimate how many of these patients have type 1 Gaucher disease.

Early type 3 Gaucher disease

Based on the importance ratings the panel provided in Round 2, the signs or co-variables identified as relevant in early type 3 Gaucher disease have been categorized as major or minor. The first question in this section will establish your level of agreement with this classification and will help us to reach a consensus.

As in previous rounds, please answer the questions based both on your clinical experience and on your broader knowledge of Gaucher disease. 'Early' disease is defined as the time before symptoms impact significantly on a patient's quality of life.

10. In Round 2, more than 75% of the panel rated the following signs and co-variables as 'important', 'very important' or 'extremely important' in early type 3 Gaucher disease. It is therefore proposed that each of these should be classified as a major sign or co-variable.

For each factor, please indicate how strongly you agree or disagree with its classification as **major**.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Age ≤ 18 years					
Anemia					
Blood relative who died of fetal hydrops and/or with diagnosis of neonatal sepsis of uncertain etiology					
Bone pain, including fractures					
Cardiovascular calcification					
Cognitive deficit					
Disturbed motor function					
Disturbed oculomotor function					
Family history of Gaucher disease					
Growth retardation, including low body weight					
Hepatomegaly					
Kyphosis					
Myoclonus epilepsy					
Pulmonary infiltrates					
Splenomegaly					
Thrombocytopenia					

11. Based on the panel's responses in Round 2, we have classified the following as minor signs or co-variables in early type 1 Gaucher disease.

Ashkenazi Jewish ancestry

Bleeding, bruising or coagulopathy

Elevated angiotensin-converting enzyme levels

Elevated ferritin levels

Family history of Parkinson disease

Fatigue

Gammopathy – monoclonal or polyclonal

If you have any comments about this classification, please add them here.

The next four questions ask you to consider whether specified levels of some of these major signs are consistent with a diagnosis of Gaucher disease, or make this diagnosis unlikely. You may check more than one box if you think more than one range is relevant. If you think that none of the proposed ranges apply, please check 'A different range' and provide the values that you think are most relevant in the comment box.

12. **Anemia** in early type 3 Gaucher disease.

	Mild (Hb >115–140 g/L)	Moderate (Hb = 95–115g/L)	Severe (Hb <95 g/L)	A different range
Consistent with early Gaucher disease				
Unlikely to be Gaucher disease				

If you think a different Hb range is relevant, please specify the range here (in g/L):

13. **Hepatomegaly** in early type 3 Gaucher disease.

	Mild (1.5–2 x enlarged)	Moderate (>2–3 x enlarged)	Severe (>3 x enlarged)	A different range
Consistent with early Gaucher disease				
Unlikely to be Gaucher disease				

If you think a different range of liver enlargement is relevant, please specify the range here:

14. **Splenomegaly** in early type 3 Gaucher disease.

	Mild (3–5 x enlarged)	Moderate (>5–9 x enlarged)	Severe (>9 x enlarged)	A different range
Consistent with early Gaucher disease				
Unlikely to be Gaucher disease				

If you think a different range of spleen enlargement is relevant, please specify the range here:

15. **Thrombocytopenia** in early type 3 Gaucher disease.

	Mild (platelet count, >100–150 x 10^9/L)	Moderate (platelet count, 50–100 x 10^9/L)	Severe (platelet count, <50 x 10^9/L)	A different range
Consistent with early Gaucher disease				
Unlikely to be Gaucher disease				

If you think a different platelet range is relevant, please specify the range here:

16. In Round 1 you were asked to estimate the total number of patients with Gaucher disease in your practice. Please estimate how many of these patients have type 3 Gaucher disease.

Barriers to diagnosis of Gaucher disease and the impact of this initiative

17. In Round 2, more than 75% of the panel rated the following barriers to diagnosis as 'important', 'very important' or 'extremely important'. To help us reach a consensus, please indicate for each statement how strongly you agree or disagree that the barrier to diagnosis it describes is among the most important in early Gaucher disease.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Owing to its rarity, there is a lack of awareness of Gaucher disease among HCPs					
Early signs can be mild and may be overlooked					
Some early signs do not seem specific to Gaucher disease, and their clinical presentation can be variable or heterogeneous					
Gaucher disease is not normally considered as a differential diagnosis					
Early signs are under-recognized as characteristic of possible Gaucher disease					
Access to diagnostic tests is poor in some countries and in some socioeconomic situations					

18. In Round 2, more than 75% of the panel rated the following statements relating to the potential impact of this initiative as 'important', 'very important' or 'extremely important'. To help us reach consensus, please indicate for each statement how strongly you agree or disagree that the potential outcome it describes is among the most important for this initiative.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Patients could be diagnosed earlier in the disease course, and monitored and managed appropriately to improve long-term outcomes and quality of life					
Earlier diagnosis would help to reduce serious or irreversible late-onset complications, and comorbidities of the disease could be avoided or managed appropriately					

HCPs' awareness of the disease might improve, and its inclusion as a differential diagnosis might avoid unnecessary invasive diagnostic procedures					
With earlier diagnosis, patients could be followed up from an earlier stage of disease, leading to a better understanding of disease phenotypes and progression					
Earlier diagnosis would allow family planning and genetic counselling to be offered earlier					
Goals for diagnosis would be clearer					
More rapid diagnosis would facilitate earlier decision-making to support patients					
It might lead to wider use and availability of diagnostic testing					

Appendix S4. Literature review of presenting signs in GD at diagnosis

A PubMed search for potentially relevant articles was conducted using the string "((Gaucher[Title/Abstract]) NOT Parkinson[Title/Abstract]) AND ("1996/01/01" [Publication Date]: "3000"[Publication Date)". From the resulting 2182 hits, any review articles or articles not written in English were excluded, yielding a total of 1827 hits. All GD types were included (i.e. perinatal lethal, GD1, GD2, GD3, GD3b, GD3c) and all ages of patient were considered; *in utero* cases were excluded. No sample size limits were applied, so all data from single cases to large retrospective studies were considered. Any studies reporting patient symptoms or progression of GD post-diagnosis were excluded. Among the 1827 articles, titles and abstracts were screened for the terms 'sign', 'symptom', diagnos*', 'presenting', 'presented', 'manifest*', 'character*', or 'feature'. A manual search of abstracts was performed to identify any irrelevant articles. These were discarded and the remaining 199 abstracts re-read in detail, after which 91 abstracts were confirmed as containing information relevant to presenting signs at diagnosis.

Appendix S5. GED-C Delphi round 1 results

Summary of phrases describing presenting signs and symptoms in early type 1 GD, grouped into 18 factors (italics) and further classified by clinical specialty.

Gastrointestinal	Hematological	Orthopedic	Pediatric	General medical
Elevated bilirubin levels – raised bilirubin ***Gallstones*** – cholelithiasis – gallstones ***Hepatomegaly*** – hepatomegaly – hepatomegaly, but invariably combined with splenomegaly – abdominal distension and pain ***Splenomegaly*** – splenomegaly – splenectomy prior to diagnosis – abdominal distension and pain	***Anemia*** – anemia ***Bleeding, bruising or coagulopathy*** – bleeding – coagulation abnormalities – coagulopathy – bruising, easy bruising – frequent bruising – bruising and factor XI deficiency in Ashkenazi Jews ***Gammopathy – monoclonal or polyclonal*** – monoclonal gammopathy – hypergammaglobulinemia – MGUS – hyperimmunoglobulinemia – monoclonal gammopathy may occur in patients with otherwise clinically mild disease – B-cell lymphoma – polyclonal gammopathy ***Leukopenia*** – leukopenia ***Thrombocytopenia*** – thrombocytopenia	***Bone issues including pain, crises, avascular necrosis and fractures*** – bone pain – bone pain with tenderness in the absence of fracture – bone crises – bone fractures are less frequent than bone crises – bone pain, i.e. bone crises but is probably captured in bone fractures – pain, especially bone pain – avascular necrosis ***Low bone mineral density*** – osteopenia/osteoporosis – low bone mineral density – low signal intensity on MRI (aspecific!)	***Growth retardation including low body weight*** – growth retardation – low body weight – Erlenmeyer flask deformity of distal femur – delayed physical milestones – radiological signs such as Erlenmeyer flask deformity or osteolysis ***Neonatal cholestasis*** – neonatal cholestasis	***Asthenia*** – asthenia – strength impairment ***Dyslipidemia*** – abnormal lipid profile – dislipidemias (high TG, low HDL cholesterol) ***Elevated ACE levels*** – elevated ACE levels ***Elevated ferritin levels*** – elevated ferritin levels – hyperferritinemia – diagnosis of iron overload without a confirmed hemochromatosis mutation ***Fatigue*** – fatigue – tireless

ACE, angiotensin-converting enzyme; GD, Gaucher disease; HDL, high-density lipoprotein; MGUS, monoclonal gammopathy of undetermined significance; MRI, magnetic resonance imaging; TG, triglyceride

Appendix S6. GED-C Delphi round 1 results

Summary of phrases describing patient co-variables in early type 1 GD, grouped into three factors.

Jewish ancestry	Family history of GD	Family history of PD
– Ashkenazi Jewish – other Jewish ancestry, e.g. Sephardic – a child of parents with Jewish and Swedish ancestry	– a family member with Gaucher disease – brother or sister with Gaucher disease – consanguinity	– a family member with Parkinson disease – perhaps in families with Parkinson disease the frequency of GD is higher, but I do not believe this is an important co-variable – family history of Parkinsonism

GD, Gaucher disease; PD, Parkinson disease

Appendix S7. GED-C Delphi round 1 results

Summary of phrases describing presenting signs in early type 3 GD, grouped into 18 factors (italics) and further classified by clinical specialty.

Gastrointestinal	Hematological	Orthopedic	Pediatric	Neurological	General medical
Hepatomegaly – hepatomegaly ***Splenomegaly*** – splenomegaly	***Anemia*** – anemia ***Bleeding or coagulopathy*** – bleeding – epistaxis ***Gammopathy – monoclonal or polyclonal*** – hyperimmunoglobulinemia ***Thrombocytopenia*** – thrombocytopenia	***Bone pain or fracture*** – bone pain – bone fractures ***Kyphosis*** – kyphosis – rarely kyphosis	***Growth retardation*** – growth retardation – developmental delay – radiological signs such as Erlenmeyer flask deformity or osteolysis	***Cognitive deficit*** – cognitive deficit – memory loss – cognitive decline – mental retardation – decrease of cognitive function ***Disturbed motor function*** – difficulty walking – unexplained general apraxia – ataxia – ataxic gait – delay in neuromotor development ***Myoclonus epilepsy*** – myoclonus epilepsy – seizure ***Disturbed oculomotor function*** – blinking may be the earliest eye sign – gaze palsy – oculomotor apraxia – convergent strabismus – strabismus – squint	***Cardiovascular calcification*** – cardiovascular calcification – valvular and coronary calcifications (very specific of GD3c) ***Elevated ACE levels*** – elevated ACE levels ***Elevated ferritin levels*** – elevated ferritin levels ***Fatigue*** – fatigue ***Pulmonary infiltrates*** – lung involvement – CXR may demonstrate pulmonary infiltrates early but this is often a later sign

ACE, angiotensin-converting enzyme; CXR, chest X-ray; GD, Gaucher disease

Appendix S8. GED-C Delphi round 1 results

Summary of phrases describing patient co-variables in early type 3 GD, grouped into five factors.

Age ≤ 18 years	Ashkenazi Jewish ancestry	Blood relative who died of fetal hydrops[a]	Family history of GD	Family history of PD
– age ≤ 18 years – age < 18 years but in particular very early presentation e.g. < 2 years	– Ashkenazi Jewish	– A family member who died of fetal hydrops and/or with diagnosis of neonatal sepsis of uncertain etiology	– a family member with Gaucher disease – family member with GD3 (not GD1) – brother or sister with Gaucher disease	– A family member with Parkinson disease

[a]and/or with diagnosis of neonatal sepsis of uncertain etiology
GD, Gaucher disease; PD, Parkinson disease

Appendix S9. Literature review findings: GD signs at diagnosis

Among the 91 relevant abstracts identified in the literature search, at least 71 different signs presenting at diagnosis were reported, ranging from general class disorders (e.g. 'bone abnormalities') through to specific signs (e.g. 'kyphosis' and 'hyperbilirubinemia'). More than two thirds of the abstracts (n = 63) reported single case studies and only six (6.6%) reported data from 100 patients or more. Notably, more than one third of the abstracts (n = 36) did not report the type of GD under consideration. In agreement with the results of the GED-C initiative, the most commonly reported presenting signs were splenomegaly (mentioned in 45 abstracts); neurological abnormalities, including seizures and disturbed motor function (38 abstracts; predominantly type 2 or 3 where reported); bone abnormalities, including pain, fracture, crises and avascular necrosis (37 abstracts); hepatomegaly (32 abstracts); thrombocytopenia (22 abstracts); and anemia (15 abstracts). Developmental issues (13 abstracts), oculomotor disturbances (12 abstracts; type 2 or 3, when reported) and musculoskeletal disorders (nine abstracts) were also reported relatively often, with fewer reports of patients presenting with dermatological (eight), immunological (eight), other visceral (seven), cardiac (seven), or respiratory (six) signs.

Splenomegaly

Splenomegaly was the sign reported most often (n = 45). Most of these reports were single cases studies (n = 29, 64.4%), although results from studies conducted in larger numbers of patients supported its ubiquity in GD. For example, longitudinal data from children and adolescents diagnosed with non-neuronopathic GD and registered in the International Collaborative Gaucher Group (ICGG) Gaucher Registry (n = 887) showed that splenomegaly was reported in 95% of patients.[1] Severe splenomegaly was more common in younger patients than in older individuals.[1] Another analysis of data from the ICGG registry that examined patients with type 1 GD at or near the time of diagnosis, who were homozygous for N370S (n = 798), found that splenomegaly was the most common presenting feature (73% of patients), and that 11% of patients had severe splenomegaly.[2] A smaller, single-centre retrospective study of patients with GD (n = 86), found that 56% presented primarily with features related to splenomegaly or thrombocytopenia.[3]

Thrombocytopenia, anemia and other hematological signs

Hematological disorders were the most commonly reported class of signs, reported 50 times among the abstracts identified, and thrombocytopenia[1-22] and anemia[1, 2, 6, 9, 14-16, 19, 21, 23-28] were reported most often within this class. For both disorders, the majority of reports were from single case studies, but larger studies reported similar findings. Respectively, thrombocytopenia and anemia occurred in 50% and 40% of patients in the ICGG registry analysis (n = 887),[1] and thrombocytopenia was the second most common sign among the patients with type 1 GD, homozygous for N370S, being present in 52% of patients.[2] Furthermore, 18% of patients had anemia, and 9% had severe thrombocytopenia.[2] A study examining the genetic and clinical characteristics of patients with GD who lived on the Iberian peninsula (n = 436) found that thrombocytopenia and anemia were present in over half (55% and

56%, respectively) of patients who had full clinical data at diagnosis (n = 357).[9] Other hematological conditions reported at diagnosis in a relatively small number of cases were pancytopenia,[25, 29-31] hemorrhage/bleeding disorders,[11, 32, 33] pallor[24, 32, 34] and leukopenia.[14, 16]

Hepatomegaly and other hepatic signs

Hepatomegaly was the second most common single sign, reported in 32 abstracts, and occurring in 87% of patients in the ICGG registry analysis (n = 887). As with splenomegaly, severe hepatomegaly was observed more often in younger than in older patients.[1] In the Iberian peninsula study (n = 436) hepatomegaly was actually the most common sign, reported in 68% of patients; it was also more likely to occur in patients who had undergone splenectomy than in those who had not.[9] Hepatic-related disorders were the second-most commonly reported class of signs, but after hepatomegaly, other individual hepatic signs were noted rarely, including cholestasis,[5, 7, 18] cirrhosis,[35] hepatic lesions,[36] hyperbilirubinemia,[4] liver disease,[37] liver failure[38] and portal hypertension.[5]

Neurological signs

A broad range of neurological abnormalities were reported, making them the third-most commonly reported sign class (38 mentions). Non-specific neurological abnormalities were reported the most (12 times),[4, 32, 39-48] followed by generalized seizures,[43, 47-49] myoclonic seizures[43, 45, 48, 49] and epilepsy.[38, 44, 50] Opisthotonus[51, 52] and muscular rigidity[51, 52] were also mentioned (twice each), and the following conditions were mentioned once: bulbar palsy,[40] deafness,[51] dementia,[53] hemiparesis,[6] hydrocephalus,[35] intrathecal sacral cyst,[50] psychomotor retardation,[6] ptosis,[53] refractory seizures,[54] retrocollis[55] and visual seizures.[49] The largest study reporting on neurological signs at diagnosis was an analysis of data from the Neurological Outcomes Subregistry of the ICGG registry (n = 131).[43] Many of the signs were identified in patients before the age of 2 years, and most related to brainstem abnormalities or to fine motor dysfunctions, including some oculomotor dysfunctions (also see below). For example, the inability to look up or down to the extremities (45% of patients), abnormally slow object tracking (43%), convergent squint (36%), ataxia (15–20%), seizures (16%) and myoclonic seizures (2%).[43] Notably, a single case of neurological abnormalities in a patient with type 1 GD was reported.[50]

Oculomotor signs

There were 13 reports of oculomotor disorders, seven of which described general oculomotor signs.[6, 43, 45, 47, 51, 54, 56] In addition to the reports from analysis of the Neurological Outcomes Subregistry of the ICGG registry,[43] case reports also described the occurrence of corneal opacity,[35, 57] exophthalmos,[4, 58] horizontal supranuclear gaze palsy[55] and reduced retinal response.[59]

Bone signs

Bone issues were common presenting features across disease phenotypes, mentioned 36 times, including 15 reports of ‘abnormalities or lesions’ at diagnosis.[1, 2, 6, 8-10, 19, 30, 42, 58, 60-64] Bone-related signs were frequently reported in the large studies already described, for example: bone disease (62–

81% of patients[1, 9]), osteopenia/osteoporosis (11–49%[2]), bone pain (27%[1]), irreversible skeletal lesions (17%[2]) and bone crises (7–9%[1, 2]). Skeletal manifestations occurred more often in older than younger children,[1] and bone disease was more likely among patients who had undergone splenectomy than among those who had not.[9] Bone pain was reported most often,[1, 33, 47, 53, 63, 65-67] then bone crises[1, 2, 58, 63] and bone fractures[58, 64, 66, 68], then avascular necrosis[47, 63] and osteopenia,[2, 14] with osteoporosis[2] and kyphosis[53] mentioned once each.

Immunological signs

Only a few instances of immunological signs at diagnosis were reported in the literature, including Epstein–Barr infection/infectious mononucleosis,[69-71] monoclonal gammopathy,[50, 61] hemophagocytic lymphohistiocytosis,[72] lymphoblastic lymphoma[73] and lymphadenopathy.[74]

Musculoskeletal signs

Several musculoskeletal abnormalities were reported, including soft tissue masses,[61, 66, 75] dysmorphic features,[55, 76] arthrogryposis,[76] cachexia,[26] coxarthritis[77] and weakness.[34]

Developmental abnormalities

There were 13 mentions of developmental abnormalities such as growth retardation,[1, 10, 12, 23, 24, 26, 28, 32] developmental delay/failure to thrive,[7, 26, 40, 74] and growth hormone deficiency.[24]

Dermatological and visceral signs

Patients presenting with dermatological and 'other visceral' signs at diagnosis were relatively uncommon. However, for those who did, the most frequent were collodion baby/congenital ichthyosis[4, 46, 76, 78, 79] and abdominal pain (4 reports[25, 28, 53, 80]). Other dermatological/visceral signs included hydrops fetalis,[76, 81] 'blueberry muffin' lesions,[78] cyanosis,[82] skin edema[46] and gallstones.[38]

Cardiac signs

There were four reports of patients being diagnosed with GD after presenting with cardiac valve abnormalities,[16, 35, 57, 83] two reports in patients with CV calcification[56, 57] and one report in a patient with pulmonary arteriovenous malformation.[58]

Respiratory signs

The class of signs reported least often at diagnosis was respiratory signs, with just two reports each for laryngospasm[55, 82] and respiratory compromise,[4, 15] and one report each for inspiratory stridor[74] and progressive dyspnea.[74]

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