Received: 28 January 2023 | Revised: 12 April 2023 | Accepted: 13 April 2023

DOI: 10.1002/jimd.12612

ORIGINAL ARTICLE

JIMD SSIEM WILEY

Key terms and definitions in acute porphyrias: Results of an international Delphi consensus led by the European porphyria network

Penelope E. Stein[1] | **Yonatan Edel**[2] | **Razan Mansour**[3] | **Reem A. Mustafa**[3,4] | **Sverre Sandberg**[5,6,7] | **Members of the Acute Porphyria Expert Panel**

[1]Haematological Medicine, King's College Hospital, London, UK

[2]Israeli Porphyria Center, Rabin Medical Hospital, Petach Tikva, Israel and Samson Assuta Ashdod Medical Center, Ashdod, Israel and Faculty of Health and Science, Ben-Gurion University in the Negev, Beer Sheva, Israel

[3]The Outcomes and Implementation Research Unit, Department of Internal Medicine, The University of Kansas Health System, Kansas City, Kansas, USA

[4]Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada

[5]Norwegian Organization for Quality Improvement of Laboratory Examinations (Noklus), Haraldsplass Deaconess Hospital, Bergen, Norway

[6]Norwegian Porphyria Centre, Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Bergen, Norway

[7]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

Correspondence
Penelope Stein, Department of Haematological Medicine, 4th Floor Hambleden Wing West, King's College Hospital NHS Foundation Trust, Denmark Hill, London, SE5 9RS, UK.
Email: p.stein@nhs.net

Funding information
European Porphyria Network (Epnet)

Communicating Editor: Areeg El-Gharbawy

Abstract

Acute porphyrias are a group of rare inherited disorders causing acute neurovisceral attacks. Many terms used frequently in the literature and clinical practice are ambiguous, which can lead to confusion in the way patients are managed, studied, and reported in clinical studies. Agreed definitions are a necessary first step in developing management guidelines and will facilitate communication of results of future clinical research. The Delphi method was used to generate consensus on key terms and definitions in acute porphyria. The process started with a brainstorming phase offered to all members of the European Porphyria Network followed by two Delphi rounds among international experts in the field of porphyria (the Acute Porphyria Expert Panel). A consensus of 75% or more was defined as the agreement threshold. A total of 63 respondents from 26 countries participated in the brainstorming phase, leading to the choice of nine terms and definitions. A total of 34 experts were

Penelope E Stein and Yonatan Edel contributed equally to this study.

Members of the Acute Porphyria Expert Panel are provided in Appendix A.

In 2023, the organisation will become international and renamed the International Porphyria Network (Ipnet).

Click here to access the podcast for this paper.

invited to take part in the Delphi rounds. Seven of the initial nine terms and definitions which entered the first Delphi round achieved the threshold for agreement. Following a second Delphi round, all nine definitions achieved agreement. Agreement on the definitions for nine important terms describing acute porphyrias represents a significant step forward for the porphyria community. It will facilitate more accurate comparison of outcomes among porphyria centres and in clinical trials and provide a strong framework for developing evidence-based clinical guidelines.

KEYWORDS

acute intermittent porphyria, acute porphyria, consensus, Delphi, hereditary coproporphyria, variegate porphyria

1 | BACKGROUND

Acute porphyrias[1] are a group of rare inherited disorders caused by partial deficiencies of certain enzymes in the haem biosynthetic pathway. Nearly all cases are one of three types, acute intermittent porphyria (AIP, OMIM #176000), variegate porphyria (VP, OMIM #176200), or hereditary coproporphyria (HCP, OMIM #121300), which are dominantly inherited disorders with very low clinical penetrance. Most people with a pathogenic gene variant never have symptoms, but a small fraction suffers from acute attacks which may be life-threatening if not recognised or if appropriate treatment is delayed.[2]

Manifestations of a porphyria attack[3] are non-specific and highly variable, including severe, poorly localised abdominal pain, vomiting, systemic arterial hypertension, tachycardia, hyponatraemia, seizures, predominantly motor peripheral neuropathy, and psychiatric symptoms. Attacks may be triggered by endogenous and/or environmental factors, including hormonal changes of the menstrual cycle, certain drugs, alcohol, fasting, and stress, which upregulate haem synthesis in the liver either by directly inducing the rate-limiting enzyme 5-aminolaevulinic acid synthase 1 (ALAS1), or indirectly by depleting the hepatic haem pool that regulates this enzyme.[4] Overexpression of ALAS1 results in increased production and accumulation of haem pathway intermediates including 5-aminolaevulinic acid (ALA) and porphobilinogen (PBG) which are thought to be responsible for the symptoms and signs of an attack through toxic damage to nerves in the central, peripheral and autonomic nervous systems. High plasma levels and urinary excretion of ALA and PBG are key findings in the laboratory diagnosis of an attack.

Treatment with human haemin to restore hepatic haem reduces elevated levels of ALA and PBG and may alleviate symptoms and shorten an attack.[5,6] A small proportion of patients have recurrent attacks requiring preventive treatment or liver transplantation.[7] Late complications of acute porphyrias may include fixed systemic arterial hypertension, chronic kidney disease, chronic neuropathy, and hepatocellular carcinoma.[8]

Two of the acute porphyrias, VP and HCP, may present with light-sensitive skin problems either alone or during an attack, which can be highly debilitating.[9] Skin manifestations of the acute porphyrias have been excluded from the current work but will be considered in the context of other cutaneous porphyrias at a later date. Rare acute porphyrias, including ALA dehydratase deficiency porphyria (OMIM *125270) and homozygous (compound heterozygous) porphyrias, have unique clinical features and are beyond the scope of the current work.

Many terms used in the extensive published literature on acute porphyrias and in clinical practice are ambiguous, with different meanings to different experts in the field, which contributes to confusion and inconsistencies in how patients are managed. Ambiguous terms are also an obstacle when comparing clinical practice and therapeutic outcomes among centres and in clinical trials, especially when developing clinical guidelines. Agreed definitions are not diagnostic or management criteria but are an essential first step in preparing guidelines for the treatment and monitoring of acute porphyrias and can facilitate and advance clinical research on these rare diseases.

Delphi is a process used to arrive at group opinions by surveying a panel of experts using a series of structured questionnaires to arrive at consensus opinions.[10,11] As a part of the process, the responses from each questionnaire are summarised and fed back to the participants. Although the Delphi method simply measures the

degree of consensus among participants, it can be modified to allow disagreements to be discussed and resolved, thereby promoting the development of consensus. The Delphi process has been successfully used in various medical fields to establish definitions, with the aim of addressing variations in clinical practice and developing management guidelines.[12–20]

This study aims to establish consensus among international clinical experts on definitions for the following terms that relate to the diagnosis, treatment, and monitoring of acute porphyrias: acute porphyria, acute porphyria attack, severe acute porphyria attack, active (symptomatic) acute porphyria (including sporadic acute porphyria and recurrent acute porphyria), latent (inactive) acute porphyria, asymptomatic acute porphyria (in remission), symptomatic high excreter, asymptomatic high excreter, prophylactic haemin, and on-demand haemin. We expect that consensus on these terms will greatly facilitate the development of guidelines for diagnosis and treatment of these disorders.

2 | METHODS

The study comprised two phases: a brainstorming phase, followed by the Delphi rounds phase. Figure 1 illustrates the steps followed to reach a consensus for acute porphyria-related definitions.

Online surveys were conducted via SurveyMonkey by the Outcomes and Implementation Research Unit at the University of Kansas Medical Center in accordance with the Declaration of Helsinki (as revised in 2013)[21]; individual consent for the survey was inferred in the cover letter of the survey.

2.1 | The brainstorming phase

The European Porphyria Network (Epnet) president, (SS) and the working group chairs (YE and PS), collectively referred to as 'chairs', drafted a list of terms considered important for acute porphyrias and proposed starting definitions for each term. A pilot survey was sent to members of the Acute Porphyria Expert Panel, subsequently referred to as the 'expert panel' to (1) agree or disagree with the proposed definitions, (2) suggest other related terms and definitions to be included, and (3) add references to support their suggestions. Members of the expert panel are international leaders in the porphyria field who were selected by the chairs to ensure global representation and a range of perspectives. They include clinicians, laboratory medicine specialists, and the leader of a patient advocacy group.

After the expert panel completed the pilot survey, the chairs incorporated their comments, and a revised survey was distributed to a broader audience of the porphyria community for further brainstorming. The broader audience included all members of Epnet who were encouraged to circulate the survey to other contacts in the porphyria community. The audience thus consisted of clinicians, patients, and laboratory specialists with an interest in and personal or clinical experience of acute porphyrias. The survey comprised a set of terms and draft definitions relating to acute porphyrias developed by the expert panel. Respondents were asked to agree or disagree with each definition and provide open-ended explanations of their responses. A meeting with the expert panel was carried out after completion of the survey to discuss areas of disagreement or uncertainty and to propose and discuss any additional terms and definitions that should be included in the survey. A map of the broader audience survey responses is illustrated in Figure 2.

2.2 | The Delphi phases

2.2.1 | Delphi 1

The terms and definitions were revised by the chairs using feedback from the broader audience survey. A survey of the revised definitions from the first Delphi round was circulated once again to the expert panel. Questions included a four-point Likert scale of agreement/disagreement, followed by opportunities for comments. The results were analysed and summarised using SurveyMonkey and Microsoft Excel. Definitions achieving at least 75% consensus were accepted and definitions achieving less than 75% were considered to require further discussion and revision.

2.2.2 | Delphi 2

The chairs reviewed the feedback from Delphi 1 and revised the definitions accordingly. The updated definitions were sent again to members of the expert panel for a second Delphi round. Definitions that still did not achieve 75% consensus or that generated helpful comments were revised and recirculated to the expert panel for additional revisions. This final Delphi round determined the final terms and definitions.

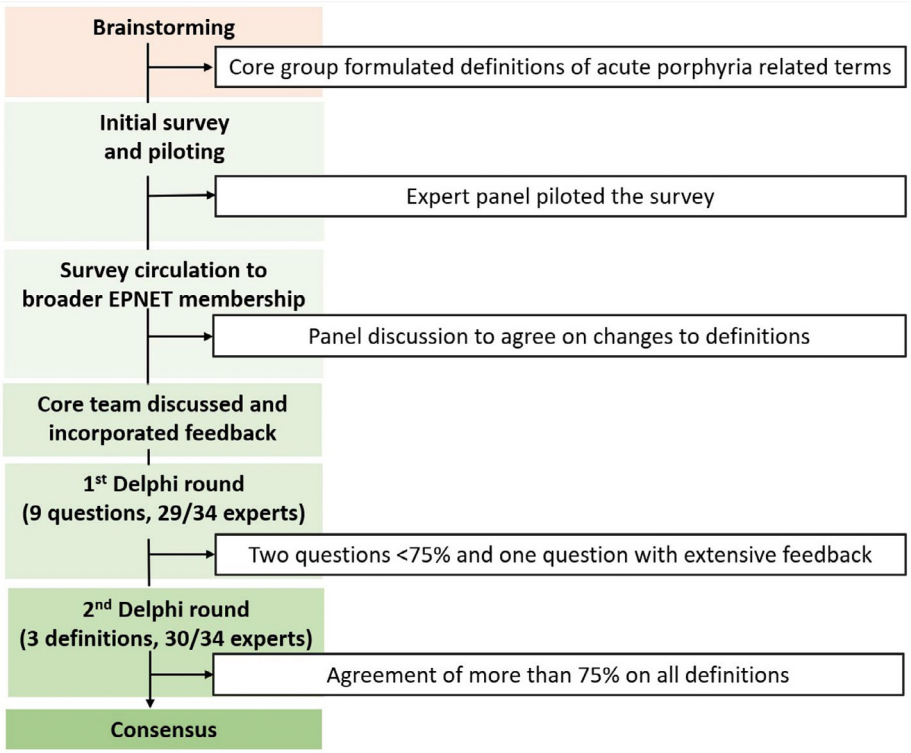


FIGURE 1 Summary of the steps in the Delphi consensus process that was used to develop definitions for the acute porphyrias.

FIGURE 2 Geographical distribution of all responses, including the initial survey and the broader audience of the porphyria community, which included 63 responses from 26 countries. Each response was from either an individual expert or a collaborating group of experts.

3 | RESULTS

Thirty-four specialists in the field of porphyria were invited to join the expert panel. They comprised 15 females and 19 males with an age range of 42–80. A total of 26 members of the panel were clinicians, 7 laboratory experts, and 1 the leader of a patient advocacy group.

The brainstorming phase involved an initial survey piloted by 20 members of the expert panel followed by a further survey among the wider porphyria community (63 responses from 26 countries). This was followed by two Delphi rounds within the expert panel. A total of nine definitions entered the first Delphi round and response rate was 85% (29/34). Seven terms had more than 75% agreement regarding definitions, and two had less than 75% agreement. Definitions for the two terms that did not achieve 75% consensus were revised and moved forward to the second Delphi round. In addition, one term and its definition achieved more than 75% consensus but generated multiple useful comments and was also revised and included in the second Delphi round. The response rate was 88% (30/34) in the second Delphi round. All nine terms and definitions, including the three revised terms, achieved more than 75% agreement by the end of the second Delphi round. The final consensus of acute porphyria-related terms and their definitions are described below and summarised in Table 1 and Figure 3.

3.1 | Final terms and definitions

1. *Acute porphyrias*

Acute porphyrias are rare inborn errors of haem biosynthesis. The three autosomal dominant acute porphyrias, AIP, VP, and HCP, result from inheritance of pathogenic variants in the hydroxymethylbilane synthase, protoporphyrinogen oxidase and coproporphyrinogen oxidase genes, respectively. The diagnoses are established by demonstrating typical patterns of haem precursor accumulation and/or a pathogenic gene variant.

The term 'acute hepatic porphyria' was simplified to 'acute porphyria' as all three of the most common forms of acute porphyria are hepatic.

Since the purpose of this work was to generate common terms and definitions but not, at this point, diagnostic criteria or treatment guidelines there was agreement that definitions should be phrased as generally as possible.

Some panel members considered that the very low clinical penetrance in the dominant acute porphyrias justified a separate term to describe people found to have a pathogenic variant but without symptoms or biochemical abnormalities. The term 'carrier' was proposed but felt to be misleading since this is more often used to describe a person with a variant for a recessive condition who usually has no risk of symptoms. There was consensus that the definition for the three most common acute porphyrias, which are autosomal dominant diseases should include all people found to have a pathogenic gene variant, whether or not symptoms have occurred since they all have some level of future risk. There is precedence for this terminology in other autosomal dominant diseases with variable penetrance, for instance, long QT syndrome.[22]

2. *Acute porphyria attack*

An acute porphyria attack is an episode that includes:

Two or more of the following manifestations typically persisting for more than 24 h in the absence of other likely explanations.

AND significantly increased urinary PBG/creatinine ratio, typically more than 10 times the upper limit of normal (or above 10 μmol/mmol creatinine if the upper limit of normal is ≤1 μmol/mmol creatinine e.g., when measured by mass spectrometry).

- *Intense pain, severe enough to require hospital admission, is a feature of nearly all attacks. Pain is most common in the abdomen but may affect other areas such as the back, legs, arms, or chest*
- *Nausea, vomiting, and/or constipation*
- *Systemic arterial hypertension and/or tachycardia*
- *Hyponatraemia*
- *Peripheral neuropathy* (*e.g., muscle weakness, paralysis, or reduced tendon reflexes*)
- *Urinary retention or incontinence*
- *Central nervous system involvement* (*e.g., seizures, confusion, reduced consciousness, psychosis, or posterior reversible encephalopathy syndrome on MRI scan*)

2a. A severe acute porphyria attack is associated with 1 or more of the following features: significant hyponatraemia, peripheral neuropathy, urinary retention or incontinence, central nervous system involvement, arrhythmias.

Note that attack severity may evolve, and any attack may rapidly become severe.

Many experts commented on the lack of evidence in relation to all aspects of the definitions related to acute attacks, as well as the difficulty and risk of categorising attack severity on the basis of a combination of symptoms and signs which are variable and non-specific.

Most favoured using urine PBG rather than urine ALA as part of this definition, since although ALA is probably more directly related to pathogenesis of symptoms, PBG is more specific for the diagnosis of acute porphyrias and the assay is more readily available in hospitals around the world. A key area of disagreement was the threshold level of urine PBG that should be used to define an attack. Experts were divided in their experience about whether a urine PBG of 5-fold or 10-fold the upper limit of normal was more appropriate. The evidence

TABLE 1 Final definitions for acute porphyria terms.

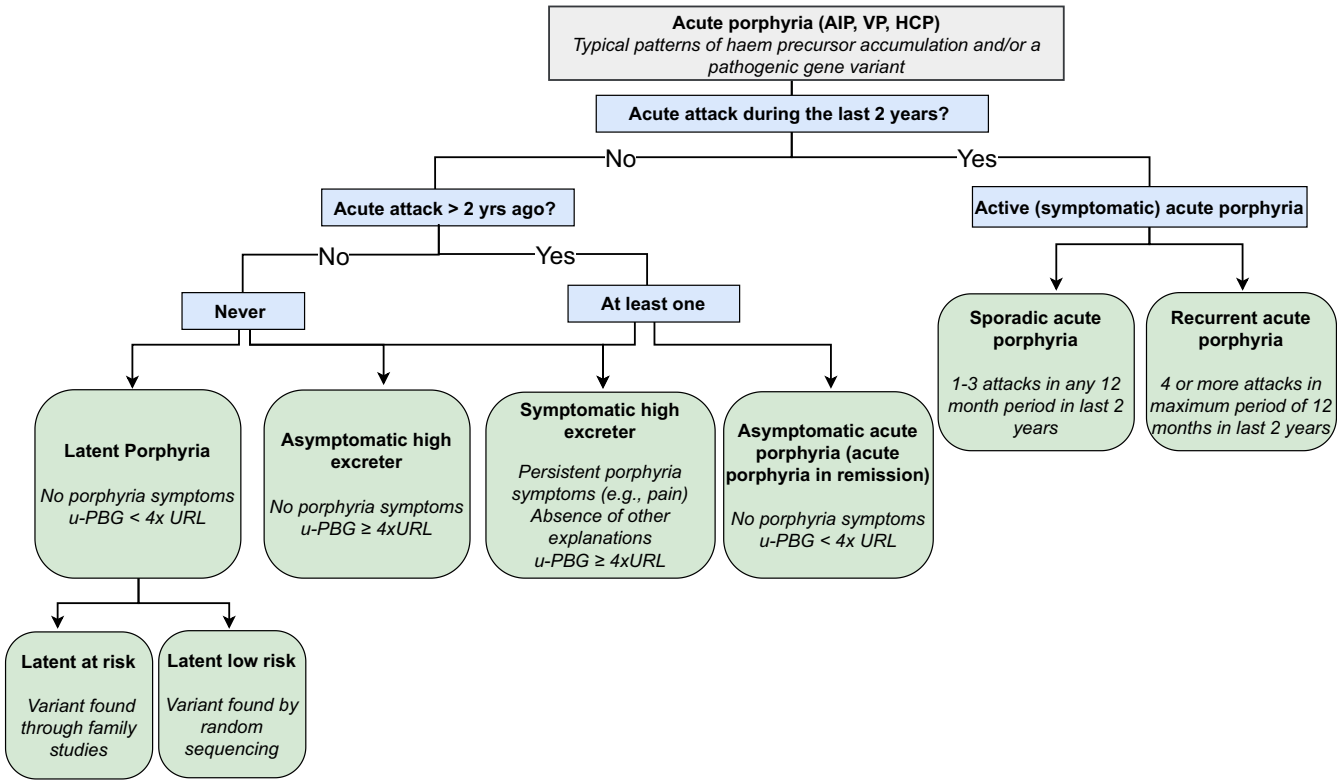
Term	Definition
1. Acute porphyria	*Acute porphyrias* are rare inborn errors of haem biosynthesis. The three autosomal dominant acute porphyrias, acute intermittent porphyria (AIP), variegate porphyria (VP), and hereditary coproporphyria (HCP), result from inheritance of pathogenic variants in the hydroxymethylbilane synthase, protoporphyrinogen oxidase and coproporphyrinogen oxidase genes, respectively.[a] The diagnoses are established by demonstrating typical patterns of haem precursor accumulation and/or a pathogenic gene variant.
2. Acute porphyria attack	*An acute porphyria attack* is an episode that includes: 2 or more of the following manifestations typically persisting for more than 24 h in the absence of other likely explanations. AND significantly increased urinary PBG/creatinine ratio.[b] • Intense pain, severe enough to require hospital admission, is a feature of nearly all attacks. Pain is most common in the abdomen but may affect other areas such as the back, legs, arms, or chest • Nausea, vomiting, and/or constipation • Systemic arterial hypertension and/or tachycardia • Hyponatraemia • Peripheral neuropathy (e.g., muscle weakness, paralysis or reduced tendon reflexes) • Urinary retention or incontinence • Central nervous system involvement (e.g., seizures, confusion, reduced consciousness, psychosis, or posterior reversible encephalopathy syndrome on MRI scan) *2a. A severe acute porphyria attack* is associated with 1 or more of the following features: significant hyponatraemia, peripheral neuropathy, urinary retention or incontinence, central nervous system involvement, arrhythmias. Note that attack severity may evolve, and any attack may rapidly become severe.
3. Active (symptomatic) acute porphyria	*Active* (*symptomatic*) *acute porphyria* refers to a patient who has experienced at least 1 acute porphyria attack within the last 2 years: *3a. Sporadic acute porphyria* refers to a patient who has experienced 1–3 attacks in any 12-month period within the last 2 years. *3b. Recurrent acute porphyria* refers to a patient who has experienced 4 or more attacks in a maximum period of 12-months within the last 2 years.
4. Latent (inactive) acute porphyria	*Latent/Inactive porphyria* refers to a person who has been found to have a pathogenic gene variant associated with acute porphyria but has never experienced definite manifestations of acute porphyria, AND whose urine PBG/creatinine ratio is lower than 4 times the upper limit of normal.[b] These may be further divided into: *4a.Latent at risk*—a person who has been found to have a pathogenic variant as part of family screening. *4b.Latent low-risk*—a person with no family history of porphyria who has been found to have an incidental pathogenic variant.
5. Asymptomatic acute porphyria	*Asymptomatic acute porphyria* (*acute porphyria in remission*) refers to a person who has experienced at least 1 acute porphyria attack in the past but has had no acute porphyria-related manifestations during the last 2 years AND urine PBG/creatinine ratio is less than 4 times the upper limit of normal.[b]
6. Asymptomatic high excreter	*An asymptomatic high excreter* refers to a person with confirmed acute porphyria who has had no porphyria-related manifestations during the last 2 years AND whose urine PBG/creatinine ratio is at least 4 times the upper limit of normal.[b]
7. Symptomatic high excreter	*Symptomatic high excreter* (*chronic high excreter*) refers to a patient with confirmed acute porphyria who has not had any acute attacks in the last 2 years but has longstanding pain or other porphyria-related manifestations in the absence of other likely explanations AND urine PBG/creatinine ratio is at least 4 times the upper limit of normal.[b]
8. Prophylactic hemin	*Prophylactic haemin* is the administration of haemin infusions at regular intervals to try to prevent acute porphyria attacks.
10. On-demand hemin	*On-demand haemin* is the administration of haemin infusions to treat very early symptoms of an acute porphyria attack to try to abort the attack.

[a]ALAD deficiency porphyria and homozygous/compound heterozygous acute porphyrias were considered to be beyond the scope of this definition.
[b]Considerations in the interpretation of Urine PBG/creatinine ratio: (1) The quality of the PBG analysis should be within specifications set by Epnet EQAS (or another EQA organisation). (2) PBG/creatinine ratio is typically increased to more than 10 times the upper limit of normal during attacks. However, if the upper limit of normal is ≤1 μmol/mmol creatinine (e.g., when measured by mass spectrometry), a result above 10 μmol/mmol creatinine is expected during attacks. (3) If the patient's PBG when asymptomatic is higher than 10 times the upper limit of normal or more than 10 μmol/mmol creatinine if measured by mass spectrometry, a significant further increase above baseline is expected during attacks. (4) In AIP, PBG/creatinine typically remains elevated for many years after or between attacks. (5) In VP and HCP, PBG/creatinine may fall to normal once the attack has resolved. (6) A PBG/creatinine ratio of 4 times the upper limit of normal is equivalent to 4 μmol/mmol creatinine if measured by mass spectrometry.

base is poor and these and other thresholds have been variably used in the literature. The problem is compounded by significant assay variability and differences in the upper limits of normal as evidenced by the results of the Epnet external quality assurance scheme (EQAS).[23] It was, therefore, emphasised that the analytical quality of PBG measurement should be verified by participating in an EQAS. Most experts agreed that the higher 10-fold threshold is more specific. However, all agreed that defining an attack does not mean a 10-fold elevation in urine PBG must be documented in every attack to justify treatment. Several experts commented that elevations of ALA and PBG may be less prominent and more transient in VP and HCP. See footnote b in Table 1 for considerations in the interetation of urine PBG.

There was extensive discussion about whether to group symptoms and signs according to a common pathogenesis or clinically. The latter was chosen as being clearer for non-experts. For example, it was considered preferable to group constipation as a gastrointestinal symptom rather than as a feature of autonomic neuropathy.

The possibility of further grading attacks according to severity was considered but it was considered potentially harmful to grade an attack as mild or moderate since all attacks are highly distressing to patients and symptoms



*An **acute attack** is an episode that includes:*

2 or more of the following manifestations typically persisting > 24 hr with no other likely explanation

AND significantly increased urinary PBG/creatinine excretion (urine PBG > 10 xURL or >10 μmol/mmol creatinine if normal ≤ 1μmol/mmol creatinine)

Intense pain usually in abdomen but may affect other sites such as back, legs, arms, chest
Nausea, vomiting and/or constipation
Systemic arterial hypertension and/or tachycardia
Hyponatraemia
Peripheral neuropathy (e.g. muscle weakness, paralysis, reduced tendon reflexes)
Urinary retention or incontinence
Central nervous system involvement (e.g. seizures, confusion, psychosis, posterior reversible encephalopathy syndrome (PRES) on MRI scan)

*A **severe acute attack** is associated with 1 or more of the following:*
significant hyponatraemia, peripheral neuropathy, urinary retention or incontinence, central nervous system involvement, arrhythmias

FIGURE 3 Flow chart summarising key terms for acute porphyria.

and signs may worsen rapidly and become severe or even life-threatening. For this reason, only 'a severe attack' was defined as a separate subcategory term, and a comment was added that attacks may progress in severity.

Some experts wished to include specific thresholds of plasma sodium and blood pressure as severity markers, but the majority felt these considerations should be based on good medical judgement and existing guidelines on severity of hyponatraemia and hypertension and should not be specific to porphyria. The panel agreed that severity markers should be restricted to features that are life-threatening or severely debilitating and should not include response to treatment (e.g., the response of pain to opiate analgesia).

3. *Active (symptomatic) acute porphyria*

Active (symptomatic) acute porphyria refers to a patient who has experienced at least 1 acute porphyria attack within the last 2 years:

3a. Sporadic acute porphyria refers to a patient who has experienced 1–3 attacks in any 12 month period within the last 2 years.

3b. Recurrent acute porphyria refers to a patient who has experienced 4 or more attacks in a maximum period of 12 months within the last 2 years.

The terms 'active', 'symptomatic' and 'sporadic' acute porphyria have been widely used but poorly defined in the past. The expert panel agreed it makes sense clinically to define all patients with recent attacks as being 'active' since these patients are at highest risk of further attacks. Although they represent a continuous spectrum, they were divided into 'sporadic attacks' or 'recurrent attacks', since treatments and risks differ for these subgroups.

Initially 'symptomatic' was defined as patients who have ever in the past suffered from attacks. However, the panel opted to change this to mean only those with attacks in the last 2 years because they considered that patients with historical symptoms, but none recently are clearly not symptomatic.

The definition of 'recurrent attacks' as meaning 'at least 4 attacks in a 12-month period' is already widely used within the porphyria community[24] and was retained. Ambiguity was reduced by changing the wording from 'within 12 months' to 'within a maximum period of 12 months' to be clear that recurrence in a patient with frequent attacks can be defined without waiting for a full 12-month period. In other words, an annualised attack rate can be calculated over a shorter period of time. Several experts commented that many patients with recurrent attacks had much higher attack frequencies than 4 per 12 months.

It was agreed that patients with porphyria-related skin symptoms as their only manifestation of acute porphyria do not meet the definition of 'active acute porphyria' for the purpose of these definitions, which focus on the neurovisceral symptoms that define the acute porphyrias. Although patients with skin manifestations only are clearly symptomatic, their disease natural history, treatment options, and risks are often completely different from those with attacks, and terms to describe them should be considered separately.

4. *Latent (inactive) acute porphyria*

Latent/Inactive acute porphyria refers to a person who has been found to have a pathogenic gene variant associated with acute porphyria but has never experienced definite manifestations of acute porphyria, AND whose urine PBG/creatinine ratio is lower than 4 times the upper limit of normal.

These may be further divided into:

4a. Latent at risk—a person who has been found to have a pathogenic variant as part of family screening.

4b. Latent low-risk—a person with no family history of porphyria who has incidentally been found to have a pathogenic variant.

'Latent porphyria' is another term that has been widely used but variously defined. The expert panel agreed this best describes people who are found to have a pathogenic variant for acute porphyria but have never had acute attacks or any definite clinical manifestations of porphyria and have a urine PBG/creatinine ratio that is within the normal range (or at most minimally elevated).

This group was subdivided into 'low-risk' and 'at-risk', as there are published evidence[25] that people with a pathogenic variant who were detected because they have relatives with active porphyria are at higher risk of symptoms than those detected for another reason, such as 'random' sequencing.

Experts disagreed on the clinical significance of pathogenic gene variants detected through random screening. Some considered the risk of attacks in these people was so low that they should be regarded as not affected, whereas others disagreed because they are at some level of risk. Because gene sequencing has previously demonstrated that the prevalence of pathogenic variants may be as high as 1 in 1600,[26] many questions about how to manage randomly detected gene variants in healthy people remain.

Panel members agreed that patients with a pathogenic variant who have features that are possibly related to their porphyria but are not specific (such as hypertension, hepatocellular carcinoma, or chronic kidney disease) in the absence of attacks, should be included within the definition of latent porphyria. Likewise, it was agreed that patients with skin symptoms as their sole manifestation of an acute porphyria would be classed as latent

porphyria for the purpose of these definitions, which currently focus on neurovisceral symptoms. This group will be considered within the definitions for cutaneous porphyrias at a later date.

5. *Asymptomatic acute porphyria*

Asymptomatic acute porphyria (acute porphyria in remission) refers to a person who has experienced at least 1 acute porphyria attack in the past but has had no acute porphyria-related manifestations during the last 2 years AND urine PBG/creatinine ratio is less than 4 times the upper limit of normal.

The panel agreed that the term 'asymptomatic acute porphyria' should be used to describe people who have had symptoms in the past, but not within the last 2 years, in contrast to those with 'latent acute porphyria' who have never had symptoms. The PBG/creatinine ratio threshold of 4 times the upper limit of normal is not evidence-based but was chosen to align with the definition of asymptomatic high excreter where this threshold had already been adopted by the porphyria community based on an empirical approach.

6. *Asymptomatic high excreter*

An asymptomatic high excreter refers to a person with confirmed acute porphyria who has had no porphyria-related manifestations during the last 2 years AND whose urine PBG/creatinine ratio is at least 4 times the upper limit of normal.

The expert panel felt these patients required a separate definition as they are believed to be at higher risk of attacks than those with asymptomatic porphyria. The PBG/creatinine ratio threshold of 4 times the upper limit of normal is in common use and has been retained.

It is important to emphasise that an 'asymptomatic high excreter' may, or may not, have had a porphyria attack in the past, in contrast to those defined as 'asymptomatic porphyria' who have had previously active porphyria with at least one attack in the past, otherwise, they are defined as 'latent'.

7. *Symptomatic high excreter*

Symptomatic high excreter (chronic high excreter) refers to a patient with confirmed acute porphyria who has not had any acute attacks in the last 2 years but has longstanding pain or other porphyria-related manifestations in the absence of other likely explanations AND urine PBG/creatinine ratio is at least 4 times the upper limit of normal.

In the past, experts have used the term 'chronic high excreter' to define this group of patients but there was agreement to change the name to 'symptomatic high excreter' for consistency with other definitions. The term describes patients with persistent chronic symptoms, typically pain, in the absence of acute attacks who also have abnormal porphyrin biochemistry, typically raised urinary PBG. Many of these patients have had porphyria attacks in the past, especially those with AIP where biochemistry remains abnormal for many years after an attack even in the absence of further attacks,[27] but some of these patients have never had a documented attack in the past. It was considered important to have a term to describe this group of patients as they are clinically complex and easily misdiagnosed; in particular, an exacerbation of chronic symptoms in a symptomatic higher excreter may be difficult to distinguish from an acute attack.

8. *Prophylactic haemin*

Prophylactic haemin is the administration of haemin infusions at regular intervals to try to prevent acute porphyria attacks.

Prophylactic haemin has been the main management strategy for recurrent acute attacks but has been superseded by givosiran in many countries. This definition has been widely agreed upon by experts for many years and was not changed.

9. *On-demand haemin*

On-demand haemin is the administration of haemin infusions to treat very early symptoms of an acute porphyria attack to try to abort the attack.

On-demand hemin is a strategy for managing patients with recurrent attacks where haemin is given promptly when the patient reports very early attack symptoms. It differs from the prophylactic use of haemin where it is given regularly regardless of symptoms or the use of haemin to treat established attacks. The goal of on-demand haemin is to prevent progression of the acute attack and avoid hospitalisation for more prolonged treatment.

4 | DISCUSSION

This is the first international effort to propose consensus definitions for key terms to describe the acute porphyrias and is a necessary first step before developing clinical guidelines. General agreement was achieved after extensive discussion among experts regarding terminology and definitions based on disease pathogenesis, clinical course, and outcomes. The respondents were from many

countries and considered a range of perspectives. Consensus was achieved through a rigorous Delphi-based process.

A frequent misconception was that these definitions might serve as diagnostic criteria or reflect treatment boundaries. However, the main purpose of this work is simply to generate common terms and definitions that can be used in the future to prepare management guidelines, which will be based on examination of the evidence for efficacy and safety. For example, while the agreed definition of 'an acute attack' included the finding of a raised urine PBG, a patient with known acute porphyria presenting with typical symptoms and signs may be judged to be having an attack that warrants treatment without the need to know the urine PBG/creatinine ratio.

We avoided proposing diagnostic criteria, so the definitions we developed are general and descriptive. For example, 'acute porphyria' is defined without proposing biochemical and genetic criteria for laboratory diagnosis. Diagnostic criteria will be addressed separately by a working group that will consider laboratory diagnostic approaches in greater detail.

Most definitions are based on consensus expert opinion and current experience since evidence to assess many implications of the definitions is sparse. For example, evidence to support definitions that include urine PBG thresholds is weak or non-existent. Therefore, many definitions will need to be updated in the future as the evidence base improves.

These terms and definitions focus primarily only on acute attacks and other neurovisceral symptoms of acute porphyrias. We acknowledge that skin symptoms, which can be particularly significant in VP, are important to consider, and will be addressed separately in future cutaneous porphyria definitions and guidelines.

We believe that our proposed terms and definitions will be a strong basis for developing evidence-based clinical guidelines for the acute porphyrias and will facilitate future clinical research and improve our understanding and management of these rare metabolic diseases.

FUNDING INFORMATION

The conduction of the survey and Delphi process was funded by the European Porphyria Network (Epnet).

CONFLICT OF INTEREST STATEMENT

Aasne Aarsand has received research grants from Western Norway Regional Health Authority and Norwegian National Advisory Unit on Rare Disorders and has a United Kingdom Patent Application for the development of a potential treatment for acute intermittent porphyria. Karl Anderson has received research grants from the US National Institutes of Health, Alnylam Pharmaceuticals, Mitsubishi Tanabe Pharma USA, Disc Medicine, Recordati Rare Diseases, and has participated on Advisory Boards for Mitsubishi Tanabe Pharma USA, Disc Medicine, and Recordati Rare Diseases. Michael Badminton has participated on an Advisory Board for Alnylam Pharmaceuticals. Manisha Balwani has received clinical trial support and related medical writing from Alnylam Pharmaceuticals, and consulting fees for participating in Advisory Boards for Alnylam Pharmaceuticals and Recordati Rare Diseases. Herbert Bonkovsky has received consulting fees from Disc Medicine and Recordati Rare Diseases and has participated on an Advisory Board for Eiger Biopharmaceuticals. Maria Cappellini has received consulting fees from Bristol Myers Squibb, Sanofi Genzyme, Agios Pharmaceuticals, and Vertex Pharmaceuticals and has participated on Advisory Boards for Bristol Myers Squibb, Agios Pharmaceuticals, and Sanofi Genzyme. Jean-Charles Deybach has received consulting fees and honoraria from Alnylam Pharmaceuticals, Mitsubishi Tanabe Pharma USA, and Disc Medicine and has participated on an Advisory Board for Alnylam Pharmaceuticals. Yontan Edel has received a speaker honorarium from Medison Pharma. Liz Gill works for the British Porphyria Association, which has received funding for educational events from Alnylam Pharmaceuticals and Recordati Rare Diseases. Laurent Gouya has received support to attend meetings from Alnylam Pharmaceuticals and has participated in Advisory Boards for Alnylam Pharmaceuticals, *Mitsubishi Tanabe Pharma USA, and Moderna*. Pauline Harper has received an unrestricted research grant from Alnylam Pharmaceuticals with all fees paid to Karolinska Institutet, Sweden. Aneta Ivanova has received a research grant from Alnylam Pharmaceuticals, consulting fees for participating on Advisory Boards for Alnylam Pharmaceuticals and Recordati Rare diseases, and a speaker honorarium from Genesis Pharma Cyprus Ltd. Janneke Langendonk has received research grants from Alnylam Pharmaceuticals and Clinuvel. Hetanshi Naik has received consulting fees for participating in Advisory Boards for Alnylam Pharmaceuticals, Disc Medicine, Mitsubishi Tanabe Pharma USA, and Recordati Rare Diseases and speaker honoraria from Sarah-Lawrence College and Keck Graduate Institute. Matteo Marcacci has received a speaker honorarium and support to attend meetings from Alnylam Pharmaceuticals. Reem Mustafa has received fees from Epnet for conduction of the survey and methods work. Elena Pischik has received a speaker honorarium from Alnylam Pharmaceuticals. Eliane Sardh has received an unrestricted research grant from Alnylam Pharmaceuticals and participated in an Advisory Board for Alnylam

Pharmaceuticals with all fees paid to Karolinska Institutet, Sweden. Sverre Sandberg has received speaker honoraria from Radiometer and Biopath and has participated on an Advisory Board for Disc Medicine. Ulrich Stölzel has received a research grant, consulting fees, and honoraria from Alnylam Pharmaceuticals, and has participated in an Advisory Board for Alnylam Pharmaceuticals. Jordi To-Figueras has received consulting fees for participating in Advisory Boards for Alnylam Pharmaceuticals and Recirdati Rare Diseases. Paolo Ventura has received consulting fees, support to attend meetings, and honoraria from Alnylam Pharmaceuticals and Recordati Rare diseases, and has participated in an Advisory Board for Alnylam Pharmaceuticals. Bruce Wang has received research grants from Alnylam Pharmaceuticals and Mitsubishi Tanabe Pharma USA, support to attend meetings from Alnylam Pharmaceuticals, and has participated in Advisory Boards for Alnylam Pharmaceuticals, Disc Medicine, Mitsubishi Tanabe Pharma USA, and Recordati Rare Diseases. Paul Wilson participated on a Data Safety Monitoring Board for Clinuvel. David Cassiman, Ibrahim El Mikati, Richard Hift, Razan Mansour, Caroline Schmitt, Mark Sonderup, Penelope Stein, David Rees, Christina Weiler-Normann, and Sharon Whatley declare that they have no conflicts of interest. This article does not contain any studies with human or animal subjects performed by any of the authors.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ETHICS STATEMENT

Approval for the online surveys were obtained by the Outcomes and Implementation Research Unit at the University of Kansas Medical Center from the Institutional Review Board (IRB) at that institution (IRB approval number: IRB00000161).

ORCID

Penelope E. Stein https://orcid.org/0000-0002-7052-6070

REFERENCES

1. Wang B, Rudnick S, Cengia B, Bonkovsky HL. Acute hepatic porphyrias: review and recent progress. *Hepatol Commun*. 2019;3(2):193-206.
2. Balwani M, Wang B, Anderson KE, et al. Acute hepatic porphyrias: recommendations for evaluation and long term-management. *Hepatology*. 2017;66(4):1314-1322.
3. Puy H, Gouya L, Deybach JC. Porphyrias. *Lancet*. 2010; 375(9718):924-937.
4. Phillips JD. Heme biosynthesis and the porphyrias. *Mol Genet Metab*. 2019;128(3):164-177.
5. Mustajoki P, Nordmann Y. Early administration of heme arginate for acute porphyric attacks. *Arch Intern Med*. 1993;153: 2004-2008.
6. Anderson KE, Collins S. Open-label study of hemin for acute porphyria: clinical practice implications. *Am J Med*. 2006; 119(801):e19-e24.
7. Marcacci M, Ricci A, Cuoghi C, Marchini S, Pietrangelo A, Ventura P. Challenges in diagnosis and management of acute hepatic porphyrias: from an uncommon pediatric onset to innovative treatments and perspectives. *Orphanet J Rare Dis*. 2022;17:160.
8. Harper P, Sardh E. Management of acute intermittent porphyria. *Expert Opin Orphan Drugs*. 2014;2(4):349-368.
9. Dawe R. An overview of the cutaneous porphyrias. *F1000Res*. 2017;6:1906. doi:10.12688/f1000research.10101.1
10. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. *J Adv Nurs*. 2000;32(4):1008-1015.
11. Brown BB. Delphi Process: a Methodology Used for the Elicitation of Opinions of Experts. 1968.
12. Allen J, Brenner M, Hauer J, Molloy E, McDonald D. Severe neurological impairment: a Delphi consensus-based definition. *Eur J Paediatr Neurol*. 2020;29:81-86.
13. Casellas-Grau A, Jordán de Luna C, Maté J, Ochoa C, Sumalla EC, Gil F. Developing a consensus definition of psychosocial complexity in cancer patients using Delphi methods. *Palliat Support Care*. 2021;19(1):17-27.
14. D'Souza N, de Neree Tot Babberich MPM, d'Hoore A, et al. Definition of the rectum: an international, expert-based Delphi consensus. *Ann Surg*. 2019;270(6):955-959.
15. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol*. 2016;48(3):333-339.
16. Hunter DJ, Arden N, Conaghan PG, et al. Definition of osteoarthritis on MRI: results of a Delphi exercise. *Osteoarthr Cartil*. 2011;19(8):963-969.
17. Rietjens JAC, Sudore RL, Connolly M, et al. Definition and recommendations for advance care planning: an international consensus supported by the European Association for Palliative Care. *Lancet Oncol*. 2017;18(9):e543-e551.
18. Sudore RL, Lum HD, You JJ, et al. Defining advance care planning for adults: a consensus definition from a multidisciplinary Delphi panel. *J Pain Symptom Manage*. 2017;53(5):821-832.e1.
19. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol*. 2006;101(8):1900-1920.
20. van der Kwast TH, van Leenders GJ, Berney DM, et al. ISUP consensus definition of cribriform pattern prostate cancer. *Am J Surg Pathol*. 2021;45(8):1118-1126.
21. World Medical Association. Declaration of Helsinki ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama
22. Alders M, Bikker H, Christiaans I. Long QT syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. *GeneReviews® [Internet]*. University of Washington; 1993–2022.
23. Aarsand AK, Villanger JH, Støle E, et al. European specialist porphyria laboratories: diagnostic strategies, analytical quality,

clinical interpretation, and reporting as assessed by an external quality assurance program. *Clin Chem*. 2011;57:1514-1523.

24. NORD rare disease Database. Acute intermittent Porphyria. https://rarediseases.org/rare-diseases/acute-intermittent-porphyria/
25. Lenglet H, Schmitt C, Grange T, et al. From a dominant to an oligogenic mode of inheritance with environmental modifiers in acute intermittent porphyria. *Hum Mol Genet*. 2018;27(7):1164-1173.
26. Chen B, Solis-Villa C, Hakenberg J, et al. Acute intermittent porphyria: predicted pathogenicity of HMBS variants indicates extremely low penetrance of the autosomal dominant disease. *Hum Mutat*. 2016;37:1215-1222.
27. Marsden JT, Rees DC. Urinary excretion of porphyrins, porphobilinogen and δ-aminolaevulinic acid following an attack of acute intermittent porphyria. *J Clin Pathol*. 2014;67:60-65.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Stein PE, Edel Y, Mansour R, Mustafa RA, Sandberg S, Members of the Acute Porphyria Expert Panel. Key terms and definitions in acute porphyrias: Results of an international Delphi consensus led by the European porphyria network. *J Inherit Metab Dis*. 2023;46(4):662-674. doi:10.1002/jimd.12612

APPENDIX A

Members of the Acute Porphyria Expert Panel

1. Aasne K. Aarsand, Norwegian Porphyria Centre, Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Bergen, Norway and Norwegian Organisation for Quality Improvement of Laboratory Examinations, Haraldsplass Deaconess Hospital, Bergen, Norway
2. Karl E. Anderson, Department of Internal Medicine, Division of Gastroenterology and Hepatology, University of Texas Medical Branch, Galveston, Texas, USA
3. Michael Badminton, School of Medicine, Cardiff University, UK
4. Manisha Balwani, Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, USA
5. Herbert L. Bonkovsky, Wake Forest University School of Medicine and Atrium Wake Forest Baptist Health, Medical Center Blvd, Winston-Salem, NC 27157, USA
6. Maria Domenica Cappellini, Foundation IRCCS Ca Granda Poiliclinico, University of Milan, Italy
7. David Cassiman, Department of Gastroenterology-Hepatology and Metabolic Center, Department of Chronic Diseases and Metabolism, University of Leuven and Leuven University Hospitals, Herestraat 49, 3000 Leuven, Belgium
8. Jean-Charles Deybach, University Denis Diderot, Paris, France and CRMR Centre Français des Porphyries, Louis Mourier hospital, Colombes, France
9. Ibrahim El Mikati, The Outcomes and Implementation Research Unit, Department of Internal Medicine, The University of Kansas Health System, Kansas City, Kansas, USA
10. Liz Gill, British Porphyria Association, UK
11. Laurent Gouya, Centre Français des Porphyries, Hôpital Louis-Mourier–APHP, Colombes, France and INSERM UMR-S 1149, Centre de recherche sur l'inflammation—Université Paris Cité, Paris, France
12. Pauline Harper, Porphyria Centre Sweden, Centre for Inherited Metabolic Diseases, Department of Medical Biochemistry and Biophysics, Karolinska University Hospital and Karolinska Institutet, Sweden
13. Richard Hift, School of Clinical Medicine University of KwaZulu-Natal, Durban, South Africa
14. Aneta Ivanova, Porphyria Center Bulgaria, St. Ivan Rilski University Hospital, 1431 Sofia, Bulgaria
15. Janneke G. Langendonk, Porphyria Expertcenter Rotterdam, Center for Lysosomal and Metabolic Disease, Department of Internal Medicine, Erasmus MC, Erasmus University Medical Center, Rotterdam, The Netherlands
16. Hetanshi Naik, Department of Genetics, Stanford University School of Medicine, California, USA
17. Matteo Marcacci, Center for Diagnosis and Management of Porphyrias, Internal Medicine Unit, University Hospital Policlinico of Modena, Dept of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Italy
18. Elena Pischik, Department of Neurology, Consultative and Diagnostic Center with Polyclinic, Saint Petersburg, Russia
19. David Rees, Haematological Medicine, King's College Hospital, London, UK
20. Eliane Sardh, Porphyria Centre Sweden, Centre for Inherited Metabolic Diseases, Department of Molecular Medicine and Surgery, Karolinska University Hospital and Karolinska Institutet, Sweden
21. Caroline Schmitt, Centre Français des Porphyries, Hôpital Louis-Mourier–APHP, Colombes, France and INSERM UMR-S 1149, Centre de recherche sur l'inflammation—Université Paris Cité, Paris, France
22. Mark Sonderup, Division of Hepatology and Lennox Eales Porphyria Laboratory, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa
23. Ulrich Stölzel, Porphyria Center Klinikum Chemnitz gGmbH/Flemmingstraße 2/D-09116 Chemnitz Hospital of Maximum Care Academic Teaching Hospital of the Universities of Leipzig and Dresden, Germany
24. Jordi To-Figueras, Biochemistry and Molecular Genetics Unit, Hospital Clinic-University of Barcelona, Barcelona, Spain
25. Paolo Ventura, Center for Diagnosis and Management of Porphyrias, Internal Medicine Unit, University Hospital Policlinico of Modena, Dept of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Italy
26. Bruce Wang, Department of Medicine, Division of Gastroenterology, University of California San Francisco, San Francisco, California, USA
27. Christina Weiler-Normann, Martin, Zeitz Centre for Rare Diseases and I. Department of Medicine, University Medical Centre Hamburg-Eppendorf, Germany
28. Sharon Whatley, Department of Medical Biochemistry, University Hospital of Wales, Cardiff, UK
29. Paul Wilson, Porphyria Expertcenter Rotterdam, Center for Lysosomal and Metabolic Disease, Department of Internal Medicine, Erasmus MC, Erasmus University Medical Center, Rotterdam, The Netherlands