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ORIGINAL ARTICLE

Rare bleeding disorders

Platelet function testing: Current practice among clinical centres in Northern Europe

Timea Szanto[1,2] | Eva Zetterberg[3] | Sofia Ramström[4,5] | Eva B. Leinøe[6] | Pål A. Holme[7] | Jovan P. Antovic[8] | Margareta Holmström[9] | Pall T. Onundarson[10] | Marika Pikta[11] | Ines Vaide[12] | Anna Olsson[13] | Maria Magnusson[14] | Satu Kärkkäinen[15] | Manar Bitar[16] | Lone Hvitfeldt Poulsen[17] | Riitta Lassila[1,2] | the Nordic Haemophilia Council[1]

[1]Coagulation Disorders Unit, Department of Hematology, Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland

[2]Research Program in Systems Oncology, Helsinki University, Helsinki, Finland

[3]Department of Translational Medicine & Centre for Thrombosis and Haemostasis, Lund University, Malmö, Sweden

[4]Department of Clinical Chemistry and Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

[5]School of Medical Sciences, Örebro University, Örebro, Sweden

[6]Department of Haematology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

[7]Department of Haematology, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[8]Coagulation Research, Institute for Molecular Medicine and Surgery, Karolinska Institute & Department of Clinical Chemistry, Karolinska University Hospital, Stockholm, Sweden

[9]Department of Health and Department of Acute Internal Medicine and Geriatrics, Medicine and Caring Sciences Linköping University, Linköping, Sweden

[10]Faculty of Medicine, University of Iceland, Reykjavik, Iceland

[11]Laboratory, North Estonia Medical Centre, Tallinn, Estonia

[12]Department of Hemato-Oncology, University of Tartu, Institute of Clinical Medicine, Tartu, Estonia

[13]Region Västra Götaland, Department of Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden

[14]Department of Haematology and Coagulation Disorders, Sahlgrenska University Hospital, Gothenburg, Sweden

[15]Hemostasis and Platelet Laboratory, Fimlab Laboratoriot, Tampere, Finland

[16]Department of Laboratory Medicine, Clinical Chemistry, Faculty of Medicine and Health, Örebro University Hospital, Örebro, Sweden

[17]Centre for Haemophilia and Thrombosis, Aarhus University Hospital, Aarhus, Denmark

Correspondence
Riitta Lassila, Unit of Coagulation Disorders, Department of Hematology and Comprehensive Cancer Center, Helsinki University Hospital, P.O. Box 372, 00029 HUS, Helsinki, Finland.
Email: Riitta.Lassila@kolumbus.fi

Abstract

Introduction: Platelet function tests are used to screen and diagnose patients with possible inherited platelet function defects (IPFD). Some acquired platelet dysfunction may be caused by certain drugs or comorbidities, which need to be excluded before testing.

Aims: To identify current practice among centres performing platelet function tests in Northern Europe.

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Methods: A total of 14 clinical centres from Sweden (six), Finland (two), Denmark (two), Norway (one), Estonia (two) and Iceland (one) completed the survey questionnaire, the population capture area of about 29.5 million.

Results: Six of the 14 (42.8%) centres providing platelet function assessment represent comprehensive treatment centres (EUHANET status). A Bleeding score (BS) or ISTH bleeding assessment tool (ISTH BAT score) is evaluated in 11/14 (78.6%) centres and family history in all. Five/14 centres (35.7%) use structured preanalytical patient instructions, and 10/14 (71.4%) recorded questionnaire on the preassessment of avoidance of any drugs or natural products affecting platelet functions. Preliminary investigations of screening tests of coagulation are performed in 10/14 (71.4%), while in 4/14 (28.6%), the diagnostic work-up of IPFD and von Willebrand disease (VWD) is performed simultaneously. The work-up of IPFD includes peripheral blood smear in 10/14 (71.4%), platelet aggregometry in all, flow cytometry in 10/14 (71.4%) and Platelet Function Analysis (PFA) in 3/11 (28.6%). Molecular genetic diagnosis is available in 7/14 (50%) centres.

Conclusions: The considerable variability in the current practice illustrates the need for harmonization between the Northern European centres according to the international registers (i.e. EUHASS) and IPFD guidelines (ISTH, EHA).

KEYWORDS
blood platelet disorders, data collection, platelet function testing, platelets, survey

1 | INTRODUCTION

Qualitative and/or quantitative platelet defects promote bleeding, whereas strong platelet reactivity may associate with thromboembolic complications. Laboratory tests of platelet function are traditionally utilised to determine the cause or potential for excessive bleeding, and/or to diagnose and manage patients with inherited (IPFD) or acquired platelet function defects.

Mucocutaneous bleeding symptom is dominant in the inherited disorders of primary haemostasis caused by von Willebrand disease (VWD), platelet or vascular wall disorders. After initial laboratory testing the prevalence of IPFD, differential diagnoses, and proportion of patients with mucocutaneous bleeding tendency of unknown cause vary. Majority of IPFD results in a mild to moderate bleeding tendency, and a significant proportion is due to presently undefined defects.[1] IPFD require comprehensive clinical and laboratory evaluation, but a consensus or standardised approach to the diagnosis is lacking.

IPFD are a heterogeneous group of diseases,[2] and their differential diagnosis encompasses a wide spectrum of entities that vary in acuity, severity, and aetiology. Diagnostic coagulation centres have an important role in establishing the diagnoses, by undertaking a comprehensive clinical and laboratory evaluation of the patients. Many laboratory techniques, including light transmission aggregometry, are not well standardised nor reproducible. Furthermore, the diagnostic approaches used by different centres are heterogeneous and acquired conditions may confound the diagnosis.[3–9] Recently, the Platelet Physiology Subcommittee of the ISTH developed consensus guidance for IPFD diagnostics, using expert opinion, a literature review and feedback from public presentations.[10] Accordingly, the first step for diagnosis of IPFD is a careful clinical evaluation of the proband, including objective personal and familial bleeding history with implementing a bleeding assessment tool (BAT).[11,12] Probands with clear abnormal clinical phenotype and/or bleeding scores, should undergo preliminary (standard) laboratory investigations, including peripheral blood smears, full blood count, screening of prothrombin time (PT), activated partial thromboplastin time (APTT) and von Willebrand factor (VWF antigen and activity), and coagulation factors VIII and IX (FVIII:C and FIX:C, clotting activity), and further coagulation factor analysis should include factor XIII (FXIII). Normal results call upon a diagnostic work-up for IPFD, including platelet function tests and next generation sequencing. Also, the European Haematology Association (EHA) established an International Working Group (IWG) and proposed a Systematic Approach to Mild and Moderate Inherited Bleeding Disorders.[13]

The primary goal of our study was to investigate practices for platelet function testing in the Nordic countries and Estonia. Particularly, we evaluated the diagnostic approach to platelet function defects, and excluded the acquired ones to cover the differential diagnosis. We used an on-line patterns-of-practice survey by focusing on how coagulation centres approached common problems of primary haemostasis, including mild VWF deficiency and platelet function disorders.

2 | METHODS

The study was conducted in accordance with the Declaration of Helsinki. To investigate practices for platelet function testing, an invitation to participate in the on-line survey was distributed electronically to the diagnostic coagulation centres, mostly members of the Nordic Haemophilia Council (NHC), including Estonia. To encourage participation, two e-mail reminders were sent before closing the survey to data entry. The aim was to gather data on both clinical and laboratory approaches, including personal and familial bleeding history, laboratory test procedures and panels. The type of anticoagulants used in routine laboratory work-up includes citrate (light transmittance aggregometer (LTA), platelet function analysis (PFA), performed either with PFA100 or PFA200), hirudin (Multiplate and flow cytometer), and citrate with formaldehyde (flow cytometry), whereas corn-trypsin inhibitor or D-Phenylalanyl-L-prolyl-L-arginine chloromethyl ketone (PPACK) are used only at research settings in rotational thromboelastometer (ROTEM) and calibrated automated thrombogram (CAT).

The survey included questions also on individual clinical diagnosis: (1) whether the centres use a bleeding assessment tool (BAT); (2) what tests were performed to investigate bleeding disorder; (3) which coagulation- and other laboratory tests were included in the bleeding disorder panels; (4) whether the centres followed a structured pre-analytical patient instructions to exclude infection and other acquired causes, such as endocrinological abnormalities; (5) time period after potential surgery, smoking, fasting or heavy exercise exertion; and (6) whether the centres use a recorded questionnaire on the avoidance of drugs (including the length of the wash-out period), over the counter products, dietary substitutions and natural products affecting platelet functions prior to testing. Participants were also instructed to list any additional investigations for bleeding disorder assessments that they performed or included in panels. There was a question on genetic counselling practices. The survey included one question about assessment of acquired platelet function defects to cover the differential diagnosis.

3 | RESULTS

3.1 | Survey participants

A total of 14 clinical centres from Sweden (six), Finland (two), Denmark (two), Norway (one), Estonia (two) and Iceland (one) were asked to complete the survey questionnaire. The share of respondents to the first round of the questionnaire was 85.7%, and 100% to the second round. Of these, 6/14 (42.8%) are comprehensive treatment centres (The European Haemophilia Network (EUHANET) status affiliated with the European Association for Haemophilia and Allied Disorders (EAHAD); http://www.euhanet.org/), 1/14 (7.3%) is a haemophilia treatment centre (EHTC), while 7/14 (50%) are not affiliated with EUHANET status. Table 1 summarises information on the countries and participant diagnostic coagulation centres.

TABLE 1 Information on the clinical and diagnostic centres in each survey participant and approximated size of referral population (*n*)

Country	Diagnostic coagulation centre	*n*
Sweden	1. Linköping University Hospital, Linköping	1,070,000
	1. Coagulation Unit, SUS, Malmö	1,870,000
	1. Adult Coagulation Unit, Karolinska University Hospital, Stockholm	
	1. Pediatric Coagulation Unit, Karolinska University Hospital, Stockholm	4,400,000
	1. Sahlgrenska University Hospital, Göteborg	1,900,000
	1. Örebro University Hospital, Örebro	2,110,000
Denmark	1. Rigshospitalet National University	2,634,950
	1. Aarhus University Hospital, Aarhus Hospital, Copenhagen	3,200,000
Finland	1. Coagulation Disorders Unit, Helsinki University Hospital, Helsinki	3,730,000
	1. Finnish Red Cross Laboratory, Helsinki	1,770,000
Estonia	1. North Estonia Medical Centre, Tallinn	1,096,000
	1. Tartu University Hospital, Tartu	380,000
Norway	1. Oslo University Hospital, Oslo	5,000,000
Iceland	1. Landspitali University Hospital. Reykjavik	340,000
Total		**29, 500,950**

3.2 | Panels of investigations used to assess the bleeding disorder

Most of the centres (84%) recommend an initial test panel for the bleeding disorder assessments.

The PT, APTT and a complete blood count are included in all screening panels, and many (85.7%) include a clot-based fibrinogen assay and assays for deficiencies of other coagulation factors. Figure 1 illustrates the subsequent instructions to order platelet function tests. Some bleeding disorder investigation panels are more comprehensive and include testing for VWD either simultaneously with platelet function testing (in 28.6%), or after excluding the coagulation factor deficiencies (in 35.7%). The first-line laboratory methods for VWD include the VWF antigen and activity (ristocetin co-factor or glycoprotein (GP) GPIb binding assay). Five (35.7%) of the participating centres adopt other strategies (Figure 1), as platelet function testing is performed only after either excluding VWD and the coagulation factor deficiencies (2/11, 14.3% of the centres). One centre first excluded abnormali-

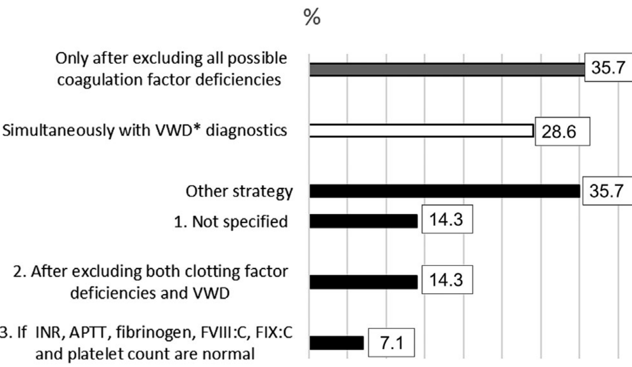

FIGURE 1 Instructions to order platelet function testing. *VWD =Von Willebrand disease, PT/INR = prothrombin time/international normalised ratio, APTT = activated partial thromboplastin time. The numbers are percentages

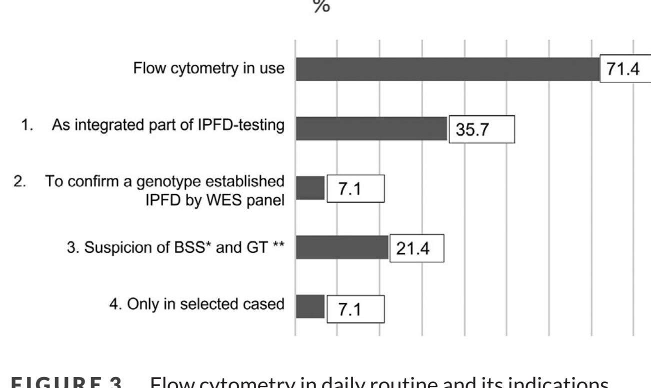

FIGURE 3 Flow cytometry in daily routine and its indications. *BSS = Bernard–Soulier syndrome, **GT = Glanzmann thrombasthenia

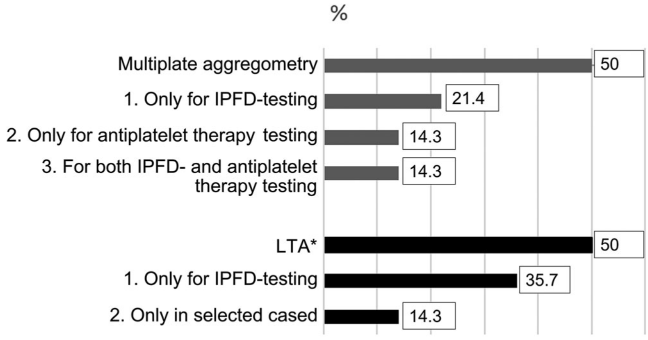

FIGURE 2 Platelet aggregation methods and their indications. LTA = Light Transmission Aggregometry.-The numbers are percentages

ties of PT, APTT, fibrinogen, FVIII:C, FIX:C and platelet counts. Two centres did not provide detailed information.

3.3 | Methods and indications of platelet aggregation studies

All laboratories evaluate platelet function disorders by aggregometry, with half of them performing light transmittance platelet aggregometry (LTA) in platelet-rich plasma (PRP) and the other half whole blood aggregometry by Multiplate®. Some (2/14; 14.3%) use both methods; LTA for IPFD testing, and Multiplate® to monitor antiplatelet therapy with aspirin or clopidogrel (Figure 2).

LTA is used only when specific criteria for IPFD are met, for example abnormal bleeding manifestations after exclusion of VWD, thrombocytopenia and/or clotting factor deficiencies. The indications for Multiplate® whole blood aggregometry are as follow: (1) suspicion of IPFD in 3/14 (21.4%), (2) assessment or exclusion of drug-induced platelet function defects in 2/14 (14.3%), and (3) assessment of both, inherited and drug-induced platelet function defects in 2/14 (14.3%) of the participants. The usual limit of thrombocytopenia for platelet aggregometry is $100 \times {}^{9}$/L. Responses to adenosine diphosphate (ADP; .2–10 μM), collagen (.5–2.5 μg/L), arachidonic acid (AA; 1.0–1.2 mmol/L), thrombin receptor-activating peptide (TRAP; 20–25 μM), to ristocetin (.3–1.2 mg/mL) and to epinephrine (5 μM) in LTA are assessed. In Multiplate, the manufacturer's standard ADP, collagen, AA, TRAP and ristocetin are used.

The number of annual LTA tests performed by the centres varies between 12 and 40.

3.4 | Indications of flow cytometry and other platelet function methods

Flow cytometry is used by most (10/14; 71.4%) of the participants, but only 35.7% perform flow cytometry routinely in the IPFD work-up. This work-up includes fibrinogen receptor GPIIb/IIIa for Glanzmann thrombasthenia, and VWF receptor GPIb/IX/V for Bernard Soulier syndrome, alpha – and dense granule defects, and phosphatidylserine (PS) expression to detect Scott syndrome (Figure 3), as recommended by the recent ISTH guidance.[14] Table 2 presents the details and agonist panel for the flow cytometry as a benchmark. For the rest of the centres, flow cytometry is restricted to selected patients: (1) to confirm an IPFD-genotype established by whole exome sequencing (WES) panel (1/14; 7.1%). (2) suspicion of Bernard Soulier syndrome or Glanzmann thrombasthenia (3/14; 21.4%), or (3) cases not responding to desmopressin (Octostim®) and/or with severe bleeding clinical features (1/14; 7.1%). The number of annual flow cytometry tests performed by the centres varies between 12 and 80.

Other methods are available in the research settings (Table 3). In response to the question about other assays, one participant listed lumi-aggregometry assay of adenosine triphosphate (ATP) release to evaluate for platelet dense granule release defects, and one used transmission electron microscopy (TEM) for platelet dense granule deficiencies.

TABLE 2 Details of flow cytometric agonist panels, a representative benchmark

Agonists (final concentrations in parenthesis):
ADP (5 µM)
PAR1-AP (SFLLRN, 10 µM)
PAR4-AP (AYPGKF, 100 µM)
CRP-XL (.15 and 2 µg/ml)
CRP-XL (2 µg/ml) + PAR1-AP (10 µM)
CRP-XL (2 µg/ml) + PAR4-AP (100 µM)
Platelet functions investigated (markers in parenthesis):
Fibrinogen receptor activation (fibrinogen binding; GPIIb/IIIa for Glanzmann thrombasthenia)
Alpha granule release (P-selectin exposure)
Dense granule release (CD63 exposure and decrease in response in presence of apyrase)
Lysosomal release (LAMP-1 (CD107a) exposure)
PS exposure (Annexin V binding)
Platelet fragmentation/microparticle formation (formation of smaller platelets and platelet fragments, i.e. CD41a-positive events with lower than normal forward scatter upon strong platelet activation)

Abbreviation: PAR1AP = protease activated receptor activating peptide, CRPXL = crosslinked collagen related peptide, GP = glycoprotein, CD = cluster differentiation antigen, LAMP1 = lysosomal associated membrane protein, PS = phosphatidylserine.
The diagnostic approach to assess platelet function defects by flow cytometry in Linköping and Örebro University Hospitals. The data are provided by Dr. Sofia Ramström.

3.5 | Pre-analytical patient instructions and clinical evaluation before laboratory investigation

The recommendations by ISTH for diagnosis of IPFD were addressed as follows: (1) how to obtain family and personal history and bleeding score to help quantitate bleeding tendency, (2) how to assure structured pre-analytics, including clear patient instructions and the use of a recorded questionnaire on drugs affecting platelet functions prior to platelet function testing, and (3) how to evaluate the laboratory work-up at participating sites. Most of the centres quantify the bleeding propensity of the probands (11/14; 78.6%) and check the avoidance of drugs affecting platelet function (10/14; 71.4%). A family history is obtained in all centres.

3.6 | Diagnostic work-up of platelet defects

As an outcome of the previous investigations, the main results of the diagnostic work-up by the centres are presented in Figure 4.

The work-up of IPFD includes peripheral blood smear (10/14; 71.4%), mean platelet volume measured by the automated blood analyser (in 8/14; 57.14% as a routine set-up) and flow cytometry (10/14; 71.4%) and platelet aggregometry in all centres (Figure 4). PFA is used in 3/11 (21.4%) centres.

TABLE 3 Alternative platelet methods for the research settings

Methods and assays	Reported availability number centres/all (%)
Thrombin generation	
• Calibrated automated thrombogram (CAT) in both PRP and PPP	7/14 (50)
Rotational thromboelastography (ROTEM/TEG)	4/14 (29)
Platelet adhesion: Cellix microfluidic method, in-house methods	2/14 (14)
Transmission electron microscopy (TEM)	3/14 (21)
Flow cytometry:	
• Residual platelet counting	
• Platelet-leukocyte conjugates	
• Bead-based adhesion assays, e.g. TRAP-6-induced adhesion to fibrinogen- and collagen-coated beads	1/14 (7)
ATP release	1/14 (7)
Changes of intracellular calcium by spectrofluorometric method	1/14 (7)
Thromboxane B2 (TXB_2) by commercial ELISA	1/14 (7)
Immunohistochemistry (MYH9, FLNA)	1/14 (7)
Monoclonal Antibody-specific Immobilization of Platelet Antigen (MAIPA)	1/14 (7)
Bleeding time according to IVY	1/14 (7)

Abbreviations: PPP = platelet-poor plasma; PRP = platelet-rich plasma, TRAP = thrombin receptor activating peptide.

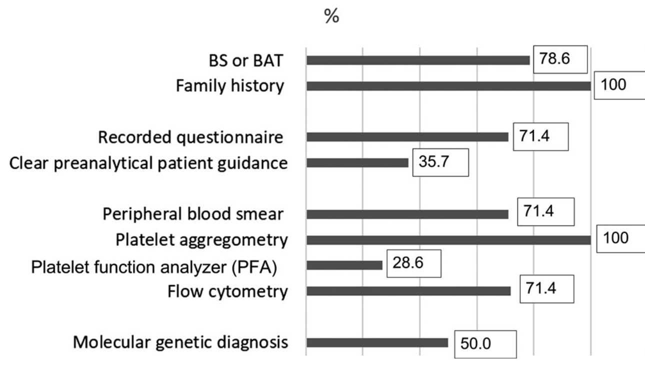

FIGURE 4 Frequency of use of the different IPFD-tests in the participating centres. BS = Bleeding Score, BAT = Bleeding Assessment Tool. The numbers are percentages

3.7 | Molecular genetic analysis

Molecular genetic diagnosis is available in half of the centres. Genetic screening is considered with (1) suspected hereditary thrombocytopenia, (2) syndromic features, (3) a strong family history, (4) a significant bleeding score, and (5) clinical and laboratory features suggestive

of a platelet disorder, but further diagnostic assays are not available. High-throughput sequencing (HTS) techniques, with targeted WES (at present 100 bleeding disorder-associated genes) combined with copy number variant analysis being available in 5/14 (35.7%) centres (in two on site, and in three in collaboration with the former). Two centres include human platelet antigens (HPA) - or other coagulation factor genotypes in their responses. Genetic counselling is only rarely offered.

Overall, before making any specific diagnosis of a platelet abnormality, platelet function test is recommended to be supplemented with another method, and NGS analysis is performed by 50% of the centres.

4 | DISCUSSION

There is a considerable variability in the current practice and therefore the need for harmonization between the Northern European centres, also to accord with the international registers (i.e. EUHANET) and IPFD guidance (ISTH, EHA). The varying diagnostic strategies lead to major uncertainties when comparing incidences of IPFD in these populations. The implementation of a uniform diagnostic algorithm for IPFD will also increase the diagnostic yield of the work-up in the future.[15,16]

All treatment centres complied with the guidance from the Platelet Physiology SSC of the ISTH to perform a careful clinical evaluation of the proband, including the personal and familial bleeding history typical for IPFD as a first step to identify patients needing further investigation. Next, clear pre-analytical rigour should be followed to control the quality and interpretation of the results. Moreover, in patients presenting with bleeding symptoms, the knowledge on clinical validity and the capture of permanent traits versus acquired tendency are critical. We should provide patients with the appropriate instructions before blood sampling regarding comorbidities and acquired conditions, including infection and endocrinological disorders, timing after potential surgery or trauma, use of a certain medications (e.g. serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs), smoking, fasting or heavy exercise exertion prior to testing. The above precautions will reduce variability, misinterpretation, and unnecessary repetition of the testing. Our study emphasises the need to improve compliance to structured pre-analytical guidance prior to IPFD testing, since only about 40% of the centres follow the current recommendations.

Our major finding was the variability in the comprehensiveness of the IPFD tests. The first-step platelet function test, including a peripheral blood smear, LTA, and flow cytometry, was available in majority of the diagnostic centres. In contrast, the ATP release assay as part of the first-step laboratory panel according to ISTH recommendations was evaluated by only one centre. Second step-test, involving LTA with an expanded agonist panel, flow cytometry with additional antibodies, clot retraction, the measurement of serum thromboxane-B_2 (TXB_2), intracellular calcium and electron microscopy were available in research set-up only in a few centres.

Recent studies have shown that a significant proportion of defective genes causing thrombocytopenia also affect platelet function.[17] However, platelet function testing in thrombocytopenia requires expertise about sensitivity and the limits of reduced platelet count should be defined for each test.[18] The lowest platelet count allowed for platelet function testing is specifically defined by most centres; and it ranges from 70 to 100 × 10^6/ml.

In addition, our survey highlights that the methodology of individual tests varies widely between laboratories, in accordance with other regional surveys of platelet function.[6] This observation underscores the importance of implementation of the standardised methodologies, as now recommended for example, LTA by the ISTH Platelet Physiology SSC.[11] The whole blood Multiplate aggregometer has a drawback of nonoptimal sensitivity.[19]

Some aspects of testing still need to be improved to ensure appropriate detection of common disorders, including control over pre-analytics and the use of agonists with concentration ranges sensitive to common platelet function disorders, such as a thromboxane A_2 analogues, epinephrine and collagen. Implementation of HTS approaches to diagnose IPFD has changed the field, and it will be incorporated into future diagnostic algorithms.[20]

Some centres use alternative methods to capture platelet functions (e.g. CAT in PRP, ROTEM with maximal clot firmness and microfluidic tests). These tests do not measure platelet function per se, but their results may be influenced by the platelet disorder.

In the past, functional platelet testing, and Sanger sequencing and linkage analysis were used for targeted molecular diagnosis. These analyses are largely replaced by HTS techniques, mostly using gene panels based on WES or NGS. NGS is available for about half of the surveyed centres aligning with the changing landscape of clinical diagnostics of IPFD. This tool is under development and needs to build on international recommendations to obtain the best and most cost-effective outcome. Overall, the implications of our study findings and the follow-up will be the next step for the participants.

Our study demonstrated considerable variability in the current practice amongst the Nordic centres when performing platelet function tests. As an outcome of this platelet function survey, a recommendation for diagnostics of IPFD in Northern Europe has been published by the NHC.[21]

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CONFLICT OF INTERESTS

No relevant conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author.

ORCID

Timea Szanto https://orcid.org/0000-0001-7006-6564
Eva Zetterberg https://orcid.org/0000-0003-1775-1727
Anna Olsson https://orcid.org/0000-0002-9974-4880
Riitta Lassila https://orcid.org/0000-0002-1911-3094

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SUPPORTING INFORMATION

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

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