

Inherited platelet function disorders: a comprehensive narrative review focusing on diagnostic and management aspects

Antonietta Ferretti,¹ Nicola Portesi,² Chiara Gorio,³ Marzia Leotta,⁴ Alessandra Strangio,⁴ Antonella Ierardi,⁴ Bianca Maria Roccon,⁵ Giulia Albrici,³ Giulia Carracchia,³ Marta Mattana,⁶ Chiara Biasoli,⁷ Cristina Santoro,⁸ Tiziano Martini,⁹ Rita Carlotta Santoro,⁴ on behalf of AICE

¹Department of Hemorrhagic and Thrombotic Diseases, "A. Gemelli" University Polyclinic Foundation IRCCS, Rome; ²Clinical Chemistry Laboratory, Diagnostic Department, ASST Spedali Civili di Brescia; ³Pediatric Onco-Hematology Unit, Children's Hospital, ASST Spedali Civili di Brescia; ⁴Hemostasis and Thrombosis Unit, Renato Dulbecco University Hospital, Catanzaro; ⁵Regional Hub Center for Hemophilia and Congenital Bleeding Disorders, University Hospital of Parma; ⁶Hematology and Rare Diseases Unit, Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello, Palermo; ⁷Hemophilia and Transfusion Center, "Bufalini" Hospital, Cesena; ⁸Department of Hematology, Policlinico Umberto I, Rome; ⁹Regional Reference Centre for Inherited Bleeding and Thrombotic Disorders, Transfusion Medicine, Città della Salute e della Scienza University Hospital, Turin, Italy

ABSTRACT

Qualitative and quantitative inherited platelet disorders (IPDs) are a heterogeneous group of rare bleeding conditions caused by inherited variants in genes that affect platelet production and function. Clinically, IPDs are characterized by significant phenotypic heterogeneity, ranging from mild mucocutaneous bleeding to severe hemorrhagic complications. In some cases, they are associated with additional systemic features, including syndromic abnormalities, or an increased predisposition to hematological malignancies. Over the past decade, the rapid implementation of next-generation sequencing technologies has transformed the field, enabling the identification of a growing number of genes involved in platelet formation and function. These advances have revealed the unexpected molecular complexity underlying platelet disorders and significantly improved the ability to establish genotype–phenotype correlations. Despite these advances, the diagnosis of IPDs remains challenging in routine clinical practice. An approach combining clinical evaluation, advanced platelet function testing and comprehensive genomic analysis is increasingly recognized as essential for accurate diagnosis

and optimal patient management. IPDs treatment is challenging too, since there are few robust therapy choices. Although promising results emerge from experimental therapies, right now therapies consist of conservative measures, platelet concentrates, tranexamic acid and recombinant activated factor VII. Aim of this narrative review is to provide a comprehensive overview of IPDs characterized primarily by platelet dysfunction.

Key words: platelets, inherited platelet function disorders, inherited bleeding disorders, thrombocytopenia, hemostasis laboratory.

Corresponding author: Nicola Portesi, Clinical Chemistry Laboratory, Diagnostic Department, ASST Spedali Civili di Brescia, 25123 Brescia, Italy.
E-mail: nicola.portesi@asst-spedalicivili.it

Contributions: AF, CG, AS, AI, BMR, GA, GC, MM, ML, NP and TM contributed to the conceptualization and writing of the original draft, as well as to the review and editing of successive versions of the manuscript. CS provided critical revision of the manuscript for important intellectual content and approved the final version for publication. RCS coordinated review and editing.

Ethical approval: not applicable.

Availability of data and materials: not applicable.

Conflict of interest: the authors declare that they have no competing interests.

Received: 16 July 2026.

Accepted: 19 September 2026.

Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

©Copyright: the Author(s), 2026

Licensee PAGEPress, Italy

Bleeding, Thrombosis and Vascular Biology 2026; 5:581

doi:10.4081/btvb.2026.581

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0).

Introduction

Qualitative and quantitative inherited platelet disorders (IPDs) are a heterogeneous group of rare bleeding conditions caused by inherited variants in genes that affect platelet production and function.¹ While these disorders are uncommon when considered individually, they collectively represent an important cause of lifelong bleeding predisposition, providing unique insights into the molecular mechanisms that regulate platelet biology and hemostasis. Clinically, IPDs are characterized by significant phenotypic heterogeneity, ranging from mild mucocutaneous bleeding to severe hemorrhagic complications.² In some cases, they are associated with additional systemic features, including syndromic abnormalities, or an increased predisposition to hematological malignancies.³

Traditionally, IPDs were classified primarily based on phenotypic characteristics identified through platelet aggregation studies and specialized functional assays.⁴ Over the past decade, however, the rapid implementation of next-generation sequencing (NGS) technologies has transformed the field, enabling the identification

of a growing number of genes involved in platelet formation and function.⁵ These advances have revealed the unexpected molecular complexity underlying platelet disorders and significantly improved the ability to establish genotype–phenotype correlations. At the same time, they have highlighted the central role of pathways regulating cytoskeletal dynamics, receptor signaling, granule biogenesis and intracellular trafficking in maintaining normal platelet function.

Despite these advances, the diagnosis of IPDs remains challenging in routine clinical practice. The rarity of many conditions, the variability of clinical presentation and the limited availability of specialized laboratory tests, all contribute to underdiagnosis and delayed recognition. Furthermore, interpreting genetic findings often requires careful integration with detailed phenotypic and functional data.⁶ Consequently, an approach combining clinical evaluation, advanced platelet function testing and comprehensive genomic analysis is increasingly recognized as essential for accurate diagnosis and optimal patient management.

Aim of this narrative review is to provide a comprehensive overview of IPDs characterized primarily by platelet dysfunction (IPFDs), giving the readers useful information for the diagnosis and management of these rare diseases.

Clinical manifestation and bleeding assessment tools

IPFDs are conditions predominantly characterized by mucocutaneous bleeding. Common manifestations include epistaxis, gingival bleeding, spontaneous petechiae or ecchymoses, heavy menstrual bleeding, postpartum hemorrhage, gastrointestinal

bleeding, and excessive post-operative bleeding. In severe cases, central nervous system or hemarthrosis may also occur.⁷ Notably, manifestations such as cephalohematomas or umbilical stump bleeding, appear in the neonatal period, and are potential early indicators of an underlying platelet defect. Symptoms usually begin early in life, and their severity varies depending on the molecular defect.⁸ Given the wide variability in clinical presentation and overlap with other conditions—such as von Willebrand disease (VWD) or inherited thrombocytopenia—the use of standardized bleeding assessment tools has become increasingly important. Among these, the ISTH Bleeding Assessment Tool (ISTH-BAT) developed by the International Society on Thrombosis and Haemostasis (ISTH) is currently the most validated (for further data, see Supplementary Table 1 in Rodeghiero *et al.*, 2010).⁹ Its effectiveness was highlighted in the BAT-VAL study, which involved a large cohort of genetically confirmed IPFDs patients.¹⁰ The ISTH-BAT demonstrated excellent ability to distinguish IPFDs from both healthy individuals and type 1 VWD patients. A score greater than 6 was associated with a >99% likelihood of an IPFD, assuming that VWD and coagulation factor deficiencies had been ruled out, thus confirming its usefulness not only as a screening tool but also for diagnostic orientation. In addition, the ISTH-BAT has shown prognostic significance: patients with high scores were more likely to experience future bleeding events requiring medical intervention or platelet transfusions. For this reason, it is recommended to assess every patient with suspected or confirmed IPFD with the ISTH-BAT at the time of diagnosis.¹¹ When the score exceeds the clinical threshold (≥ 4 for adult men, ≥ 6 for adult women and ≥ 3 for children) closer follow-up and a more aggressive prophylactic approach is advised in situations of high bleeding risk, such as surgery or invasive procedures. Its moderate specificity means that additional confirmatory testing

Table 1. Relevant critical points for each phase of the analytical process.²¹

Preanalytical phase	
Patient preparation	- <i>Sampling Day</i>: Subjects should be resting and fasting - <i>Restrictions</i>: Refrain from smoking (30 minutes prior) and coffee/caffeine consumption (2 hours prior) - <i>Medication</i>: For 3-14 days prior, patients should avoid drugs affecting platelet function if medically possible. Otherwise, the laboratory must be informed of any recently taken medications
Sampling	- Needles smaller than 21 gauge are not recommended - Smaller tubes (<i>e.g.</i>, 1 mL) are not recommended - Tourniquet use is not recommended
Transportation	- Avoid vibration, shaking, or agitation - Maintain room temperature (20-25°C) - The time delay between sampling and analysis should be 30-120 minutes - Test runs can be lengthy, so samples should reach the lab as soon as possible
Clinical information	- This impacts the choice of tests/methods and their proper interpretation
Analytical phase	
Test selection criteria/flow charts	- Not explicitly reported in the International Society on Thrombosis and Haemostasis algorithm¹⁶ - Lack of detailed reporting on sensitivity, specificity, and cost²¹
Standardization	- Many functional assays lack standardization and validation^{17,24} - Multicenter studies, standard operating procedures, and external quality assurance are needed to improve reproducibility and diagnostic accuracy^{15,20}
Post-analytical phase	
Reference range	- CLSI rules for establishing reference intervals are not applicable to platelet functional tests - Reference ranges must be determined on a population of healthy volunteers for each laboratory
Interpretation	- Consider clinical and therapeutic information, as well as complementary tests (<i>e.g.</i>, flow cytometry or genetic analyses) - Abnormal findings should be confirmed on a different specimen

is often required, particularly in borderline cases. This limitation is especially evident in pediatric patients, in whom the ISTH-BAT has shown limited sensitivity for detecting mild IPFDs.¹² To address these specific challenges in pediatric patients, the Pediatric Bleeding Questionnaire (PBQ) was developed with an abnormal bleeding score (BS) defined as ≥ 2 (resource available at <https://elearning.wfh.org/resource/pediatric-bleeding-questionnaire-pbq/>).¹³ The PBQ includes bleeding symptoms unique to childhood (e.g., umbilical stump bleeding, post-circumcision hemorrhage, macroscopic hematuria) and assigns a quantitative bleeding score. In a study involving 23 children aged 0.6 to 18 years with confirmed platelet function disorders, 96% had a PBQ score ≥ 2 , with a median of 8 (range: 1–20), confirming the tool's high sensitivity for identifying bleeding tendency.¹⁴

Overall, tools like the ISTH-BAT and PBQ are essential for improving the diagnostic and prognostic evaluation of IPFDs. While they cannot replace functional platelet testing, their integration into clinical practice allows for earlier, more accurate, and individualized care for patients with suspected or confirmed platelet function defects.

Laboratory diagnostics

The diagnostic approach for IPFDs involves several laboratory tests. These tests should only be performed on patients carefully selected through a precise clinical evaluation, ideally by hemostasis experts.¹⁵ The current reference algorithm for IPFDs diagnosis was proposed by the SSC of ISTH in 2015 and revised in 2016 (Figure 1).^{16,17} More recently, Hoepner *et al.* proposed a reinterpretation of this diagnostic workup, further complemented by Gresele *et al.*, who provided an updated review of IPFDs and platelet functional tests, delineating a refined laboratory framework.^{18,19} These approaches outline a stepwise methodology, starting with preliminary tests and progressing to advanced functional, non-functional, and genetic assays. This approach should be flexible, adapting to individual clinical cases and allowing for the skipping or combining of steps based on specific diagnostic hypotheses.¹⁸ The British Society of Haematology published updated guidelines for IPFDs diagnostic workup in 2021.²⁰ Subsequently, a 2024 review by the Société Française de Thrombose et d'Hémostase integrated various guidelines and recommendations, including the aforementioned British work, to formulate specific statements on functional testing, especially light transmission aggregometry (LTA).²¹

For a more comprehensive overview of clinical, laboratory, and genetic features, see Supplementary Materials.

Preliminary tests

Preliminary tests are designed to exclude other bleeding disorders, such as VWD, plasmatic defects, or acquired hematologic disorders.^{15,18} These should include a full blood count, prothrombin time, partial thromboplastin time, fibrinogen, and VWF parameters.¹⁵ Some authors also suggest dosing coagulation factor XIII and coagulation factor IX.¹⁸ Blood group should be determined in cases of borderline VWF levels to exclude physiologically normal levels in group O individuals. ISTH does not recommend the use of the Platelet Function Analyzer as a screening tool for IPFDs due to its lack of sensitivity and specificity.²² However, other authors propose using PFA or whole blood impedance aggregometry in restricted settings, such as time-critical situations like urgent surgery.¹⁸

Functional tests

All platelet functional tests require samples acquired with utmost care from correctly prepared patients to prevent premature platelet activation or inhibition. These tests should be performed in specialized laboratories to ensure proper handling and interpretation by skilled and experienced personnel (Table 1).²¹

Light transmission aggregometry

LTA is considered the gold standard for platelet function evaluation.¹⁵ It measures the amount of light transmitted through a stirred sample of platelet-rich plasma (PRP) maintained at 37°C. The induction of platelet aggregation by agonist addition increases light transmission, with autologous platelet-poor plasma used as a comparator.²¹ In addition to the critical points mentioned above, LTA requires a significant blood volume (20 mL), a normal platelet count ($150\text{--}600 \times 10^9/\text{L}$), and clear plasma specimens.²¹ All guidelines recommend several platelet agonists for LTA, but there is no consensus on their choice or concentration. The general approach is to start with a first-line panel of agonists, which should be expanded after the initial test. Extended panels should also include first-line agonists at different concentrations (Table 2).²¹ Despite its central role, LTA remains affected by substantial interlaboratory and interindividual variability. An ISTH SSC multicenter study involving 28 laboratories compared locally used agonists with standardized comparator reagents and demonstrated relevant differences in agonist potency, particularly for TRAP-6, arachidonic acid, and epinephrine, whereas ADP and ristocetin showed greater consistency.²³ These findings support the adoption of simple standardization principles for agonist sources and emphasize that results obtained at low or threshold agonist concentrations should be interpreted cautiously, taking into account both reagent-related and biological variability.

Mixing test

Mixing tests in LTA should be performed after observing enhanced agglutination to low-dose ristocetin. This helps differentiate between defects of plasmatic VWF (Type 2B VWD) and defects of VWF receptors expressed on platelets (Platelet-Type von Willebrand Disease, PT-VWD) (Table 3).

Platelet secretion assays

Laboratory assays assessing platelet granule content and release are pivotal in diagnosing IPFDs. Although various platelet secretion assays (PSAs) have been developed, evidence-based information on their diagnostic performance for IPFDs and comparative studies are currently lacking. The ISTH recommended performing PSAs as first-line tests in IPFDs, despite a previous survey indicating that over half of specialized laboratories worldwide consider PSAs as second-line tests.²⁴

Lumiaggregometry

Light transmission lumiaggregometry allows for the continuous measurement of platelet ATP release upon agonist stimulation, simultaneously assessing both secretion and aggregation in PRP. It is the most frequently used test, despite its cost and uncertainties regarding sensitivity and specificity with weak agonists.²⁴

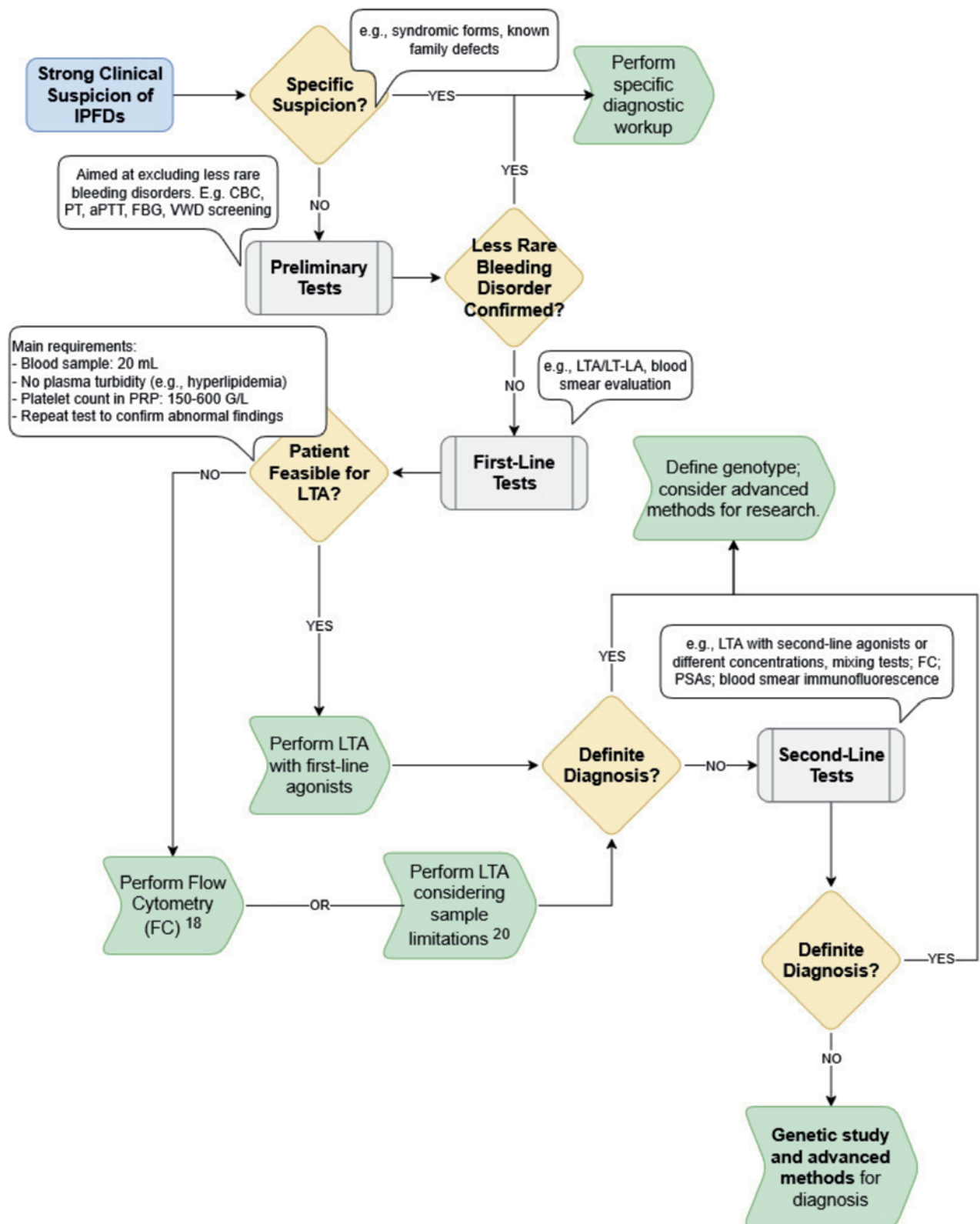


Figure 1. Proposed diagnostic algorithm for inherited platelet function disorders (adapted from Gresele *et al.*, 2015, 2016).^{16,17} aPTT: Activated Partial Thromboplastin Time. CBC: Complete Blood Count. FBG: Fibrinogen. FC: Flow Cytometry. IPFDs: Inherited Platelet Function Disorders. LTA: Light Transmission Aggregometry. LT-LA: Light Transmission Lumiaggregometry. PRP: Platelet-Rich Plasma. PSAs: Platelet Secretion Assays. PT: Prothrombin Time. VWD: von Willebrand Disease.

Flow cytometry

Flow cytometry analysis (FCM) can be used to investigate platelet phenotype and platelet activation parameters; in detail, it is useful to study: surface platelet glycoprotein deficiencies; platelet aggregation or secretion; platelet procoagulant function.²⁵ If platelet aggregation tests do not allow a final diagnosis of an IPFD, FCM is recommended to specify the diagnosis.¹⁶ Platelets are labelled with monoclonal fluorochrome-conjugated antibodies directed against platelet-specific surface antigens such as CD41/CD61 (fibrinogen receptor integrin $\alpha\text{IIb}\beta_3$ /GPIIb/IIIa) or CD42a (subunit GPIX of von Willebrand factor receptor complex GPIb/V/IX) in combination with gating by size (forward scatter/FSC) and granularity (side scatter/SSC); platelet agonists (*e.g.*, TRAP-6, ADP) used for aggregation tests can also be employed in FCM.¹⁸ Depending on the assay specifications, platelet phenotype and function analysis are performed in whole blood (WB) or platelet-rich plasma (PRP); great advantages of FCM are represented by the small amount of blood requested (*e.g.* 1.8 mL), that makes it feasible also for pediatric patients, and the reliability of this test even in presence of thrombocytopenia. Platelet volume can instead alter results, with higher glycoprotein expression reported in macrothrombocytopenia, in which larger platelets may produce apparently increased glycoprotein expression because of their greater surface area, potentially generating a misleading interpretation if absolute MFI values are considered in isolation: to mitigate this limitation, the MFI of the glycoprotein under investigation may be expressed as a relative ratio to another platelet glycoprotein, such as GPIIb/IIIa (CD41 or CD61), used as an internal platelet reference; this approach has

been applied to normalize the expression of GPIb α /GPIb-IX-V and may help distinguish a true relative deficiency from an apparent increase related to platelet size.^{18,26-29} Weak points of FCM are: availability restriction to specialized centers; relative time-consuming nature; moderate susceptibility to sample handling and preanalytical variables.³⁰

Immunofluorescence microscopy on the blood smear

The principle of the test is the visualization, on a blood smear, of alterations in the distribution of platelet proteins by using monoclonal antibodies. Immunofluorescence microscopy (IFM) can be applied to identify deficiencies in membrane proteins, altered distribution of cytoskeletal proteins, alpha and delta granules defects.¹⁸ A retrospective study on 3217 IPFD patients demonstrated a prediction power of IFM in about 30% of the cases.³¹ IFM was successively validated, by comparison with genetic testing, for nine types of IPFD: MYH9-related disease, Bernard-Soulier Syndrome (classical and monoallelic), Glanzmann Thromboasthenia (types 1 and 2), TUBB1-related thrombocytopenia, GF11B defect, filamin A-related thrombocytopenia, Delta-storage pool disease, WAS/X-linked thrombocytopenia.³² IFM advantages include: relatively low costs, not excessively time-consume and the possibility to perform on shipped samples. The reproducibility of this approach has recently been assessed in a blinded interlaboratory validation study promoted by the ISTH SSC.³³ Native air-dried blood smears from healthy controls and patients with genetically confirmed IPDs were distributed to seven laboratories, which used a shared antibody panel and formulated diagnostic predictions

Table 2. Proposed light transmission aggregometry first- and second-line agonists in different guidelines with the concentration indicated by the International Society on Thrombosis and Haemostasis.²¹

Concentration	
First-line agonists*	
Adenosine diphosphate	2 μM initial
Epinephrine/adrenaline	5 μM initial
Collagen	2 $\mu\text{g/mL}$ initial horm collagen (equine tendon)
Arachidonic acid	1 mM initial
Ristocetin	1.2 mg/mL initial
	If normal: 0.5 to 0.7 mg/mL
	If absent: 2 mg/mL
Second-line agonists**	
Thromboxane A2 mimetic U46619	1 μM
Thrombin-receptor activating peptides	10 μM
Gamma thrombin [#]	50 to 200 ng/mL
Calcium ionophore a23187 [#]	1.25 to 10 μM
Collagen-related peptides [#]	10 to 1000 ng/mL
Convulxin [#]	1 to 1000 ng/mL

*Usually include; **Used in ample panels after the first test, can include. [#]Concentration non stated by International Society on Thrombosis and Haemostasis, reported only by British Society for Haematology Committee.

Table 3. Agglutination after addition of low dose ristocetin.

Test result	Type 2B von Willebrand disease	Platelet-type von Willebrand disease
Healthy control plasma + patient platelets	No	Yes
Patient plasma + healthy control platelets	Yes	No

solely on the basis of immunofluorescence findings. All laboratories correctly identified MYH9-related disease, Bernard–Soulier syndrome, Glanzmann thrombasthenia, and GFI1B-related thrombocytopenia; six of seven laboratories correctly recognized TUBB1-related disorder and quantitative δ -storage pool disorder, whereas GATA1-related thrombocytopenia was correctly identified by five laboratories. These findings support the reproducibility of immunofluorescence microscopy for selected IPDs, while also indicating that standardized procedures, appropriate training, and external quality assessment remain important for broader implementation.

Advanced methods

Several advanced methods can be employed to further investigate platelet function and thrombus formation, particularly when prior tests yield inconclusive results. These tests can advance our understanding of IPFDs physiopathology but can only be performed in highly specialized research laboratories.¹⁸

Genetic diagnosis

Over the past decade the genetic basis of numerous hereditary thrombocytopenias and platelet function disorders has been elucidated. Molecular genetic testing is indicated to confirm affected individuals within families, particularly when phenotypic platelet testing is impractical and for prenatal diagnosis. In 2015 the American College of Medical Genetics and Genomics and the Association for Molecular Pathology published guidelines for the interpretation of genetic variants.³⁴ To date, approximately 50 genetic causes of IPFDs have been identified.³⁵ The genetic analysis has been particularly useful for diagnosing biallelic Bernard–Soulier syndrome (BSS), Glanzmann thrombasthenia (GT), and Gray Platelet Syndrome, where the number of candidate genes is limited and accessible databases allow confirmation of pathogenic nucleotide variations. However, only a small proportion of patients with suspected IPFDs currently benefit from the substantial advances in this field. Diagnosis still requires specialized laboratory techniques available primarily in reference centers. In the last decade, the application of NGS, including whole exome sequencing, and the use of gene panels for rapid testing have greatly accelerated the discovery of causal genes and expanded the list of variants in more common disorders.^{5,6,36} Current challenges include the integration of NGS into first-line screening and improving the prediction of bleeding risk and therapeutic management. Careful phenotyping combined with NGS has led to the identification of numerous novel genes responsible for inherited thrombocytopenia, with or without large platelets or associated platelet function defects.^{5,6,37} Diagnosis is established when a genetic mutation is identified, standard laboratory tests (such as flow cytometry) confirm the disorder, or when the patient's clinical characteristics are consistent with descriptions reported in the literature. Below we report some examples of the best characterized IPFDs:

BSS is an autosomal recessive disorder caused by pathogenic variants in the GPIBA, GPIBB, and GP9 genes. No clear genotype–phenotype correlations have been described, and genetic testing is not routinely performed, except for the Bolzano variant in the context of prenatal diagnosis.³⁶

GT is an autosomal recessive inherited disorder. Affected in-

dividuals harbor homozygous or compound heterozygous biallelic pathogenic variants in the *ITGA2B* (30 exons) or *ITGB3* (15 exons) genes, located on chromosomes 17q21.31 and 17q21.32, respectively. In homozygous cases, the same pathogenic variant is present on both alleles, whereas in compound heterozygous cases, two different pathogenic variants are present, one on each allele. Although simple heterozygosity is relatively common in the general population, homozygosity or compound heterozygosity occurs more frequently in consanguineous settings. To date, at least 126 pathogenic variants have been reported, including 68 in *ITGA2B* and 58 in *ITGB3*. These variants comprise missense mutations (52%), nucleotide insertions and deletions (28%), nonsense mutations (14%), and splice-site variants (6%).^{36,38,39}

Storage Pool Disease (SPD) may have autosomal dominant or recessive inheritance and represents a genetically heterogeneous group. The molecular basis of isolated inherited δ -SPD remains largely unknown. NGS approaches are expected to facilitate the identification of causative genes. SPD can also be associated with congenital syndromes such as Hermansky–Pudlak and Chediak–Higashi syndromes.⁴⁰

Aspirin-like Platelet Function Defects have been reported as autosomal recessive in one study, with variants in *PTGS1* identified in a cohort of 15 cases.⁴¹ Two individuals carried rare variants in *PTGS1*, the gene encoding COX-1, which catalyzes the conversion of arachidonic acid to prostaglandin H₂. One case presented a homozygous missense variant (p.Trp322Ser) with a Combined Annotation Dependent Depletion (CADD) score of 31.0. Additional studies reported autosomal dominant inheritance of *PTGS1* variants acting as modifiers in a family with hemophilia A and platelet function disorder and rare heterozygous variants in two individuals with bleeding tendency.^{42–44}

Platelet-type von Willebrand disease exhibits autosomal dominant inheritance due to a point mutation (A→G, codon 239) in the GPIBA gene. Because platelet aggregometry results are often ambiguous, genetic confirmation of the mutation is typically required to establish the diagnosis.^{38,45,46}

Chediak–Higashi Syndrome is an autosomal recessive disorder caused by mutations in *LYST* (lysosomal trafficking regulator; also known as *CHS1*). Molecular diagnosis is confirmed by the identification of biallelic pathogenic or likely pathogenic variants in *LYST*.^{47,48} The *LYST* mRNA (NM_000081) contains 53 exons encoding a 3801-amino-acid protein (NP_000072). *LYST* is widely expressed, with higher levels in certain tissues. Its carboxy-terminal region contains three key domains: Pleckstrin-homology, Beige and Chediak–Higashi (BEACH), and WD-40 repeats, which are primarily involved in vesicular trafficking. Most patients harbor private mutations, including nonsense, missense, frameshift, and splice-site variants, distributed throughout the gene, particularly in ARM/HEAT, BEACH, and WD-40 domains. A recent study identified 11 novel pathogenic *LYST* variants, totaling 147 variants: 61 frameshift (41%), 44 nonsense (30%), 23 missense (16%), 13 splice site or small deletions (9%), 5 in-frame (3%), and 1 start-loss variant (1%). Notably, a genotype–phenotype correlation was observed: individuals with at least one missense or in-frame variant generally exhibit milder disease, whereas those with two nonsense or frameshift variants tend to have more severe phenotypes.⁴⁸

Hermansky–Pudlak syndrome (HPS) is inherited in an autosomal recessive manner. Once the pathogenic variants causing HPS are identified in an affected family member, carrier testing

for at-risk relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible. Homozygosity for HPS1 c.1472_1487dup16 is found in approximately 80% of affected individuals of Puerto Rican ancestry. HPS3 deletion/duplication analysis for the common 3.9-kb deletion (g.339_4260del3904) is found in 20% of individuals of central Puerto Rican ancestry. The HPS3 splice site variant c.1163+1G>A occurs in individuals of Ashkenazi Jewish ancestry, while the HPS6 frameshift variant c.1065dupG is found in individuals of Israeli Bedouin descent.⁴⁹

Gray platelet syndrome (GPS) is inherited in an autosomal recessive manner (autosomal dominant inheritance has been reported in only 1 family). Siblings of an affected patient are at 25 % risk for GPS, while the risk for offspring of a GPS patient is not significantly higher than for the general population. It is caused by mutations in the *NBEAL2* gene. Absence or marked reduction of alpha-granules in platelets underlies the disorder. In addition to the classical hematologic manifestations, immune dysregulation, including autoimmune disease and recurrent infections, has also been described among the manifestations of GPS.⁵⁰⁻⁵²

Treatment

Despite the heterogeneity of IPFDs, prophylactic and therapeutic options remain relatively limited. Prophylactic options include educational and preventive measures to minimize risk of bleeding (avoiding activities with risk of trauma, dental hygiene, no platelet function-interfering drugs, such as aspirin, clopidogrel, non-steroidal anti-inflammatory drugs, necessity of immunization against hepatitis viruses, inclusion in registries, and regular follow-up by a specialized hematology service.⁵³ The main topical measures are compression with gauze soaked with tranexamic acid, fibrin sealants, splints for dental extractions and packing for nose bleeds. Antifibrinolytic agents, such as ϵ -aminocaproic acid and tranexamic acid, are quite effective in controlling epistaxis, gingival bleeding, and menorrhagia, as well as in preventing bleeding during minor surgical procedures. Tranexamic acid is generally administered at a dose of 15-25 mg/kg every 6-8 hours, while ϵ -aminocaproic acid can be administered at a dose of 50-60 mg/kg every 4-6 hours. They can be administered either as monotherapy or in combination with desmopressin, platelet transfusions, or recombinant activated factor VII (rFVIIa).⁵³ Desmopressin, which is approved for the management of VWD and hemophilia A, has also demonstrated efficacy in both the treatment and prophylaxis of bleeding episodes in select patients with IPFDs. Desmopressin is generally administered at a dose of 0.3 μ g/kg, usually 30-60 minutes before a procedure, and may be repeated every 12-24 hours when necessary.⁵⁴ Recombinant activated factor VII acts by increasing thrombin generation, enhancing platelet adhesion to the extracellular matrix and promoting platelet aggregation. It was approved by the FDA in 2014 for GT and particularly in patients refractory to platelet concentrates. In patients with GT, rFVIIa is generally administered at a dose of 90 μ g/kg every 2-6 hours until hemostasis is achieved.⁵⁵ Due to the risks of alloimmunization, anti-Rh immunization, infections, and allergic reactions, platelet transfusion should be reserved for cases in which local measures or antifibrinolytic agents are ineffective, for major surgical procedures or childbirth. Donors

should be HLA-matched to prevent alloimmunization.^{56,57} Allo-genic hematopoietic stem cell transplantation (allo-HSCT) has proven successful in patients with very severe bleeding symptoms or with high risk of transformation to bone marrow aplasia or acute leukemia. Considering the high morbidity and mortality, the risk-benefit analysis of performing allo-HSCT must be considered on an individualized basis.⁵⁸ Excessive bleeding at surgery is a feared complication of IPFDs and the risk is determined by the type of platelet disorder and eventually the severity of thrombocytopenia, bleeding history, type of surgery. It has been observed that the risk of bleeding is higher in IPFDs than in thrombocytopenias; specifically, biallelic BSS and GT patients carry the highest risk. The risk is empirically prevented or treated with platelet transfusions, antifibrinolytic agents, desmopressin (in patients at lower bleeding risk), or rFVIIa.⁵⁹

Gynecological and obstetric management

Menometrorrhagia represents a frequent and clinically relevant complication in women with IPFDs, significantly impairing quality of life and often leading to iron deficiency anemia. Management should be individualized and multidisciplinary, taking into account bleeding severity, reproductive goals, and the underlying platelet defect. First-line therapeutic options include antifibrinolytic agents and hormonal therapies, including combined oral contraceptives, progestin-only regimens, and the levonorgestrel-releasing intrauterine system, which have demonstrated efficacy in reducing menstrual blood loss. However, the use of hormonal therapy may hinder conception and complicate pregnancy planning, particularly in women actively seeking fertility. IPFDs are associated with significant risk of primary and secondary PPH, and wound hematoma. Women known to have a platelet disorder should receive pre-pregnancy counselling from a multidisciplinary team with expertise in caring for IPFDs patients. Women should be informed of their risk before becoming pregnant.⁶⁰ Peripartum hemostatic management should be guided by assessment of the individual phenotype. Patients with a bleeding history should be given a platelet transfusion prophylactically at delivery or before caesarean section, in combination with tranexamic acid. Tranexamic acid should be given at the onset of labor and continued regularly through the postpartum period until lochia is minimal. Desmopressin has variable efficacy and is unlikely to be useful as sole therapy in IPFDs. Central neuraxial anesthesia should be avoided. In patients with GT, rFVIIa could be given prophylactically, at delivery, for patients with a history of bleeding. One of the main risks associated with platelet transfusion is alloimmunization. Maternal anti- α IIb β 3 IgG antibodies may cross the placenta, leading to adverse fetal and neonatal outcomes, including thrombocytopenia, bleeding, and death.⁶¹⁻⁶³

Future therapeutic perspectives

As previously highlighted, IPFDs currently lack long-term prophylactic treatment options. Consequently, patients experience recurrent bleeding episodes, which are managed acutely.

In recent years, novel therapeutic strategies have been developed, including HMB-001, a subcutaneously bispecific antibody that binds and stabilizes endogenous factor VIIa with one antibody arm and binds to TLT-1 on activated platelets with the other arm.⁶⁴ This allows the accumulation of endogenous factor VIIa in the body, recruitment of factor VIIa directly to the sur-

face of the activated platelets, where it is known to facilitate hemostatic plug formation. Study results indicate that HMB-001 has the potential to offer subcutaneous prophylactic treatment to prevent bleeds in people with GT and other inherited bleeding disorders, with a low-frequency dosing regimen. Interim pharmacokinetic data from the Phase 1/2 study of HMB-001 indicate a reduction of over 50% in treated bleeding episodes at all tested dose levels.⁶⁵ An additional therapeutic approach might be the use of TF pathway inhibitor (TFPI). TFPI is a multivalent Kunitz-type serine protease inhibitor that modulates coagulation through feedback inhibition of the TF-FVIIa complex, with a dependence on FXa; it also blocks early forms of the prothrombinase complex with partially cleaved FVa.⁶⁶ Concizumab is a humanized monoclonal antibody directed against the second Kunitz domain of TFPI, that by binding and thereby inhibiting FXa, abolishes the inhibitory effect of TFPI. This mechanism has been demonstrated to enhance thrombin generation in hemophilia A and B patients.⁶⁷ Concizumab could have a potential role in prophylaxis for patients with GT. Dubut *et al.* have provided in vitro proof-of-concept data demonstrating that TFPI inhibition improves hemostasis in GT.⁶⁸ If corroborated by clinical evidence, concizumab may represent a prophylactic option to reduce bleeding episodes in GT patients.

Conclusions

IPFDs are a heterogeneous group of diseases, with different phenotype. As we reported in this review the diagnosis is complex and necessitates of many different tests which not always are performed in a single institution; therefore, we underscore the necessity to organize a laboratory network for a global evaluation of samples, leading to a correct diagnosis. IPFDs treatment is challenging too, since there are few robust therapy choices. Although promising results emerge from experimental therapies, right now therapies consist of conservative measures, platelet concentrates, tranexamic acid and rFVIIa. It is also important to highlight the fundamental role of a multidisciplinary approach in such rare diseases.

With this work we aimed to focus on IPFDs which are *neglected diseases* to improve the management of affected patients.

References

1. Sánchez-Fuentes A, Pérez-Botero J, Bastida JM, et al. Diagnosis of inherited platelet disorders: clinical evaluation and functional and molecular assays. *Biomolecules* 2025;15:846.
2. Nurden AT, Nurden P. Congenital platelet disorders and understanding of platelet function. *Br J Haematol* 2014;165:165-78.
3. Simon D, Kunicki T, Nugent D. Platelet function defects. *Haemophilia* 2008;14:1240-9.
4. Nurden AT, Freson K, Seligsohn U. Inherited platelet disorders. *Haemophilia* 2012;18:154-60.
5. MacLachlan A, Watson SP, Morgan NV. Inherited platelet disorders: insight from platelet genomics using next-generation sequencing. *Platelets* 2017;28:14-9.
6. Leo VC, Morgan NV, Bem D, et al. Use of next-generation sequencing and candidate gene analysis to identify underlying defects in patients with inherited platelet function disorders. *J Thromb Haemost* 2015;13:643-50.
7. Bury L, Falcinelli E, Gresele P. Qualitative disorders of platelet function. In: Greer JP, Arber DA, Glader B, et al, eds. *Wintrobe's Clinical Hematology*. 15th ed. Philadelphia: Wolters Kluwer; 2023. p. 1182-201.
8. Palma-Barqueros V, Revilla N, Sánchez A, et al. Inherited platelet disorders: an updated overview. *Int J Mol Sci* 2021;22:4521.
9. Rodeghiero F, Tosetto A, Abshire T, et al. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. *J Thromb Haemost* 2010;8:2063-5.
10. Gresele P, Orsini S, Noris P, et al. Validation of the ISTH/SSC bleeding assessment tool for inherited platelet disorders: a communication from the Platelet Physiology SSC. *J Thromb Haemost* 2020;18:732-9.
11. Gresele P, Orsini S, Noris P, et al. The ISTH bleeding assessment tool as predictor of bleeding events in inherited platelet disorders: communication from the ISTH SSC Subcommittee on Platelet Physiology. *J Thromb Haemost* 2021;19:1364-71.
12. Alhaj D, Hagedorn N, Cuntz F, et al. ISTH bleeding assessment tool and platelet function analyzer in children with mild inherited platelet function disorders. *Eur J Haematol* 2024;113:54-65.
13. Bowman M, Riddel J, Rand ML, et al. Evaluation of the diagnostic utility for von Willebrand disease of a pediatric bleeding questionnaire. *J Thromb Haemost* 2009;7:1418-21.
14. Biss TT, Blanchette VS, Clark DS, et al. Use of a quantitative pediatric bleeding questionnaire to assess mucocutaneous bleeding symptoms in children with a platelet function disorder. *J Thromb Haemost* 2010;8:1416-9.
15. Gresele P, Falcinelli E, Bury L. Laboratory diagnosis of clinically relevant platelet function disorders. *Int J Lab Hematol* 2018;40:34-45.
16. Gresele P, Subcommittee on Platelet Physiology. Diagnosis of inherited platelet function disorders: guidance from the SSC of the ISTH. *J Thromb Haemost* 2015;13:314-22.
17. Gresele P, Bury L, Falcinelli E. Inherited platelet function disorders: algorithms for phenotypic and genetic investigation. *Semin Thromb Hemost* 2016;42:292-305.
18. Hoepner G, Althaus K, Müller J, et al. The diagnostic assessment of inherited platelet function defects—part 1: an overview of the diagnostic approach and laboratory methods. *Hämostaseologie* 2025;45:229-42.
19. Gresele P, Falcinelli E, Bury L. Investigation of bleeding disorders: when and how should we test platelet functions? *Hämostaseologie* 2025;45:335-46.
20. Gomez K, Anderson J, Baker P, et al. Clinical and laboratory diagnosis of heritable platelet disorders in adults and children: a British Society for Haematology guideline. *Br J Haematol* 2021;195:46-72.
21. Stépanian A, Fischer F, Flaujac C, et al. Light transmission aggregometry for platelet function testing: position paper on current recommendations and French proposals for accreditation. *Platelets* 2024;35:2427745.
22. Hayward CPM, Harrison P, Cattaneo M, et al. Platelet function analyzer (PFA)-100 closure time in the evaluation of platelet disorders and platelet function. *J Thromb Haemost* 2006;4:312-9.

23. Alessi MC, Coxon C, Ibrahim-Kosta M, et al. Multicenter evaluation of light transmission platelet aggregation reagents: communication from the ISTH SSC Subcommittee on Platelet Physiology. *J Thromb Haemost* 2023;21:2596-610.
24. Mezzano D, Harrison P, Frelinger AL, et al. Expert opinion on the use of platelet secretion assay for the diagnosis of inherited platelet function disorders: communication from the ISTH SSC Subcommittee on Platelet Physiology. *J Thromb Haemost* 2022;20:2127-35.
25. Bourguignon A, Tasneem S, Hayward CPM. Screening and diagnosis of inherited platelet disorders. *Crit Rev Clin Lab Sci* 2022;59:405-44.
26. Perez Botero J, Di Paola J. Diagnostic approach to the patient with a suspected inherited platelet disorder: who and how to test. *J Thromb Haemost* 2021;19:2127-36.
27. Vettore S, Scandellari R, Moro S, et al. Novel point mutation in a leucine-rich repeat of the GPIIb α chain of the platelet von Willebrand factor receptor, GPIIb/IX/V, resulting in an inherited dominant form of Bernard-Soulier syndrome affecting two unrelated families: the N41H variant. *Haematologica* 2008;93:1743-7.
28. Leinøe E, Brønns N, Rasmussen AØ, et al. The Copenhagen founder variant GPIIbA c.58T>G is the most frequent cause of inherited thrombocytopenia in Denmark. *J Thromb Haemost* 2021;19:2884-92.
29. Savoia A, Pastore A, De Rocco D, et al. Autosomal dominant macrothrombocytopenia in Italy is most frequently a type of heterozygous Bernard-Soulier syndrome. *Blood* 2001;97:1330-5.
30. Frelinger AL 3rd, Rivera J, Connor DE, et al. Consensus recommendations on flow cytometry for the assessment of inherited and acquired disorders of platelet number and function: communication from the ISTH SSC Subcommittee on Platelet Physiology. *J Thromb Haemost* 2021;19:3193-202.
31. Zaninetti C, Greinacher A. Diagnosis of inherited platelet disorders on a blood smear. *J Clin Med* 2020;9:539.
32. Zaninetti C, Leinøe E, Lozano ML, et al. Validation of immunofluorescence analysis of blood smears in patients with inherited platelet disorders. *J Thromb Haemost* 2023;21:1010-9.
33. Zaninetti C, Bury L, Bozzi V, et al. Interlaboratory exercise on the use of immunofluorescence microscopy on the blood smear for recognizing inherited platelet disorders: communication from the ISTH SSC Subcommittee on Platelets in Health and Disease. *J Thromb Haemost* 2026;24:1923-32.
34. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405-24.
35. Greinacher A, Pecci A, Kunishima S, et al. Diagnosis of inherited platelet disorders on a blood smear: a tool to facilitate worldwide diagnosis of platelet disorders. *J Thromb Haemost* 2017;15:1511-21.
36. Perez Botero J, Lozano ML, Rivera J, et al. Glanzmann thrombasthenia: genetic basis and clinical correlates. *Haematologica* 2020;105:888-94.
37. Nurden AT, Nurden P. Inherited thrombocytopenias: history, advances and perspectives. *Haematologica* 2020;105:2004-19.
38. Carubbi C, Masselli E, Nouvenne A, et al. Laboratory diagnostics of inherited platelet disorders. *Clin Chem Lab Med* 2014;52:1091-106.
39. Althaus K, Hoepner G, Zieger B, et al. The diagnostic assessment of platelet function defects—part 2: update on platelet disorders. *Hämostaseologie* 2025;45:243-53.
40. Masliah-Planchon J, Darnige L, Bellucci S. Molecular determinants of platelet delta storage pool deficiencies: an update. *Br J Haematol* 2013;160:5-11.
41. Sivapalaratnam S. Congenital aspirin-like defect as a result of autosomal recessive variants in PTGS1. *Blood* 2018;132:1156.
42. Nance D, Campbell RA, Rowley JW, et al. Combined variants in factor VIII and prostaglandin synthase-1 amplify hemorrhage severity across three generations of descendants. *J Thromb Haemost* 2016;14:2230-40.
43. Bastida JM, Del Rey M, Lozano ML, et al. Design and application of a 23-gene panel by next-generation sequencing for inherited coagulation bleeding disorders. *Haemophilia* 2016;22:590-7.
44. Rolf N, Knoefler R, Bugert P, et al. Clinical and laboratory phenotypes associated with the aspirin-like defect: a study in 17 unrelated families. *Br J Haematol* 2009;144:416-24.
45. Russell SD, Roth GJ. Pseudo-von Willebrand disease: a mutation in the platelet glycoprotein Ib alpha gene associated with a hyperactive surface receptor. *Blood* 1993;81:1787-91.
46. Othman M, Gresle P. Guidance on the diagnosis and management of platelet-type von Willebrand disease: a communication from the Platelet Physiology Subcommittee of the ISTH. *J Thromb Haemost* 2020;18:1855-8.
47. Sharma P, Nicoli ER, Serra-Vinardell J, et al. Chediak-Higashi syndrome: a review of the past, present, and future. *Drug Discov Today Dis Models* 2020;31:31-6.
48. Morimoto M, Nicoli ER, Kuptanon C, et al. Spectrum of LYST mutations in Chediak-Higashi syndrome: a report of novel variants and a comprehensive review of the literature. *J Med Genet* 2024;61:212-23.
49. Tondi F, Cirsmaru RA, Conti C, et al. Hermansky-Pudlak syndrome: from molecular pathogenesis to targeted therapies. *IUBMB Life* 2025;77:e70025.
50. Glembotsky AC, De Luca G, Heller PG. A deep dive into the pathology of gray platelet syndrome: new insights on immune dysregulation. *J Blood Med* 2021;12:719-32.
51. Alamelu J, Liesner R. Modern management of severe platelet function disorders. *Br J Haematol* 2010;149:813-23.
52. Sims MC, Mayer L, Collins JH, et al. Novel manifestations of immune dysregulation and granule defects in gray platelet syndrome. *Blood* 2020;136:1956-67.
53. Al-Huniti A, Kahr WH. Inherited platelet disorders: diagnosis and management. *Transfus Med Rev* 2020;34:277-85.
54. Coppola A, Di Minno G. Desmopressin in inherited disorders of platelet function. *Haemophilia* 2008;14:31-9.
55. Poon MC. Clinical use of recombinant human activated factor VII in the prevention and treatment of bleeding episodes in patients with Glanzmann's thrombasthenia. *Vasc Health Risk Manag* 2007;3:655-64.
56. Grainger JD, Thachil J, Will AM. How we treat the platelet glycoprotein defects; Glanzmann thrombasthenia and Bernard-Soulier syndrome in children and adults. *Br J Haematol* 2018;182:621-32.

57. Lee RH, Kasthuri RS, Bergmeier W. Platelet transfusion for patients with platelet dysfunction: effectiveness, mechanisms, and unanswered questions. *Curr Opin Hematol* 2020;27:378-85.
58. Cid AR, Montesinos P, Sánchez-Guiu I, et al. Allogeneic hematopoietic cell transplantation in an adult patient with Glanzmann thrombasthenia. *Clin Case Rep* 2017;5:1887-90.
59. Orsini S, Noris P, Bury L, et al. Bleeding risk of surgery and its prevention in patients with inherited platelet disorders. *Haematologica* 2017;102:1192-203.
60. Bolton-Maggs PHB, Chalmers EA, Collins PW, et al. A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO. *Br J Haematol* 2006;135:603-33.
61. Harrison P, Mackie I, Mumford A, et al. Guidelines for the laboratory investigation of heritable disorders of platelet function. *Br J Haematol* 2011;155:30-44.
62. Peitsidis P, Datta T, Pafilis I, et al. Bernard-Soulier syndrome in pregnancy: a systematic review. *Haemophilia* 2010;16:584-91.
63. Siddiq S, Clark A, Mumford A. A systematic review of the management and outcomes of pregnancy in Glanzmann thrombasthenia. *Haemophilia* 2011;17:e855-69.
64. Gandhi PS, Zivkovic M, Østergaard H, et al. A bispecific antibody approach for the potential prophylactic treatment of inherited bleeding disorders. *Nat Cardiovasc Res* 2024;3:166-85.
65. Sivapalaratnam S, et al. A phase 1/2, first-in-human study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of HMB-001 in participants with Glanzmann thrombasthenia. *Blood* 2023;142:1225.
66. Chowdary P. Anti-tissue factor pathway inhibitor therapy: a novel approach to the treatment of haemophilia. *Int J Hematol* 2020;111:42-50.
67. Castaman G, Jimenez-Yuste V, Mahlangu J. Concizumab, a non-replacement therapy for persons with hemophilia with inhibitors. *J Clin Med* 2025;14:2961.
68. Dubut J, Goin V, Derray C, et al. Targeting tissue factor pathway inhibitor with concizumab to improve hemostasis in patients with Glanzmann thrombasthenia: an in vitro study. *J Thromb Haemost* 2024;22:2589-600.

Online supplementary material:

Supplementary Table S1. IPFDs clinical, genetic and laboratory features for defect type.