La diagnostica delle piastrinopatie congenite

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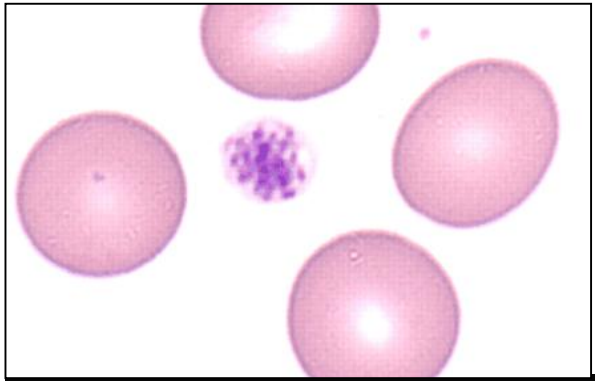
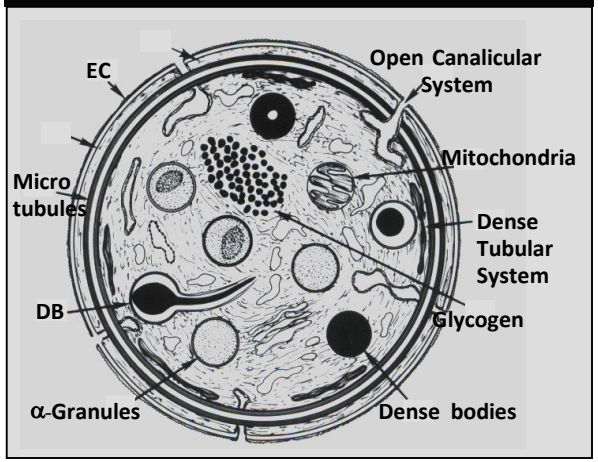
Platelets

- Thrombocytes
- Cell fragments circulating in blood (size: 1.5–3.0 µm)
- Shape: anuclear and discoid cell → spiny sphere when activated
- Life span: 9–10 days
- Crucial function in primary hemostasis leading to the formation of normal blood clots
- Total platelet mass: 10^{12}
- Bleeding disorders may derive from alterations in platelet number and/or functions





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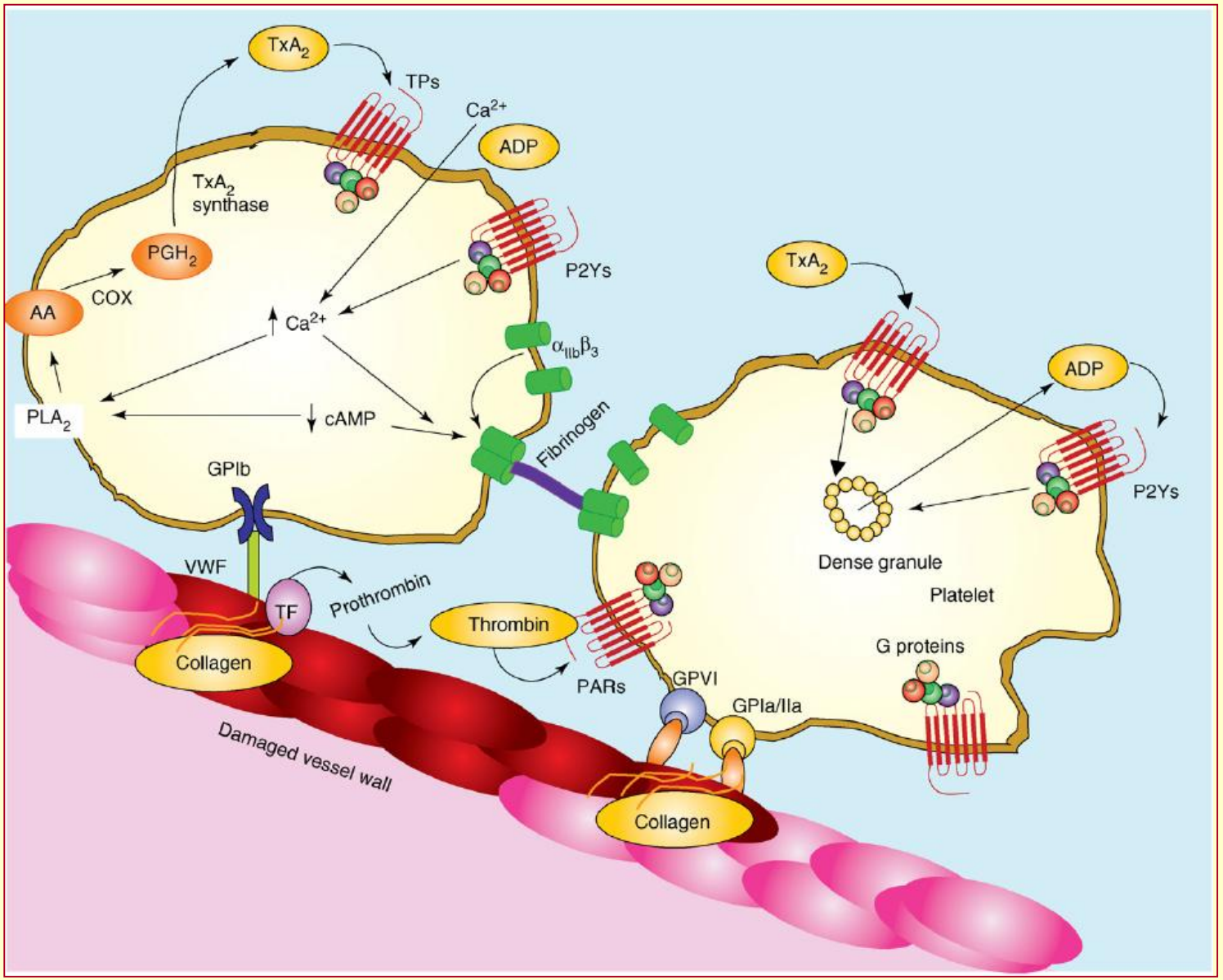
Platelet activation at a vascular wall damage area



Gresele P et al., TiPS 2008;29:352

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INHERITED PLATELET FUNCTION DISORDERS

- A heterogeneous group of rare congenital hemorrhagic disorders with normal (or reduced) platelet number and an altered platelet function
- Mucocutaneous bleeding diathesis of variable severity
- Large heterogeneity in terms of molecular/genetic defect (for several forms not yet identified)

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Diagnosis of suspected IPFD: **results of a worldwide survey**

- Many laboratories worldwide are involved in the diagnosis of IPFD
- Tests for IPFD represent a major committment these diagnostic laboratories (>14.000 patients studied each year)
- High variability in the diagnostic approaches
- In 40-60% of studied patients with confirmed platelet dysfunction, a diagnosis is not achieved despite demanding laboratory investigations

Gresele P et al, J Thromb Haemost 2014; 12:1562

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Diagnosis of suspected IPFD:
results of a worldwide survey

Conclusive informations

N. of patients/year with suspected inherited platelet function disorders	14451 (72 patients/center)
N. of cases explored with no real platelet defect	8676 of 14451 (60.04%)
N. of patients with identified known inherited platelet function disorder	3113 of 5775 (53.90%)
N. of patients who receive diagnosis at molecular level	502 of 5775 (8.70%)
N. of patients with undefined diagnosis although confirming a platelet function disorder	2233 of 5775 (34.10%)

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INHERITED PLATELET FUNCTION DISORDERS
A revised classification

1-ADHESIVE PROTEIN RECEPTOR DEFECTS

BSS, GT, PT-VWD, VCF, $\alpha_2\beta_1$, GPVI, GPIV

2-SOLUBLE AGONIST RECEPTOR DEFECTS

P_2Y_{12} receptor, TP receptor , α2 adrenergic receptor

3-DEFECT OF PLATELET GRANULE CONTENTS (isolated/syndromic)

α-granules, δ-granules, α+δ granules

4-DISORDERS OF SIGNALLING PATHWAYS

Gs platelet defect, Tx-synthase deficiency, $cPLA_2$, PKA, LADIII, CalDAG-GEFI

5-DEFECTS OF MEMBRANE PHOSPHOLIPIDS

Scott syndrome, Stormorken syndrome

6- DEFECTS OF TRANSCRIPTION FACTORS

FPD/AML/MDS, FLI1-related dense granule defect, Paris-Trousseau syndrome, GATA1

7- DEFECTS OF CYTOSKELETAL PROTEINS

Filaminopathy, WAS/XLT, Cytosolic adaptor protein (ADAP)

8- UNCLASSIFIED

SLFN14-related thrombocytopenia

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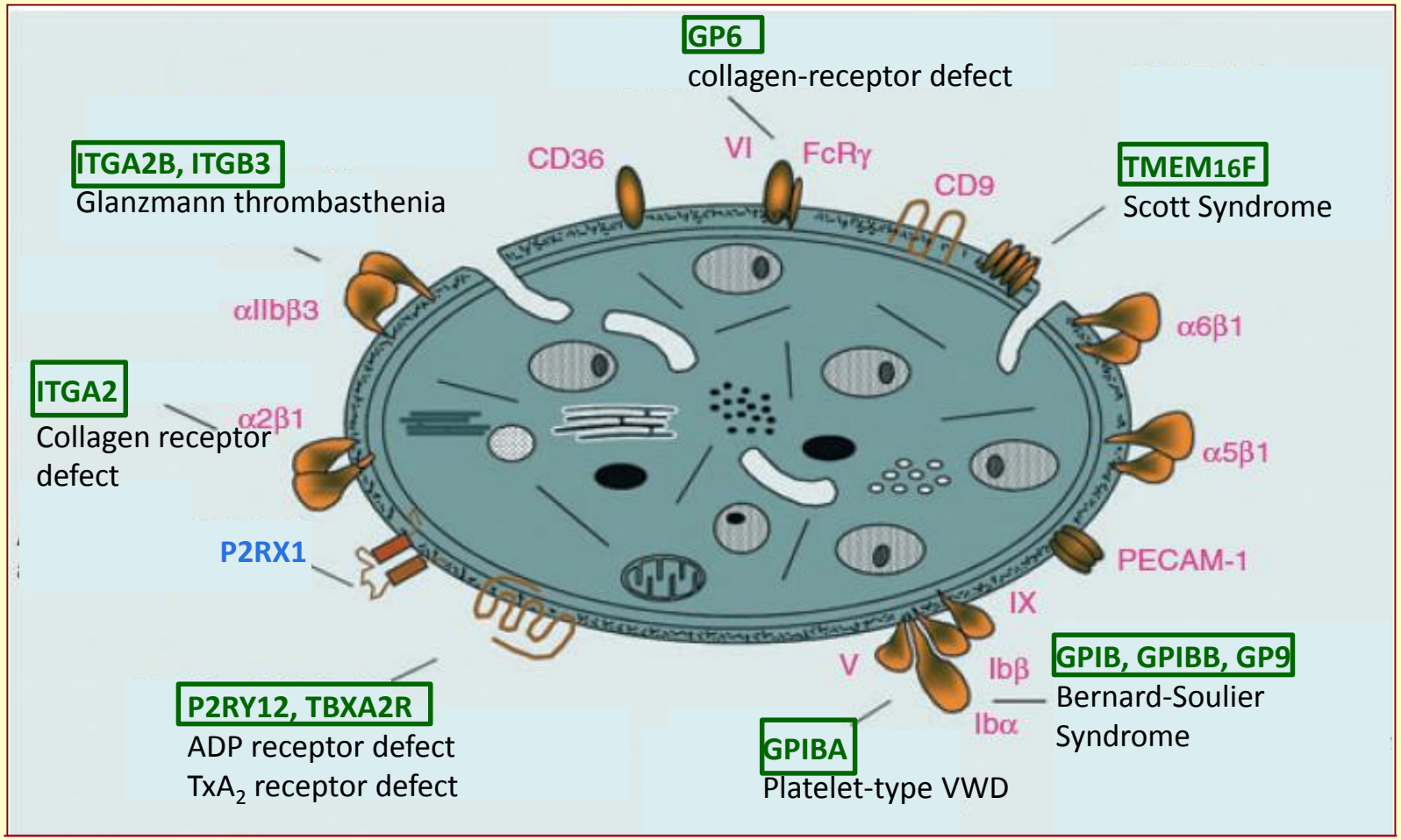
Gresele P, Bury L, Falcinelli E, Hämostaseologie 2016 - Epub

Inherited platelet function disorders due to surface defects



modified from Nurden P, Nurden AT. J Thromb Haemost. 2015;13:S2-9

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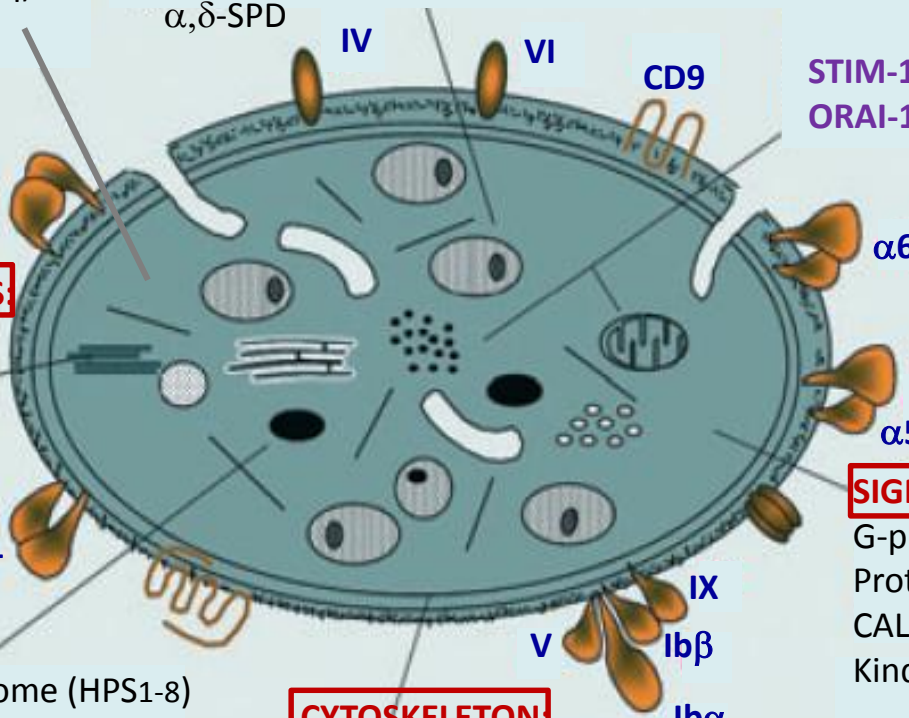
Inherited platelet function disorders due to defects of internal platelet components



TRANSCRIPTION FACTORS:
FPD/AML/MDS (RUNX-1)
FLI-1
Paris-Trousseau (del11q)
GATA-1

α-GRANULES:
Gray platelet syndrome (NBEAL2, GFI1B)
ARC syndrome (VPS33B)
Quebec platelet syndrome (PLAU duplication)
α,δ-SPD

STIM-1 (Stormorken
ORAI-1 syndrome)

SIGNALING PATHWAYS:
TxA2 synthase (TxAS)
Cyclooxygenase-1
Phospholipases

SIGNALING PATHWAYS:
G-proteins (Gαq-Gα1-Gs)
Protein kinases
CALDAG-GEFI (RASGRP2)
Kindlin-III (FERMT3)

DENSE GRANULES:
Hermansky-Pudlak syndrome (HPS1-8)
Chediak-Higashi syndrome (LYST)
Griscelli syndrome (MYO5A, RAB274, MLPH)
δ–SPD

CYTOSKELETON:
FLNA-related disorder
ADAP
Wiskott-Aldrich syndrome (WASP)

modified from Nurden P, Nurden AT. J Thromb Haemost. 2015;13:S2-9

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Platelet function assays

- **GLOBAL TESTS OF PLATELET FUNCTION**
  - Bleeding time
  - PFA-100®
  - Parallel-plate perfusion chambers

- **PLATELET AGGREGATION TESTS**
  - Light transmission aggregometry
  - Lumiaggregometry (secretion)
  - Impedance aggregometry
  - VerifyNow
  - Platelet Works
  - Others

- **PLATELET ACTIVATION INDUCED BY HIGH SHEAR STRESS**
  - Whole blood O'Brien filtration test
  - Cone and Plate(let) Analyzer

- **FLOW CYTOMETRY**

- **PLASMA SOLUBLE PLATELET ACTIVATION MARKERS**
  - β-TG, PF-4, sPsel, sCD40L,...

- **URINARY MARKERS OF PLATELET ACTIVATION**
  - 11-dehydro-thromboxane B2, urinary β-TG, …

modified from Harrison P, in Gresele P et al. Eds, 2008.
Platelets in Hematologic and Cardiovascular Disorders –Clinical Handbook – Cambridge University Press 2008.

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Applications of Platelet Function Assays

-Diagnosis of platelet function defects

-Detection of antiplatelet antibodies

-Detection of circulating activated platelets

-Study of platelet hyperreactivity

-Monitoring of antiplatelet therapy (and perioperative hemostasis)

-Evaluation of platelet banking (transfusion medicine)

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The skin bleeding time

ALTERED IN

- Thrombocytopenia
- Von Willebrand Disease
- Inherited Platelet Function Disorders
- Acquired Platelet Function Disorders
- Some Blood Clotting or Connective Tissue Disorders
- Drugs

ADVANTAGES

- It is the only diagnostic test assessing platelet function in vivo
- It is simple
- It is fast
- It is a besides test
- Does not imply sample manipulation
- It assesses platelet function in the presence of all the cellular components involved
- It assesses platelet function under flow conditions

DISADVANTAGES

- Low reproducibility
- Wide variation of the normal range
- Requires skilled technician
- It is strongly influenced by many variables (skin thickness, room temperature, venous pressure, position and orientation of the skin wound, patient cooperation, etc)
- It is invasive; it may leave scars

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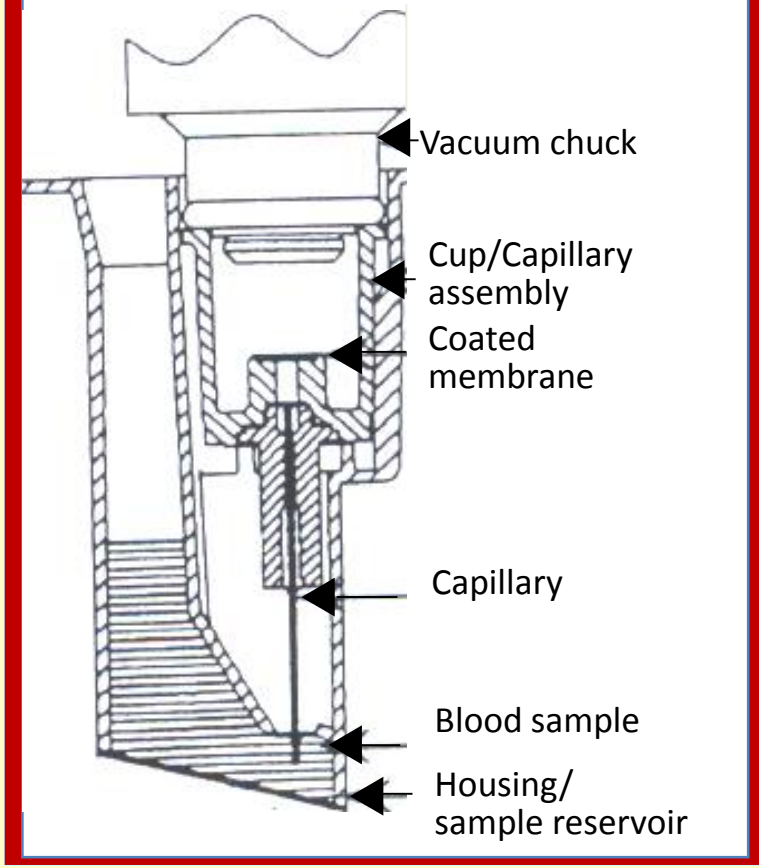
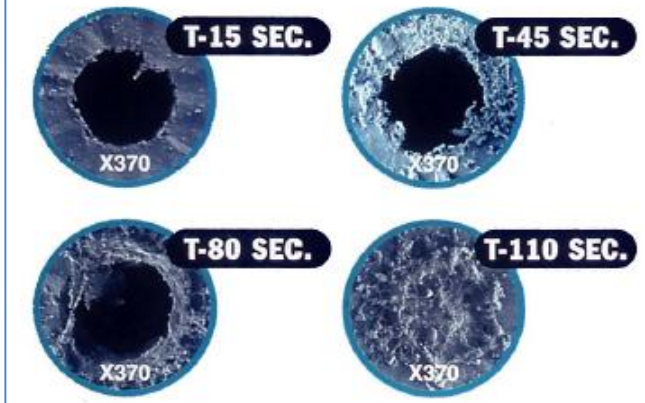
PFA-100® (200®)
Principle of the method



- 0.8 ml anticoagulated whole blood
- High shear rate (5-6000 s^{-1})
- Membrane: COLL/EPI; COLL/ADP; ADP/PGE_1

Membrane occlusion



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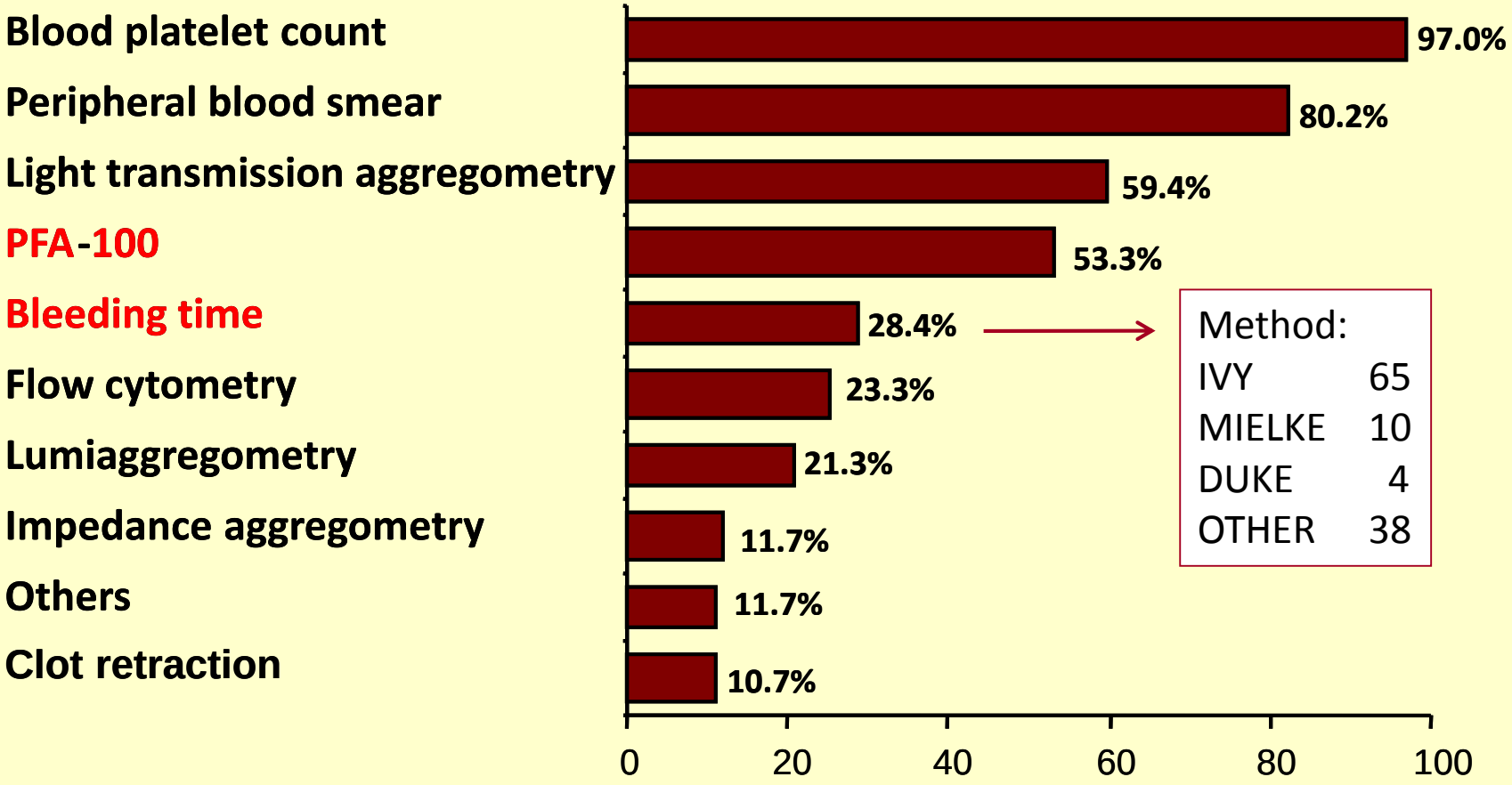
Diagnosis of suspected IPFD: results of a worldwide survey

What kind of first step (screening) tests do you perform in patients with a suspected inherited platelet function disorder?



N. of respondents: 197/202 (97.5%)

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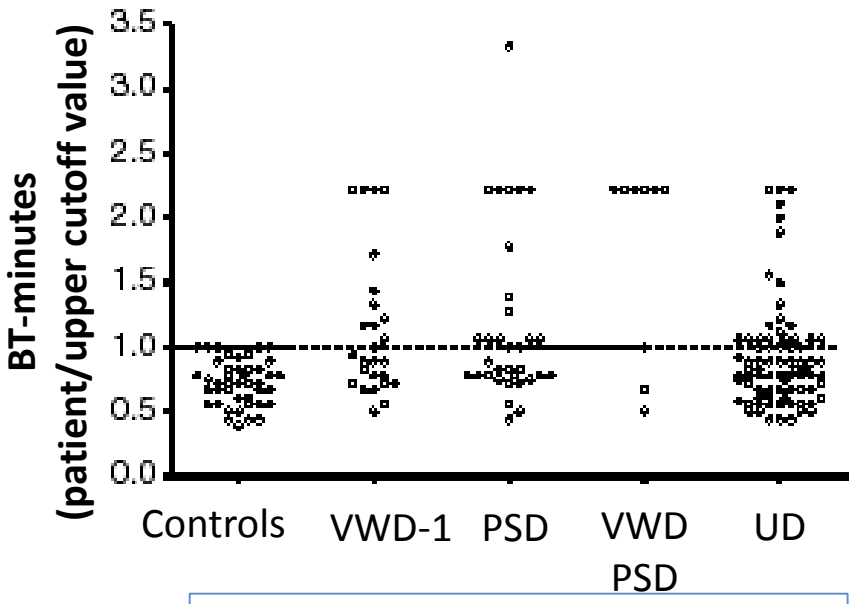
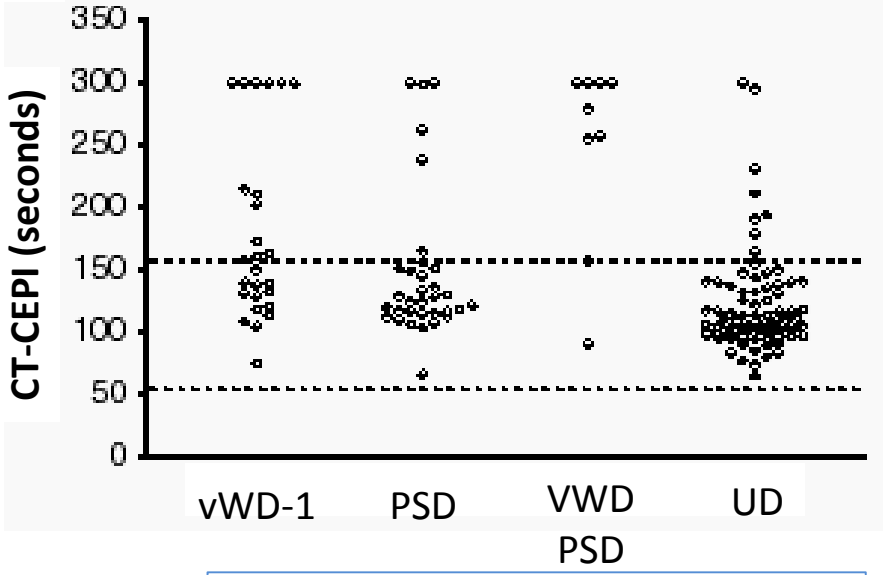
Gresele P et al., J Thromb Haemost 2014; 12:1562

Skin Bleeding Time and PFA-100® have low sensitivity to screen patients with hereditary, mucocutaneous hemorrhages



- Prolonged in 35.8% of all patients
- Prolonged in 43.0% of PSD



- Prolonged in 29.7% of all patients
- Prolonged in 24.0% of PSD

- 148 patients with unequivocal mucocutaneous bleeding and positive family history
- Low correlation coefficient between the two tests (0.51%)

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Quiroga T, J Thromb Haemost 2004, 2: 892

PFA-100® findings in congenital platelet disorders

	Total nr. of subjects	ADP-CT	EPI-CT
Disorders with normal platelet counts			
Glanzmann thrombasthenia	23	P	P
P2Y12 deficiency	4	N or P	N or P
Dense granule deficiency	30	N or P	N or P
Hermansky-Pudlak syndrome	44	N or P	N or P
Primary secretion defects	30	N	N or P
Disorders with reduced or normal platelet counts			
Bernard-Soulier syndrome	8	P	P
Wiskott-Aldrich syndrome	5	N or P	N or P
Hereditary macrothrombocytopenia MHY9-related	5	N	N or P

Sensitivity to platelet disorders ranged from 24 to 80%

"… test optional in the evaluation of platelet disorders and function…"

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Modified from Hayward CPM et al., J Thromb Haemost 2006, 4: 312.

Diagnosis of inherited platelet function disorders: guidance from the SSC of ISTH

- PFA-100® and Template Skin Bleeding Time: **not recommended** because of their poor diagnostic accuracy and low sensitivity (although still widely used by several laboratories as screening tests).

They may be used as optional test in single laboratories if a stringent cut off threshold is applied

(CP Hayward for the SSC Platelet Physiology, JTH 2006; 4:312-9
Gresele P for the SSC Platelet Physiology, JTH 2015;13:314-22)

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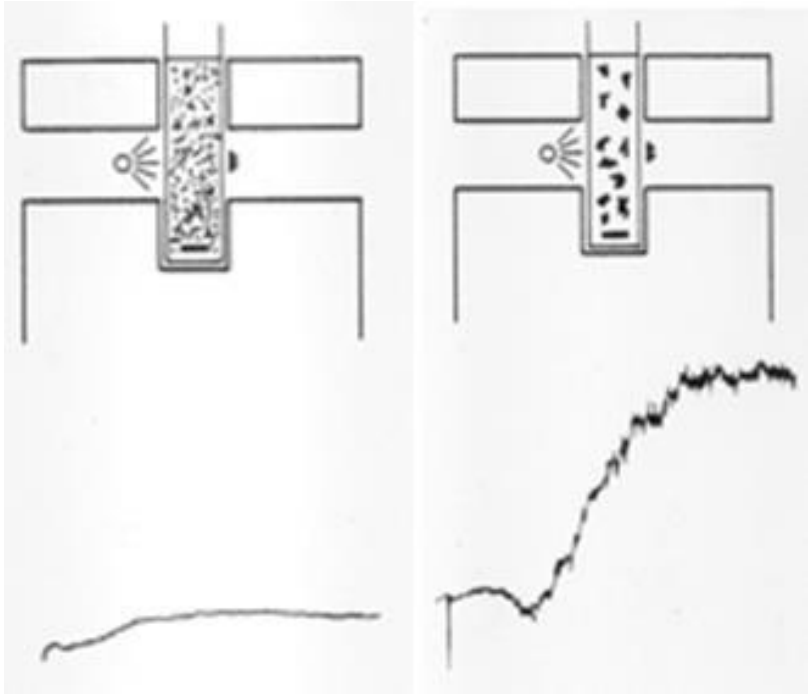
Light transmission aggregometry (LTA)



Basic principle:
to measure the increase of light transmission through a suspension of platelets during platelet clump formation

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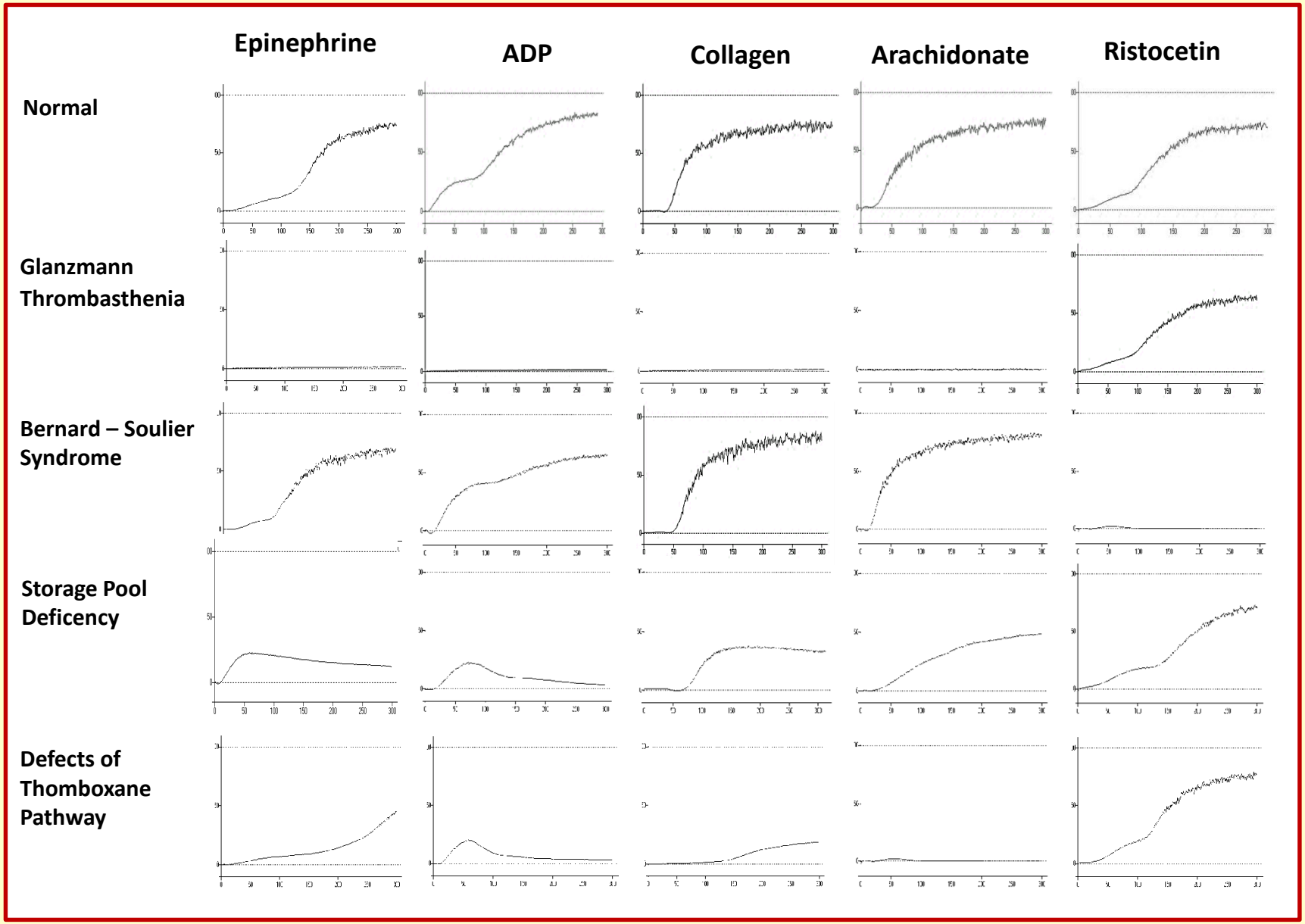
Diagnosis of inherited platelet function disorders by LTA



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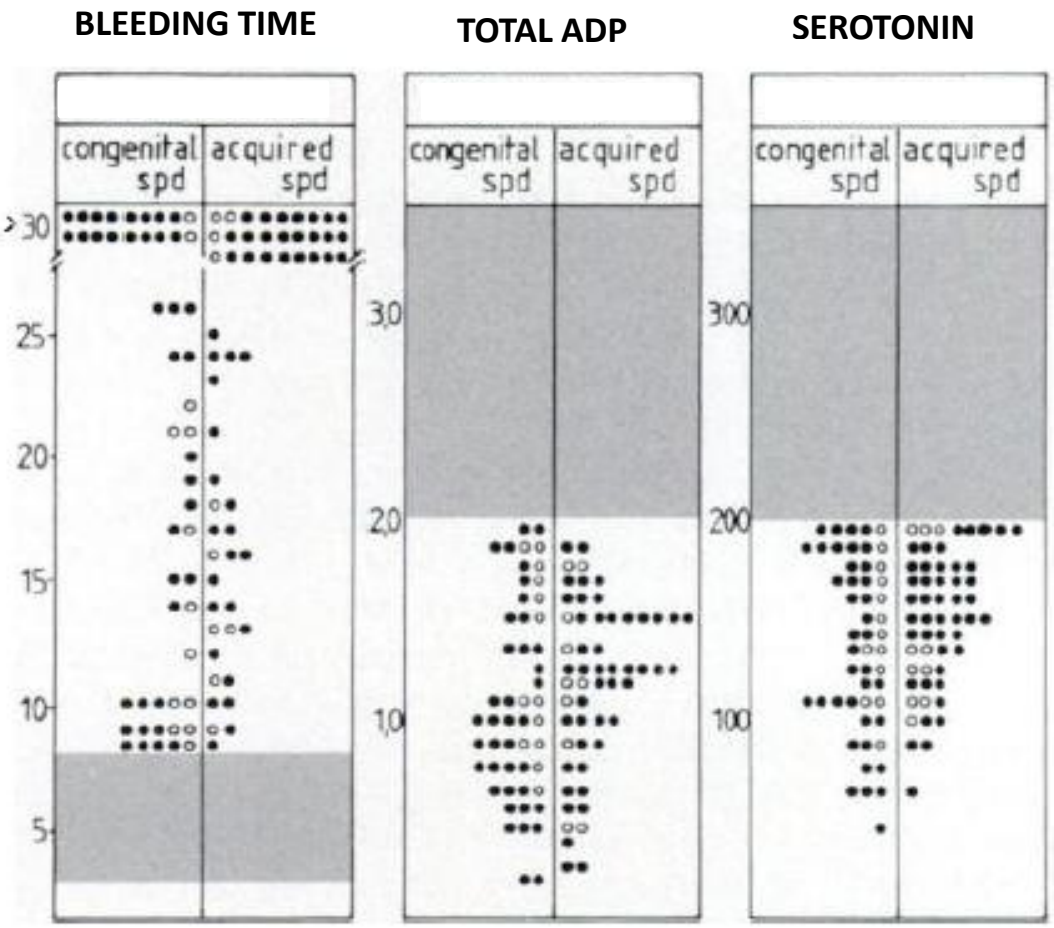
Defective platelet secretion with normal aggregation in δ-SPD



106 patients with δ-SPD

Nieuwenhius HK et al., Blood 1987;70:620

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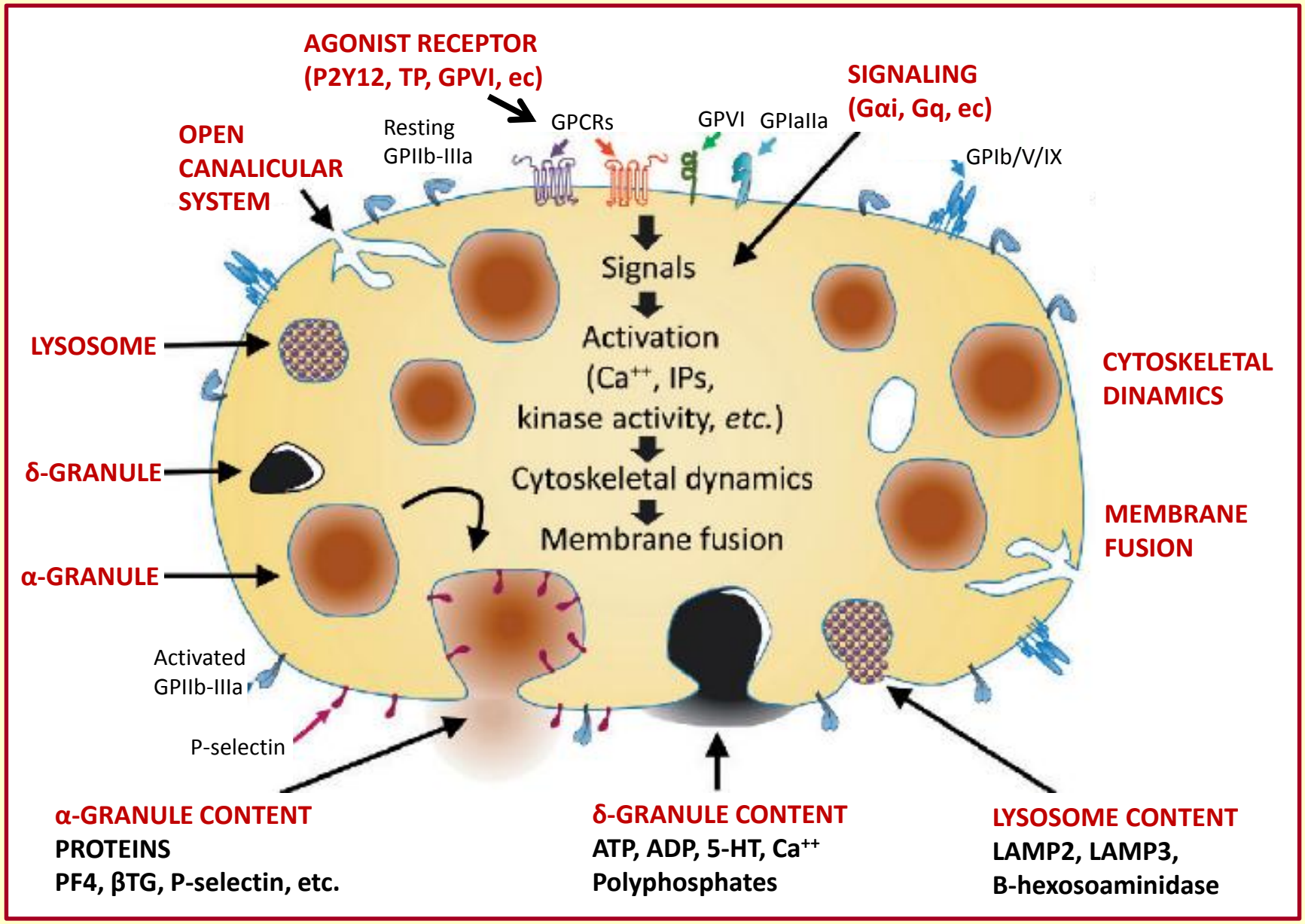
Pathways regulating platelet granule release



modified from Mumford AD et al., Thromb Haemost 2015, 114: 14

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Types of tests used for the assessment of platelet secretion

1. Quantitative assays for specific granule components:

- ADP, ATP
- 5-HT
- PF4 (CXCL4); β-TG (CXCL7)
- Platelet membrane P-selectin measured by FC*
- TLT-1

4. Surrogate, indirect assessment of platelet secretion defects:

- Whole mount EM: semi-quantitative measurement of δ-granules number
- Observation of platelets in blood smears allows suspecting GPS
- Transmission EM, Immune EM and IF-confocal microscopy

- Mepacrine fluorescence assay: for counting the number of δ-granules
- δ-granule 5-HT assessment by FC and immunocytochemical microscopy
- Measurement of different platelet components in lysate fractions, i.e. fibrinogen, PF4, β-TG and many other proteins, before and after activation

Mumford AD et al., Thromb Haemost 2015, 114: 14

FC: Flow Cytometry

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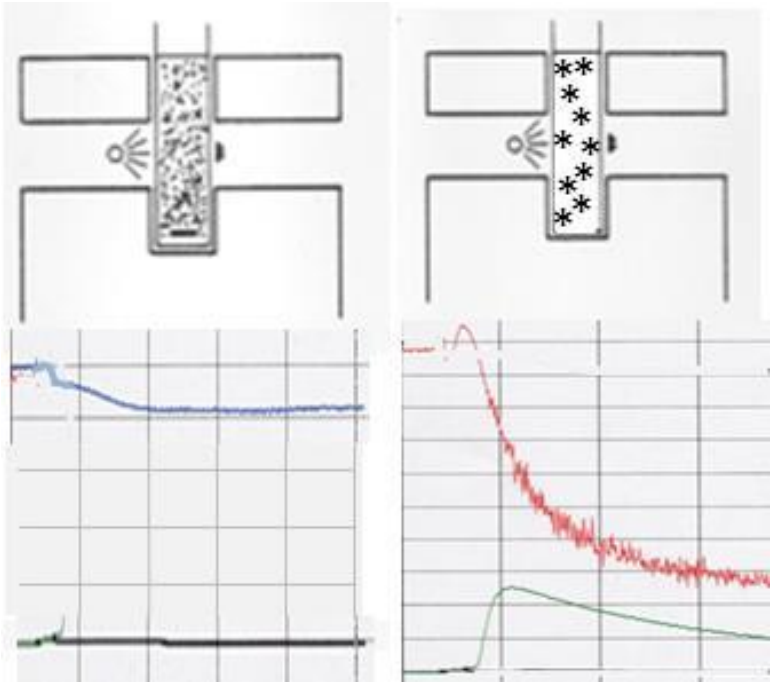
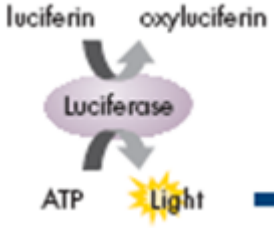
Lumiaggregometry (LA)



Basic principle:
to measure secretion through ATP release (firefly luciferin-luciferase) in combination with the simultaneous measurement of aggregation



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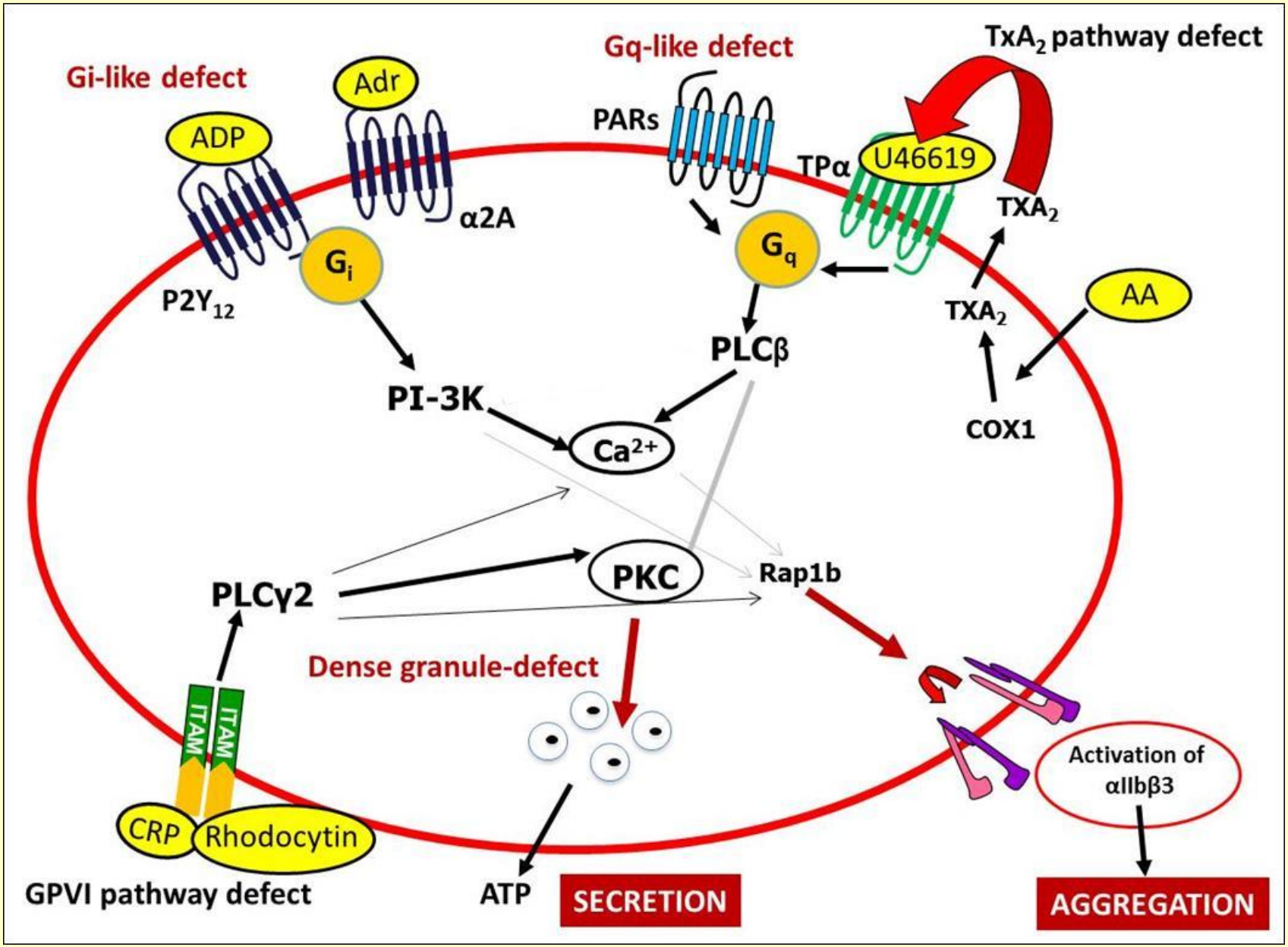
Diagnosis of IPDF at a pathway level



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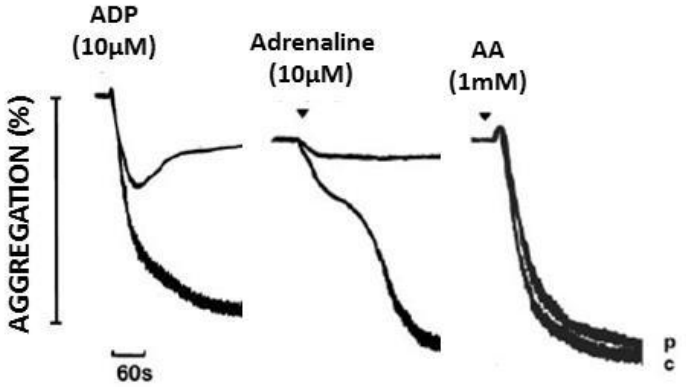
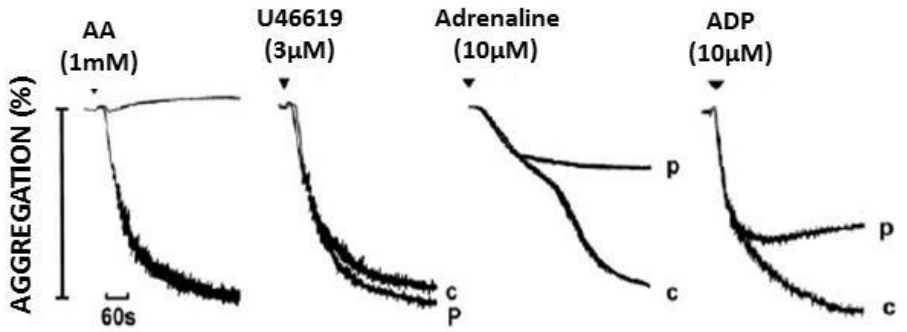
Diagnosis of IPD by lumiaggregometry using a streamlined agonist panel

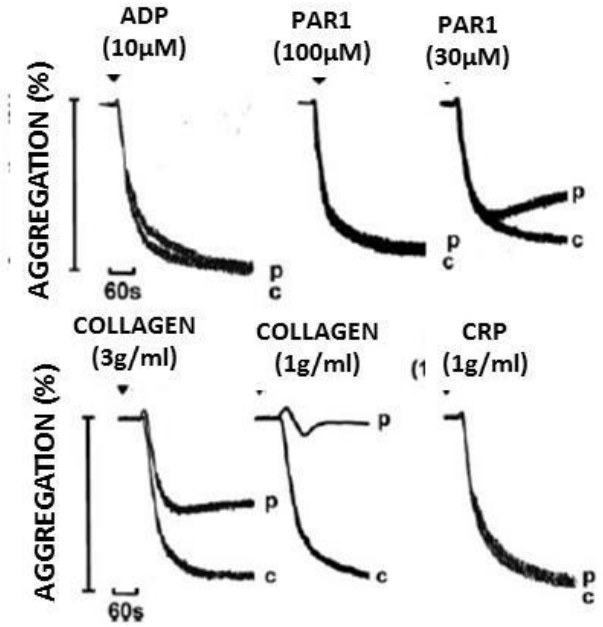
GI signaling defect



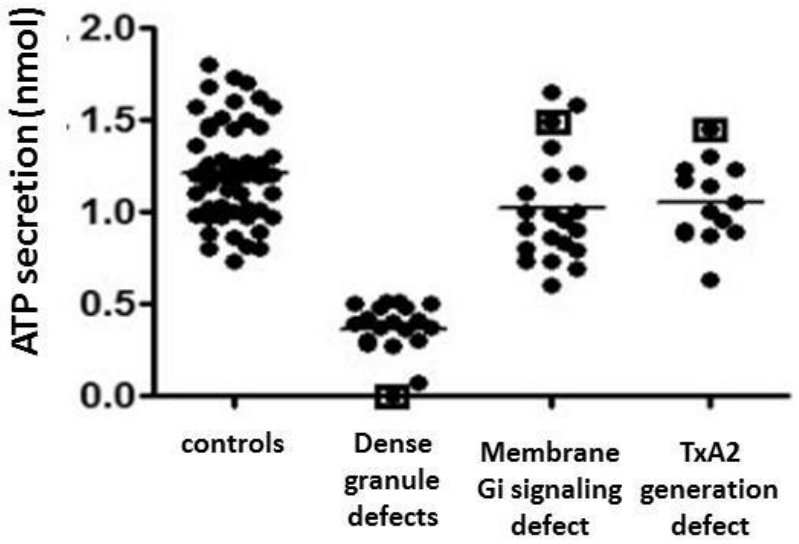
TxA_2 generation defect



Dense granule defect



ATP secretion



-111 subjects with suspected IPFD (70 healthy controls)
-in 58% abnormal lumiaggregometry
-targeted genotyping: 3 new $P2Y_{12}$/TxA_2 receptor mutations

Dawood BB et al., Blood 2012;120:5041

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Flow cytometry in hemostasis and thrombosis

ADVANTAGES	DISADVANTAGES
• Small sample volume • Short time of analysis • Possibility to study platelets in whole blood • Possibility to study platelet characteristics/function in thrombocytopenic patients	• Expensive • Technically complex • Lack of standardization • Need to process the sample immediately after blood collection

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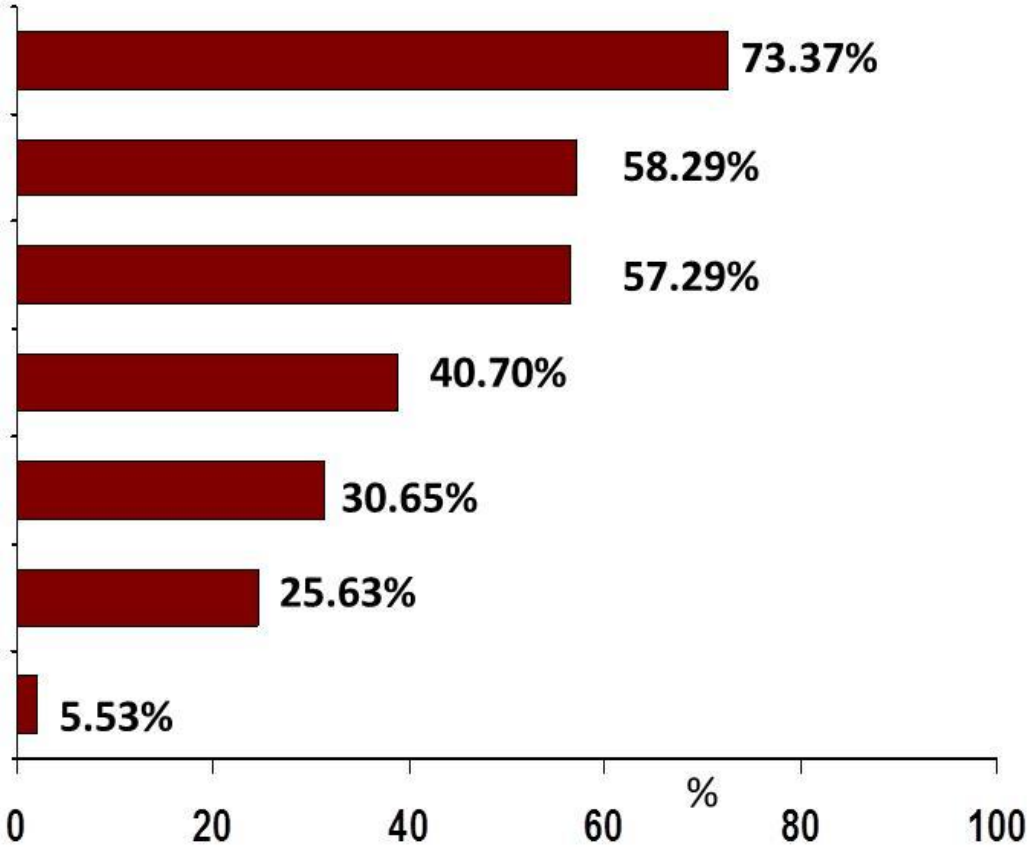
Diagnosis of suspected IPFD: results of a worldwide survey

Instruments available in the laboratory

- Light transmission aggregometer
- PFA-100
- Flow-cytometer
- Lumiaggregometer
- Impedance aggregometer
- Other
- HPLC



Other:

microscopy	(27.45%)
platelet function devices	(13.72%)
thromboelastography	(13.72%)
adhesion assay	(7.84%)

N. of respondents: 199/202 (98.5%)

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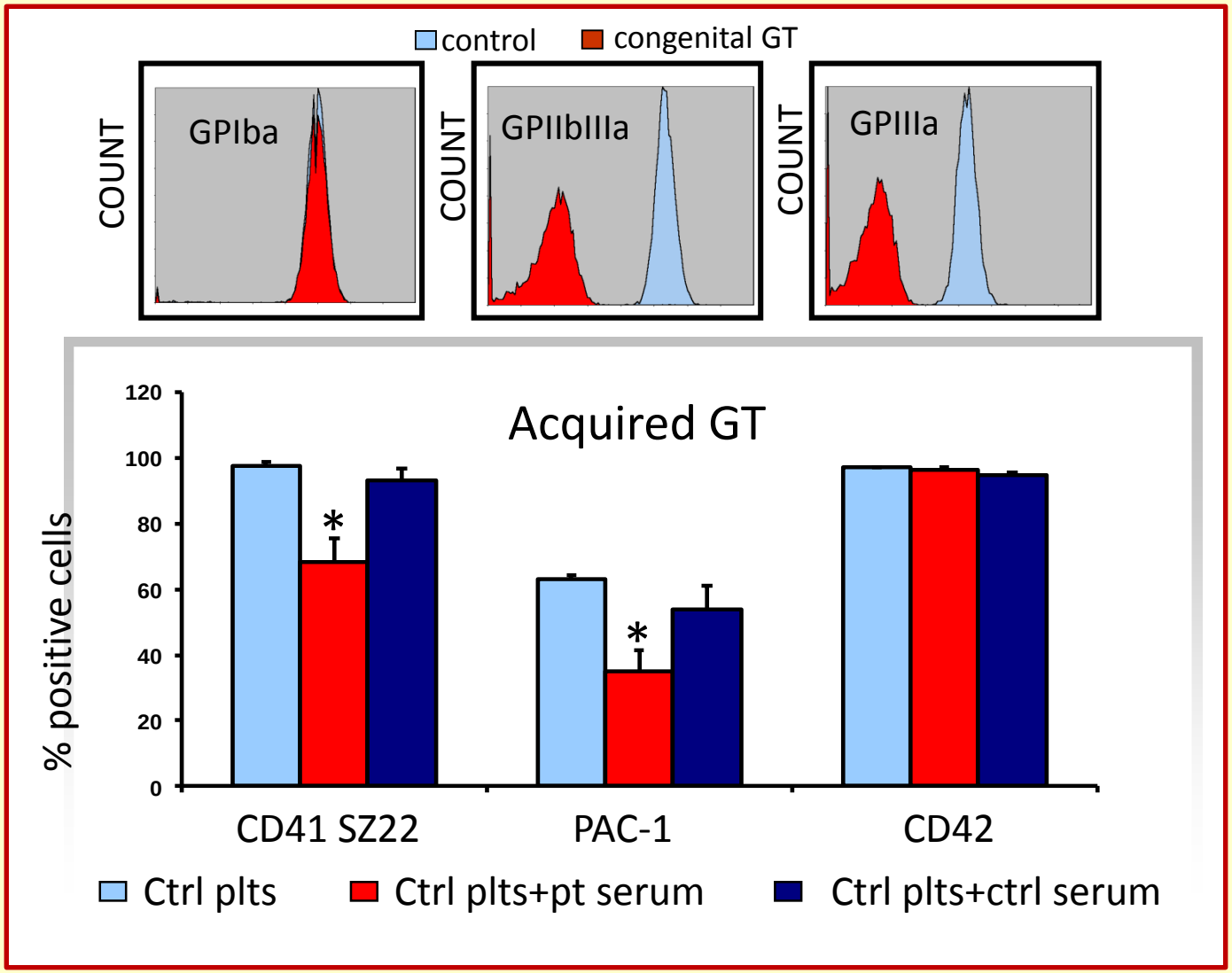
Gresele P et al., J Thromb Haemost 2014; 12:1562

Flow cytometry in the diagnosis of IPFD

Glanzmann Thrombasthenia



Giannini S et al., Cytometry B Clin Cytom 2008, 74:194

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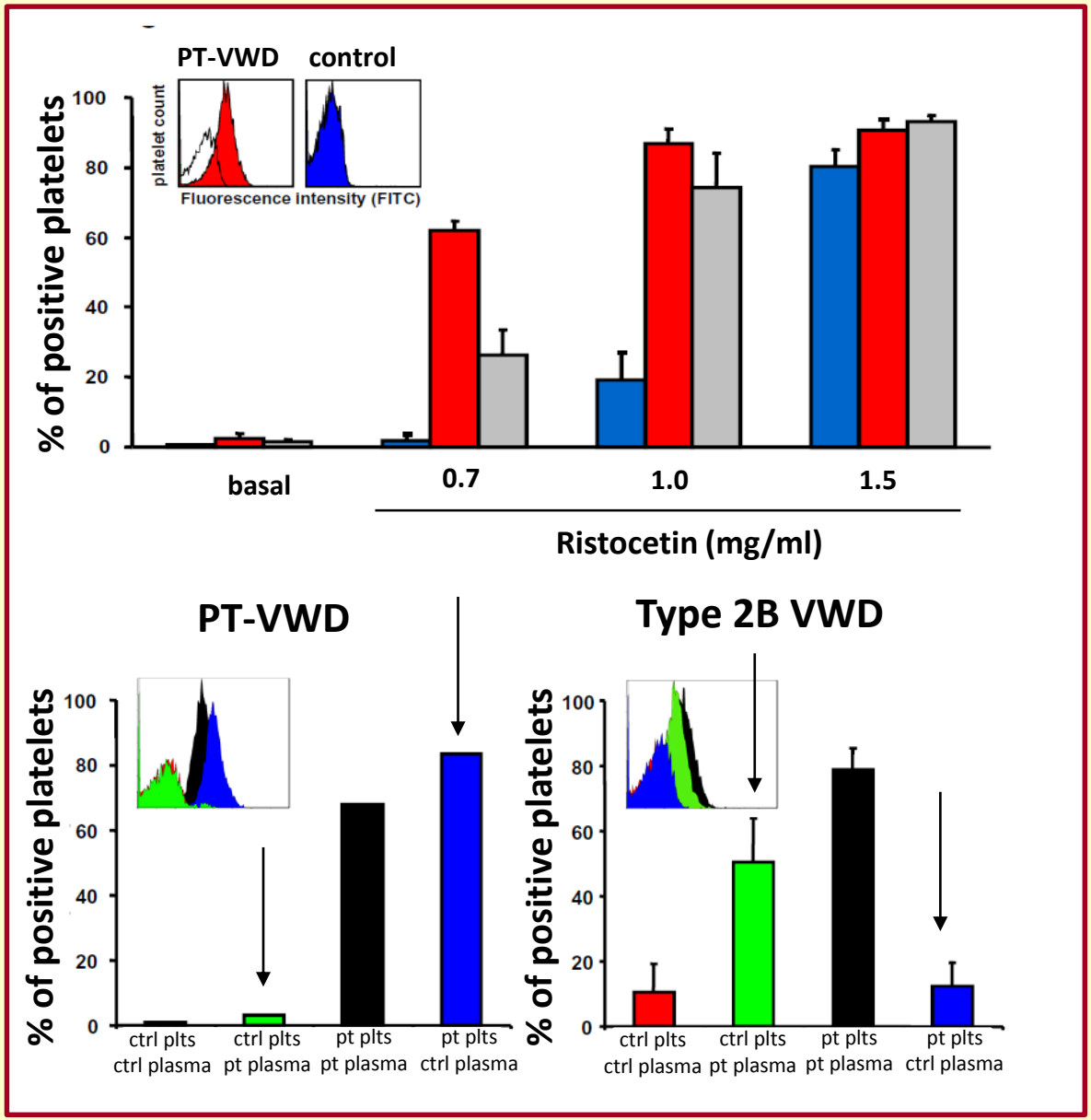
Differential diagnosis of Platelet Type-Von Willebrand Disease and Type 2B VWD by flow cytometry



Giannini S, et al., Haematologica 2010; 95:1021

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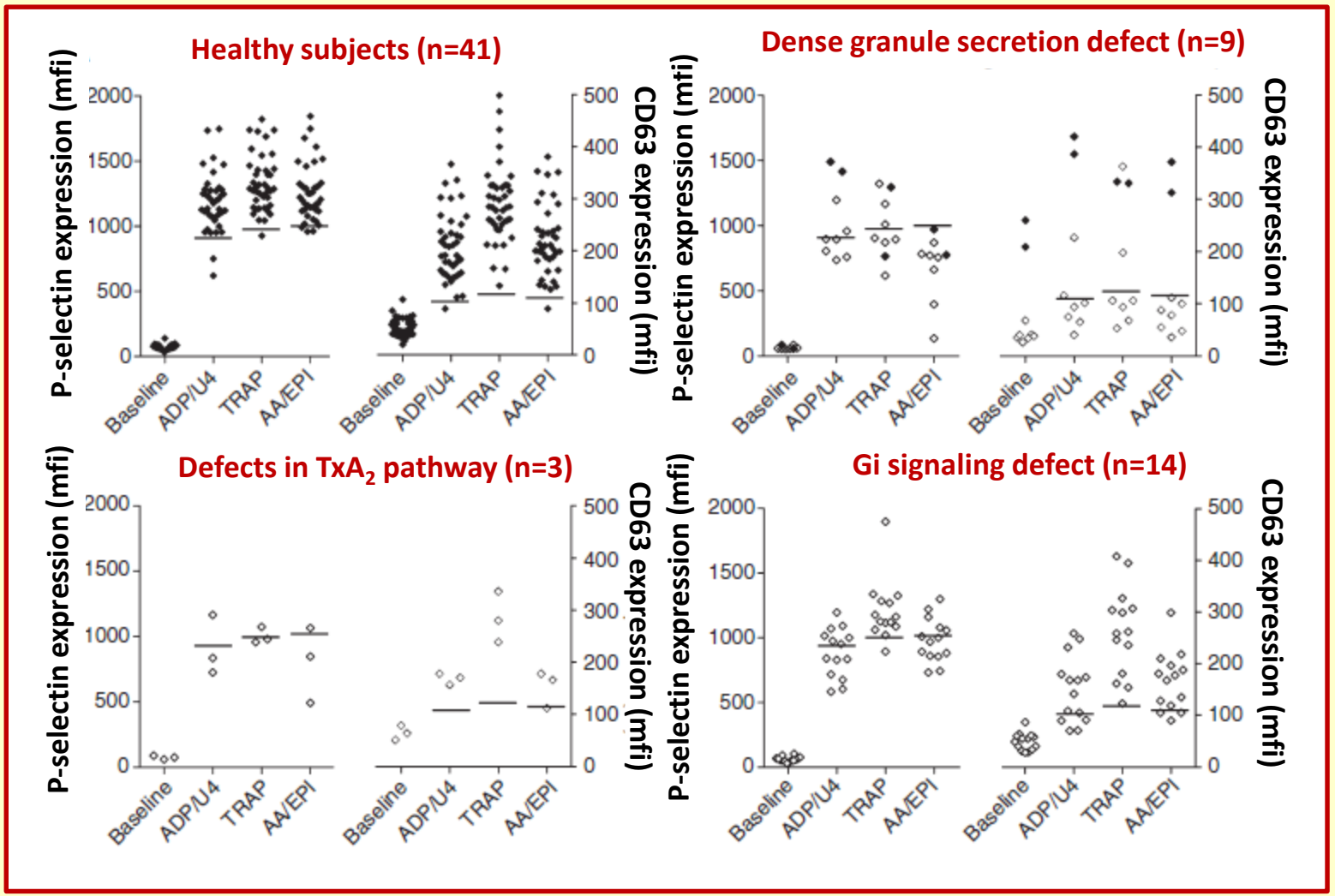
Use of a whole blood remote flow cytometry platelet function test for the diagnosis of mild bleeding disorders



-61 patients; samples fixed and analyzed within 3 days
-Lumiaggregometry vs remote flow cytometry: concordance 84% ($p<0.0001$)

Dovlatova N et al, J Thromb Haemost 2014;12:660

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Guidelines for the diagnosis of **PATIENTS WITH SUSPECTED INHERITED PLATELET FUNCTION DISORDERS**

Who should be studied?

- Patients with history of mucocutaneous bleeding (familial or not) for whom an acquired or drug-induced cause of platelet dysfunction was excluded
- Patients for whom the following conditions have been excluded (when they fully explain the severity of the bleeding diathesis)
    - Acquired thrombocytopenia
    - Von Willebrand disease
    - Blood clotting defect
    - Afibrinogenemia

Gresele P; SSC Platelet Physiology, J Thromb Haemost 2015, 13:314

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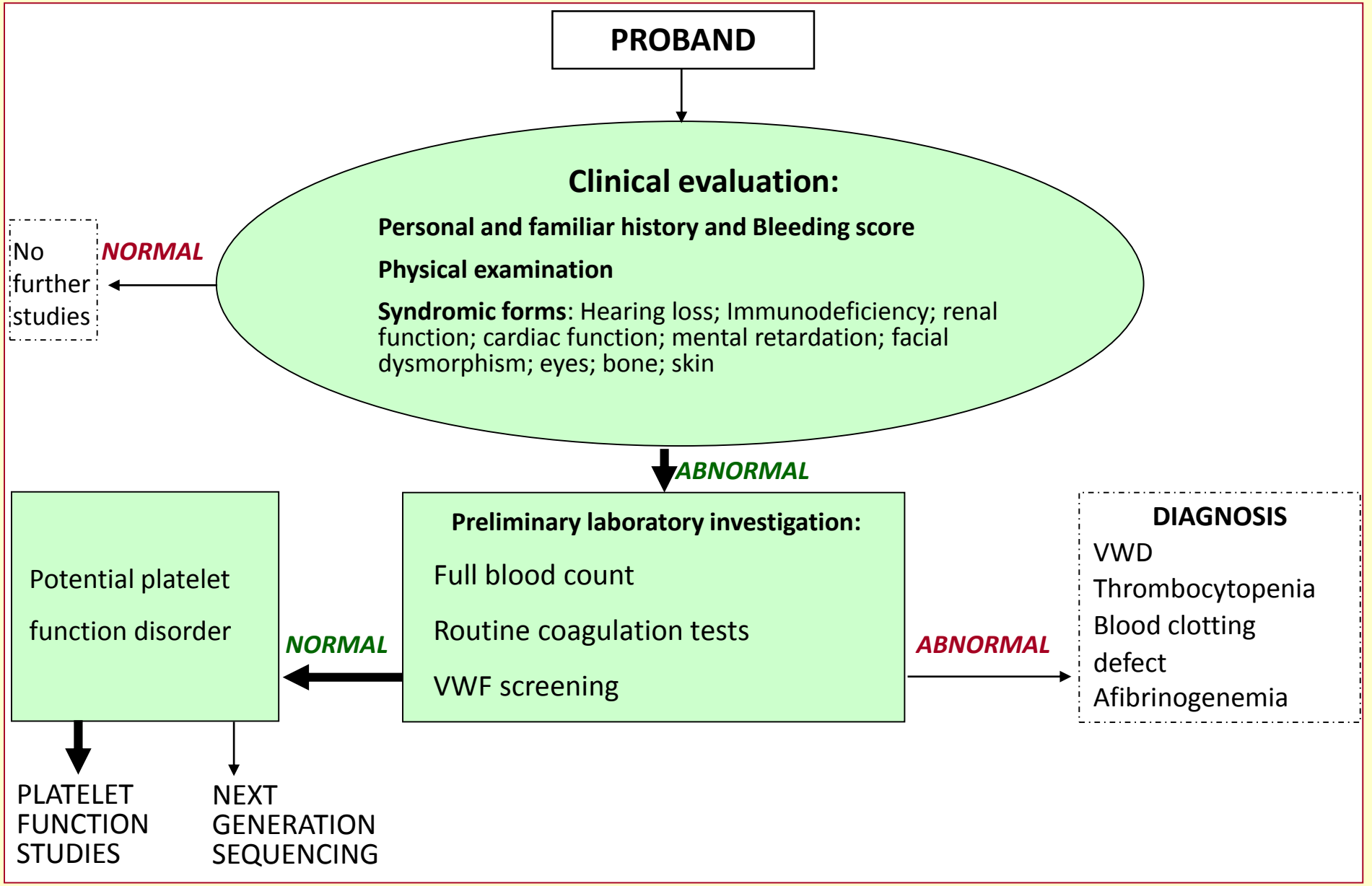
DIAGNOSTIC ALGORITHM - Flowchart



Gresele P; SSC Platelet Physiology, J Thromb Haemost 2015, 13:314

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Clinical evaluation of the patient with a suspected inherited platelet function disorder

- Personal and family bleeding history
- Drug and food history
- Sites of bleeding (easy bruising, epistaxis, gum bleeding, menorrhagia)
- Severity (objective assessment?), recurrence
- Concomitant systemic alterations

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The ISTH Bleeding Assessment Tool for the evaluation of IPFDs

- BATs have been developed to standardize the bleeding history with the aim to improve diagnostic accuracy, quantify symptom severity, inform treatment, and predict future bleeding
- The ISTH-BAT has been validated for VWD and shown to be predictive of bleeding outcome
- Very little information is available on the utility of the ISTH-BAT for patients with IPDs
- The ISTH-BAT evaluation study for IPD is a large cross-sectional and prospective study to test the diagnostic utility of the ISTH-BAT for IPFDs, in comparison with VWD-1 and healthy volunteers, and its possible prognostic significance

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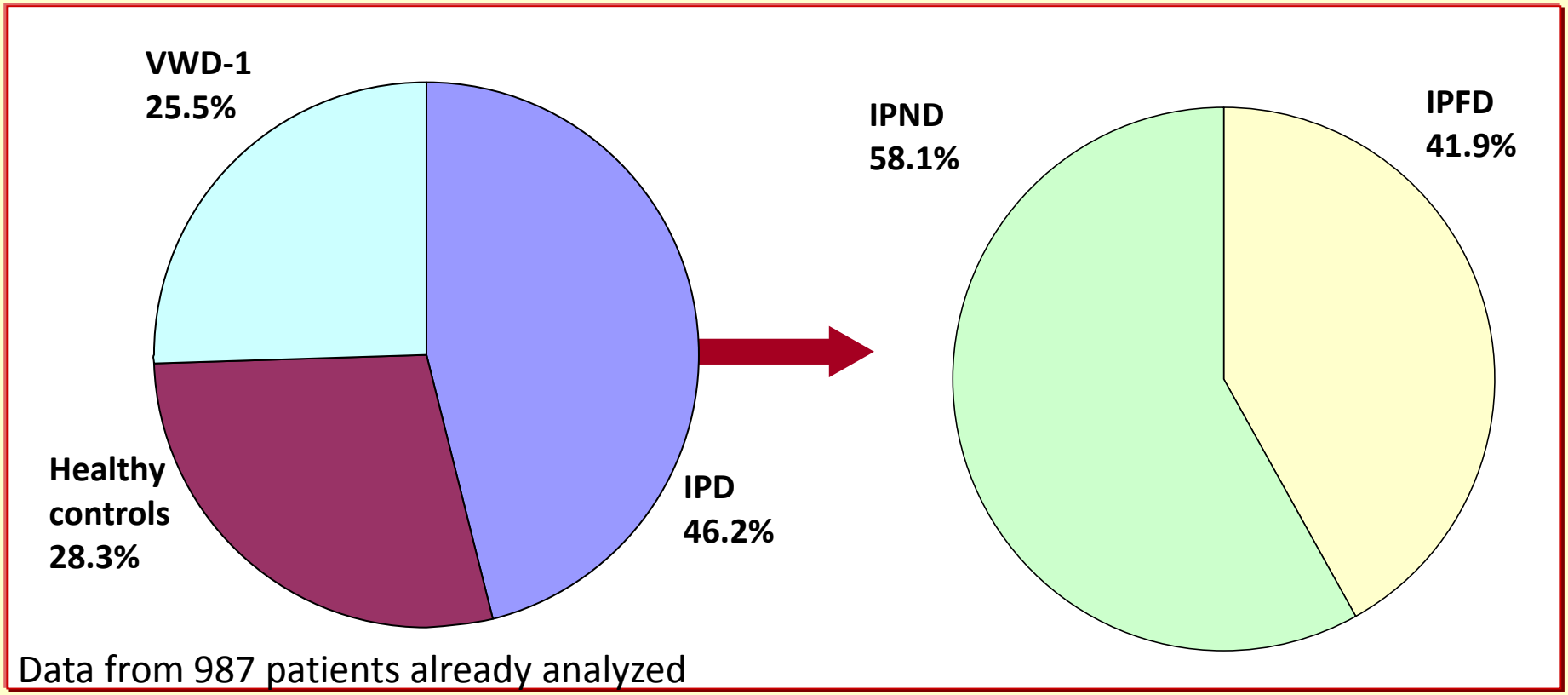
ISTH-BAT evaluation study in IPFDs

Patients enrolled according to disease groups

1042 subjects enrolled from 42 centers



Data from 987 patients already analyzed

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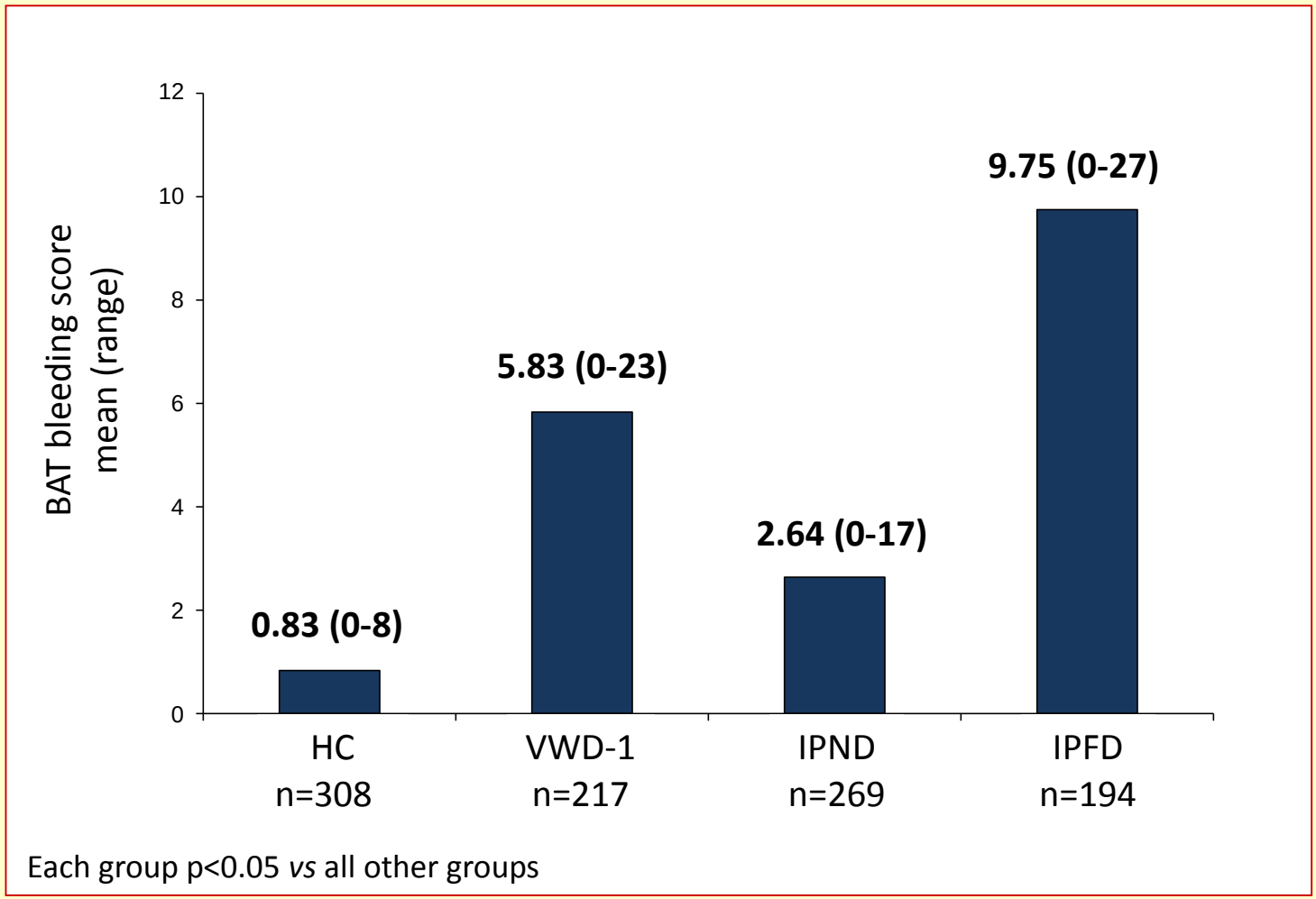
BAT bleeding score according to disease group



Each group p<0.05 *vs* all other groups

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Syndromic IPFDs

Disorder	Associated abnormalities
Arthrogryposis renal dysfunction and cholestasis syndrome	Arthrogryposis, renal dysfunction, cholestasis, cerebral malformations, dysmorphic features
Filaminopathy related macrothrombocytopenia	Skeletal dysplasia, mental retardation, cardiac valvular dystrophy, congenital intestinal pseudo-obstruction, terminal osseous dysplasia
Gsα platelet defect	Short stature, mental disability, brachydactyly. Pseudohypoparathyroidism Ib (PHPIb)
Hermansky-Pudlak syndrome, Chediak-Higashi syndrome	Skin, ocular and hair hypopigmentation, nystagmus Immunodeficiency
Leukocyte adhesion deficiency III	Leukocytosis, recurrent bacterial infections
Paris-Trousseau syndrome	Psychomotor retardation, facial and cardiac abnormalities
Stormorken syndrome	Miosis, muscle weakness, dyslexia, ichthyosis, asplenia
Velocardiofacial syndrome	Cardiac abnormalities, learning disabilities, velopharyngeal insufficiency, immunodeficiency, facial dysmorphisms and thymic hypoplasia
Wiskott-Aldrich syndrome	Eczema, immunodeficiency

Gresele P et al., Semin Thromb Haemost 2016;42:292

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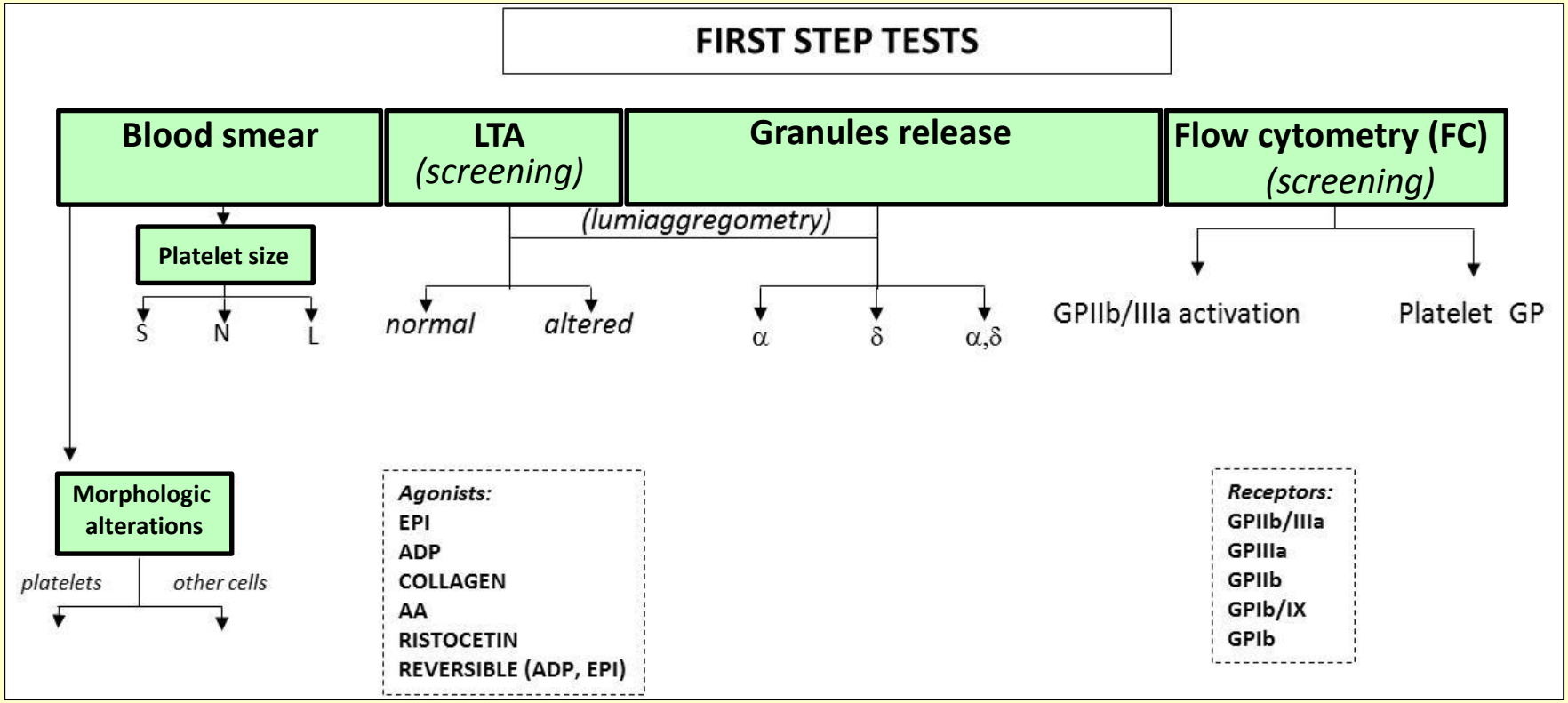
Diagnosis of IPFD: guidance from the SSC of ISTH



Gresele P; SSC Platelet Physiology, J Thromb Haemost 2015, 13:314

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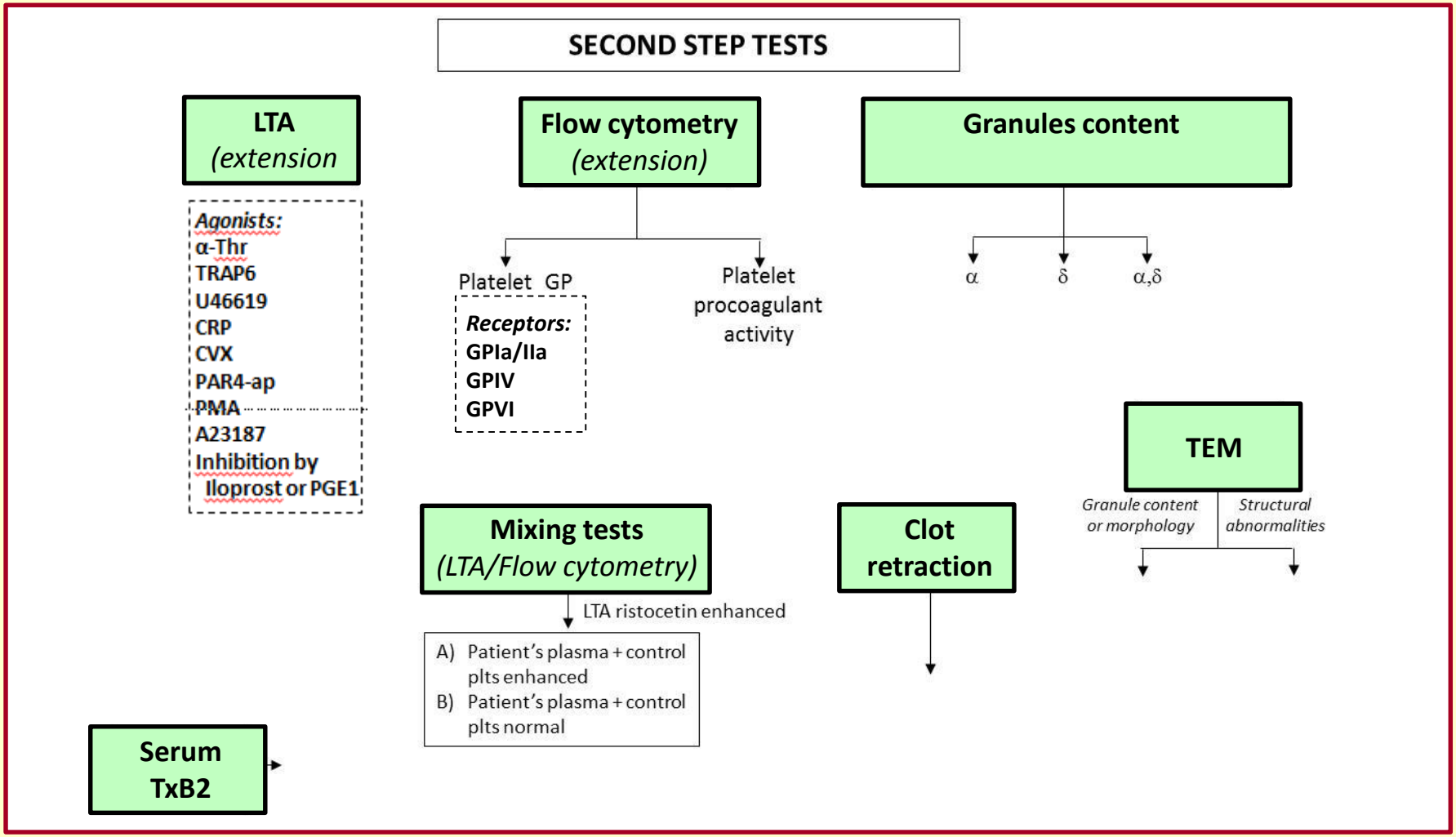
Diagnosis of IPFD: guidance from the SSC of ISTH



Gresele P; SSC Platelet Physiology, J Thromb Haemost 2015, 13:314

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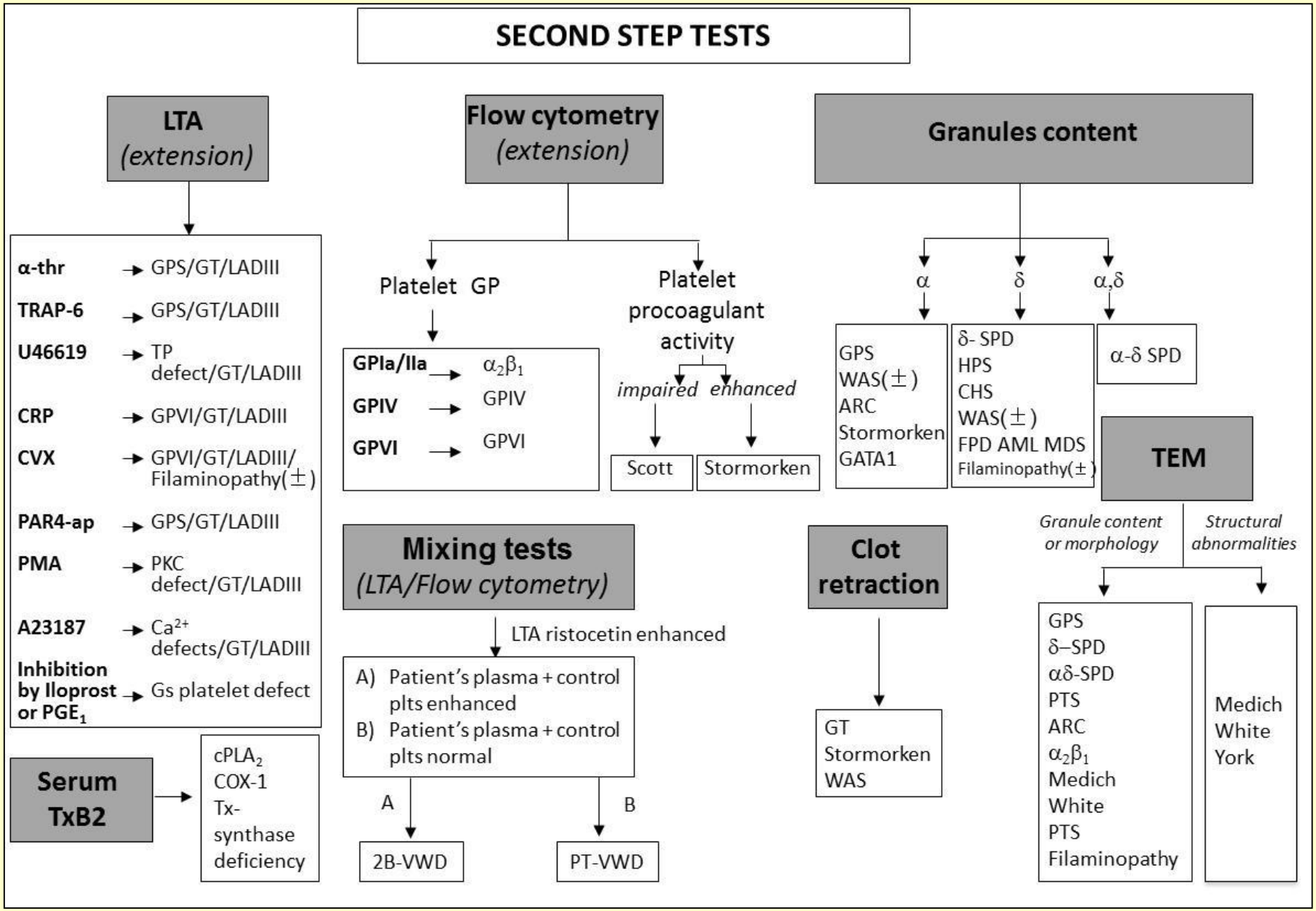

Gresele P et al., J Thromb Haemost 2015, 13:314-22

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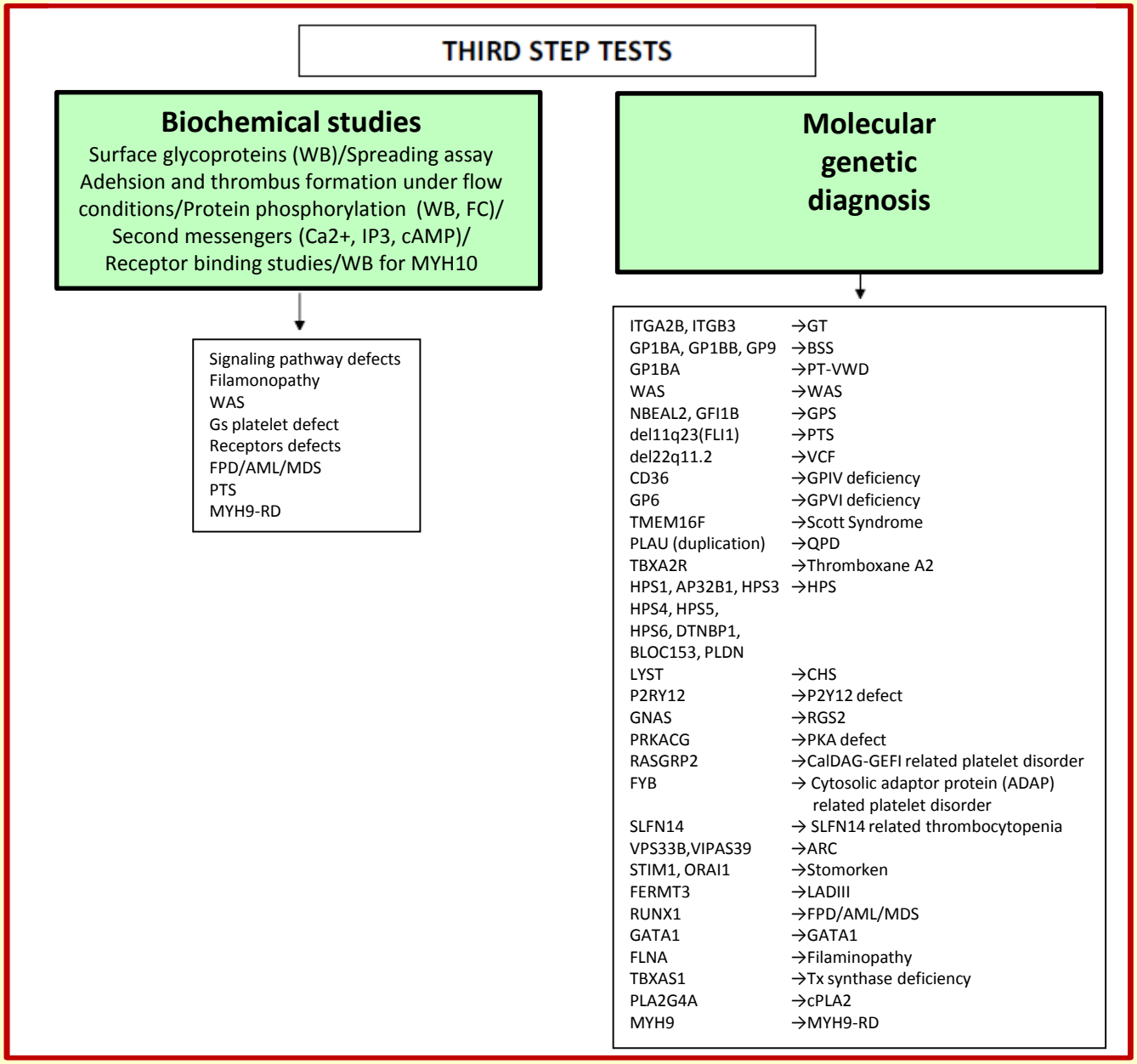
Diagnosis of IPFD: guidance from the SSC of ISTH



Gresele P; SSC Platelet Physiology, J Thromb Haemost 2015, 13:314

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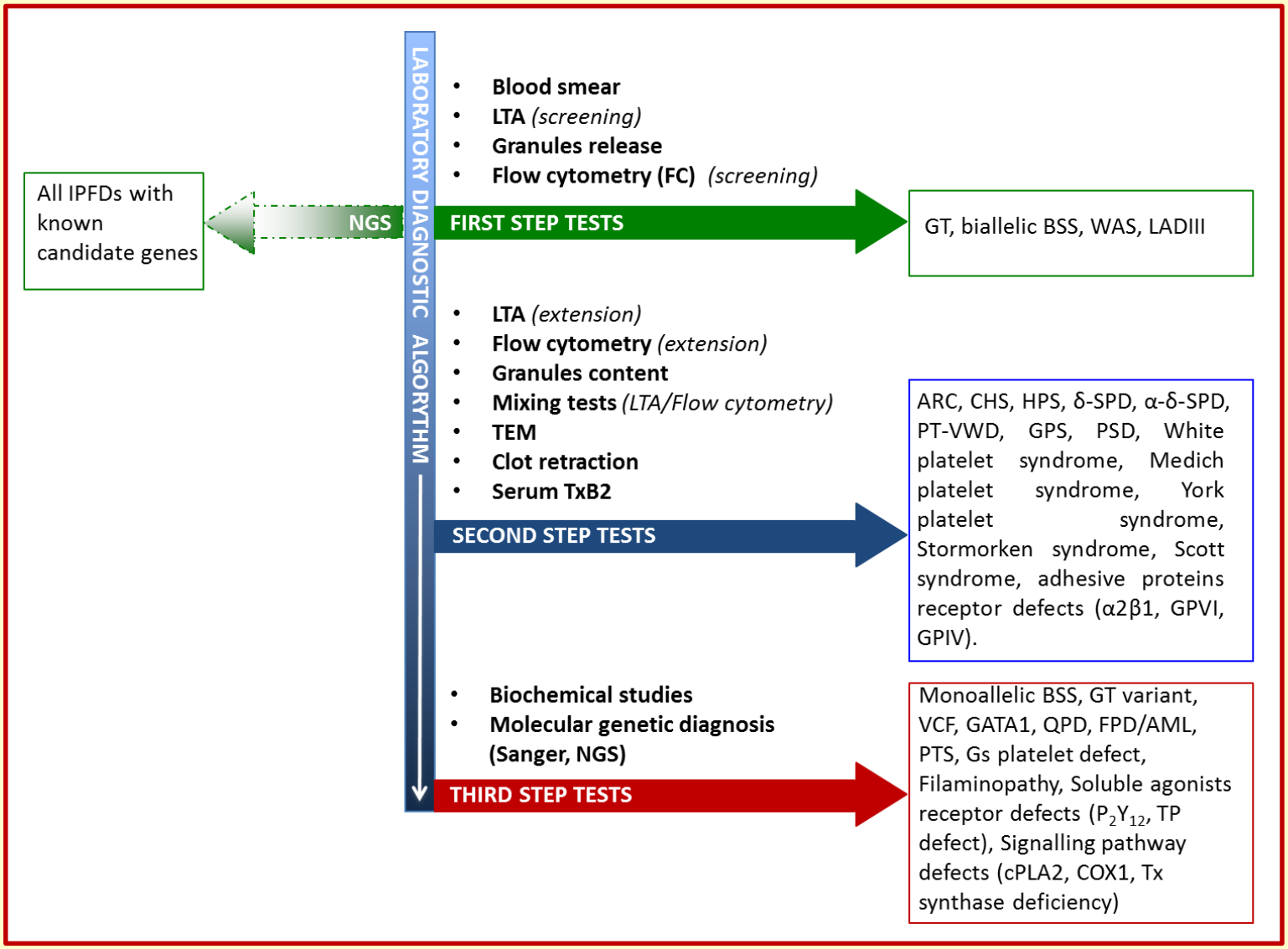
Diagnoses of IPFDs made by the application of a standardized diagnostic algorithm



Gresele P et al., Semin Thromb Haemost 2016, 42:292

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Genetic Diagnosis: pros and cons

- Next Generation Sequencing enables the simultaneous analysis of large groups of candidate genes, allowing the rapid identification of a mutation in a known gene.
- Diagnosis of some IPFD can be reached only after genetic analysis (e.g. GT Variants).
- For some disorders (e.g. MYH9-RD) a phenotype/genotype correlation exists.

however

- We need to consider that several centers still do not have access to molecular testing.
- Genetic testing (especially WES) is a potentially valuable investigation for gene discovery only if backed up by good phenotyping.
- Ethics of predictive testing should be considered (e.g. diagnosis of FPD/AML)
- It can not be considered yet as an initial diagnostic test, but rather as complementary and/or confirmatory.

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Indications to genetic diagnosis of IPFDs

- **Not required:** when clinical phenotype or first/second step tests are sufficient for a conclusive diagnosis (e.g. GT, BSS, PT-VWD)
- **Advisable:** when the platelet phenotype may not be undisputably attributed to a specific disorder (e.g. Stormorken syndrome) or when genotype/phenotype prognostic correlations exists (e.g. MYH9-RD, HPS)
- **Recommended:** when the clinical and laboratory picture is disorienting, functional alterations are heterogeneous, or characterization is uncertain for too few cases described (e.g. GT variants, $cPLA_2$ deficiency, etc.)

Gresele P et al., Semin Thromb Haemost 2016;42:292

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The ThromboGenomics platform

- Currently, 90% of patients with an heritable bleeding disorder with the exception of hemophilia and VWD never receive a conclusive molecular diagnosis.
- Targeted sequencing platform covering 63 genes linked to heritable bleeding, thrombotic and platelet disorders.
- The Thrombogenomics platform provides a sensitive genetic test to obtain molecular diagnoses in patients with a suspected etiology.

Simeoni I et al. Blood 2016;127:2791

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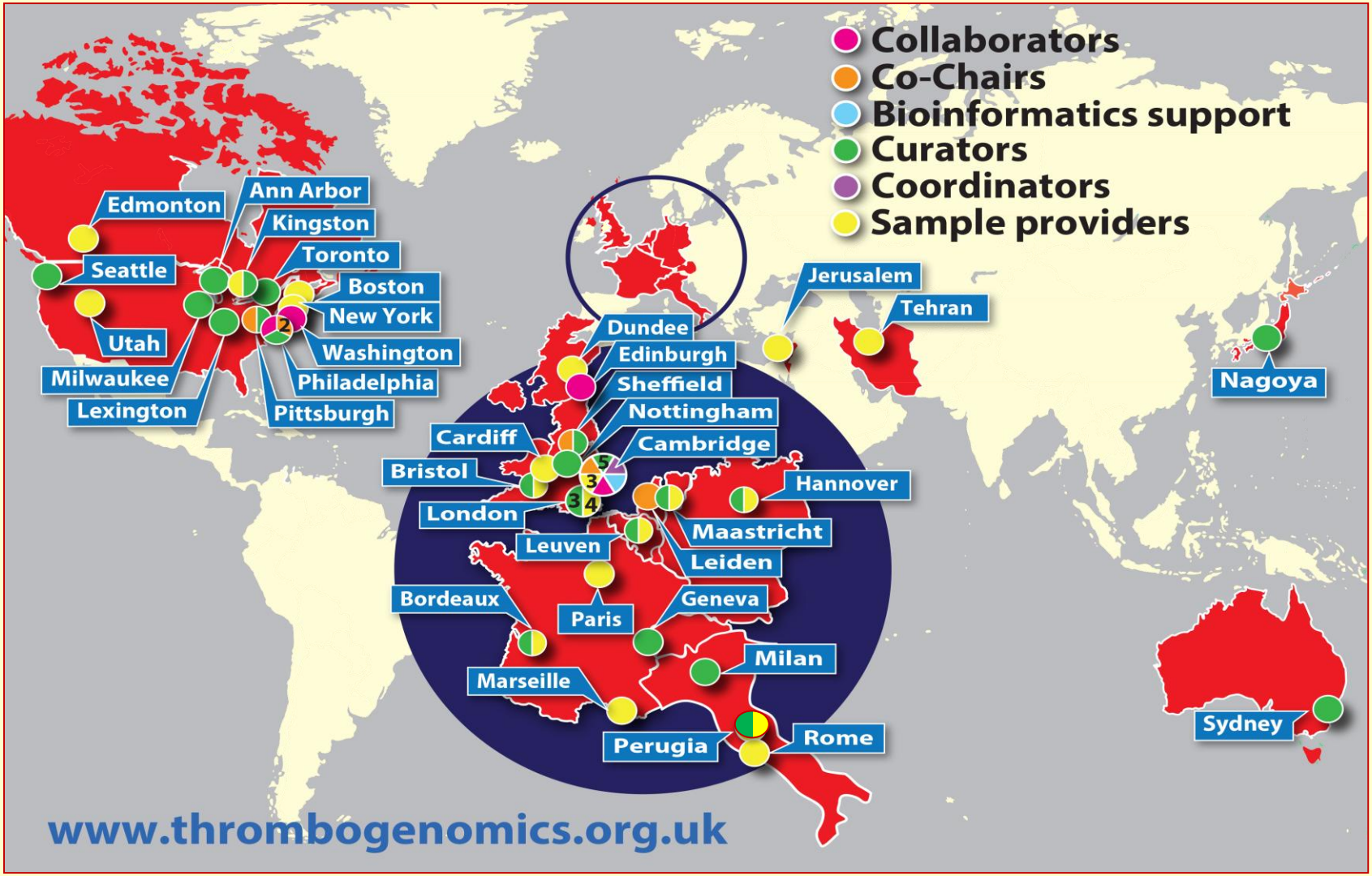
ThromboGenomics - Network



Simeoni I et al. Blood 2016;127:2791

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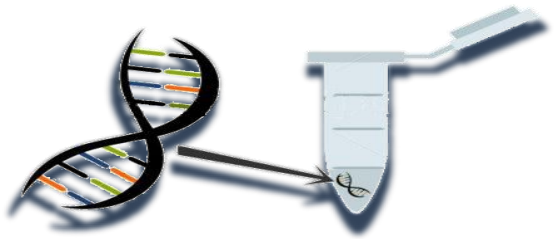
ThromboGenomics - Methods

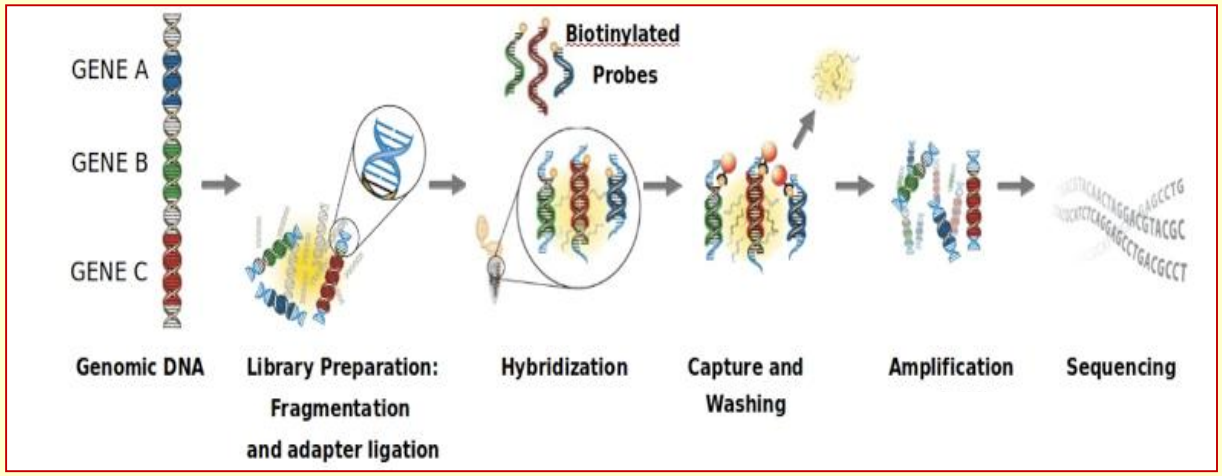
1. Patient phenotyping (HPO terms)

- Mucocutaneous bleeding
- Impaired aggregation ADP
- Impaired aggregation collagen
- Impaired aggregation epinephrine
- Impaired aggregation arachidonic acid
- Normal aggregation ristocetin
- Defective CD41/CD61 expression
- Absent clot retraction
- Normal granule content

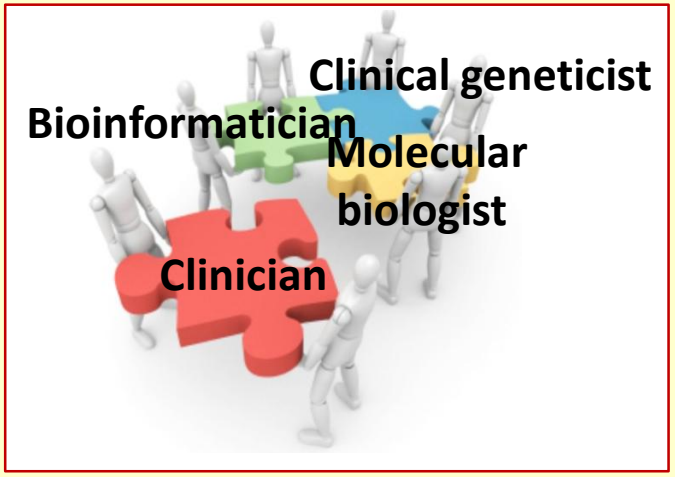
2. DNA extraction



3. Next Generation Sequencing: targeted sequencing of 63 genes from 24 samples simultaneously



4. Results analysis
(Multi-disciplinary team)



Simeoni I et al. Blood 2016;127:2791

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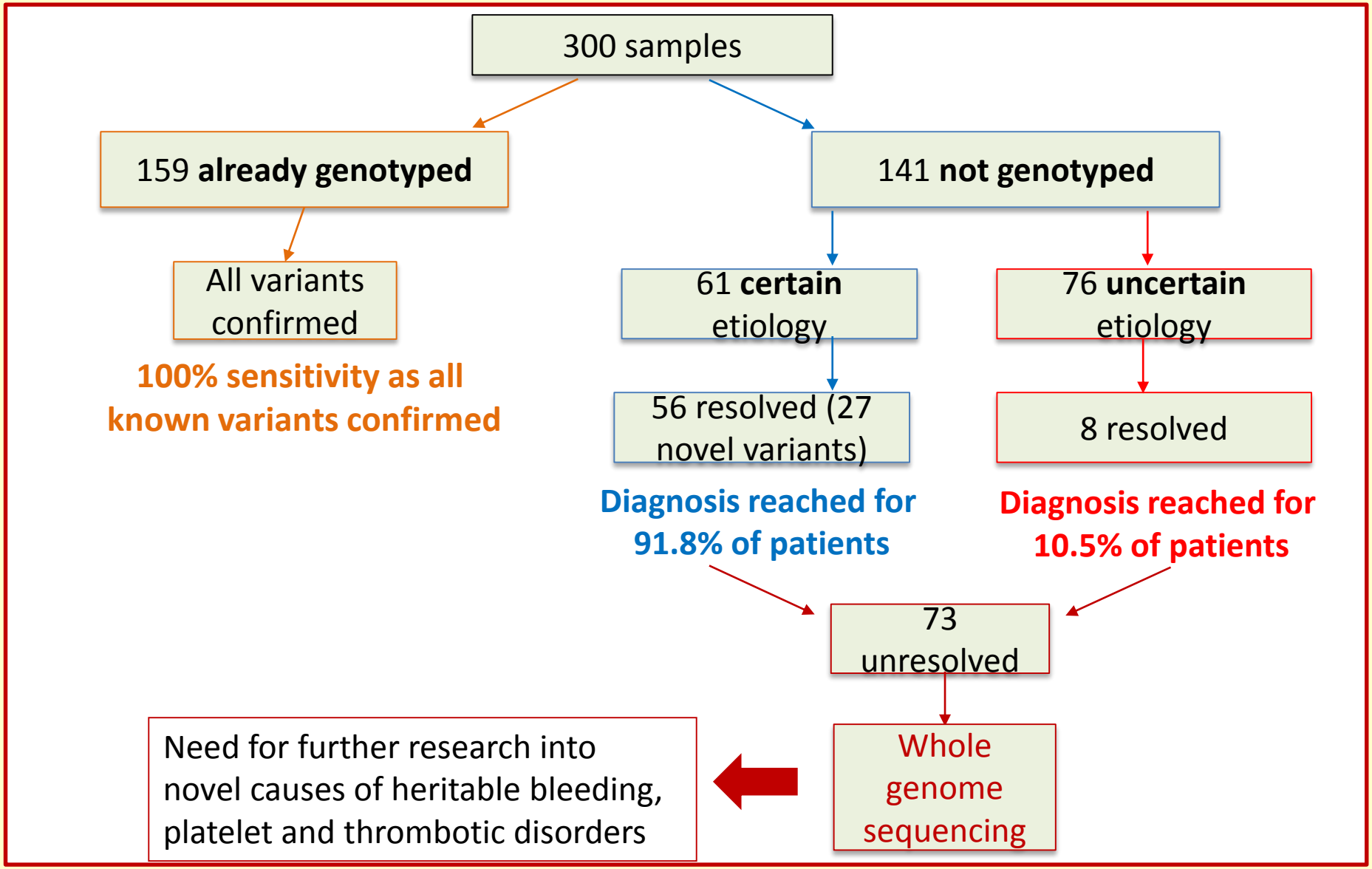
ThromboGenomics - Results



Simeoni I et al. Blood 2016;127:2791

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Conclusions

- IPFDs are a heterogeneous group of bleeding diseases which represent a significant fraction of all the bleeding diatheses
- A careful clinical evaluation and a rational diagnostic algorithm based on a streamlined panel of tests allows diagnosis in a large part of the cases.
- Genetic diagnosis is becoming a conceivable alternative to extensive platelet function testing for many IPFDs
- IPFDs are associated with a significant bleeding risk
- Correct diagnosis and the use of prompt and appropriate treatment may minimize bleeding risk

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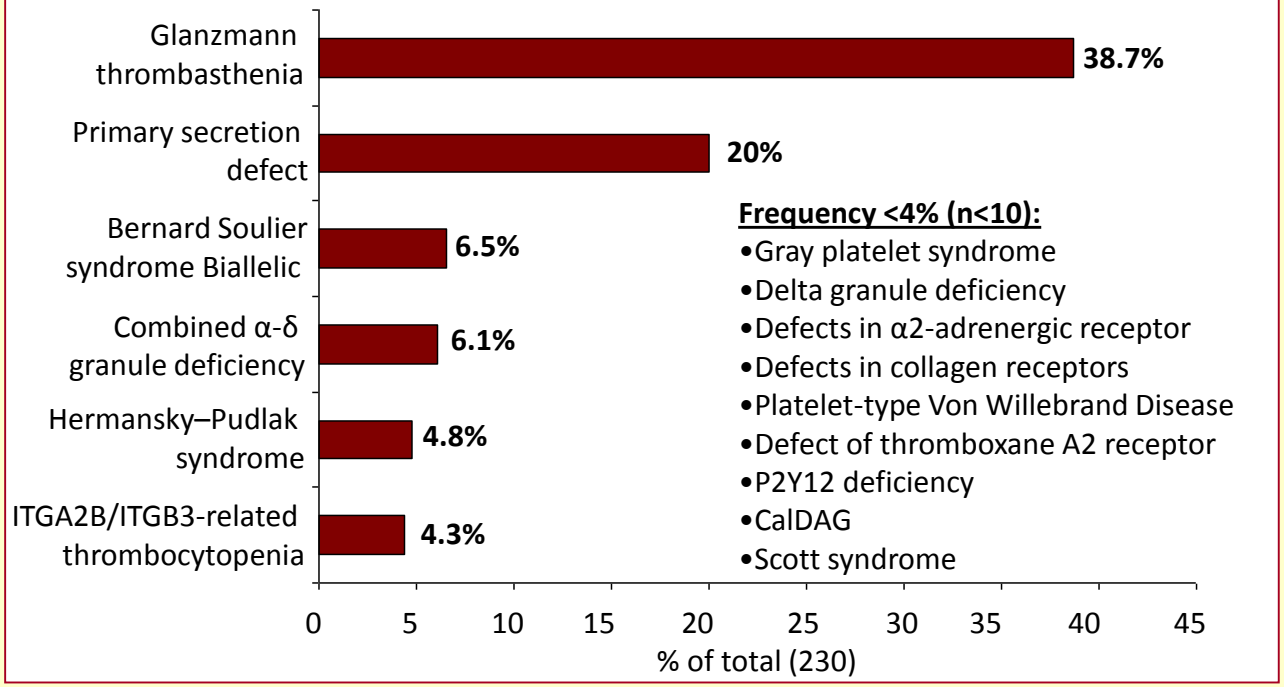
Bleeding risk of surgery in IPFD

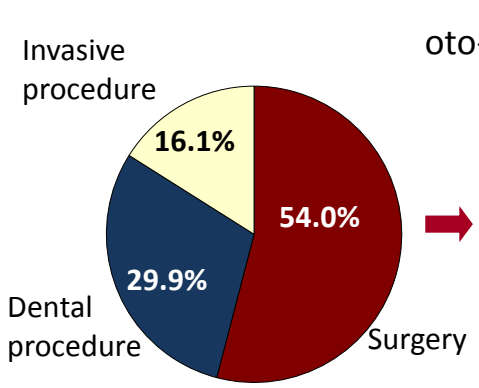
- Excessive bleeding during invasive procedures is a feared complication in patients with IPFD.
- However, very few studies have evaluated the bleeding risk associated with surgery in patients with IPFDs and most data come from case reports or small case series.
- The exact bleeding risk of surgery and the most appropriate management options in IPFDs are therefore unknown
- SPATA Study: retrospective, multicentre, worldwide study involving clinical centers managing IPFDs.
- Participants were asked to enroll all IPFD patients they had on file who had undergone surgery and to examine their records.

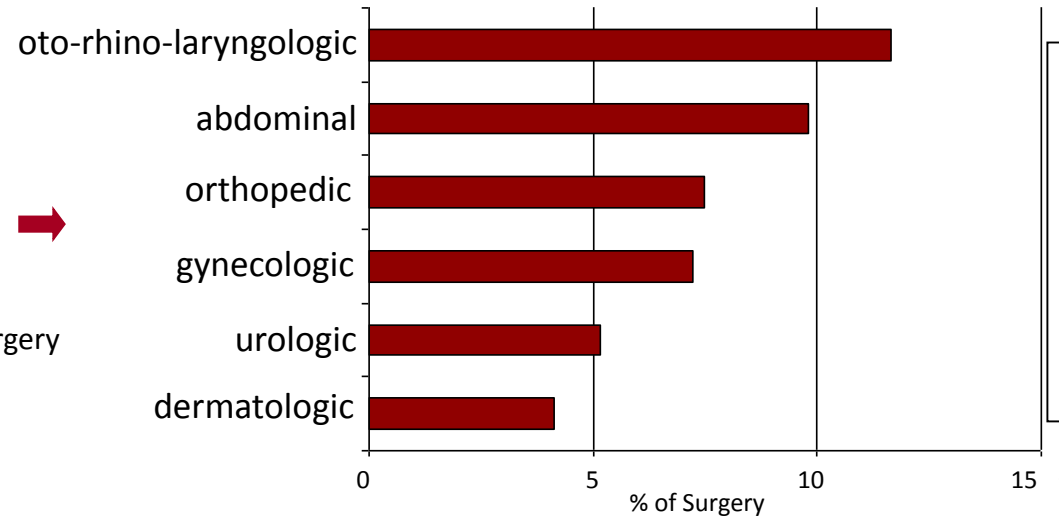
IPFD and procedures



230 IPFD patients
42 centers, **16** countries
Median age: 40 years
(IQR 23.5-54)
Women: 58.26%

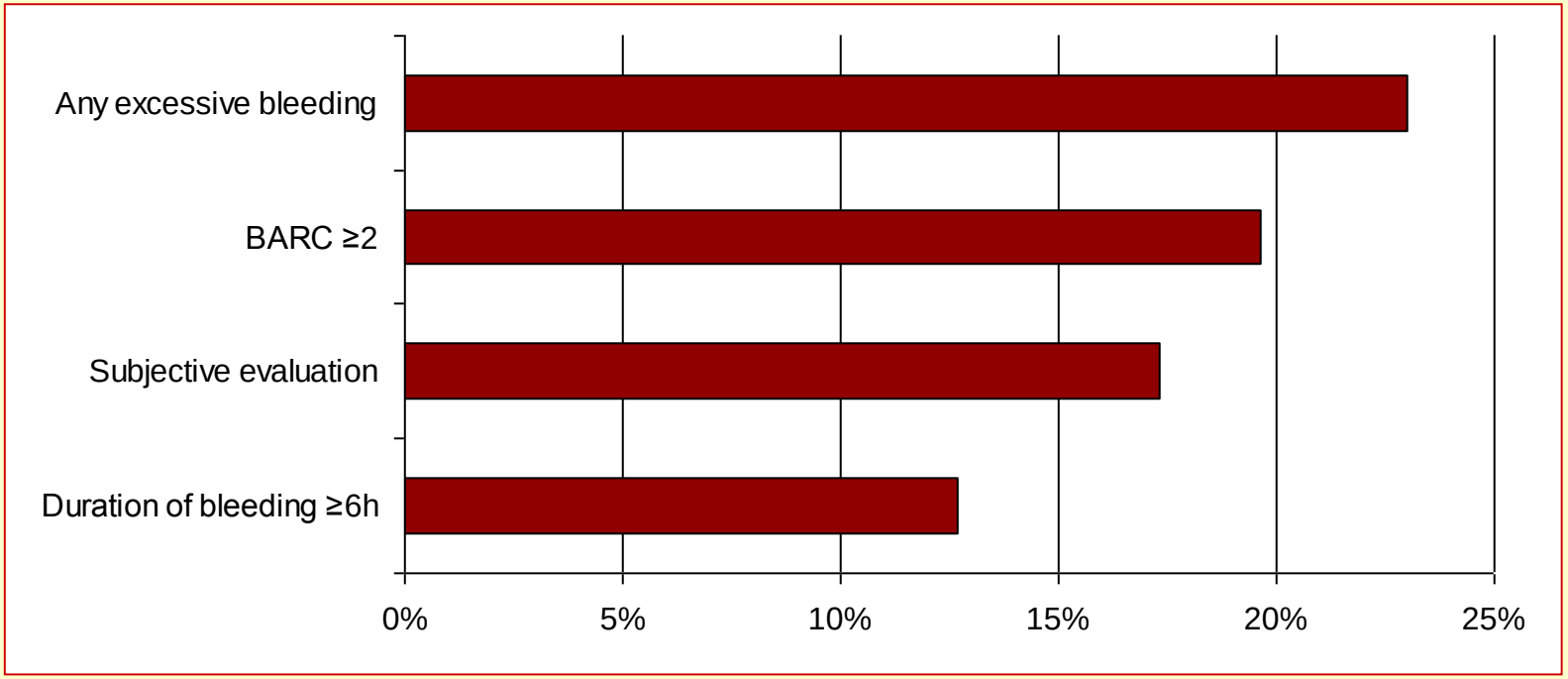
442 procedures
Median age at surgery: 31 years
(IQR 15-52)





Frequency <4%:
•eye
•breast
•cardiovascular
•colorectal
•neurological
•plastic
•thoracic

Frequency of excessive bleeding at surgery in the overall IPFD population



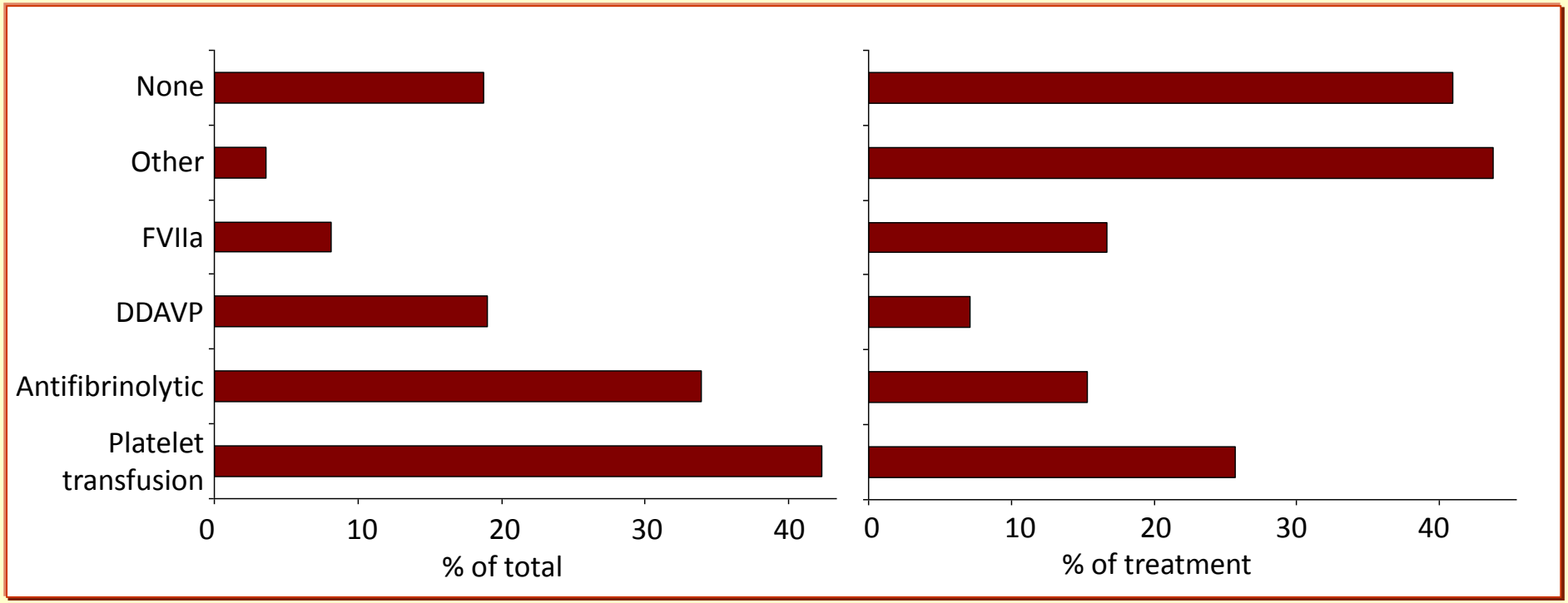
Treatment options for IPFDs

- **Antifibrinolytic agents**: local or systemic; arrest/prevent epistaxis, gingival bleeding or menorrhagia; used for the prevention of bleeding for minor surgery
- **DDAVP:** i.v., s.c., nasal spray; efficacious in preparation to invasive procedures or surgery (contraindicated in PT-VWD; uncertain efficacy in some IPFDs)
- **Platelet transfusion:** treatment of acute bleeding or prior to surgery; should be used only when other agents have failed (alloimmunization and infectious risks)
- **rFVIIa:** approved for treatment of acute bleeding and for perioperative management of GT refractory to platelet transfusions; little or no informations for other IPFDs

Prophylactic antihemorrhagic preparation and outcome

Antihemorrhagic preparation

Any excessive bleeding according to antihemorrhagic preparation



OTHER: cryoprecipitate; fibrin-glue, fibrinogen, FFP, IVIG, local hemostatic agent, suture, local tranexamic acid

OR for bleeding depending on prophylactic preparation:

-Any prophylaxis	OR 0.38 (0.23-0.63)
-Antifibrinolytic	OR 0.43 (0.26-0.72)
-DDAVP	OR 0.19 (0.08-0.45)
-Platelet transfusion	OR 1.10 (0.71-1.70)

Management of patients

Patients with mild platelet disorders

⇩

Local haemostatic measures
Antifibrinolytic
Desmopressin

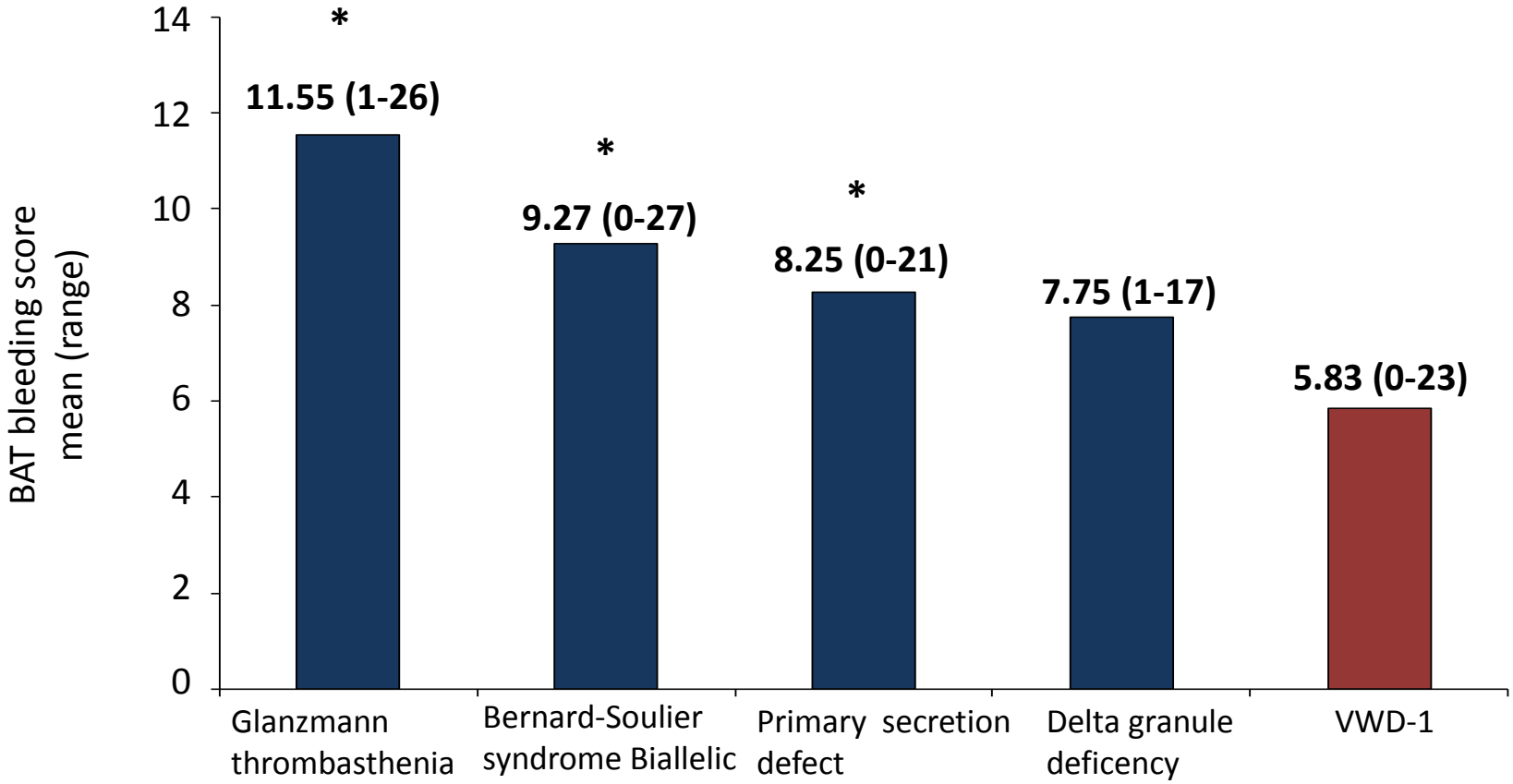
Patients with severe platelet disorders
(Glanzmann thrombasthenia and Bernard-Soulier syndrome)

⇩

Local haemostatic measures
Antifibrinolytic
Desmopressin
Platelet transfusion
rFVIIa (GT)

Valera MC et al., J Oral Pathol Med 2013;42:115.

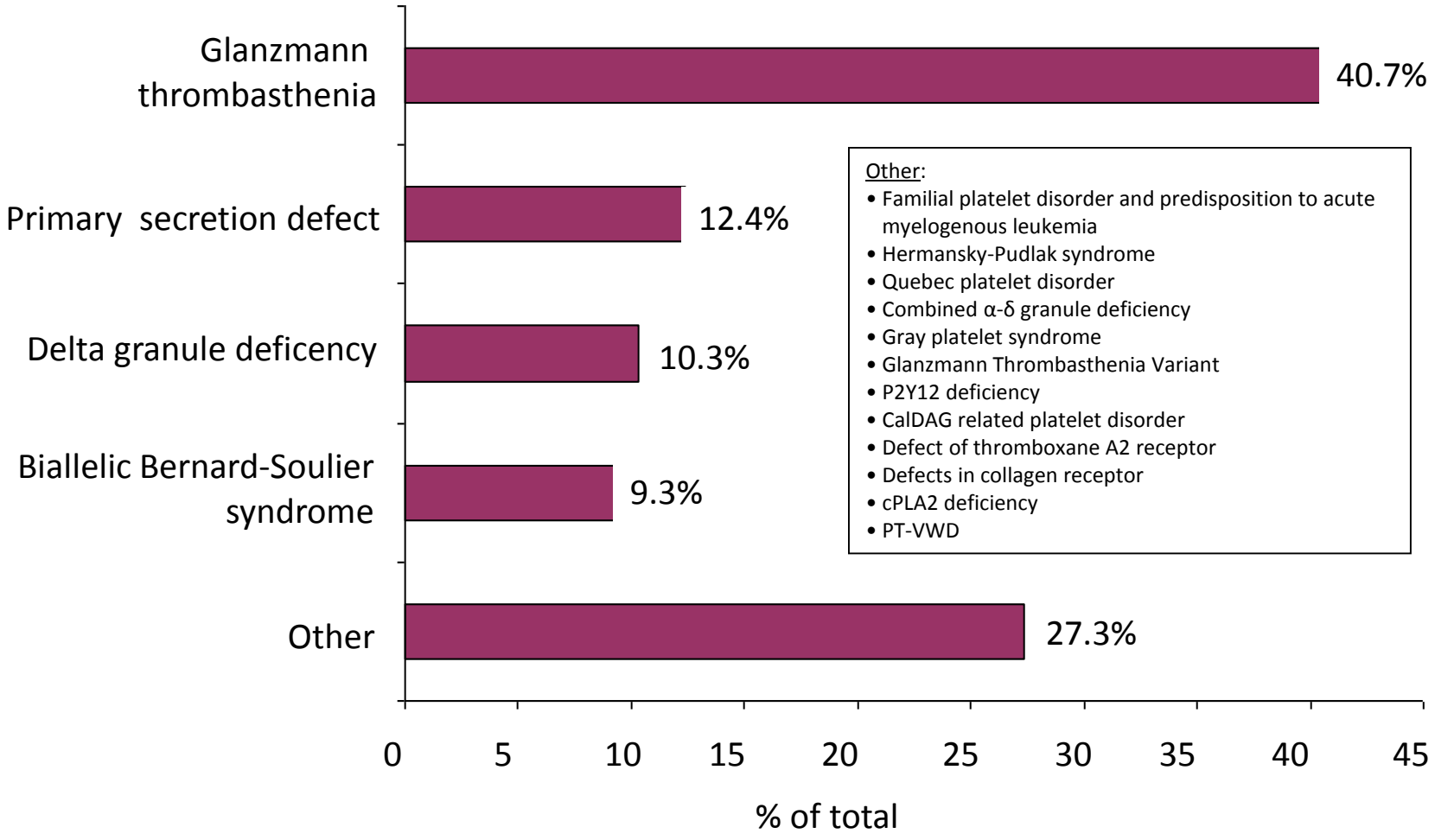
BAT bleeding score in IPFD by principal diagnoses



*** p<0.05 vs VWD-1**

IPFD patients enrolled according to diagnosis

194 IPFD patients enrolled



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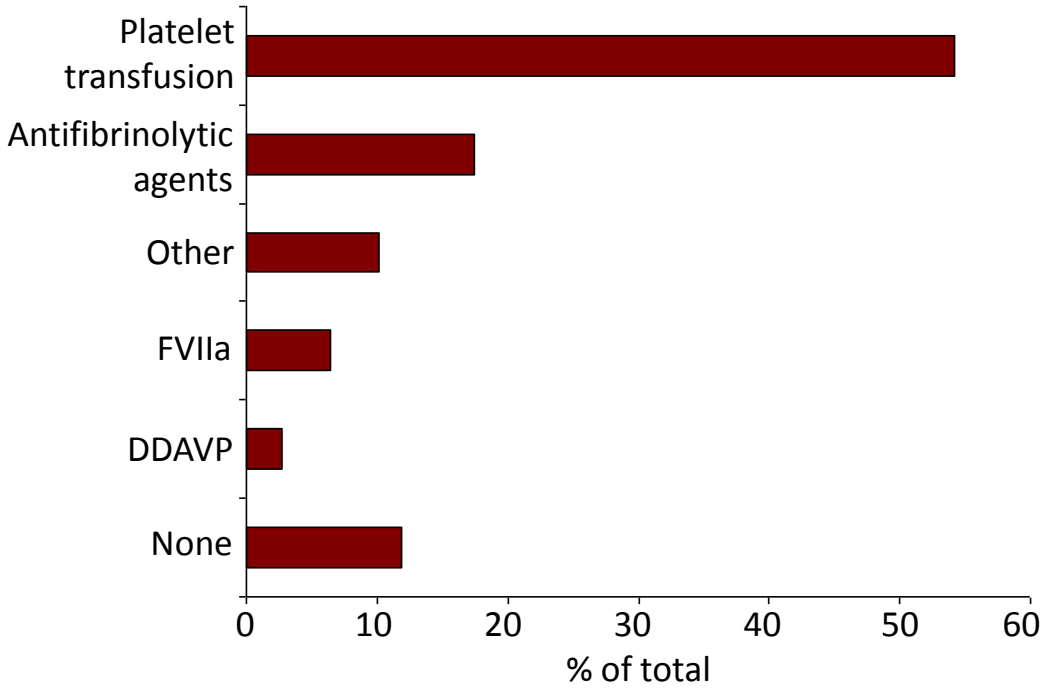
Emergency treatment of bleeding

Excessive bleedings requiring treatment: **109** patients
31.2% of which did not undergo
antihemorrhagic prophylaxis

Treatment



OTHER: cryoprecipitate, local ice, i.v. sandostatine, stitches, surgery.

BAT bleeding score according to diagnoses