ERN-EuroBloodNet Topic on Focus on Inherited Platelet Function Disorders (IPFD)

webinar

HEALTH PROFESSIONALS

Genetic testing for IPFD - Advantage, limitations and future perspectives

Kathleen Freson
KU Leuven

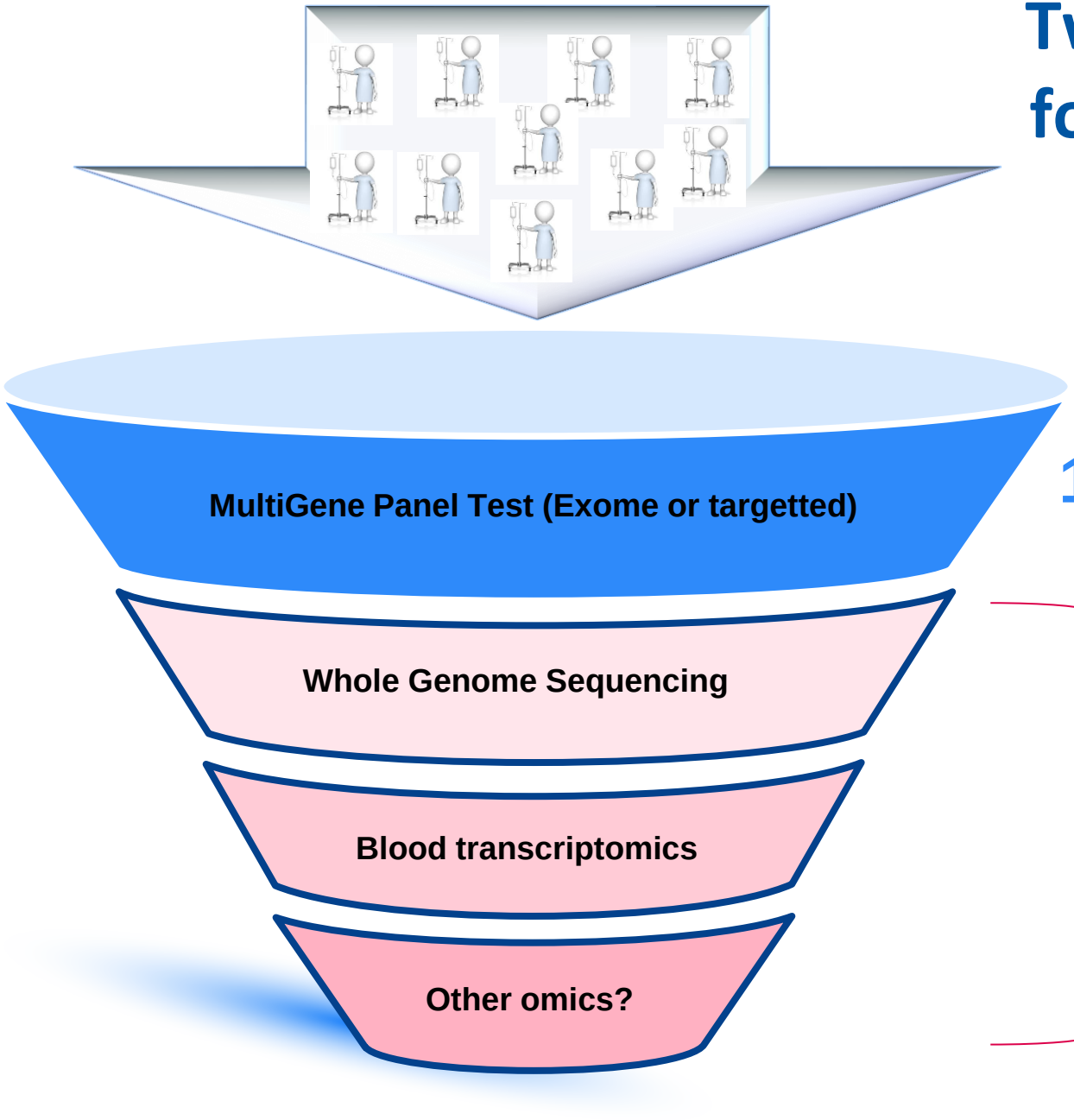
February 11, 2026

CRPP Centre de Référence Pathologies Plaquettaires
MHEMO La Filière des maladies rares de l'hémostase
ebn ERN | EuroBloodNet

Disclosure for conflict

Research Grant	Swedish Orphan Biovitrum (SOBI)

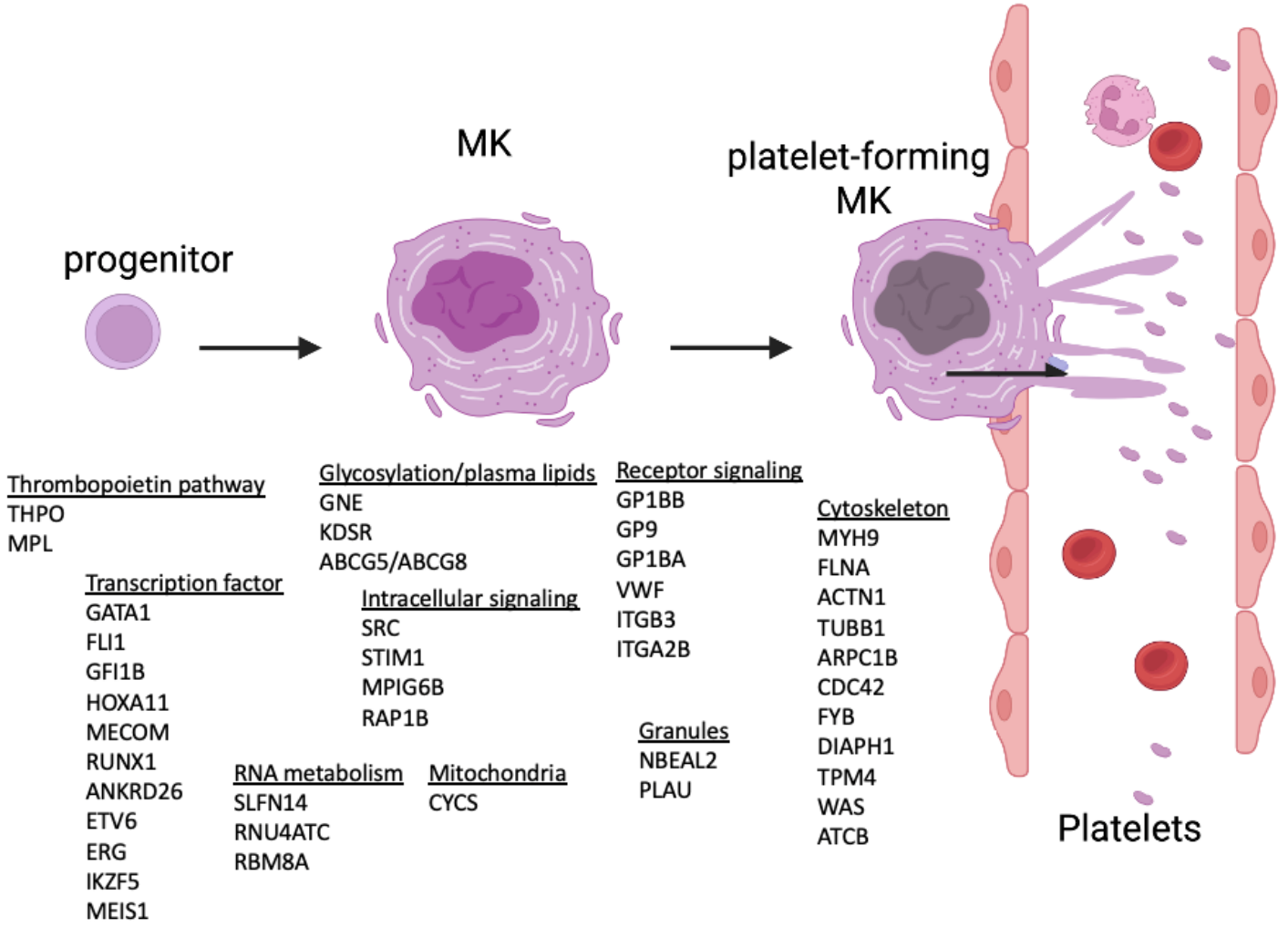
Two Genetic Testing Pathways for Inherited Platelet Function Disorders



1. Genetic testing in the clinic

2. Genetic testing in research

Inherited platelet disorders are heterogeneous (68 genes) & many are ultra rare

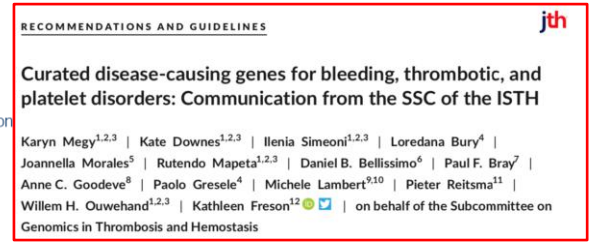


Receptors and Intracellular signalling
P2RY12
TBXA2R
TBXAS1
ABCC4
PTGS1
PLA2G4A
RASGRP2
FERMT3
GP6

Procoagulant activity
ANO6

Granule biogenesis secretion
HPS1, AP3B1, HPS3, HPS4, HPS5, HPS6, DTNBP1, BLOC1S3, BLOC1S5, BLOC1S6, AP3D1, LYST, NBEA, VPS33B, VIPAS39, STXBP2

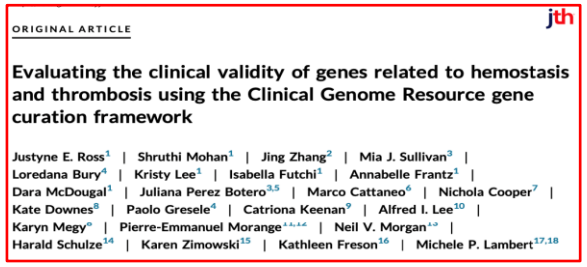
SSC Scientific and Standardization Committee


RECOMMENDATIONS AND GUIDELINES

jth

Curated disease-causing genes for bleeding, thrombotic, and platelet disorders: Communication from the SSC of the ISTH

Karyn Megy[1,2,3] | Kate Downes[1,2,3] | Ilenia Simeoni[1,2,3] | Loredana Bury[4] | Joannella Morales[5] | Rutendo Mapeta[1,2,3] | Daniel B. Bellissimo[6] | Paul F. Bray[7] | Anne C. Goodeve[8] | Paolo Gresele[4] | Michele Lambert[9,10] | Pieter Reitsma[11] | Willem H. Ouwehand[1,2,3] | Kathleen Freson[12] | on behalf of the Subcommittee on Genomics in Thrombosis and Hemostasis


ORIGINAL ARTICLE

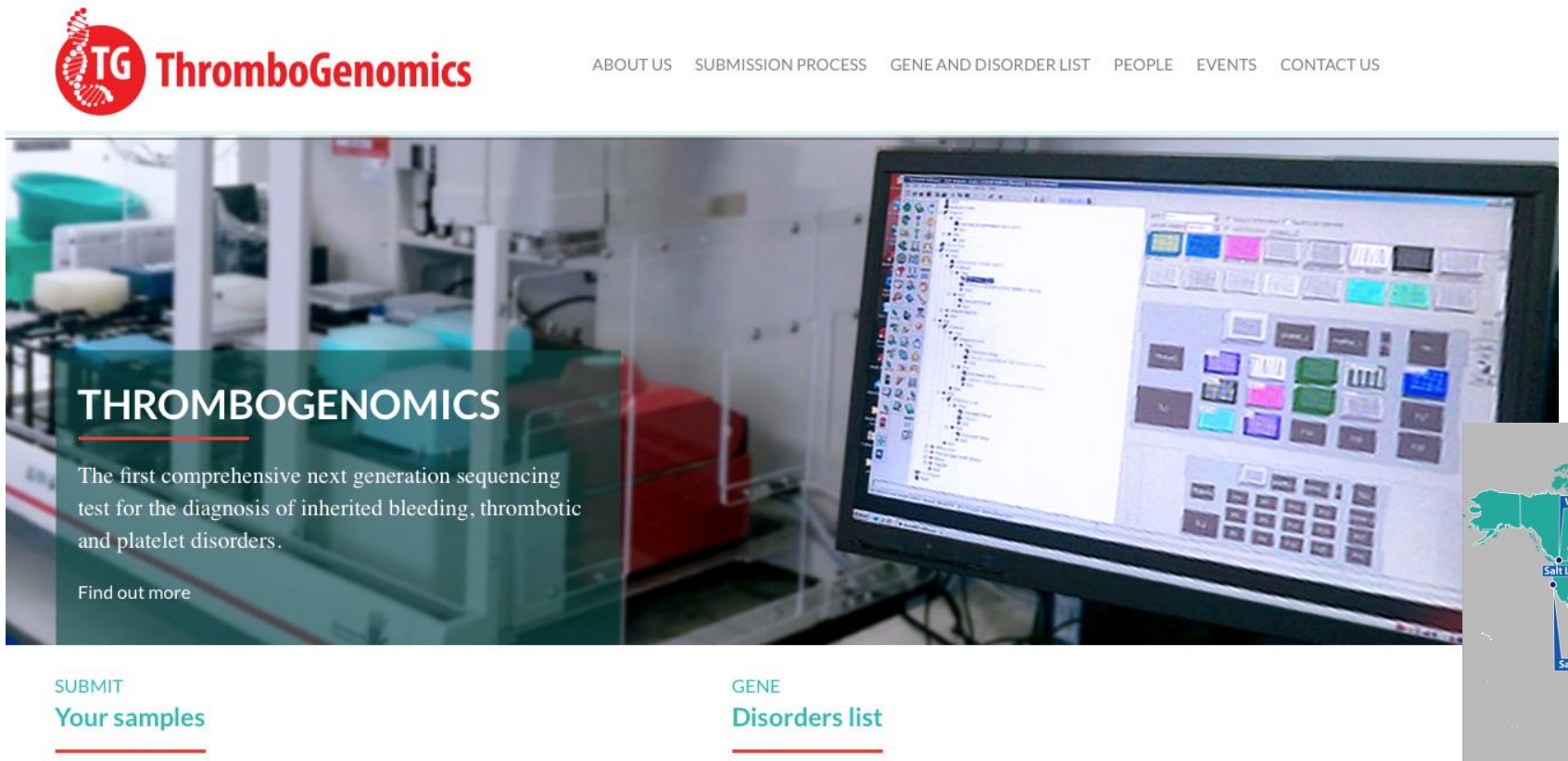
jth

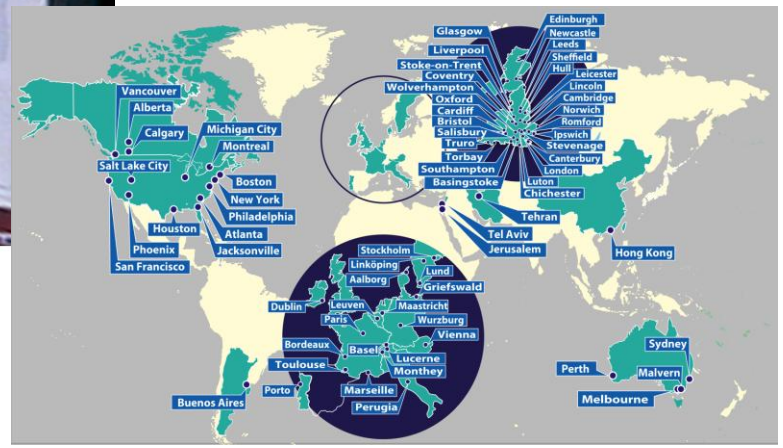
Evaluating the clinical validity of genes related to hemostasis and thrombosis using the Clinical Genome Resource gene curation framework

Justyne E. Ross[1] | Shruthi Mohan[1] | Jing Zhang[2] | Mia J. Sullivan[3] | Loredana Bury[4] | Kristy Lee[1] | Isabella Futchi[1] | Annabelle Frantz[1] | Dara McDougal[1] | Juliana Perez Botero[3,5] | Marco Cattaneo[6] | Nichola Cooper[7] | Kate Downes[8] | Paolo Gresele[4] | Catriona Keenan[9] | Alfred I. Lee[10] | Karyn Megy[11] | Pierre-Emmanuel Morange[12,13,14] | Neil V. Morgan[1,3] | Harald Schulze[14] | Karen Zimowski[15] | Kathleen Freson[16] | Michele P. Lambert[17,18]

ClinGen Clinical Genome Resource

Implementation of multigene panel test : ThromboGenomics study

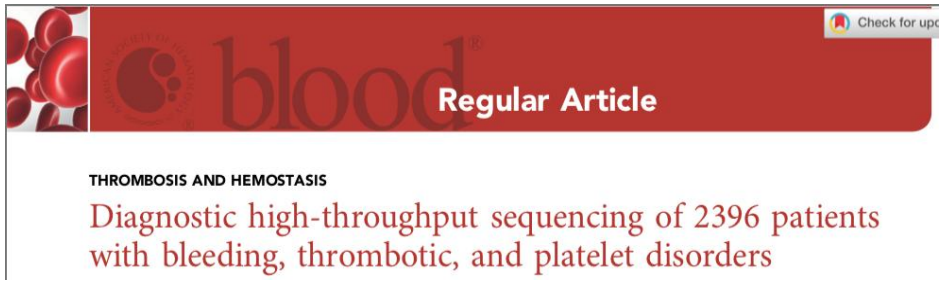




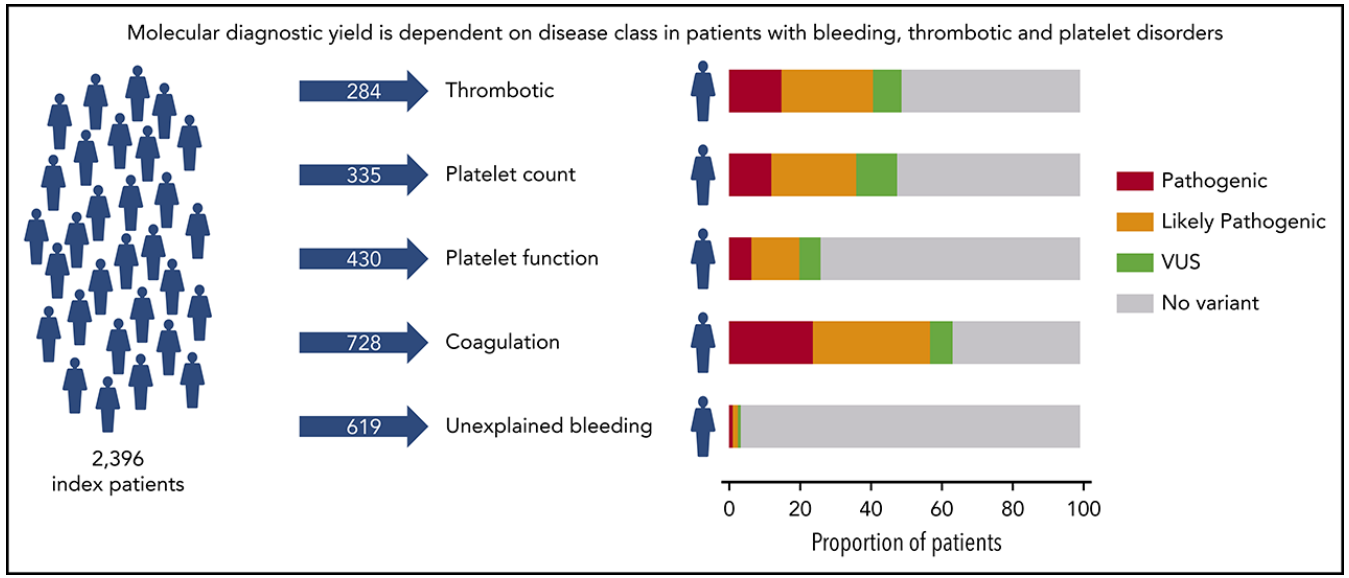
Simeoni I, et al. Blood. 2016

Panel name	Diagnostic-grade (TIER1) genes
Platelet defects gene panel* *Including genes for thrombocytopenia*	ABCC4, ABCG5, ABCG8, ACTB, ACTN1, ANKRD26, ANO6, AP3B1, AP3D1, ARPC1B, BLOC1S3, BLOC1S5, BLOC1S6, CDC42, CYCS, DIAPH1, DTNBP1, ERG, ETV6, FERMT3, FLI1, FLNA, FYB1, GATA1, GFI1B, GNE, GP1BA, GP1BB, GP6, GP9, HOXA11, HPS1, HPS3, HPS4, HPS5, HPS6, IKZF5, ITGA2B, ITGB3, KDSR, LYST, MECOM, MPIG6B, MPL, MYH9, NBEA, NBEAL2, P2RY12, PLA2G4A, PLAU, PTGS1, RASGRP2, RAP1B, RBM8A, RNU4ATAC, RUNX1, SLFN14, SRC, STIM1, STXBP2, TBXA2R, TBXAS1, THPO, TPM4, TUBB1, VIPAS39, VPS33B, VWF, WAS

Diagnostic rates obtained in the ThromboGenomics study



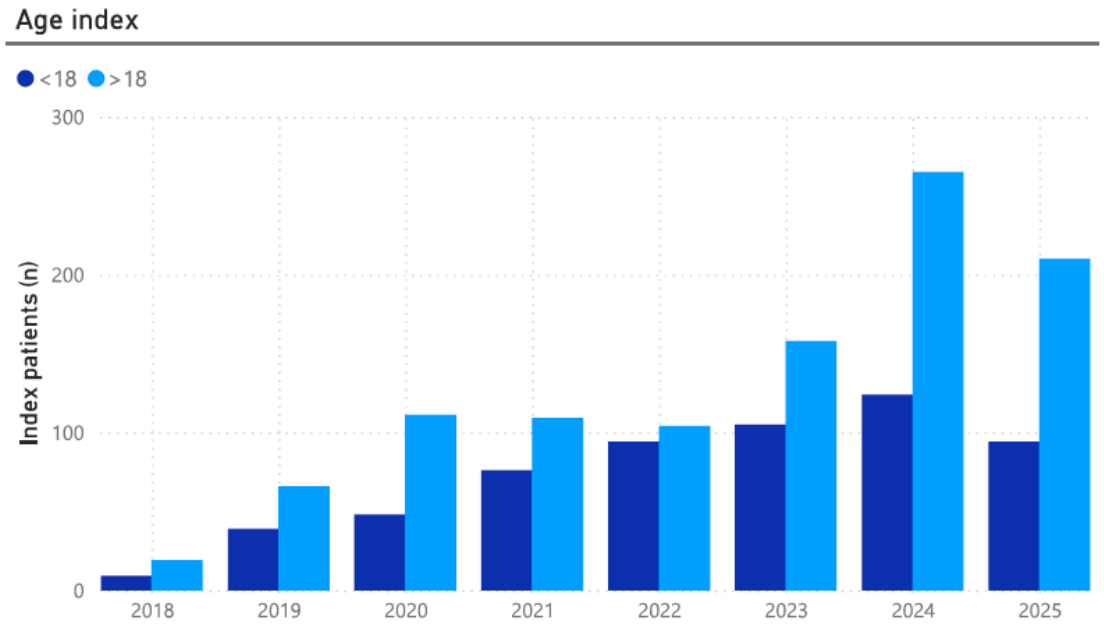
Kate Downes, Blood 2019



Diagnostic rates for

- **Thrombocytopenia 50%**
- **Platelet function disorders 27%**

WES-based panel for bleeding @UZLeuven



Christine Van Laer

- Referral center in Belgium
- Part of NHS (1200 euro/panel – 8 euro/patient), strict inclusion:
  Platelet function disorders: no storage pool disease !
- TAT 3 months
- Accredited test (100% coverage, variants are validated)

J Thromb Haemost. 2023;21:887–895

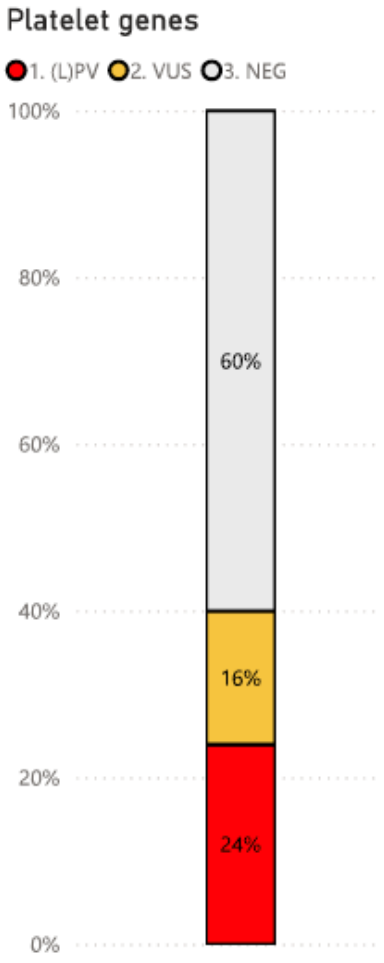
https://doi.org/10.1016/j.jtha.2022.12.007

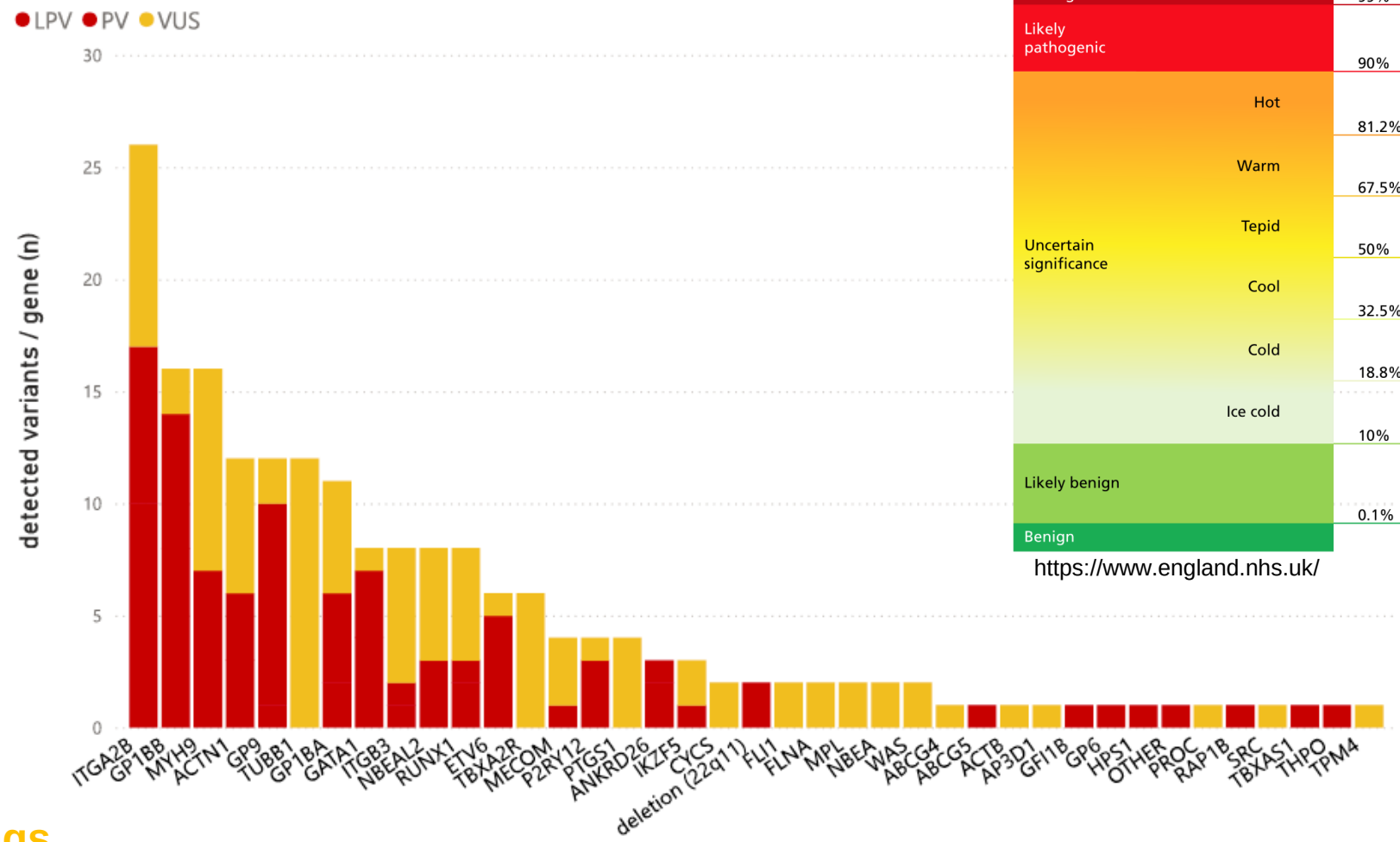
BRIEF REPORT

Interim analysis

Clinical application of multigene panel testing for bleeding, thrombotic, and platelet disorders: a 3-year Belgian experience

Christine Van Laer[1,2] | Marc Jacquemin[1,2] | Sarissa Baert[3] | Veerle Labarque | Chantal Thys[1] | Thomas Vanassche[1,5] | Chris Van Geet[1,4] | Peter Verhamme | Karen Willekens[3] | Anniek Corveleyn[3] | Kathelijne Peerlinck[1,5] | Kathleen Freson[1]





https://www.england.nhs.uk/

These are all “HOT” VUS findings

Most patients have thrombocytopenia, most common function disorders are

- Glanzmann thrombasthenia
- Dominant TBXA2R, P2RY12 and PTGS1 defects

ARTICLE IN PRESS

Received: 24 February 2025 | Revised: 21 April 2025 | Accepted: 28 April 2025

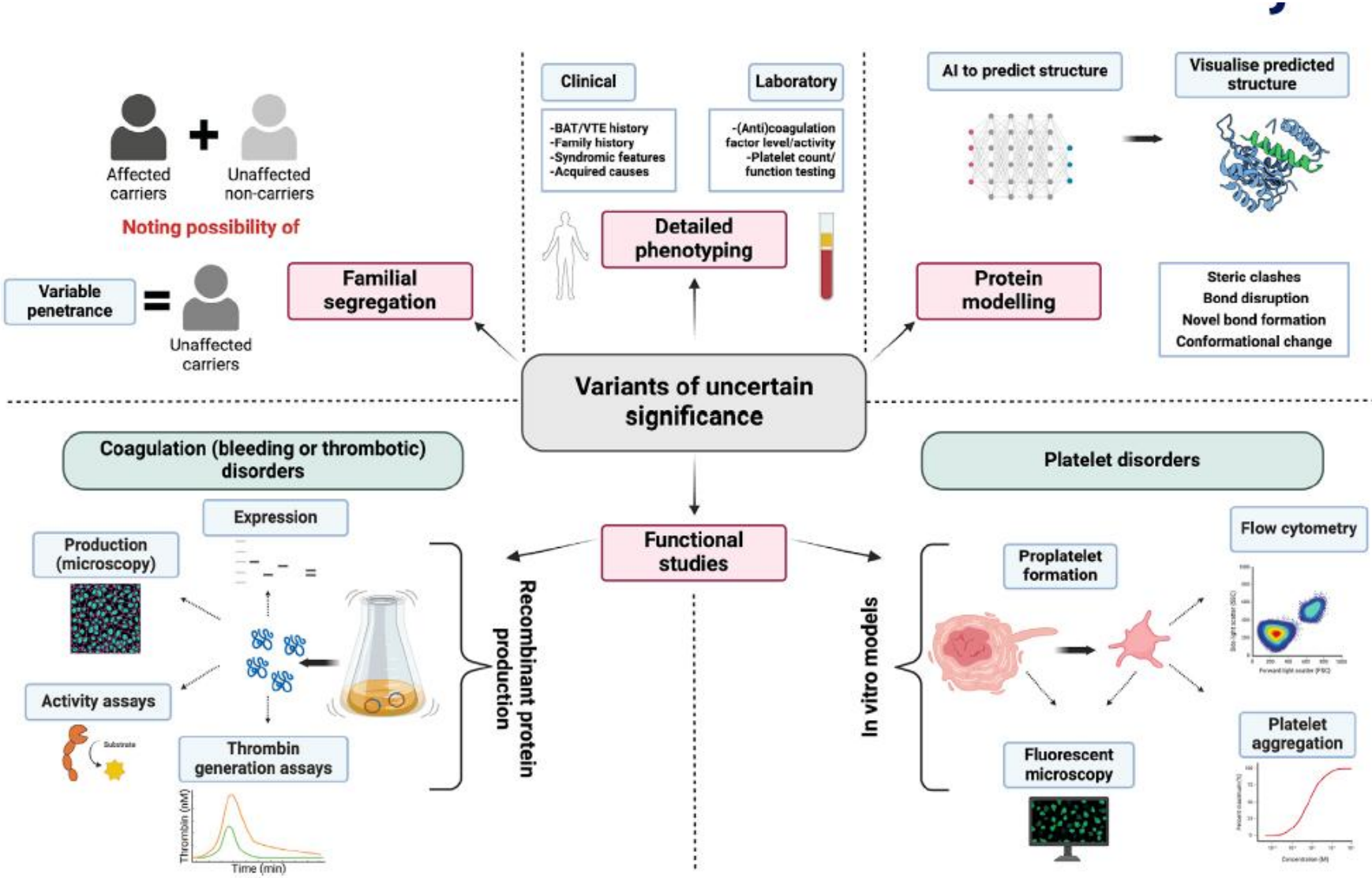
https://doi.org/10.1016/j.jtha.2025.04.026

REVIEW

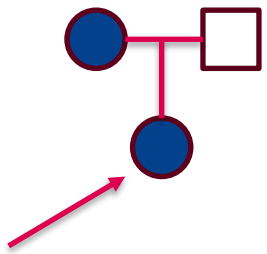
Implementation and clinical utility of multigene panels for bleeding, platelet, and thrombotic disorders

Radha Ramanan[1,2,3] | Andreas Verstraete[1,4] | Christine Van Laer[1,5] | Kathleen Freson[1]

How to reclassify a VUS to LPV?



Additional lab tests for variant reclassification



Index case, 35 y

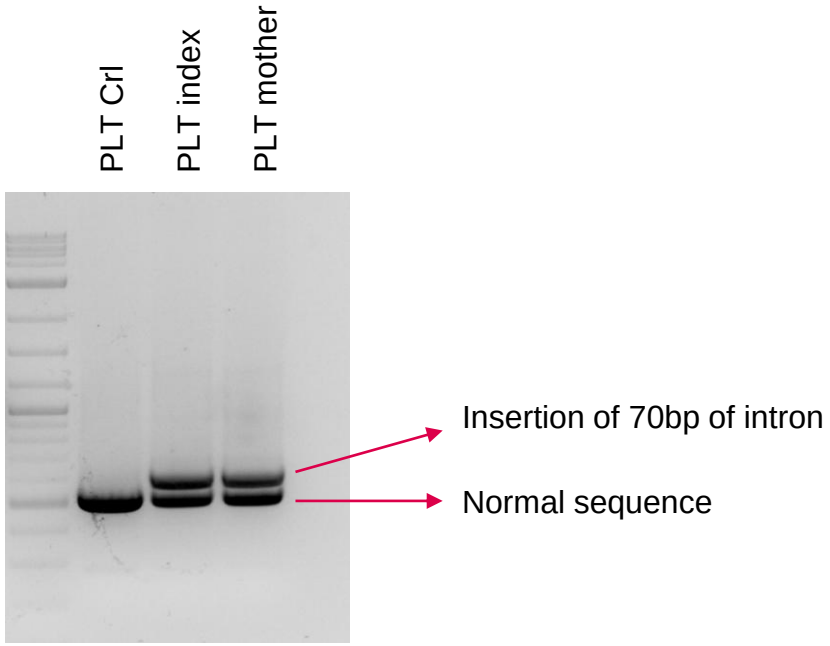
No bleeding symptoms

Platelet count 99-134 K (nl MPV)

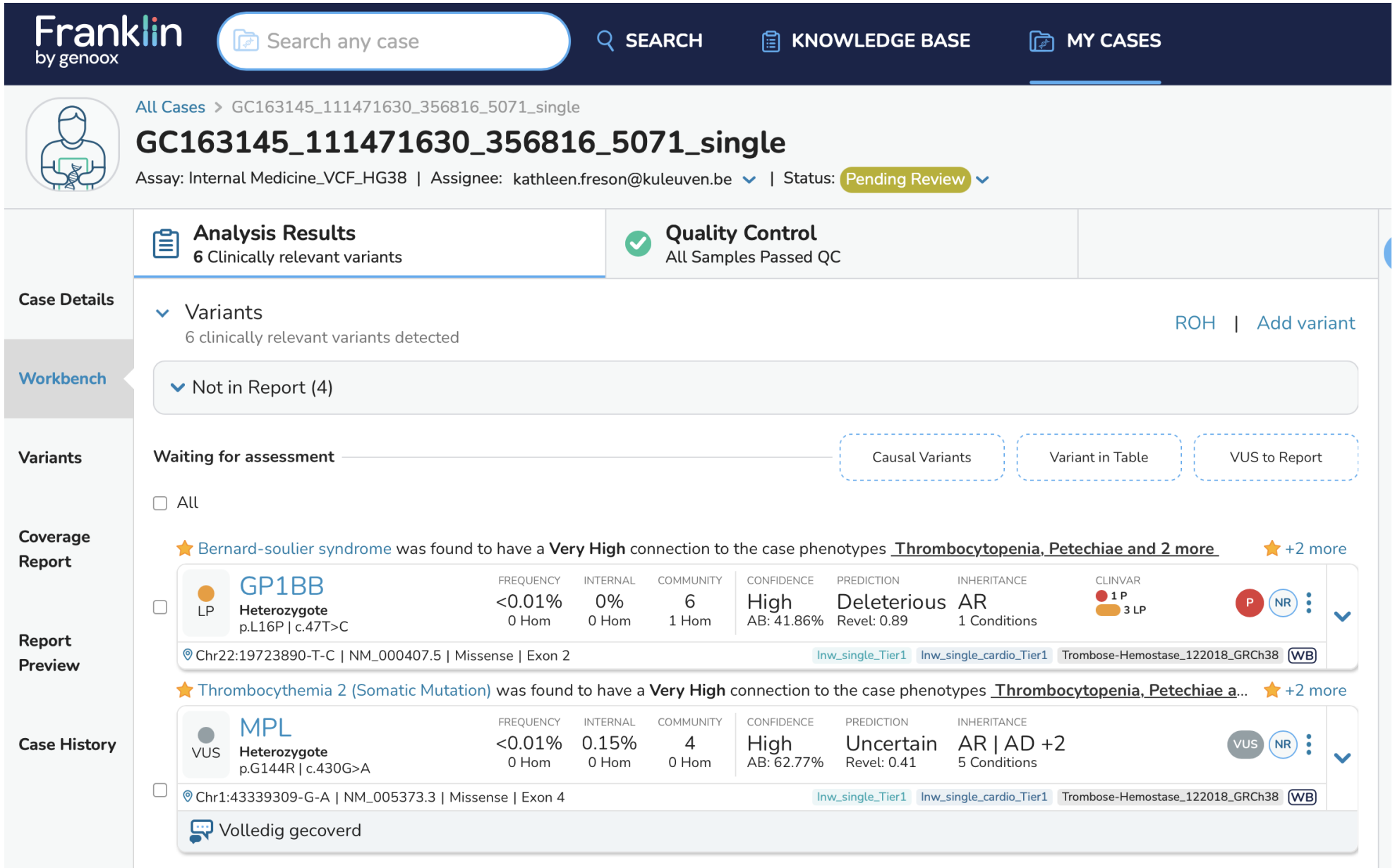
Autosomal dominant TP

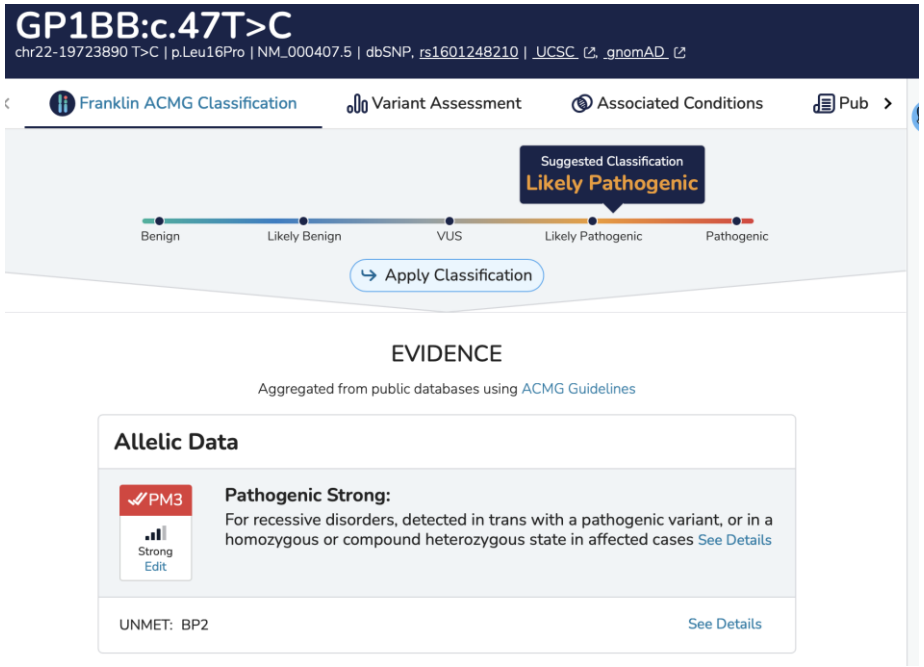
ETV6 c.1254-2A>C VUS

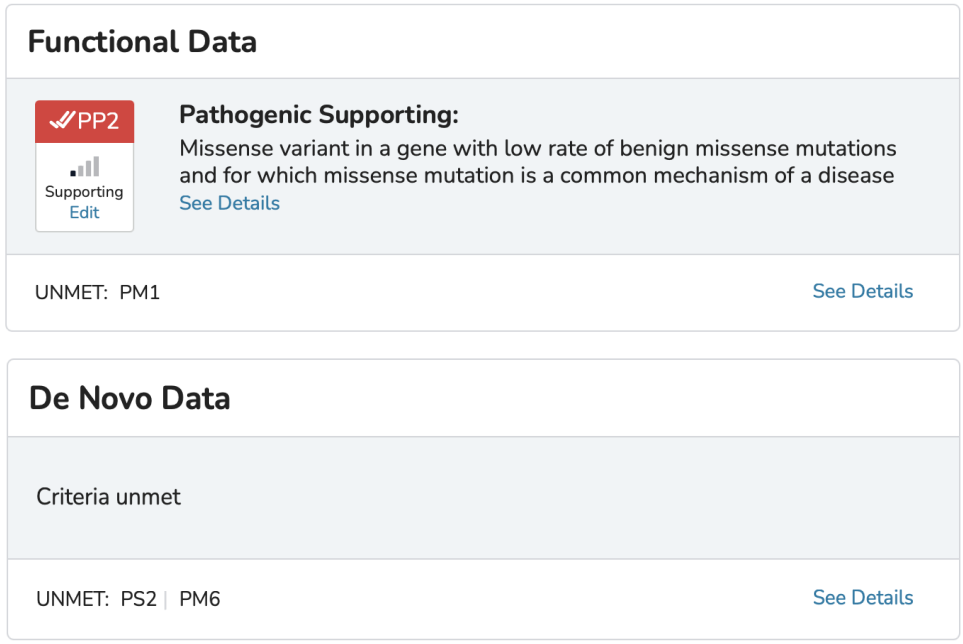
ETV6 c.1254-2A>C LPV



Patient with mild macrothrombocytopenia (100K, MPV 12 fL), mild bleeding, family history with dominant TP

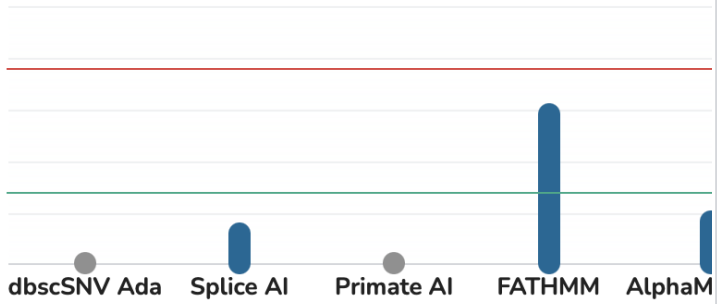



GP1BB:c.47T>C
chr22-19723890 T>C | p.Leu16Pro | NM_000407.5 | dbSNP, rs1601248210 | UCSC, gnomAD
Franklin ACMG Classification
Variant Assessment
Associated Conditions
Pub
Suggested Classification
Likely Pathogenic
Benign
Likely Benign
VUS
Likely Pathogenic
Pathogenic
Apply Classification
EVIDENCE
Aggregated from public databases using ACMG Guidelines
Allelic Data
PM3
Strong
Edit
Pathogenic Strong:
For recessive disorders, detected in trans with a pathogenic variant, or in a homozygous or compound heterozygous state in affected cases See Details
UNMET: BP2
See Details
Population Data
PM2
Moderate
Edit
Pathogenic Moderate:
Extremely low frequency in gnomAD population databases See Details
UNMET: BA1 | BS1 | BS2
See Details
In-silico Predictions
PP3
Moderate
Edit
Pathogenic Moderate:
For a missense or a splicing region variant, computational prediction tools unanimously support a deleterious effect on the gene See Details
Franklin uses the latest recommendations (2022) for PP3/BP4 rules Learn how
UNMET: BP4
See Details


Functional Data
PP2
Supporting
Edit
Pathogenic Supporting:
Missense variant in a gene with low rate of benign missense mutations and for which missense mutation is a common mechanism of a disease
See Details
UNMET: PM1
See Details
De Novo Data
Criteria unmet
UNMET: PS2 | PM6
See Details

Predictions

*Prediction scores were normalized to allow integrated graph view



See detailed pr

4 evidences

Submissions: LP(3) P(1)

CLINVAR

Franklin Community (0)

Clinvar (4)

Clinvar Clinical Significance: **Likely pathogenic**

Thrombocytopenia

Review Status: ★☆☆☆ | RCV000852142 | Clinvar

Last evaluated: Feb 16, 2023 | 1 submitter

Clinvar Clinical Significance: **Pathogenic**

Bernard Soulier Syndrome

Review Status: ★☆☆☆ | RCV002222630 | Clinvar

Last evaluated: Feb 16, 2023 | 1 submitter

Clinvar Clinical Significance: **Likely pathogenic**

Not Provided

Review Status: ★☆☆☆ | RCV003324792 | Clinvar

Last evaluated: Feb 16, 2023 | 1 submitter

Clinvar Clinical Significance: **Likely pathogenic**

Macrothrombocytopenia

Review Status: ☆☆☆☆ | RCV001003916 | Clinvar

Internal Frequency

0%
Very Rare variant in your Samples

0
Number of Homozygote

Sample	Phenotypes	Affected status	Ethnicity	Zygosity	Depth
GC163145_111471630_356816_5071	Thrombocytopenia, Petechiae, Epistaxis, Menorrhagia	Affected	N/A	Het	43
GC164574_111844541_361920_6271	N/A	Affected	N/A	Het	52

Phenotypes

Click the tag to disable the phenotype

No Phenotype was added

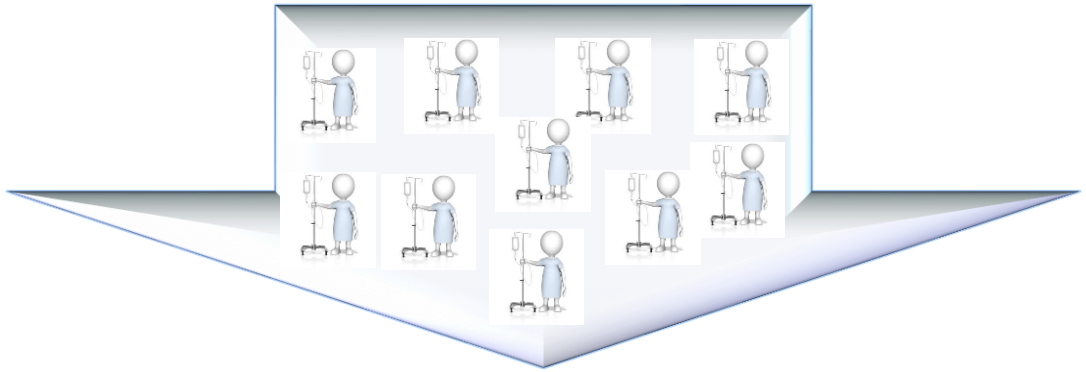
Add / Remove Phenotypes

Case Comments

Fenotype: trombopenie, verhoogde bloedingsneiging
Voorafgaand onderzoek: /
Familiegeschiedenis: vader milde trombopenie
Minimize

Add / Edit

Two Genetic Testing Pathways for Inherited Platelet Function Disorders



40%

MultiGene Panel Test (Exome or targetted)

Whole Genome Sequencing

Blood transcriptomics

Other omics?

1. Genetic testing in the clinic

2. Genetic testing in research

Gene discovery using WGS

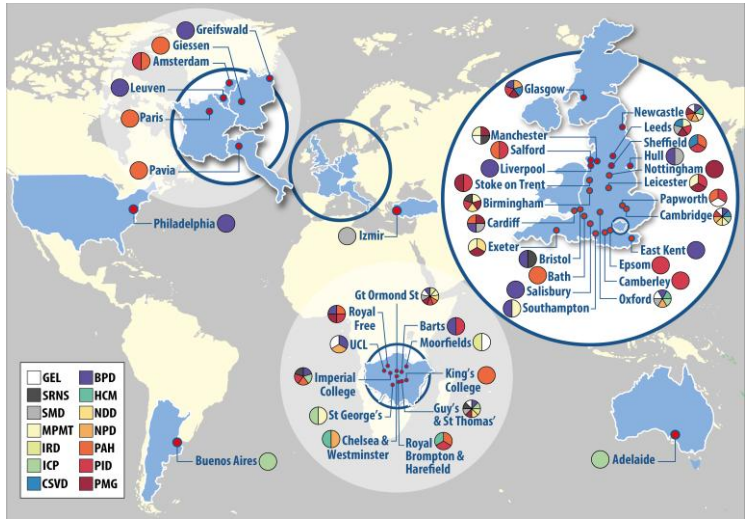
NIHR BioResource
Rare Diseases

Bleeding, thrombotic and Platelet Disorders	BPD		Multiple Primary Malignant Tumours	MPMT
Cerebral Small Vessel Disease	CSVD		Neurological and Developmental Disorders	NDD
Ehler-Danlos Syndromes	EDS		Neuropathic Pain Disorders	NPD
Genomics england Rare Diseases Pilot-II	GEL		Pulmonary Arterial Hypertension	PAH
Hypertrophic Cardiomyopathy	HCM		Primary Immune Disorders	PID
Intrahepatic Cholestasis of Pregnancy	ICP		Primary Membranoproliferative Glomerulonephritis	PMG
Inherited Retinal Disorders	IRD		Stem cell and Myeloid Disorders	SMD
Leber Hereditary Optic Neuropathy	LHON		Steroid Resistant Nephrotic Syndrome	SRNS
biobank uk Improving the health of future generations		UK Biobank – Extreme Red Cell Traits		UKBio

- **57** NHS Hospitals and **26** non-UK Hospitals

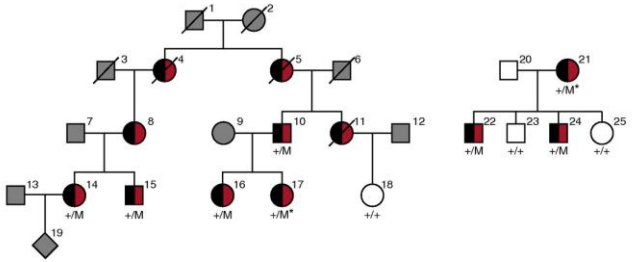
  (Bleeding & Platelet Disorders 1916 patients)

- **13,037 index patients**

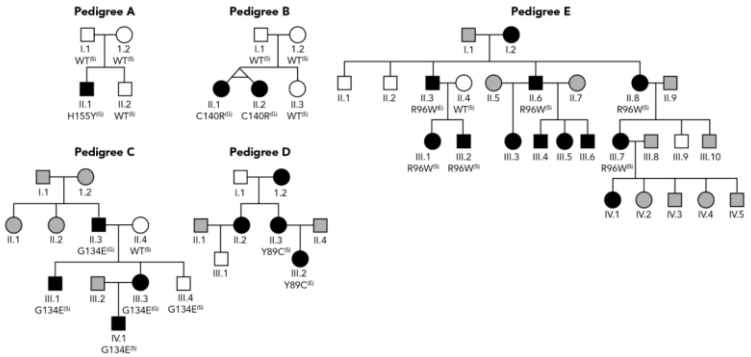


Additional gene discovery in a genome

DIAPH1-related thrombocytopenia + deafness



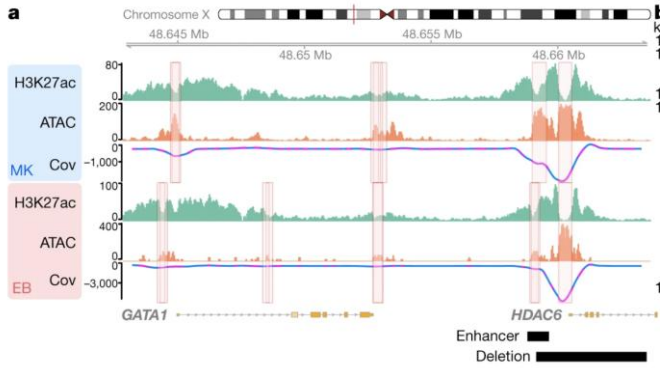
IKZF5-related thrombocytopenia



Deletions in noncoding DNA

Turro et al, 2020, Nature

GATA1/HDAC6-related thrombocytopenia + Autism

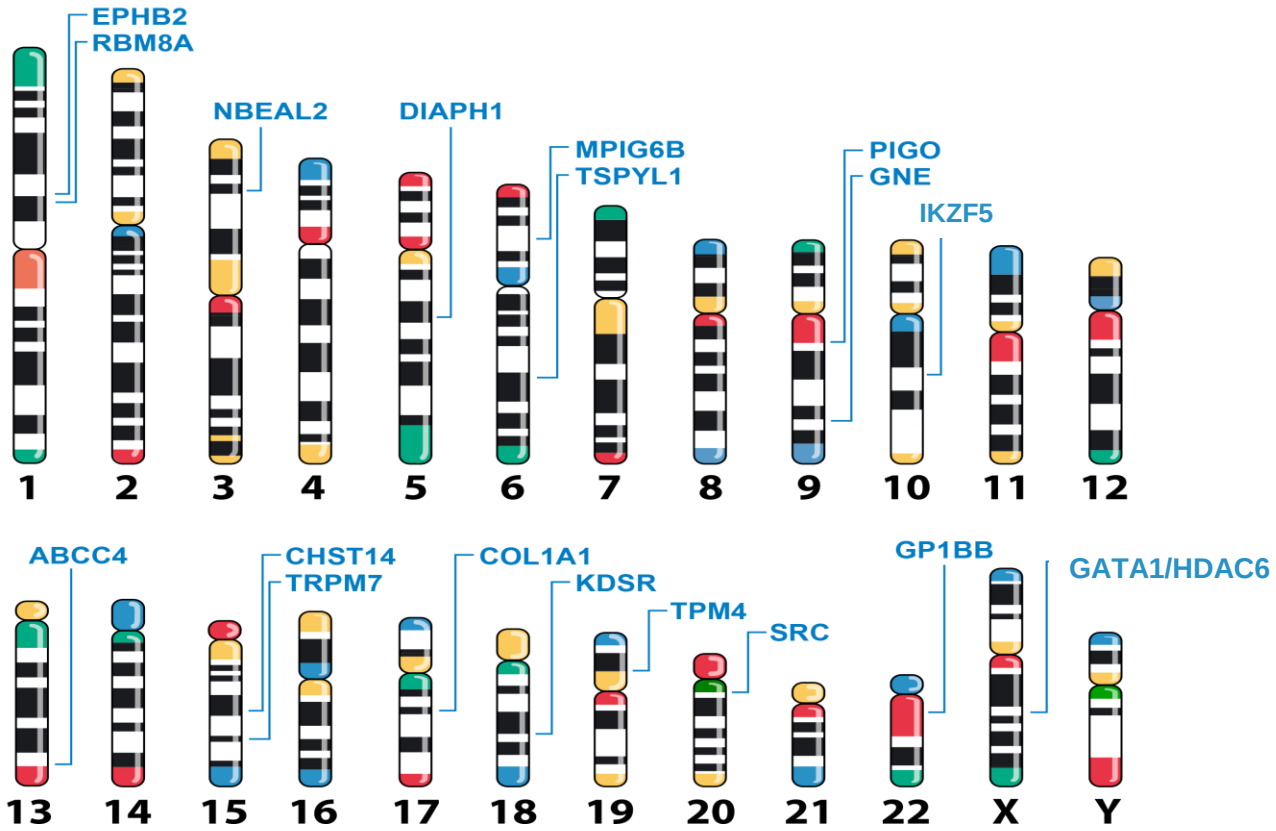


Statistical driven discoveries:

Unrelated patients with same genotype-phenotype using BeviMed (Ernest Turro, Daniel Greene)

Stritt et al, 2016, Blood
Lentaigne et al, 2019, Blood

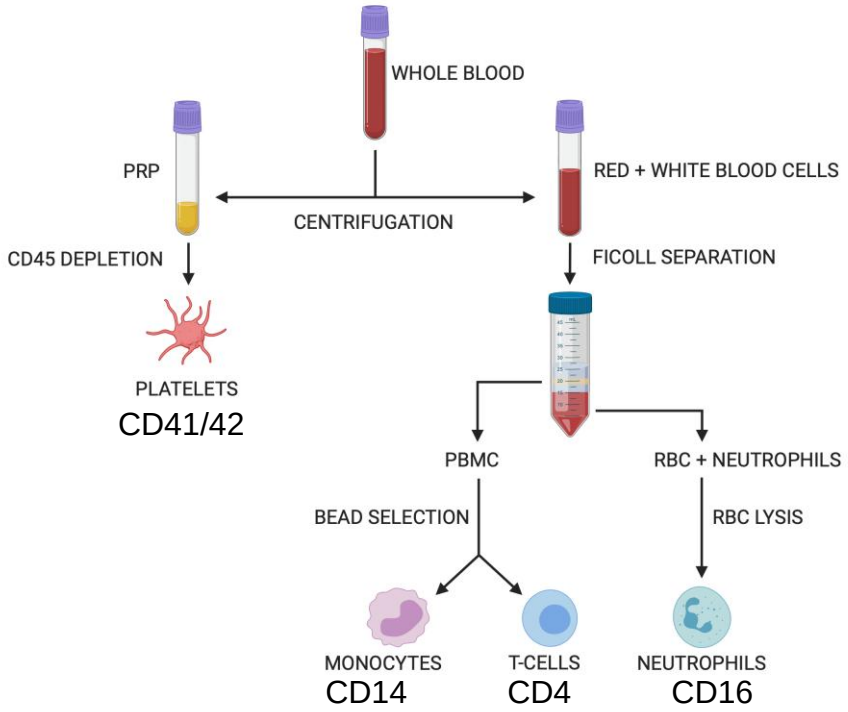
2011-2020: 18 new genes for bleeding & platelet disorders



UZLeuven (543 patients): Only 10% diagnostic rate

Albers *et al*, Nat Genetics 2011; Albers *et al*, Nat Genetics 2012; Cvejic *et al*, Nat Genetics 2013; Chen *et al*, Science 2014; Westbury *et al*, Genome Medicine 2015*;* Green *et al,* AJHG 2016; Stritt *et al*, Nat Comm 2016; Turro *et al,* Science Transl Med 2016; Stritt *et al*, Blood 2016; Simeoni *et al*, Blood 2016; Lentaigne e*t al*, Blood 2016; Poggi *et al,* Haematologica 2016; Bariana *et al*, BJH 2017; Siva-palaratnam *et al,* Blood 2017; Pleines *et al*, JCI 2017; Greene *et al*, AJHG 2017; Westbury *et al,* Blood 2017; Sivapalaratnam *et al,* BJH 2017; Morren *et al,* Orphanet 2017*; Freson et al,* JTH 2017; Sowerby *et al,* JCI 2017; Mayer *et al*, Blood 2018; Revel-Vilk *et al,* Blood 2018; Berrou *et al*, Blood 2018; Hofman *et al*, Blood 2018; Bariana *et al,* Haematologica 2018; Westbury *et al,* Blood Adv 2018; Lentainge et al, Blood 2019; Buyse et al, HMG 2021

Added value of (blood cell) transcriptomics?

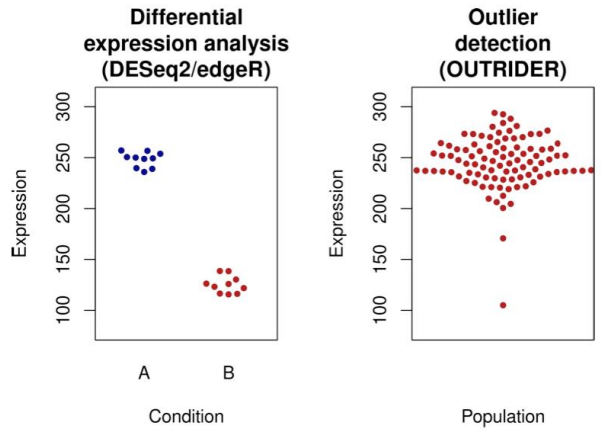


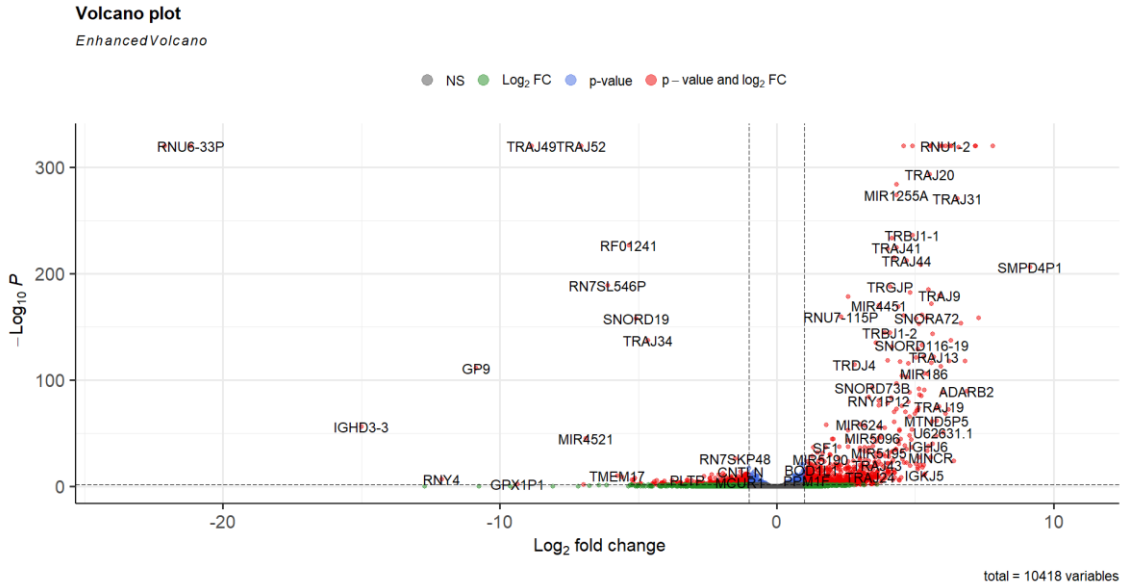
Information about gene expression and splicing outliers using ML-based approaches
OUTRIDER and FRASER

Brechtmann et al OUTRIDER: A statistical method for detecting aberrantly expressed genes in RNA sequencing data; *AJHG,* 2018
Scheller et al Improved detection of aberrant splicing with FRASER 2.0 and the intron Jaccard index. AJHG, 2023

Platelet transcriptome analysis with OUTRIDER

Koen De Wispelaere

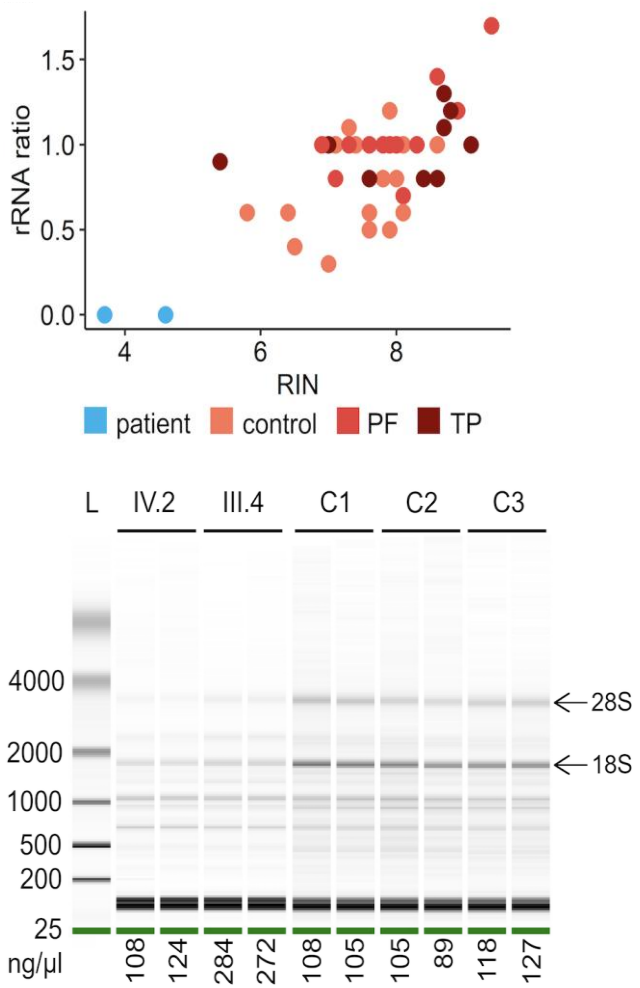


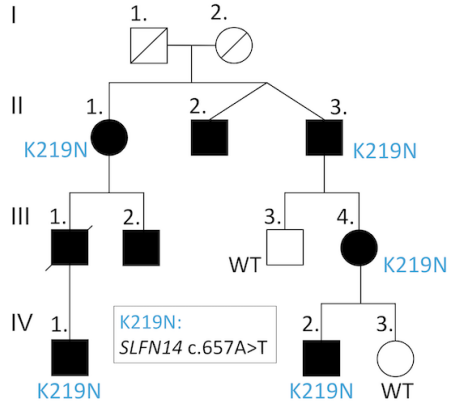


Validation in a Bernard Soulier Syndrome patient
(GP9 homozygous deletion)

ISTH 2026 abstract

Transcriptomics for understanding of disease mechanism



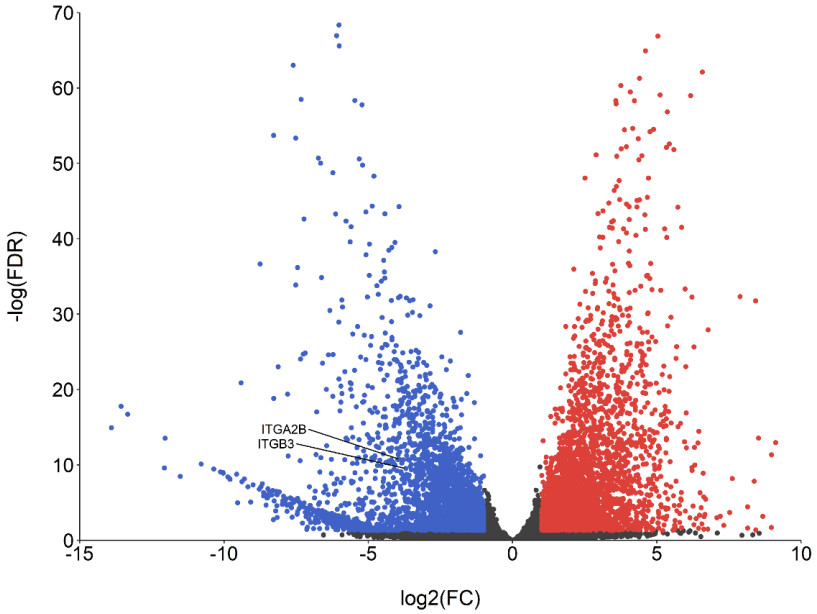


SLFN14 –K219N (endoribonuclease with an unknown role in blood)

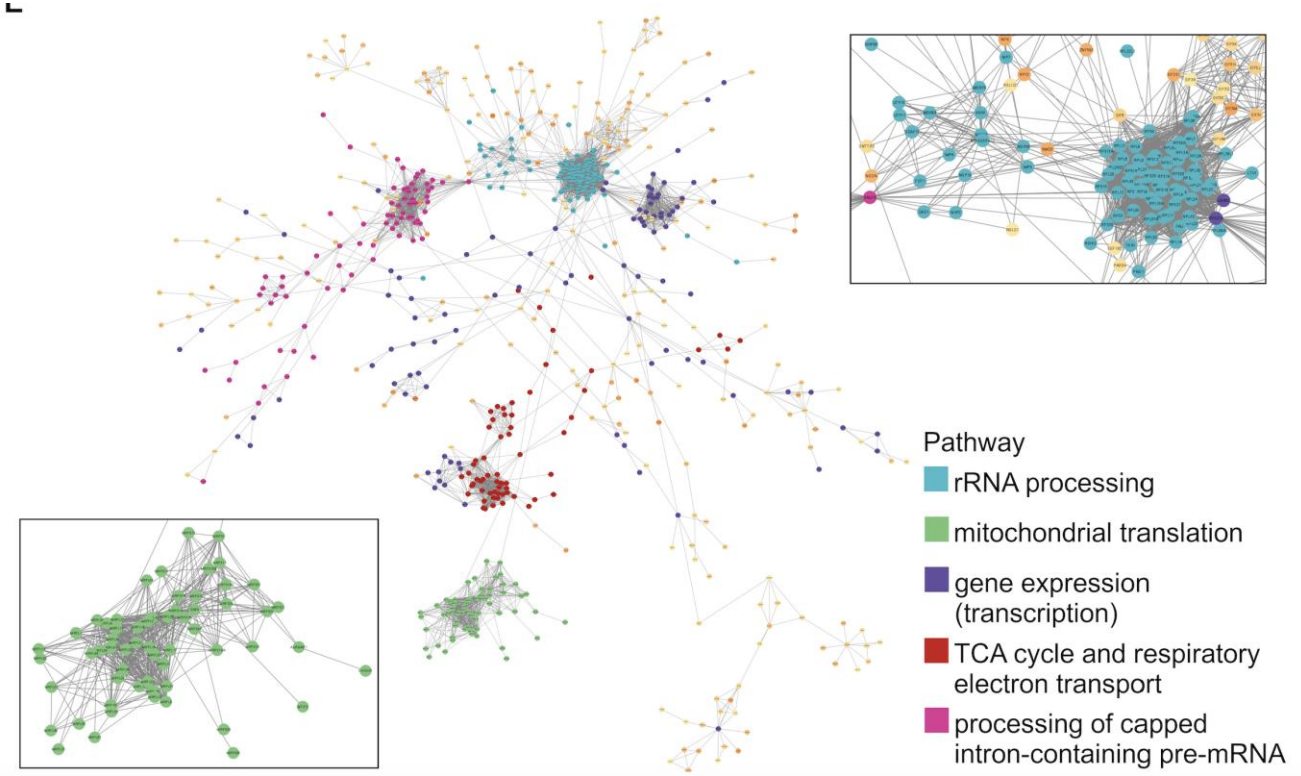
Mild thrombocytopenia + Mild PLT dysfunction + “Obvious bleeding”

Ver Donck et al, Blood, 2023

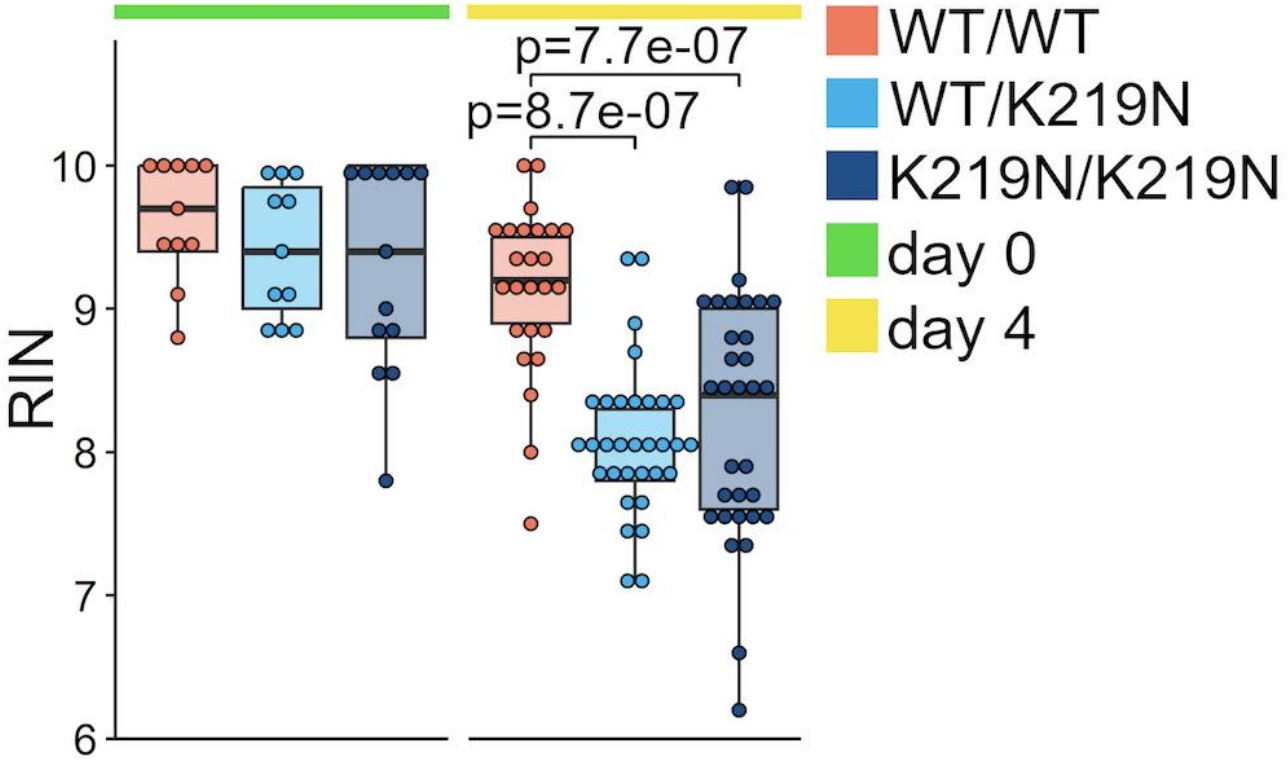
Extensive RNA dysregulation in SLFN14 defective platelets

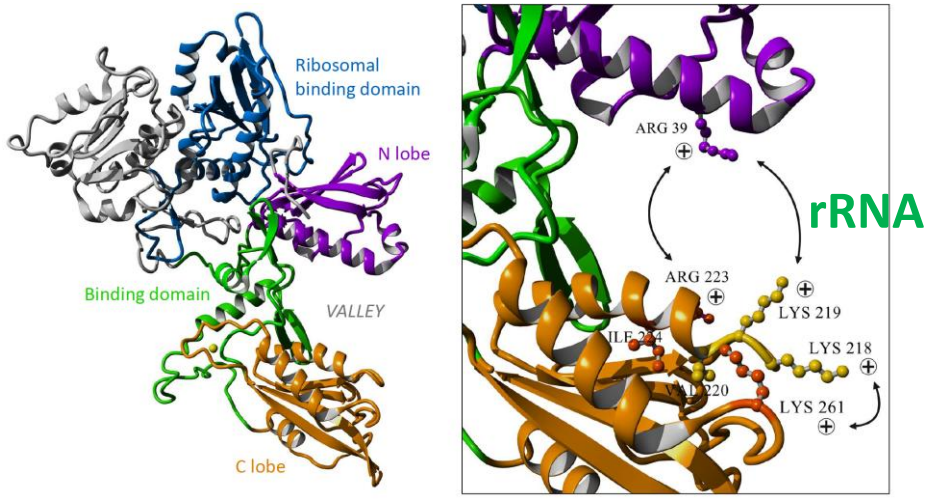


2888 DOWN & 2999 UP
(|log2FC|>1, FDR<0.05)



Cell model for the disease :
rRNA degradation in SLFN14 defective megakaryocytes



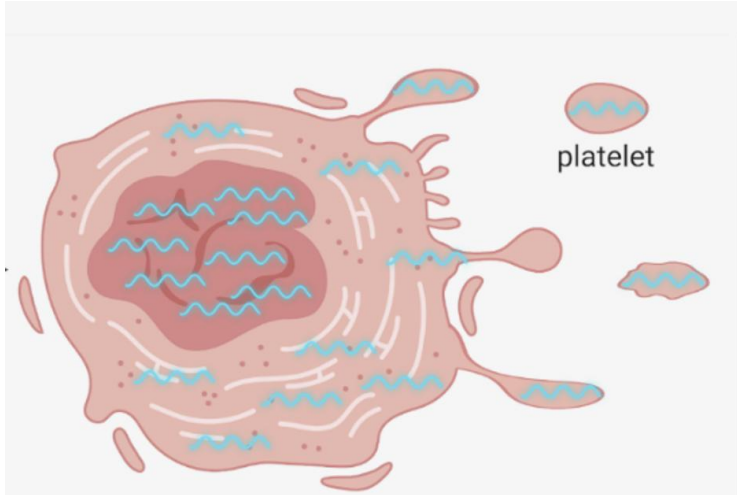


SLFN14 structure

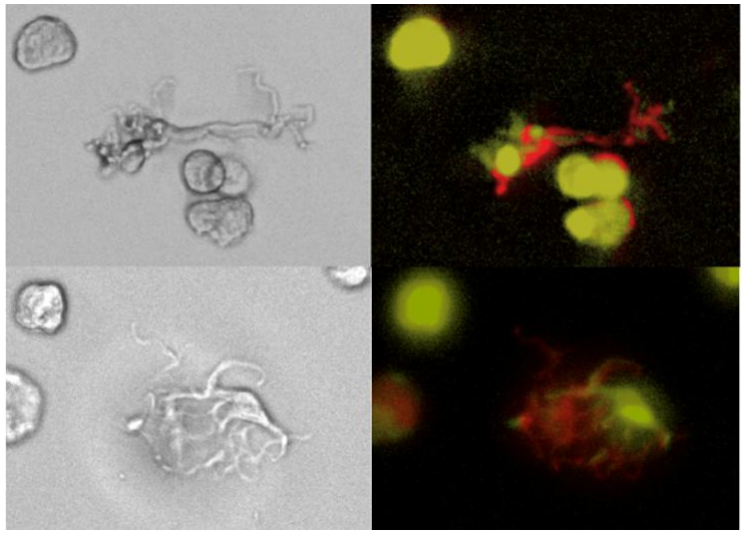
Can platelet transcriptomes (no nucleus) be used ?

What will happen in case of thrombocytopenia?

Koen De Wispelaere



De Wispelaere et al, IJMC, 2022



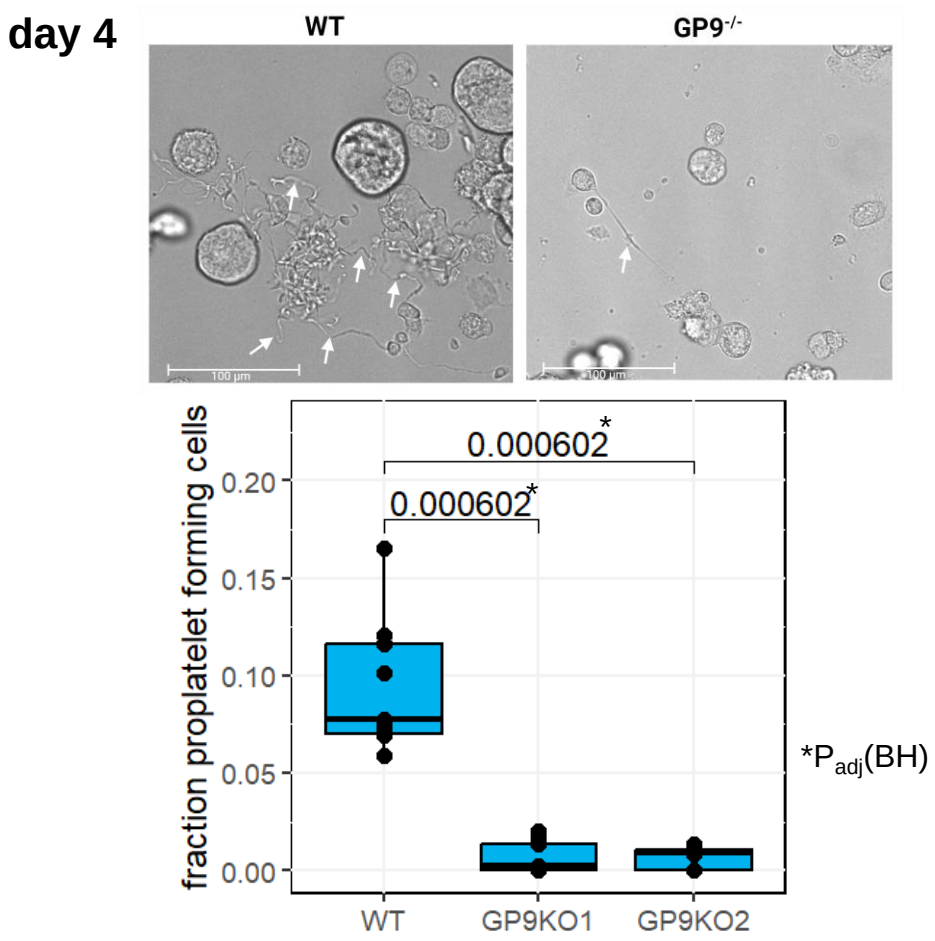
StrandBrite RNA
SiR-Actin

De Wispelaere et al, HemaSphere, 2025

imMKCL disease models for BSS and IKZF5-related thrombocytopenia

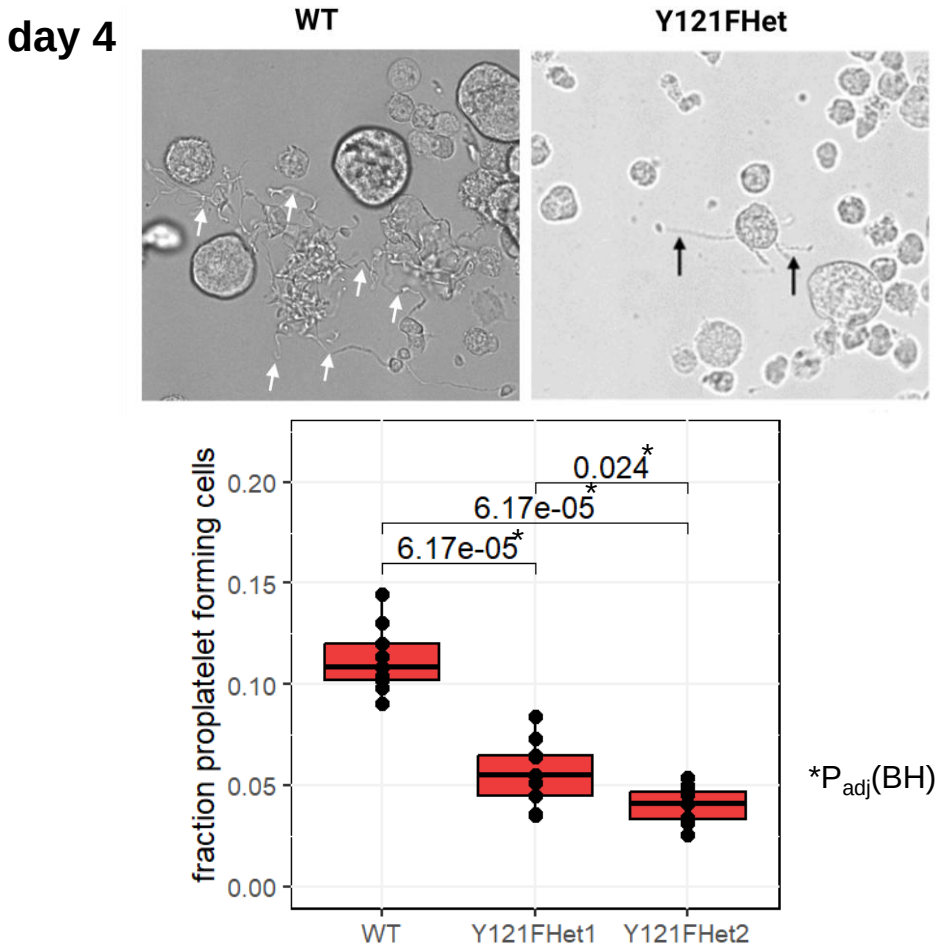
Bernard Soulier Syndrome GP9$^{-/-}$

VWF receptor



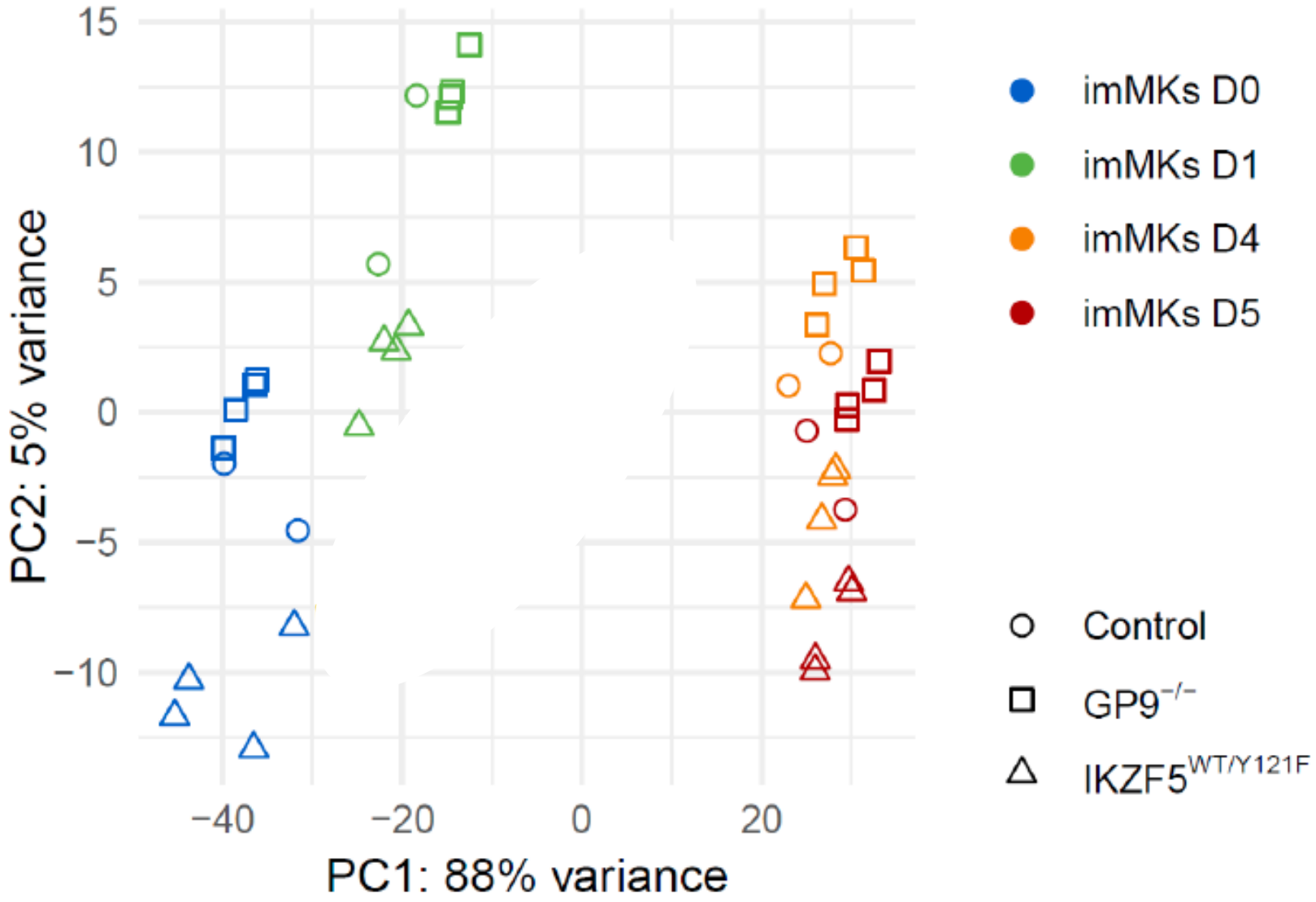
IKZF5-related thrombocytopenie IKZF5$^{Y121F/WT}$

Transcription factor

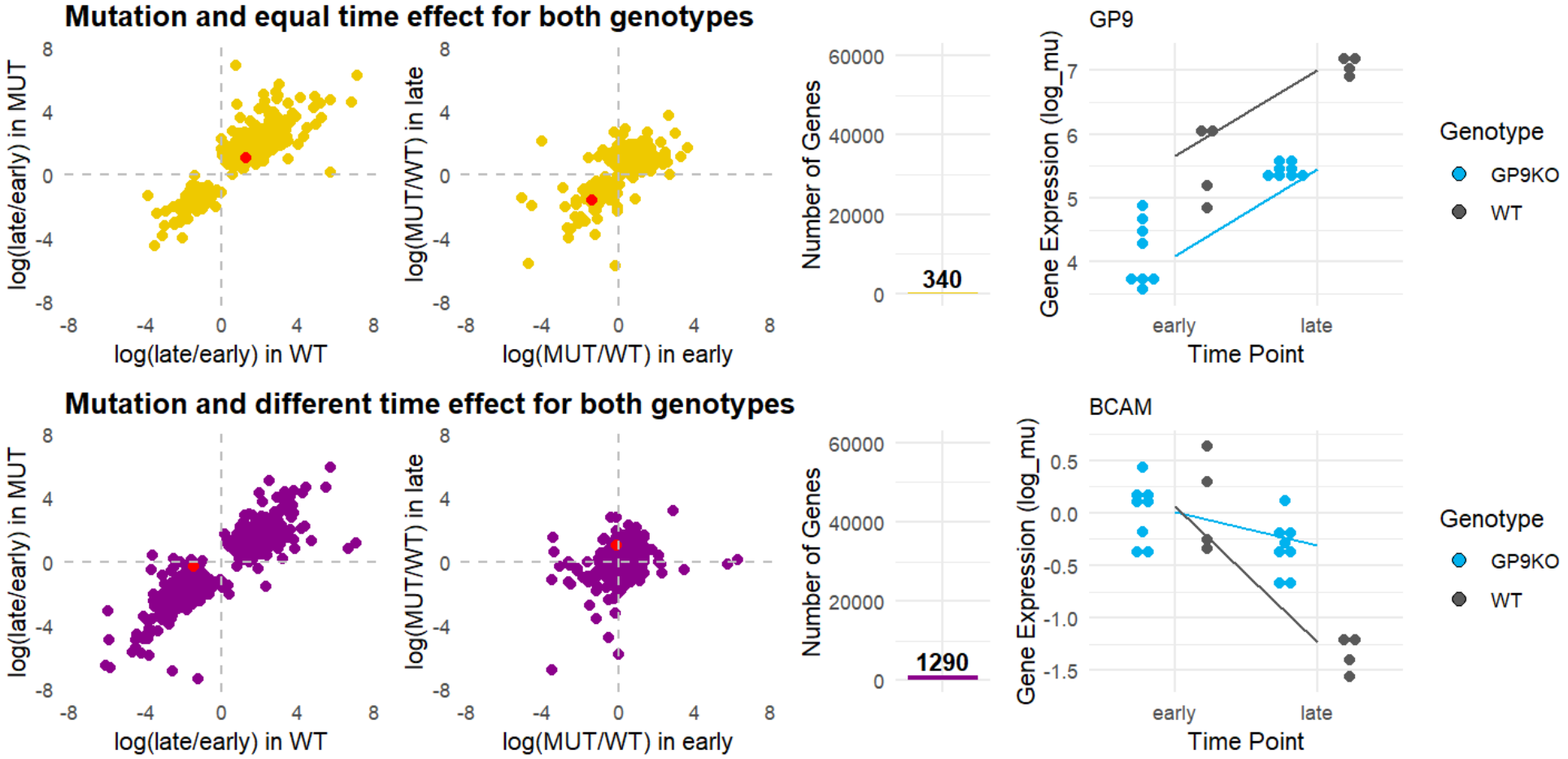


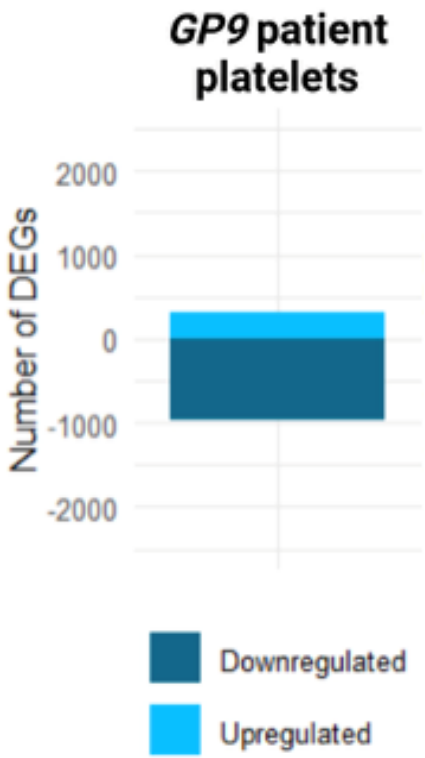
De Wispelaere et al, HemaSphere, 2025

Transcriptome analysis of GP9$^{-/-}$ and IKZF5$^{Y121F/WT}$ deficient MKs (in vitro) and platelets (patients)

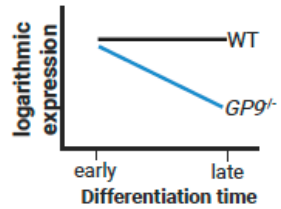


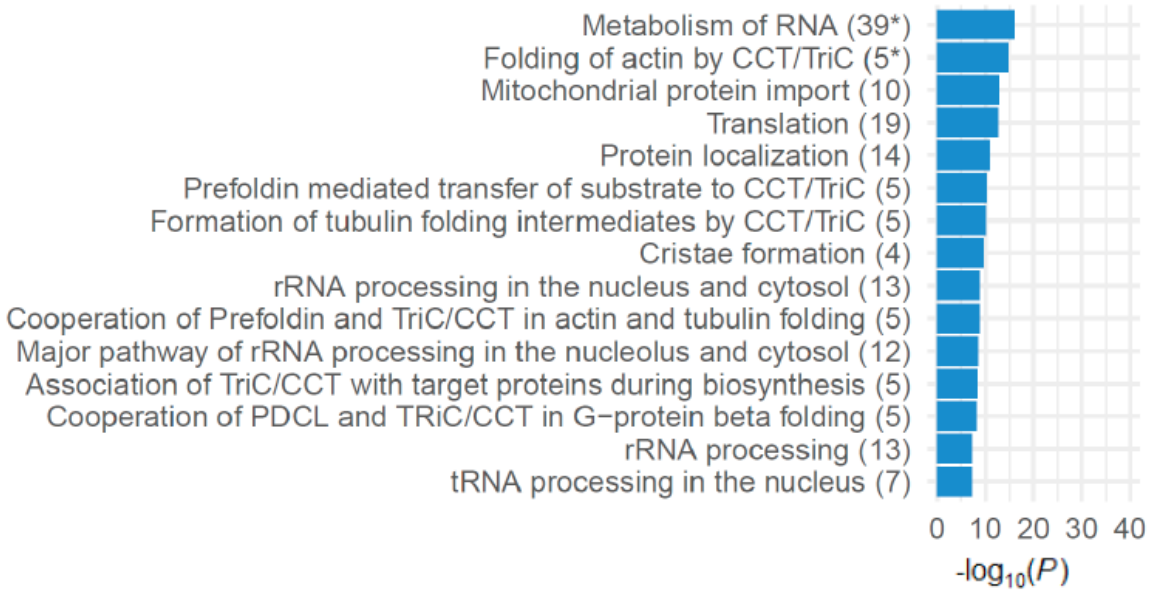
Longitudinal gene expression during MK differentiation

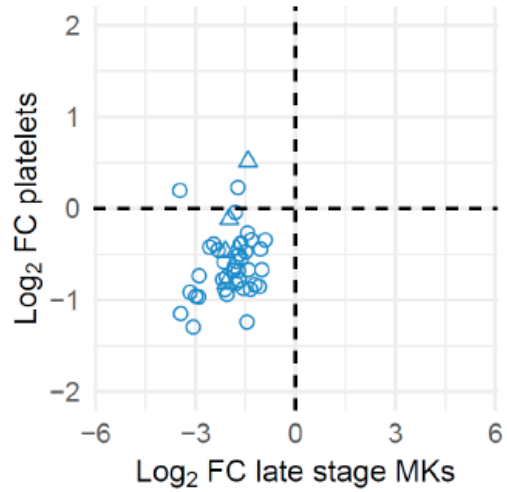




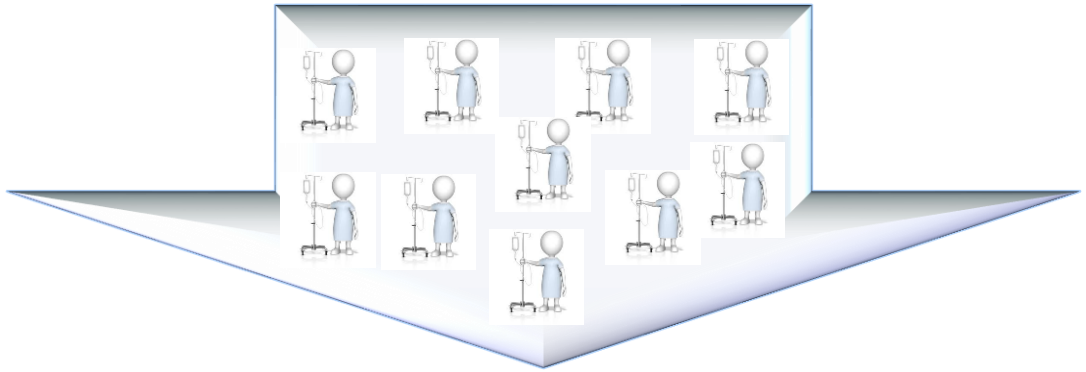
Late downregulation in *GP9*$^{-/-}$ MKs (289 genes)

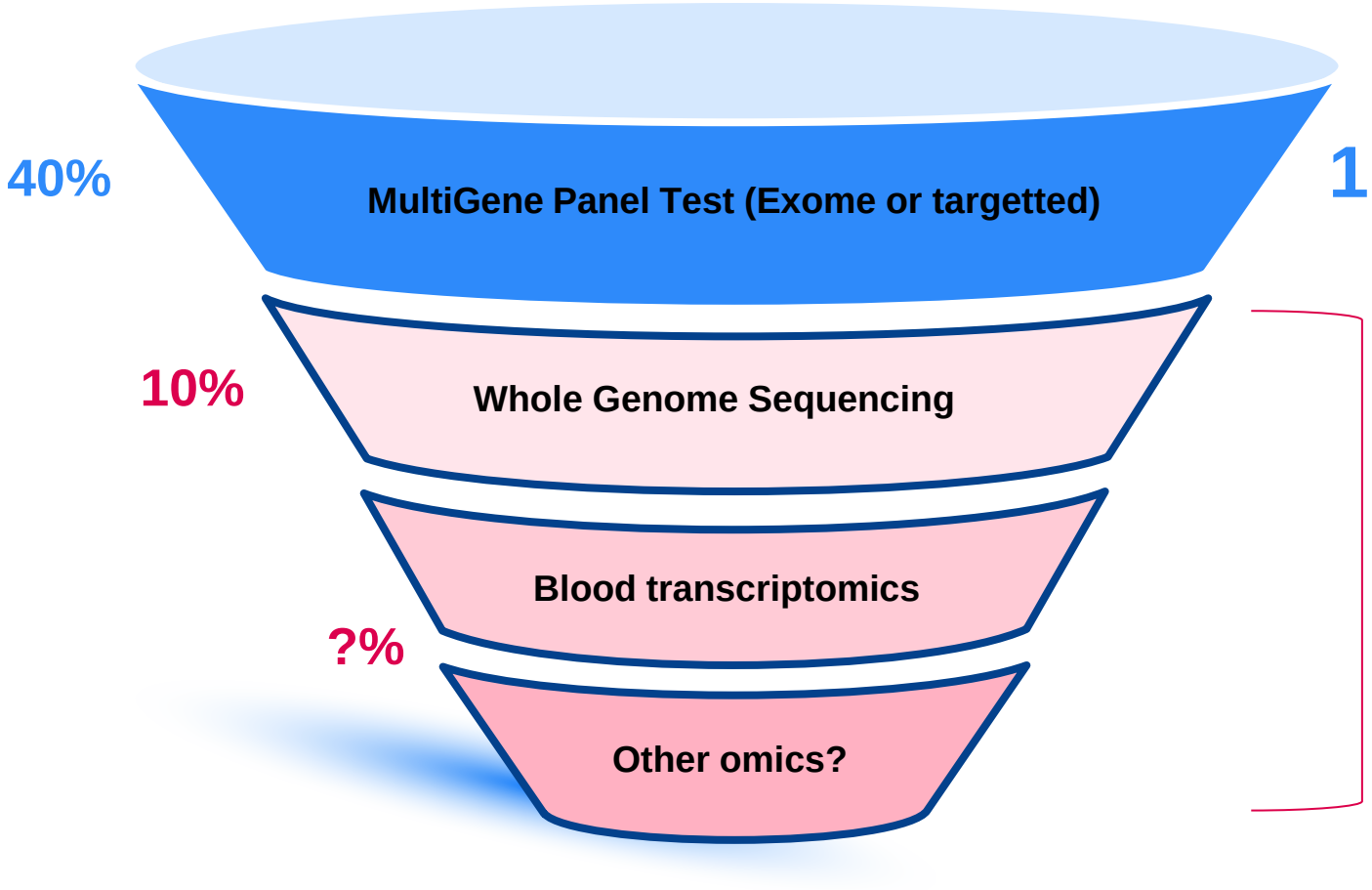






Two Genetic Testing Pathways for Inherited Platelet Function Disorders





1. Genetic testing in the clinic

2. Genetic testing in research

Take home messages

- NGS for clinical purposes: use of a multigene panel results in 30 (function disorders) - 60% (thrombocytopenia) diagnostic rate
- Whole genomes are useful for gene discovery, but it feels like finding a needle in the haystack at the single patient level
- Transcriptomes can contribute to disease understanding but their added value for gene discovery is not yet clear

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KU LEUVEN

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