Molecular Testing in the Diagnosis of Inherited Bleeding Disorders – Insights and Advances

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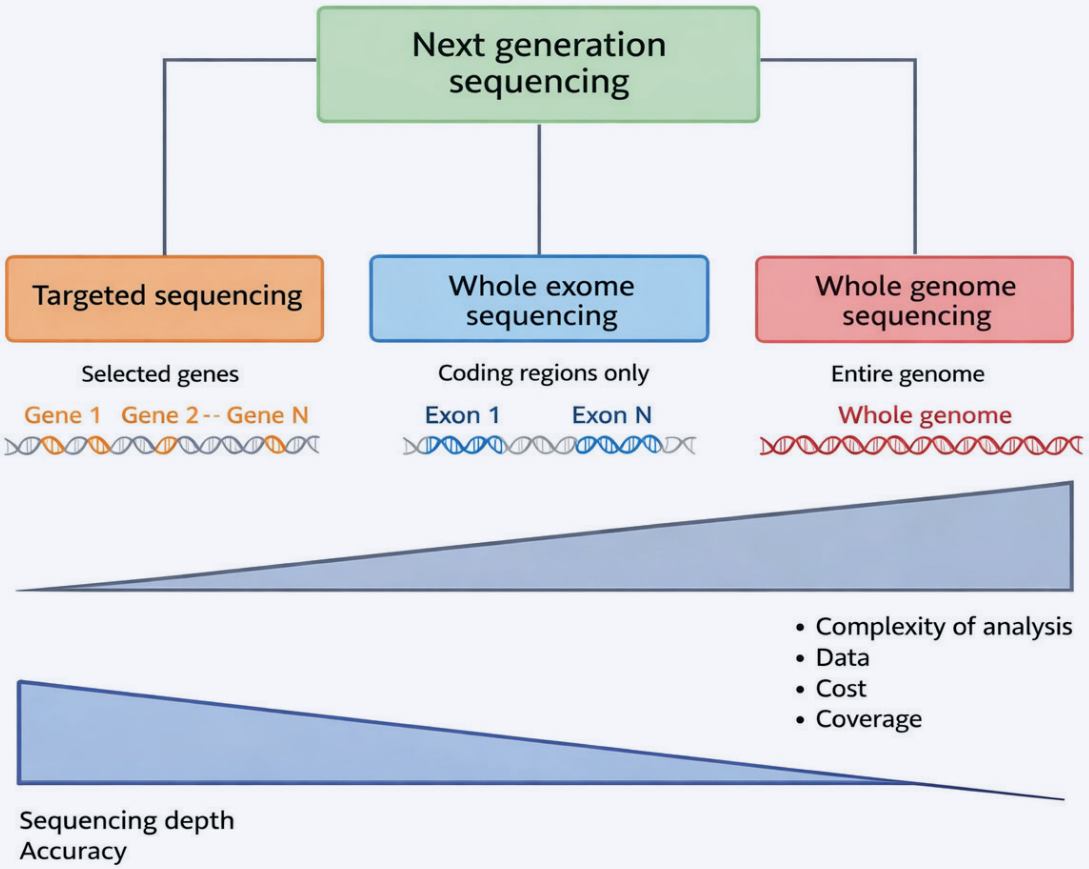
Abstract
Inherited bleeding disorders represent a diverse group of conditions characterized by an increased bleeding tendency that is most often caused by defects in platelets or coagulation factors. The clinical and genetic heterogeneity of these disorders entails significant diagnostic challenges, as traditional approaches based on clinical evaluation, family history and specialized laboratory assays often lack both sensitivity and specificity, especially for rare or atypical presentations. Recent advances in molecular genetics, particularly high throughput sequencing (HTS), have transformed the diagnostic landscape of inherited bleeding disorders. HTS enables the simultaneous analysis of multiple genes, facilitating the identification of causative DNA variants in an increasing number of patients. Targeted gene panels, whole exome sequencing, and whole genome sequencing each offer unique advantages in terms of coverage, depth, and the ability to detect a broad spectrum of genetic alterations. The implementation of multigene panels has led to a significantly increased diagnostic yield and reduced diagnostic delays. Despite these advances, important challenges remain, particularly regarding the interpretation of variants of uncertain significance, detection of complex rearrangements, and the management of incidental findings. In this review, we describe recent insights and advances in the application of HTS for the diagnosis of inherited bleeding disorders and discuss the implications for clinical practice.

Introduction

Inherited bleeding disorders represent a highly heterogeneous group of conditions, characterized by a lifelong increased bleeding diathesis. These disorders are broadly categorized into inherited platelet disorders (IPDs) and inherited coagulation disorders. IPDs include quantitative defects (thrombocytopenia) and qualitative defects known as thrombocytopathies (impaired platelet function). Inherited coagulation disorders involve deficiencies or dysfunction of specific clotting factors, with von Willebrand disease (VWD) and haemophilia A being the most common inherited coagulation disorders (1,2). Traditionally, the diagnosis of inherited bleeding disorders has relied on a combination of clinical evaluation, family history, and specialized laboratory investigations, with functional assays - such as platelet function tests and coagulation factor activity measurements - serving as the cornerstone of the initial diagnostic process (3). Despite their central role, these functional assays also present notable limitations, and therefore the diagnostic journey can be complicated. Clinical symptoms often overlap among different disorders, and functional assays may be unable to distinguish between them. Additionally, functional assays may lack sensitivity and specificity, particularly in mild or atypical forms of inherited conditions. They can fail to distinguish between inherited and acquired causes of bleeding, and results can be influenced by preanalytical factors such as the time between sample collection and processing, as well as external factors like stress, fever, and pregnancy. For example, acute stress can significantly increase plasma levels of von Willebrand factor (VWF) and factor VIII (FVIII) due to endothelial cell release triggered by catecholamine surges. Similarly, during pregnancy, VWF and FVIII levels can rise threefold as part of the body's physiological preparation for delivery (4). These elevations may transiently normalize abnormal values, thereby masking an underlying inherited bleeding disorder and producing false-negative results. Currently, there are no functional assays available to directly assess the integrity or function of the vascular wall; as a result, endothelial dysfunction cannot be evaluated using standard laboratory testing. In clinical practice, some patients present with a clear bleeding phenotype despite entirely normal results on comprehensive functional haemostatic assays - referred to as having a bleeding disorder of unknown cause (BDUC) (5). This underscores a key limitation of functional testing to detect bleeding defects: while valuable, our current assays may not detect all defects, particularly when the underlying pathophysiology lies outside the scope of what these tests can measure.

All these factors can result in diagnostic delays and uncertainty. In recent years, the advent of molecular diagnostic testing has revolutionized the approach to inherited bleeding disorders by enhancing diagnostic capabilities and improving the accuracy of identifying underlying genetic causes (6,7). This review explores the evolving role of molecular testing in the diagnosis of inherited bleeding disorders. We describe the advances in HTS technologies, the application of gene panels, and the implementation of molecular testing into clinical and research settings, with the overarching goal of improving diagnostic precision and patient outcomes.

FIGURE 1: Overview of next-generation sequencing technologies: targeted panel sequencing, whole exome sequencing (WES), and whole genome sequencing (WGS). The figure illustrates differences in genomic coverage, sequencing depth, cost, and suitability for detecting various types of genetic variants. Targeted panels focus on selected genes and offer high depth for specific clinical questions. WES captures all coding regions (exons), providing a balance between coverage and cost. WGS covers the entire genome and is most comprehensive, enabling detection of structural variants and non-coding mutations. CNV: copy number variation



Advancements in sequencing methods

Prior to the advent of high throughput sequencing (HTS), Sanger sequencing, a method that allows for the targeted analysis of a specific gene or gene region, was used to confirm a functional diagnosis. Sanger sequencing remains the gold standard for variant validation and is still used for the analysis of single genes or for familial segregation studies (8). By genetically validating a functional diagnosis, it is possible to offer appropriate genetic counselling, establish a prenatal diagnosis, or identify carriers (e.g., women who are carriers of pathogenic variants in the coagulation factor 8 (F8) or 9 (F9) but who have normal factor levels). However, the labour-intensive nature and substantial cost, coupled with its low throughput, make it impractical to simultaneously investigate multiple candidate genes, which is often required due to the genetic heterogeneity of bleeding disorders. HTS platforms, which can sequence millions of DNA fragments in parallel, facilitate the simultaneous analysis of multiple genes, exomes, or even the entire genome, offering a faster and more cost-effective alternative to Sanger sequencing. HTS can be used both to provide molecular confirmation of an established clinical or functional diagnosis, and to identify a genetic diagnosis in cases where a clear functional diagnosis has not yet been established. HTS comprises several techniques, each with its own applications, which we will provide a brief overview of here (Figure 1) (9).

Targeted gene panels are designed to capture and sequence a predefined set of genes that are known to be associated with specific conditions (10). The use of targeted panels offers several advantages, including high sequencing depth, rapid turnaround, and cost-effectiveness compared to broader approaches. This approach is particularly valuable in the diagnosis of disorders where pathogenic variants may occur in different genes, such as for congenital thrombocytopenia. Panels can in theory also detect copy number variations (CNVs), including larger deletions and duplications, within the targeted gene set. However, the ability of panels to detect CNVs is dependent on the design of the panel and bioinformatics pipelines (11). Whole exome sequencing (WES) analyses the entire exome, which is the protein-coding portion of the genome. The exome accounts for about 1-2% of the total genome and encompasses approximately 23 000 genes (12). WES is especially useful where targeted panel testing fails to identify a causative variant, as it allows for the discovery of novel disease genes or the confirmation of atypical presentations of known disorders (13). However, it also presents challenges, including the interpretation of incidental findings unrelated to the phenotype and the increased burden of data analysis. Whole genome sequencing (WGS) provides the most extensive analysis, where the entire genome (coding and non-coding regions) is examined. The complexity and cost of WGS remain significant, and its use is currently limited to research settings or particularly challenging diagnostic cases.

Each of these techniques has its own advantages and disadvantages (14). Firstly, the major difference between the three methods is the volume of data that are generated. WGS produces substantially more data than targeted sequencing,

and the complexity of analysis is inherently linked to this data volume, making WGS analysis far more complex compared to targeted sequencing. Secondly, as the volume of data analysed increases, so do the associated costs. Lastly, targeted sequencing demonstrates the highest accuracy, while WGS has the lowest accuracy, with a higher likelihood of errors. Consequently, findings from WES or WGS are routinely confirmed using Sanger sequencing. Although traditional short-read next generation sequencing (NGS) was previously limited in detecting certain CNVs, current WES and WGS methods, equipped with advanced bioinformatics pipelines, are now sufficiently sensitive to detect most deletions and duplications. Despite advances in short-read NGS, challenges remain in identifying complex structural variants, such as large inversions and repeat expansions. These limitations can lead to certain complex insertions being missed when relying solely on standard targeted HTS panels (15). To overcome these limitations, complementary techniques such as multiplex ligation-dependent probe amplification (MLPA) and array comparative genomic hybridization (aCGH) arrays are widely employed. MLPA offers targeted, sensitive detection of exon-level deletions and duplications in genes like VWF, F8, and F9 (16,17). These confirmatory methods remain essential for the validation of certain complex genomic alterations.

A major recent advancement in sequencing technology is the development of long-read sequencing methods (18). Most current high-throughput sequencing in clinical diagnostics rely on short-read sequencing, where DNA is fragmented into short stretches of approximately 100–300 base pairs. While highly effective for detecting single nucleotide variants and small indels, short-read methods are inherently limited in their ability to map large structural variants, repetitive elements, and complex rearrangements. Long-read sequencing platforms can sequence much longer DNA fragments (thousands to tens of thousands of base pairs), greatly increasing the ability to resolve complex structural variants, large inversions, repeat expansions, and other changes in challenging genomic regions. Several recent studies illustrate the growing clinical utility of long-read sequencing in inherited bleeding disorders. For example, Chatron et al. used nanopore long-read sequencing to identify an unbalanced chromosomal rearrangement responsible for severe haemophilia A (19). This complex structural variant had eluded detection and characterization by conventional genetics sequencing. Another study applied targeted long-read sequencing in cases of inherited platelet disorders, successfully identifying and precisely characterizing structural variants - including deletions, insertions, and complex rearrangement - that were missed or incompletely resolved by short-read approaches and conventional diagnostic tests (20). These initial studies show that long-read sequencing can improve the detection and precise characterization of genetic variants in certain bleeding disorders, leading to more accurate diagnoses.

Variant interpretation and clinical significance

Variants identified through molecular testing are systematically categorized to guide clinical interpretation and patient management. Each variant is assessed based on available evidence and classified as benign (class 1), likely benign (class 2), variant of uncertain significance (VUS; class 3), likely pathogenic (class 4), or pathogenic (class 5) (21). This standardized framework supports consistent reporting and facilitates communication between laboratories and clinicians, guiding genetic counselling and clinical decision-making. In accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines, certain laboratories implement additional stratification within the VUS category (21,22). Specifically, they further distinguish between standard VUS and VUS+ classifications. The VUS+ designation is applied to variants for which there is preliminary—yet insufficient—supporting evidence for pathogenicity, but not enough to justify reclassification as likely pathogenic.

Application of molecular testing in inherited bleeding disorders

The International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee Subcommittee (SSC) has curated a list of disease-causing (TIER1) genes specifically associated with bleeding and thrombotic disorders, which is updated annually (23). To date, 109 TIER1 genes have been recognized as causative for (anti)coagulation and platelet defects (Table 1). These genes form the basis of multigene panels used in clinical molecular testing of bleeding and thrombotic disorders. Our UZ Leuven multigene panel has included an additional third subpanel with genes that are not part of the ISTH TIER1 list (Table 1). These genes are related to vascular disorders such as Hereditary Haemorrhagic Telangiectasia and Ehlers-Danlos syndrome. This subpanel is used for screening patients with BDUC.

To evaluate the effectiveness of implementing a multigene panel in clinical practice, it is important to consider the diagnostic yield. Several studies have reported their diagnostic rates; however, direct comparison is challenging, as the composition of multigene panels can differ between centres. Additionally, differences in patient selection criteria, sequencing methods, and variant interpretation guidelines may further complicate meaningful comparisons. The ThromboGenomics study represents the largest international evaluation to date of multigene panel sequencing for patients with suspected inherited coagulation, thrombotic and platelet disorders (25). In this cohort of 2,396 patients, the panel achieved an overall diagnostic rate of 49.2% among those with thrombotic, coagulation, platelet count, or platelet function disorders, but only 3.2% in BDUC patients. Building on this international framework, UZ Leuven implemented a similar HTS panel for inherited bleeding disorders in clinical diagnostics from early 2019 onward. Over a three-year period, the clinical application of this multigene panel testing was evaluated (24). A total of 487 patients from 27 hospitals were tested, with at least one genetic variant detected in 58% of cases, indicating a substantial and similar diagnostic yield. These figures refer to bleeding and thrombosis. Of these genetic variants, half were classified as likely pathogenic or pathogenic, while the remainder were VUS.

The clinical advantages of molecular testing, particularly NGS, are considerable and extensive. This technology has advanced diagnostic capabilities in haematology and beyond, enabling more precise, timely, and informative assessments of hereditary conditions. Firstly, genetic testing offers the ability to establish a definitive molecular diagnosis. In many cases, clinical features alone may be insufficient to distinguish between phenotypically similar disorders. NGS enables the precise identification of the causative genetic variant, thereby providing diagnostic certainty. This allows clinicians to transition from a presumptive or phenotypic diagnosis to a definitive molecular diagnosis. This certainty is not only important for patient management, but also for communication with patients and families, as it provides a clear explanation for symptoms and test results that may have previously remained inconclusive (26). Secondly, a molecular diagnosis enables more accurate risk stratification and prognostic assessment. Different genetic variants, even within the same gene, can be associated with variable disease severity, progression, and response to treatment. Identifying the precise genetic cause enables clinicians to anticipate potential complications, monitor for disease-associated risks, and make well-informed decisions regarding surveillance and intervention strategies. For example, in Glanzmann Thrombasthenia, specific genetic variants within the *ITGA2B* or *ITGB3* genes are associated with differences in bleeding

severity and the risk of alloimmunization, which significantly influence clinical management, including the need for platelet transfusion support or the use of alternative therapies such as recombinant factor VIIa (27,28). Thirdly, genetic testing can reveal a broader and clinically significant underlying pathology that may not be apparent based on clinical features alone. Certain genes, such as *RUNX1*, *ETV6*, *ERG* and *ANKRD26*, are known not only for their role in inherited thrombocytopenia with increased bleeding tendencies, but also for their association with an increased risk of haematological malignancies, including myelodysplastic syndrome and acute leukaemia (29–32). In these cases, the identification of a pathogenic variant has implications beyond the immediate presentation, prompting the need for proper counselling, long-term monitoring, and early detection of malignant transformation. Fourthly, the identification of a pathogenic variant has profound implications for genetic counselling and family planning. Molecular testing remains essential not only in cases where the diagnosis cannot be established through functional assays, but also when functional testing provides a clear diagnosis, as it is crucial for genetic counselling, targeted carrier screening, and predictive testing. Once a causative variant is known, at-risk relatives can be offered predictive testing, and carriers can be identified with accuracy. This enables tailored counselling regarding inheritance patterns, recurrence risks, and reproductive options, including prenatal and preimplantation genetic diagnosis (33). Fifthly, a molecular diagnosis can prevent inappropriate or unnecessary treatments. For instance, distinguishing a case of inherited thrombocytopenia from immune thrombocytopenia, based on genetic findings may prevent the initiation of immunosuppressive therapies, which would be ineffective and potentially harmful in the inherited context (26). Finally, NGS is considered cost-effective, particularly given the complexity and genetic heterogeneity of inherited bleeding disorders which often require the simultaneous analysis of multiple candidate genes.

Despite the significant advances in molecular testing, several challenges remain. One of the most prominent issues is the interpretation of VUS, which complicates the process of determining their clinical relevance. To further elucidate a VUS, further investigation is critical to clarify its clinical impact (34). Segregation studies within affected and non-affected family members help determine whether the variant co-segregates with the disease phenotype, providing important clues about its potential pathogenicity. It is important to keep incomplete penetrance in mind, which can complicate the interpretation of segregation analyses. Furthermore, the variant frequency in large population databases, such as gnomAD, is evaluated; a variant that is rare or absent in healthy populations but more common in affected individuals may suggest a pathogenic role. In parallel, curated databases like ClinVar offer clinical interpretations of variants based on submitted evidence, aiding the assessment of their significance in a diagnostic context (21). Other supportive strategies include literature reviews for new case reports, the use of computational prediction tools to evaluate the variant's likely effect, and periodic reanalysis of genomic data as scientific knowledge evolves. Lastly, sometimes functional testing, which may include in vitro or in vivo assays, is conducted to assess the effect of the variant on protein function or cellular processes. All these mechanisms may be conducted to reclassify a VUS. However, despite these supplementary investigations, it is by far not always feasible to definitively reclassify a VUS. This uncertainty can pose substantial difficulties in clinical decision-making, as it leaves both clinicians and patients uncertain about the potential impact of these variants on disease manifestation or prognosis. In addition, incomplete coverage of certain genes can lead to missed diagnoses, as not all regions of the genome may be fully captured or sequenced. NGS platforms may have limitations in detecting large-scale genomic alterations, such as large deletions or duplications. Furthermore, the association of certain genes related to inherited bleeding disorders with an increased risk of malignancies offers a clear clinical benefit, as it enables early detection, appropriate counselling, and timely surveillance. However, this advantage is accompanied by important ethical considerations, particularly regarding the disclosure of incidental findings and the psychological burden such information may place on patients and their families.

NGS-based approaches in diagnostically challenging bleeding disorders

It is acknowledged that NGS has significantly transformed the diagnostic landscape of inherited bleeding disorders. However, despite the implementation of multigene panels, in some cases no definitive functional or genetic diagnosis can be established. This encompasses clinical scenarios in which the underlying pathobiology remains insufficiently understood or the relevant genes have yet to be identified (as observed in patients with BDUC), as well as individuals diagnosed with a known bleeding disorder—even when functionally characterized—who lack an identifiable pathogenic variant (e.g., certain patients with haemophilia). This section will outline the research-based approaches that may be pursued in such cases to further investigate the underlying genetic causes.

RNA sequencing (RNAseq) has become an essential tool for uncovering the molecular consequences of genetic variants, especially those outside coding regions, by enabling the detection of aberrant splicing events, altered gene expression, and the functional impact of non-coding variants. It should be noted, however, that this approach depends on the gene being sufficiently expressed in the analysed tissue, often blood cells, which may not always apply to the specific genes that are being studied. For example, in haemophilia A, systematic analysis combining NGS of the entire F8 locus and mRNA from patients without detectable coding variants, confirmed that deep intronic variants could create new splice sites, leading to the aberrant inclusion of intronic DNA into the mature mRNA and premature stop codons, thereby establishing their pathogenicity. It is important to note that the cDNA analysed in this study was derived from RNA extracted from blood cells, which are not primary sites of factor VIII synthesis. Therefore, tissue-specific alternative splicing events occurring in factor VIII-producing cells may not be represented (35). Similarly, in von Willebrand disease, transcriptomics of platelets and leukocytes has revealed that deep intronic and synonymous VWF mutations can cause aberrant splicing, with RNAseq data providing direct evidence of their functional impact (36). These findings underscore the essential role of RNAseq in uncovering the pathogenic consequences of non-coding and intronic mutations that are missed by conventional genomic approaches, thereby improving the molecular diagnosis and understanding of inherited bleeding disorders.

In addition to facilitating variant detection, NGS has significantly advanced the understanding of the underlying pathobiology of rare bleeding disorders. *SLFN14*-related thrombocytopenia serves as a notable example (37). Pathogenic missense variants in *SLFN14*, which encodes for an endoribonuclease involved in ribosome degradation, have been identified as the cause of an autosomal dominant form of thrombocytopenia with increased bleeding tendency through WES and RNAseq. Transcriptomic analyses of patients carrying the *SLFN14 K219N* variant revealed extensive dysregulation of gene expression, including marked upregulation of ribosomal protein genes and activation of mitochondrial translation and transcription pathways. This transcriptomic signature indicates ribosomal stress and a compensatory response mediated by mTORC1 signalling, which appears central to disease pathogenesis. These insights illustrate how NGS technologies not

only enable genetic diagnosis but also contribute to the elucidation of molecular mechanisms underlying rare platelet disorders.

Genetic manipulation of immortalized megakaryocyte progenitor cell lines (imMKCLs) could be a powerful research tool to further unravel the underlying pathophysiology and validate the functional consequences of genetic variants identified in patients with inherited platelet disorders (38). These imMKCLs are derived from human induced pluripotent stem cells and can be expanded in culture for several months and differentiate into functional platelets. By using CRISPR-Cas9, researchers can introduce patient-specific mutations into imMKCLs and study their impact on megakaryocyte differentiation, platelet production, gene expression, and signalling pathways. This approach not only helps to confirm or deny the pathogenicity of a VUS but also provides mechanistic insights into disease development. For example, Lo et al. investigated the molecular mechanisms underlying Gray Platelet Syndrome, a rare inherited bleeding disorder caused by pathogenic variants in the *NBEAL2* gene, leading to the absence of α-granules in platelets and resulting in bleeding symptoms (39,40). Using imMKCLs, they demonstrated that the endoplasmic reticulum protein SEC22B physically interacts with *NBEAL2* and is essential for proper α-granule biogenesis. Importantly, disease-associated variants in *NBEAL2* disrupt this interaction, and genetic knockout of SEC22B in imMKCLs results in a failure to produce α-granules, recapitulating key features of Gray Platelet Syndrome. These findings provide new insights into the pathogenesis of Gray Platelet Syndrome using the imMKCL-based model.

Conclusion

The diagnosis of inherited bleeding disorders has been fundamentally transformed by advances in genetic testing. The transition from phenotype-driven algorithms to molecular diagnostics has enabled the identification of causative variants in an increasing proportion of patients, improving risk stratification, guiding management, and facilitating genetic counselling. While targeted gene panels remain the first-line approach in clinical practice, WES and WGS, along with emerging research tools such as RNAseq, are essential for resolving undiagnosed cases and for expanding our understanding of the genetic architecture of these disorders. Despite these advances, it remains essential that diagnostic requests continue to be targeted and guided by clinical expertise to ensure appropriate test selection, efficient resource use, and meaningful interpretation of results.

Challenges remain, including the interpretation of variants of uncertain significance, the need for equitable access to testing, and the ethical considerations associated with incidental findings. The future of diagnostics in inherited bleeding disorders will be shaped by the integration of multi-omics data and the continued collaboration between clinicians, geneticists, and researchers.

Statements

There are no competing interests to disclose.

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TABLE 1: Overview of the multigene Thrombosis and Haemostasis panel of UZ Leuven, divided in the three subpanels.

Subpanel	Gene	Related Disorder(s)
Coagulation*	ADAMTS13	Thrombotic thrombocytopenic purpura
Coagulation	F2	Prothrombin deficiency Prothrombin G20210A mutation-associated thrombophilia
	F5	F5 deficiency Factor V Leiden thrombophilia
	F7	Factor VII deficiency
	F8	Haemophilia A
	F9	Haemophilia B
	F10	FX deficiency
	F11	FXI deficiency
Coagulation ***Angioedema***	F12	FXII deficiency
Coagulation	FGA	Fibrinogen deficiency
	FGB	Fibrinogen deficiency
	FGG	Fibrinogen deficiency
	GGCX	Vitamin K-dependent coagulation factor deficiency
	HRG	Histidine-rich glycoprotein deficiency
	KLKB1	Hereditary prekallikrein deficiency (Fletcher factor deficiency)
	KNG1	Kininogen deficiency
	LMAN1	Combined FV and FVIII deficiency
	MCFD2	Combined FV and FVIII deficiency
	PIGA	Paroxysmal nocturnal haemoglobinuria
	PLG	Plasminogen deficiency
	PROC	Protein C deficiency
	PROS1	Protein S deficiency
	SERPINC1	Antithrombin deficiency
	SERPIND1	Heparin cofactor 2 deficiency
	SERPINE1	Plasminogen activator inhibitor 1 deficiency
	SERPINF2	Alpha 2 antiplasmin deficiency
	THBD	Thrombomodulin deficiency
	VKORC1	Vitamin K-dependent coagulation factor deficiency
	VWF	Von Willebrand Disease

Subpanel	Gene	Related Disorder(s)
Unexplained bleeding	ACVRL1	Hereditary Haemorrhagic Telangiectasia
	CHST14	Ehlers-Danlos syndrome
	COL1A1	Ehlers-Danlos syndrome, arthrochalasia type, 1
	COL3A1	Ehlers-Danlos syndrome, vascular type
	COL4A1	Brain small vessel disease with or without ocular anomalies
	COL4A2	Brain Small Vessel Disease 2
	COL5A1	Ehlers-Danlos syndrome, classic type, 1
	COL5A2	Ehlers-Danlos syndrome, classic type, 2
	ENG	Hereditary Haemorrhagic Telangiectasia
	GDF2	Hereditary Haemorrhagic Telangiectasia
	SMAD4	Hereditary Haemorrhagic Telangiectasia

* The coagulation subpanel includes genes related to bleeding and thrombosis.

Subpanel	Gene	Related Disorder(s)
Platelet	ABCC4	Reduced ADP-induced platelet aggregation
	ABCG5	Sitosterolemia with macrothrombocytopenia
	ABCG8	Sitosterolemia with macrothrombocytopenia
	ACTB	Baraitser-Winter syndrome with macrothrombocytopenia
	ACTN1	Macrothrombocytopenia
	ANKRD26	Thrombocytopenia and increased risk for cancer
	ANO6	Scott syndrome (platelet function disorder)
	AP3B1	Hermansky Pudlak syndrome (platelet function disorder)
	AP3D1	Hermansky Pudlak syndrome (platelet function disorder)
	ARPC1B	Platelet abnormalities and immune-mediated inflammatory disease predisposition
	BLOC1S3	Hermansky Pudlak syndrome (platelet function disorder)
	BLOC1S5	Hermansky Pudlak syndrome (platelet function disorder)
	BLOC1S6	Hermansky Pudlak syndrome (platelet function disorder)
	CDC42	Takenouchi-Kosaki syndrome with thrombocytopenia
	CYCS	Thrombocytopenia
	DIAPH1	Macrothrombocytopenia and sensorineural hearing loss
	DTNBP1	Hermansky Pudlak syndrome (platelet function disorder)
	ERG	Thrombocytopenia and susceptibility to cancer
	ETV6	Thrombocytopenia and increased risk for cancer
	FERMT3	Leukocyte Adhesion deficiency type III (platelet function disorder)
	FLI1	Paris-Trousseau syndrome and Jacobsen syndrome (TP)
	FLNA	Syndrome with macrothrombocytopenia
	FYB1	Thrombocytopenia
	GATA1	Thrombocytopenia with dyserythropoiesis
	GFI1B	Macrothrombocytopenia
	GNE	Myopathy associated with thrombocytopenia
	GP1B1	Bernard-Soulier syndrome Macrothrombocytopenia (mild) Platelet-type VWD
	GP1BB	Bernard-Soulier syndrome Macrothrombocytopenia (mild)
	GP6	Glycoprotein VI deficiency
	GP9	Bernard-Soulier syndrome
	HOXA11	Amegakaryocytic thrombocytopenia with radio-ulnar synonstosis syndrome
	HPS1	Hermansky Pudlak syndrome (platelet function disorder)
Platelet	HPS3	Hermansky Pudlak syndrome (platelet function disorder)
	HPS4	Hermansky Pudlak syndrome (platelet function disorder)
	HPS5	Hermansky Pudlak syndrome (platelet function disorder)
	HPS6	Hermansky Pudlak syndrome (platelet function disorder)
	IKZF5	Thrombocytopenia, Pegasus syndrome
	ITGA2B	Glanzmann Thrombasthenia
	IGAB3	Glanzmann Thrombasthenia
	KDSR	Thrombocytopenia and erythrokeratoderma
	LYST	Chediak-Higashi syndrome
	MECOM	Amegakaryocytic thrombocytopenia with radio-ulnar synostosis syndrome
	MPIG6B	Thrombocytopenia, anaemia and myelofibrosis
	MPL	Amegakaryocytic thrombocytopenia
	MYH9	Macrothrombocytopenia, sensorineural hearing loss, kidney disease, cataracts
	NBEA	Autism with platelet dense granule defect
	NBEAL2	Gray platelet syndrome
	P2RY12	ADP receptor defect
	PLA2G4A	Phospholipase A2 deficiency, group IV A
	PLAU	Quebec platelet disorder
	PTGS1	Platelet function disorder
	RAP1B	Syndromic thrombocytopenia
	RASGRP2	Platelet function disorder
	RBM8A	Thrombocytopenia-absent radius (TAR) syndrome
	RUNX1	Thrombocytopenia and increased risk for haematological cancer
	SLFN14	Platelet function disorder
	SRC	Thrombocytopenia
	STIM1	Stormorken syndrome = York platelet syndrome (thrombocytopenia)
	STXBP2	Familial hemophagocytic lymphohistiocytosis type 5
	TBXA2R	Thromboxane A2 receptor defect
	THPO	Thrombocytopenia progressing to bone marrow failure
	TPM4	Macrothrombocytopenia
	TUBB1	Macrothrombocytopenia
	VIPAS39	Arthrogryposis, renal dysfunction, and cholestasis
	VPS33B	Arthrogryposis, renal dysfunction, and cholestasis
	VWF	Von Willebrand disease
	WAS	Wiskott-Aldrich syndrome

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