

ILLUSTRATED REVIEW

Bleeding disorder of unknown cause: an illustrated review on current practice, knowledge gaps, and future perspectives

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Abstract

In more than half of the individuals with a clinically relevant bleeding tendency who are referred to hemostasis experts, no biological etiology can be found after extensive laboratory testing. These persons are diagnosed with an unexplained bleeding tendency or “bleeding disorder of unknown cause” (BDUC). The mucocutaneous bleeding phenotype of individuals with BDUC is generally comparable to that of individuals with inherited bleeding disorders such as von Willebrand disease or platelet function disorders. BDUC definitions applied in literature are heterogeneous, but all comprise 2 main criteria: (1) there is an increased bleeding tendency based on the clinical view of the physician and/or an increased bleeding score; (2) no abnormalities are found with available hemostasis laboratory tests. This is reflected in the recent published BDUC

Amaury L.L. Monard and Caroline M.A. Mussert share the first authorship and contributed equally to this work.

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definition by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis, stating that BDUC is a diagnosis of exclusion, characterized by normal hemostatic investigations despite a clinically significant bleeding tendency. Importantly, other nonhemostatic and acquired causes of bleeding should be excluded, but details on exclusion criteria and associated diagnostic testing remain undefined. Patients and health care providers are challenged by the uncertainty and lack of formal diagnosis particularly as there is no clear consensus regarding treatment. Research on the diagnostic value of new laboratory tests in individuals with BDUC has not yet been productive. In this illustrative review, the current practice and knowledge gaps in BDUC are addressed, previous research on BDUC is outlined and future directions with outstanding questions for future research in BDUC are highlighted.

KEYWORDS

bleeding disorder of unknown cause, diagnosis, hemostasis, review, treatment

Essentials

- Bleeding Disorder of Unknown Cause (BDUC) is defined by a positive personal and/or family history of bleeding with normal laboratory test results.
- More than half of patients with bleeding symptoms seen in hemostasis clinics are diagnosed with BDUC.
- There are major knowledge gaps and lack of consensus on the approach to treatment.
- Research is critically required to better understand the impact and determinants of BDUC.

1. Table of contents for this BDUC illustrated review

An introduction to BDUC

Bleeding disorder of unknown cause



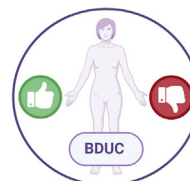
Definition



Patient characteristics



Bleeding phenotype

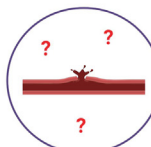


Implications

Current knowledge gaps



Definition of increased bleeding tendency



Pathophysiological mechanism



Diagnostic process



Treatment & management

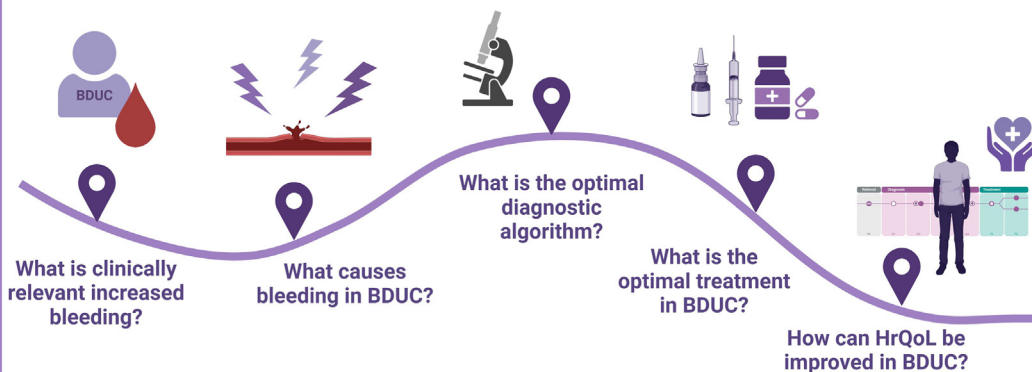


Patient reported outcomes

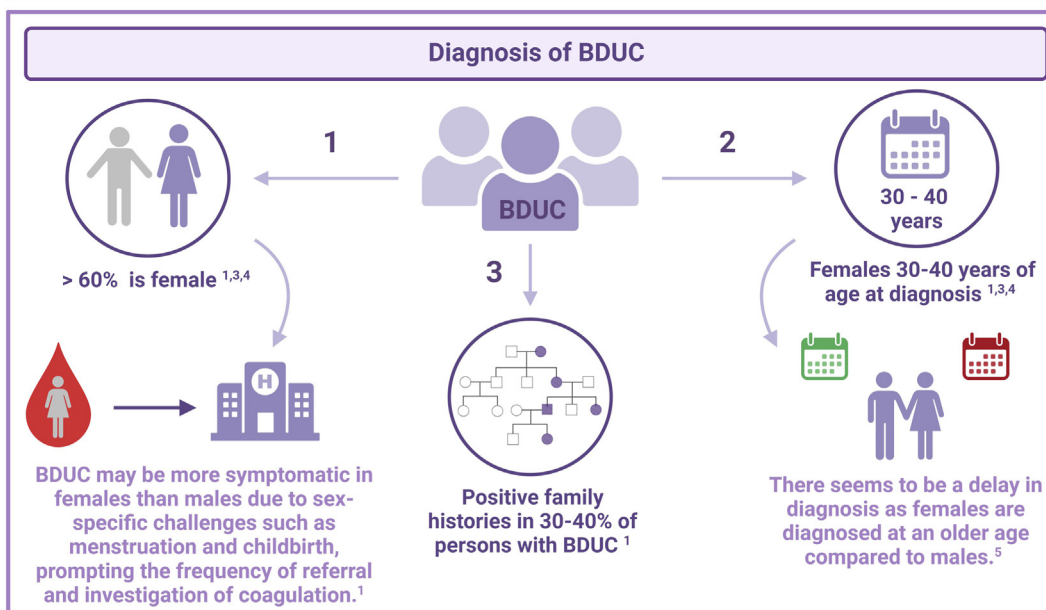
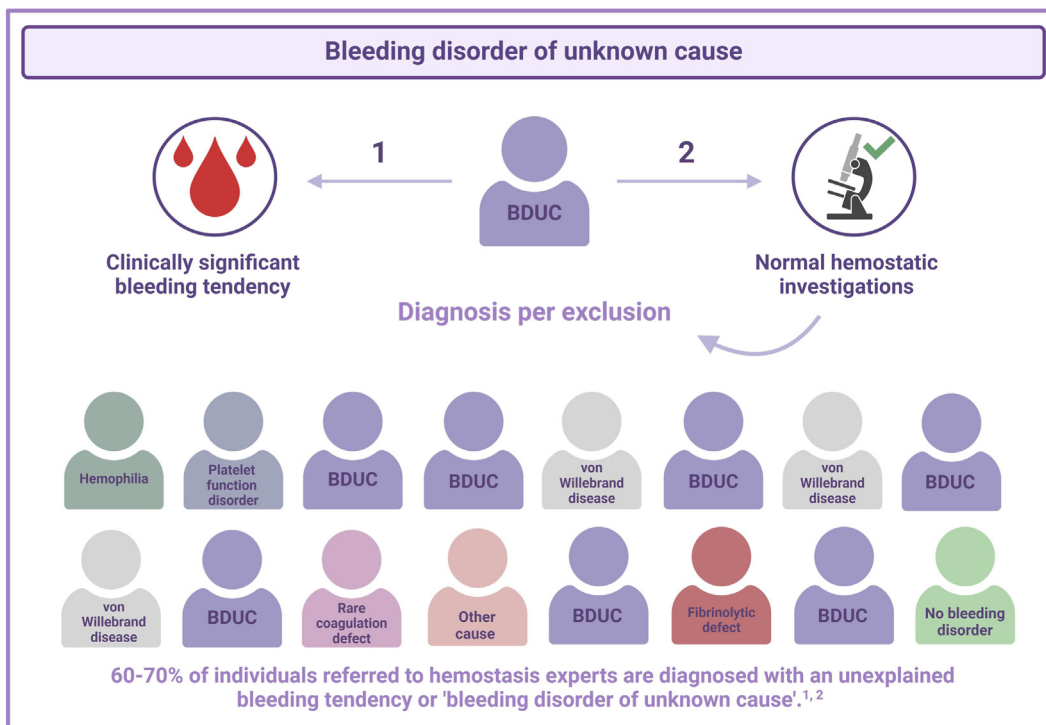


Care pathway & patient journey

Future perspectives



2. What is Bleeding Disorder of Unknown Cause (BDUC)?

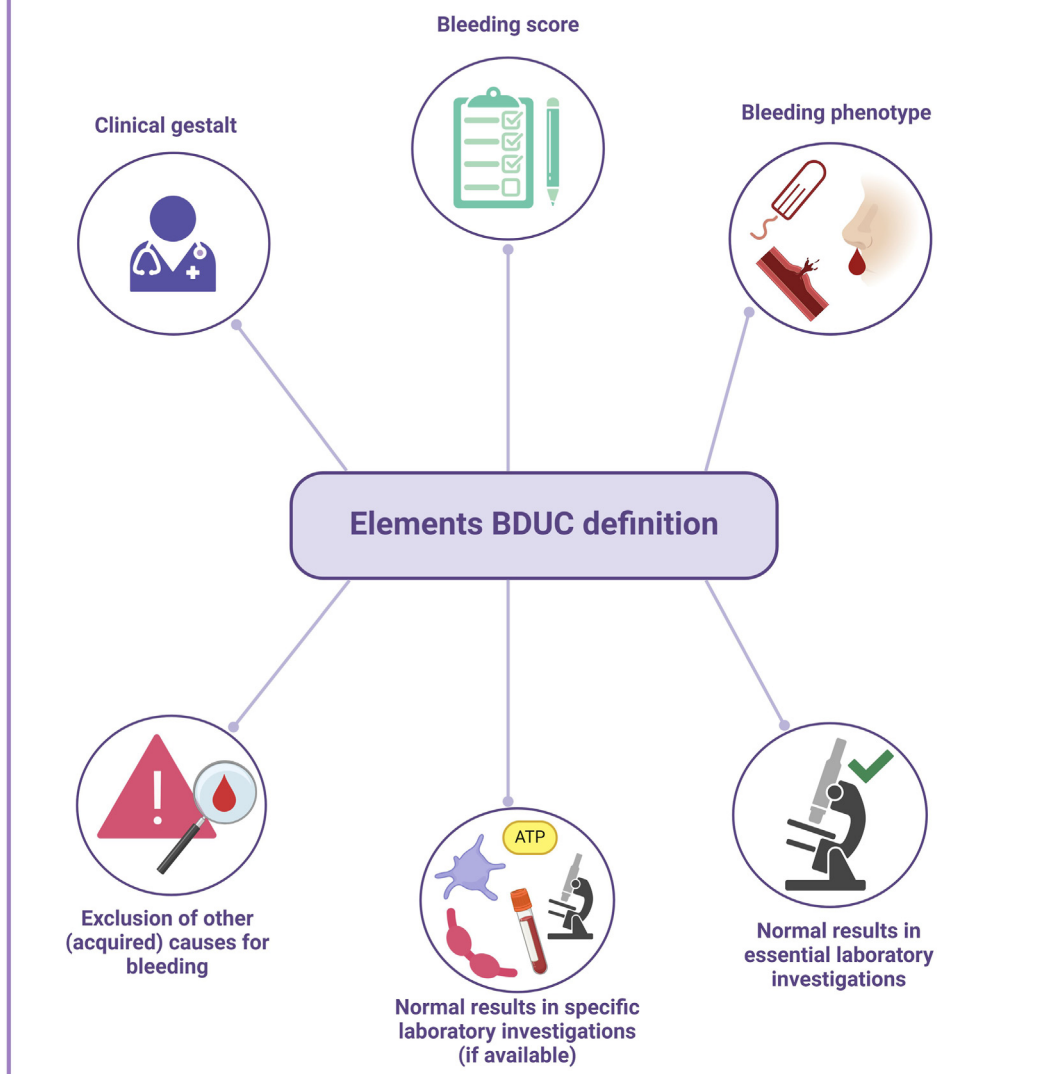


3. Elements of the BDUC definition

Previously used definitions applied in literature were heterogeneous, but all comprised two main criteria:

1. There is an increased bleeding tendency based on the clinical view of the physician (clinical gestalt) and/or increased bleeding score assessed by a validated bleeding assessment tool (BAT)
2. There are no abnormal results from available hemostasis laboratory tests⁴⁻⁷

Recently, the ISTH SSC published a BDUC definition, containing the following elements.²

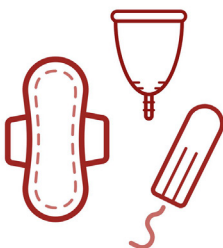


4. Bleeding phenotype

The bleeding phenotype of individuals with BDUC is typically characterized by mucocutaneous bleeding as well as bleeding around medical and dental procedures.^{3-5,8-10}

Gynecologic & obstetric bleeding

Heavy menstrual bleeding



60% - 90% of females with BDUC^{3-5,10}

Gynecologic cause should be excluded²

Post partum bleeding



30% - 65% of females with BDUC^{3-5,9,10}

Mucocutaneous bleeding

Hematomas/easy bruising



66% - 78%^{3-5,10}

Epistaxis



31% - 79%^{3-5,10}

Oral mucosal



19% - 53%^{3,4,10}

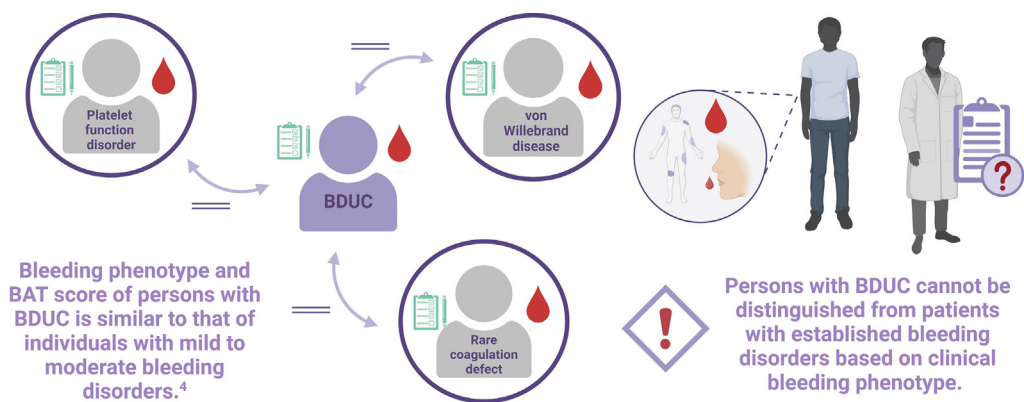
Bleeding during or after medical & dental procedures



44% - 75%^{3-5,9,10}

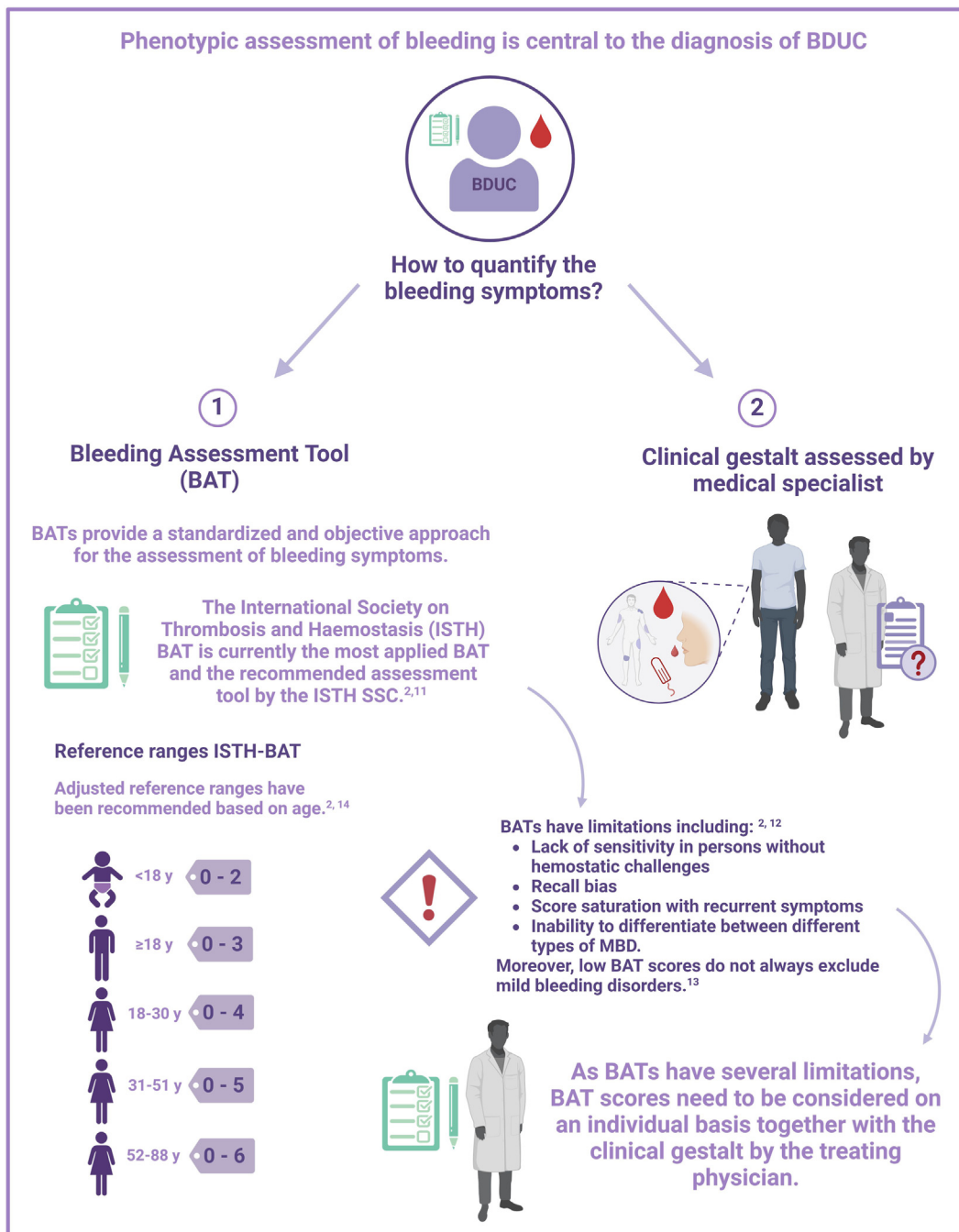


36% - 84%^{3-5,10}



5. Assessment of bleeding phenotype

Phenotypic assessment of bleeding is central to the diagnosis of BDUC

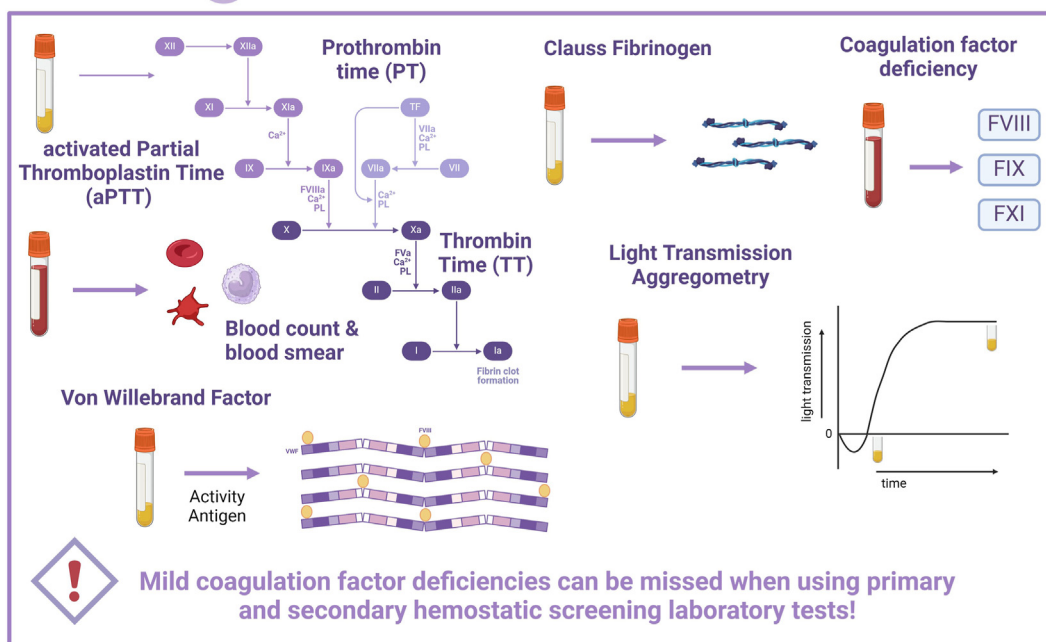


6. Laboratory tests

Laboratory testing is indispensable in the diagnostic process of bleeding disorders. Various diagnostic algorithms for laboratory testing leading to BDUC diagnosis have been described. Recently, the ISTH SSC recommended a stepwise approach.² In addition, other causes for bleeding symptoms should be excluded.¹⁵ In case of a clinically relevant bleeding tendency without any abnormal laboratory test results, BDUC may be diagnosed.

1

Essential Laboratory Investigations

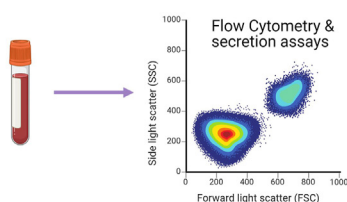


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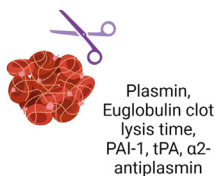
Specific Laboratory Investigations (if available)

Additional laboratory tests can be performed if available. These investigations can include platelet assays, fibrinolysis assays, rare clotting factor deficiencies and other specialized assays.²

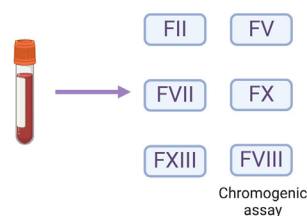
Platelet function



Fibrinolysis assays

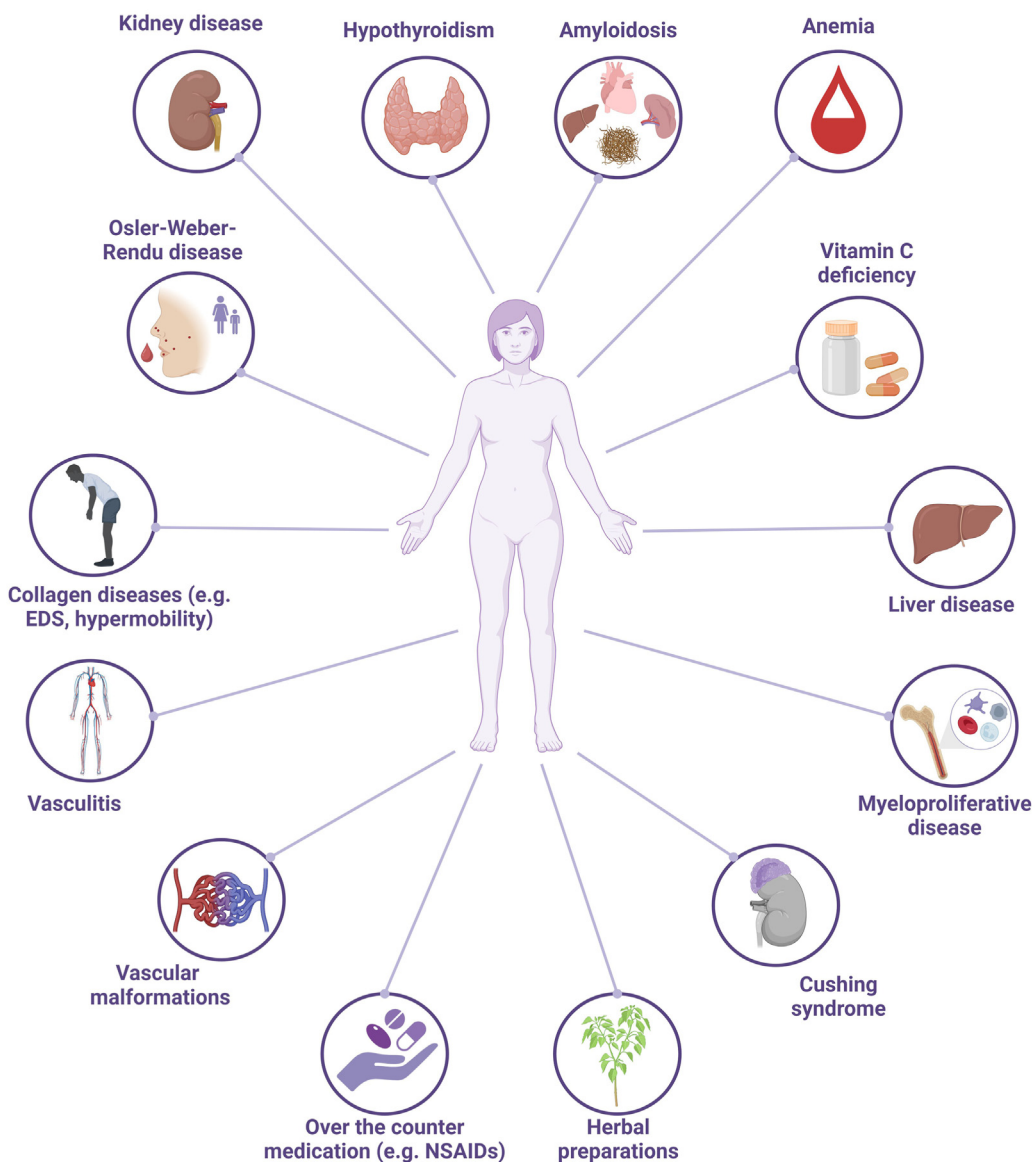


Rare clotting factor deficiencies



7. Other causes for bleeding

Other conditions are associated with an increased bleeding tendency, without detectable abnormalities in the coagulation cascade.¹⁵ To exclude other causes, additional (laboratory) tests should be performed when clinically indicated.



8. Current treatment

Indications for treatment



Bleeding e.g. heavy menstrual bleeding



Dental procedures



Surgeries and other medical interventions



Pregnancy and delivery



Persons with BDUC have an increased bleeding risk around hemostatic challenges!



Regularly, a treatment plan is composed for these circumstances.¹⁵



Clear guidelines on treatment in persons with BDUC are lacking.

Currently used treatments

A step-wise treatment plan is suggested for persons with BDUC, based on previous bleeding complications and severity of the bleeding tendency:^{2,15}

Tranexamic acid (TxA)



Minor and major medical and dental procedures



- 1g 3x/day¹⁵
- 15-25 mg/kg (up to 1g) 3x/day⁵
- 500-1000 mg 3x/day¹⁶



Single dose 10 mg/kg (up to 1g) continued orally¹⁶

Desmopressin (DDAVP)



Minor and major medical and dental procedures, often combined with TxA



0.3 µg/kg^{5, 15, 16}

Platelet transfusions



Preventative and/or therapeutic in high risk situations

* Consider risk on alloimmunization!



Some case studies report the use of fresh frozen plasma in persons with BDUC.¹⁷

Recombinant activated FVII



Last resort in case of major, life threatening bleeding complications

Treatment knowledge gaps

Only few studies have investigated treatment and bleeding complications around hemostatic challenges in persons with BDUC.^{5, 9, 16} Consequently, there is little evidence regarding efficacy and safety, and unknowns remain.

Best treatment per medical intervention



Efficacy



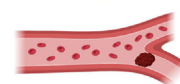
Bleeding complications



Safety



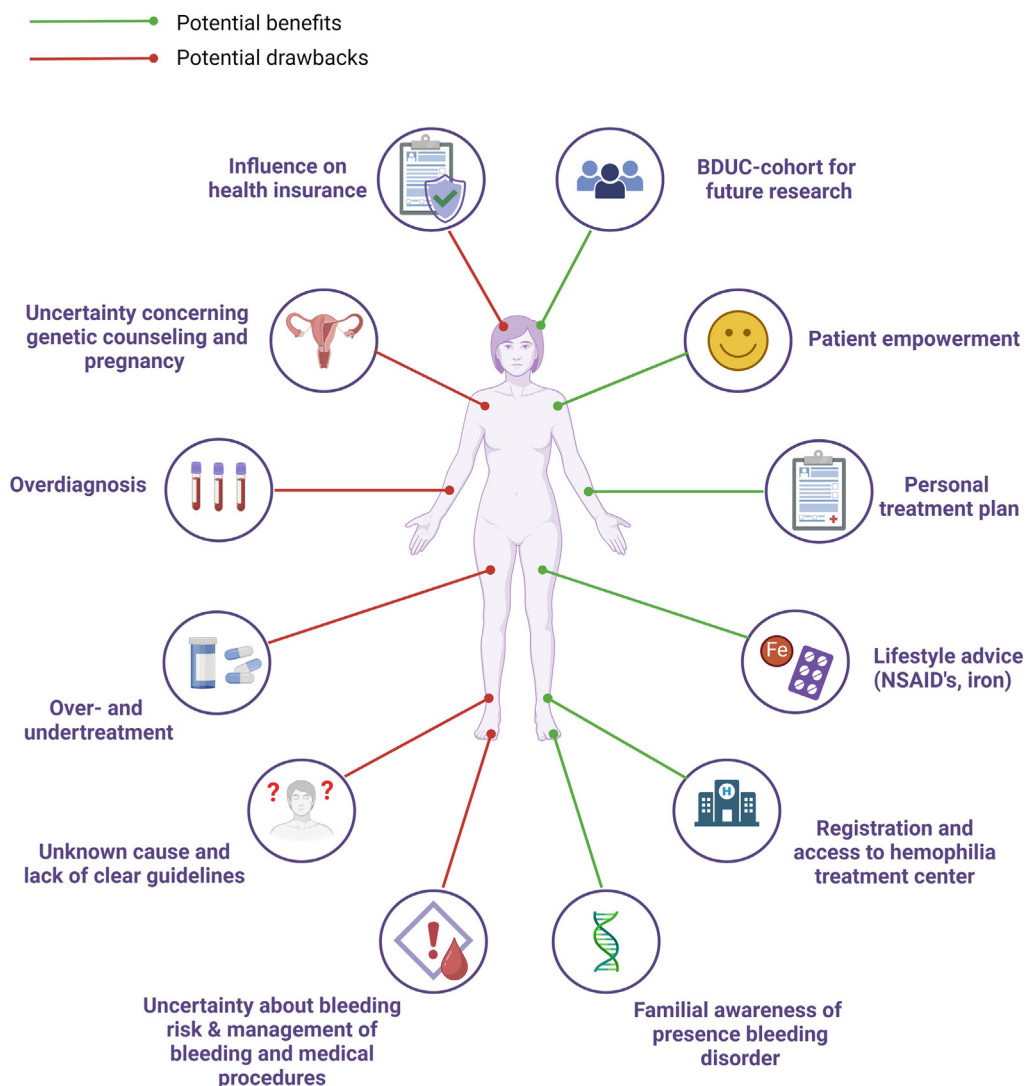
Thrombotic risk



Bleeding complications still occur which suggests that the currently applied prophylactic treatment in BDUC is often not adequate.⁹

9. Benefits and drawbacks of BDUC diagnosis

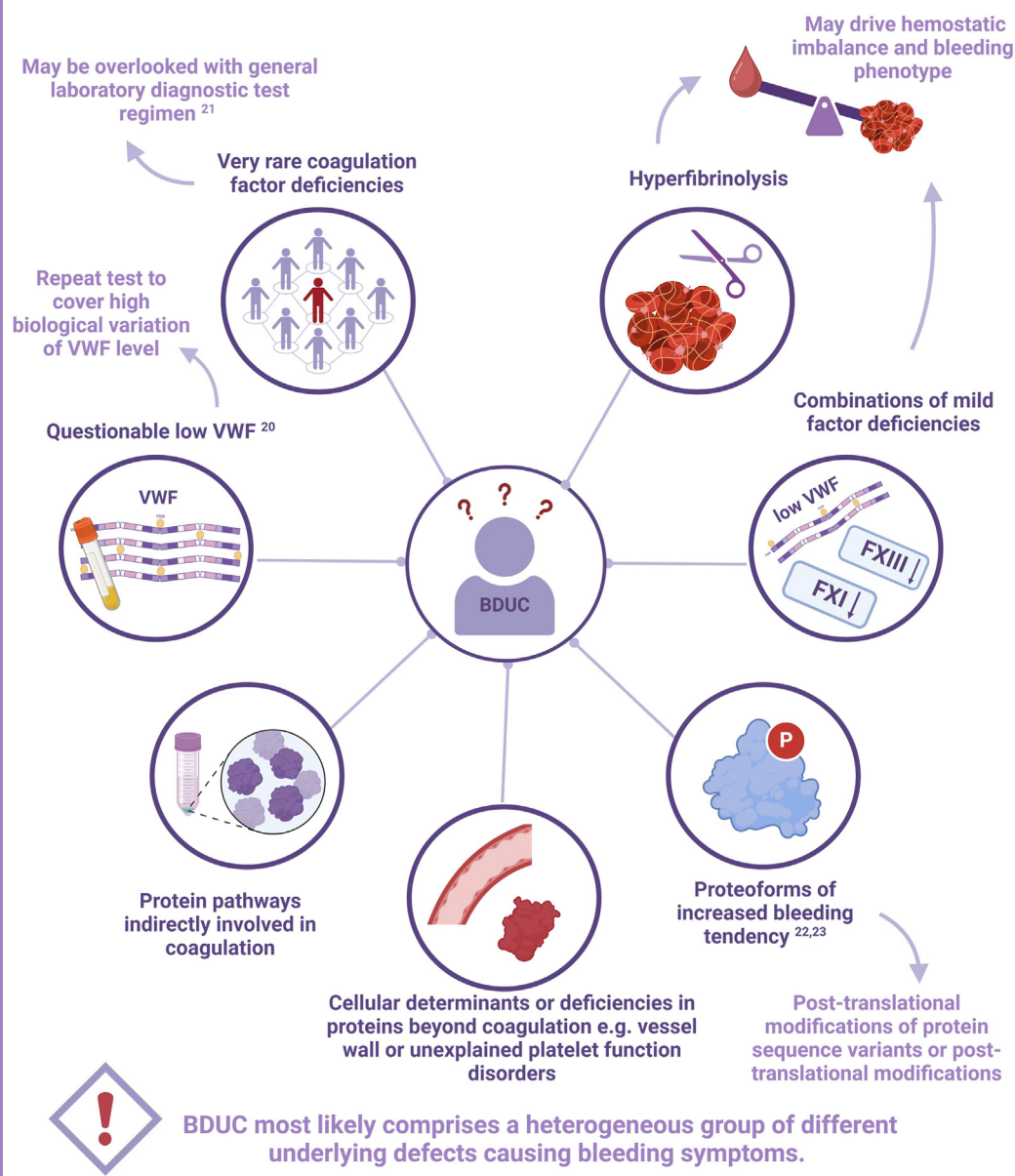
As the bleeding phenotype of BDUC patients is similar to patients with other bleeding disorders, it is not surprising that BDUC patients also present with an increased morbidity and lower quality of life. The diagnosis of BDUC has various positive and negative implications.^{7,15,18}



Adapted from Baker et al. 2021

10. Suspected hemostatic etiologies underlying BDUC

A variety of pathologies can be associated with an increased bleeding tendency or prolonged bleeding episodes.^{19, 20} The underlying pathophysiology behind the bleeding tendency in persons with BDUC is yet unknown.



11. Advanced hemostatic laboratory testing

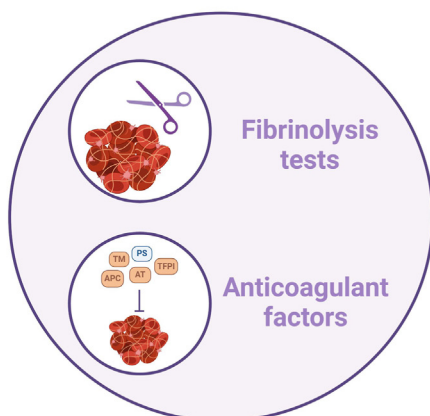
Besides the broadly available hemostatic laboratory tests, additionally more advanced hemostatic laboratory tests can be used to investigate underlying pathophysiological mechanisms.



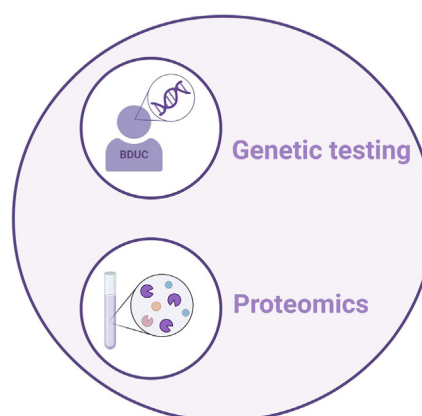
These tests are currently mainly used in research settings and their diagnostic value in the BDUC population is unclear.



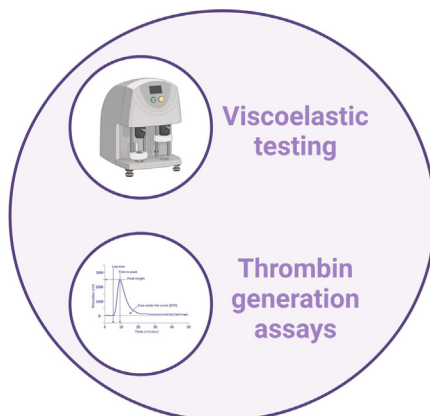
Functional testing



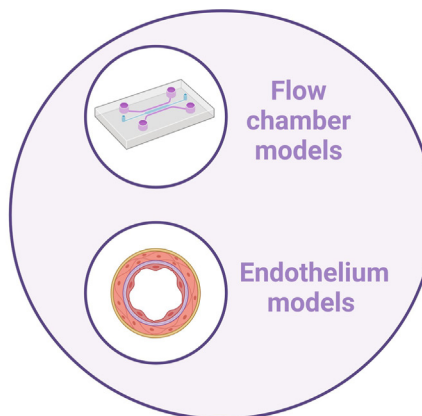
Genomics and proteomics



Global hemostasis



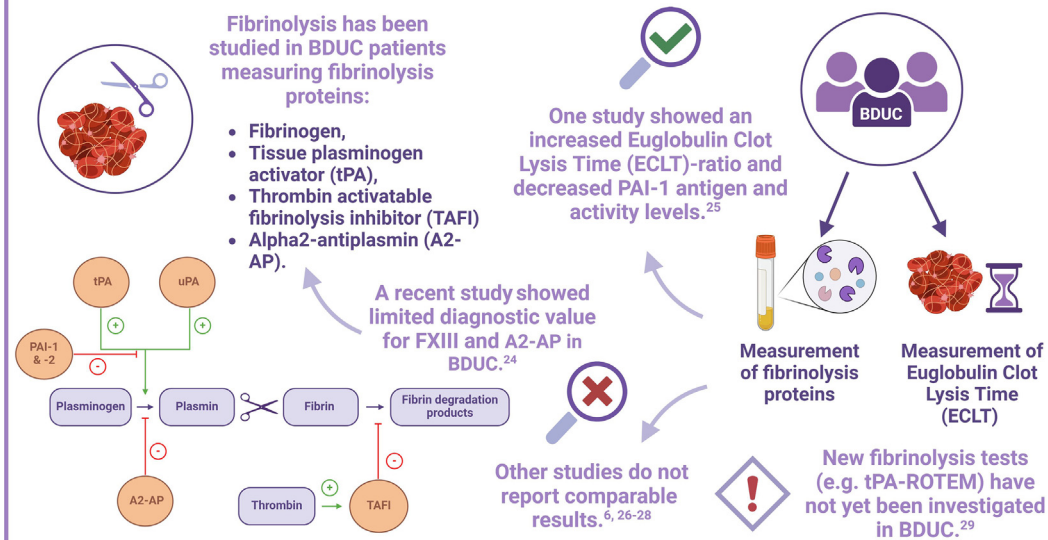
Microfluidics



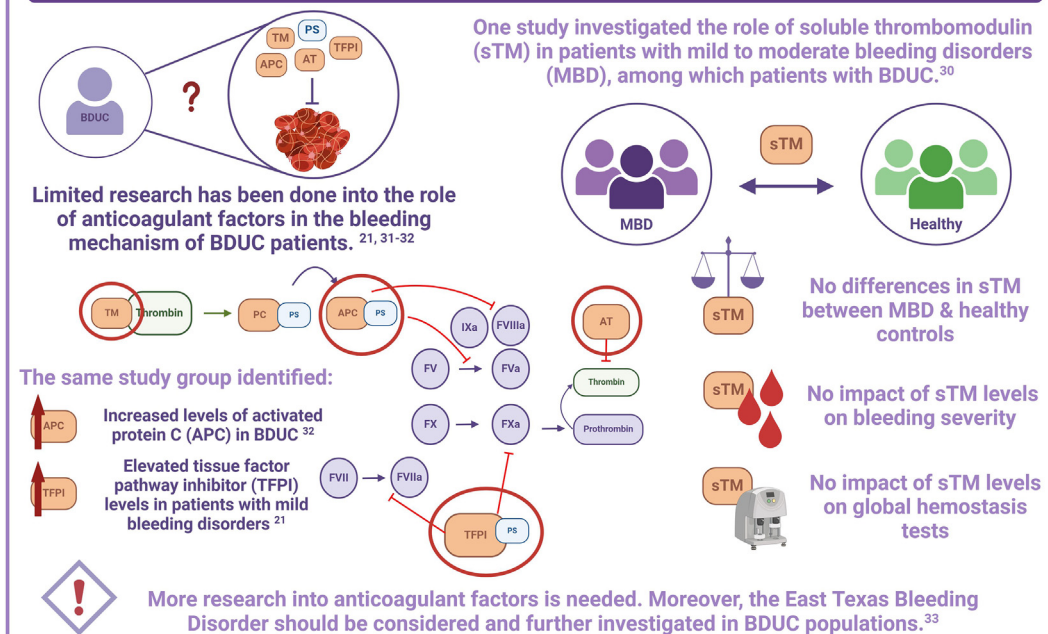
In the next four capsules current research and knowledge gaps on advanced hemostatic laboratory testing in BDUC are highlighted.

12. Functional testing

Fibrinolysis tests

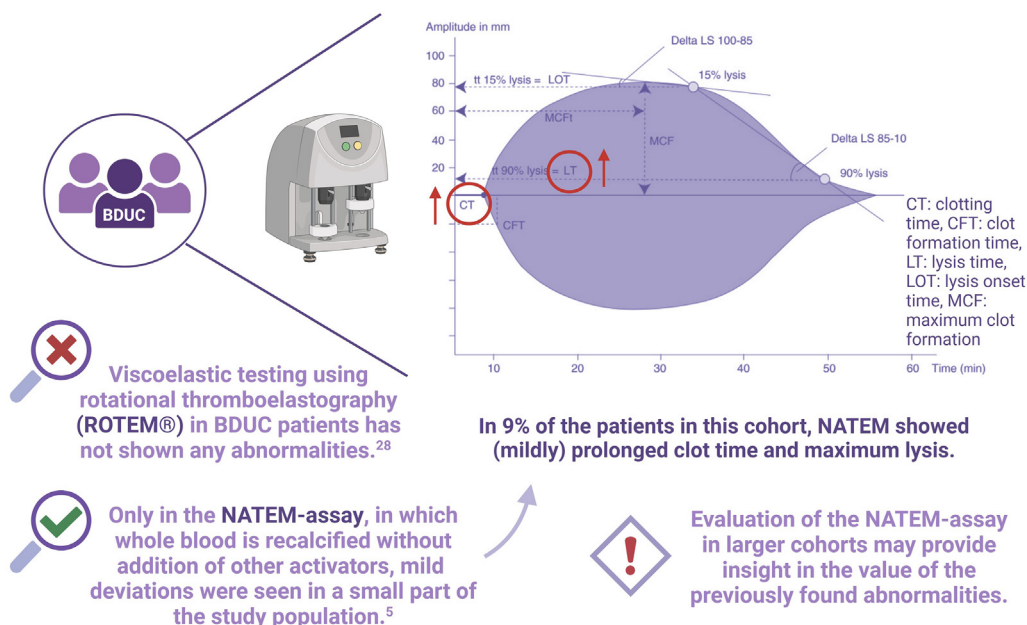


Anticoagulant factors

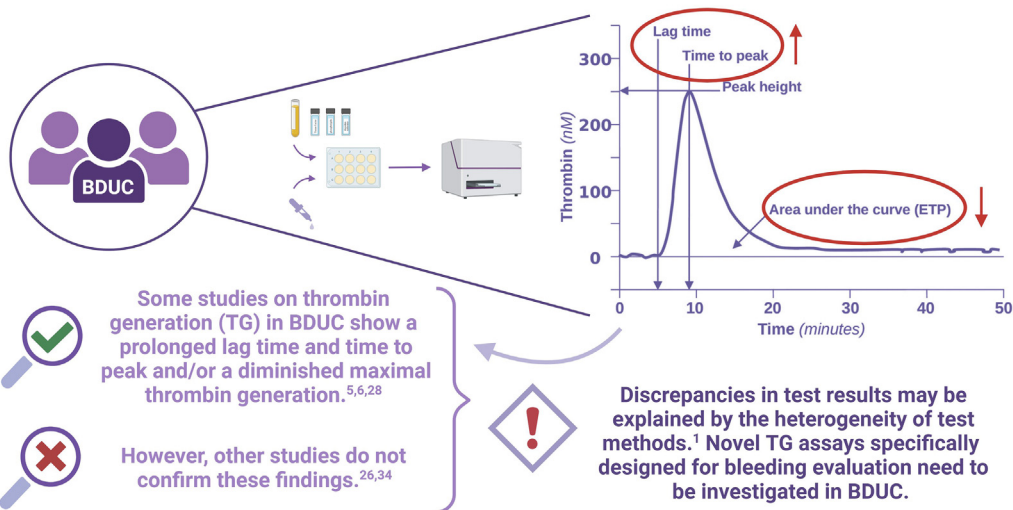


13. Global hemostasis

Viscoelastic testing



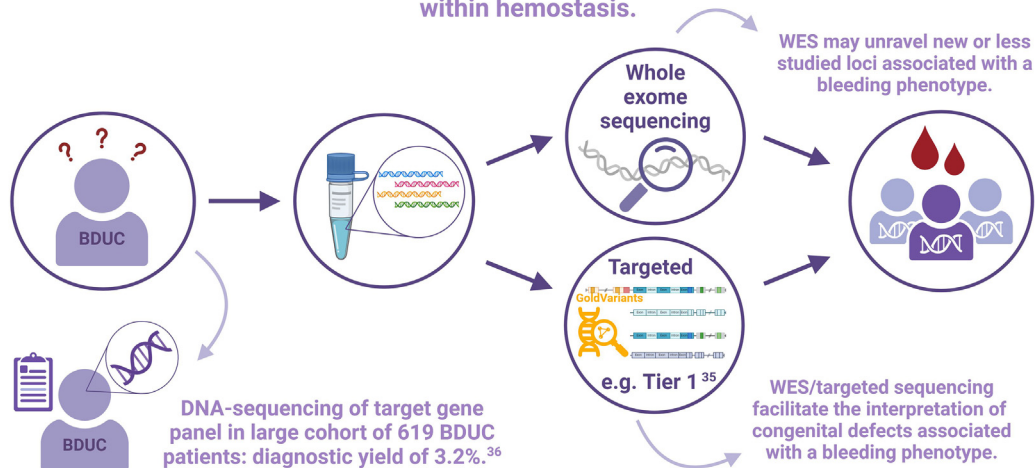
Thrombin generation assays



14. Genomics & proteomics

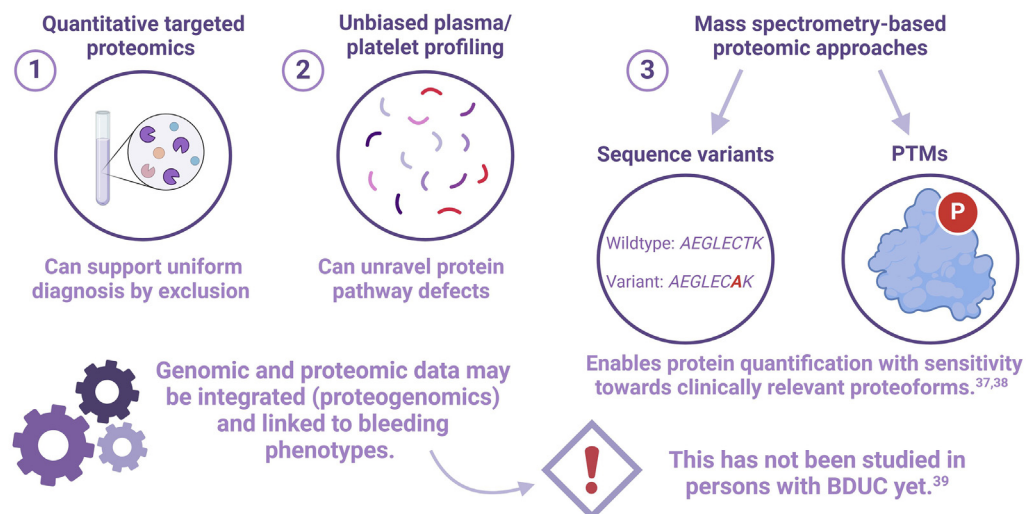
Genomics

The etiology underlying BDUC may be caused by a genetic abnormality. Exome variants resulting in altered protein biosynthesis may affect protein functionality within hemostasis.



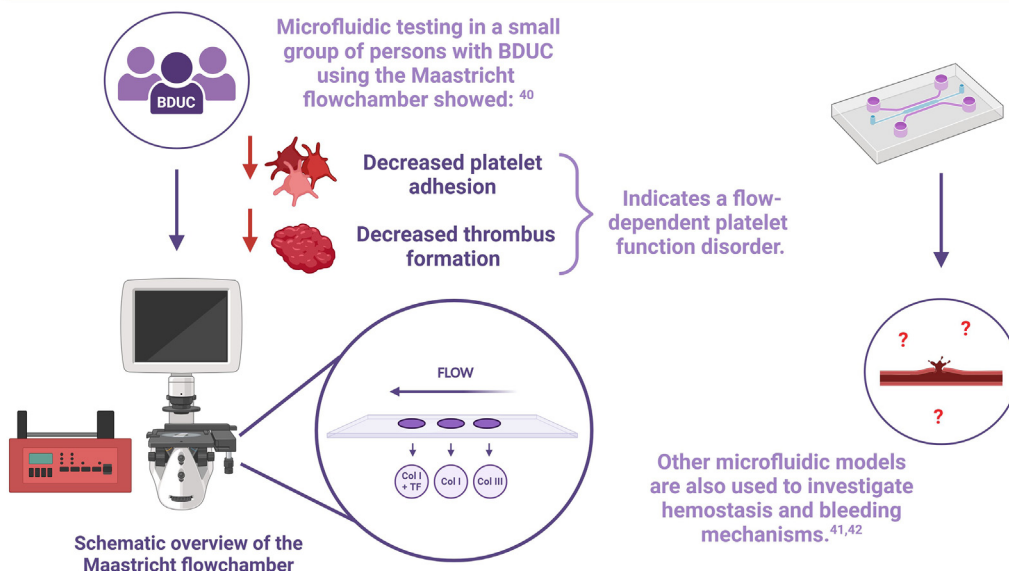
Proteomics

Powerful strategy to screen for rare protein deficiencies or abnormal protein signatures.

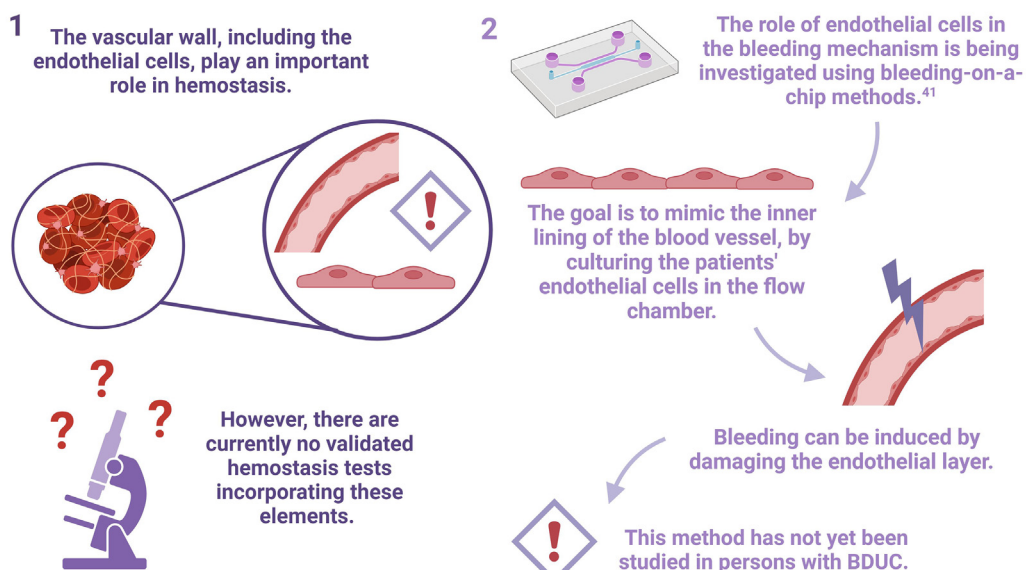


15. Microfluidics

Flow chamber models



Endothelium models



16. Quality of life

Patient-reported outcomes measurement information system (PROMIS)

Tool to precisely and efficiently measure:



Patient reported symptoms



Functioning



Health-related quality of life

Consisting of person-centered measures that evaluates and monitors:⁴³



Physical health



Social health



Mental health



General population



Chronic conditions

Validation of PROMIS

PROMIS items validated in hemophilia patients:⁴⁴



Hemophilia



Physical function



Pain interference



Fatigue



Depression



Anxiety



Ability to participate in social roles & activities



Satisfaction with social roles and activities

PROMIS reliable and useful instrument to measure patient-reported outcomes in hemophilia.



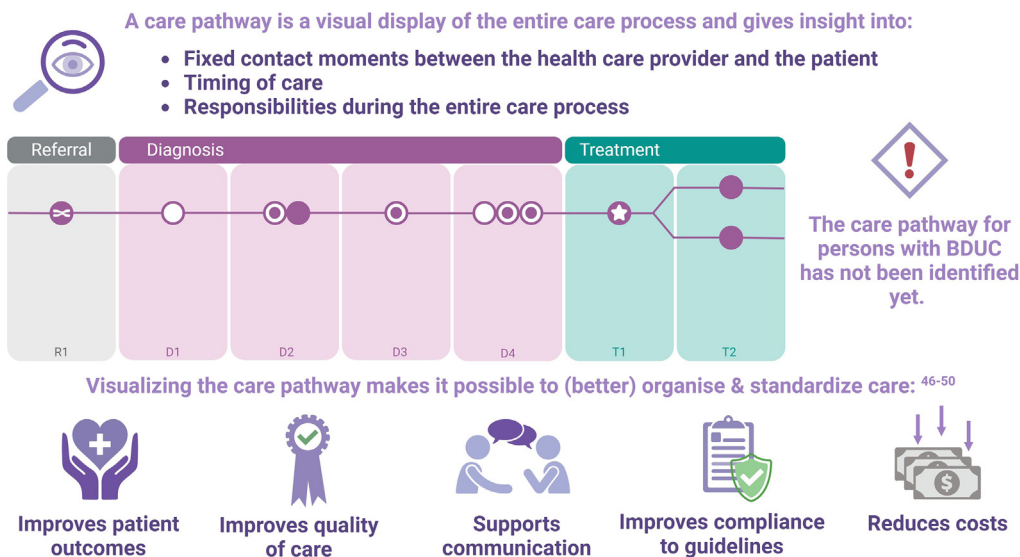
BDUC

- Limited research has been performed into quality of life and/or PROMIS in BDUC.
- One recent paper by Mehic et al. reported impaired physical and mental health-related quality of life in persons with BDUC using the RAND-36.⁴⁵
- The Reliability of PROMIS to measure PROs in BDUC is unknown.

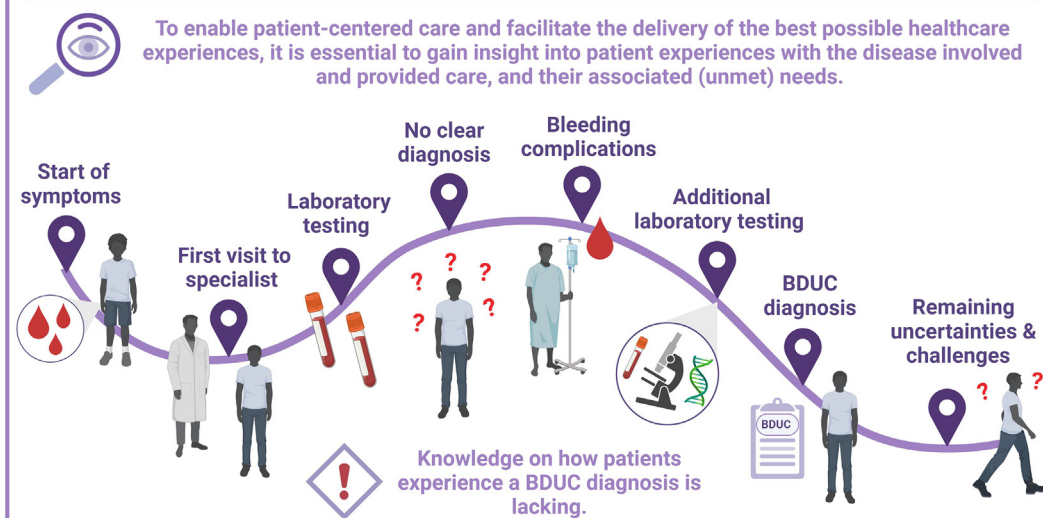
17. The BDUC health journey

Identifying care pathways and patient experiences are essential to generate meaningful insights into the perceived challenges and areas for improvement in the currently provided care.

Identifying the BDUC care pathway



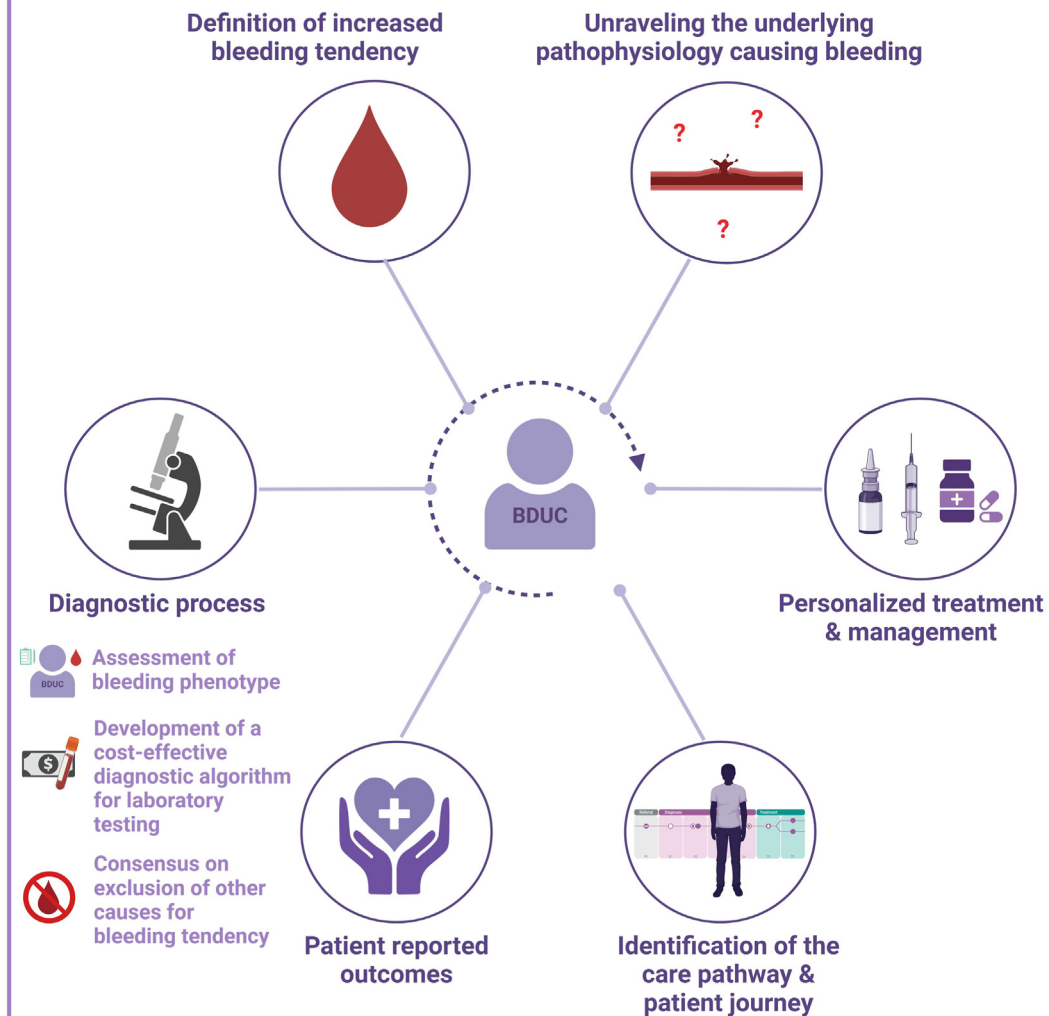
The BDUC patient journey



18. Future directions of BDUC research

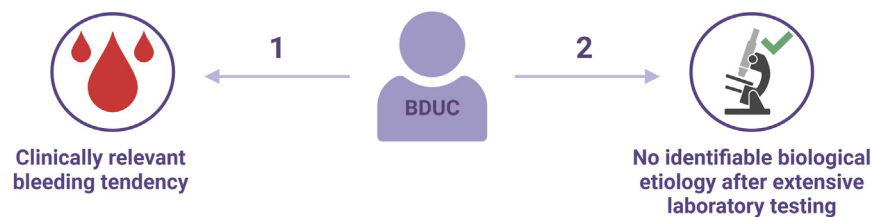
In this illustrated review we have identified current knowledge gaps regarding BDUC, highlighting the need for consensus and guidelines on several topics.

Future studies should focus on:

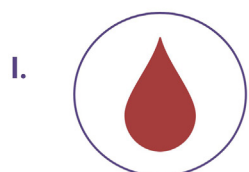


19. Key takeaways

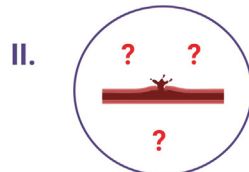
- 1 In half of individuals referred for a bleeding tendency analysis a clear diagnosis cannot be made. This is then referred to as an unexplained bleeding tendency or 'bleeding disorder of unknown cause' (BDUC).



- 2 Identified knowledge gaps & future research topics:



Definition of increased bleeding tendency



Pathophysiological mechanism



Diagnostic process



Treatment & management



Patient reported outcomes



Care pathway & patient journey

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Figures are created in BioRender.com

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AUTHOR CONTRIBUTION

A.L.L.M. and C.M.A.M. share first authorship and wrote original draft, designed the capsule, and reviewed the process. T.T.v.D., M.J.H.A.K., Y.M.C.H., M.v.d.B., R.E.G.S., S.E.M.S., K.J.F., K.M., P.L.d.E., L.N., I.v.M., R.I.B., and J.S.O'D. reviewed and edited the manuscript. M.H.C. and F.C.J.I.H-M. reviewed, edited, and supervised the study.

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