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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

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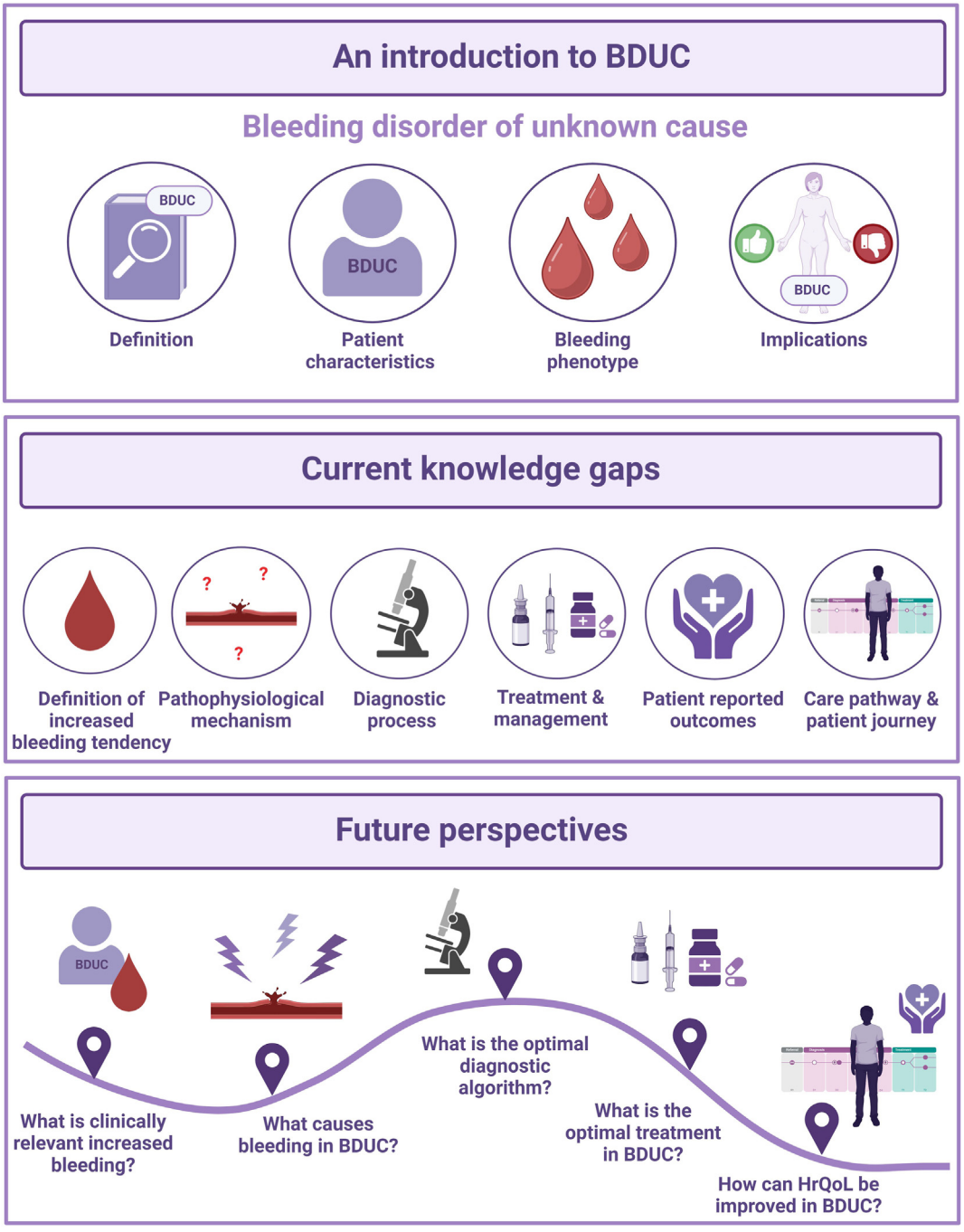
definition by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis, stating that BDUC is a diagnosis of exclusion, characterized by normal hemostatic investigations despite a clinically significant bleeding tendency. Importantly, other nonhemostatic 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

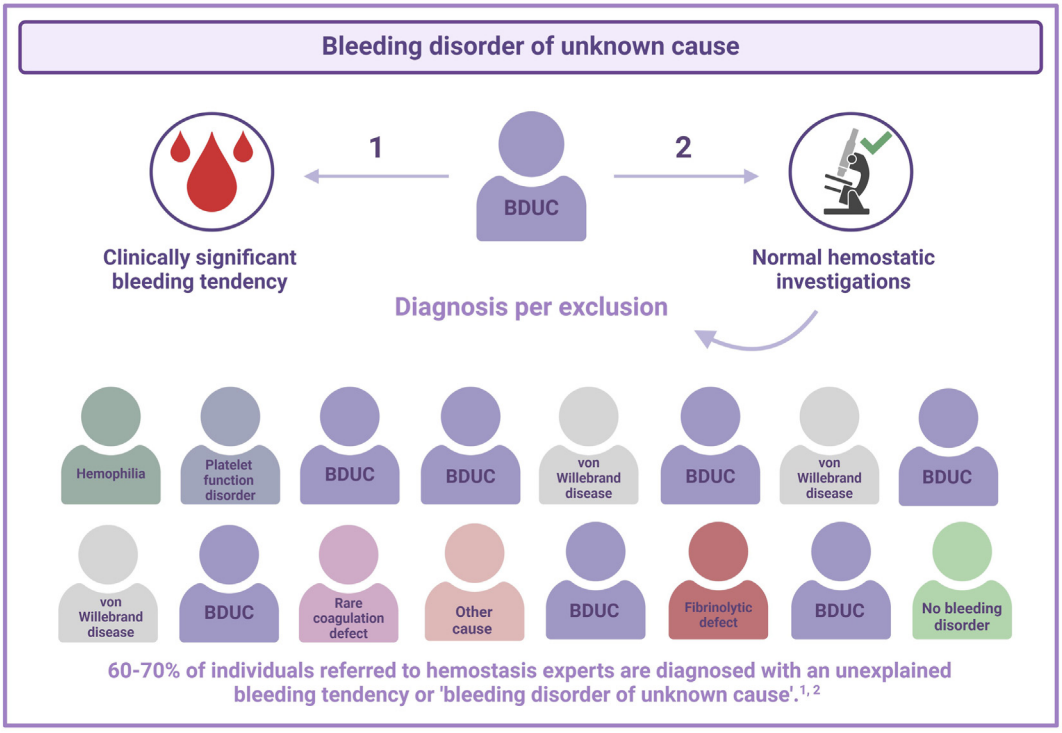
Essentials

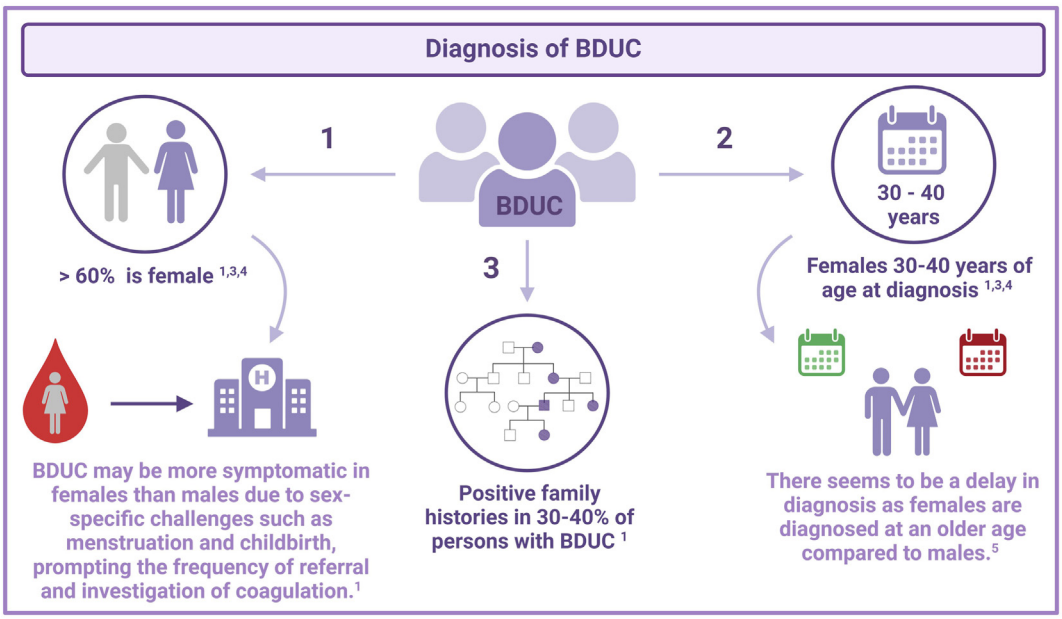
- Bleeding Disorder of Unknown Cause (BDUC) is defined by a positive personal and/or family history of bleeding with normal laboratory test results.
- More than half of patients with bleeding symptoms seen in hemostasis clinics are diagnosed with BDUC.
- There are major knowledge gaps and lack of consensus 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



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



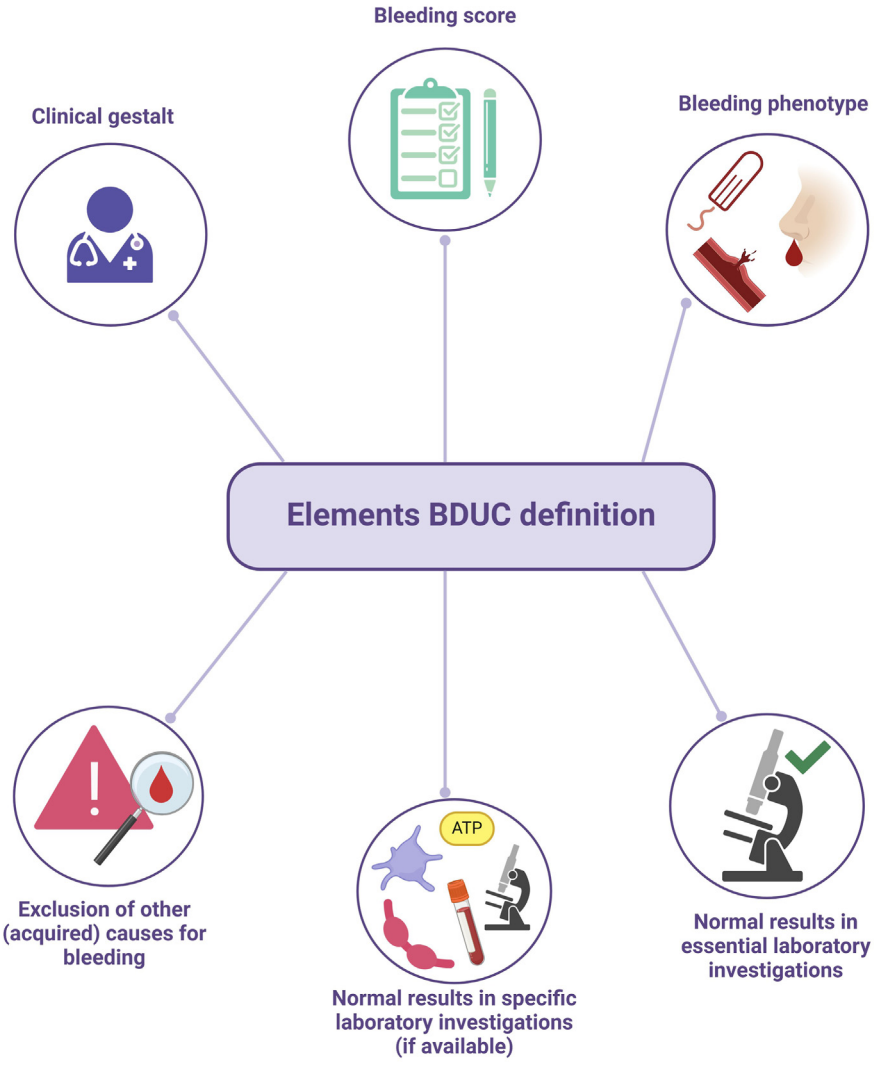


3. Elements of the BDUC definition

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 tests [4-7]

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

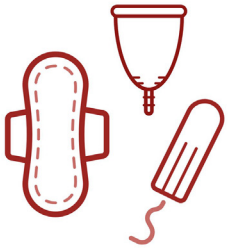


4. Bleeding phenotype

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

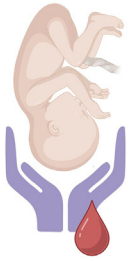
Heavy menstrual bleeding



60% - 90% of females with BDUC [3-5, 10]

Gynecologic cause should be excluded [2]

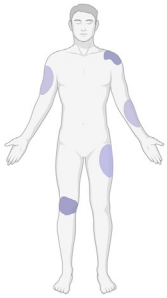
Post partum bleeding



30% - 65% of females with BDUC [3-5,9,10]

Mucocutaneous bleeding

Hematomas/easy bruising

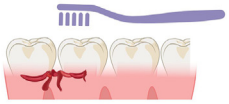


66% - 78% [3-5, 10]

Epistaxis

31% - 79% [3-5, 10]

Oral mucosal

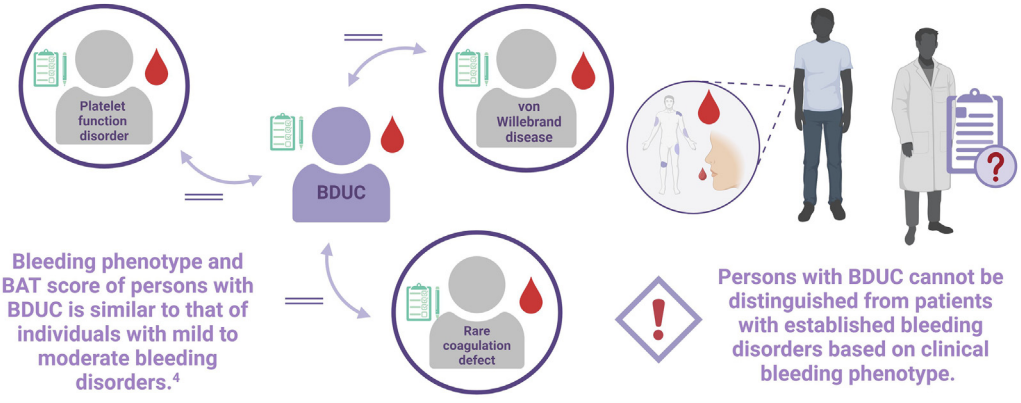


19% - 53% [3,4,10]

Bleeding during or after medical & dental procedures

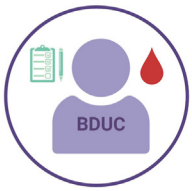
44% - 75% [3-5,9,10]

36% - 84% [3-5,10]



5. Assessment of bleeding phenotype

Phenotypic assessment of bleeding is central to the diagnosis of BDUC



How to quantify the bleeding symptoms?

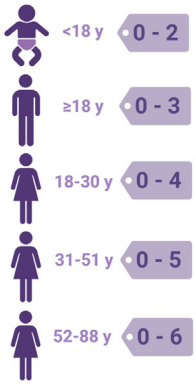
1 Bleeding Assessment Tool (BAT)

BATs provide a standardized and objective approach for the assessment of bleeding symptoms.

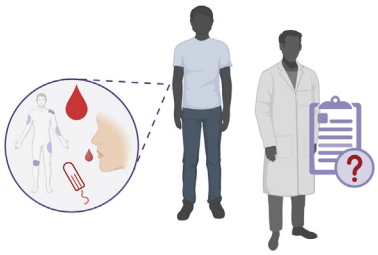
The International Society on Thrombosis and Haemostasis (ISTH) BAT is currently the most applied BAT and the recommended assessment tool by the ISTH SSC.[2,11]

Reference ranges ISTH-BAT

Adjusted reference ranges have been recommended based on age.[2, 14]



2 Clinical gestalt assessed by medical specialist



BATs have limitations including: [2, 12]

- Lack of sensitivity in persons without hemostatic challenges
- Recall bias
- Score saturation with recurrent symptoms
- Inability to differentiate between different types of MBD.

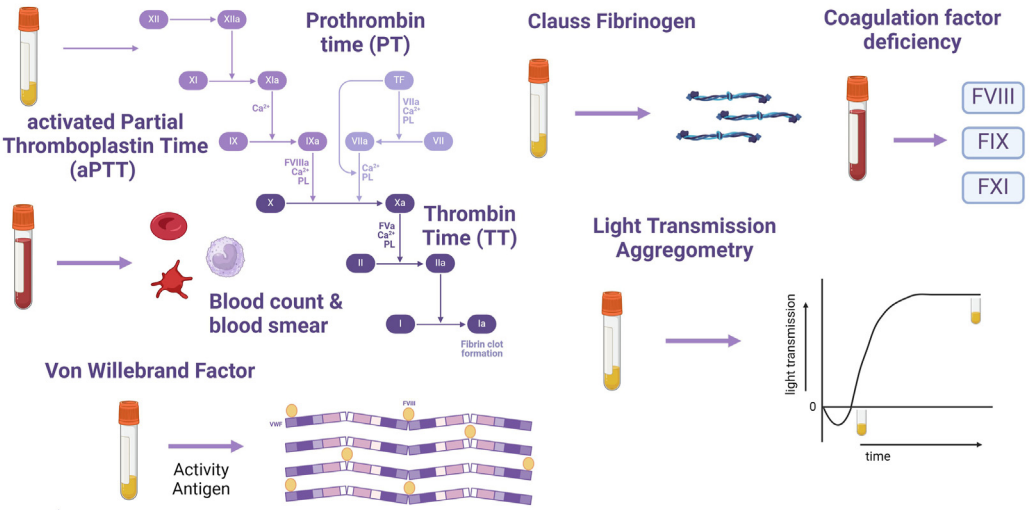
Moreover, low BAT scores do not always exclude mild bleeding disorders.[13]

As BATs have several limitations, BAT scores need to be considered on an individual basis together with the clinical gestalt by the treating physician.

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.

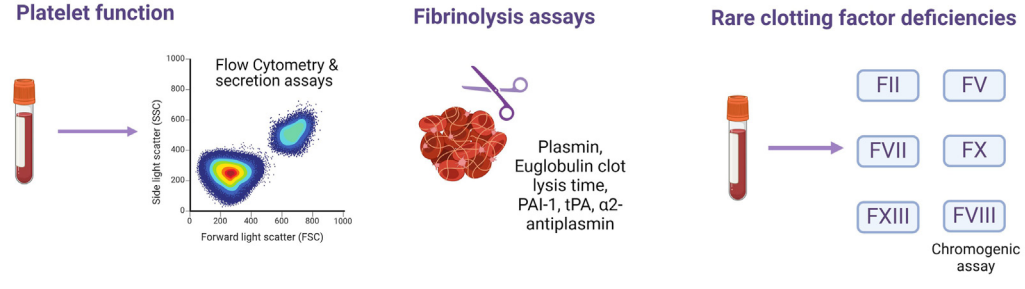
1 Essential Laboratory Investigations



Mild coagulation factor deficiencies can be missed when using primary and secondary hemostatic screening laboratory tests!

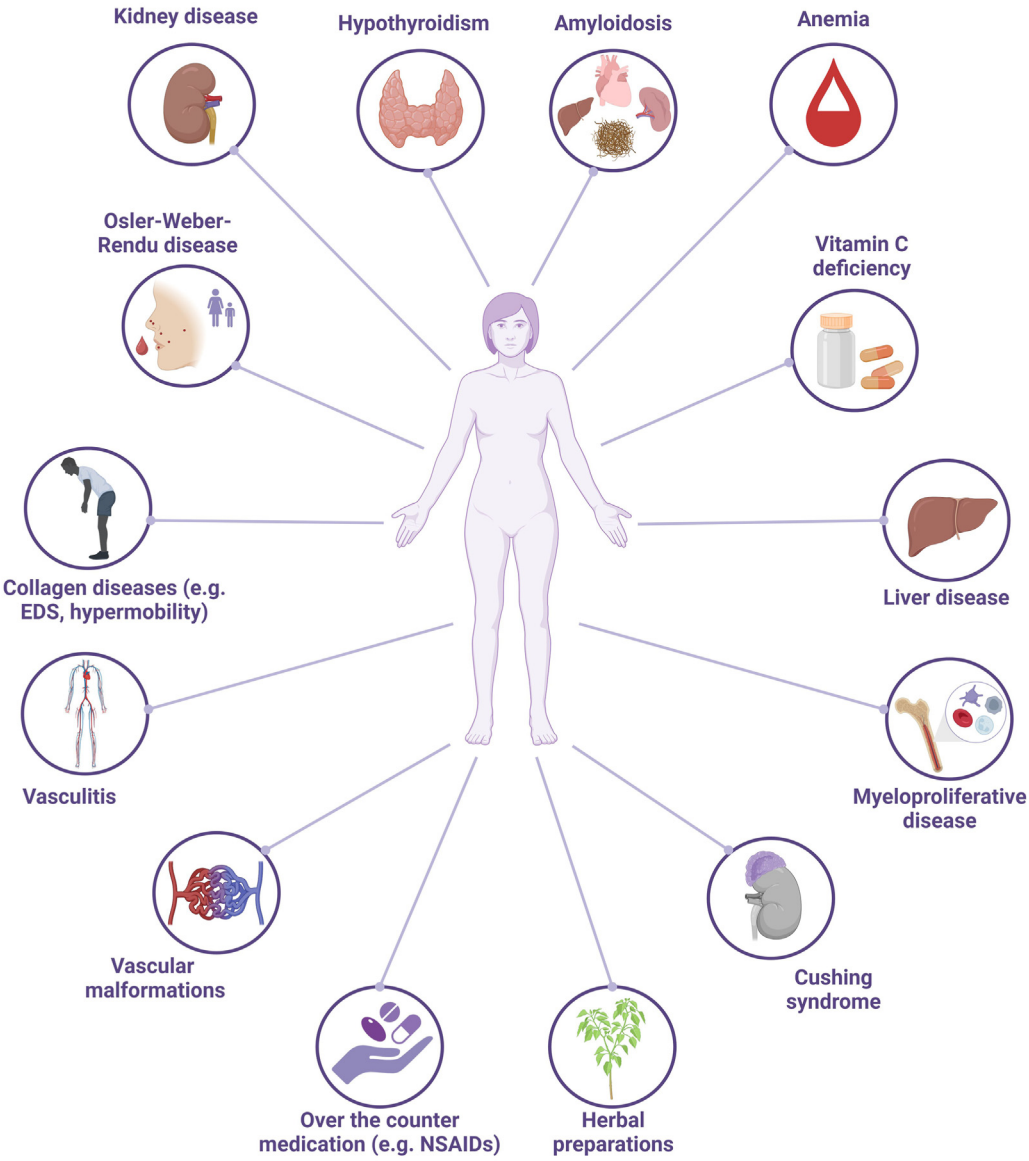
2 Specific Laboratory Investigations (if available)

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]



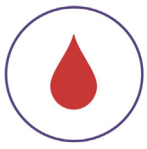
7. Other causes for bleeding

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

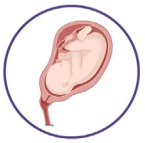
Indications for treatment



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]

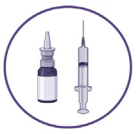
Tranexamic acid (TxA)

Minor and major medical and dental procedures

- 1g 3x/day [15]
- 15-25 mg/kg (up to 1g) 3x/day [5]
- 500-1000 mg 3x/day [16]

Single dose 10 mg/kg (up to 1g) continued orally [16]

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.

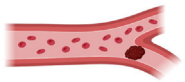
Best treatment per medical intervention

Efficacy

Bleeding complications

Safety

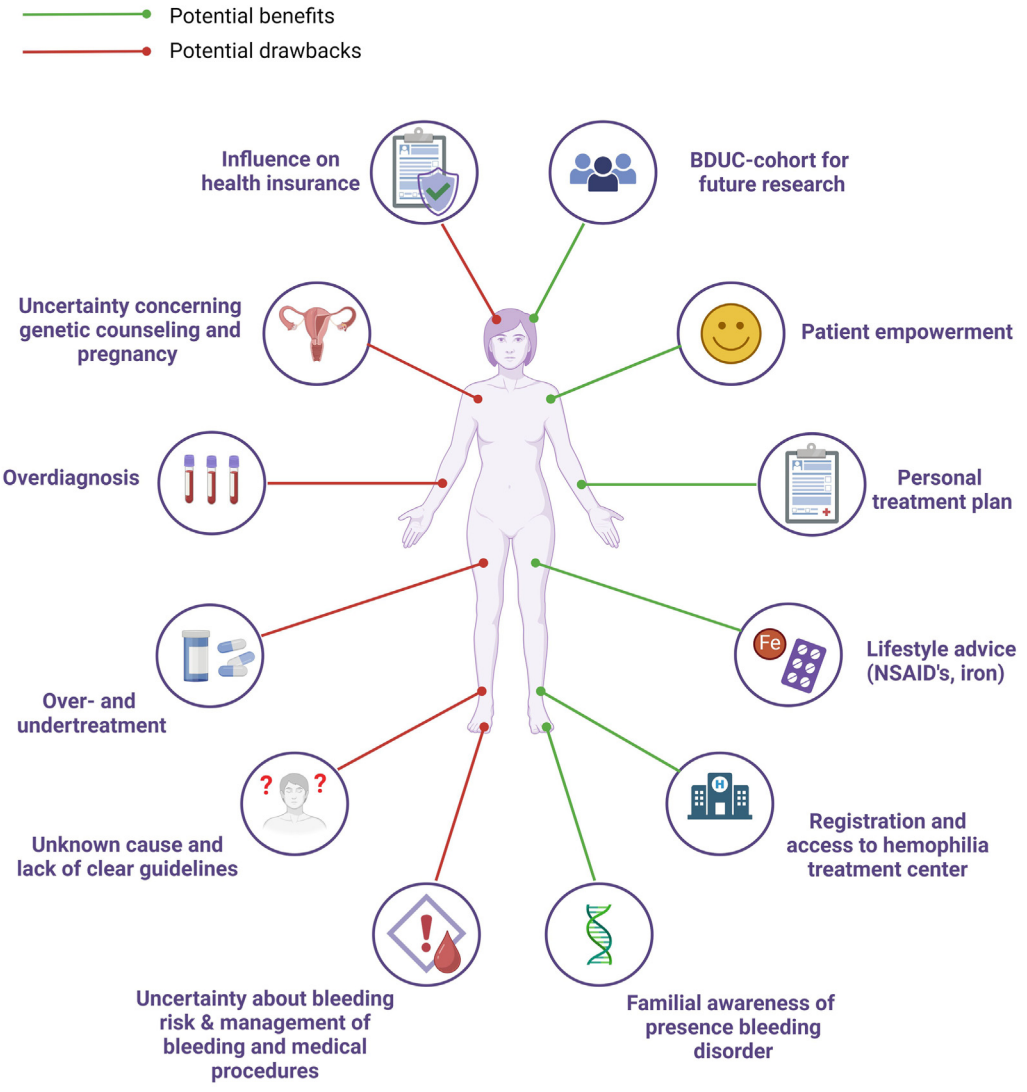
Thrombotic risk



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

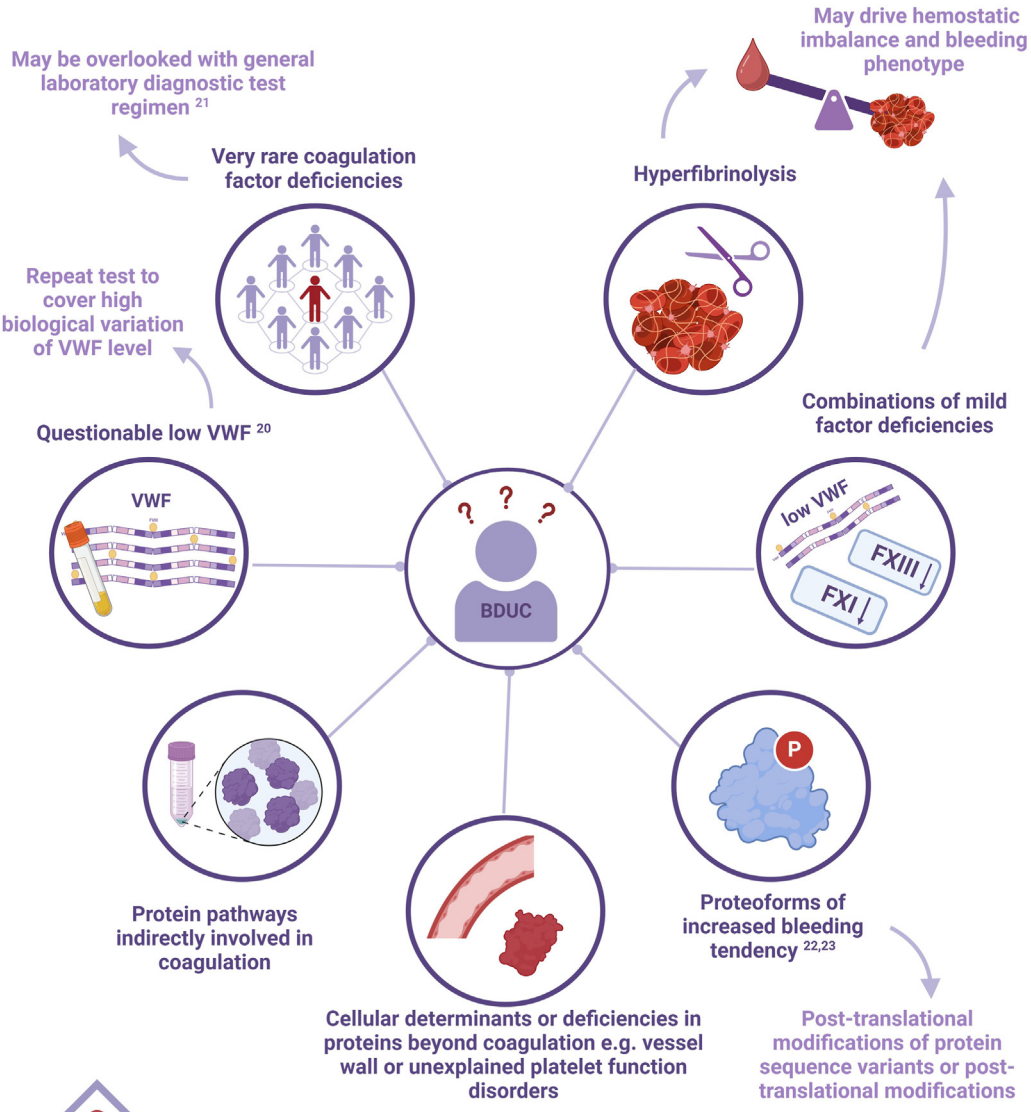
As the bleeding phenotype of BDUC patients is similar to patients with other bleeding disorders, it is not surprising that BDUC patients also present with an increased morbidity and lower quality of life. The diagnosis of BDUC has various positive and negative implications.[7,15,18]



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.



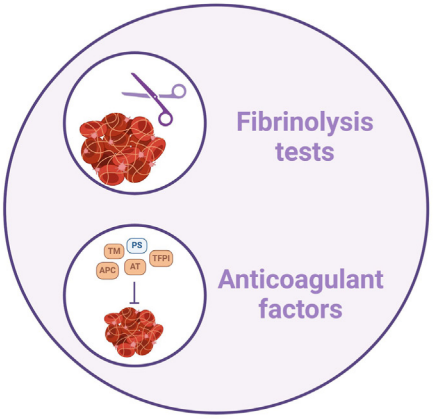
BDUC most likely comprises a heterogeneous group of different underlying defects causing bleeding symptoms.

11. Advanced hemostatic laboratory testing

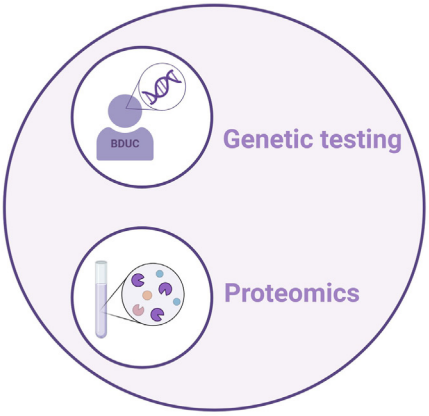
Besides the broadly available hemostatic laboratory tests, additionally more advanced hemostatic laboratory tests can be used to investigate underlying pathophysiological mechanisms.

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

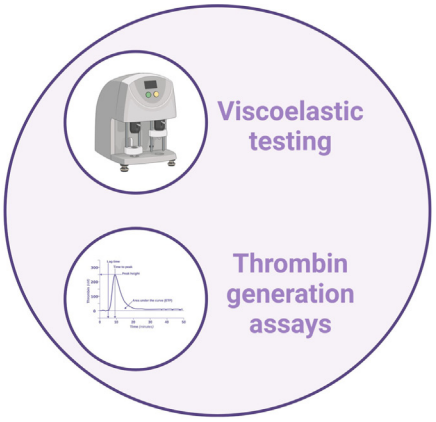
Functional testing



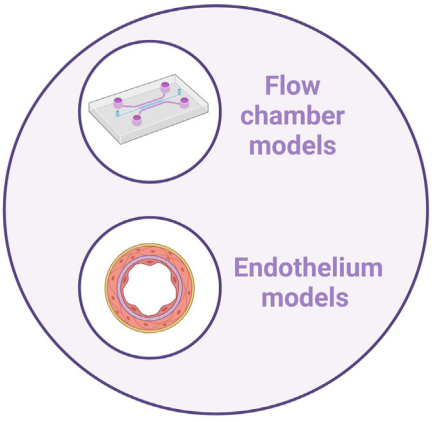
Genomics and proteomics



Global hemostasis

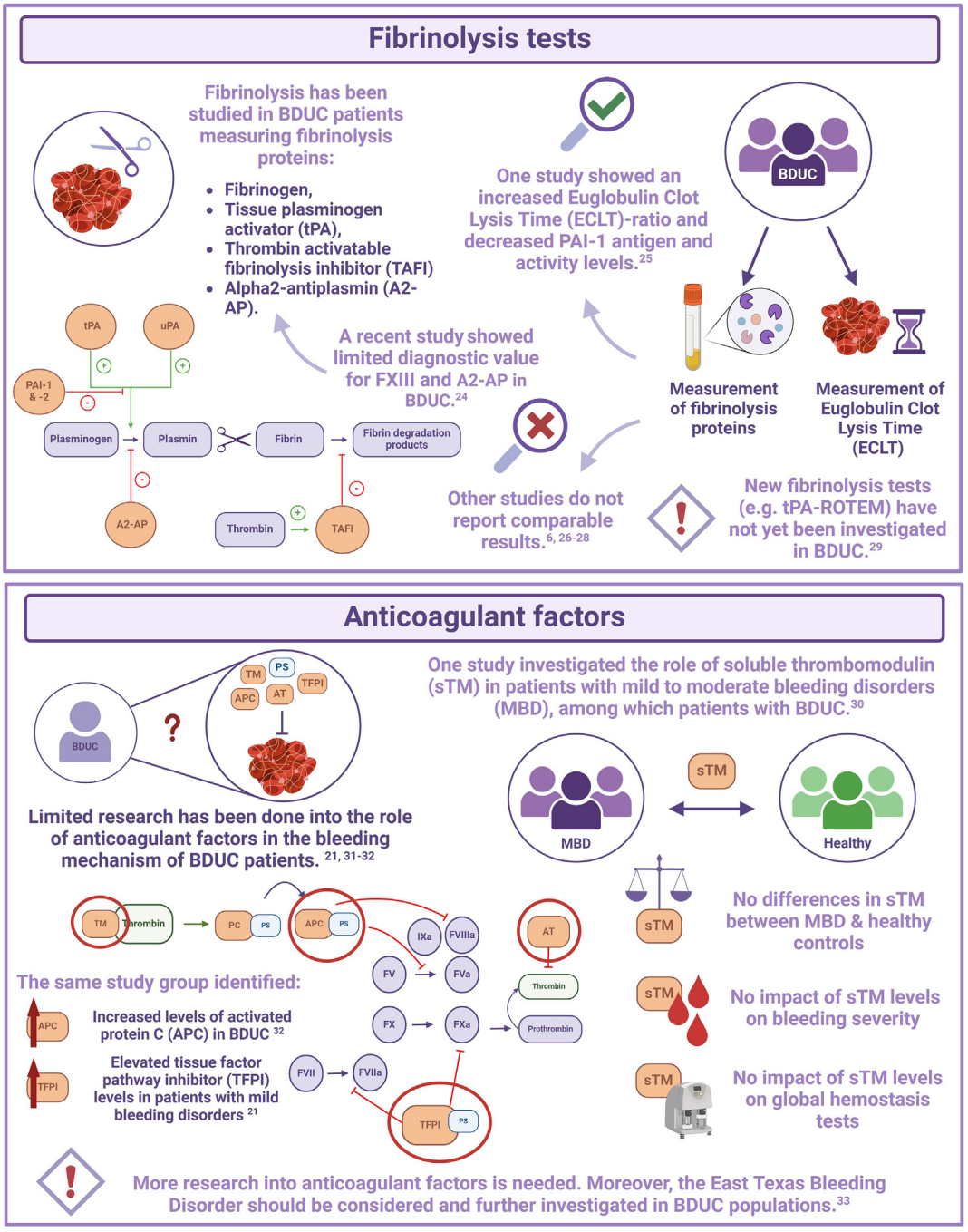


Microfluidics



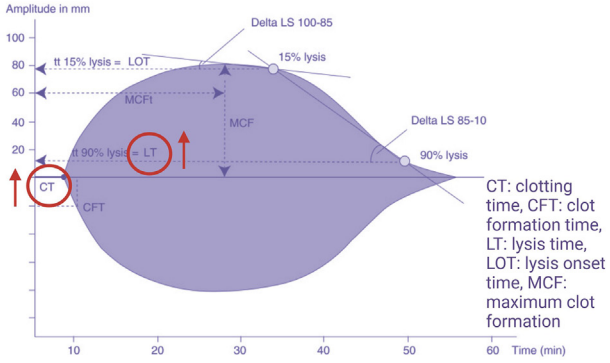
In the next four capsules current research and knowledge gaps on advanced hemostatic laboratory testing in BDUC are highlighted.

12. Functional testing



13. Global hemostasis

Viscoelastic testing



CT: clotting time, CFT: clot formation time, LT: lysis time, LOT: lysis onset time, MCF: maximum clot formation

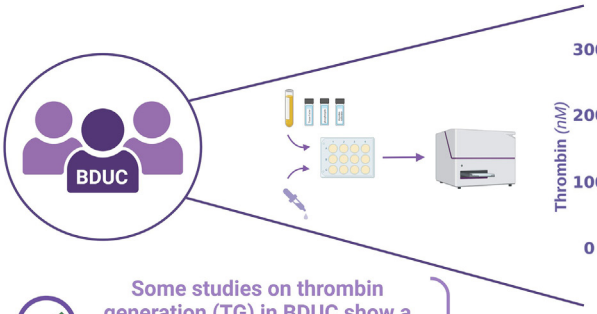
Viscoelastic testing using rotational thromboelastography (ROTEM®) in BDUC patients has not shown any abnormalities.[28]

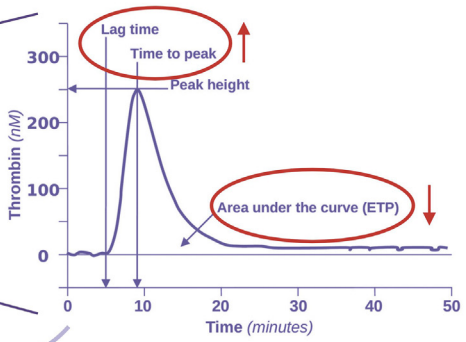
In 9% of the patients in this cohort, NATEM showed (mildly) prolonged clot time and maximum lysis.

Only in the **NATEM-assay**, in which whole blood is recalcified without addition of other activators, mild deviations were seen in a small part of the study population.[5]

Evaluation of the NATEM-assay in larger cohorts may provide insight in the value of the previously found abnormalities.

Thrombin generation assays





Some studies on thrombin generation (TG) in BDUC show a prolonged lag time and time to peak and/or a diminished maximal thrombin generation.[5,6,28]

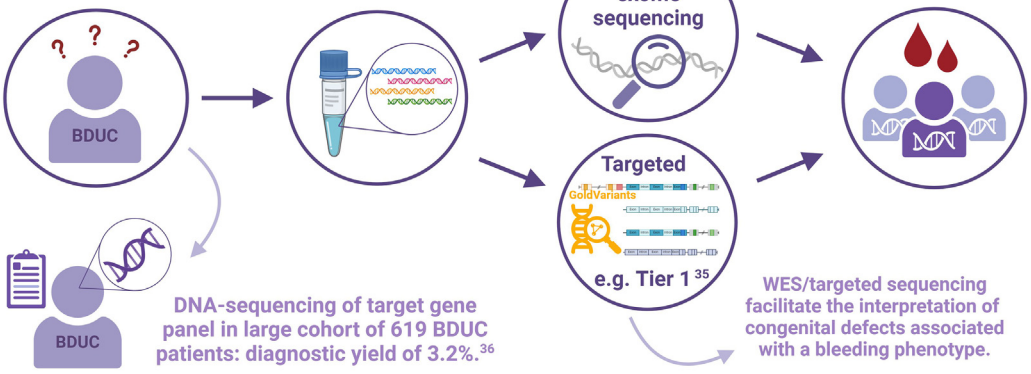
However, other studies do not confirm these findings.[26,34]

Discrepancies in test results may be explained by the heterogeneity of test methods.[1] Novel TG assays specifically designed for bleeding evaluation need to be investigated in BDUC.

14. Genomics & proteomics

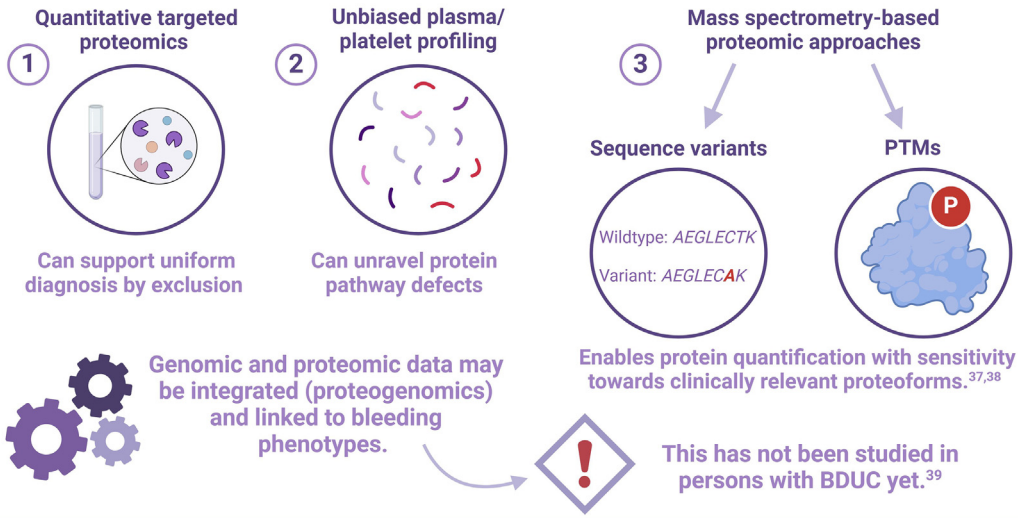
Genomics

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



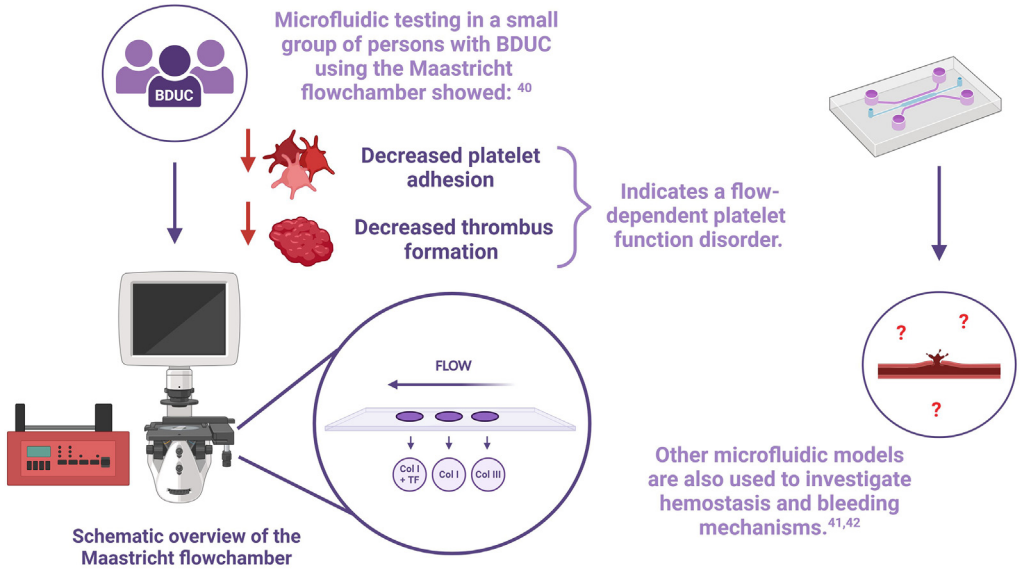
Proteomics

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

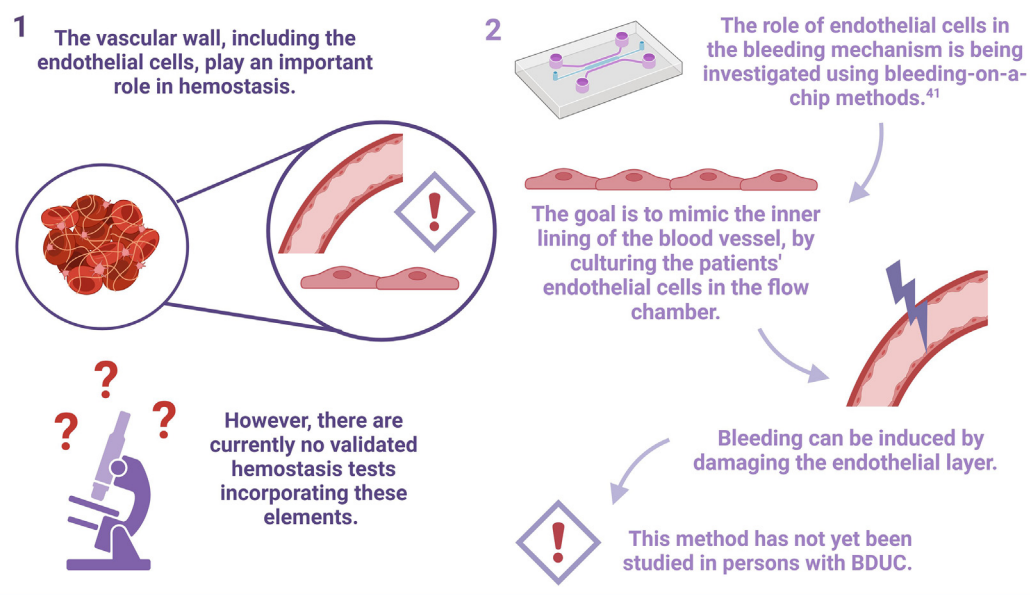


15. Microfluidics

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.

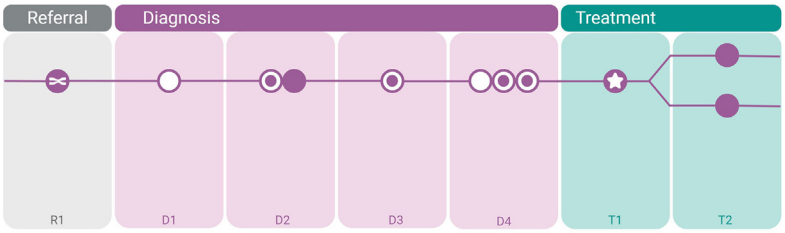
17. The BDUC health journey

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

A care pathway is a visual display of the entire care process and gives insight into:

- Fixed contact moments between the health care provider and the patient
- Timing of care
- Responsibilities during the entire care process



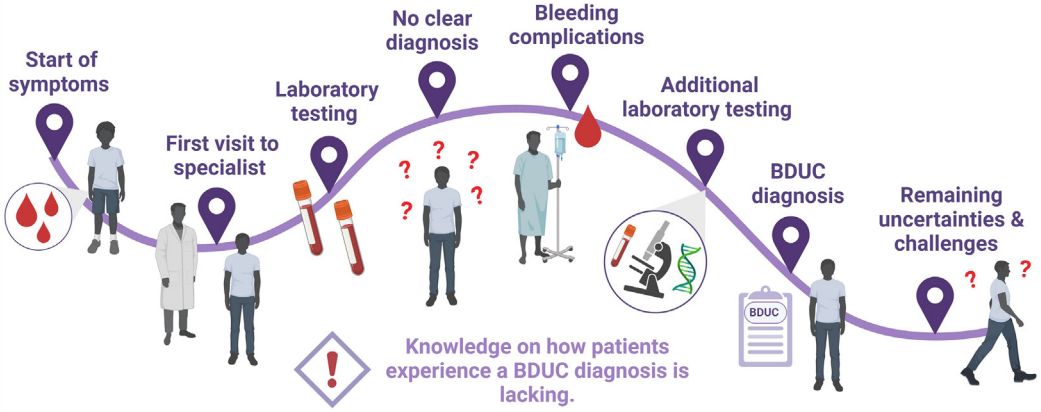
The care pathway for persons with BDUC has not been identified yet.

Visualizing the care pathway makes it possible to (better) organise & standardize care: [46-50]

- Improves patient outcomes
- Improves quality of care
- Supports communication
- Improves compliance to guidelines
- Reduces costs

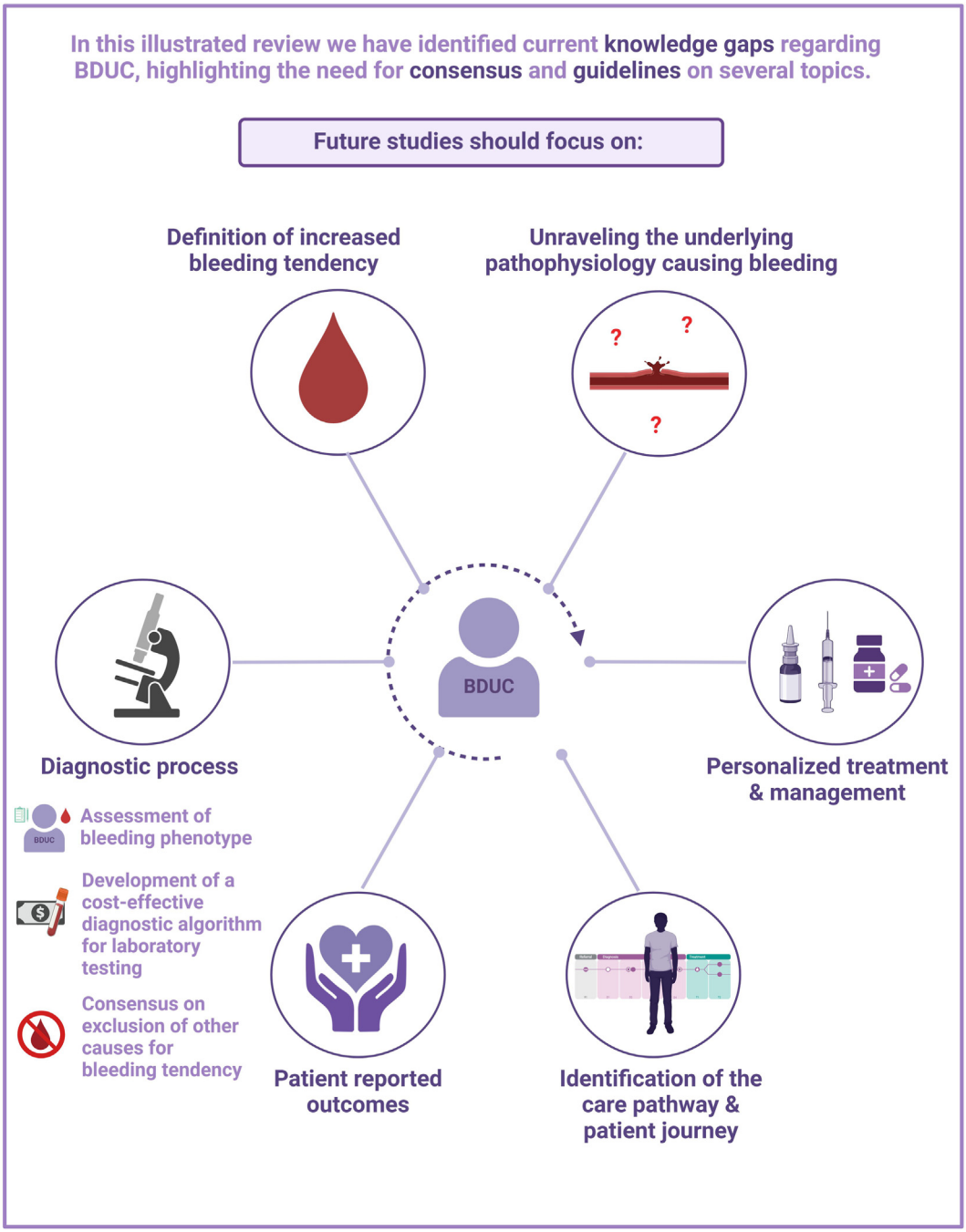
The BDUC patient journey

To enable patient-centered care and facilitate the delivery of the best possible healthcare experiences, it is essential to gain insight into patient experiences with the disease involved and provided care, and their associated (unmet) needs.



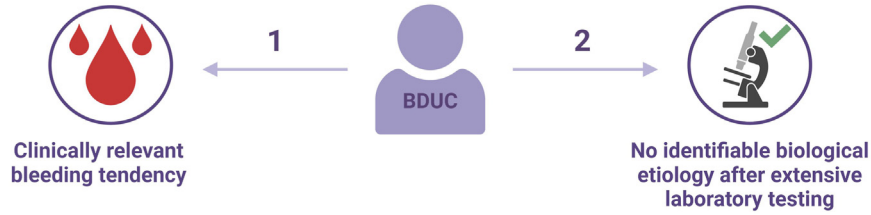
Knowledge on how patients experience a BDUC diagnosis is lacking.

18. Future directions of BDUC research

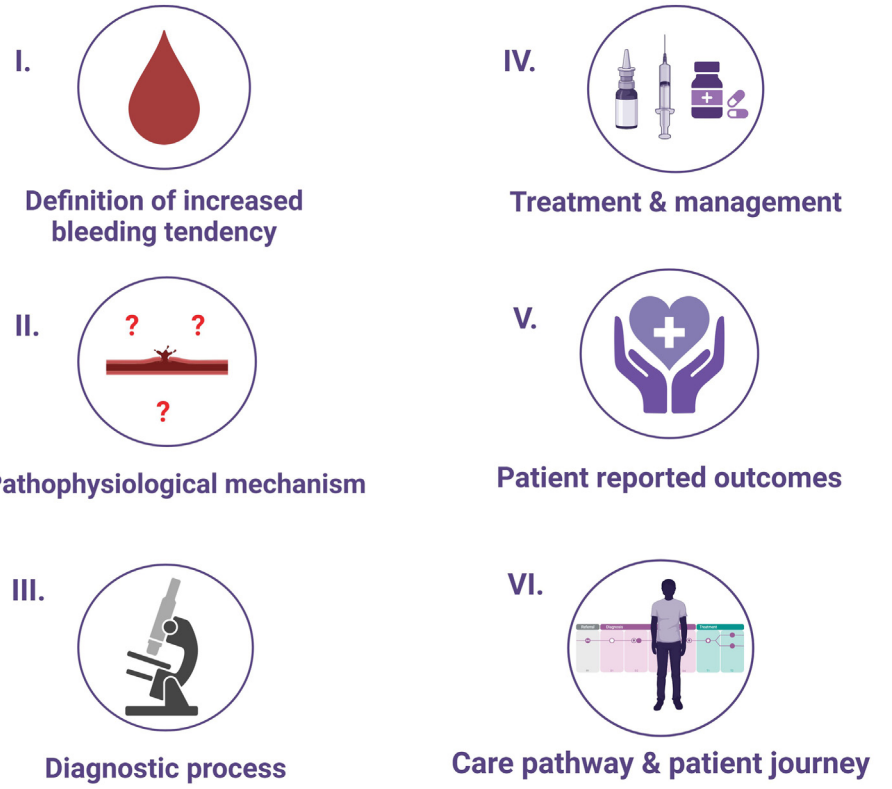


19. Key takeaways

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:



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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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