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National Bleeding Disorder Foundation Clinical Practice Recommendations for Laboratory Screening of Iron Deficiency With and Without Anemia in the Inherited Bleeding Disorders Population

Glaivy Batsuli[1] | Magdalena D. Lewandowska[2] | Ming Y. Lim[3] | Kelly Tickle[4] | Maureen K. Baldwin[5] | Rose Bender[6] | Jennifer Davila[7] | Brendan Hayes[8] | Amanda Jacobson-Kelly[9] | Peter Kouides[10] | Michele P. Lambert[11] | Shilpa Nataraj[1] | Michelle Sholzberg[12] | Roona Sinha[13] | Hanny Al-Samkari[14] | Amy L. Dunn[9]

[1]Department of Pediatrics, Stanford University, Palo Alto, California, USA | [2]Innovative Hematology/Indiana Hemophilia & Thrombosis Center, Indianapolis, Indiana, USA | [3]Division of Hematology and Hematologic Malignancies, Department of Internal Medicine, University of Utah, Salt Lake City, Utah, USA | [4]Hemophilia of Georgia Center For Bleeding and Clotting Disorders At Children's Healthcare of Atlanta, Atlanta, Georgia, USA | [5]Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland, Oregon, USA | [6]Yale University School of Medicine, New Haven, Connecticut, USA | [7]Children's Hospital at Montefiore and Albert Einstein College of Medicine, Bronx, NY, USA | [8]National Bleeding Disorders Foundation, New York, NY, USA | [9]Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, Ohio, USA | [10]Mary M. Gooley Hemophilia Treatment Center, Rochester, NY, USA | [11]Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA | [12]St. Michael's Hospital, Li Ka Shing Knowledge Institute, University of Toronto, Toronto, Ontario, Canada | [13]Royal University Hospital, Division of Pediatric Hematology-Oncology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada | [14]Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

Correspondence: Amy L. Dunn (amy.dunn@nationwidechildrens.org)

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ABSTRACT

Introduction: The National Bleeding Disorder Foundation (NBDF) Medical and Scientific Advisory Council (MASAC) was formed in 1954 and issues recommendations and advisories pertinent to the bleeding disorders community. MASAC is comprised of > 25 rotating members from different medical disciplines and lived experience experts.

Aim: The Iron Deficiency Taskforce was formed to address the concern for undertreatment and misdiagnosis of iron deficiency with and without anemia in the inherited bleeding disorder community. Members included MASAC members and individuals outside of MASAC with clinical, research, and lived experience expertise and/or interest in iron deficiency and screening in the bleeding disorders community. Currently, there are no published standardized approaches, guidelines, or recommendations that address iron deficiency screening for a population of individuals at high risk of experiencing iron deficiency and its associated complications

Method: Due to the limited published peer-reviewed data on the prevalence of iron deficiency and anemia in this population, this document was devised by consensus recommendations amongst members of the Iron Deficiency Taskforce with additional review and feedback from all MASAC members.

Result: This document identifies individuals within the inherited bleeding disorder population at risk for iron deficiency with and without anemia providing consensus recommendations on indications for screening, approach to screening, and general

management considerations if iron deficiency and anemia are identified. Recommendations for higher hemoglobin (< 13 g/dL) and ferritin (< 50 ng/mL) thresholds for anemia and iron deficiency diagnoses, respectively, are also discussed.
Conclusion: Further research is necessary to understand the impact of iron deficiency in inherited bleeding disorders.

1 | TOPIC 1: The Impact of Iron Deficiency

1.1 | Background

An estimated 24% of the world's population, or ~2 billion individuals, has anemia [1]. Iron deficiency anemia is the most common cause of anemia and is associated with significant morbidity and mortality in high-risk populations [2]. Iron deficiency without anemia is an under recognized and undertreated public health issue that affects males and females across the lifespan. Iron deficiency is especially prevalent among women and girls, affecting 40% of this population between the ages of 12–21 years when applying current standards for reference ranges of ferritin [3]. Severe iron deficiency, with or without anemia, may be the first indication of an underlying inherited bleeding disorder that warrants additional evaluation, while individuals with an inherited bleeding disorder are at an increased risk of developing iron deficiency due to iron loss from bleeding.

Untreated iron deficiency ultimately evolves into IDA. Screening and correction of iron deficiency is critical, particularly during high-risk periods such as childhood, adolescence, and pregnancy. Diets consisting of low iron, excessive cow's milk intake, or disordered eating can further increase one's risk of iron deficiency. Because iron is a vital micronutrient for development, iron deficiency has been associated with motor and cognitive impairment and poor physical growth in children even in the absence of anemia [4, 5]. Iron deficiency can affect quality of life through reduced physical productivity and work capacity in adults [6, 7]. It has also been associated with decreased effectiveness of some childhood vaccines, placing children at risk for severe infections [8]. It is important to recognize the wide spectrum of symptoms associated with iron deficiency (Table 1) [9–12].

1.2 | Recommendation 1.1

- **MASAC recommends that all individuals with an inherited bleeding disorder should be routinely and periodically screened for iron deficiency and anemia irrespective of sex, age, or bleeding disorder severity (Figure 1).**
  - REMARK: All inherited bleeding disorder diagnoses should be considered when pursuing laboratory screening. Inherited bleeding disorders include (in no particular order):
    - Hemophilia A (Factor VIII deficiency)
    - Hemophilia B (Factor IX deficiency)
    - Von Willebrand Disease (VWD)
    - Rare Coagulation Factor Deficiencies (e.g., Fibrinogen disorders, Factor II deficiency, Factor V deficiency, Combined Factor V and VIII deficiency, Factor VII deficiency, Factor X deficiency, Factor XI deficiency, and Factor XIII deficiency)
    - Congenital Platelet Disorders (e.g., Platelet storage pool disorders, Glanzmann Thrombasthenia, Bernard Soulier Syndrome, and other inherited platelet disorders)
    - Hemophilia A and B Carriers - defined as individuals with a factor VIII or factor IX gene mutation and normal factor VIII/IX activity levels [13, 14]

TABLE 1 | Signs and symptoms of iron deficiency with or without anemia.

Breath holding spells in infants/toddlers	Increased bruising
Cheilitis (inflammation of the lips)	Insomnia
Chills	Pale mucous membranes
Cognitive decline in the elderly population	Pale skin
Cognitive impairment	Pagophagia (craving of ice)
Deformed or "spoon" shape to nails	Passing out (syncope) or almost passing out (near syncope)
Depressed mood or irritability	Pica (craving of non-food substances)
Dizziness	Restless legs syndrome
Dry skin or hair	Ringing in the ears
Exercise intolerance	Shortness of breath
Fatigue	Smooth or glossy appearance of the tongue
Hair loss	Tachycardia/palpitations
Headache	

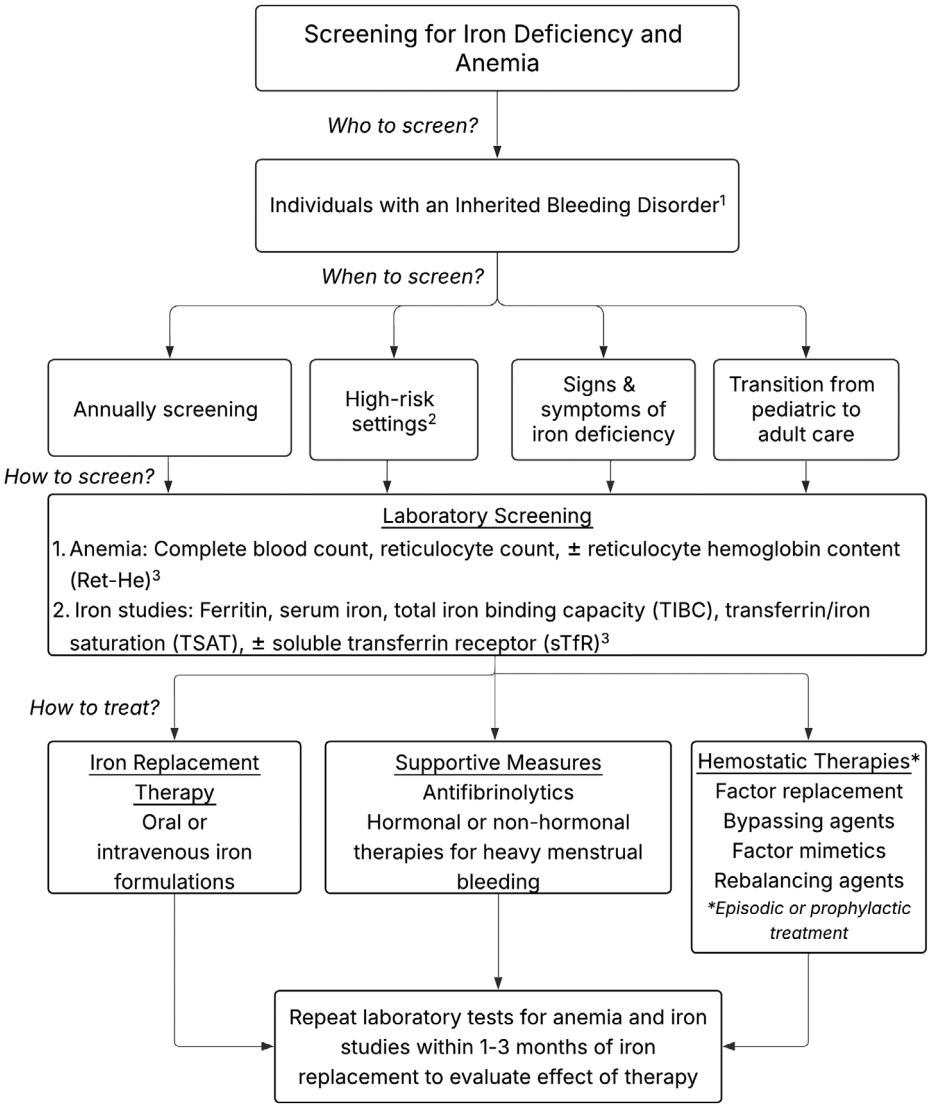

FIGURE 1 | Flow chart of screening recommendations for iron deficiency and anemia in the inherited bleeding disorders population. [1]Applies to males and females at all ages with an inherited bleeding disorder diagnosis: von Willebrand Disease (VWD), hereditary hemorrhagic telangiectasia (HHT), hemophilia A and B including carriers, rare coagulation factor deficiencies, congenital platelet disorders, and bleeding disorder of unknown cause (BDUC). 2High-risk settings include: During or after treatment for a severe bleeding episode, report of recurrent breakthrough bleeds such as mucocutaneous bleeds, after a major surgery/procedure, pregnancy/postpartum, onset of menses, history of iron deficiency with or without anemia within the past 6 months, history of requiring iron replacement therapy within the past 6 months, dietary history concerning for low iron intake or disordered eating, or history/concern for gut malabsorption of iron (i.e., inflammatory bowel disease, celiac disease, chronic proton pump inhibitor/antacid use). [3]Serum iron, TIBC, and TSAT should be obtained if the test is available. Ret-He and/or sTfR should be obtained if there is a concern for inflammation and the test is available.

- Hereditary hemorrhagic telangiectasia (HHT) [15]
- Bleeding Disorder of Unknown Cause (BDUC) - defined as a diagnosis of exclusion in an individual with a clinically significant bleeding tendency but normal hemostatic evaluation [16]

1.3 | Recommendation 1.2

- **MASAC recommends a multi-disciplinary approach to laboratory testing for iron deficiency and anemia including collaboration between primary care providers (PCPs) and specialists to ensure timely diagnosis, monitoring, and resolution of iron deficiency.**
  - REMARK: This guidance is intended for clinical providers including PCPs, obstetricians/gynecologists, oncologists, other pertinent specialists (i.e., cardiologist, nephrologists, or gastroenterologists/hepatologists), and hematology-focused physicians and advanced practice providers (APPs) who provide care to individuals with inherited bleeding disorders within and outside of Hemophilia Treatment Centers (HTCs) or comprehensive bleeding disorders clinics. These recommendations are also intended for individuals within the inherited bleeding disorders

community to promote self-advocacy when concerns for iron deficiency are present.

2 | TOPIC 2: Frequency of Laboratory Screening for Iron Deficiency and Anemia

2.1 | Background

Due to the risk of chronic blood loss from bleeding events, the prevalence of iron deficiency and IDA in the inherited bleeding disorders population may be higher than the general population. Laboratory screening for iron deficiency varies widely among HTCs. Query of the American Thrombosis & Hemostasis Network (ATHN) dataset revealed that only ~4% of 10,527 females with bleeding disorders aged 13–40 years had laboratory screening for iron deficiency between 2015–2019, but 72% of the screened individuals met criteria for iron deficiency [17]. Heavy menstrual bleeding, a common bleeding symptom and cause of iron deficiency, affects up to 80% of women and girls with inherited bleeding disorders [18–20]. A case-series of 14 male and female children with qualitative platelet disorders Glanzmann Thrombasthenia and Bernard Soulier Syndrome reported that while 79% of patients required iron replacement therapy for IDA, all the patients met the criteria for iron deficiency (ferritin < 20 ng/mL) at least once [21]. A single-institution retrospective review of hemophilia B carriers and females with mild/moderate hemophilia B between 10–74 years old reported 93% of the 57 individuals had documented ferritin levels < 50 ng/mL, consistent with iron deficiency [22]. More recently, adult individuals in an Austrian study with mild and moderate bleeding disorders including a large cohort of individuals with BDUC reported a prevalence of 39% with iron deficiency (ferritin < 30 μg/L) [23, 24]. These studies suggest that the true prevalence of iron deficiency and anemia in the inherited bleeding disorders population is likely significantly underestimated. Despite the risk of bleeding related-complications, there are no existing recommendations or guidelines addressing screening for iron deficiency and anemia in this population.

2.2 | Recommendation 2.1

- **MASAC recommends that laboratory screening for iron deficiency and anemia should be performed annually in all individuals with an inherited bleeding disorder at all ages**.
  - REMARK: In the inherited bleeding disorders population where individuals are at a higher risk of chronic blood loss and experiencing complications from untreated iron deficiency, routine individual risk assessment in combination with laboratory screening for iron deficiency and anemia is strongly recommended on an annual basis.
  - REMARK: Laboratory screening should be performed in all individuals irrespective of sex, age, or disease severity/phenotype.

2.3 | Recommendation 2.2

- **MASAC recommends additional laboratory screening for iron deficiency and anemia during high-risk settings (outside of routine annual screening) when clinically indicated in all individuals with inherited bleeding disorders**.
  - REMARK: individuals with inherited bleeding disorders are at a higher risk for iron deficiency during high-risk settings when evaluated in the outpatient clinical setting [25, 26]. High-risk settings include:
    - During/following the treatment of a severe or prolonged bleeding episode*
    - Following hospitalization for the treatment of a bleeding episode*
    - Reported history of recurrent breakthrough bleeds, particularly mucocutaneous bleeds (i.e., mouth, nose, or gastrointestinal bleeding)
    - Following a major surgery or report of excessive blood loss during a surgery/procedure
    - During pregnancy and postpartum (see **Topic 3**)
    - At the onset of menarche in adolescents
    - Report of heavy menstrual bleeding (defined as menstrual bleeding lasting more than 7 days, soaking through 1 or more pads/tampons in less than 2 hours, or passing large clots)
    - History of iron deficiency or IDA within the past 6 months
    - History of requiring iron replacement therapy within the past 6 months
    - History of Helicobacter pylori gastritis, inflammatory bowel disease, celiac disease, prior bariatric surgery, or other risk factors for acute or recurrent iron malabsorption
    - Dietary history concerning for low iron intake, limited access to iron-rich foods, disordered eating, avoidant/restrictive food intake disorder, etc.
    - Report of frequent or long-term use of proton pump inhibitors (PPIs), H2 blockers, and antacids
  - REMARK: It is important to note that a normal or high ferritin during acute treatment for a bleed or hospitalization does not rule out iron deficiency. Ferritin is an acute phase reactant that can be falsely high or normal in the setting of inflammation. It is important to repeat laboratory testing at a later time point to confirm the presence or absence of iron deficiency in these situations.*

2.4 | Recommendation 2.3

- **MASAC recommends that laboratory screening for iron deficiency and anemia should be performed at any time an individual with an inherited bleeding disorder presents with signs or symptoms suggestive of iron deficiency with or without anemia**.

2.5 | Recommendation 2.4

- **MASAC recommends that laboratory screening for iron deficiency and anemia should be considered prior to**

the transition of adolescents and young adults with inherited bleeding disorders to adult providers if not previously performed.

3 | TOPIC 3: Risk of Iron Deficiency During Pregnancy and Postpartum in the Inherited Bleeding Disorders Population

3.1 | Background

IDA, the most frequent cause of anemia during pregnancy, is a common but preventable complication affecting nearly 1 in every 5 pregnant persons in the United States [27]. Each pregnancy requires approximately 1,000 milligrams (mg) of total iron to support increased red blood cell (RBC) production, normal placental and fetal development, and anticipated blood loss at delivery [28]. Persons with inherited bleeding disorders who become pregnant have an increased risk of IDA, given the risk of lower baseline iron stores from blood loss. Furthermore, the diagnosis of physiologic versus pathologic cause of anemia in pregnancy poses a significant challenge on account of plasma volume expanding by 40%–50% with erythrocyte mass expansion of only 15%–25%. IDA during pregnancy is associated with an increased risk of maternal death, postpartum depression, preterm birth, low birth weight, cesarean delivery, longer hospital stays after delivery, postpartum hemorrhage, and perinatal blood transfusion [29–32]. Additionally, persons who are iron deficient during pregnancy are at higher risk of delivering infants who are iron deficient, which has been linked to neurological impairment [29, 33, 34]. Postpartum IDA is underrecognized yet associated with fatigue, depression, and negative impact on cognition functioning, which can ultimately affect maternal-infant bonding and maternal care of the infant [35–39].

3.2 | Recommendation 3.1

- **MASAC recommends that individuals with inherited bleeding disorders should be screened for iron deficiency and anemia prior to conception, at least once in the first trimester, and again during the second or third trimester of pregnancy**.

3.3 | Recommendation 3.2

- **MASAC recommends that individuals with inherited bleeding disorders should be screened for iron deficiency and anemia after delivery and at 6–12 weeks postpartum**.

4 | TOPIC 4: Recommended Tests for Laboratory Screening of Iron Deficiency and Anemia

4.1 | Background

Laboratory screening should consider that signs and symptoms of iron deficiency can occur with or without anemia. Hemoglobin alone is not a good predictor of iron deficiency. Moreover, IDA does not typically present until severe iron deficiency has developed and even before microcytosis ensues. It is important to directly measure an individual's iron status alongside tests for anemia to ensure accurate diagnosis and enable prompt treatment.

Most organizations and clinical laboratories differentiate the hemoglobin reference values used to define anemia based on biological sex in which females have a lower cut-off value of hemoglobin to be considered anemic. This is in part due to the effect of testosterone on RBC production resulting in a higher upper range of hemoglobin values for males [40]. The World Health Organization (WHO) defines anemia as a hemoglobin < 12 g/dL in nonpregnant women and < 13 g/dL in men [41]. The WHO differentiates reference values for hemoglobin based on biologic sex at the onset of menarche, while the reference range recommended for hemoglobin levels prior to menarche and after menopause are equivalent between females and males. The hemoglobin reference ranges identified were primarily chosen based on mean hemoglobin values in various populations of women and men. This has led to a growing debate on whether sex-based reference ranges are appropriate, particularly in light of the lack of physiologic data demonstrating differences in oxygen uptake, oxygen carrying capacity, and oxygen delivery by sex [9, 42]. For instance, there is no sex-based difference in the hemoglobin threshold for preoperative or other indications for blood transfusions. In addition, mild anemia (hemoglobin < 13 g/dL or hematocrit < 36%) in the preoperative setting is associated with increased length of hospital stay and higher 30-day morbidity & mortality rates after major non-cardiac surgery irrespective of sex [43]. As a result, sex-specific reference values for defining anemia may enable permissive iron deficiency among females, placing these individuals at increased harm from iron deficiency and anemia [43–45].

For ferritin values, there are no physiologic reasons to support separate reference ranges between males and females. A recent Delphi consensus review concluded that the minimum ferritin for females should be 30 ng/mL [46]. This document has been a helpful reference for caregivers and clinical providers to educate their laboratory colleagues, as many laboratories still use a female specific cutoff in the 10–13 ng/mL range compared to 30 ng/mL in males [46]. However, more recent studies performed in healthy women between 18–50 years of age assessing ferritin levels that correspond with physiological upregulation of iron absorption and hepcidin levels identified a ferritin cutoff of < 50 ng/mL as an indicator of iron deficiency [47, 48]. Parenteral iron administration in women with iron deficiency defined as a ferritin ≤50 ng/ml with a normal hemoglobin also resulted in improved quality of life [49]

4.2 | Recommendation 4.1

- **In individuals with inherited bleeding disorders, MASAC recommends that laboratory screening should include testing for anemia and iron studies (**Table 2**)**.
  - REMARK: Pregnant persons should be screened for iron deficiency and anemia with CBC, reticulocyte count, fer-

TABLE 2 | Laboratory tests for anemia and iron studies.

Tests for anemia	Tests of iron status
Complete blood count (CBC)	Ferritin
Reticulocyte count	Serum Iron[b]
Reticulocyte hemoglobin content (CHr or Ret-He)[a]	Total iron binding capacity (TIBC)[b]
	Transferrin or iron saturation (TSAT)[b]
	Soluble transferrin receptor (sTfR)[a]

[a]If available and concerned about concurrent inflammation.

[b]Serum iron, TIBC, and TSAT are often performed in combination with ferritin. If not readily accessible, would add the serum iron, TIBC, and TSAT if concerned about concurrent inflammation or other causes of anemia.

ritin, and iron studies (iron, total iron binding capacity, transferrin saturation, and soluble transferrin receptor).

- REMARK: The reticulocyte hemoglobin content (CHr or Ret-He) provides an indirect measure of the functional iron available for new RBC production over the previous 3 to 4 days [50]. A low Ret-He is seen in IDA and thalassemia. If there is concern for inflammation and clinically accessible, testing of the Ret-He should be considered. The Ret-He can help to distinguish IDA from anemia of inflammation in which Ret-He will be normal in anemia of inflammation. It is important to note that the Ret-He is not reliable in individuals with a hemoglobinopathy (i.e., sickle cell disease, thalassemia, etc.) or hemoglobinopathy trait (i.e., sickle cell trait, thalassemia trait/thalassemia minor).
- REMARK: A low serum iron level alone is insufficient for the diagnosis of iron deficiency because a low serum iron level is also seen in anemia of inflammation. Additionally, serum iron levels can be affected by recent dietary iron intake. As such, a normal or high serum iron level does not rule out iron deficiency. If there is concern for falsely normal or high serum iron levels due to recent intake of an iron-rich meal, repeat testing can be performed when fasting.
- REMARK: The soluble transferrin receptor (sTfR) measures the receptor for iron that is bound to transferrin and is helpful in cases where anemia of inflammation versus IDA needs to be clarified [48]. The sTfR is not an acute phase reactant (like ferritin) and values will be high in the setting of iron deficiency, but normal in anemia of chronic inflammation. It is also helpful for interpreting iron tests in the setting of class 2 or 3 obesity, but the sTfR values are age and sex dependent. A ratio of sTfR to the logarithm of the ferritin level (referred to as the sTfR/log ferritin index) is another helpful way to determine the difference between IDA and anemia of inflammation. A sTfR/log ferritin index ≤ 1 suggests anemia of inflammation while a sTfR/log ferritin index ≥ 2 suggests IDA or a mixed picture of IDA with anemia of inflammation.

4.3 | Recommendation 4.2

- **MASAC recommends a hemoglobin level < 13 g/dL as the cut-off for diagnosing anemia in males and females with inherited bleeding disorders**.
  - REMARK: This recommendation ensures that the diagnosis of IDA is properly identified in a high-risk population to address under-recognition of this bleeding-related complication. However, the clinical provider can take into consideration their knowledge of the individual's personal history in combination with their clinical judgement when applying this recommendation.
  - REMARK: Neonates and infants have a dynamic physiologic hemoglobin range from birth (mean hemoglobin 13.5 – 18.5 g/dL) up to 6 months of age (mean hemoglobin 9.5 – 11.5 g/dL). This can be further complicated by prematurity. The appropriate hemoglobin range for this age group should be referenced in the diagnosis of anemia [51].
  - REMARK: A hemoglobin of $\leq$ 10.5 g/dL in children 6 months to 2 years of age and a hemoglobin $\leq$ 11.5 g/dL in children 2 to 12 years old are used to define anemia in these age groups based on population studies [52].
  - REMARK: Anemia in pregnant persons in the general population is defined as a hemoglobin < 11 g/dL by the American College of Obstetrics and Gynecology [28].

4.4 | Recommendation 4.3

- **MASAC recommends a ferritin level of < 50 ng/mL as the cut-off for diagnosing iron deficiency in males and females with inherited bleeding disorders at all ages**.
  - REMARK: Iron deficiency in pregnant persons with inherited bleeding disorders should be defined as ferritin < 50 ng/mL.
  - REMARK: A higher ferritin threshold is strongly recommended to prevent unrecognized or misdiagnosed iron deficiency [21, 53, 54].
  - REMARK: While there is evolving data on the optimal ferritin threshold in the general population, it is important to emphasize that there is very limited to no data on the optimal ferritin thresholds for individuals with inherited bleeding disorders. The clinical provider can take into consideration their knowledge of the individual's personal history in combination with their clinical judgement when applying this recommendation.
  - REMARK: It is important to note that ferritin is an acute phase reactant in which high ferritin or falsely normal values can be seen when there is inflammation, including autoimmunity, certain infections, cancer, or liver disease.

TABLE 3 | Summary of reference values for iron studies.

	Normal	Iron deficiency
Ferritin (ng/mL or mcg/L) [9, 47, 48]	50–300[a]	< 50
Serum iron** (mcg/dL) [79]	60–150[b]	< 60
TIBC (mcg/dL) [80]	250–450	> 450
Transferrin Saturation (%) [79, 81]	20–60	< 20
Reticulocyte hemoglobin content (pg) [50, 82]	> 30	≤ 30
Absolute reticulocyte count (per μL) [51]	25,000–75,000	< 75,000[c]

[a]The upper limit of ferritin values is 200 ng/mL for women and 300 ng/mL for men.

[b]The serum iron level may be affected by recent consumption of an iron-rich meal. If there is concern for an iron-rich meal affecting the lab results, the serum iron level should be repeated when fasting.

[c]An absolute reticulocyte count less than 75,000 per μL is considered low when anemia is present and indicates a hypoproliferative process such as iron deficiency anemia.

4.5 | Recommendation 4.4

- **MASAC recommends that the levels and pattern of the iron studies (i.e., ferritin, serum iron, TIBC, and TSAT) are evaluated collectively with the hemoglobin and reticulocyte count to confirm the diagnosis of iron deficiency and anemia (**Table 3).
  - REMARK: Ideally, the serum iron level should be performed when the individual is fasting. However, this is not always feasible. If there is concern for falsely normal serum iron level due to recent intake of an iron-rich meal, repeat testing should be performed when fasting.

5 | TOPIC 5: Diagnostic Considerations for Laboratory Screening

5.1 | Background

Although individuals with an inherited bleeding disorder are at risk for blood loss from the underlying bleeding disorder, there are other potential sources of blood loss or diagnoses that may cause anemia, such as a malignant lesion, arteriovenous malformation, thalassemia trait or other RBC disorder, or anemia of inflammation. Other diagnostic considerations include the impact of anemia on coagulation laboratory tests. Clinical providers should be aware of several studies showing that anemia can "mask" the diagnosis of VWD by falsely elevating factor VIII activity and von Willebrand factor (VWF) levels [55–57]. Clinical providers should also be aware that anemia can cause platelet dysfunction, which will affect platelet function testing [58, 59].

5.2 | Recommendation 5.1

- **MASAC recommends that other causes of anemia are considered if 1) the laboratory pattern of iron indices is not consistent with iron deficiency, 2) the individual is not responsive to iron replacement therapy, or 3) there are additional signs/symptoms concerning for alternative causes of anemia when accounting for the individual's medical and/or family history**.
  - REMARK: Thalassemia and other RBC disorders such as sideroblastic anemia should be considered in the evaluation of anemia. Individuals with thalassemia or thalassemia trait without concomitant iron deficiency typically have a high/normal serum iron, normal TIBC, normal TSAT, and normal/high ferritin in addition to an increased or normal RBC count. In contrast, iron deficiency is associated with a low serum iron, TSAT, ferritin, and RBC count. Additionally, the Mentzer index assessing the ratio of the RBC count to mean corpuscular volume (MCV) is a helpful calculation. An RBC count/MCV ratio < 12 is typically consistent with thalassemia and a ratio > 13 with iron deficiency.

5.3 | Recommendation 5.2

- **If another cause of anemia or specific site of blood loss is identified (i.e., gastrointestinal bleeding), MASAC recommends subspecialty consultation where applicable and further diagnostic evaluation per standards of care**.

5.4 | Recommendation 5.3

- **MASAC recommends that diagnostic VWF panels and platelet function testing are performed in the non-anemic state, if possible. If anemia is present at the time of initial testing, repeat testing is recommended once the anemia is corrected**.

6 | TOPIC 6: Management of Iron Deficiency and Anemia

6.1 | Background

The beneficial effects of treating IDA with oral and/or intravenous (IV) iron replacement therapy on symptom resolution and improving one's health status are well documented. Treating iron deficiency without anemia is just as beneficial to individuals as treating IDA. Studies have shown that iron replacement therapy for iron deficiency without anemia can improve an individual's cognition (particularly memory and verbal language), mood, and reduce fatigue [60, 61]. While an individual's dietary intake of iron should be optimized, timely implementation of iron replacement therapies with oral or intravenous iron formulations coupled with response monitoring is critical.

6.2 | Recommendation 6.1

- **MASAC recommends that iron replacement with oral or IV iron formulations should be implemented in a timely manner once iron deficiency with or without anemia has been identified**.
  - REMARK: Dosing regimens for oral iron replacement are generally recommended as 3 mg/kg elemental iron once daily in children or 1 tablet elemental iron (e.g., 65 mg elemental iron with ferrous sulfate) once daily in adolescents/adults [62, 63]. In adults with iron deficiency without anemia, every other day dosing of oral iron is better tolerated and absorbed than higher dosing regimens [64]. Oral iron should not be prescribed or administered more than once a day (i.e., avoid 2 or 3 times a day dosing) [63]. There are many different types of oral iron available in different forms including liquid, powder, tablets, and capsules. Although ferrous sulfate is the most readily available and used oral iron formulation, gastrointestinal side effects (i.e., nausea/vomiting, metallic taste, abdominal pain, and constipation) are common and can reduce oral iron tolerance and adherence. It is recommended that an oral iron formulation most likely to be tolerated, accessible, and adhered to by the individual with iron deficiency is initiated and reassessed after initiation per the provider's clinical judgment.
  - REMARK: The use of IV iron replacement should be strongly considered in individuals with an inherited bleeding disorder with chronic blood loss that is challenging to manage with oral iron alone, oral iron intolerance/allergy, persistent severe symptomatic anemia (hemoglobin < 10 g/dL), persistent fatigue despite a ferritin between 30–50 ng/ml, or the need for rapid correction of iron deficiency [10, 49, 65].
  - REMARK: We recommend the use of the following IV iron formulations in the inherited bleeding disorder population: iron sucrose (primarily used in children), low molecular weight iron dextran, ferumoxytol, and ferric derisomaltose [66, 67].
  - REMARK: It is important to acknowledge that acute reactions to IV iron infusions can occur with any of the IV iron formulations. Acute IV iron reactions are generally self-limited and can vary from mild/moderate symptoms (i.e., itching, hives, chest tightness, back/joint pain, shortness of breath, cough, and increased heart rate) to rare but severe or life-threatening symptoms (i.e., anaphylaxis) [67]. For this reason IV iron infusions typically occurs in a hospital or infusion center. However, there are individuals who are safely able to receive IV iron infusions at home per guidance of their clinical provider. This risk should be discussed between the individual and provider through shared-decision making, and should not prevent utilization of IV iron infusion as a therapeutic option if deemed medically appropriate.
  - REMARK: The use of certain IV iron replacement formulations, including ferric carboxymaltose and iron polymaltose, have very high rates of treatment-emergent hypophosphatemia (upwards of 50%–75% in persons receiving ferric carboxymaltose for a single course of iron repletion) [68–71]. This hypophosphatemia occurs due to an acquired renal lesion from these products, often lasts for weeks to months, may be severe, and is strongly resistant to oral or IV phosphate repletion. Given that people with inherited bleeding disorders, particularly those with chronic ongoing bleeding, will often require repeat courses of IV iron repletion, ferric carboxymaltose and iron polymaltose should be avoided when at all possible. Repeat infusions of these formulations may result in hypophosphatemic osteomalacia and insufficiency fractures as well as kidney stones and fatigue [72]. Formulations allowing for full-dose iron repletion (1,000 mg elemental iron or more) with a negligible risk of treatment-emergent hypophosphatemia are considered optimal for this population. This includes iron sucrose (primarily available for use in the pediatric population), low molecular weight iron dextran, ferumoxytol, and ferric derisomaltose.

6.3 | Recommendation 6.2

- **During second and third trimester of pregnancy, MASAC recommends iron replacement with IV iron formulations over oral iron formulations for rapid correction of iron deficiency in individuals with inherited bleeding disorders**.
  - REMARK: There is very limited data on the safety of IV iron infusions in the first trimester of pregnancy. IV iron infusions are generally deferred until the second trimester when possible. However, the decision of whether to administer intravenous iron should be individualized and made utilizing shared decision making with the pregnant individual, hematologist, and obstetrician/gynecologist.
  - REMARK: During the second and third trimesters of pregnancy, rapid correction of iron deficiency is important to optimize the health of the mother and baby. This is more easily accomplished with IV iron replacement. There have been several studies that show IV iron infusions significantly increase hemoglobin, ferritin, and iron levels in pregnant individuals in the general population with IDA compared to oral iron taken during pregnancy [73, 74]. One study of pregnant individuals with IDA found that IV iron resulted in a reduced need for blood transfusions compared to oral iron (0% vs 15%) [75]. Rapid correction of IDA is especially important during the second and third trimester of pregnancy, where oral iron is much less effective that IV iron at improving the baby's cord blood ferritin level at birth [76].
  - REMARK: In the postpartum period, IV iron replacement is associated with higher hemoglobin and ferritin levels up to 6 weeks postpartum compared to oral iron replacement [77].

6.4 | Recommendation 6.3

- **MASAC recommends that the response to treatment should be monitored until resolution of iron deficiency and anemia, with repeated treatment as necessary**.
  - REMARK: The effect of oral iron replacement therapy should be evaluated within 1 month of initiation at

minimum and continued until iron deficiency correction. In many individuals, iron stores are replenished after 3 months of oral iron therapy but it can take up to 6 months in others. The individual's clinical circumstances, medication tolerance, and adherence to oral iron replacement therapy should be considered when determining the follow up interval and frequency of monitoring of iron correction and recurrence.
    - REMARK: The effect of IV iron therapy should be evaluated within 1 month of completion of IV iron administration and re-evaluated within 6 months for iron deficiency recurrence.

6.5 | Recommendation 6.4

- **MASAC recommends assessment for the need of supportive measures or hemostatic therapies (either episodically or prophylactically) to prevent chronic blood loss and iron deficiency in the inherited bleeding disorders population**.
    - REMARK: In inherited bleeding disorders, it is important to address the source of bleeding symptoms that may be contributing to iron deficiency through supportive measures (i.e., antifibrinolytic agents for mucosal bleeds; topical measures or surgical interventions for nosebleed prevention) and/or hemostatic therapies (i.e., factor replacement therapies, bypassing agents, factor mimetics, or rebalancing agents) depending on the bleeding severity and underlying diagnosis [53]. Antiangiogenic agents can also be considered in HHT.
    - REMARK: For individuals with heavy menstrual bleeding, supportive therapies such as hormone-based therapies or non-hormone-based therapies should be strongly considered to minimize bleeding at least until iron repletion. Additionally, a referral to gynecology may be helpful in heavy menstrual bleeding management.
    - REMARK: In some circumstances, chronic blood loss resulting in iron deficiency may justify the need to initiate prophylactic hemostatic therapies to optimize disease management, prevent further blood loss, and enable resolution of iron deficiency. Initiation of prophylactic hemostatic therapy should be discussed with clinical providers with expertise in the management of inherited bleeding disorders and preferably located at HTCs.

6.6 | Recommendation 6.5

- **MASAC recommends addressing any other risk factors (i.e., long-term PPI use, poor dietary intake of iron, excessive cow's milk intake in children, etc.) that may be contributing to iron deficiency and anemia when applicable**.
    - REMARK: A table identifying food sources of iron is provided in Supplemental Table S1.

7 | Future Research Needs

The purpose of the MASAC Iron Deficiency Screening Taskforce was to generate initial recommendations for clinical providers and Lived Experienced Experts on laboratory screening for iron deficiency in the inherited bleeding disorders population across the age spectrum and regardless of sex. Individuals with inherited bleeding disorders are at high risk of developing iron deficiency resulting from bleeding episodes. However, the prevalence of iron deficiency in the inherited bleeding disorder population is not fully understood owing to the limited research dedicated to this specific topic area. Further research is necessary to understand the impact of iron deficiency across all inherited bleeding disorders and to help define the optimal testing frequency, laboratory cut-off values, and ideal treatment approaches. Further investigation on the impact of iron deficiency and anemia on coagulation laboratory testing is also recommended. The availability of clinical trials and real-world data affects the development of guidelines or consensus statements on the approach to or frequency of screening for iron deficiency and IDA in this population. Increased research dedicated to understanding the prevalence and impact of iron deficiency in the inherited bleeding disorders population across the lifespan is warranted. It is expected that increased screening for iron deficiency and a higher ferritin threshold will result in increased diagnosis of iron deficiency and more aggressive treatment as with IV iron infusions, which may result in increased healthcare costs. However, recent cost analysis of routine screening for iron deficiency with higher ferritin threshold and utilization of IV iron infusions for iron deficiency correction demonstrated this approach to be more cost effective than a lower ferritin threshold and no screening largely due to the positive impact on quality-adjusted life expectancy [78]. Future research on the economic impact of increased iron deficiency screening, increased treatment for iron deficiency correction including utilization of IV iron formulations, and associated effect on quality of life outcomes, such as less missed days from work/school, will be equally informative to the inherited bleeding disorders community. Several organizations are developing or revising recommendations and guidelines for diagnosing and management or iron deficiency with and without anemia that will help to further increase awareness of this issue.

Author Contributions

G.B. led the Iron Deficiency Taskforce through the NBDF and A.D. oversaw the generation of this document as the NBDF MASAC Chair. G.B., M.D.L, M.Y.L., K.M.T., M.K.B., R.B., J.D., B.H., A.J.K., P.K. M.P.L, S.N., M.S., R.S., H.A., and A.L.D. all participated in drafting, editing, critical review, and approved the final draft of this document.

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Conflicts of Interest

G.B. has received honorarium for participation in advisory boards from Octapharma, Genentech, and Sanofi, is a scientific collaborator with Genentech (no funding received), and has clinical research funding from Wayne State University via Genentech. M.D.L. does not accept any honoraria personally, has served as a consultant for Alnylam, and Roche/Genentech, advisory board member for HEMA biologics, speaker for Pfizer and Novo Nordisk. M.Y.L. has received honorarium for participation in advisory boards for Hema Biologics, BioMarin, Sanofi, Takeda, and SeraGene. K.M.T has participated in advisory boards with Genentech, Sanofi and Hema Biologics and received honoraria for speaking events through Hemostasis and Thrombosis Research Society and Sanofi. M.K.B. has a consulting contract with Spark Biomedical. J.D. has received honorarium for advisory board participation with Genentech, Sanofi, Octapharma, Novo Nordisk, and Biomarin and consulting with Genentech and Novo Nordisk. J.D. has also received research funding from Genentech. A.J.K. is the Nationwide Children's Hospital site primary investigator for the Pharmacosmos P-Monofer-peds trial: A phase III, prospective, open-label, multi-center trial of ferric derisomaltose in children 0 to < 18 years of age with iron deficiency anemia due to non-dialysis dependent chronic kidney disease or with iron deficiency anemia who are intolerant or unresponsive to oral iron. A.J.K. does not receive any salary support or direct payment as the site primary investigator. M.P.L. an advisory board member for Janssen, Sobi, Argenx, PDSA, 22qSociety and CdLS Foundation and a consultant for Novartis, Argenx, Agios, Sobi, Sanofi and Janssen. M.P.L. has also received research funding from FWGBD, PDSA, NIH, Sysmex, Novartis, Principia, Janssen, Argenx, Dova, Octapharma, Sobi and Sanofi. S.N. is a paid consultant to Star Therapeutics. M.S. has unrestricted funding to the institution from Pfizer and Octapharma and has received honorarium for speaking engagements with Octapharma, Sobi, Werfen, and Rocher. H.A. has received research funding via his institution from Agios, Amgen, Vaderis, Novartis, and Sobi, and consultancy from Agios, Amgen, Alnylam, Alpine, Takeda, Pharmacosmos, Sobi, Sanofi, and Novartis. A.L.D. is on the board for the National Bleeding Disorder Foundation (MASAC Chair), World Federation of Hemophilia—USA, and Cascade. She has received research/foundation support from Novo Nordisk, Sanofi/Sobi, Biomarin, Genentech, Pfizer, Spark, ATHN, Regeneron, and Takeda. A.D. has been a consultant for Hema Biologics and CSL Behring. R.B., P.A.K., B.H. and R.S. stated that they have no interests which might be perceived as posing a conflict or bias.

Data Availability Statement

Not applicable. No data generated for this manuscript.

Ethics Statement

Not applicable.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting file 1: hae70227-sup-0001-SuppMat.docx