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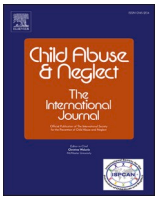

Traumatic intracranial hemorrhage in pediatrics: Implications of factor XIII deficiency and consumptive coagulopathy in abusive head trauma evaluation

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ABSTRACT

For infants that present with intracranial hemorrhage in the setting of suspected abusive head trauma (AHT), the standard recommendation is to perform an evaluation for a bleeding disorder. Factor XIII (FXIII) deficiency is a rare congenital bleeding disorder associated with intracranial hemorrhages in infancy, though testing for FXIII is not commonly included in the initial hemostatic evaluation. The current pediatric literature recognizes that trauma, especially traumatic brain injury, may induce coagulopathy in children, though FXIII is often overlooked as having a role in pediatric trauma-induced coagulopathy. We report an infant that presented with suspected AHT in whom laboratory workup revealed a decreased FXIII level, which was later determined to be caused by consumption in the setting of trauma induced coagulopathy, rather than a congenital disorder. Within the Child Abuse Pediatrics Research Network (CAPNET) database, 85 out of 569 (15 %) children had FXIII testing, 3 of those tested (3.5 %) had absent FXIII activity on qualitative testing, and 2 (2.4 %) children had activity levels below 30 % on quantitative testing. In this article we review the literature on the pathophysiology and treatment of low FXIII in the setting of trauma. This case and literature review demonstrate that FXIII consumption should be considered in the setting of pediatric AHT.

1. Introduction

Intracranial hemorrhage (ICH) is a key component of abusive head trauma (AHT). Subdural hematomas are the most common type of intracranial hemorrhage in cases of AHT; however, epidural hematomas, subarachnoid, and parenchymal hemorrhages may also be present. ICH can also be the presenting symptom of an inherited bleeding disorder, thus, hemostatic evaluation is the standard protocol for cases of suspected abuse where bleeding is a prominent symptom.

In August 2022, the American Academy of Pediatrics (AAP) issued updated guidelines to evaluate children with intracranial hemorrhage for underlying bleeding disorders, including thorough history and physical examination, diagnostic imaging and

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laboratory testing (Anderst et al., 2022). Clues from the history that may indicate an increased probability of a bleeding disorder include bleeding from the umbilical cord, bleeding complications after dental procedures, circumcision, surgery, as well as family history of heavy menstrual bleeding, prolonged epistaxis, or hemarthroses. Findings on physical exam, including bruising, petechiae, and hemarthrosis may also be seen. The diagnosis of ICH should always be followed by a dilated fundoscopic exam to evaluate for retinal hemorrhages and other signs of ocular trauma. Ophthalmologic exam and neuroimaging help characterize the bleeding, in which findings from trauma are often readily distinguished from other disease processes (Christian & Levin, 2018; Levin, 2010; Thau et al., 2021).

Currently the AAP recommends basic hemostatic laboratory workup for all children with intracranial bleeding suspected of abuse, except for independently witnessed or verifiable trauma, or the presence of other injuries concerning for abuse such as fractures, burns, abdominal visceral trauma (Anderst et al., 2022). The initial testing panel recommended in cases of ICH can be seen in Table 1. The studies included in this panel test for the most common bleeding disorders associated with ICH.

Tests for conditions with extremely rare population prevalence or rare association with ICH (<1 in 1 million) are not included (Anderst et al., 2022). Congenital Factor XIII (FXIII) deficiency is a rare disease, the probability an ICH is caused by congenital FXIII deficiency is <1 in 6 million, therefore it is not included in first line screening in cases of suspected AHT. This updated version of guidelines also takes into consideration the epidemiologic aspects of congenital FXIII deficiency, the cluster of congenital FXIII deficiency that is known to be in Iran due to consanguinity, and that even though congenital FXIII deficiency has one of the highest risks for ICH out of bleeding disorders, the majority of ICH in congenital FXIII deficiency is intraparenchymal. Of note, von Willebrand Factor (VWF) antigen and activity levels are included in the AAP's recommended workup for isolated bruising, but not in the workup for ICH. This is because although von Willebrand Disease (VWD) is the most common inherited bleeding disorder, and may explain easy bruising, ICH is extremely rare in patients with VWD (Anderst et al., 2018).

Abnormalities in this initial workup would prompt further investigation and consultation with a pediatric hematologist. The full hemostatic evaluation is often not completed during the patient's hospitalization, especially if the patient has received transfusions of blood products, which may complicate laboratory interpretation. Patients often require outpatient hematology follow up for repeat laboratory testing, genetic workup, or other confirmatory testing. By this time, transient coagulopathies due to trauma would have resolved, but abnormalities related to primary bleeding disorders would persist. Furthermore, the presence of a bleeding disorder does not preclude the possibility of abuse.

2. Suspected AHT or bleeding disorder? Approach to a case

A 10-month-old male presented to a community emergency room with seizures and posturing after an unwitnessed fall from a bed (3–4 ft. height) onto a hard floor. Head computed tomography (CT) revealed a large 15 mm mixed density subdural hemorrhage along the right cerebral convexity with significant mass effect. The patient underwent emergent decompression of the hematoma and hemicraniectomy (Fig. 1). The operative note confirmed the subdural hemorrhage was hyperacute, without signs of chronicity. After stabilization and initial surgical management, he was transferred to Texas Children's Hospital, a level I trauma center, for further care. He did not receive a plasma or cryoprecipitate infusion prior to transfer. Upon arrival, he was evaluated by the neurosurgery team and an external ventricular drain (EVD) was placed with improvement in mass effect (Fig. 1). Ophthalmology evaluation revealed bilateral retinal hemorrhages too numerous to count in all four quadrants, with ora serrata hemorrhages, strongly suggestive of abusive head trauma. Further evaluation later in his course revealed a negative skeletal survey. The Child Abuse Team was consulted and recommended a comprehensive hematology evaluation for a possible underlying bleeding disorder, due to the presence of extensive hemorrhages. There was no history of prior bleeding as newborn, or umbilical hemorrhage. He was circumcised without bleeding complications and did not have a history of easy bruising. Mother did have a prior miscarriage, the cause of which was unknown.

Initial hemostatic evaluation demonstrated a normal prothrombin time (PT) and activated partial thromboplastin time (aPTT), ruling out severe deficiencies of coagulation factors VII, VIII, IX, X, XI, V, and II (thrombin). Initial fibrinogen (125 mg/dL, normal 220–440 mg/dL) and platelet values (117,000 cells/uL, normal 150,000–450,000 cells/uL) were low, likely secondary to consumption in the setting of a large acute intracranial hemorrhage. Both fibrinogen and platelets normalized by day 3 of hospitalization. Further workup was obtained to rule out VWD, platelet function disorder, and FXIII deficiency all of which can present with bleeding in the setting of a normal PT and aPTT. Von Willebrand factor diagnostic studies and platelet function studies were reassuring, while quantitative antigen FXIII level was decreased at 28 % (normal range 75.2–154.8 %). However, whether the low levels of FXIII were due to an inherited bleeding disorder or acquired due to consumption remained uncertain at this point. The diagnostic impression of the Child Abuse Team was initially indeterminate for inflicted injury due to the uncertainty of whether his FXIII deficiency was

Table 1
Recommended laboratory testing for cases of intracranial hemorrhage.[a]

Initial testing	Prothrombin time (PT)
	Activated partial thromboplastin time (aPTT)
	Complete blood cell count with platelet count
Suspected trauma	Factor VIII level
	Factor IX level
Neurologic compromise	D-dimer
	Fibrinogen

[a] Modified from algorithm published at Anderst et al., Pediatrics, 2022.

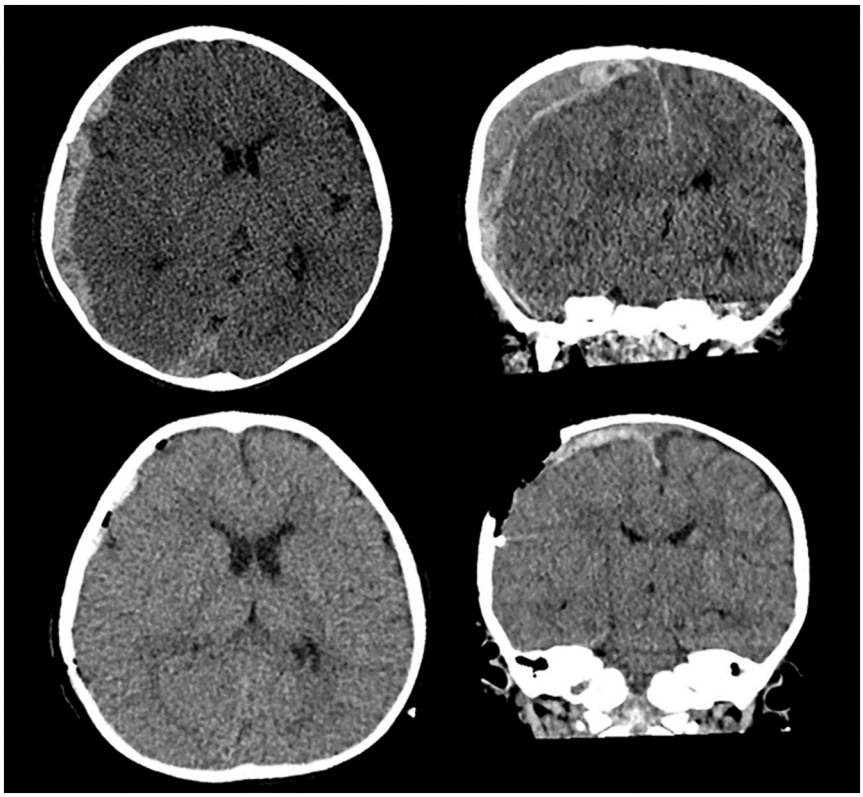

Fig. 1. Patient head computed tomography (CT). Top row: axial non-contrast enhanced CT including coronal Multiplanar Reconstruction (MPR) reveals a large undulated subdural, mixed hyper- and hypodense hematoma overlying the right cerebral hemisphere with resultant significant mass effect. The right cerebral hemisphere including right lateral ventricle is herniating across the midline with bowing of the falx to the left. Bottom row: subsequent follow up CT shows a marked improvement of the midline shift after evacuation of the subdural hematoma. Air inclusions are seen along the craniectomy site, part of the fronto-parietal bony skull has been removed.

congenital or acquired. Factor XIII infusions were started, and the only other blood products that this patient received were red blood cells for anemia.

3. Evaluation for FXIII deficiency in suspected AHT: a multicenter experience

To put FXIII testing into the broader context of AHT evaluations we used data from the Child Abuse Pediatrics Research Network (CAPNET), an initiative funded by the National Institutes of Health (NIH) to build a multinetwork research database. IRB approval was obtained from Baylor College of Medicine. CAPNET consists of 10 children's hospitals across the US that contribute data using a common data collection form on all child abuse physician consultations with concern for physical abuse (Kratchman et al., 2022). According to CAPNET data, from February 2021 to February 2022, 569 children received a physical abuse evaluation by the child abuse team with injuries that included intracranial hemorrhage. Of these children, 85 (15 %) were tested for FXIII deficiency, including 60 (71 %) that had qualitative testing, 27 (32 %) that had quantitative testing. Two children had both qualitative and quantitative testing, which is likely due to reflexive quantitative testing if the qualitative test is abnormal. Overall, of the 85 children tested for FXIII, 3 (3.5 %) children had absent FXIII activity on qualitative testing, and 2 (2.4 %) children had activity levels below 30 % on quantitative testing. The type of testing completed also varies by hospital. In this multicenter cohort, 8 out of the 10 children's hospitals sent qualitative testing, 6 hospitals sent quantitative testing, and 3 hospitals sent both sent both types of testing. All the hospitals sent some form of FXIII testing. At this time, CAPNET does not collect data on either treatment or follow-up lab values. CAPNET data is also subject to data entry errors. The type of testing likely contributes the number of abnormal results discovered, since the qualitative testing will only result abnormal if there is a severe deficiency of <3 %.

3.1. Factor XIII testing approaches

A variety of in vitro assays can be used to evaluate for FXIII deficiency, including clot solubility test, FXIII qualitative activity assay, FXIII quantitative antigen assay, and inhibitor assay. However, the FXIII activity assays are the first-line screening tests when available (Karimi et al., 2018). There are different modalities of FXIII activity assays, from these, the ammonia release assay requires the shortest

timeframe for performance, making it the most common and more convenient method (Katona et al., 2012). If screening test is positive, plasma antigen assays are required to classify the deficiency as subtype A, or subtype B. Genetic defects in the A subunit can cause severe and spontaneous bleeding in homozygous and heterozygous patients, and these are the most common defects (Dorgalaleh & Rashidpanah, 2016). Deficiency in subunit B leads to shorter half-life of FXIII subunit A, and has a less severe phenotype due to the remaining FXIII activity. Subtype B deficiency accounts for <5 % of FXIII deficiency cases (Dorgalaleh & Rashidpanah, 2016). However, realistically many laboratories do not have the equipment required for FXIII activity assays; in those instances clot solubility tests are used as a screening tool, although these are not standardized and have low sensitivity and can only detect severe deficiency (Karimi et al., 2018). For the patient described above we obtained FXIII quantitative antigen levels, a study that was available at our institution, which allowed us to obtain results in a timely manner; however, we recognize this test might not be available at many institutions.

3.2. Factor XIII deficiency classic presentation

Factor XIII works at the final stage of the coagulation cascade by catalyzing the crosslinking of fibrin chains. Inherited FXIII deficiency is a rare autosomal recessive disorder, with an incidence of one per 1–2 million (Karimi et al., 2018). It typically presents with umbilical cord bleeding, seen in >80 % of severely deficient cases, and soft tissue hematomas. In women of childbearing age, FXIII deficiency can present with recurrent miscarriages (Karimi et al., 2018). Patients can also have more severe presentations including spontaneous ICH, seen in approximately 33 % of affected patients (Dorgalaleh et al., 2016; Ivaskevicius et al., 2007). However, the most common site for ICH is generally intraparenchymal, and subdural hemorrhages (SDH) are notably rare (Naderi et al., 2014).

Although ICH is a known presentation of FXIII deficiency, retinal hemorrhages in the setting of FXIII deficiency have yet to be reported (Thau et al., 2021). In a large case series of 93 Iranian patients with severe FXIII deficiency 23/93 patients (25 %) developed spontaneous ICH; however, there is no mention of retinal hemorrhages or fundoscopic exam evaluation (Lak et al., 2003). In a case report by Gordon et al., an 8-month-old developed bilateral subdural hematomas. Initially there was concern for non-accidental trauma and the patient was removed from his home environment; however, the same child continued with unexplained bruising and later was confirmed to have FXIII deficiency (Gordon et al., 2008). In this case report, however, there is no mention of fundoscopic exam. A case report of a 38-month-old patient with known FXIII deficiency who had ICH at 4-months of age, and another episode at 8.5-months of age without known trauma described a fundoscopic exam which revealed no retinal hemorrhages (Larsen et al., 1990).

3.3. Factor XIII physiology in trauma-induced coagulopathy

Patients who present with trauma and hemorrhage are at risk for further bleeding due to a combination of multiple factors, which fall into five main categories: dilution of coagulation factors, platelet activation, activation of the vascular endothelium, exposure of the subendothelial matrix to blood, and activation of inflammation (Moore et al., 2021). Coagulopathy, itself, is part of the "lethal triad" (i.e., coagulopathy, acidosis, and hypothermia) that portends a high mortality (~20–40 %) in patients with trauma (Mitra et al., 2012; Smith et al., 2021). Trauma non-survivors have significantly elevated international normalized ratios and aPTT and lower fibrinogen levels.

Although the role of FXIII in stabilizing fibrin clots is known, its importance in trauma has been less well defined. Factor XIII crosslinks fibrin strands to stabilize clots. It also is an adjunct antifibrinolytic through its ability to crosslink α2 antiplasmin into the fibrin meshwork to prevent plasmin-induced fibrinolysis (Fraser et al., 2011; Mutch et al., 2010).

In trauma patients, traditional coagulation tests include quantification of platelets and fibrinogen concentrations and measurement of the contact and tissue factor pathways of the coagulation cascade. While these standard tests are widely available and useful for the initial evaluation of patients, there are important pathways that are missed with these tests. These include platelet function defects (e.g., Glanzmann thrombasthenia), anti-platelet use (e.g., aspirin), VWD, and FXIII deficiency. Viscoelastic hemostatic assays (VHA) are real-time methods to assess a patient's hemostatic status using whole blood. These tests, rotational thromboelastometry and thromboelastography, can be performed at the bedside in real-time to help guide hemostatic resuscitation in the bleeding patient. As opposed to the routine coagulation tests, VHA can suggest FXIII deficiency through a decreased maximal amplitude/clot firmness and/or increased fibrinolysis when overall platelet count and fibrinogen levels are normal (Zia et al., 2015). However, suspicion of FXIII deficiency should be confirmed with quantitative FXIII activity testing (Ivaskevicius et al., 2007; Kohler et al., 2011).

Although there are fewer publications regarding outcomes in trauma patients with low FXIII levels as compared to conventional coagulation assays, some data do exist, albeit primarily in adult populations. In a study of isolated traumatic brain injuries, Bohm et al. found that adults with initial INR $\geq$ 1.2 had significantly lower FXIII activity levels than those with normal INR (68 % vs. 88 %, respectively), suggesting a global consumptive coagulopathy (Böhm et al., 2021). In a larger study of adults undergoing intracranial surgery, Gerlach et al. reported that post-operative FXIII activity levels <60 % were associated with a >6-fold increase in bleeding intracranial hematoma post-operatively (Gerlach et al., 2002). Katzensteiner et al. evaluated the effect of FXIII replacement in trauma patients admitted to an intensive care unit. They found a modest negative correlation between initial FXIII activity and number of surgical procedures performed and blood products transfused. Despite this correlation, they did not observe a benefit in replacing FXIII in patients after matching for initial FXIII level and severity of injury (Katzensteiner et al., 2022). However, the initial FXIII levels in the replacement group was ~60 %. This level is higher than what has been recommended by the European Task Force for Advanced Bleeding Care in Trauma which recommends FXIII replacement for FXIII activity <30 % and bleeding; so replacement of FXIII may be warranted, especially with active bleeding (Spahn et al., 2019). If FXIII replacement is warranted, the most efficient method is through plasma-derived FXIII concentrates (Nugent, 2012) and recombinant FXIII (Inbal et al., 2012), although fresh frozen plasma and

cryoprecipitate do contain FXIII and may be more readily available.

4. Case evolution: inherited factor XIII deficiency or trauma induced coagulopathy?

Factor XIII infusions were initiated due to the decreased FXIII antigen level. Published regimens include FXIII replacement every other day for 10 days with an initial dose of 750 IU and subsequent infusions of 500 IU every other day for 10 days in adults, and an initial infusion of 30 IU/kg followed by 10–26 IU/kg for 10 days (Dorgalaleh & Rashidpanah, 2016; Ribizzi et al., 2015). In the setting of major neurosurgical interventions, FXIII supplementation is recommended pre-operatively to increase levels to 60–100 % (Janbain et al., 2015). Due to the severity of the intracranial hemorrhage and the need for possible repeat neurosurgical interventions, we aimed for a FXIII goal of >90 % for 10 days. This required 5 FXIII infusions in the span of 10 days with doses as follows: initial dose of 40 Units/kg, followed by 4 additional doses of 10–20 Units/kg (See Fig. 2). Genetic testing for defects in *F13A* or *F13B* was also sent.

After the fifth FXIII infusion, he had surpassed the 10 days post-trauma; therefore, we monitored FXIII levels in absence of supplementation. As shown in Fig. 2, FXIII levels normalized over time and remained stable for 60 days in absence of additional supplementation, during which he was followed in the outpatient hematology clinic. No defects in *F13A* or *F13B* were found, ruling out an inherited FXIII disorder and confirming that consumption from acute hemorrhage was the cause of his initial low FXIII levels.

Due to the lack of pediatric literature on FXIII being affected in trauma-induced coagulopathy and/or consumptive etiologies, and this child's lack of injuries outside of hemorrhage, the Child Abuse Team's impression remained indeterminate for inflicted injury until after the information that was added after the hematology clinic follow-up visit at 60 days post-injury. After this hematology follow-up visit with negative genetic testing and normalization of FXIII levels without further supplementation, the Child Abuse Team's impression changed to high concern for inflicted injury. Since the child remained in the same care environment that he was in at the time of his injury, the results and final impression of the child abuse team was also directly communicated to the parents. Clinically, the patient was continued on anti-epileptic medications after discharge and his developmental delay was closely followed with physical and speech therapy.

5. Lessons learned and clinical implications

For clinicians it is important to be aware not only of bleeding disorders, but also the possibility of trauma induced coagulopathy in cases of suspected AHT. Standardized guidelines for hematology workup in cases of suspected AHT usually primarily focus on uncovering or ruling-out potential underlying bleeding disorders, and not on identifying trauma-induced-coagulopathy. In addition, if the adult trauma literature recognizes FXIII deficiency due to consumption in trauma cases and demonstrates improved outcomes with FXIII replacement, replacement may be considered in pediatric trauma as well. Hospitals using only qualitative testing may underdiagnose cases of mild to moderate FXIII deficiency from consumption, missing a chance to improve outcomes by supplementation of FXIII during the acute trauma phase where the risk for continued bleeding remains elevated.

6. Importance of clear communication with child protective services and law enforcement agencies while workup in undergoing

One of the most important roles of the medical provider, especially the child abuse pediatrician, in cases of suspected AHT is communicating the medical findings to Child Protective Services (CPS) and Law Enforcement. The distinction between whether an injury is abusive versus not may not be immediate. The gradual, stepwise accumulation of medical data that alters and refines the diagnostic impression is a normal part of medical practice but can be misunderstood by those outside the medical field. Thus, while the

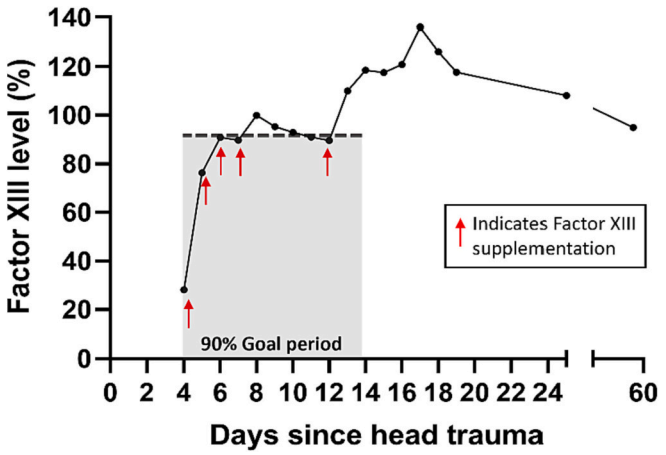

Fig. 2. Factor XIII infusion schedule for patient.

diagnostic workup is still in process, it is crucial to clearly communicate to our community partners what uncertainties remain. Understanding that FXIII deficiency seen in the setting of possible trauma can be caused by trauma-related consumptive process may prevent the premature conclusions of an underlying medical disorder – potentially placing the child at risk of future injury or death. CPS, Law Enforcement, and court systems frequently demand immediate medical answers in cases of suspected abusive head trauma. Medical testing does not always abide by the desired timeline. Medical information communicated to non-medical investigators at any point in the evaluation can easily be misunderstood as the "final answer", therefore it is crucial that the medical team clearly communicate with these other agencies what may change depending on outstanding tests or evaluation.

In this case, despite communicating with outside agencies that medical tests were pending and would not result for up to two-three months, the outside agencies proceeded with their decisions as if there was little to no concern for inflicted trauma. The absence of strong, definite communication of concern for inflicted trauma appeared to be interpreted as little to no concern for inflicted trauma. By the time the genetic testing had resulted and proof that FXIII remained normal without infusions, the outside agencies had made their decisions, moved forward, and this new information did not change the plan.

7. Conclusion

In the setting of a child with suspected AHT complicated by hemorrhage, clinicians should consider FXIII deficiency as a contributor to the clinical picture. As demonstrated in our case, AHT may result in a transient, consumptive FXIII deficiency that may require FXIII replacement, especially in the setting of neurosurgical procedures or worsening hemorrhages. Consultation with a coagulation and hematologic expert is warranted in these challenging cases.

CRediT authorship contribution statement

Arianexys Aquino López: Conceptualization, Writing – original draft. **Clay T. Cohen:** Conceptualization, Writing – review & editing. **Amanda Small:** Conceptualization, Writing – review & editing. **Fong Wilson Lam:** Conceptualization, Writing – review & editing. **Angela N. Bachim:** Conceptualization, Writing – review & editing.

Declaration of competing interest

AAL has no conflicts of interest.

CTC declares conflicts of interest of participation on an advisory board for Bayer Pharmaceuticals and as a consultant for Oliver Wyman.

AS has no conflicts of interest.

FWL has no conflicts of interest.

ANB has no conflicts of interest.

Data availability

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