

Overcoming the Diagnostic and Monitoring Challenges for Very Rare Bleeding Disorders in the US: The Potential Benefits of a Centralized Laboratory

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Abstract: 198 words (200 max)

Advancing the care for individuals with rare bleeding disorders (RBDs) has been challenging due to the limited number of patients and their variable phenotypes, leading to the establishment of global registries. Outside of registries and trials, a critical issue involves diagnosing and monitoring treatment of RBDs using laboratory assays in “real time” in a reliable and reproducible manner across the network of institutions caring for these patients. While there are many College of American Pathologists - Clinical Laboratory Improvement Act certified specialty coagulation laboratories and considerable expertise in these laboratories in tertiary-care centers in the US, the assays needed to diagnose and monitor the very rare bleeding disorders are performed too infrequently and employ varying methodologies, often without FDA approval (Research Use Only), to justify having them established, standardized, and readily available for such a projected small demand. A central laboratory or network of laboratories with expertise in particular RBDs could be developed in consultation with key stakeholders under a model similar to the Children’s Oncology Group. With quality control over assays supporting diagnosis and treatment monitoring, the community can then address key scientific questions, such as the correlation of genotype, factor level, and phenotype, while also supporting public health surveillance, and support the development of new therapeutic products.

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While there are challenges to understanding more about bleeding disorders through research due to the orphan nature of disorders such as the congenital hemophilias, the challenge is even

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greater for the much less common group of clotting factor deficiencies, qualitative platelet disorders, and other rare clinical conditions, designated collectively as rare bleeding disorders (RBDs). For hematologists treating these patients, collaboration around global registries is often required to help shed light on best practices in management.

Between 2008 and 2011, two registries that provided post-marketing surveillance data around the use of recombinant factor VIIa (rFVIIa) in Acquired Hemophilia (AH) closed. The EACH-2 registry captured data between 2003 and 2008 and included 501 patients with AH from 117 centers and included data on 474 bleeding episodes, follow-up for post-partum hemorrhage, and outcomes of immunosuppression.¹⁻⁴ The Hemostasis and Thrombosis Research Society (HTRS) registry captured data between 2000 and 2011 and included 166 patients with AH with 237 bleeding episodes and 58 surgical procedures.⁵⁻⁷

In 2011, two additional registries, which were designed in part to capture post-marketing surveillance data around the use of recombinant factor VIIa (rFVIIa) closed, capping a multi-year effort by dedicated hematologists around the world to track treatment of Glanzmann's Thrombasthenia and congenital Factor VII (FVII) Deficiency, irrespective of treatment product. Initiated in 2006, the Glanzmann's Thrombasthenia Registry (GTR) captured data on 218 patients with Glanzmann's Thrombasthenia from 45 sites in 15 countries with 1073 admissions for 870 bleeding episodes and 204 surgical procedures.⁸ The Seven Treatment Evaluation Registry (STER) captured data on 75 patients with FVII deficiency from 15 countries with 101 bleeding events.⁹ STER also captured data on 38 patients with 38 surgical procedures, along with data on 34 patients treated with routine FVII replacement.^{10,11}

There certainly is the temptation to move right from the "need" to capture data about a rare disorder to choosing a registry or electronic medical record platform. Recent approval of plasma derived replacement for fibrinogen and factor XIII (FXIII), as well as a recombinant FXIII concentrate highlight the need for accumulating such post-approval data.

One of the key issues around the accumulation of clinical or registry/trial data is that the data would have little or no utility for either clinical management or scientific research without assurances that the laboratory diagnosis and monitoring assays of the RBDs were accurate and consistent. Many of the participating institutions in clinical studies, registries, and database

platforms possess their own internal College of American Pathologists - Clinical Laboratory Improvement Act (CAP-CLIA) certified specialty coagulation laboratories and were experienced in supporting clinical research trials in any number of medical diseases, including trials of RBDs that used central laboratories. Yet, most institutions only infrequently perform clotting factor assays for RBDs within their institutions and instead rely on outside commercial concerns for their “send outs.” This is a fiscal, reimbursement, and man-power necessity for hospital-based laboratories, particularly since many of these laboratory assays have not been approved for clinical care decision making by the United States Food and Drug Administration (FDA) and are thus labeled “research use only” (RUO). Such designation often compromises the ability to obtain insurance reimbursement for testing and limits the number of labs where the testing can be performed.

One example is testing for congenital factor XIII (FXIII) deficiency, where a widely used assay is the clot-solubility test, a screening test for FXIII deficiency only sensitive to levels less than 1%. The standard quantitative functional assay (Berichrom, Seimens Diagnostic), used both in clinical trials and for adjusting treatment in routine clinical practice, is insensitive below 5-10% and is RUO.¹² A United Kingdom National External Quality Assessment Service (UK NEQAS) study in 2003 showed significant variability in laboratory results from 147 centers for these assays, especially in patients with mild to moderate FXIII deficiency or in the presence of residual FXIII activity following treatment.¹³ Guidelines developed by the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee (ISTH-SSC) recommend further characterization of FXIII A and B subunit deficiency through enzyme-linked immunosorbent assay (ELISA) and genotyping.¹⁴ Well-characterized ELISA test kits, such as those developed by Muzbeck and colleagues and marked by Technoclone for quantifying antigenic A and B subunits, are RUO and are not currently being manufactured or distributed globally.¹⁵⁻¹⁷ The CDC in the US has now developed and launched a free program which allows hematologists to send plasma from patients with confirmed FXIII deficiency to have their FXIII molecules analyzed for the a subunit genotype, and quantitative immunoblotting in conjunction with Dr. Diane Nugent’s lab, thus facilitating physician ability to capture FXIII cases for public health surveillance.

Establishment of a central laboratory with expertise in these types of assays may eliminate this variability and provide more confidence in the accuracy, reliability, and reproducibility of diagnostic tests. The use of a central laboratory in the global STER registry provided an example of quality control over laboratory values performed locally, and provided a critical function when it came to determination of inhibitors to factor replacement.^{9,18} Outside of STER and since its termination, FVIIa ELISA, FVII inhibitor assays, and FVII genotyping are not readily available. In contrast, the GTR did not use a central laboratory and throughout the study assessment of, for example, anti-HLA and anti-platelet antibodies were reported with inconsistent nomenclature and detail.

It has been suggested that proteomic and genomic technologies may become the focus in the analysis of patients with inherited platelet disorders and that whole exome or whole genome sequencing may become a first line to identify the molecular basis of rare diseases.¹⁹ The BRIDGE consortium in the United Kingdom aims to discover the genetic basis of the inherited Rare Diseases and the Bleeding and Platelet Diseases substudy specifically aims to develop and validate a sensitive Next Generation Sequencing-based test to detect clinically relevant variants in bleeding and platelet diseases, and in order to do so, aims to first identify the genetic basis of rare bleeding and platelet disease.^{20,21} The BRIDGE study is using a central BRIDGE Sample Intake Laboratory to collect and sequence all DNA samples, including samples from other BRIDGE studies in pulmonary arterial hypertension, primary immune disorders, steroid resistant nephrotic syndrome, and Ehlers-Danlos syndromes.²¹

Also in the United Kingdom, through collaboration with the ISTH-SSC, the National Institute for Biological Standards and Control (NIBSC) provides plasma and coagulation factor standards calibrated by laboratories of SSC-associated investigators.²² NIBSC is a World Health Organization (WHO) international laboratory for biological standards and prepares, evaluates and distributes International Biological Standards.²³ In addition, NIBSC is responsible for regulatory testing of biological medicines in the European Union.²³ The presence of such a regulatory body allows for strict oversight of the laboratories which use these assays for the diagnosis and treatment of RBDs. **In the United States and North America, the CAP (College of American Pathology) offers a similar laboratory accreditation program. In addition the Centers for Medicare and Medicaid Services (CMS) regulates all testing through the Clinical Laboratory**

Improvements Amendments (CLIA). CAP and CLIA certifications are however voluntary and are for standardized tests only. They are not available for tests required for the diagnosis of RBD such as FXIII deficiency. They also do not mandate a specific assay or assay platform and therefore allow for great inter-laboratory variability. Research testing is allowed by CLIA but it does not allow the laboratory to report patient specific results and therefore cannot be used for diagnostic purposes. The UK also has the advantage of a significantly smaller geographic area allowing limited number of laboratories to provide services. Unfortunately such consolidation of services is not possible to serve the wide spread needs of the USA and North America. Also unique to the USA is that the CMS does not guarantee that laboratory workups will be reimbursed for, through the health mechanisms available in the USA.

Children's Oncology Group (COG) provides perhaps some guidance on the ability to implement a national central lab resource in the US. COG is a National Cancer Institute (NCI) supported clinical trials group uniting more than 8,000 experts at more than 200 children's hospitals, universities and cancer centers across North America, Australia, New Zealand and Europe. More than 90% of the 13,500 children and adolescents diagnosed with cancer in the US each year are treated within the network, and there are at any time about 100 active trials. COG has complex risk classification systems that are used to deliver risk-stratified therapy for many pediatric cancers, and classification of patients is based on biological, clinical, and genomic data obtained and entered automatically from both treating institutions and central laboratories.²⁴

While there is overlap between the hematology community (including the hemophilia treatment center network) and the oncology community that already is accustomed to having central laboratory functions under federal (NCI) funding, autonomy and practical logistical considerations might limit applicability of a central lab function in hematology and especially coagulation testing. Establishment of a central lab would require the transportation of specimens to the central laboratory. In the study of platelet disorders which forms a significant proportion of RBD's, it is not possible to transport the specimen (whole blood or platelet rich plasma) as platelet lysis during transportation is inevitable and would make the sample useless. Further, many of the specialty coagulation laboratories already have CAP-CLIA certification and can perform many of these assays. Regional/local differences in insurance coverage might limit the ability for payor funding of confirmatory tests, most of which may be classified as RUO.

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Assuming funding wasn't an issue, would such local/regional/national labs be willing to send samples to another academic institution or commercial laboratory that was designed as the central lab? Given some labs may have specific expertise in a particular RBD, either through epidemiologic differences or by serving central lab roles in compassionate use programs in RBDs (e.g. congenital FXIII deficiency), should there be more than one central lab or specifically a central lab designed by disease?

So, if for RBDs a centralized RBD laboratory function were felt to be advantageous in the US or more broadly in North America, how could this be developed and implemented? Some key points are illustrated below:

- All key stakeholders need to be involved in the discussions including federal entities, professional societies, the hemophilia and RBD treatment center network, specialty coagulation laboratories, and patient advocacy organizations (**Table 1**).
- Agreement would need to be reached as to the scope of specific testing available, but likely including uncommon coagulation or platelet function tests, factor assays including testing to determine inhibitors (Bethesda-type assays), and perhaps genotyping.
- There would need to be consensus on a more standardized diagnostic approach, perhaps following ISTH-SSC or other guidelines where available and applicable.
- The allocation of specific diseases/tests to several laboratories or development/engagement of a single central laboratory would need to be determined.
- The funding for such a project would need to be secured, whether initially as a pilot (specific tests or diseases) or as a more complete project.

The role of pharmaceutical companies in such an RBD diagnostic laboratory network also deserves some consideration. Certainly, as manufacturers for products, companies are responsible for pre-approval clinical trials and post-approval surveillance of patients to determine safety and efficacy. This implicitly requires accurate diagnosis and the ability to monitor patients treated outside of prospective trials that end with a product's launch. It would be preferable for companies to assure the central lab's role throughout their clinical development,

facilitating the development and maintenance of expertise. However, any support in general from industry should be as broad based as possible. An example in that regard could involve a commitment by pharmaceutical industry members to fund investigator initiated studies which are focused on maintenance of a nationwide repository for collection of patient plasma/tissue specimens for future studies. This could be coordinated under the auspices of a national cooperative research group, such as ATHN or HTRS. Another example includes support of investigator initiated initiatives targeting the development of laboratory tools to facilitate diagnoses of rare bleeding disorders, e.g. designing and development of a genetic platform for the diagnosis of FXIII deficiency, Glanzmann's thrombasthenia, and other hereditary platelet qualitative defects. We have been gratified that Novo Nordisk has moved in this direction and anticipate that other pharmaceutical members will follow suit.

There could be additional benefits to considering a centralized laboratory for uncommon RBD assays.

- Validation studies to support FDA approval of the assays would be much easier if a single central laboratory or group of laboratories could pool dozens of samples from across the US, and thus support uniform insurance coverage. Availability of approved tests would allow for more specific diagnostic and monitoring recommendations in package labelling.
- Cost-efficiencies can be achieved by pooling many samples to run assays together. For example, reagent kits for ELISA assays where available (e.g. FXIII A₂, B₂ and A₂B₂ antigen)¹³ can be costly if only used for one patient.
- In association with refinements to ICD-9CM/ICD-10 to support individual codes for each rare disorder (currently pooled under 286.4/D68.2 for other clotting factor deficiencies as well as other codes for congenital and acquired bleeding disorders), data from a central laboratory would help with epidemiologic study of these rare diseases.
- By identifying the experts in each of these RBDs in this process, it would also connect the physician caring for the patients with RBDs to the experts in the field providing better standardization of care.

In the “real world” of medical care outside of the clinical research environment, there is a critical need for health care practitioners to recognize and diagnose bleeding disorders in an efficient and timely manner. Research has indicated that the physicians who encounter patients with RBDs often overlook RBDs as a differential diagnosis and do not approach the laboratory confirmation in an adequate, targeted, or cost efficient manner. Further, they may not receive insightful guidance from their non-clinically oriented coagulation laboratory directors. In an effort to assist healthcare practitioners in the diagnosis of bleeding disorders and to ultimately facilitate appropriate referrals to knowledgeable hematologists, one pharmaceutical company (Novo Nordisk) has developed a “user friendly” educational resource around diagnostic assays, the Coags Uncomplicated iPhone/Android/web application.²⁵ As part of the application, the Lab Value Analyzer first allows healthcare practitioners to screen for medication-related abnormalities, then pattern-matches lab values entered with disease profiles and lists potentially matching diagnoses. The Diagnostic Algorithm provides a resource to help healthcare practitioners in considering appropriate additional lab tests.

When a RBD is suspected in an acute bleeding emergency, the central laboratory probably will not allow relevant patient management in real time. These situations are often managed with traditional therapies such as Cryoprecipitate and FFP prior to establishment of the diagnosis . The diagnostic samples are frequently obtained prior to this intervention and would be the target of the " central laboratory" to facilitate the establishment of the correct diagnosis which can then lead to more targeted intervention.

In this call to action and to address these concerns, objective data need to be gathered to survey the coagulation laboratories around the US and Canada (in commercial, tertiary care hospitals, and research laboratories) to determine current capabilities and to identify unmet needs. It is possible that this could lead to improved accessibility to laboratories established by a consortium of the FDA, industry, professional advocacy groups (ISTH-SSC, THSNA, HTRS), NIH, university research laboratories, and the CDC.

With adoption of this type of central laboratory model for RBDs, the needs of the stakeholders and the patient community can be served efficiently (both from the healthcare and fiscal

perspectives). Third party payers also have an obligation to ensure that patients have received the correct diagnosis and treatment and therefore would be an equal stakeholder in this effort.

Further, availability of accurate, reproducible, and reliable laboratory data would support public health and product surveillance, clinical research, and quality improvement initiatives in care of patients with RBDs.

Table 1. (REVISED)

ORGANIZATION	MISSION
Centers for Disease Control (CDC)	Component of the department of health and human services, with a major role in developing a comprehensive public health agenda to promote and improve the health of people with blood disorders.
National Heart Lung and Blood Institute (NHLBI)	Provides global leadership for promoting research and mentoring of scientists and physicians in the field of blood disorders.
Food and Drug Administration (FDA)	Responsible for protecting public health by assuring the safety and efficacy of drugs, biologics and medical devices.
American Society of Hematology	Professional society dedicated to furthering the understanding of disorders of the blood, bone marrow, immunologic and vascular systems by promoting research, education and training in hematology.
American Society of Pediatric Hematology and Oncology (ASPHO)	Multidisciplinary organization dedicated to promoting the optimal care of children with

	blood disorders and cancer by advancing research and education.
Hemostasis and Thrombosis Research Society (HTRS)	North American professional medical society dedicated to supporting investigator-initiated research, mentoring, and continuing medical education.
International Society on Thrombosis and Haemostasis (ISTH)	International professional medical organization with a goal to generate reliable and standardized clinical and basic science tools.
North American Society of Coagulation Laboratories (NASCOLA)	Non-profit organization that provides laboratory external quality assessment and develops guidelines for the appropriate use, performance and interpretation of coagulation tests.
American Thrombosis and Hemostasis Network (ATHN)	Nonprofit organization that manages a national database of patients with bleeding and thrombotic disorders that can be used to improve care and support research.
National Hemophilia Foundation (NHF)	Patient advocacy organization for patients with inherited bleeding disorders in the United States of America.
World Federation of Hemophilia (WFH)	Global patient advocacy organization for patients with inherited bleeding disorders.

Potential role of the above organizations in this effort:

CDC, NHLBI, FDA: Provide organizational guidance and assist in the development of tests that are extremely essential for many of the RBD's.

ASH, ISTH, HTRS, ATHN: Provide network of physicians with expertise in rare bleeding disorders

NASCOLA, CAP: Provide information on laboratories with expertise in the area of RBD that could potentially serve as the central labs, assist in test development and ensure EQA.

NHF, WFH: Provide guidance to the community on the availability and importance of accurate diagnosis.

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