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Perspective

Thrombotic Microangiopathy: A Multidisciplinary Team Approach

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Thrombotic microangiopathy (TMA) is characterized by the presence of microangiopathic hemolytic anemia and thrombocytopenia along with organ dysfunction, and pathologically, by the presence of microthrombi in multiple microvascular beds. Delays in diagnosis and initiation of therapy are common due to the low incidence, variable presentation, and poor awareness of these diseases, underscoring the need for interdisciplinary approaches to clinical care for TMA. We describe a new approach to improve clinical management via a TMA team that originally stemmed from an Affinity Research Collaborative team focused on thrombosis and hemostasis. The TMA team consists of clinical faculty from different disciplines who together are charged with the responsibility to quickly analyze clinical presentations, guide laboratory testing, and streamline prompt institution of treatment. The TMA team also includes faculty members from a broad range of disciplines collaborating to elucidate the pathogenesis of TMA. To this end, a clinical database and biorepository have been constructed. TMA leaders educate front-line providers from other departments through presentations in various forums across multiple specialties. Facilitated by an Affinity Research Collaborative mechanism, we describe an interdisciplinary team dedicated to improving both clinical care and translational research in TMA. *Am J Kidney Dis.* 70(5):715-721. © *2017 by the National Kidney Foundation, Inc.*

INDEX WORDS: Thrombotic microangiopathy (TMA); multidisciplinary team; complement-mediated hemolytic uremic syndrome (CM-HUS); thrombotic thrombocytopenic purpura (TTP); clinical care; rare disorder; translational research; nephrology; hematology.

Development of a Thrombotic Microangiopathy Team

Rationale

Thrombotic microangiopathy (TMA) is a rare life-threatening condition characterized by the widespread formation of microthrombi, resulting in multiorgan failure in its severe and disseminated form.[1,2] TMA is identified by laboratory abnormalities such as thrombocytopenia, microangiopathic hemolytic anemia, and decreased glomerular filtration rate, and clinically, by end-organ injury primarily affecting the kidneys and central nervous system.[2,3] Pulmonary, cardiac, and gastrointestinal manifestations are also common in severe TMA.[4] Classically, microangiopathic hemolytic anemia presents with elevated lactate dehydrogenase concentration, low haptoglobin concentration, negative direct antiglobulin (Coombs) test, and the presence of schistocytes in the peripheral-blood smear.[5] However, these tests can be insensitive to early detection of TMA and discrepant results may confuse the picture. Some guidelines no longer require all parameters to be present to diagnose TMA.[6-9]

TMA comprises multiple acquired and hereditary conditions, including thrombotic thrombocytopenic purpura, Shiga toxin–mediated and complement-mediated hemolytic uremic syndrome (CM-HUS), and drug-induced TMA, among others (Box 1).[1,2] The pathophysiologic processes leading to some TMA syndromes are relatively well understood. For example, acquired thrombotic thrombocytopenic purpura results from reduced ADAMTS13 (von Willebrand factor protease) activity secondary to an acquired inhibitor in the more common sporadic (nonhereditary) form.[10] Shiga toxin mediates HUS and mutations in the complement system mediate CM-HUS.[1] Moreover, many conditions (Box 2) mimic the laboratory abnormalities of TMA, resulting in delay in the diagnosis and treatment for the underlying cause.

Early detection and diagnosis of TMA are essential to improve clinical outcomes. A delay in the diagnosis and treatment of the cause of TMA may result in irreversible end-organ damage, including kidney failure, stroke, and cardiac dysfunction. As an example, untreated CM-HUS is associated with a 50% risk for end-stage renal disease and a 25% mortality rate.[2] In CM-HUS, these outcomes are

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Box 1. Classification of Primary TMA

Thrombotic thrombocytopenic purpura
- Hereditary
- Acquired (inhibitory autoantibody)

Shiga toxin–mediated HUS
- *Shigella dysenteriae*
- *Escherichia coli*, serotypes O157:H7 and O104:H4

Complement-mediated TMA[a]
- Loss-of-function mutations: CFH, CFI, MCP, thrombomodulin, and CFHRs
- Gain-of-function mutations: CFB, C3

Drug-induced TMA
- Quinine, gemcitabine, quetiapine, mitomycin, cyclosporine, tacrolimus, sirolimus, opioids, others[b]

Metabolism-mediated TMA
- Mutations affecting cobalamin (vitamin B_{12}) metabolism

Coagulation-mediated TMA
- DGKE, thrombomodulin and plasminogen mutations

Abbreviations: CFB, complement factor B; CFH, complement factor H; CFHR, complement factor H–related proteins; CFI, complement factor I; DGKE, diacylglycerol kinase epsilon; MCP, membrane cofactor protein; TMA, thrombotic microangiopathy.

[a]All have acquired and hereditary forms.

[b]For a detailed review of agents associated with TMA, see reviews by George and Nester,[1] 2014, and Noris and Remuzzi,[2] 2009.

Box 2. Causes of Secondary Thrombotic Microangiopathy

Pregnancy
- HELLP syndrome, preeclampsia

Hypertension
- Malignant hypertension

Infectious
- Bacterial: infective endocarditis, pneumococcal, rickettsia, brucella, borrelia
- Viral: HIV, CMV, HBV, HCV, influenza A, parvovirus B19, EBV, dengue
- Fungal: aspergillus, blastomyces, *Candida* spp, *Cryptococcus* spp
- Parasitic: *Babesia* spp, *Plasmodium falciparum*

Malignancy
- Breast, ovarian, gastric, colorectal, lung, pancreatic, lymphoma, myelodysplastic syndrome

Autoimmune disorders
- SLE, antiphospholipid antibody syndrome, scleroderma, dermatomyositis

Transplantation
- Allogeneic bone marrow transplantation, solid-organ transplantation

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HELLP, hemolysis, elevated liver function test, low platelet; HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus.

significantly improved by the early administration of complement inhibitor therapies.[11,12]

Adding to the difficulty in rapidly diagnosing the cause of TMA is the long-standing approach of relying on hematology or nephrology consultants working independently, and sometimes with limited communication between them. Additionally, these 2 specialties are focused on their specialty-specific differential diagnoses, leading to a narrower vision of the full clinical picture. Moreover, individual consultants have varying degrees of experience with diagnosing and managing specific TMA causes, which may lead to errors in management. Therefore, new approaches to uncommon and high-mortality illnesses such as TMA are needed to improve clinical outcomes.[9]

Goals of a TMA Team

In response to the need to facilitate more rapid diagnosis and institution of TMA therapy, we created a multidisciplinary TMA team composed of individuals with an interest and expertise in managing this rare disorder. The active participation of clinicians with our department's Thrombosis and Hemostasis Affinity Research Collaborative (ARC) facilitated creation of the TMA team. As we published earlier,[13] an ARC consists of investigators from different disciplines with a shared interest in a biomedical problem with the ultimate goal of improving clinical care. The TMA team is designed to address 3 major goals. First, we aimed to improve clinical outcomes through rapid diagnosis and treatment, with a goal to improve patient morbidity and mortality and decrease inpatient length of stay and health care delivery costs. Second, we aimed to educate a wide range of front-line clinicians to increase awareness of TMA. Finally, we aimed to develop research on the pathogenesis of TMA. Our team represents a novel model of a multidisciplinary assembly in the inpatient and outpatient settings for the management of a rare disorder such as TMA. In order to bring together the relevant disciplines needed to diagnose and treat TMA, we sought an interdisciplinary paradigm to address the unmet clinical need of a rare disorder such as HUS, with an estimated incidence of 4 to 6 per million.[2]

In the current article, we describe our approach and the role of the TMA team in increasing TMA awareness throughout the hospital, facilitating the early diagnosis of TMA and early treatment implementation directed at the underlying condition. We also describe how such an effort can result in a better understanding of this complex condition by enhancing research.

Clinical Aspects of the TMA Team

The first step toward our goal has been to determine the scope of TMA expertise in the team. To

standardize the approach to potential TMA cases, we selected a small group of individuals with clinical experience managing TMA. The current TMA team includes 2 adult nephrologists, an adult hematologist, a pediatric hematologist, the apheresis director, and a clinical pharmacist. An expert in high-risk materno-fetal obstetrics recently has been recruited to our team due to the high frequency of TMA presentations in this patient population. Selection of these specialties was based on the most commonly consulted services related to potential TMA cases, as well as those essential to making the diagnosis and implementing treatment. The role of the pharmacist is not limited to approval of therapeutic agents, but extends to assistance in potential drug-induced TMA cases and with meningococcal vaccination and prophylactic antibiotics before the use of complement inhibitors. The TMA team is led by 2 codirectors, a nephrologist and hematologist, who centralize and oversee all activities.

Our next goal has been to create an algorithm to facilitate the differential diagnosis of TMA in a timely manner. Because of the clinical overlap between the relatively uncommon TMA cases and the far more frequent occurrence of associated laboratory abnormalities such as thrombocytopenia, hemolytic or nonhemolytic anemia, and decreased glomerular filtration rate, we focused on clinical triggers designed to alert the primary clinical team and/or the nephrology and hematology consult services to consider activating the TMA team.[9] We developed an algorithmic approach to identify possible TMA cases and assist the primary team in ordering appropriate diagnostic studies essential to confirm the diagnosis of TMA and identify its cause. The algorithm identifies specific laboratory abnormalities that should prompt consideration of the diagnosis of TMA and lead to further investigation to rule out other diseases that could mimic TMA. The algorithm also helps distinguish primary TMA from systemic diseases associated with TMA features. A systematic scheme to the approach to TMA is now available[14] and has been distributed widely across several specialties at our institution.

At least one physician member of the TMA team is available on call at all times. The other TMA team members are available through e-mail or by telephone to consult with one another to achieve rapid consensus about the diagnostic workup and management strategy for every TMA team consultation. This unique feature of prompt communication between team members has led to faster and more focused diagnostic workup, quicker turnaround time for key laboratory test results, and more accurate diagnosis (Table 1). Importantly, the TMA team does not replace the primary consult services for nephrology and hematology, but instead supplements these services by delivering the clinical expertise of TMA

Table 1. Examples of Cases Managed by the TMA Team Since Its Inception

Date	Final Diagnosis	Time to Diagnosis, h	Time to Treatment, h	Patient Outcome
October 2015	DIC	<24	<24	Recovered from *Streptococcus pneumoniae* sepsis
October 2015	Hypertensive emergency	96	96	Blood pressure controlled but patient remained dialysis dependent
November 2015	Hypertensive emergency	48	48	Blood pressure controlled with return of kidney function to baseline
February 2016	G6PD deficiency	48	48	Resolution of hemolysis with discontinuation of offending agent
March 2016	Drug-induced TMA	72	72	Discontinuation of calcineurin inhibitor with improved kidney function
April 2016	Drug-induced TMA	96	96	Discontinuation of gemcitabine, administration of complement inhibitor, resolution of hematologic abnormalities, and partial recovery of kidney function
May 2016	Dermatomyositis-induced TMA	72	72	Died of pulmonary hemorrhage despite initiation of complement inhibitor
July 2016	TTP due to ADAMTS13 inhibitor	<24	<24	TTP under long-term management with plasma exchange and immunosuppressive agents
September 2016	SLE-induced TMA with WHO class IV SLE nephritis	48	48	Administration of complement inhibitor, resolution of hematologic abnormalities, but no recovery of kidney function

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; DIC, disseminated intravascular coagulopathy; G6PD, glucose-6-phosphate dehydrogenase; SLE, systemic lupus erythematosus; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; WHO, World Health Organization.

team members and the availability of immediate consultation with all specialties represented on the team (Fig 1). Team members bill for professional services if they are consulted without the involvement of the primary inpatient consult services for hematology or nephrology. All TMA team members have previous clinical experience in TMA, including management of relevant pharmacologic agents or plasma exchange. TMA team members from hematology examine daily peripheral-blood smears on suspected TMA cases to identify schistocytes. Although tissue diagnosis is not always required for TMA, we work closely with members of the Pathology Department, who are well versed in identifying TMA in biopsy specimens of kidney and other tissues, with biopsy results generally available within 24 hours. Our pathologists routinely stain tissues for C5b-9 deposition as a helpful adjunct for TMA diagnosis. When complement inhibitors are considered, we adhere to standard vaccination and antibiotic prophylaxis protocols.

We worked with the laboratory medicine department at our hospital to identify mechanisms to achieve faster turnaround time and optimal performance characteristics for the diagnostic laboratory tests required to diagnose TMA, as well as to determine its cause (Fig 1). For instance, we improved the turnaround time for ADAMTS13 testing from 7 to 10 days to 24 to 48 hours. We also created a quick laboratory panel order set in the electronic medical record for diagnostic tests frequently required to investigate potential TMA. TMA team members also have experience ordering genetic and specialized complement testing as required for the workup of TMA cases. On an ongoing basis, TMA team members evaluate whether any rate-limiting steps are delaying TMA diagnosis. The time to diagnosis and treatment initiation has dramatically improved since

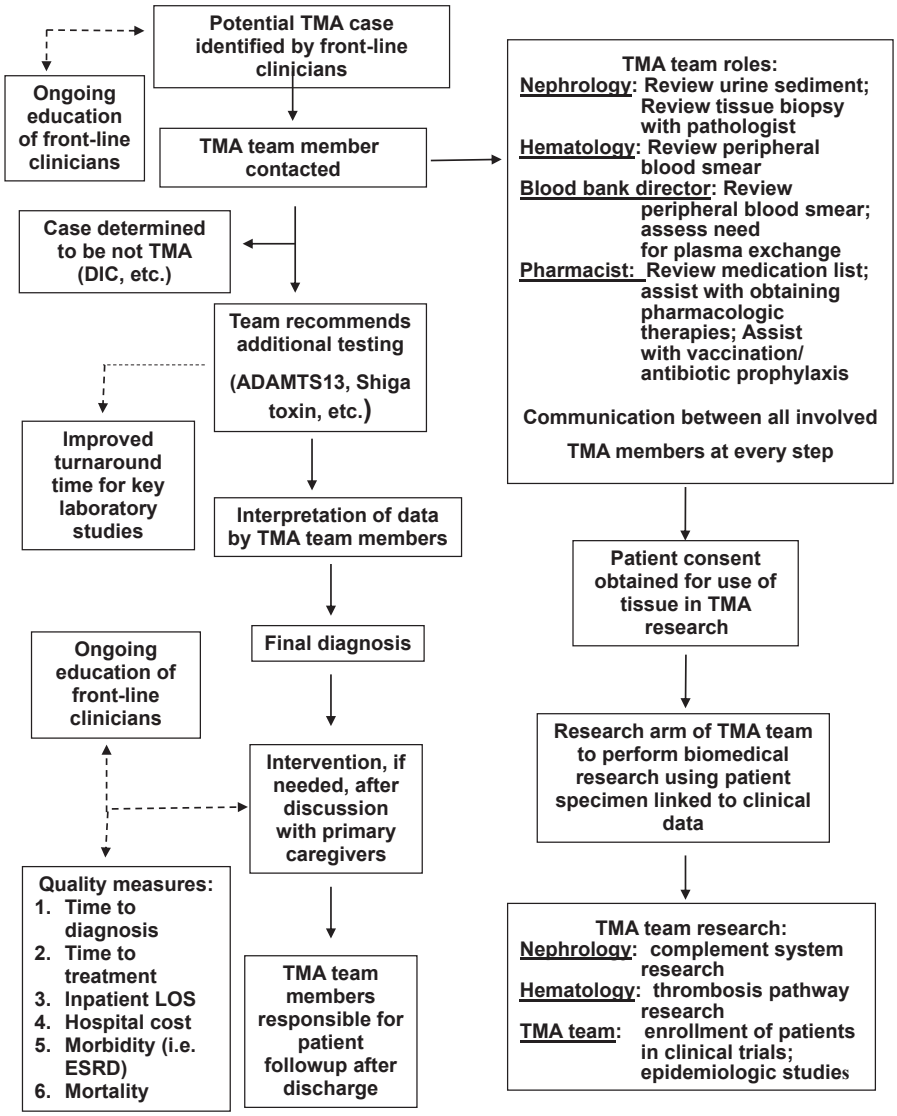

Figure 1. Process map for thrombotic microangiopathy (TMA) management. Solid lines represent the processes involved in clinical, educational, and research arms of the TMA team. Dashed and bidirectional lines represent rate-limiting steps we encounter and sources of continual improvement to the diagnosis and management of TMA. Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; DIC, disseminated intravascular coagulopathy; ESRD, end-stage renal disease; LOS, length of stay.

formation of the TMA team (Table 1). We expect that this will result in improved clinical outcomes, shorter lengths of stay, and cost savings from reducing the use of expensive medications or interventions (such as a prolonged course of plasma exchange with normalization of hematologic parameters but not reversal of organ injury) that are not indicated or effective.

Educational Aspects of the TMA Team

We anticipate that the major barrier to successfully improving care of patients with TMA will be the lack of awareness of TMA in the differential diagnosis and initial workup. Lack of familiarity by the front-line services with the laboratory abnormalities that serve as early diagnostic clues to TMA could lead to delayed identification and treatment of TMA disorders. Thus, since launching the TMA team in October 2015, the strategy for improving the recognition and management of TMA has been disseminated to the entire medical campus community through workshops, lectures, and educational symposia. The goal has been to familiarize the institutional community with the pathogenesis, presentation, differential diagnosis, intervention, and management strategies for the various forms of TMA. In a recent mini-symposium, nationally and internationally recognized experts in TMA and the complement system were invited to lecture on the approach to suspected TMA, the complement system in reference to TMA, treatment of CM-HUS, TMA after kidney transplantation, and genetic variants implicated in CM-HUS from the international atypical HUS registry. Events such as this one are attended by clinical and research faculty from hematology/oncology, nephrology, transplantation surgery, laboratory medicine, emergency medicine, hospital medicine, and critical care medicine and research faculty interested in TMA and related disorders.

In addition, we have initiated teaching conferences led by the TMA team directors with internal medicine residents through various educational conferences (medical grand rounds and mortality and morbidity conference, among others) in their teaching curriculum. We have scheduled similar educational sessions with faculty and trainees in other key front-line clinical and consulting departments, including the high-risk maternofetal pregnancy program, the emergency department, and intensive care units. Our goal is to increase awareness of both TMA as a disease and the presence of the TMA team. This educational enterprise is a continuous effort to educate new health care providers who join the workforce in our institution.

Finally, with the assistance of the Clinical and Translational Science Institute (CTSI) at Boston University, we have reached out to other CTSI hubs, also through the development of a TMA team website,[15] which will allow dissemination on a broader scale. This interactive site provides a diagnostic algorithm, detailed instructions for the diagnostic workup, and approaches to therapeutic interventions. The site also contains updates on recent advances, interesting case reports, research activities, and clinical trials in the field.

Research Aspects of the TMA Team

In line with the complex nature of TMA, its pathogenesis is polygenic, multifactorial, and dynamic. It involves several different cell types in various vascular beds, mediators, regulators, and disease modifiers, all of which orchestrate an intricate and dynamic process influencing the clinical phenotype and overall prognosis. Though some triggers (infections, pregnancy, and drugs) and predisposing conditions (loss-of-function mutations of complement regulators or mutations in diacylglycerol kinase epsilon, among others listed in Box 1) have been well described, several aspects of TMA warrant further investigation. For example, although genetic variants predisposing to CM-HUS have been identified in half the cases, the causative gene(s) remain unknown in the rest. Although aberrant hyperactivation of the alternative complement pathway is a well-accepted mediator of primary CM-HUS, recently identified genetic variants in complement mediators and regulators in patients with secondary HUS implicate its broader role in TMA.[1,2]

Several aspects of TMA pathogenesis that require further insight include the dynamic interaction of genetic and environmental factors, specific organ tropism and the contribution of various cell types, signaling cascades triggered by the initial insult, and the mediators and regulators of the pathogenic targets. Better understanding of these processes will help identify potential risk markers and novel targets that can be further developed in the future for therapeutic purposes. The latter is especially important because therapies exist for only a small proportion of all TMA cases, namely CM-HUS and thrombotic thrombocytopenic purpura.[16]

The TMA team also provides an excellent vehicle for research. Its availability allows the creation of a registry and biorepository to facilitate translational and basic science research to help further clarify the pathophysiology of TMA syndromes. If this model is implemented by individual institutions or via a nationwide initiative such as the CTSI program at several academic institutes, it might lead to interinstitutional collaboration to facilitate discoveries related to TMA. The Evans Center for Interdisciplinary Biomedical Research at Boston University Medical Campus has a novel ongoing initiative that

draws investigators, clinicians, and researchers within Boston University campuses and from surrounding institutes to form ARCs with the primary objective of encouraging collaborations.[13] The center provided resources to build a clinical TMA task force and a research program that can leverage the development of the TMA database and biosamples.

The database includes relevant clinical, biochemical, hematologic, infectious, and immunologic panels and will provide a rich resource for phenotypic analysis for predictive purposes. Given the low incidence of TMA, such a database will also provide an opportunity to understand the natural history of TMA specific to various causes and will record the diagnostic and therapeutic steps in the management of an individual patient for quality improvement purposes.

TMA research poses challenges from other perspectives. Though there are different small- and large-animal models, as well as knockout and transgenic models, of TMA,[17,18] they are trigger specific and do not adequately represent the human disease or emulate the heterogeneous clinical course of an individual TMA case. Given the multicomponent pathogenesis of the disease, transitioning from animal models to clinical research in humans remains challenging. This makes the research with human samples especially valuable to probe the disease heterogeneity and examine the mechanistic aspects of disease.

As a result of the low incidence of TMA, availability of sufficient samples representative of the TMA disease spectrum is important. Garnering a sufficiently large sample size for required statistical power is a major bottleneck in TMA translational research, a limitation that can be addressed by our TMA team. An accompanying biobank with isolated, stored, and catalogued biospecimens including blood, urine, and tissue samples tagged to deidentified individual patient data is an invaluable resource for probing novel mediators[19-21] and signaling events triggered in various vascular cell types.[22,23] Serial urine samples can be explored for biomarker(s) that can serve as a surrogate for the microangiopathic hemolytic anemia process within the microvasculature of the kidney. Extracted genomic DNA can be subjected to deep sequencing for novel variants and for risk allele or polymorphisms analysis.[24] Such a resource is more likely to provide the critical sample size required for hypothesis testing and assist with research proposals even for investigators outside the institution. At this stage, our goal is to collect clinical data and corresponding biosamples to be available for basic research within and outside of our institution. Adaptation of this team model by other centers may facilitate multicenter research collaboration. enhancing the ability to better understand TMA disorders.

Sustainability

An important facet of the new TMA team development is a plan for its sustainability. In our case, the ARC program supported by the Department of Medicine ($50,000 yearly for up to 3 years) provided funds to build the TMA biobank. Beyond the first 3 years, continuous support of the research branch of TMA will be derived from extramural funding, as well as institutional pilot funding mechanisms offered through the Department of Medicine and the CTSI.

Concluding Remarks

Although the ARC mechanism has served as a springboard to creating a TMA team, we posit that such initiative is possible in other medical centers even if the research program part is not feasible. The key determinants of success are the team members with different backgrounds and expertise necessary to deliver comprehensive care that addresses the patients' needs throughout their disease course. Creation of a TMA team allows clinical expertise from different disciplines and perspectives to be rapidly mobilized for early diagnosis and initiation of potentially life-saving treatment. We believe a preassembled team is critically important for improving clinical outcomes for patients with TMA. The benefits of a multidisciplinary team approach have been well described, but its application to the management of a rare, difficult-to-diagnose, potentially fatal disease that is treatable in many cases when implemented expeditiously may serve as a paradigm for other similar conditions. Multidisciplinary teams have been shown to improve clinical care in other diseases such as systemic amyloidosis, which is similar to TMA in involving multiple organs.[25]

Our TMA team approach could serve as a model for similar teams and structures adopted by other institutions. This not only will allow the delivery of better care, but also might enhance multicenter collaboration to standardize the approach to TMA and facilitate partnerships between medical centers to affect patient care, education, and research related to TMA. The shared experience derived from a standardized approach and creation of a TMA network will offer learning and research opportunities not possible in individual programs due to the rarity of the diseases that make up TMA.

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