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Coagulation Function Testing Clinical Demand and Current Status in China

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Abstract

Diseases or symptoms related to coagulation function are widely present in clinical daily work, as coagulation function plays a central role in maintaining homeostasis in the internal environment. Therefore, coagulation dysfunction often leads to serious harm to patients. At the same time, coagulation related treatments such as the use of anticoagulants or transfusion therapy have potential serious side effects, even leading to patient death. For many years, balancing the bleeding or embolism caused by anticoagulants has been a challenge that clinical workers have to face, which poses great challenges to clinical work. Therefore, monitoring coagulation function is very important for clinical diagnosis and treatment. The rapid and accurate completion of coagulation function diagnosis conclusions and early transmission to clinical workers are important guarantees for patient life. However, at present, due to technical limitations and the complexity of the detection process, this demand cannot be met. At present, in China, coagulation function testing is mostly concentrated in laboratory departments, and the limitation of distance may affect the timeliness of coagulation function testing. Therefore, many clinical departments of institutions tend to conduct coagulation function testing themselves, which has led to many new demands for coagulation function testing, such as fast and convenient POCT coagulation function testing and coagulation function testing of cell models that are more in line with clinical needs, More joint detection of coagulation markers and so on, of course, these needs must be established on the premise that clinical testing equipment and laboratory testing results are consistent. However, in order to meet the needs of miniaturization and rapid testing, the coagulation function testing equipment used in clinical departments often has significant methodological differences from laboratory testing equipment, which further leads to differences in testing results. Based on this situation, many new technologies, including microfluidic technology, as well as more detection techniques, have been widely and deeply applied to clinical coagulation function testing, which has brought a lot of good news to clinical coagulation function diagnosis to a large extent.

Keywords: coagulation, point-of-care testing, microfluidics, detection technology, quality management, clinical diagnosis

1. Introduction

The coagulation system is an important mechanism for maintaining the stability of the internal environment in the human body. On the one hand, coagulation function is one of the main mechanisms by which the body resists external infections and repairs damage. It interacts with various blood cells, vascular endothelium, inflammatory

mechanisms, the complement system, and other regulatory mechanisms in the body, forming a complex network of cross-interactions (Foley JH & Conway EM, 2016). Coagulation dysfunction, caused by various reasons, is widely present in clinical settings.

On the one hand, coagulation function is also referred to as the coagulation cascade or "coagulation waterfall." This is because symptoms associated with coagulation dysfunction often occur rapidly, are severe, and progress quickly. This makes the timeliness of coagulation function testing crucial. Furthermore, due to the presence of significant technical interference in the coagulation function testing system, the timeliness of coagulation function testing is highly correlated with the clinical diagnostic consistency of coagulation function test results.

Moreover, due to the complex dynamic mechanisms of coagulation function, coagulation-related treatments often need to be based on the balance between coagulation and anticoagulation. In other words, both excessive anticoagulation and insufficient anticoagulation can lead to corresponding adverse symptoms in patients, and in severe cases, it may even threaten the patient's life. Therefore, whether it is based on the stability of the patient's internal environment or the efficacy and adverse effects monitoring of anticoagulant therapy, the monitoring system of coagulation function and coagulation-related biomarkers is of great significance for the treatment and prognosis of patients (Nimah M & Brilli RJ, 2003; Vanderschueren S, Weerda A, Malbrain M, et al, 2000; Levi M, Schouten M & van der Poll T, 2008).

Currently, coagulation function testing technology is still in its developmental stage. While existing technologies are quite classic, new technologies are constantly emerging. Especially with the continuous development of microfluidic technology, there is an abundance of rapid coagulation function testing platforms that can be applied in clinical settings. These platforms are advantageous because they are compact, have fast detection speeds, and are easy to operate, meeting the clinical requirements for timely coagulation function testing. However, due to limitations in clinical settings and differences in report interpretation methods, there are still many limitations in the use of coagulation function testing devices in the current clinical scenario. This article will review the current status of coagulation function testing based on the clinical characteristics of coagulation function and common coagulation function testing technologies.

2. Clinical Characteristics of Coagulation Function

Coagulation function disorders are common complications in critically ill patients and are related to mortality (Ecaterina S, D M L, J N W, et al, 2018; Amaral A, Opal SM & Vincent JL, 2004). Additionally, coagulation dysfunction can cause or exacerbate clinical emergencies.

Clinical coagulation function disorders are both systemic and complex. A large number of studies (Jackson SP, Darbousset R & Schoenwaelder SM, 2019; Asakura H & Ogawa H, 2021; Colling ME, Tourdot BE & Kanthi Y, 2021; Iba T, Levy JH, Warkentin TE, Thachil J, van der Poll T, Levi M, Scientific and Standardization Committee on DIC, and the Scientific and Standardization Committee on Perioperative and Critical Care of the International Society on Thrombosis and Haemostasis, 2019; Levi M & van der Poll T, 2010; de Bont CM, Boelens WC & Pruijn GJM, 2019; Rawish E, Sauter M, Sauter R, Nording H & Langer HF, 2021) have revealed that there are complex crosstalk mechanisms between various blood components (cells, proteins, inorganic ions) involved in coagulation function, inflammation mechanisms, complement systems, etc. (Van der Poll T & Levi M, 2012; O`Brien M, 2012; Oikonomopoulou K, Ricklin D, Ward PA & Lambris JD, 2012). These complex crosstalk mechanisms mediate various physiological and pathological processes and play an extremely important role in maintaining the stability of the body's internal environment. In contrast, coagulation mechanisms, except for the role of promoting potential pathological progression due to the activation of multiple enzymes in the cascade process, generally manifest as symptoms of bleeding or thrombosis, which are often important causes of death in critically ill patients. Therefore, the relationship between coagulation function and clinical emergencies is extremely close.

Common clinical symptoms such as trauma, infection, tumors, pregnancy, and their corresponding treatment methods can all lead to symptoms of bleeding or thrombotic embolism in patients.

Starting from clinical symptoms.

Coagulation and tumors: Studies have shown that the occurrence of deep venous thrombosis (DVT) and pulmonary embolism thrombosis (PET) is associated with various malignant tumors (Yap KP & McCready DR, 2004; Guo X, et al, 2018; Fujiwara R, et al, 2020; Lopez-Ruz S, Barca-Hernando M & Jara-Palomares L, 2021; Bauersachs R, 2023; De Robertis R, et al, 2018; Khorana AA, et al, 2022; Falanga A, et al, 2017; Hisada Y & Mackman N, 2018). On the one hand, the tumor immune microenvironment (TME) provides conditions that favor the formation of blood clots (Magnus N, D'Asti E, Garnier D, Meehan B & Rak J, 2013; Saidak Z, et al, 2021; Galmiche A, Rak J, Roumenina LT & Saidak Z, 2022). This is reflected not only in the interactions of various physiological proteins and tumor-related proteins in the tumor immune microenvironment but also in further research showing that multiple cancer genes potentially participate in the regulation of coagulation

function (Tawil N & Rak J, 2022). In various cancers, the core factor of the current thrombosis model, Tissue Factor (TF), has been found to be highly expressed. This is not only related to the destruction of vascular tissue during tumor progression but also to changes in gene expression and the local immune microenvironment, such as extracellular vesicles enriched with TF on the surface identified in tumor-mediated extracellular vesicles (Galmiche A, Rak J, Roumenina LT & Saidak Z, 2022). On the other hand, ample data indicate that coagulation-related proteins also promote the development and metastasis of tumors. Currently, there is a large amount of research on inhibiting coagulation to suppress tumor growth (Nadir Y, 2019). Therefore, anticoagulant therapy is both a guarantee for managing thrombosis and bleeding during tumor treatment and also has potential therapeutic benefits for tumors (Schrag D, Uno H, Rosovsky R, Rutherford C, Sanfilippo K, Villano JL, Drescher M, Jayaram N, Holmes C, Feldman L, Zattra O, Farrar-Muir H, Cronin C, Basch E, Weiss A, Connors JM, CANVAS Investigators, 2023; Choi JU, et al, 2021; Ruf W, Rothmeier AS & Graf C, 2016; Martins MA, Silva TF & Fernandes CJ, 2023).

Coagulation and pregnancy: Blood in pregnant women is in a hypercoagulable state, and pregnancy-related deep venous thrombosis (DVT) and pulmonary embolism thrombosis (PET) are the leading causes of maternal mortality (Kalaitzopoulos DR, et al, 2022). Additionally, defects in coagulation function and platelets are also important reasons for infertility and recurrent miscarriages during pregnancy (Bick RL, 2000). In cases where childbirth complications, such as placental abruption, result in intrauterine trauma for various reasons, it may lead to the entry of amniotic fluid into the maternal circulation. This can further lead to the symptoms of Anaphylactoid Syndrome of Pregnancy (ASP), formerly known as amniotic fluid embolism (AFE) (Haftel A, Carlson K & Chowdhury YS, 2024). This is mainly due to the hypersensitive reaction caused by fetal components in the amniotic fluid entering the maternal circulation. This hypersensitive reaction may lead to coagulation disorders, resulting in systemic disturbances and ultimately leading to the occurrence of disseminated intravascular coagulation (DIC) (Tamura N, Farhana M, Oda T, Itoh H & Kanayama N, 2017).

Coagulation and trauma: Coagulation function is closely related to trauma (Zanza C, et al, 2023), and this relationship is not only manifested in the hemostasis and repair of trauma by coagulation function, but also in the complex regulation of the innate immune system during the trauma process (Pape HC, Moore EE, McKinley T & Sauaia A, 2022; Luyendyk JP, Schoenecker JG & Flick MJ, 2019; Messerer DAC, et al, 2021). Trauma disrupts vascular tissue, exposes collagen and tissue factor (TF) in the extracellular matrix, which activates the coagulation function, leading to hemostasis and subsequent repair of the trauma. In this process, coagulation mechanisms are activated by endothelial and inflammatory factors, and they also participate in the regulation of inflammatory mechanisms, thus playing a role in resisting external infections. Therefore, coagulation function is considered as the “first line of defense” against external interference during trauma (Colling ME, Tourdot BE & Kanthi Y, 2021). Moreover, more research has revealed the important role of coagulation function in tissue trauma repair, which is reflected in its regulatory effect on the microenvironment of the injured area (Velnar T, Bailey T & Smrkolj V, 2009; Reinke JM & Sorg H, 2012). Various factors such as hypothermia, acidosis, and hypoperfusion after trauma can lead to acute disorders of coagulation function, resulting in trauma-induced coagulopathy (TIC). TIC manifests as an early bleeding tendency and a later hypercoagulable state. In the later stages, patients often present with multiple thromboembolism and multiple organ failure (Moore EE, et al, 2021). Studies have found that the mortality rate of trauma patients with TIC is much higher than that of trauma patients without TIC (CRASH-3 trial collaborators, 2019).

Coagulation and sepsis: With increased understanding, sepsis is no longer considered a simple response to infection, but rather an immune imbalance caused by infection (Hotchkiss RS, et al, 2016). Coagulation dysfunction is often associated with sepsis, and a previous review (Amaral A, Opal SM & Vincent JL, 2004) summarized the changes in coagulation factors in sepsis. These changes include increased tissue factor (TF), thrombin and antithrombin complex (TAT), and D-dimer (D-dimer), as well as decreased factor VII, antithrombin (AT), and activated protein C (APC). These changes indicate that coagulation and fibrinolysis are activated during the pathological process of sepsis and create conditions for potential disseminated intravascular coagulation (DIC). Studies have revealed that the coagulation activation associated with sepsis-induced DIC is not due to widespread tissue damage-induced contact activation of coagulation, but rather due to the immune dysregulation in the systemic environment, such as the generation of cytokine storms and activation of complement, leading to coagulation dysfunction (Iba T, Connors JM, Nagaoka I & Levy JH, 2021).

Coagulation dysfunction can also lead to the further development of related critical illnesses. Prolonged coagulation dysfunction can cause the occurrence of disseminated intravascular coagulation (DIC), which is a depletion syndrome characterized by systemic dysregulation of the internal environment. Studies have shown that sepsis-related DIC is not simply a result of a single coagulation disorder, but rather a complex outcome of the interactions of multiple systemic networks in the internal environment (Levi M & Sivapalaratnam S, 2018; Levi M, 2007; Iba T, Levi M & Levy JH, 2020; Unar A, Bertolino L, Patauner F, Gallo R & Durante-Mangoni E, 2023). This further explains the complex role and important status of coagulation function in maintaining

immune homeostasis. DIC is common in departments such as oncology, obstetrics, burns, and neonatology (Levi M & Sivapalaratnam S, 2018; Adelborg K, Larsen JB & Hvas AM, 2021; VanVooren DM, Bradshaw WT & Blake SM, 2018; Takeda J & Takeda S, 2019; Vincent JL, et al, 2018; Morikawa M, et al, 2021; Hisamune R, Mochizuki K & Yamakawa K, 2023; Ten Cate H & Leader A, 2021). DIC can cause microcirculatory disorders in patients due to excessive coagulation activation, and secondary depletion of procoagulant function can lead to depletion of anticoagulant and fibrinolytic functions, resulting in bleeding symptoms in patients while experiencing microcirculatory disorders. This may further lead to multifunctional organ failure (MOF), shock, and ultimately patient death.

Starting from clinical treatment needs, anticoagulant therapy is a "double-edged sword", as inadequate or excessive anticoagulation can cause serious harm to patients (Dhakal P, et al, 2017). Many anticoagulant drugs themselves also have potential side effects, such as heparin-induced thrombocytopenia (HIT) (Prince M & Wenham T, 2018; Warkentin TE & Greinacher A, 2009; Junqueira DR, Carvalho Md & Perini E, 2013), which refers to heparin-induced adverse reactions mediated by antibodies during the use of heparin drugs. HIT is mainly characterized by a decrease in platelet count and can cause venous and arterial thrombosis, and in severe cases, even death. Anticoagulant therapy is not only used to balance the high coagulation and thrombosis risks caused by various underlying diseases but is also an important clinical treatment auxiliary method. For example, in the establishment of cardiopulmonary bypass (CPB), extracorporeal membrane oxygenation (ECMO), and continuous renal replacement therapy (CRRT), direct anticoagulants such as heparin are generally used to prevent the physiological coagulation of blood and maintain the natural flow of blood to ensure circulation while avoiding the secondary harm caused by thrombosis. Anticoagulant therapy is the basis for the implementation of extracorporeal circulation technology, but it is ultimately a "double-edged sword", and adverse reactions such as secondary bleeding, thrombocytopenia, and thrombosis caused by excessive anticoagulation are not uncommon in anticoagulant therapy during extracorporeal circulation (Prince M & Wenham T, 2018; INSPIRATION Investigators, et al, 2021; Boer C, Meesters MI, Veerhoek D & Vonk ABA, 2018; Jámbor C, et al, 2008).

Taking cardiac direct visualization surgery mediated by CPB as an example, a large amount of heparin is needed during the bypass process to ensure the establishment and flow of CPB. During the perioperative period, the reasons for blood coagulation tendency include not only surgical procedures (Ranucci M, 2015) such as thoracotomy and intubation but also the inflammatory response, complement activation, and interference between inflammation and coagulation caused by contact changes, oxidative stress, and ischemia-reperfusion during the CPB process (Paparella D, Brister SJ & Buchanan MR, 2004). Therefore, anticoagulant therapy related to cardiac direct visualization surgery mediated by CPB is not a simple anticoagulation process. In this case, the systemic role of coagulation function in the internal environment needs to be further studied and discussed.

In terms of anticoagulant drugs, there are currently a variety of anticoagulant drugs available, including direct anticoagulants such as heparin, dabigatran, and rivaroxaban, indirect anticoagulants such as warfarin, and platelet antagonists such as clopidogrel and aspirin. In clinical practice, the use of these anticoagulant drugs needs to constantly adhere to the requirements of the anticoagulation balance point. Insufficient dosage or inadequate efficacy may fail to effectively eliminate the potential thrombotic risk caused by underlying diseases, while excessive dosage may cause bleeding due to excessive anticoagulation (Lip GYH, et al, 2018; Hindricks G, et al, 2021; Levine GN, et al, 2022; Bikdeli B, et al, 2022). Due to significant individual differences among patients, there is often a lack of unified and effective standards for the use of anticoagulant drugs (Oldgren J, et al, 2022; Harrington J, et al, 2023; Kent DM, et al, 2015), leading to frequent occurrence of bleeding in clinical practice due to improper drug use.

The use of blood products is also closely related to coagulation function (Madisetty J, Wang C, 2017; Meier J, 2016; Kozek-Langenecker SA, 2014; Yoon U, et al, 2022). Massive transfusion (MT) is an effective method for treating hemorrhagic shock. However, the core fatal adverse reactions of MT are acidosis, hypothermia, and coagulation dysfunction caused by excessive transfusion, which are highly related to the patient's mortality rate (Sihler KC & Napolitano LM, 2010). The transfusion process may provide the body with a large number of cell factors from allogeneic sources, leading to an inflammatory response. Changes in circulating volume can also cause tissue damage, which may result in coagulation dysfunction (van Manen L, et al, 2022; Tuinman PR, et al, 2011).

3. The Characteristics of Coagulation Detection Technology

Classification of coagulation testing items: From the perspective of detection technology, coagulation function testing can be classified according to detection items. At present, coagulation function testing can be divided into coagulation function testing and coagulation function related biomarker testing according to detection items. Functional testing mainly detects various indicators such as viscoelasticity during sample coagulation time and coagulation process, which often express the systemic state of activation of the entire active part of the

coagulation mechanism to sample coagulation, for example, activation of prothrombin time (PT), thromboelastography, etc., the characteristic of this type of detection is that it utilizes the coagulation mechanism to cause blood coagulation, activates the coagulation mechanism of the sample through activators (such as kaolin, tissue factors, etc.), and causes sample coagulation. By detecting coagulation time, or the physical properties such as changes in viscoelasticity during the coagulation process can be used to determine the overall tendency of the sample's coagulation state (high or low coagulation), the ability to form blood clots, and the progress of coagulation mechanisms (Winter WE, Flax SD & Harris NS, 2017; Carll T & Wool GD, 2020).

In contrast, the detection of coagulation function related biomarkers is mostly carried out through immunological techniques such as immunoturbidimetry, chemiluminescence, etc. The detection targets are mostly the blood concentration of a certain biomarker (including a complex) in the coagulation mechanism, such as fibrinogen degradation products (FDP), D-dimer (D-Dmier), TAT, and plasmin- α Fibrinolytic enzyme complex- α 2 plasma inhibitor complex (PIC), etc. (Weitz JI, Fredenburgh JC & Eikelboom JW, 2017; Uenomachi H, et al, 1996).

At the same time, the colorimetric substrate method can also be used to detect the activity of specific biomarkers, such as the detection of antithrombin (AT) activity. This is achieved by adding a known amount of excess thrombin to the plasma. As thrombin forms a 1:1 complex with antithrombin in the plasma, the remaining thrombin acts on the chromogenic agent through its protease activity, cleaving the chromogenic groups and causing a color change in the reaction system, the final degree of color development is negatively correlated with the antithrombin activity in plasma. Similarly, by increasing the affinity between heparin and FX, a known amount of excess FX is added to the sample plasma. Heparin in the sample antagonizes it in a 1:1 ratio, and the remaining FX cleaves the chromogenic groups of the reagent through its enzyme activity, resulting in a color change in the reaction system. The degree of color change is inversely proportional to the residual heparin in the plasma, and the quantitative results of the patient's residual heparin in vivo are obtained based on this result.

Functional indicators and related biomarkers each have their own characteristics and complement each other (Favaloro EJ & Lippi G, 2017).

From the perspective of interpreting test results, functional indicators often reflect the systemic overall tendency of the coagulation mechanism, without being able to pinpoint a specific point in the coagulation mechanism. The qualitative nature of functional testing outweighs the quantitative aspect, while biomarker testing can pinpoint a specific point in the coagulation mechanism. By measuring the specific content (concentration value) of a biomarker, not only can it indirectly reflect the overall status of the coagulation mechanism, but its quantitative nature also provides advantages in terms of accuracy. For a long time, routine coagulation function tests in China (such as PT, APTT, TT, FIB) could only reflect the state of hemostatic tendency, without showing the full picture of the entire coagulation system. Therefore, in order to comprehensively understand the state of the coagulation system, testing items such as AT activity, D-dimer, and FDP are widely used in conjunction with functional coagulation testing, which allows for a more comprehensive assessment of the coagulation system. This approach not only meets the demand for comprehensive evaluation of the coagulation system but also provides valuable diagnostic information for treatments like thrombolysis and heparin therapy.

From the perspective of reaction systems, coagulation assays, as the main methodology for functional coagulation testing, measure the coagulation time or other physical properties of the sample after activation. These results are generally obtained directly through instrument sensors, rather than through a calibration system that establishes a conversion system between reaction results and test results. Therefore, the nature of its reaction determines the difficulty of constructing a unified standardization calibration system. In many cases, the accuracy of test results is based on the reliability of the testing platform and reaction reagents, which further leads to numerous influencing factors, making it difficult to achieve high comparability between instruments. In contrast, coagulation-related biomarker testing measures the concentration of biomarkers through techniques such as immunoassay and colorimetry. As the reaction results and test results are corresponded by the calibration function curve established through a calibration system, this testing system generally has a traceable calibration system. Interference factors affecting the test results can be effectively controlled by introducing calibration standards, ensuring not only the precision and reliability of the test results but also achieving high comparability between instruments.

Precisely because of this, on one hand, in order to supplement the lack of details in functional coagulation testing, and on the other hand, to achieve more accurate quantitative measurements through biomarkers, at the current stage, coagulation testing primarily relies on functional coagulation testing supplemented with coagulation-related biomarker testing as the main clinical diagnostic method (Favaloro EJ, 2010).

4. Coagulation Function Testing Equipment

Coagulation analyzers are the most widely used platforms for functional coagulation testing. The output parameters mainly include the prothrombin time (PT), which reflects the functionality of the extrinsic

coagulation pathway, the activated partial thromboplastin time (APTT), which reflects the functionality of the intrinsic coagulation pathway, the thrombin clotting time (TT), which reflects fibrinogen functionality, and the concentration of fibrinogen (FIB). In order to meet clinical needs, current coagulation analyzers generally incorporate additional biomarker detection channels using optical detection systems. This enables the use of immuno-turbidimetric assays and chromogenic substrate assays. Some coagulation analyzers also have additional channels for platelet aggregation function detection through optical pathways.

As the most mainstream platform for functional coagulation testing, coagulation analyzers use a reaction methodology that involves anticoagulation of whole blood with sodium citrate in vitro (blocking the coagulation reaction chain by chelating calcium ions), followed by separation of plasma and activation of the coagulation cascade through exogenous calcium addition. The evaluation of the sample's coagulation tendency is achieved by measuring the sample's clotting time, which is mainly determined by measuring PT, APTT, and TT. Biomarker detection, such as DD and FDP, is achieved through immuno-turbidimetric assays or chromogenic substrate assays using optical detection modules, while fibrinogen detection is achieved through quantitative measurement using a coagulation-based assay.

The reason why coagulation analyzers have become the most popular coagulation functional testing technology is because of their extensive and deep clinical application over the past few decades. This has enabled them to accumulate a wealth of clinical experience, establish complete clinical guidelines and expert consensus, and ultimately form a highly recognized diagnostic and treatment testing system for clinical coagulation function.

On a technical level (Huber AR, Méndez A, Brunner-Agten S, 2013; Lippi G, Plebani M & Favaloro EJ, 2014), coagulation analyzers used in the laboratory mostly implement high-speed and high-throughput fully automated detection systems. This allows the laboratory to efficiently and accurately process large volumes of samples, and the automated detection process further improves the accuracy and convenience of the testing process, reducing the need for repeat testing and fundamentally improving the efficiency of testing. On the other hand, with the application of microfluidic technology in coagulation function testing (Branchford BR, Ng CJ, Neeves KB & Di Paola J, 2015), rapid coagulation function analyzers for point of care testing (POCT) have also rapidly developed. Various handheld or cart-based whole blood sample coagulation function analyzers have also met the needs of rapid bedside diagnosis in clinical settings (Beynon C, Unterberg AW & Sakowitz OW, 2015).

The detection principle of coagulation analyzer: The most mainstream detection methods for coagulation analyzers are optical detection system and magnetic bead detection system, each with its own advantages.

The optical method (Sevenet PO & Depasse F, 2017) refers to the use of an optical detection system to measure changes in the transmittance or absorbance of a light beam passing through the analyzed sample to identify the clot formation process. Over time, the transmittance or absorbance is continuously recorded. The magnetic bead method, on the other hand, uses a magnetic detection system to add magnetic beads to the reaction system. The magnetic beads continuously oscillate in the magnetic field. As the coagulation end products continuously cross-link fibrinogen in the reaction system, the degree of coagulation increases, and the resistance experienced by the magnetic beads during oscillation increases, leading to a decrease in the oscillation amplitude. An algorithm is then constructed to detect the oscillation of the magnetic beads in the reaction system and obtain the corresponding sample clotting time.

Although the detection principles of the two methods are different, both are essentially detecting the coagulation process in the reaction system. In comparison, each has its own advantages and disadvantages (Geens T, et al, 2015; Lefkowitz JB, et al, 2000). The optical method theoretically has higher sensitivity compared to the magnetic bead method, as the latter requires a higher degree of coagulation to obtain the detection endpoint. Therefore, the optical method may have a more sensitive detection linearity for samples with low coagulation. However, the detection characteristics of the optical method determine that it lacks sufficient anti-interference ability for clinical samples with higher turbidity, such as chyle and lipemic samples, whereas the magnetic bead method avoids interference caused by sample turbidity by measuring the viscous elasticity of the reaction system through mechanical principles (Jilma-Stohlawetz Petra, Lysy Katharina, Belik Sabine et al, 2019).

Viscoelastic testing (VET) of coagulation function (Carll T & Wool GD, 2020) is a type of coagulation function detection system based on whole blood samples. It activates the coagulation mechanism of ex vivo samples using different activators, continuously monitoring the shear modulus, resonant waves, and other parameters throughout the process of the reaction system transitioning from a liquid state to a gel state (which may include the gel state reverting back to a liquid state due to fibrinolysis). Through algorithms, the overall state of the coagulation function of the reaction system is obtained. Currently, there is a rich variety of systems based on viscoelastic testing, including thromboelastography detection systems connected to rotating shafts or suspended wires with thrombus elasticity graphs, as well as systems using acoustic wave detection for resonant testing. VET testing systems can effectively assess the activation time of procoagulants, platelet and fibrinogen levels (count and function), and also have the ability to evaluate fibrinolysis. However, VET testing systems are not

sensitive to the natural anticoagulant system.

Taking thromboelastography as an example of a viscoelastic experiment, thromboelastography (Salooja N & Perry DJ, 2001) is a detection platform based on whole blood coagulation for VET. It can output parameters such as R-time, which reflects the activation time of coagulation factors, K-time and α-angle, which reflect the rate of clot formation, and MA, which can largely reflect the interaction between platelets and fibrinogen in the clot. Through the output of the coagulation index CI, it can effectively comprehensively evaluate the overall coagulation function of the patient being tested. As a comprehensive and strong coagulation function detection platform, thromboelastography can achieve an activated coagulation detection mode that reflects the overall coagulation process, a detection mode for platelet aggregation via the arachidonic acid pathway and adenosine diphosphate pathway inhibition rates, a heparin clearance comparison experiment mode to reflect the efficacy of heparin therapy, a fibrinogen function detection mode, and an activated coagulation detection mode that speeds up the reaction process by adding tissue factor. This makes thromboelastography have a wider range of applications in clinical coagulation function detection.

Thromboelastography (TEG) constructs a cell-based coagulation function analysis system by activating the coagulation mechanism of whole blood samples and continuously monitoring the viscoelasticity during the clotting process. Theoretically, it is more in line with the cell-based model of coagulation mechanism (Ho KM & Pavey W, 2017; Ho KM & Pavey W, 2017; Smith SA, 2009) as the blood cells are fully involved in the reaction process. This reaction system fulfills the three main stages of the cell-based model of coagulation mechanism, including the activation process mainly carried out by “TF-bearing cells,” the amplification and propagation process carried out by platelets as the core reaction-carrying cells. However, currently, there is no clear research indicating that thromboelastography as an in vitro experiment can truly and completely reflect the cell-based coagulation mechanism in vivo.

Moreover, thromboelastography not only detects the coagulation activation process, but also provides more comprehensive and effective information for assessing clot formation ability by measuring the degree of clot formation and the viscoelasticity of the sample after coagulation. The actual strength of clot formation through the interaction between platelets and fibrinogen, as well as the rate of clot dissolution by fibrinolytic enzymes, can reflect a more comprehensive and systematic coagulation function status, which is valuable for clinical evaluation of coagulation function.

Compared to the traditional coagulation function analyzers that output PT and APTT as the most commonly used clinical coagulation functional testing parameters, research has shown (Shaydakov ME, Sigmon DF & Blebea J, 2024; Chee YL, 2014; Adcock DM & Gosselin RC, 2017; Thom I, Cameron G, Robertson D & Watson HG, 2018; Frendl G, 2019) that they have significant limitations. The fundamental reason lies in the fact that PT and APTT are based on the coagulation cascade theory, which has certain flaws (Smith SA, 2009). For example, when the body lacks FXII, the test results may indicate prolongation, but patients generally do not exhibit a bleeding tendency. When there is a deficiency of endogenous coagulation factors FVIII and FIX, the body may experience severe bleeding, but the exogenous coagulation pathway does not contribute to hemostasis. Additionally, there is often a delay before the explosive generation of thrombin.

Another study has shown that thromboelastography, as a whole blood reaction system, can to some extent more fully reflect the impact of the immune environment’s multi-system interactions on the coagulation mechanism (Swanepoel AC, Nielsen VG & Pretorius E, 2015). Thromboelastography has certain application value and advantages in the field of coagulation function diagnosis in sepsis (Samuels JM, Moore HB & Moore EE, 2018). However, in China, thromboelastography is mainly used to guide coagulation function testing for transfusion and related medication (Maier, Cheryl L., Sniecinski & Roman M, 2021; Bolliger D, Seeberger MD & Tanaka KA, 2012).

1) Despite the advantages of thromboelastography in principle, compared to coagulation analyzers, it still has many clinical application limitations, such as:
2) Compared to coagulation analyzers, the clinical diagnostic guidelines and standardized diagnostic systems constructed by thromboelastography still need further development.
3) Long testing time. The complete testing process of thromboelastography takes approximately 1-2 hours continuously, and even when using the maximum amplitude (MA) value as the output parameter endpoint, the testing time still exceeds 20 minutes. Although the use of tissue factor-activated clotting test improves the testing speed, it cannot measure the clotting activation time (R value), limiting its clinical application. Therefore, its use is relatively limited in China.
4) Currently, thromboelastography is mostly used with semi-automatic machines, which have complex manual operations and low throughput. Platelet testing requires the simultaneous testing of 3-4 cups, resulting in low testing efficiency and difficulty in meeting the demand for multi-point monitoring.

5) The currently available fully automated thromboelastography platforms on the market still face issues such as large size, heavy weight, and limited throughput, which fundamentally do not overcome the clinical application limitations of thromboelastography.

6) Traditional suspension wire method of thromboelastography is heavily influenced by horizontal factors, while the new testing principles used in high-throughput fully automated thromboelastography have not yet been widely validated clinically, and their accuracy needs further refinement in clinical diagnosis.

ACT Function Analyzer: The output parameter of the ACT function analyzer (Horton S & Augustin S, 2013) is the activated clotting time (ACT). Its testing principle involves collecting whole blood samples, which are activated by white clay or diatomaceous earth as the activator of the coagulation mechanism (intrinsic coagulation pathway) through sample contact, and the sensor detects the sample coagulation time, which is the ACT measurement result. The advantage of the ACT function analyzer is that, compared to traditional coagulation analyzers, its testing principle is similar to the activated partial thromboplastin time (APTT), but the ACT function analyzer uses whole blood samples, which are theoretically closer to the cell model of the coagulation mechanism. Compared to thromboelastography, although ACT only reflects the process of coagulation activation, which is similar to the ACT of the activated clotting test, and clinically similar to the R-time of the activated clotting test, its testing speed is faster and more suitable for the clinical point-of-care testing scenario. Therefore, most clinical ACT function analyzers have a small size and simple operation, and ACT testing is widely used in scenarios such as heparin medication, surgery, and extracorporeal circulation. Regarding heparin medication, although APTT is also used as a monitoring index, ACT has greater advantages in high-dose heparin medication situations (Wehner JE, et al, 2020, Liu Y, Yuan Z, Han X, Song K & Xing J, 2023; Simko RJ, Tsung FF & Stanek EJ, 1995). Therefore, in situations such as CPB and ECMO that require high-dose heparin application, ACT is often used as the core coagulation function monitoring index to assist anticoagulation treatment. Although ACT is widely used in monitoring heparin anticoagulation treatment, it is not fundamentally a heparin medication monitoring index. Its essence is still a systemic manifestation of coagulation function, and therefore, ACT has many interfering factors in heparin medication monitoring, which also leads to the actual correlation between ACT and heparin is not high (Cunningham D, Besser MW, Giraud K, Gerrard C & Vuylsteke A, 2016; Bode AP & Lust RM, 1994). From another perspective, even if there is the same ACT target point, the starting dose of heparin in extracorporeal circulation varies greatly among different institutions (Shibasaki M, et al, 2010). From the perspective of testing platform design, the current ACT function analyzers basically adopt a design that is more suitable for clinical departments rather than laboratory centers. The positioning of ACT is also often positioned as a clinical point-of-care device and is widely used in ICU, operating rooms, and other clinical scenarios.

5. Interference of Coagulation Functional Testing System

Compared to other clinical tests, the interference system of coagulation function testing is more diverse and complex (Winter WE, Pittman DL & Harris NS, 2023). Even though coagulation function testing has a complete quality control process, it cannot achieve the same level of excellence in terms of improving the accuracy of individual institutions' test results and the consistency of test results among institutions, as other types of testing (Plebani M, Sanzari MC & Zardo L, 2008).

Research has shown (Lippi G, et al, 2006) that rapid coagulation function testing can improve its accuracy (Boldt J, et al, 1998; Sahli SD, et al, 2020; Despotis GJ, Joist JH & Goodnough LT, 1997), and the fundamental reason for this is the limitations of the coagulation function testing technology system, which mainly lie in the diversity and complexity of interfering factors in traditional coagulation function testing systems.

Interference from the sample. Coagulation function testing mainly uses sodium citrate anticoagulant samples. The collection of sodium citrate anticoagulant samples requires high standards because the citrate in the blood collection tube must be in an appropriate proportion with the sample to ensure the accuracy of the test results. Too little sample, excessive anticoagulation, or sample dilution can lead to test result deviation. Conversely, too little sample can result in insufficient anticoagulation, which can also affect the test results. The anticoagulation principle of sodium citrate mainly relies on its chelation with calcium ions in the sample, which interrupts the coagulation cascade process because of the absence of calcium ions. However, it should be noted that sodium citrate anticoagulation only interrupts the coagulation cascade rather than completely inhibiting the coagulation mechanism. Coagulation factors can still be activated for various reasons and lose their activity over time. The collection of coagulation function testing samples involves the separation of blood from the body, whether it is from the median cubital vein, fingertip blood collection, or sample collection in extracorporeal circulation. These involve the formation of trauma or contact with foreign bodies, which can activate the coagulation mechanism. Therefore, the stability of coagulation function samples is much lower than that of samples from other tests, and this stability gradually decreases with time. Studies have shown that the results of PT, APTT, and FIB testing samples, regardless of whether they are stored at room temperature or refrigerated, will change continuously

with time (Plebani M, Sanzari MC & Zardo L, 2008).

Research has found (Clinical and Laboratory Standards Institute, 2008; Ren TY & Zheng L, 2014; Harms CS, 1982) that ex vivo coagulation function samples can experience a decrease in the accuracy of test results due to changes in the environmental conditions they are exposed to. Factors such as pH value, temperature, contact surfaces, mechanical changes, etc., can all lead to changes in coagulation function test results. For example, when performing APTT testing on a coagulation function analyzer, the test results can be influenced by the pH value. If an uncovered sample causes an increase in pH value due to the release of carbon dioxide, the test results will be altered. Studies have shown that for every 0.8 increase in pH value, APTT will be extended by approximately 20 seconds. Additionally, when a sample undergoes centrifugation and the plasma is directly exposed to air, the increase in pH due to the release of carbon dioxide will be even more pronounced.

Interference from the testing platform: As mentioned earlier, the stability and accuracy of coagulation function test results depend on the stability of the hardware and reagents of the testing platform. Testing systems that use clotting time as the result generally lack a traceable calibration system and are difficult to control for quality. This means that changes in the expiration date of reagents after opening may directly affect the accuracy of test results, especially prominent in multi-dose reagents. Additionally, during the instrument testing process, environmental interference factors such as voltage fluctuations and vibrations affecting the hardware will also be directly reflected in the results.

"Vector nature" of systematic result errors: The so-called "vector nature" is reflected in two aspects: "direction" and "degree". Due to the cascading amplification effect of coagulation function, the coagulation function in the body may rapidly change and cause functional disorders and systemic disruptions due to various pathological factors. In contrast, ex vivo samples undergo changes in their coagulation properties over time due to environmental changes and the activation of coagulation mechanisms during the sampling process. This ultimately results in increasing errors between ex vivo samples, which should accurately reflect the body's coagulation function status, and the body's coagulation status over time. This is determined both by the continuous changes in the body's coagulation function over time due to pathological factors, and by the continuous changes in ex vivo samples over time due to environmental interference.

Therefore, the accuracy of clinical coagulation function testing not only needs to ensure the stability and reliability of the testing platform and reagents, but also a fast and convenient testing system is an effective guarantee of accurate results.

6. A Rapid Coagulation Detection System Equipped with Microfluidic Chips

The coagulation function detection platform built by microfluidic technology is widely used in clinical testing due to its unique technological advantages (Jigar Panchal H, Kent NJ, Knox AJS & Harris LF, 2020).

The detection platform built by microfluidics technology is also known as Lab on a chip (LOC) or micro Total Analytical System. The biggest advantage and feature of microfluidic chip technology is that many technical units and processes can be connected through microfluidic channels, achieving flexible combination and large-scale integration on the micro platform, which can be fast, automatic, high-throughput low cost local detection of biological and chemical indicators to achieve complex functions of a complete laboratory. Due to its small size, microfluidic chip detection only requires processing extremely small amounts of fluid, which can greatly save expensive biochemical detection reagent costs (Kulkarni MB, Ayachit NH & Aminabhavi TM, 2022; Whitesides GM, 2006).

Essentially, microfluidic technology builds a reaction platform for the detection of coagulation function, which involves mixing and processing various components in the reaction system through microfluidic technology, integrating them into a specially designed fluid channel chip system with micrometer to nanometer scales. Finally, the reaction is carried out at specific positions on the chip, and the reaction process is detected by a biosensor detector to obtain detection results. Coagulation function testing, whether it is coagulation function testing or coagulation related biomarker testing, can be achieved through microfluidic technology on micro nano scale chips (Jigar Panchal H, Kent NJ, Knox AJS & Harris LF, 2020).

Microfluidic technology is very suitable for the needs of coagulation function detection (Ziółkowski R, et al, 2021). Through microfluidic technology, coagulation function, platelets, and various coagulation related drugs can be detected. The entire detection process can be controlled through the design of microfluidic channels, which can further achieve the construction of dynamic or static detection systems.

The biggest advantage of the coagulation function analyzer equipped with microfluidic technology is that it achieves miniaturization and convenient system construction. Because the coagulation function reaction system is concentrated in the microfluidic chip through the construction of microfluidic chips, the reaction process often only requires simple operations, and only a detection mechanism with biosensors needs to be constructed to achieve the output of detection results. Therefore, the detection platform can be reduced to the size of handheld

devices, and the diversification of detection principles or sample preprocessing achieved through microfluidic chips, the coagulation analyzer equipped with microfluidic chip technology can not only detect plasma, but also directly detect whole blood. These advantages in details enable clinical departments with very limited detection conditions to improve both detection efficiency and accuracy, ensuring the timeliness and accuracy of clinical diagnosis.

7. Detection Methodology for Microfluidics

Electrochemical detection (Matsumoto Y, Fujita T, Fukushima S, et al, 2018; Gkouziouta A, Aravanis N, Zarkalis D, et al, 2019; Hawkins B M, Ventresco C, Hellinger A, et al, 2020; van den Heuvel J K, Kena N, van Hattum T et al, 2019): The principle of that mainly involves the blood sample entering the microfluidic coagulation function analyzer equipped with electrochemical detection. The blood sample binds with reagents and initiates a reaction, leading to the generation of thrombin in the reaction system. Thrombin then decomposes the substrate in the chip, producing electroactive compounds that generate an electrochemical signal. The instrument records the time from the start of measurement to the first appearance of this signal and converts it into corresponding parameters for the coagulation function detection results through built-in algorithms. This method is widely used for routine monitoring of patients undergoing anticoagulant therapy, such as those after heart valve replacement surgery. The main drawback of electrochemical detection is that its principle is based on the generation of thrombin rather than the production of cross-linked fibrinogen, which is the endpoint product of coagulation function. This fundamental difference in detection systems from the mainstream methods used in clinical practice for coagulation function testing platforms makes it challenging to ensure consistency in the detection results.

Dynamic current method: The detection principle used is similar to electrochemical methods. In a specific area of the microfluidic chip, there is a silver plated ion electrode. The blood sample flows through the reaction zone and mixes with the reagent before finally flowing into the electrode zone; As blood coagulates, its resistance gradually increases, and the starting and ending points of the reaction are calculated by detecting the current at both ends of the electrode. This method has been widely used in anticoagulant therapy monitoring in recent years due to its convenient operation and relatively low cost (Zhu S, et al, 2015).

The mechanical optical method (Yu SJ, Guo Y & Tang L, 2010) uses a detection technology based on optical detection, but its principle is very different from the mainstream optical detection system of coagulation method. Its detection principle is that when the blood sample enters the microfluidic chip of the microfluidic coagulation function analyzer equipped with electrochemical method, the blood sample combines with the reagent and begins to react. The coagulation cascade of the reaction system starts, and the viscosity of the blood sample changes, causing changes in the flow behavior of microfluidics that were originally in a flowing state in microfluidic capillary circuits. Record the behavior changes of blood samples flowing back and forth in the test channel through LED optical detection, and ultimately form a solidification curve. One of the advantages of mechanical optics lies in the construction of microfluidic channels, which endow the reaction system with a certain “dynamic blood flow” mechanical structure, reflecting that the blood samples flowing during the process are to some extent closer to the coagulation mechanism of blood dynamics in human blood vessels.

Limitations of microfluidic coagulation analyzers: At present, most microfluidic coagulation function testing platforms have the problem of having fewer testing items. The vast majority of microfluidic coagulation function detection platforms can only achieve PT detection (including INR detection) and APTT detection, and some can achieve detection of TT, FIB, and ACT. However, based on clinical testing needs, coagulation biomarker detection and other immune items such as inflammatory factors and myocardial indicators that have joint detection value with coagulation function indicators may be more attractive for clinical applications if they can achieve joint detection.

Meanwhile, like traditional coagulation analyzers, microfluidic technology coagulation detection platforms also have common issues with traditional coagulation analyzers - significant differences in detection results, which are a common product of physiological and pathological factors of coagulation function and limitations of detection technology. Furthermore, due to the differences between the detection methodology used in the coagulation detection platform constructed by microfluidic technology and the commonly used detection methodology in the laboratory, this often leads to poor consistency in the detection results of different detection systems for the same project, The issue of consistency in test results has become an important issue and urgent issue that is constantly being discussed and addressed in the standardization and normalization of clinical laboratory testing (Cai PP, Zhang W, Zhou LQ, et al, 2018; Fan HY & Lu HX, 2019; Yu SJ, Guo Y & Tang L, 2010), as chaotic and even erroneous test data greatly interfere with normal clinical diagnosis (Cai PP, et al, 2018; Wilkieson TJ, Ingram AJ, Crowther MA, et al, 2011).

Disc centrifugal microfluidic coagulation function detection chip (Yin YP, Yang XC & Xue J, 2012; Huang XB, Li SY, Wang X, Sun Y & Jiang H, 2013; Lin JJ, Fan H, Chen LX, et al, 2015): Its main feature is to

construct microfluidic channels at the micrometer to nanometer level on a disc-shaped microfluidic chip, and use centrifugation to achieve liquid separation and whole blood plasma separation, so that it does not require additional pre-treatment steps for sample centrifugation separation. At the same time, the most widely used optical coagulation detection system is adopted, maintaining methodological consistency. The disc microfluidic chip stores the mainstream coagulation function detection platform and a centrifuge at the size of a palm, achieving both POCTization of the mainstream coagulation function analyzer and multi technology integration of POCT coagulation function analyzer, i.e. synchronous detection of different detection methods on the same platform. At the same time, the disc chip used further reduces the optical distance of the reaction system to the level of 1mm due to its nanoscale microfluidic system. Compared with other microfluidic chips, disc microfluidic chips have the ability to centrifuge and separate whole blood samples due to their structural advantages. On this basis, disc microfluidic technology can directly carry detection methods consistent with laboratory tests, which is more conducive to building a diagnostic system for consistency between clinical and laboratory coagulation function test results (Lin CH, et al, 2015).

The centrifugation function of the disc-based microfluidics has potential advantages in the detection process. Research has shown that the sodium citrate has an important anticoagulant mechanism in anticoagulated samples, due to its acid-base buffering effect that maintains the pH value of the sample between 7.30-7.45. However, in vitro samples lose their buffering effect on Hb after centrifugation, leading to easier changes in sample pH (Clinical and Laboratory Standards Institute, 2008). Experimental results have shown that uncovered in vitro samples after centrifugation experience an increase in pH within 30 minutes due to the release of CO2 (Ren TY & Zheng L, 2014). Studies have demonstrated that a pH increase of 0.8 units will prolong the APTT detection result by approximately 20 seconds (Harms CS, 1982). Therefore, centrifugation of the whole sample is not conducive to sample waiting and retesting consistency, while the on-board centrifugation of the disc-based chip effectively achieves segmented centrifugation of the sample, allowing the in vitro sample in the collection tube to remain uncentrifuged.

1) Research has shown that coagulation factors are more sensitive to temperature. After a period of storage at high temperatures of 58 ℃, all coagulation factors in the ex vivo samples become inactive, while platelets are easily activated and undergo release and aggregation at low temperatures, thereby affecting coagulation factors. Further research has confirmed that this temperature affected property is further strengthened after centrifugation (Shaoxing Pushkin Biotechnology Co., Ltd. 2018), thereby affecting the storage quality of ex vivo samples, Therefore, it is not conducive to the consistency of sample waiting and re-examination. The disk chip in machine centrifugation system can solve the problem of unfavorable preservation of in vitro samples by achieving segmented centrifugation of in vitro samples.

2) The microfluidic disc chip has a light distance as low as 1mm, which can make high turbidity samples such as chyle and lipid blood samples have stronger transparency in reaction systems with thinner optical paths (thickness). Therefore, it can effectively avoid the interference of detection results caused by sample turbidity, while maintaining the sensitivity of optical detection for low coagulation samples.

3) Through the integration of upper level detection technology and the construction of nanoscale microfluidic channels, an integrated POCT detection platform can be achieved for coagulation function, thromboelastography, coagulation biomarkers immune markers, and even molecular diagnosis.

8. Conclusion and Outlook

On the one hand, coagulation dysfunction is an important cause of serious injury or death to patients in clinical practice (Ding T & Zhou X, 2021). At the same time, the use of coagulation related drugs or blood products is a double-edged sword. While ensuring its efficacy, it is more necessary to prevent adverse reactions caused by excessive use.

On the other hand, coagulation dysfunction often occurs in critical illnesses, as the process of coagulation mechanism is divided into “initiation, amplification, and amplification”. Therefore, coagulation dysfunction often develops rapidly, and the timeliness of coagulation function testing is very important. The more critical reason is the collection method of coagulation function testing samples, as well as the exposure of samples in the external environment, which leads to continuous changes in sample testing results over time, this results in a vector property error between the coagulation function in the internal environment and the results of in vitro sample detection. Therefore, the timeliness of coagulation function detection is largely a guarantee of accuracy. Coagulation function testing technology is advancing rapidly.

In terms of testing items, whether it is coagulation function testing or coagulation function related biomarkers, the types of items available for clinical selection and reference are becoming more and more comprehensive. From the perspective of the integrity of coagulation mechanisms, a reasonable combination of coagulation function testing and coagulation biomarker testing is needed, the systemic overall state of coagulation function

reflected by functional indicators and the detailed information reflected by various coagulation function related biomarkers can construct a more comprehensive overall information of coagulation function, providing more complete and reliable detection results as diagnostic basis and drug efficacy and side effect evaluation for clinical diagnosis. Meanwhile, traditional coagulation function indicators can provide stable and reliable results for clinical practice, while new coagulation function biomarkers such as coagulation viscoelasticity detection systems based on cell model coagulation mechanisms can further provide more diagnostic value information for clinical diagnosis.

From a technical perspective, mature coagulation function testing technology has achieved centralized processing and detection of large quantities of coagulation function samples in the central laboratory of the laboratory. With the continuous development of microfluidic technology over the years, the POCT coagulation function testing platform based on microfluidic technology has been widely used for rapid detection in clinical departments by fully leveraging its advantages, this is not simply a demand created by the application of technology in clinical practice, but rather a result of clinical demand reacting to technological research and development. Undoubtedly, the timely demand for rapid detection of coagulation function in clinical practice is essentially based on the diagnostic need for coagulation function to accurately reflect the patient's coagulation function status, and ultimately this demand will not be limited to routine coagulation function testing, The demand for more systematic multi project joint detection, especially convenient, fast, and efficient detection of coagulation function related biomarkers, may be an important direction in the future. Therefore, the future market demand for coagulation testing is likely to gradually establish a demand for rapid diagnosis in clinical settings and a demand for centralized coagulation function screening in central laboratories.

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