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Research Progress on the Causes and Mechanisms of Ischemic Stroke

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Abstract: Ischemic stroke (CIS) is a general term for cerebral vascular occlusion and other causes of insufficient blood supply and necrosis in brain tissue, and is a common acute cerebrovascular disease with a complex pathogenesis, mostly related to blood circulation and inflammatory response induced by oxygen free radicals. The pathogenesis of this disease has many subtypes and is prone to a variety of complications and sequelae, which significantly reduces the quality of life of patients. Chinese medicine has unique insights into CIS, and has the characteristics of personalized and multi-targeted treatment by guiding treatment through theories such as key points of identification as well as differentiation and treatment. According to TCM, the main causes and mechanisms of CIS are old age and weakness, internal injury and accumulation of damage, emotional stress, fire and wind, phlegm and turbidity, heat and wind, and sudden changes in climate and blockage of qi and blood. Most of the blame is on qi, blood, deficiency, wind, phlegm, fire and stasis. Secondly, it is also necessary to define the meridians and internal organs, the acute, recovery and post-acute periods, the closed and decompensated periods, and the oblique and rebellious phases of the disease. CIS is located in the brain and is closely related to the heart, liver, spleen and kidney. We need to combine the holistic concept of Chinese medicine and the identification of internal organs to improve clinical efficacy by treating patients according to their conditions. Therefore, the aim of this paper is to identify the etiology, pathogenesis and disease of CIS in order to provide a theoretical basis for clinical diagnosis and treatment.

1. Introduction

Cerebral ischemic stroke is a common disease characterized by brain tissue ischemia, hypoxia, and necrosis. Its signs and symptoms include sudden numbness or weakness in the arms or legs, facial drooping, difficulty speaking or understanding, confusion, problems with balance or coordination, and vision loss[1]. CIS can be classified into three pathological types based on the mechanisms of local brain tissue ischemia and necrosis: cerebral embolism, hemodynamic mechanisms, and cerebral infarction caused by cerebral thrombosis. The first two account for about 80%-90% of all acute ischemic strokes, while local brain tissue hypoperfusion due to hemodynamic factors accounts for

10%-20%[2]. With improved living standards, less physical activity, and increased life stress, the incidence of CIS is rising. Severe cases can threaten life, and some patients may suffer sequelae, lowering their quality of life and increasing economic burden. Modern medical treatment for CIS mainly includes general management, blood pressure and blood sugar control, oxygen therapy, and nutritional support. For patients within a treatment window, intravenous thrombolysis or thrombectomy may be applied, along with antiplatelet therapy, anticoagulation, neuroprotection, and Chinese medicine or acupuncture treatment. However, there are issues with unstable efficacy, potential worsening of the condition, and increased risk of complications like bleeding. In traditional Chinese medicine (TCM), CIS falls under the categories of “stroke” and “partial paralysis.” TCM offers multiple treatment targets, a holistic approach, and personalized treatment plans based on syndrome differentiation, which can be advantageous for stroke management. This article reviews TCM understanding of CIS, summarizing its causes, mechanisms, affected areas, and risk factors. It also discusses treatment strategies based on organ pattern differentiation and acupuncture meridian theory, aiming to provide a theoretical basis for clinical diagnosis and treatment.

2. The causes and mechanisms of CIS

2.1 Theory of internal injury accumulation in the elderly and weak

Traditional Chinese Medicine (TCM) believes that CIS is mainly caused by an imbalance of yin and yang, and the disordered flow of qi and blood affecting the brain. It is more common in middle-aged and elderly people. According to 'Zabing Yuanliu Xizhu - Zhongfeng Yuanliu': 'When people reach fifty or sixty years old, their qi and blood decline, and they may get a stroke.' The onset of CIS often involves various risk factors such as long-term high blood pressure and high blood sugar, which can act together[3]. Middle-aged and elderly people's lifestyles and diets are relatively stable; diets high in salt and oil, along with little and short-duration exercise, can damage the body's organs and cause high blood pressure, and long-term exposure forms CIS risk factors. Wei Julin[4] and others conducted a retrospective study of middle-aged and elderly CIS patients, evaluating their MRI, MRA, and risk factors compared to younger patients, and found that acute CIS in older patients involves more intracranial blood vessels and a larger affected area, with higher degrees of atherosclerosis and higher rates of arterial narrowing than in younger patients. Older patients also have a higher frequency of lacunar infarction and worse prognosis, often leaving mild to severe limb movement disorders or difficulties with speech and swallowing. The study also found that older people often have more complex underlying conditions, and the risk factors for CIS are commonly seen in diseases and unhealthy habits typical in older adults, such as high blood pressure, diabetes, smoking, high homocysteine, and family history of high triglycerides. Research by Liu Shanshan and others shows that CIS in older adults is mainly lacunar infarction, with hypertension as the primary risk factor to address[5]. On MRI, lesions are often located in the basal ganglia, and transcranial Doppler ultrasound shows significantly increased blood flow velocity in the anterior and middle cerebral arteries, with carotid plaques much higher than in healthy people. Therefore, with more underlying diseases, weaker organ function, and insufficient vital energy to resist pathogens, older adults can reduce the risk of CIS by controlling blood pressure and sugar, maintaining good lifestyle and diet habits, and reducing long-term exposure to and the combined impact of risk factors, offering new directions for clinical prevention and treatment.

2.2 Emotional injuries turn fire into wind

The onset of disease usually comes from external factors like the six excesses, internal injuries from the seven emotions, or other internal and external causes. Joy, anger, worry, thought, sadness,

fear, and shock can each harm the body on their own or work together to cause illness, leading to imbalances in the organs. The 'Su Wen: Treatise on Vital Energy Connecting to Heaven' says, 'If one gets extremely angry, the body's energy will be cut off, and blood will rush upward, causing fainting.' Of all the seven emotions, anger harms the liver most easily, leading to liver qi stagnation, poor blood flow, and blockage of the brain's channels; or yin deficiency with excessive liver yang; or excessive heart fire causing blood to rebel upward and disturb the spirit. When emotions are too intense or last too long, far beyond normal experiences, it's called excessive five emotions, which can disrupt the flow of qi and blood in the body. Sudden emotional swings are a main trigger, with the disease mechanisms mainly involving excessive heart fire, kidney deficiency, or imbalance of yin and yang[6]. During the Jin and Yuan periods, the cause of stroke began to focus more on internal wind. Liu Wansu believed that strokes were mostly caused by extreme emotions (joy, anger, thought, sadness, fear), rather than 'external wind.' Anger affects the liver; patients who get easily irritated and have uncontrolled emotions will have liver qi stagnation. Over time, this transforms into heat, generating wind and depleting liver yin, and since yin can't control yang, internal wind forms, disturbing the clear orifices and resulting in stroke. Excessive joy affects the heart; if it goes too far, it excites the heart fire, causing qi and blood to reverse into the brain, triggering a stroke. Worry affects the spleen; excessive thinking leads to qi stagnation, which stops blood flow, eventually forming blood stasis that can rise and block the brain's channels, inducing stroke. Long-lasting sadness and worry affect the lungs; they subtly consume heart yin, depriving the heart of nourishment, damaging vital energy, and disrupting lung functions, producing pathological factors like phlegm that increase stroke risk. Stroke patients also often have sleep problems, irritability, and anxiety[7]. Therefore, it's important to help patients manage their emotions, calm liver wind, promote qi and blood circulation, as well as use psychological, verbal, and music therapy to relax them. Keeping patients happy is key in treating emotional triggers of CIS.

2.3 Phlegm and dampness build up inside, turning into heat that causes wind

Phlegm pathogens often cause disease by obstructing the flow of qi and blood, affecting the metabolism of body fluids throughout the body, and easily clouding the mind. Treating this type of disease is quite broad and varied. The 'Tangtou Gejue: Mengshi Guntan Wan' says, 'Many diseases are caused by mischief from phlegm.' The 'Clinical Guide Cases: Stroke' states, 'Excessive alcohol and meat consumption in the past brings heat and wind, causing illness.' Overeating rich foods can easily lead to a weak spleen, which can't properly transport nutrients, causing dampness to accumulate and produce phlegm; prolonged stagnation may transform into heat. Excessive liver activity can affect the spleen, producing damp-phlegm internally; liver fire can dry fluids into phlegm, which then blocks the orifices leading to stroke. Zhu Danxi believed that stroke often involves blood deficiency complicated by phlegm, aligning with Liu Wansu's 'internal wind' theory; treatment should first address the phlegm, then nourish and invigorate the blood. The principles of 'fluids and blood have the same origin' and 'phlegm and stasis have the same source' indicate that phlegm turbidity often obstructs qi movement, affecting fluid distribution and leading to phlegm formation. Since phlegm and blood stasis are both yin pathogens, they are prone to causing clumping, disrupting the flow of qi and blood, and ascending to the brain[8]. Buyang Huanwu Tang, created by Wang Qingren in the Qing Dynasty, can activate blood, remove stasis, and nourish blood to unblock channels. Modern pharmacological studies show that Buyang Huanwu Tang can dilate blood vessels, inhibit platelet activation and clear free radicals, improve ischemia-reperfusion injury, and aid in neuron repair[9]. Phlegm-dampness is a yin pathogen that can transform when warmed; studies show that Banxia Baizhu Tianma Tang can significantly improve neurological functions in patients with phlegm-damp stroke[10]. A systematic review indicates that Mingluo Chengqi Tang can enhance the daily living

abilities of patients with phlegm-heat and organ-fullness syndrome and improve hemodynamics and systemic inflammation[11]. Using methods to resolve phlegm and remove blood stasis can help alleviate symptoms and signs in CIS patients, offering a path for CIS treatment.

2.4 Sudden changes in the weather are causing blood and energy to get blocked

In elderly people who are frail, with stagnant qi and blood, accumulated phlegm and dampness, and imbalance of yin and yang, sudden changes in climate can cause external wind to invade. The cold makes the blood coagulate, qi and blood circulation is hindered, and the primordial spirit is unnourished. The “Treatise on Cold Damage and Miscellaneous Diseases” says: 'When the pulse at the inch position is floating and tight, tightness indicates cold, floating indicates deficiency; cold and deficiency attack each other... When evil enters the bowels, one becomes unrecognizable; when evil enters the organs, speech is difficult, and saliva is expelled from the mouth.' Yan Yonghe pointed out that 'internal deficiency causing stasis leads to stroke.' The “Golden Chamber” states: 'If the capillary blood overflows, the meridians retain blood; if the blood is stasis, it leads to stroke.' Ren Jixue believes the mechanism of stroke is 'reverse disorder of qi and blood, and phlegm-stasis accumulation,' and clinically, promoting blood circulation and removing stasis is commonly used to treat CIS[12]. Traditional Chinese medicine for blood stasis often uses safflower, leech, and notoginseng to reduce blood viscosity, decrease platelet aggregation, and promote new blood formation. Modern pharmacological research confirms that these blood-activating and stasis-removing drugs can dilate blood vessels, improve microcirculation, thin the blood, and reduce clot formation[13]. Therefore, sudden climate changes are considered an external pathogenic factor, and when it seriously affects the organs, it can cause confusion or unclear speech. Early detection and removal of the pathogenic factor is key to treatment. Qi and blood disorder with blood stasis ascending to the brain can block cerebral circulation, slow or even obstruct blood flow, causing local ischemia and hypoxia necrosis of brain tissue, resulting in serious consequences. Using remedies that move qi, invigorate blood, and remove stasis can reduce platelet aggregation and thin the blood, making it very necessary for treating CIS.

3. Syndrome differentiation and treatment of internal organs

3.1 Treating based on the brain theory

The brain is one of the extraordinary organs, formed by the convergence of marrow, and is also called the 'sea of marrow.' In the 'Ling Shu: On the Sea,' it is believed that 'when the sea of marrow is insufficient, it can cause symptoms such as dizziness, tinnitus, leg weakness, blurred vision, and lethargy.' Wang Ang of the Qing Dynasty recorded in 'Bencao Beiyao' that 'a person's memory all lies in the brain,' emphasizing the brain's role in thinking and memory. Wang Qingren believed that the brain can regulate sensory functions like memory, vision, hearing, smell, and speech, and pointed out that 'the mind and memory are not in the heart but in the brain.' The brain plays an important role in a person's life, spirit, and sensory activities. It is linked with the Du meridian and the Foot Jueyin Liver meridian, and participates in vision, hearing, and thinking. According to TCM's Zangxiang theory, thinking belongs to the heart and is classified under the five organs, so treatments for brain-related diseases often start from the five organs, especially the heart, which is closely related to the pathogenesis and treatment of CIS. The heart governs the mind; if the heart's spirit is sufficient, the brain is nourished. The liver stores the soul; when the soul is in its place, a person can perform normal life activities. The spleen stores intention, which helps generate ideas. The lungs store the corporeal soul, governing instincts and controlling movement. The kidneys store wisdom, enabling proper thinking and rational analysis. If the functions of the five organs are abnormal, this affects the brain's

normal function and leads to abnormal life activities. The fundamental pathogenesis of CIS lies in brain dysfunction, which is closely related to the physiological function of the five organs, phlegm, fire, and wind, so treatment is based on principles like opening the orifices, calming wind, resolving phlegm, and clearing the bowels. Research by Chen Jianhua et al. showed that Binghuang Wuling San can improve brain edema in rats with middle cerebral artery occlusion, thereby protecting neurological function[14]. Huang Lina et al. found that multiple active ingredients such as naphthofuran lactones in the Yinao Tongluo formula can act on multiple targets and activate multiple pathways, playing anti-apoptotic roles in CIS treatment[15]. Pu Fang et al. demonstrated that acupuncture combined with medication can lower Hamilton Depression Rating Scale scores in patients with post-CIS depression, improve mood, and alleviate symptoms. Therefore, in CIS treatment, going from the brain as the starting point plays an important role.

3.2 Treating heart and brain together

The heart in the Five Elements belongs to fire and is the yang within yang. It governs the body's blood vessels, nourishes the internal organs, stores the spirit, and regulates a person's mental and cognitive activities. The heart is the 'main master of the five zang and six fu organs,' holding the primary position among the body's organs. The 'Lei Jing' says, 'When worry moves the heart, the lungs respond; when thought moves the heart, the spleen responds; when anger moves the heart, the liver responds; when fear moves the heart, the kidneys respond; all emotional injuries... originate from the heart.' The heart governs the blood vessels, and blood circulates continuously in the vessels. If there is excessive blood loss, it can cause consciousness to become faint, and in severe cases, spiritual collapse. Insufficient brain marrow or pathological products like phlegm can cause blood stasis, leading to dizziness and memory decline. If heart fire is excessive, causing liver wind to stir internally, blood may rush upward, resulting in confusion and hemiplegia. If the heart is diseased and loses control over the spirit, a person may experience mental unrest, and in severe cases, delirium or coma. If febrile diseases cloud the heart spirit, it can lead to coma or convulsions. Therefore, the heart and brain are closely related physiologically and influence each other in the onset and pathology of CIS. Treating CIS from the heart-brain perspective follows the basic principle of clearing fire, unblocking the bowels, and opening orifices. Current studies have confirmed that this approach can be effective. For example, Chen Meiling's research showed that combining sublingual acupuncture with the Brain-Heart Tong capsule improved treatment outcomes in the acute phase of stroke, enhanced neurological function scores, reduced limb spasticity, and relieved clinical symptoms with high safety[16]. Liu Qun and colleagues found that heart-regulating and calming acupuncture could effectively improve Hamilton Depression Scale (HAMD) and Self-Rating Depression Scale (SDS) scores in CIS patients with post-stroke depression, reduce adverse drug reactions, and regulate serum serotonin (5-HT) and norepinephrine (NE) levels[17]. Guo Wei's research demonstrated that modified Xixin Decoction could raise Mini-Mental State Examination (MMSE) scores, adjust serum neuron-specific enolase (NSE) levels, improve mild cognitive impairment in elderly CIS patients with deficiency-stasis-toxin syndrome, enhance cognitive function and daily living abilities, improve local brain blood flow, and reduce damage to neurological functions[18]. Therefore, in treating CIS, the heart-brain theory also plays an important role.

3.3 Treatment based on the liver

The liver is one of the five viscera in the body, characterized by a yin nature and yang function. On one hand, the liver governs the smooth flow of qi throughout the body, regulates emotions, and manages blood circulation, which is why it’s considered a 'firm organ'; it prefers openness and dislikes repression. On the other hand, the liver stores blood, nourishes the body and the organs, and governs

the tendons, so when it’s in a pathological state, it affects a person’s movement. CIS can be caused by emotional damage, which generates wind and fire. The liver is closely connected to emotions, and when liver wind stirs internally or liver stagnation transforms into heat, it can produce fire and deplete liver yin. Yin can’t control yang, which leads to internal wind, disturbing the sensory orifices, resulting in stroke. Hence, liver yin deficiency is one of the pathological bases for stroke, and clinically, treatment can be based on the liver, with the principle of clearing heat and calming wind. Up to now, some studies have confirmed the effectiveness of liver-based treatments for CIS. Zhao Huan and others used Naqing Tong Decoction to improve symptoms in patients with liver-heat blood-stasis type CIS prodromes, lowering their LDL, blood glucose, uric acid, and homocysteine levels, and reducing the occurrence of CIS[19]. Zheng Wenxu found that Shugan Huoxue Jieyu Decoction could relieve depressive symptoms in post-CIS patients, achieving both physical and mental treatment with minimal side effects, widely used in clinics[20]. Wang Weixing showed that a nourishing liver and kidney and activating blood formula could improve the life and mobility of patients in the recovery phase of CIS with liver and kidney deficiency combined with blood stasis, aiding recovery[21]. Zheng Longfei confirmed that Zhen Gan Xi Feng Decoction with modifications could lower neurological deficit scores and improve daily living ability scores in acute CIS patients, showing clear clinical effects[22]. Yue Jiaojiao and colleagues found that Shugan Chi Jin Formula combined with a spasm muscle therapy device was effective in treating post-CIS limb spasms, reducing the severity of spasticity and improving vascular endothelial function[23]. Therefore, these studies highlight the significant role of liver-based treatment in CIS.

3.4 Treatment based on the spleen and stomach

The spleen and stomach are the source of the body's qi and blood production and the foundation of acquired constitution. It mainly produces the qi of the middle qi, the spleen and stomach organs, the body's vital qi, and the qi of grains. The spleen and stomach mature the grains and produce the essence and their substances, distributing them throughout the body, which is the nourishment of the body's essence from the grains. The spleen belongs to earth, governs muscles and limbs, resides in the middle burner, and can nourish heart fire; the heart is in the upper burner and can warm spleen earth. The spleen and stomach are the hub for the rise and fall of qi. Normal operation of the spleen and stomach promotes digestion and absorption of food. The spleen is the source of phlegm production, and spleen deficiency easily leads to phlegm-dampness. From 'Taiping Shenghui Fang ·Prescriptions for Treating Spleen Stroke': “When spleen qi is weak and wind pathogens take advantage of the deficiency and enter the Foot Taiyin meridian, the body becomes lethargic, excessive sweating and aversion to wind, the tongue is stiff, speech is slurred and unclear, the mouth and face are deviated, and the skin is numb and numb. The mind is drunk and drunk in thought. These are signs of spleen stroke.” “CIS can be caused by internal generation of phlegm turbidity, transforming heat into wind. Over time, phlegm turbidity accumulates into heat, and together with blood stasis, it is one of the mechanisms for the onset or worsening of CIS. Therefore, diagnosis and treatment should focus on tonifying the spleen and transforming dampness, resolving phlegm, and calming wind. Clinically, the spleen-strengthening method has shown significant efficacy in treating CIS. Li Futian et al. have shown that self-formulated Jian Pi Hua Yu Decoction for treating patients with acute atherosclerotic CIS can effectively improve serum levels of brain-derived neurotrophic factor (BDNF), thereby protecting brain nerves and enhancing motor function [24]. Li Lei et al. found that after Guipi Tang was modified and combined with paroxetine, it was effective in treating depression after heart and spleen deficiency type CIS. It could lower patients' Pittsburgh Sleep Quality Index (PSQI) and Stroke Scale (NIHSS) scores, significantly improve insomnia and neurological deficit symptoms, improve patients' Daily Living Ability Scale (ADL) scores, promote limb function

recovery, and enhance daily living abilities [25]. Zhang Shijie and colleagues have shown that Huo Pei Erzhu Drink can be aromatic, dispel odor, strengthen the spleen, dispel dampness, and remove turbidity, and is effective in treating patients with dysphagia caused by post-CIS dysphagia [26]. Wang Jia summarized Wang Chunsheng's clinical experience in treating CIS with the spleen and stomach, finding that the spleen and stomach theory can be applied throughout the entire CIS: the prodromal phase can achieve preventive measures before illness, the acute phase can prevent deterioration after illness, and the recovery phase can prevent recurrence after illness [27].

3.5 Treatment based on the kidneys

The kidneys are considered the foundation of congenital constitution, and having sufficient kidney essence promotes normal growth and development. The kidneys govern the bones, generate marrow, and are connected to the brain. CIS (Cerebral Ischemic Stroke) can be linked to aging, frailty, and internal injuries, all closely related to the kidneys, which are also closely connected to the brain. Kidney yin deficiency is the pathological basis of CIS; when kidney essence is insufficient, the brain's marrow lacks the material for biochemical processes, leading to emptiness in the brain. Kidney deficiency can also cause blood stasis, impairing the meridians, so kidney essence cannot rise and exert its function. Loss of kidney qi can lead to a decline in body functions. Moreover, the kidneys regulate fluids; modern medicine has found that the kidneys excrete body water and toxins and participate in endocrine regulation. When kidney metabolism is impaired, electrolyte levels can become disordered, blood pressure and lipids may rise, which can trigger other diseases. In particular, patients with renal insufficiency may see an increase in cardiovascular and cerebrovascular disease risk. Overall, abnormal kidney function is related to CIS, and treatment should focus on nourishing kidney yin. Research by Chen Ying shows that clinical use of Dabuyuan Decoction combined with donepezil hydrochloride can improve post-CIS cognitive decline in patients with kidney essence deficiency, enhancing attention, calculation, and language ability, and improving daily life abilities. Guo Yanlin and others summarize that long-term clinical practice shows kidney deficiency with brain marrow consumption may be seen as local brain tissue necrosis; the ischemic penumbra after CIS can be seen as a micro-sign of blood stasis, and surrounding edema corresponds to phlegm obstruction. Kidney deficiency, blood stasis, and phlegm obstruction can lead to CIS, and clinical treatment using kidney tonics, blood circulation promotion, and phlegm removal is effective. Research by Huang Renfeng suggests that using Guizhi Fuling Wan combined with Shenqi Wan in patients with kidney deficiency and blood stasis in acute CIS can effectively improve treatment outcomes, lower pulsatility index (PI) and resistance index (RI), improve local cerebral microcirculation, protect brain nerves, and restore patients' daily living abilities. Therefore, in CIS treatment, nourishing yin and tonifying the kidneys should be part of the approach.

4. Summary

CIS, as a common clinical condition, still isn’t fully understood in terms of its causes, and treatment options are somewhat limited. It can affect various aspects of a patient’s thinking, understanding, language, orientation, and memory, and can even disrupt daily life. It often leads to complications like paralysis, swallowing issues, insomnia, unclear speech, and other aftereffects, and in severe cases, it can be life-threatening. This seriously impacts a person’s life and work, so figuring out the causes and mechanisms of CIS is really important for trying to treat and prevent it effectively.

Traditional Chinese medicine has a unique understanding and approach to treating CIS through the perspective of the internal organs and other aspects. Therefore, this article studies the causes and mechanisms of CIS based on basic TCM theories and finds that it is related to aging and physical weakness, internal injuries and losses; the internal generation of phlegm-dampness leading to heat

and wind; excessive emotions turning into fire and wind; sudden climate changes causing stagnation of qi and blood, with dysfunction of the internal organs as the main reason. CIS can arise from issues with qi, blood, deficiency, wind, phlegm, fire, stasis, or a combination of these. This article recognizes that the onset of CIS is not only related to the brain but is also closely connected to the heart, liver, spleen, and kidneys, and they can affect each other. Therefore, treating CIS based on the theory of the internal organs while also paying attention to the relationships between qi, blood, wind, and phlegm can make diagnosis and treatment more logical. In clinical treatment, it is important to observe the patient as a whole, combine the four diagnostic methods, identify the functions of the internal organs clearly, and adjust the treatment flexibly according to the pattern.

Overall, traditional Chinese medicine has some understanding of the causes and mechanisms of CIS, but there is currently a lack of clinical data and laboratory support, which limits deeper research into the causes, mechanisms, and organ-based therapies for CIS. Therefore, further studies on how organ-based treatment affects CIS should be conducted, aiming to provide reliable evidence-based support for clinical treatment of CIS.

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