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Analysis on the current quality standards of Chinese materia Medica used in COVID-19 prevention and treatment

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ABSTRACT

Purpose: Traditional Chinese medicine (TCM) has fully engaged and played an essential role in the prevention and treatment of Coronavirus Disease 2019 (COVID-19). This study compares relevant standards on high-frequency Chinese Materia Medica (CMM) used in this pandemic aiming at reaching a global consensus and ensuring the use of Chinese medicines safely.

Methods: 141 representative Chinese formulas and Chinese Patent Medicines from the National Protocol and the most of Provincial Protocols for controlling COVID-19 in China have been collected to statistical analyze the composition and characteristics of CMM. Among them, the domestic and international standards of 47 varieties with the frequency usage over 10 times were selected to compare their quality requirements in the mainstream pharmacopoeias and international standards.

Results: The quality requirements of used CMM for fighting COVID-19 on the terms of overall quality control, marker compounds, and safety indicators showed different patterns in these mainstream pharmacopoeias and international standards. The uniformed and scientific quality standards of CMM were urgently needed to promote global acceptance and trade.

Conclusions: These findings will provide evidence for building unified quality and safety standards that can adapt to the characteristics of CMM and promote international trade, and also will be stated that it is of the highest priority for ISO/TC 249 to formulate high-quality standards that consolidate international consensus to ensure quality and safety of the urgently needed CMM.

1. Introduction

Since the outbreak of Coronavirus Disease 2019 (COVID-19) in China in December 2019, in the absence of a specific Western medicine and vaccine, traditional Chinese medicine (TCM) has played an essential role in COVID-19 prevention and treatment in China. From the third trial version onwards of the seventh edition of Diagnosis and Treatment Protocol for COVID-19 (the National Protocol) issued by the General Office of National Health Commission of China and State Administration of TCM, it has been clarified that COVID-19 falls under the category of 'pestilences' in TCM. In accordance with the treatment principle of abidance by individuality, locality and seasons and the National Protocol, China's provinces (autonomous regions and municipalities directly under the Central Government) have formulated and released regional-specific TCM treatment and prevention protocols based on regional characteristics (the Provincial Protocol) [1,2]. With the full play of the characteristics and advantages of TCM, integrated Chinese and Western treatment has achieved satisfactory result [3–6].

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It is widely acknowledged that TCM plays an important role and is one of the merits in the epidemic prevention and control. A press conference held on the effectiveness of TCM in the treatment of COVID-19 cases in Wuhan reported that clinical observation showed that TCM has proven to be effective in the treatment of over 90 % of all confirmed COVID-19 cases on the Chinese mainland, said a TCM official on March 24, 2020. Among these confirmed cases, 74,187 were given TCM products, accounting for 91.5 % of the total [7]. It was found that TCM helped to relieve the symptoms, reduce the progression from mild to severe and critical, increase recovery rate, decrease mortality rate, and bring the convalescent to normal body functions [8–11]. Meanwhile, we noticed that China has adopted the methods of integrating traditional Chinese medicine with western medicine which led to a better outcome of this pandemic.

As Chinese Materia Medica (CMM) played a key role in this pandemic, its standards on quality and safety are attracting more attentions from the public. ISO/TC 249 has accumulated rich experience in developing international standards on CMM and relevant monographs have been recorded in national pharmacopoeias which enable CMM to be used globally. In this study, we aimed at analyzing the above-mentioned standards on CMM to recognize the current challenges in the process of their development.

2. Materials and methods

141 representative formulas and Chinese Patent Medicines from the National Protocol (the third trial version onwards of the seventh edition) and the main 25 Provincial Protocol of China [1,2] were selected and the usage frequency of each herbal medicine was counted. There are 47 varieties of CMM with the usage frequency over 10 times. Their botanical origins, morphological identification, and qualitative identification, quantification of marker compounds, heavy metals and residual pesticides in the following mainstream pharmacopoeias and international standards were summarized and compared.

Chinese Pharmacopoeia (ChP),
The Japanese Pharmacopoeia (JP),
The Korean Pharmacopoeia (KP),
European Pharmacopoeia (EP),
U.S. Pharmacopoeia (USP),
U.S. Pharmacopoeia-Herbal Medicine Compendium (USP-HMC),
WHO monographs on selected medicinal plants, and ISO standards.

3. Results and discussions

3.1. Statistical analysis of Chinese Materia Medica used in the Chinese formulas and Chinese Patent Medicines for COVID-19 prevention and treatment

There are 231 varieties of CMM used in the 141 representative formulas and Chinese Patent Medicines, covering botanical medicines, mineral medicines, and animal medicines. Among them, botanical medicines account for 83.55 % (193 varieties), mineral medicines for 8.66 % (20 varieties) and animal medicines for 7.79 % (18 varieties), and the number varieties types between mineral medicines and animal medicines is close to each other. The CMM used in the formulas over 10 times account for 20.35 % (47 varieties), including 45 varieties of botanical medicines, one variety of mineral medicine, and one variety of animal medicine (Table 1).

The commonly used CMM are Glycyrrhizae Radix et Rhizoma (gān cǎo), Armeniacae Semen Amarum (xìng rén), Gypsum Fibrosum (shí gāo), Scutellariae Radix (huò xiāng), Forsythiae Fructus (lián qiào), Ephedrae Herba (má huŏng), Lonicerae Japonicae Flos (jīn yīn huă-liăn qiào), Lepidii Semen-Gypsum Fibrosum (tíng lì zī-shí gāo).

3.2. Current situations of quality standards for CMM and comparative analysis

The quality standards of CMM is a key technical link for CMM to break the barriers of international trade and gain access to international markets. Under the framework of the globalization of CMM, with the ultimate goal to gain access to international markets, it is indispensable to promote internationalization of CMM by formulating a scientific, advanced and applicable system for quality standards with international recognition to effectively ensure efficacy and safety of CMM.

The current quality standards of the above selected 47 varieties of CMM in the mainstream pharmacopoeias and international standards are shown as follows.

3.2.1. Situation of the standards
3.2.1.1. Situation of standards collected by the mainstream pharmacopoeias [12–17]. All varieties of used CMM have corresponding quality standards in ChP, with more than 85 % collected in JP and KP but with fewer description in EP and USP/USP-HMC for 31.91 % and 25.53 %, respectively (Table 2).

3.2.1.2. Situation of standards collected by WHO monographs and ISO [18,19]. There are 14 varieties included in WHO monographs on selected medicinal plants, and 16 varieties included in ISO international standards. For ISO standards, 2 varieties of CMM, Lonicerae Japonicae Flos and Scutellariae Radix have been officially published, and 14 varieties are under development stage (Table 3).

3.2.1.3. Situation of standards collected by the mainstream pharmacopoeias and international standards. The standard of Scutellariae Radix is the only CMM that has been recorded in ChP, JP, KP, EP, USP, ISO and WHO monograph. The standards of Glycyrrhizae Radix et Rhizoma, Ginseng Radix et Rhizoma, and Schisandraceae Chinensis Fructus have been recorded in ChP, JP, KP, EP, USP and WHO other than ISO.

3.2.2. Comparative analysis of the standards and current challenges

Based on the characteristics of CMM, the standards of the mainstream pharmacopoeias and international standards mainly focus on the safety issues of CMM, such as botanical origins, morphological identification, and qualitative identification, quantification of marker compounds, heavy metals and residual pesticides [11–18]. However, the mainstream pharmacopoeias and international standards have different emphases on standards in terms of overall quality control of CMM, selection of marker compounds, safety issues and others. Taking Scutellariae Radix as an example, the comparative analysis of the standards among the mainstream pharmacopoeias, ISO and other international standards is as follows (Table 4):

1) Apart from the basic contents such as botanical origins, morphological features, microscopic characteristics, qualitative identification, purity test, assay, and storage, etc. of the CMM, ChP has included other factors including nature, flavor and meridian distribution, functions and indications, usage and dosage; while ISO and USP standards elaborate on packaging, transportation and labeling.
2) Purity test includes moisture and total ash contents, but with differences in limit values of each standard.
3) The regulations and requirements on safety indicators such as heavy metals and residual pesticides showed a different pattern in these mainstream pharmacopoeias and international standards.
safety management of medicines in different countries and the legal characteristics of ISO/TC 249 international standards for CMM.

4) The main differences of the standards are the gaps in the selection of marker compounds and limitation regulation. The single marker compound of baicalin is used for quantitative analysis in ChP, EP, and USP. Marker compounds and limitation regulation. The single marker compound of baicalin is used for quantitative analysis in ChP, EP, and USP.

3.3. Necessity of formulating international standards for CMM and characteristics of ISO/TC 249 international standards for CMM

Pharmacopoeias are the important technical code for quality and safety management of medicines in different countries and are the legal norms and evidence for the entry to the pharmaceutical markets. Through the coordination of pharmacopoeia standards, global free trade of high-quality pharmaceutical products can be promoted. Although TCM has been widely promoted globally, due to the inherent characteristics of CMM and the sparks between traditional and modern evaluation systems, CMM has been variously identified in different countries and has difficulties in international registration [20–22]. The phenomena mainly result from the barriers to connect the quality standards for CMM with the mainstream markets in Europe and US, and restrictions of medical regulations and policies in different countries/regions. Major differences were identified in the classification of CMM.
The list of 47 varieties of Chinese Materia Medica with usage frequency ≥ 10 times included by ISO/TC 249 platform.

Table 2
The status of the collection of standards for 47 varieties of Chinese Materia Medica (usage frequency ≥ 10 times) in the mainstream pharmacopeias and international organizations.

| Rank | Pharmaceutical Name | ChP | JP | KP | EP | USP | ISO | WHO |
|------|-----------------------|-----|----|----|----|-----|-----|-----|
| 1    | Glycyrrhiza Radix et Rhizoma | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 2    | Armeniaca Semen Amarum  | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 3    | Gypsum Fibrosum         | ✓  |   | ✓  | ✓  | ✓   | ✓   | ✓   |
| 4    | Scutellariae Radix      | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 5    | Forsythiae Fructus      | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 6    | Poria                  | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 7    | Ephedrae Herba          | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 8    | Citri Reticulatae Pericarpium | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 9    | Pogostemonis Herba      | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 10   | Lonicerae Japonicae Flos | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 11   | Platycodonis Radix      | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 12   | Pinelliae Rhizoma       | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 13   | Magnoliae Officinalis Cortex | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 14   | Ophiopogonis Radix       | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 15   | Atractylodis Macrocephalae Rhizoma | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 16   | Atractylodis Rhizoma    | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 17   | Rhei Radix et Rhizoma   | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 18   | Astragali Radix         | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 19   | Phragmisis Rhizoma      | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 20   | Ginseng Radix et Rhizoma | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 21   | Descurainiae Semen/ Lepidii Semen | ✓  |   | ✓  | ✓  | ✓   | ✓   | ✓   |
| 22   | Schisandraceae Chinensis Fructus | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 23   | Anemarrhenae Rhizoma    | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 24   | Panoniae Radix Rubra    | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 25   | Trichosanthis Semen     | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 26   | Bupleuri Radix          | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 27   | Persicae Semen          | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 28   | Rehmanniae Radix        | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 29   | Pseudostellariaceae Radix | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 30   | Morix Cortex            | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 31   | Tsaoke Fructus          | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 32   | Arecae Semen            | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 33   | Cocos Semen             | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 34   | Artemisiae Annuae Herba | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 35   | Corni Fructus           | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 36   | Perillae Folium         | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 37   | Acorni Lateralis Radix Praeparata | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 38   | Codonopsis Radix        | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 39   | Lophatheri Herba        | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 40   | Saposhnikoviae Radix    | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 41   | Zingiberis Rhizoma      | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 42   | Picrorrhizae Rhizoma    | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 43   | Gardeniae Fructus       | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 44   | Fritillariase Thunbergii Bulbus | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 45   | Menthae Haplocalycis Herb | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 46   | Notopterygii Rhizoma et Radix | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |
| 47   | Bulbali Cornus          | ✓  | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   |

Coverage ratio of standards for the 47 varieties (%) 100.00 87.23 85.11 31.91 25.53 30.04 29.79

* These CMM as new work item proposal (NWIP) have been submitted into ISO/TC 249 platform, and they have not been officially approved as new projects.

Table 3
The list of 47 varieties of Chinese Materia Medica with usage frequency over10 times included by ISO/TC 249 platform.

| No. | English Name                          | Chinese Name | Sponsor Countries | Current Stage |
|-----|---------------------------------------|--------------|-------------------|--------------|
| 1   | ISO 21317:2019 Traditional Chinese medicine—*Lonicera japonica flower* | 中医药—金银花 | China             | Published    |
| 2   | ISO 22988:2020 Traditional Chinese medicine—*Astragalus mongholicus root* | 中医药—蒙古黄芪 | China             |              |
| 3   | ISO 23,962 Traditional Chinese Medicine—Processed Aconitum carmichaeli lateral root | 中医药—附子 | China             | Draft international Standard (DIS) |
| 4   | ISO 23,585 Traditional Chinese Medicine—*Codonopsis pilosula root* | 中医药—党参 | China             | Working Draft |
| 5   | ISO 23,965 Traditional Chinese Medicine—*Bupleurum chinense and Bupleurum scorzonfolium root* | 中医药—槟榔 | China             |              |
| 6   | ISO 4564 Traditional Chinese Medicine—*Scutellariabacalenis Georgii root* | 中医药—黄芩 | China             |              |
| 7   | Traditional Chinese Medicine—*Panax ginseng root* | 中医药—人参 | China             | New Work Item Proposal (NWIP) |
| 8   | Traditional Chinese medicine—*Glycyrrhiza uralensis root and rhizome* | 中医药—甘草 | China             |              |
| 9   | Traditional Chinese medicine—*Paeoniae Radix rubra* | 中医药—半夏 | China             |              |
| 10  | Traditional Chinese medicine—*Rehmannia glutinosa root* | 中医药—地黄 | China             |              |
| 11  | Traditional Chinese Medicine—*Areca Semen* | 中医药—槟榔 | China             |              |
| 12  | Traditional Chinese Medicine—*Saposhnikoviae variata root and rhizome* | 中医药—防风 | China             |              |
| 13  | Traditional Chinese Medicine—*Platycodon grandiflorum root* | 中医药—桔梗 | Republic of Korea |              |
| 14  | Traditional Chinese medicine—*Schisandra chinensis fruit* | 中医药—五味子 | Republic of Korea |              |
| 15  | Traditional Chinese Medicine—*Rheum root and rhizome* | 中医药—大黄 | Germany           |              |
| 16  | Traditional Chinese Medicine—*Coptis rhizome* | 中医药—黄连 | Canada            |              |
and its products, market entry pathways, requirements of compliance with Good Manufacturing Practices; and level of evidence to demonstrate safety and efficacy based on historical use, non-clinical and clinical studies. Variations in the evaluation standards adopted by regulatory authorities pose a number of barriers and opportunities for the internationalization of TCM products [22].

It is not easy to fully understand the properties and curative effects of CMMs under the current knowledge and methodologies we have had. On the other hand, some western countries still have stipulated strict regulations on the registration of Chinese medicines before they could be sold. Such is the dilemma we meet: trying to follow the modern evidence-based approaches for registration while retaining unique characteristics of TCM. It can be highly desirable to develop ISO standards on each herbal medicine to serve as a reference during those registration processes.

Although the pharmacopoeias of different countries have a certain global impact, due to the disparities in initial motivations and target groups of the pharmacopoeias, it is difficult to apply to the standard of a specific country as supporting evidence for arbitration in international arbitration once a trade dispute occurs. Furthermore, due to the limited varieties of CMM included in the pharmacopoeias of Europe, US and other countries, or the disputes in the selection of the marker compounds, it is difficult for the existing standards to adapt to the needs of international trade of CMM.

Based on consultative and consensus-based processes, ISO/TC 249 provides a platform to develop standards which represent global expert opinion across consumers, practitioners, industry, academics from universities, and government. For standards on CMMs, there are still large disparities in the levels of requirements between a range of countries and their national pharmacopoeias. Therefore, ISO/TC 249 can serve the purpose of filling the gaps and supporting the appropriate use of CMMs. With a focus on the demands for the international market, ISO/TC 249 has been dedicated to filling in the blanks of the universal standards for international trade of CMM, stipulating international standards for CMM, strengthening quality control and safety requirements of CMM, and conducting a large amount of research on the detection of residual pesticides and heavy metals, etc. In order to complete the above tasks in an organized manner, ISO/TC 249 have formulated and released ‘ISO/TR 23975: 2019 Traditional Chinese medicine—Priority list of single herbal medicines for developing standards’ [23] from the needs of international trade, the status of pharmacopoeias in different countries, the degree of safety issues of CMM, the status of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) collection, and the consensus of experts in all countries. It aims at establishing unified quality standards that can adapt to the characteristics of CMM, ensure safety and effectiveness, and are applicable to international trade. With the new challenges and suggestions that COVID-19 brings us, the commonly used CMM in COVID-19 prevention and treatment need to be prioritized more appropriate, and the international standards should be published in a timely manner. With the endorsement of ISO international standards, TCM should play its role in the prevention and treatment of major infectious diseases worldwide. By comparative studies, the data has shown that among the 47 varieties of CMM with a usage frequency over 10 times for fighting COVID-19, only 22 varieties (46.81 %) are currently included in ISO/TR 23975. In other words, there is much to be engaged for ISO international standards in this field.

3.4. Further thoughts on international standards of ISO/TC 249 in responding to major emergencies of public health

The outbreak of COVID-19 reminds us that in dealing with major emergencies of global public health, it is of great importance to transcend the borders and build a global community of shared wellbeing now. The understanding and diagnosis and treatments of TCM for diseases and health care, over hundreds of years’ application supports the efficiency and safety of Chinese medicines, and its contribution to the wellbeing should be shared by the mankind. It is an important mission of ISO/TC 249 to promote TCM contribution to the wellbeing of the mankind by stipulating international standards of high quality.

CMM have the characteristics of diversity and complexity of ingredients, which is difficult to comprehensively evaluate by the quality control and assessment mode of single ingredient of modern chemical medicines. For the key scientific problems urgently needed to be solved in the internationalization and standardization of CMM, with the focus on the methodology for comprehensive characterization of the overall composition of CMM and the establishment of quality evaluation system, the demarcation of toxic CMM between effectiveness and safety, and the formulation of the limitation range of effect-toxic ingredients [24–26], we need to integrate the concepts of stipulating standards of the mainstream pharmacopoeias and ISO standards, etc., and to establish a scientific quality standard system that can adapt to the characteristics of CMM and can be generally recognized by the international community. Based on the experience of fighting COVID-19, it is urgent for ISO/TC 249 to formulate high-quality standards that consolidate international consensus to ensure the quality and safety of

### Table 4

The comparative analysis of quality standards for Scutellariae Radix in the standards of the mainstream pharmacopoeias, WHO and ISO.

| Items                  | ChP, 2015 | JP, 17th | KP, 11th | EP, 9.0 | USP-HMC | WHO monograph | ISO |
|------------------------|-----------|----------|----------|---------|---------|---------------|-----|
| Loss on drying         | ≤10.0 %   | ≤12.0 %  | ≤15.0 %  | ≤12.0 % | ≤12.0 % | ≤15.0 %       |     |
| Total ash              | ≤6.0 %    | ≤5.0 %   | ≤6.0 %   | ≤6.0 %  | ≤6.0 %  | ≤6.0 %        |     |
| Acid-insoluble Ash     | —         | ≤1.0 %   | ≤2.0 %   | ≤1.0 %  | ≥1.0 %  | —             |     |
| Ethanol-soluble extracts| ≥40.0 %  | —        | —        | ≥18.0 % | ≥15.0 % | ≥26.0 %       |     |
| Water-soluble extracts | —         | —        | —        | ≥28.0 % | ≥40.0 % | —             |     |
| Assay                  | Baicalin: ≥9.0 % | — | — | — | — | — | — |
| Heavy metals           | —         | —        | —        | —       | —       | —             |     |
| Pesticide residuals    | —         | —        | —        | —       | —       | —             |     |
| Sulfur dioxide         | —         | ≤ 150 ppm | ≤ 30 ppm | — | — | —             |     |
the urgently needed CMM.

4. Conclusions

In this study, the characteristics of used CMM for prevention and treatment of COVID-19, and the quality requirements of 47 main varieties of CMM in mainstream pharmacopoeias and international standards were comprehensively analyzed and compared. These findings provide evidence for developing harmonized standards which can be relied on to guarantee the safety and quality of CMM. This study also stated that it is of the highest priority for ISO/TC 249 to formulate high-quality standards that can consolidate global consensus and contain the characteristics of CMM at most.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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