Combining 'omics and comparative effectiveness research: Evidence-based clinical research decision-making for Chinese medicine

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Systematic reviews and meta-analyses of Chinese medicine trials have demonstrated issues with consistent quality, and an evidence gap between the practice of, and research on, traditional treatments. Clinical practice is built on knowledge, clinical experience, and patient preferences, all of which can be influenced by values and belief systems. A current movement in clinical medicine research, known as comparative effectiveness research, supports the development of evidence-based recommendations to enable more informed decision-making in the clinic and more valid health policies that also meet the criteria for practicing "P4" (predictive, preventive, personalized, and participatory) medicine. Creating a modern, strategic research framework for Chinese medicine that takes into account the stakeholders' perspectives, follows a patient-centered approach, uses mixed methods research methodologies, and combines modern scientific techniques such as systems-biology–based 'omics technologies would be beneficial for bridging the gap between Chinese medicine theory and modern clinical research methodologies.

Background

The most prominent medical research model compares "one disease, one treatment;" however, this strategy often does not have comparable clinical practices. Further, clinical trials based on such research models are usually performed in a standardized setting with a carefully selected patient group, and often produce results that are neither generalizable nor able to guide and inform clinical care. Systematic reviews and meta-analyses summarizing such trials might even be misleading for various chronic diseases, but especially for complex conditions such as diabetes, cardiovascular disease, and pain, which often occur in patients with multiple comorbid diseases who are receiving a number of different treatments. Decision makers—clinicians, patients, and funders—require studies that are comparable with actual treatment options in real life settings (*1*). Comparative effectiveness research (CER) is intended to provide real-world evidence that helps clinicians and patients choose the options that best fit the individual's needs and preferences (*2*). CER involves the stakeholders' needs at all relevant steps and includes a number of different types of research designs, clinical trials being one of them. These so called pragmatic trials are characterized by including more "real-life" patients presenting in routine clinical care including those that have comorbidities and use comedication, providing more individualized treatments, using patient-relevant outcomes, and being performed in a setting that is "in line" with routine clinical care (*3*).

Chinese medicine has been historically based on a descriptive and phenomenological approach and has relied on complex mixtures of herbal medicines as well as nonpharmacological interventions such as acupuncture and lifestyle advice. Research on some of the individual treatment components of Chinese medicine (e.g., acupuncture) have already made relevant contributions to CER evidence (*4*) and provided guidance for the design of further acupuncture CER (*5*). However, in clinical practice Chinese medicine is a complex intervention that focuses on the whole system's organization, and not on physiological pathways or single targets. Treatments are built on knowledge accumulated from ancient texts, experts, clinical experiences, and patient preferences, which are influenced by values and belief systems (*6*). Chinese medicine has a fundamental patient participation element, including general lifestyle aspects (e.g., diet and exercise) in the complex intervention strategies. Traditional Chinese diagnoses (or "syndrome differentiation"), a comprehensive analysis of clinical information from a Chinese medicine perspective (e.g., information derived from case taking, examining the patient's pulse and tongue), is used to guide personalized treatment options (*7*). Each syndrome consists of symptoms that determine their own unique treatment protocol.

Integrating syndrome differentiation with the biomedical techniques of modern clinical practice would be helpful for determining personalized treatments (*8*). The beta version of the International Classification of Diseases (ICD) 11 already allows Chinese syndrome coding in addition to Western diagnoses (*9*). Currently, these Chinese syndromes are considered important tools for predicting disease (*10, 11*) and ongoing efforts are correlating them with measurable biomarkers. Recently, a systems-biology–based approach has been utilized for Chinese medicine syndrome differentiation studies enabling the stratification of patient populations (*8*). This strategy may help researchers optimize their clinical trial design by having the ability to determine which patients are most appropriate for a specific intervention. One advantage of a systems biology approach is that it aims to understand both the connectivity and interdependence of individual components within a dynamic and nonlinear system, such

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as traditional medicine, as well as the properties that emerge at different organizational levels. In addition, the use of 'omics techniques (including genomics, proteomics, metabolomics, transcriptomics, and lipidomics) align very closely with the concepts and practices of Chinese medicine (*8*). Using 'omics-based techniques in Chinese medicine presents the unique opportunity to better understand both personalized diagnoses and the systems-based interventions of Chinese medicine (*12*). Two recent studies on rheumatoid arthritis have demonstrated the potential of this approach for conventional medicine. By combining Chinese syndrome diagnoses with the identification of biomarkers and the use of genomics to determine the diagnostic subgroups, opportunities for better treatment outcomes were provided (*13, 14*).

In the future, it is hoped that P4 medicine will enable the prediction and prevention of diseases rather than reactive health care (*15*). Understanding how genomic differences in individuals, along with an individual's environmental exposures, influence biological systems has the potential to enable medical professionals to make patient-specific predictions followed by personalized treatments or, even better, preventive interventions. In the future, health care consumers will be increasingly equipped with their personal health information, including genome sequences, molecular profiles of diseased tissues, and biomarker panels (*16*). Participation from all major stakeholders will be needed to provide clinical and health policy guidance for this new medical era.

Moreover, one strategy CER could benefit from is incorporating at least genomics as part of a future research approach (*17*). Including 'omics techniques into CER would be a new area for Chinese medicine—one yet to be incorporated into methodological CER guidance (*18*). It could directly bridge the gap between the personalized approach of Chinese medicine theory and Western science. The trend toward P4 medicine in CER also creates an ideal setting to provide information from large, real-life populations. Furthermore, the characteristics of P4 medicine dovetails well with the foundations of Chinese medicine.

Below, we have proposed some recommendations that combine the underlying concepts of CER with systems biology based 'omics technologies in order to collect scientific evidence for Chinese medicine that can be used to broaden the use of traditional medicine and optimize clinical decision-making.

Recommendations

When there is insufficient evidence for a treatment, a combination of both existing data from trials and systematic reviews of the literature should be used to inform future research and support clinical decision-making. This requires:

- Tools for systematic reviews and meta-analyses that provide comprehensive information about both the context of the studies and the extent to which the results are generalizable
- Secondary data-analyses of existing studies that have utilized a systems biology approach to identify possible associations between syndrome differentiation in Chinese medicine, other patient characteristics, and disease progression.

Future clinical research on Chinese medicine would benefit from combining the evolving CER methodology, modern systems biology 'omics approaches, and patients' needs during routine care. In practice, this would require:

1. Strategic clinical trial designs:

- Trials that include heterogeneous and "realistic" patient samples, are performed in settings reflective of a patient's routine care, and have sample sizes that facilitate further subgroup analyses
- Trial designs that balance multiple factors, including the type of study and context of the relevant diagnostic scenarios with both qualitative information (e.g., Chinese syndrome differentiation, patient preferences, and expectations) and quantitative parameters (e.g., systems biology including 'omics analysis)
- The development of guidance on the appropriate outcome measures for future research
- Realistic treatment protocols that shift patient treatments toward a personalized care model that allows the use of complex interventions, including lifestyle factors, and reflects the changes patients experience during routine clinical practice; 'omics-based analyses should be used to answer open questions about the complex pharmacological networks that are activated by complex herbal preparations (*12*)
- More studies with a diagnostic focus are needed to learn how predictive factors from Chinese medicine correlate with modern quantitative parameters.

2. Stakeholder involvement:

- Each stakeholders' needs (patients, clinicians, government, and payers) should be taken into account when identifying a study's focus, planning clinical trial designs, and interpreting results; to allow a high level and systematic inclusion of stakeholder viewpoints, both qualitative and quantitative research methodologies would need to be applied (*19*).

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