



Precision cardiovascular medicine in China

Jie LIU¹, Ru-Tai HUI¹, Lei SONG^{1,2,#}

¹State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

²Cardiomyopathy Ward, National Clinical Research Center for Cardiovascular Diseases, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

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1 Introduction

In mainland China, hospitalization expenses for patients with cardiovascular and cerebrovascular diseases have rapidly increased since 2004 and currently exceed the growth rate of the national gross domestic product.^[1] One reason for these high expenses is that the traditional “one-size-for-all” medical model results in low treatment efficacy. Precision and individualized medical models may help reduce the medical burden and provide a sustainable medical model.

2 Initiatives and organizations to promote precision medicine

The essence of precision medicine has long been embodied in the philosophy of traditional Chinese medicine, such as the ideas of bianzheng shizhi, tongbingyizhi, and yibingtongzhi. In recent years, Chinese society has made great efforts to develop precision medicine. The government, academia, enterprises, health care providers, patients and the public are working together to establish precision medicine as the driver of the medical and healthcare system in China. In 2014, the National Health Commission of the People’s Republic of China assigned the first high-throughput sequencing technology pilot units for clinical applications in three areas: genetic disease diagnosis, prenatal screening and diagnosis, and preimplantation genetic diagnosis (PGD). The Chinese Central Government launched a precision medicine initiative on July 29, 2015. Immediately, after former U.S. president Obama announced the Precision Medicine Initiative, the “China Precision Medicine” programme, an independent national project, was integrated into the 13th Five-Year National Science and Technology

Innovation Plan and the Healthy China 2030 Plan. A total of \$9 billion was allocated, compared with \$215 million announced for the Precision Medicine Initiative in the United States.^[2]

In the area of genomic data collection and analysis, the Beijing Genome Institute is one of the world’s largest sequencers and repositories of genetic material. In early 2017, the China National GeneBank in Shenzhen had over 500 million genetic sequences from over 8,000 species, stored in more than 40 databases.^[2] The Chinese Academy of Medical Sciences collaborated with Oxford University in the UK to launch a study, called the China Kadoorie Biobank, to investigate the main genetic and environmental causes of common chronic diseases among the Chinese population between 2004 and 2008. More than 510,000 adults were recruited from ten geographically defined regions in China.^[3]

Under the auspices of the China International Exchange and Promotive Association for Medical and Health Care, scientists from various fields of precision medicine, including cardiovascular disease, cerebrovascular disease, genetics, molecular imaging, reproductive medicine, medical statistics, bioinformatics and big data analysis, established a national professional academic organization known as the Precision Cardiovascular Medicine League (PCML). The PCML’s goals are to (1) establish a precision-based system for diagnosing cardiovascular diseases (CVDs) for clinical decision making; (2) search for genetic markers, risk factors and targets to improve clinical outcomes, minimize or avoid adverse effects, and guide drug treatment; (3) train personnel and formulate industry standards, norms and guidelines of Chinese precision cardiovascular medicine (PCM); and (4) construct a nationwide network to promote the clinical translation and application of the results of scientific research in precision medicine. During the past four years, the

#Correspondence to: E-mail: songlqd@126.com

PCML established countrywide PCM collaboration centres and conducted basic and clinical studies on monogenic and polygenic (or complex) CVDs, covering half of the Chinese population.

3 Precision medicine for monogenic CVDs

In China, approximately 20 million patients have monogenic CVDs, and at least half of these patients have detectable specific pathogenic mutations.^[4-7] The “Guideline for Diagnosis and Treatment of Chinese Adult Hypertrophic Cardiomyopathy” and the “Guideline for Genetic Diagnosis of Monogenic Cardiovascular Disease” were published in 2017 and 2019, respectively.^[8,9] Twenty-three relatively common monogenic CVDs, including a variety of cardiomyopathies, ion channel diseases, monogenic pathogenic hypertension, hereditary diseases of the aorta, familial pulmonary hypertension, hereditary thrombophilia and inherited lipid metabolic abnormalities, were systematically discussed. New precision medicine concepts, such as “gene diagnosis”, “genetic interruption” and “genetic counselling”, were formally put forward in clinical CVD guidelines for the first time. These guidelines will help promote the use of rational and standardized gene detection methods by hospitals, institutions, and commercial companies throughout China.

In 2013, researchers from China and other countries identified the type 13 long QT syndrome genotype in a cooperative study.^[10] Arrhythmogenic cardiomyopathy has recently been classified based on its clinical features, histopathology and genotype and was named “the Fuwai Classification”.^[11,12]

Diagnosing single-gene diseases and chromosomal aneuploidy usually requires 3–5 cells biopsied from a preimplantation embryo. A team from Peking University developed a new PGD method, known as mutated allele revealed by sequencing with aneuploidy and linkage analyses (MARSALA), which is based on single-cell genome sequencing, to simultaneously detect chromosomal abnormalities and point mutations and perform linkage analyses of single genes.^[13] Hundreds of healthy babies, free of known genetic diseases, were born after a PGD using MARSALA.

Genetic counselling in China remains in its infancy. The genetic counselling profession remains to be established; experienced genetic counsellors are scarce, and the public’s awareness of genetic counselling is limited. In recent years, the Chinese Genetic Society has organized training courses and trained more than 4,000 medical staff members on genetic counselling, but the number of genetic counsellors still does not meet China’s clinical needs.^[14]

Some issues in this field remain perplexing, including the

dilemma of genotype-phenotype associations due to heterogeneity. Furthermore, the relatively low incidence of monogenic diseases makes it difficult to obtain comprehensive and representative data. With the development of the high-throughput sequencing technology, many “pathogenic mutations” discovered in the past were found to be non-pathogenic single-nucleotide polymorphisms, and multiple gene variants were revealed to be associated with one disease. Thus, stricter requirements are needed to interpret sequencing results. Finally, most genetic testing is conducted in individual centres or by third parties in China, and the results are often difficult to repeat and interpret.^[15] Therefore, multicentre, large-scale studies, with long-term follow-ups, big data analysis techniques and shared genomic databases, are crucial.^[16,17]

4 Precision medicine for polygenic CVDs

In precision medicine for polygenic (or complex) CVDs, which include coronary heart diseases and hypertension, pharmacogenomics is thus far the most practical and reliable approach. Data from pharmacogenomic studies help guide tailored therapeutics using an individual’s genetic makeup, rational drug development and repurposed medications.

Many studies have demonstrated that the sensitivity to warfarin differs between Chinese and Caucasian populations and that variations in metabolism-related genes can alter the efficacy of warfarin.^[18,19] A meta-analysis of randomized controlled trials found that genotype-guided warfarin dosing algorithms could improve the efficacy and safety of anticoagulation with warfarin.^[20] The heritability of a platelet response to clopidogrel has also been found to be highly divergent among individuals and associated with clopidogrel resistance.^[21-23] Individual antiplatelet therapy guided by *CYP2C19* gene detection was reported to significantly reduce the incidence of major adverse cardiovascular events without increasing bleeding rates in the Chinese population.^[24] Implementation of genetic testing has been suggested to prevent statin-induced myopathy, an adverse side effect of statin drugs.^[25] Elevated blood homocysteine concentrations increase the risk of stroke, and the methylenetetrahydrofolate reductase (*MTHFR*) *C677T* genotype can significantly modify this effect in Chinese hypertensive patients.^[26] Many attempts have been made to investigate the association between gene polymorphisms and blood pressure response to antihypertensive drugs, such as β -blockers, angiotensin II receptor blockers and calcium channel blockers.^[27-30] However, most clinicians in China do not routinely use pharmacogenomics because of the lack of Chinese data regarding evidence-based medicine.

5 Future perspectives

There are several challenges ahead for PCM as follows:

(1) Ethnic differences. Native Chinese populations exhibit genetic mutation profiles different from those in Western populations.^[31] Much of these variations may be due to individual environmental adaptations to pathogens, climate, altitude, diet and possibly cognitive challenges.^[32] China has fifty-six ethnic groups with different geographic environments, lifestyles and cultures. Therefore, genomic data of transethnic origins must be evaluated before genomic information can be applied in the clinic.

(2) Talent training. For clinicians, the amount of data needed for genetic testing is too large, the genomic analysis process is daunting, and the results may be inaccurately interpreted. These issues may discourage clinicians from trying to apply precision medicine-based diagnoses and treatments. Moreover, no national institution exists to conduct formal training, certification and assessment in genomics for clinicians.

(3) Economic burden. Advances in genomics over the past quarter century have substantially reduced the costs of genome sequencing, but the expense of genetic testing remains too high for many patients (whole-exon sequencing services are commercially available or provided by a university laboratory at a cost of approximately \$1,000). It may be years before China's health insurance and commercial insurances begin covering these tests.

(4) Propaganda and education. Propaganda and education should be organized to help patients, doctors, researchers, the government and relevant enterprises understand the benefits and disadvantages of precision medicine to broaden the knowledge of PCM and prevent doctors and patients from having unrealistic expectations to prevent "overselling" precision medicine.

6 Summary

In China, although there is a long way to go, we firmly believe that making efforts to implement PCM will be fruitful in reducing CVD incidence, mortality and medical costs, bringing new opportunities for early warning and intervention, improving patient's quality of life, and extending their life expectancy.

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