

Improving Quality of Genetic Testing through Participation in International Proficiency Testing Programs

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Over the past decade, China has experienced rapid growth in the field of clinical genetic testing. However, considerable variations exist in testing practices among the laboratories, in part due to the lack of comprehensive standards, guidelines, and inter-laboratory proficiency testing programs. Here, we report the quality improvement experience of a major academic genetic testing center in China through participation in American proficiency testing programs for newborn screening and cytogenetics. Our experience highlights the importance of inter-laboratory proficiency testing in improving genetic testing quality, and the needs to develop robust proficiency programs to advance the field of genetics and genomics medicine in China.

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INTRODUCTION

Genetic diseases are common in China, with more than 3,000 genetic disorders reported, and approximately 3% of all births having genetics based diseases.^{1,2} In China, cytogenetics testing became available for patients with chromosomal abnormalities in the early 1980s,³ and newborn screening for congenital conditions in 1981.⁴ Over the past decade, genetic testing in China has expanded rapidly, with a wide range of cytogenetic and molecular genetic tests available in most major medical centers and diagnostic laboratories, along with the recent introduction of next generation sequencing including whole genome sequencing testing.⁵ However, considerable variation exists regarding the quality and testing methods among the laboratories. Differences in the socioeconomic development in different parts of the country, the lack of national standards and guidelines for genetic testing, and the limited number of inter-laboratory proficiency testing (PT) programs all create challenges for the medical genetics community.

PARTICIPATION IN INTERNATIONAL PT PROGRAMS

In 2007, the Center for Clinical Molecular Medicine (CCMM) was established at the Chongqing Children's Hospital in Chongqing, China. It is one of the first genetic testing centers in China to provide cytogenetics, molecular genetics, and biomedical genetic testing for congenital disorders and cancer, as well as newborn screening, and is situated in a region with a population of over 30 million.⁶ In 2010, CCMM began newborn screening tests for phenylketonuria (PKU), congenital hypothyroidism (CH), glucose-6-phosphate-dehydrogenase (G6PD) deficiency, and congenital adrenal cortical hyperplasia (CAH). However, before 2013, inter-laboratory proficiency tests were only available for PKU and CH. In 2012, CCMM expanded its screening to 17 amino acids and 30 acylcarnitines, using tandem mass spectrometry to screening for six disorders related to amino acid metabolism, nine disorders for organic acid metabolism, and five fatty acid oxidation defects. These newborn screening tests are recommended by the US Department of Health and Human Services expert group and the American College of Medical Genetics and Genomics (ACMG),⁷ but they have not been widely adopted among newborn screening programs in China.

In 2013, six amino acids (phenylalanine, leucine, methionine, tyrosine, valine, and citrulline) and seven acylcarnitines (free carnitine, propionylcarnitine, isovalerylcarnitine, octanoylcarnitine, dodecanoylcarnitine, palmitoylcarnitine, and stearoylcarnitine) were included in the newborn screening PT program administrated by the Chinese National Clinical Laboratory Center (NCLC). However, CCMM

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currently performs testing for 17 amino acids and 30 acylcarnitines, and many are not included in the NCLC PT programs. As well, the number of laboratories enrolled in the NCLC PT program is small, as only a few laboratories in China perform newborn screening for amino acid and fatty acid disorders. Moreover, the lack of standardization and financial parity results in considerable variation in methodologies and practices between the participating laboratories. Therefore, aggregated data from the participating facilities is often insufficient in statistical power to reach meaningful conclusions or for comparisons. As well, the supplies provided by the NCLC PT program have occasionally been of suboptimal quality, thus interfered with

test results. All of these factors undermine the ability of PT programs in China to evaluate the quality performance of participating laboratories. Many large international PT programs have much more comprehensive panels of tests, such as the program commissioned by the Center for Disease Control and Prevention (CDC) in the US. The CDC newborn PT program evaluates disorders related to metabolism defects in 7 amino acids and 21 acylcarnitines, includes a large number of participants worldwide, and is compatible with a variety of testing methodologies. The CDC program provides reliable reference values that are derived from “golden standard” methodologies. These reference values are suitable for comparing the performance of participating laboratories.

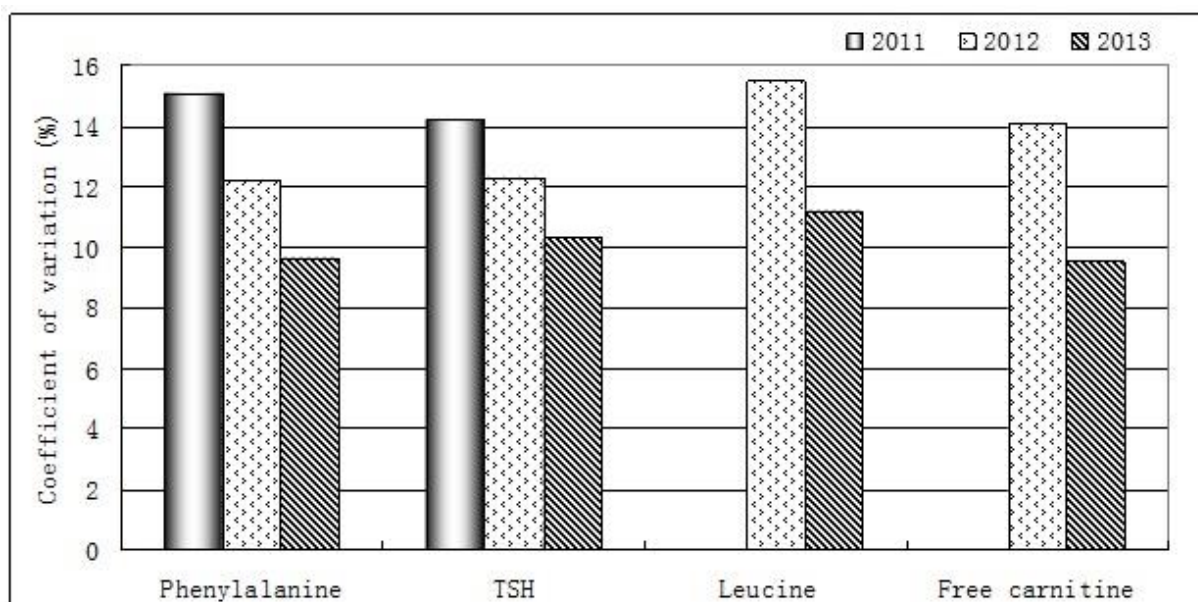


Figure 1. Annual average coefficients of variation for phenylalanine, thyroid stimulating hormone, leucine, and free carnitine testing. The annual average coefficients of variation were calculated relative to the values derived from the internal controls. The coefficients of variation for phenylalanine, thyroid stimulating hormone (TSH), leucine, and free carnitine tests declined from 2011 to 2013.

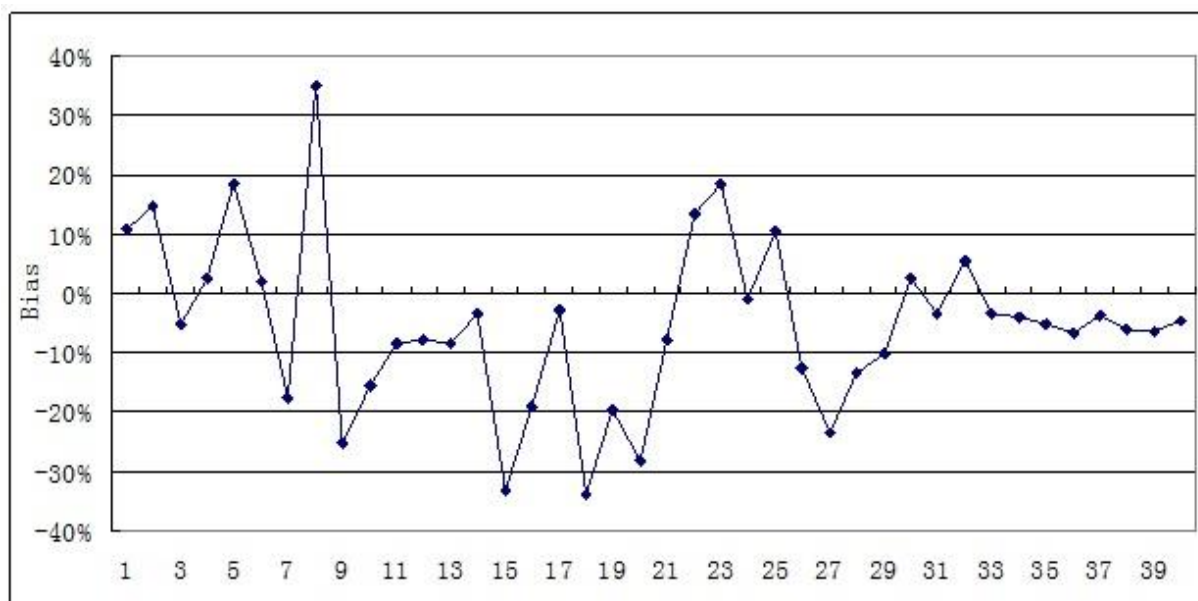


Figure 2. Variation in results of PT phenylalanine tests performed at CCMM. The degree of deviation relative to reference values (%) (Y-axis) of 39 phenylalanine tests (X-axis) performed at CCMM between 2012 and 2014. The results indicate a trend towards better results over this period.

In 2012, CCMM enrolled in the US CDC newborn screening PT program as part of its quality control and assurance program. Since then, CCMM has introduced automation to several of its assays, including the Dissociation-Enhanced Lanthanide Fluorescent Immunoassay (DELFI) (Wallac Oy, Turku, Finland), which has helped minimize variations between test runs. We have also included additional quality controls for several tests, in accordance with the CDC's recommendations. As a result, the average coefficients of variation for the tests including phenylalanine, thyroid stimulating hormone, leucine, and free carnitine have improved (**Figure 1**), and our CDC PT results have become closer to their reference values (**Figure 2**).

Genetic testing among other disciplines in China also faces similar challenges. For example, comprehensive technical standards are still lacking for cytogenetics, and although there are several regional inter-laboratory specimen exchange programs, they are all relatively small. The differences in the methodologies among participating laboratories has often made comparing their results difficult, and thus in 2011 we chose to enroll in the cytogenetic PT survey program administrated by the US College of American Pathologists (CAP). Since then, the cytogenetics laboratory at CCMM has adopted new procedures to improve chromosome band levels, resulting in bone marrow chromosome band levels increasing from 371 to 471. Additionally, the failure rate for constitutional cytogenetics testing decreased from 1% to 0.03%, and the oncology cytogenetic failure rate decreased from 7.9% to 3.8%. We also use the PT survey materials for staff continuing education and training. CCMM's cytogenetic abnormal rate for new leukemia cases, a major indicator of oncology cytogenetics quality, has been consistently maintained at approximately 70%, which is comparable with its peers in the West. We have also achieved a 100% correction rate for the CAP PT tests we have performed thus far. In 2013, CCMM collaborated with the Chinese NCLC to successfully conduct the first nationwide cytogenetics proficiency testing trial in China. One hundred and thirty-nine laboratories participated in the trial, and the success of

this collaboration has laid the groundwork for formal cytogenetics PT programs in China, which are scheduled to launch in 2015.

CONCLUSION

Inter-laboratory PT is essential for genetic testing quality control and quality assurance. Our experience in participating in international PT programs demonstrates that such programs would provide valuable alternatives to laboratories in China, where similar domestic programs are not available. As genetic testing plays an increasingly important role in modern medical practices, and the demands for quality genetic testing in China continue to rise, robust PT programs for genetic testing will be critical to standardizing practices and providing quality testing results. With more laboratories in China gaining experience in international PT programs, as well as the new initiatives for genetic testing in China, we believe that China will be able to develop PT programs for genetic testing that are in line with the international standards to advance medical genetics in China.

CONFLICT OF INTEREST

None

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