Implementing comprehensive genetic carrier screening in China—Harnessing the power of genomic medicine for the effective prevention/management of birth defects and rare genetic diseases in China

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ABSTRACT
Carrier screening had been demonstrated as a powerful practice in preventing selected severe genetic disorders. This practice is expanding its scope and impact in the era of next-generation sequencing. Empirical and theoretical data support the utility of expanded carrier screening. The authors propose a comprehensive carrier screening program as a main component of the first-tier measure in preventing severe genetic disorders and birth defects in China. We discussed the key principles and important aspects to ensure the success of such a program. The authors believe this program will play a pivotal role in our endeavor for a healthier nation.

KEYWORDS
Carrier screening, Next generation sequencing, Birth defect, Genetic disease

Most babies are born healthy but there is a small chance of having a baby with a severe genetic disease or birth defect even to healthy couples without positive personal or family history. The risk differs from couple to couple, depending on the carrier status of the couples for pathogenic mutations in disease causing genes. There are hundreds of severe recessive genetic diseases that every couple could be a carrier for. One study showed an average carrier burden of 2.8 (0–7) pathogenic variants in 448 genes associated with severe childhood onset recessive diseases. The carrier burden could differ significantly from one population to another. The higher the incidence of a certain disease in a population, the higher the risk being a carrier for an individual. For example, individuals in the Guangxi Zhuang Autonomous Region of China have almost one out of four chances to carry a disease-causing gene mutation for thalassemia due to high prevalence of this condition in this region. Carrier screening is a type of genetic test to determine what this risk is for each couple. Knowing the risk of being a carrier before or during pregnancy provides couples with options for making appropriate reproductive decisions.

Initially carrier testing was done for one or few relatively common recessive disorders associated with significant morbidity, reduced life-expectancy in a specific population with a high carrier rate. Tay-Sachs disease (TSD) had been the prototype and model of carrier screening for effective prevention of the disease since 1970s. A more than 90% reduction of children born with Tay-Sachs disease in the United States and Canada was observed in the Ashkenazi Jewish (AJ) community as a result of carrier screening, followed by prenatal diagnosis when indicated. The effectiveness of carrier screening can also be appreciated from the thalassemia carrier screening program in China. For example, in Guangxi, the birth rate of severe thalassemia patient dropped from 2.47‰ in year 2009 to 0.6‰ in year 2017, a 80% reduction in less than 10 years as a result of the population level extensive carrier screening effort. Currently, diseases recommended by professional societies for carrier screening are very limited. The American College of Medical Genetics and Genomics (ACMG) recommended screening cystic fibrosis (CF) and spinal muscular atrophy (SMA) for people of all races, and screening Bloom syndrome, Canavan disease, familial dysautonomia, Fanconi anemia type C, Gaucher disease, mucolipidosis IV, Niemann-Pick disease type A and Tay-Sachs disease for AJ population. The American Congress of Obstetricians and Gynecologists (ACOG) only recommended screening CF for all groups, fewer diseases in AJ panel and recommended screening for Hemoglobinopathies for African or African American, Southern Asian and Southern European.

Entering the era of genomic medicine, the so called “expanded carrier screening” became available since 2009. The expanded carrier screening test included severe genetic diseases much beyond the lists recommended by professional societies. We are at a very early stage of this new practice and generally there is a lack of specific guidelines for it. In 2013, ACMG issued a policy statement regarding expanded carrier screening, acknowledging the coming of age for expanded screening. In 2015, ACMG/ACOG/National Society of Genetic Counselors (NGSC)/perinatal quality foundation/Society for Maternal-Fetal Medicine (SMFM) issued a joint statement addressing many issues and challenges for implementing expanded carrier screening in US. This joint statement set the stage for wide-spread implementations of expanded carrier screening. Currently, the conditions and genes included in the expanded panels differ from one provider to another. The clinical utility and social impact are just beginning to be evaluated. Based on data from an expanded carrier screening program involving 94 severe or profound conditions among 346 790 individuals, it was shown that expanded carrier screening modeled more hypothetical fetuses at risk for severe or profound conditions than did screening based on current professional guidelines (Mann-Whitney P < 0.001). More strikingly, 94% of hypothetical fetuses affected for East Asian couples would be missed if only screening for conditions within guidelines. Even for the well-implemented thalassemia screening in China, utilizing the next generation sequencing (NGS)-based molecular screening test as a new approach could significantly improve the detection rate as over 12% of the
pathogenic or likely pathogenic variants identified by NGS assay would be undetectable by traditional methods. Such findings are of very instructive importance for us to consider developing and implementing expanded carrier screening on top of the successful thalassemia program in China. We believe a comprehensive genetic carrier screening program will dramatically reduce the rates of birth defect and rare disease in China. It should be a very important component of our measure to prevent birth defect and improve population health. NGS-based technologies and innovative new assay platforms will replace existing approach with better sensitivity, efficiency and cost-effectiveness. Yet there are many issues need to be discussed for a successful development and implementation of such a comprehensive genetic carrier screening program in China. Due to different health care infrastructure and culture value, we cannot adopt the panel or system that is implemented in the western world. Here we offer our thoughts, comments and points to consider for designing, developing and implementing a comprehensive genetic carrier screening program for populations across China.

PRINCIPLES AND CONSIDERATIONS FOR DEVELOPING THE COMPREHENSIVE GENETIC CARRIER SCREENING PROGRAM IN CHINA

The main purpose of carrier screening is to identify variants of clinical significance and to use the information for couples to make informed decision regarding reproduction. As for any genetic tests, such service should follow the four basic principles of ethics, specifically:

1. Respect for autonomy: The decision to participate in carrier screening should be made by the couple themselves based on the sufficient information and adequate genetic counseling provided to them; participates should sign informed consent. Those who do not agree to participate in carrier screening should be provided with the same level of information and care. In carrier test, parents are acting on behalf of their children in making decision before they can make decision themselves. In this regard, adult onset disorders should not be part of carrier screening since the children can make their own decision by the time they are capable of.

2. Beneficence: The benefit of carrier screening test can be applied to both individual family and society as a whole. This has been demonstrated as an effective way of preventing diseases that have significant impacts to individual life and society. This is of somewhat similar benefit as the employment of vaccines but it is carried out not as mandatory, even though in some Middle Eastern and Mediterranean regions, screening for beta thalassemia is mandatory.

3. Nonmaleficence: It is important to know even though there is very limited physical harm to the participates for undergoing carrier screening, the potential harm to unborn individuals and psychological impact to parents can be significant. The service provider should use best of their knowledge to ensure the information provided to the participants is accurate and correct based on the most current scientific evidence. The test process should follow all the guidelines to ensure high quality, which includes test design, data generation as well as data analysis and reporting.

4. Justice: The test should not be offered only to selected individuals. It is not intended for individuals with indications for specific genetic test or with family history. In order to offer equal access to this service, all couples should be offered information and genetic counseling. The cost associated with this test should be kept as low as possible. Government may consider subsidizing the test. In addition, local government should set up infrastructure to make access to such test more feasible for a larger population. The successful experience for thalassemia screening program in Guangxi for example can be of great value while implementing the comprehensive carrier screening program in China.

In general, a test should be validated following ACCE (analytic validity, clinical validity, clinical utility and associated ethical, legal and social implications) model developed by CDC’s Office of Public Health Genomics (OPHG). Specifically: 1. Analytical validity: NGS technical platform is the best platform at the moment and the technology is improving rapidly and will further increase its technical validity. Yet, certain types of pathogenic variants are not reliably detectable and should be addressed separately (e.g. CGG repeat expansion in FMR for Fragile X syndrome) or need to have a well validated informatic procedure (e.g. Copy number in SMN1 for SMA).

2. Clinical validity: Positive predictive value is influenced by disease prevalence, penetrance of variants and distribution of pathogenic variants (e.g. hotspot mutation). Negative predictive value is of critical importance for genetic counseling and additional medical screening protocol and follow-up treatment plan.

3. Clinical utility: It should be monitored by measuring the reduction of severe disease incidence after the screening program is put in place. The program should be piloted in certain regions in order to demonstrate its effectiveness. The clinical utility can also be modeled by the detected variants from a defined population. The clinical utility may differ from region to region.

4. Ethical, legal and (psycho)social issues: Individual autonomy should be respected and informed consent should be a normal process; the genetic counseling should
be provided to help couple make informed deciding as well as psychological support. Individuals should be protected from any discrimination and stigmatization based on carrier status. China needs to put in place such a law as Genetic Information Nondiscrimination Act (GINA) in US.

With respect to the specific features of the comprehensive carrier screening, the test has the same goal as the traditional carrier screening, that is to provide couples with information to optimize pregnancy outcomes based on their personal values and preference. While the standard for considering a pregnancy outcome optimal differs from person to person, from one culture to another, the criteria for including disorders to be screened should be based on a consensus generated by the target population.

Many rare genetic diseases are included in the expanded screening panel; disease prevalence is a less critical factor to consider when selecting diseases for screening. It is particular relevant when NGS-based test platform is used since the cost of the test is not directly proportional to the gene number included in the panel. Furthermore, we have very limited knowledge regarding the rare disease prevalence in China, so the disease selection for the Chinese comprehensive carrier screening panel should not be based on disease prevalence.

Residue risk is an important concept for carrier screening and should be provided as accurate as possible. Yet residue risk cannot always be calculated for all diseases in the panel. It is encouraged to determine the frequency of variants in previously untested ethnic and racial groups. This point is particularly relevant to China since the large high-quality genome sequencing data is not yet available and shared. We have limited knowledge regarding the mutation spectra of disease genes in Chinese patients. We call on to develop shared genomic database of Chinese population.

Carrier testing is most commonly used to screening for variants in autosomal recessive (AR) genes but it is not limited to these AR genes. X-linked and autosomal dominant (AD) genes can also be targeted for screening. The selections for AD conditions need to be carefully vetted and should be limited to childhood onset conditions with potential severe clinical consequences.

The condition selected should be of reasonable incidence and recurrence. Variants need to be reliably detected by the defined technical platform, with defined positive and negative predictive value.

There should be reproductive options available for the conditions selected. Those options include pre-implantation genetic diagnosis (PDG), prenatal diagnostics (non-invasive is preferred), use of non-carrier donor sperm and/or oocytes, refraining from pregnancy or adoption.

**CRITERIA FOR DISEASE/GENE INCLUSION AND VARIANT REPORTING**

In order to minimize potential harm and maximize the benefit of the comprehensive carrier screening, the medical genetics professional societies (e.g. The Chinese Medical Doctor Association Medical Genetics Physicians Chapter; the Chinese Obstetricians and Gynecologists Association; the Medical Genetics Branch and the Chinese Society of Laboratory Medicine of the Chinese Medical Association; The Genetics Society of China, Human and Medical Genetics branch and the Chinese Board of Genetics Counseling; Chinese Preventive Medicine Association, the birth defect prevention and control branch; China Healthy Birth Science Association, the birth defect prevention branch; March of Dimes Birth Defects Foundation of China) should work with government and patient advocate groups (e.g. the Chinese Organization for Rare Diseases) to develop the appropriate comprehensive carrier screening panel for Chinese population. It is recommended by the authors of this commentary to set up an ad hoc working group (i.e. The Chinese comprehensive carrier screening work group) to take on this task. The comprehensive screening panel will evolve over time so the working group will be a long-term team. The work group should collect and curate evidence to be used for design panel, as well as provide professional advice for the technical and clinical aspect of the screening.

The working group should first develop disease/gene inclusion criteria and then use evidence-based approach to determine the level of evidence to be used to decide what diseases/genes to be screened. The following factors should be considered as criteria:

1. **Disease severity.** Diseases included in the comprehensive carrier screening panel should be the ones with significant medical problems. The severity of disease is evaluated based on the life expectancy, quality of life of the affected and the availability/effectiveness/affordability of treatment options for the condition. Perinatal lethality, pediatric death and significantly shorten life span are considered as severe consequences, moderate to severe intellectual disability and severe physical disability that significantly impact the quality of life are also considered as severe consequences. The conditions included in the screening panel usually do not have effective or available treatment. The evidence for evaluating disease severity is not always available particular for populations not well-studied. The evaluation should not only consider the disease prognosis in the defined environment but also consider the availability of medical service that affects the quality of life of affected. The panel design has to be population specific and should evolve when situation changes (e.g. the availability of affordable and effective treatment for a disease will eliminate the necessity of screening for genes responsible).
2. Gene curation (ascertaining the gene-disease causal relationship) needs to be done following the ClinGen SOP for the genes to be included in the screening panel. Only genes at strong or definitive level to be associated with severe disease should be considered to be included in the screen panel. In US, options are provided to include diseases with variable expressivity or incomplete penetrance and those known to be associated with mild phenotype as along as the information is made available and transparent. In China, we think those conditions are not to be included in the screen panel for the concerns of improper use of the screening findings. Adult-onset and diseases with low-penetrance should be omitted from the panel, such examples included but not limited to genes responsible for α-1-antitrypsin deficiency; MTHFR and hereditary hemochromatosis and variants associated with mild thalassemia.

3. It is challenging to interpret all variants for its causal relationship and its association with outcome severity. Variant classification in general should be done by well-trained personnel following the ACMG/AMP guidelines. Only the pathogenic and like pathogenic variants should be considered as positive findings. On special cases, professional judgement should be exercised to decide two rare VUS as likely disease-causing variants. It is particularly critical when we perform preimplantation genetics diagnosis (PGD) based on the variant classification. Considering the limitation of the current ACMG/AMP variant classification guideline, when we encounter situations with potential disease-causing variants which cannot reach the level of likely pathogenic, the obstetricians and medical geneticist along with genetic counselor (GC) should work together to assess the risk before proceeding with PGD.

ENSURING THE SUCCESS OF COMPREHENSIVE CARRIER SCREENING IN CHINA

A successful carrier screening program depends on many factors. The education for physicians and other healthcare providers is critical for proper implementation of the population-based carrier screening. We need to develop professional training courses specifically for this program, professionals involved with carrier screening, prenatal diagnosis, PGD, genetic counseling should be trained.

Population education is also very important. The professional society should develop education materials for general population. Online knowledgebase should be developed for professional and general population. The attitude and acceptance of expanded carrier screening by population is a key to ensure the success. Guangxi had a well-implemented thalassemia screening program, and the pre-marital screening rate is the highest in China. While the pre-marital screening rate is down to less than 10% in major cities like Shanghai, Beijing, the rate is as high as 95% in Guangxi. The governmental and societal supporting systems that had been established in Guangxi predict the best chance of success in implementing the new screening program as a pilot. Nevertheless, the expanded screening program is much more complicated and requires an extensive educational program for both professionals and general population.

The implementation of expanded carrier screening needs a large number of GCs. This is in urgent shortage. The government should develop a certification pathway to formally establish GC training programs and certify qualified GC. Establish GC position in hospitals of all level and in diagnostic labs. Certified GC should also be allowed to practice independently.

Assessment regarding the attitude and concerns about the screening should be conducted. Screening approaches and panel design should be adjusted to best benefit the population and minimize the potential harm.

The cost of the screening test should be kept low as much as possible. This requires to utilize the most advanced and reliable technical platform with high efficient and high throughput, much automated operation. The central and local government should consider to subsidize the screening program. Other agencies such as March of Dimes Birth Defects Foundation of China can play important roles in facilitating the implementation as they have done a great job for newborn screening program in China. The program should also be considered to be covered by the basic health insurance policy.

A stringent quality control program should be in place for laboratories carrying out the comprehensive carrier screening. The personnel should be properly trained and certified. In-lab proficiency test and inter-lab comparison should be part of routine quality monitoring program.

The participants should be properly consented and this is of huge logistic challenge. But a well-developed consent material will help to facilitate such a process. The key points for consent is discussed below:

Test result should be confidential. Such mechanism should be put in place in labs, hospitals and diagnostic companies. Information should be released to participants first unless it was decided to be delivered to the couple together at the time of pre-test counseling.

Paternity has to be certain for risk assessment. Negative result does not mean zero risk.

Genes and diseases included in the screening panel are selected based a set of rules. Only pathogenic (P) and likely pathogenic (LP) variants are reported. Thus the screening program will not detect all possible diseases. It is mainly designed to significantly reduce such risk in a cost-effective manner.
Everyone has a risk to be a carrier. Being a carrier does not mean inferiority. Usually one, sometimes two or more P/LP variants are detected in an individual. Being a carrier for autosomal recessive (AR) disorders does not mean the individual is affected. If the screening panel include X-linked and autosomal dominant genes, it is possible that an individual carrying P/LP variants, or an individual carrying compound heterozygous or homozygous P/LP variants in a AR gene maybe affected. Genetic counseling and medical management are strongly recommended.

**OTHER POINTS TO CONSIDER FOR IMPLEMENTING THE COMPREHENSIVE CARRIER SCREENING IN CHINA**

**Time of screening**

The best time for undergoing screening is preconception. It provided couples with a variety of preventive measures, including PGD, use of donor gametes, adoption and prenatal diagnosis with a choice of pregnancy termination in cases with severe condition.

For provinces that have a strong premarital screening program, we encourage carrier screening being an important part of the program offered to every couple and provide adequate education and counseling. For provinces without a well participated premarital screening program, couples could be offered information and counseling while applying for marriage license. Sequential test (test one of the reproductive partner first, if positive, test the other partner for variants in the specific gene(s)) would be a better choice over testing both parties simultaneously. But in either case, blood samples should be collected at the same time. Premarital carrier screening is not intended to decide if the couple is fit to get married. Counseling should be provided to the couple in order for them to understand the meaning of the carrier test. In order to avoid complications, carrier test result can be considered to be released after marriage before pregnancy.

Carrier testing can also be carried out at prenatal stage. It is encouraged to do carrier testing at early stage of pregnancy as possible. It may be preferred to do on both parents simultaneously to make sure there is enough time to make decision.

Carrier testing is suitable for reproductive-aged individuals. Testing of minors for carrier status is not considered as necessary at this point.

**Region and ethnicity**

Allele frequency differs significantly across different populations from different regions or of different ethnic background. This is the basis for ethnic/region specific carrier test done before. For example, carrier screening for thalassemia is still mainly performed in the southern provinces in China. But due to the extensive cross-province population migration that had been happening in China during the last several decades, the traditional population boundary is no longer distinct. Furthermore, most of region/ethnicity specific alleles are not exclusive, they occur at lower level but nevertheless exist in other populations. Empirical data that have shown ~40% of individuals screened positive by expanded carrier screening were not from indicated regions or of indicated ethnicities by previous guidelines. Thus, expanded carrier screening should not be limited to offer to certain selected populations. Certain population or people of certain ethnic background will be detected to have much higher probability to carry positive variants, they should have stronger motivation to go carrier screening. But even though the positive screening rate and variant profile will differ from one population to another, a single uniform screening panel should be used for the same reason discussed above. Such an approach can also reveal unbiased information regarding the allele frequencies and disease prevalence across different regions/ethnic groups, since currently, we do not have a good understanding of allele distribution profile across China at granular scale.

**Detection methods**

For most disease-causing genes, pathogenic mutation can occur along entire gene sequence. For those genes, sequencing all the coding regions of the gene, as well as known intronic pathogenic variants are desirable. For genes with hotspot mutation, covering those variants are essential and genotyping for specific mutation can be performed. Copy number variants (CNV) need to be detected through specific methods until sequencing-based assay can detect single exon level CNV reliably.

Although the joint statement indicated that NGS-based screening is not always the best technical platform choice for some diseases, the rapid improvement of NGS and its capability to detect previously undetectable variants are making this platform an increasingly suitable for carrier screening. For example, SMA is mainly due to deletion of SMN1 gene which share high homology with SMN2 gene; it has been a challenge to detect deletion carriers. Recently, NGS-based test was able to reliably detect heterozygous deletion of SMN1, as well as point mutations within SMN1. Similarly, the mutation spectra of HBB and HBA genes associated with thalassemia are also challenge for NGS-based test but with careful design of capture probes and custom informatic data analysis pipeline, they can be well covered by NGS-based test. It is predicted that NGS-based test will replace traditional approaches using mean corpuscular volume and hemoglobin electrophoresis for thalassemia screening.

**SUMMARY**
Preventing severe birth defect and rare genetic disorders is of national strategic importance for improving the overall health and life quality of our nation. A well developed and implemented nation-wide comprehensive carrier screening program will be one of the most effective approaches to reduce the birth defect and severe genetic disorders including rare disease that was not possible to detect before. We will be able to learn the genome and the pathogenic variant profile of our population during this practice which will constitute the critical piece of large-data-based future healthcare system. We call on all stakeholders to actively participate and play respective roles in this worthy endeavor.

CONFLICT OF INTEREST
The authors have no conflict of interests relevant to this article.

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