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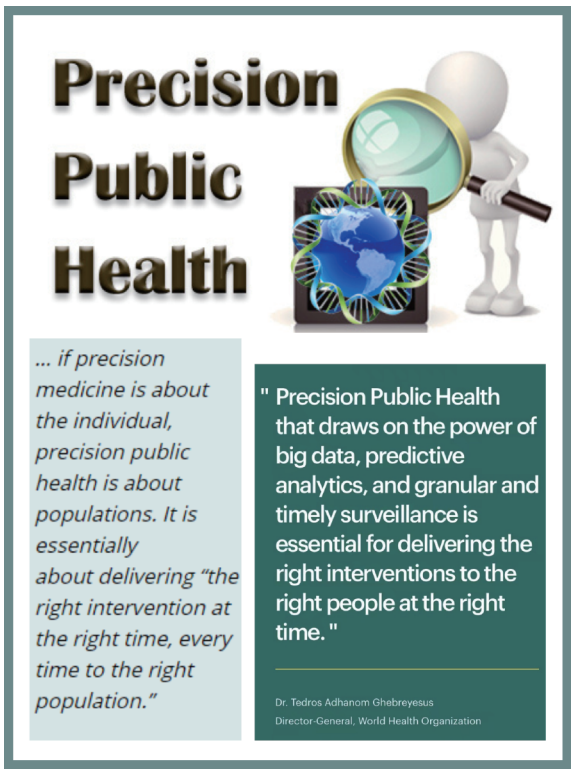

PRECISE PUBLIC HEALTH ISSUE

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Cover Image: adapted from the US Center for Disease Control and Prevention, https://blogs.cdc.gov/genomics/2018/05/15/precision-public-health-2/

This week's issue was organized by Guest Editor Zhuo Chen.

Foreword

Precision Public Health in China: Opportunities and Challenges

Zhuo Chen[1, 2,#]

"Precision Public Health," a term proposed in 2013, had riled up mixed feelings and intense debates during the early days of its use (*1*–*6*). Critics often considered "Precision Public Health" as a version of "Precision Medicine" at the population level and fretted over the prospect that the concept may take focus away from social determinants of health (*1*–*2*). In defense, Richard Horton argued that "Precision public health is about using the best available data to target more effectively and efficiently interventions of all kinds to those most in need." (*3*). Khoury et al. defined "Precision Public Health" as "the delivery of the right intervention to the right population at the right time, and includes consideration of social and environmental determinants." (*4*). Khoury and colleagues reviewed the evolution of the field of public health genomics, its relations to the core public health functions, and how it contributed to the emergence of the concept of precision public health (*5*). The coronavirus disease 2019 (COVID-19) pandemic further highlighted the importance of precision public health, a key tool of surveillance through both laboratory tests among infected and at-risk persons and wastewater sequencing (*7*–*8*). Genomic information is also critical for the rapid development of COVID-19 therapeutics, in addition to the more prominent case of messenger ribonucleic acid (mRNA) vaccines (*9*).

As one of the six countries involved in the Human Genome Project, China is a critical player of the global genomic research community (*10*–*12*). National registries with genomic information include the China Kadoorie Biobank and the Chinese National Twin Registry (*13*–*14*). Home to one of the fastest-growing genomics markets, China has immense potential for its precision public health research and practice (*15*).

The collection of articles in this special issue addresses aspects of precision public health in the context of China. Sun et al. examined the practice of breast cancer genetic testing in China and suggested that the benefit of genetic testing at breast cancer diagnosis in China could be larger than in Caucasian populations (*16*). Zhu used a discrete choice experiment and a mixed logit model to assess the preference over direct-to-consumer genetic testing among a Chinese population and provided estimates on the willingness-to-pay for genetic testing for physical traits, personality, and dietary recommendations (*17*). Jiang reviewed the guidelines for disclosure of secondary (or incidental) genomic findings, i.e., the risks of genetic-related conditions not requested by the patient, and advocated for the creation of local guidelines on secondary findings in China (*18*). Chen et al. provided a scoping review of studies on ethical, legal, and social implications of genomics in Chinese language and summarized them in four broad themes, i.e., ethical considerations, regulatory framework, perceptions of genomics and precision medicine, and future directions (*19*).

Indeed, as prior literature forcefully argued, precision public health encompasses the use of genomic information, big data, and traditional means of risk stratification, as well as their ethical, legal, and social implications (*4*–*5*,*20*). This special issue is an attempt to bring together perspectives from public health, economics, ethics, and health policy to understand the opportunities and challenges related to Precision Public Health in China. There is much to be accomplished in using Precision Public Health to improve population health in China and elsewhere.

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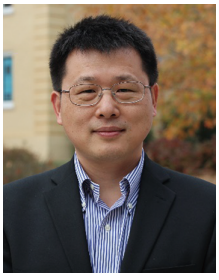

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Review

A Scoping Review of Global Guidelines for the Disclosure of Secondary Genomic Findings to Inform the Establishment of Guidelines in China

Shan Jiang[1,#]

ABSTRACT

The detection and disclosure of secondary findings (SFs) is a preventive strategy for medically-actionable hereditary health conditions. Some countries have guidelines on management and disclosure of SFs, while others avoid detection and disclosure of SFs. This study is a review of clinical guidelines from six countries and the European Union to identify similarities and differences among SF guidelines. Evidence from this review supports harmonization of guidelines across countries to promote broad international collaborations on genomics and to benefit precision medicine. This study can serve as a reference for development of SF management guidelines in China by contributing evidence from other countries to the ethical and methodological challenges under debate.

INTRODUCTION

Genome sequencing provides information about disease risk, prognosis, or treatment response, and is rapidly becoming an affordable and useful tool for patients (*1*–*2*). Sequencing occasionally identifies gene variants, called secondary findings (SFs), that are neither relevant to the primary intention of sequencing nor to the patient's health condition. Disclosure of these SFs to patients is much debated (*3*–*5*). Some pathogenic variants are not medically actionable, and the disclosure of these variants may cause the patient anxiety (*6*), psychological harm (*7*), or information overload (*8*). However, non-disclosure of some SFs may miss opportunities to encourage patients to consider life-planning options or accept interventional recommendations (*9*–*10*).

The lack of consensus on SF management has led to differences in clinical guidelines across countries (*11*). For example, the American College of Medical Genetics and Genomics (ACMG) recommends returning SFs that are medically-actionable and have high penetrance, and has published a list of gene-condition pairs that should be returned to patients on a consent basis (*12*). As a result, disclosure of SFs becomes a preventive strategy to increase health outcomes from genomic interventions, such as population genetic screening and opportunistic screening. In contrast, Canada takes a different approach and recommends avoiding detection and return of SFs to patients (*13*).

In the era of precision medicine (succinctly described as providing tailored treatments to the right patients), maintenance of public health and development of healthcare technologies have benefited from the accumulation of vast amounts of genomic data worldwide (*14*). Since SFs contribute a large proportion of the available genomic data, discordance between countries' SF management and disclosure guidelines may hinder the accumulation of genomic data and the development of precision medicine to address patient- and population-level health (*15*). In contrast, harmonized international guidelines on disclosing SFs would benefit genomic data accumulation and precision medicine research based on genomics. Therefore, it is useful to examine county-level SF guidelines and their concordance to inform the development of harmonized global guidelines. Such an examination can provide a global landscape of guidelines for stakeholders in China, where no guidelines on SF disclosure currently exist, and can serve as a reference for the establishment of national guidelines.

METHODS

Search Strategy

This scoping review compared clinical guidelines on disclosing SFs derived from genome sequencing. EMBASE, PubMed, MEDLINE, Web of Science, and

HumGen, an international database of law and policies related to human genetics (*16*), were searched for published guidelines. The "grey literature" was searched using Google and Google Scholar. The search terms were "incidental findings," "secondary findings," "unanticipated findings," "unsolicited findings," "ancillary findings," "opportunistic findings," and "accessory findings" (*3*–*4*), accompanied by terms related to genome sequencing and communication of results.

Inclusion Criteria

The study included documents published by professional organizations, governments, and bioethical committees that were relevant to SF disclosure in a clinical setting. The review was limited to documents written in English and published after 2010, when genome sequencing was initially used. The selection process included two rounds: screening by title and abstract, followed by full-text review (Figure 1).

Summary and Comparison

Characteristics and major contents of the guidelines were extracted from the original documents and included guideline title, source country, publication year, responsible professional organization, and major recommendations. Characteristics and recommendations were summarized by country, separately for adults and children.

To further compare guidelines, the major recommendations were summarized as succinct points, and the guidelines for each jurisdiction were checked for the presence or absence of these points. Results of the presence check were placed in a table to display similarities and differences of the guidelines.

RESULTS

Characteristics of Selected Articles

Thirteen articles were included in the review (Table 1) and covered the leading countries in genomics research and practice: the United States (US), the United Kingdom (UK), Canada, Australia, Germany, Denmark, and the European Union (EU). Contents of the clinical guidelines are shown in Table 2.

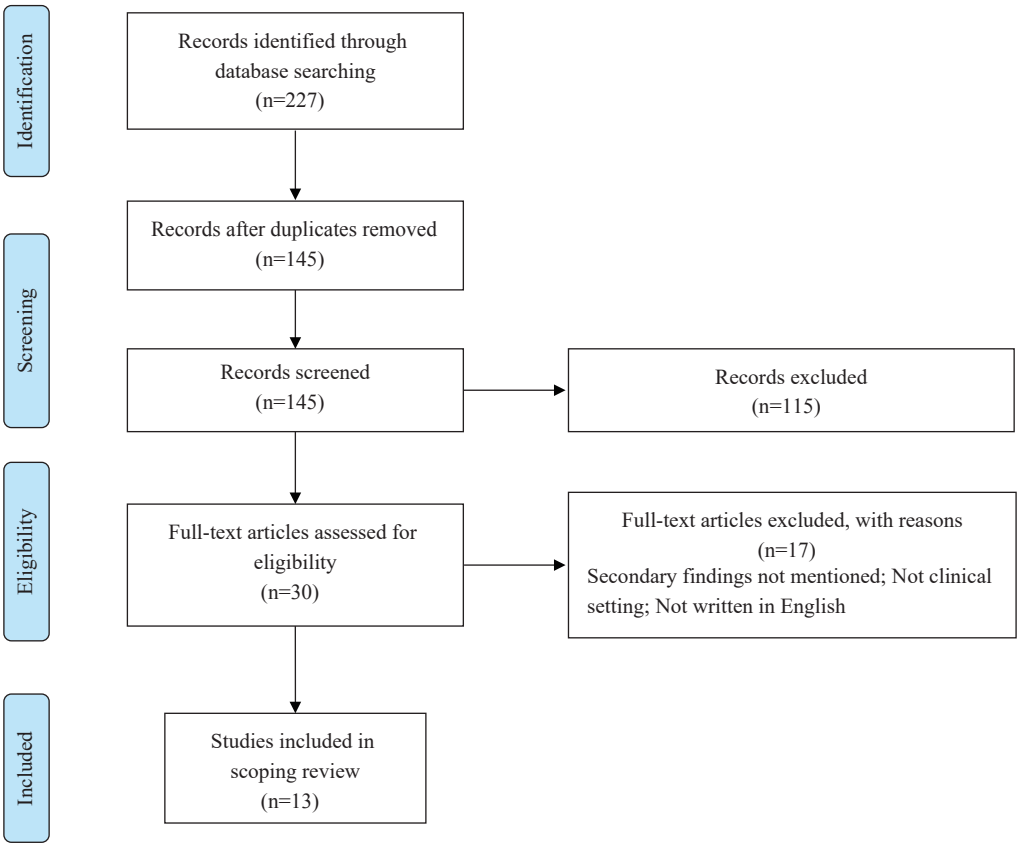

FIGURE 1. Article selection process.

TABLE 1. Characteristics of included clinical guidelines.

No.	Country (s)	Time	Organization	Targeted population	Title
1	US	2013	Presidential Commission for the Study of Bioethical Issues	Adults; children and adolescents	Anticipate and communicate. Ethical management of incidental and secondary findings in the clinical, research, and direct-to-consumer contexts (*17*)
2	US	2013	ACMG	Adults; children and adolescents	Points to consider for informed consent for genome/exome sequencing (*18*)
3	US	2013	ACMG	Adults; children and adolescents	ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing (*19*)
4	US	2014	ACMG	Adults; children and adolescents	ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing (*20*)
5	US	2015	ASHG	Children and adolescents	Ethical, legal, and psychosocial implications of genetic testing in children and adolescents (*21*)
6	US	2017	ACMG	Adults; children and adolescents	ACMG Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0) (*22*)
7	Canada	2015	CCMG	Adults; children and adolescents	Position statement of the Canadian college of medical geneticists (*13*)
8	EU	2013	ESHG	Adults; children and adolescents	Whole-genome sequencing in health care: recommendations of the European Society of Human Genetics (*23*)
9	EU	2015	P^3G, ESHG, HUGO, and PHG Foundation	Children and adolescents	A statement on the continued importance of targeted approaches in newborn screening programmes (*24*)
10	UK	2014	AGNC	Adults; children and adolescents	Position statement on opportunistic genomic screening (*25*)
11	UK	2014	PHG Foundation	Adults	Realising genomics in clinical practice (*26*)
12	Germany	2013	German Ethics Council	Adults	The future of genetic diagnosis: from research to clinical practice (*27*)
13	Australia	2014	RCPA	Adults	Implementation of massively parallel sequencing in diagnostic medical genetic testing (*28*)

Abbreviation: ACMG=American College of Medical Genetics and Genomics; AGNC=Association of Genetic Nurses and Counsellors; ASHG=American Society of Human Genetics; CCMG=Canadian College of Medical Geneticists; ESHG=European Society of Human Genetics; EU=European Union; HUGO=Human Genome Organization; P^3G=Public Population Project in Genomics and Society; RCPA=Royal College of Pathologists of Australasia; UK=the United Kingdom; US=the United States.

TABLE 2. Contents of guidelines by country on the return of SFs in a clinical context.

Guideline	Key points
US, 2013	• A minimum list of conditions, genes and variants should be routinely evaluated and reported to the ordering clinician who can place them into the context of that patient's medical and family history, physical examination and other laboratory testing. • Any findings included by the list should be reported by laboratories without seeking consents from the patient and family. • A clinician should be trained to communicate and interpret the results of incidental findings.
US, 2014	• Before performing the clinical sequencing, a written consent should be obtained from the patient, describing the interpretive uncertainty, privacy, possible impact on other family members, and the inevitable generation of data. • Patients have the right to opt out of the analysis of the medically actionable gene list, so that they can choose not to receive the results of IFs. • Same policies apply to children as to adults. • Patients must decide whether to analyze the whole set of medically actionable genes (gene list) or none of them. It is infeasible to analyze a subset of the genes due to practical difficulties.
US, 2015	• The disclosure of IFs should occur only when the information has clear clinical utility. • Informed consent should be obtained if there is a substantial likelihood of generating clinically relevant IFs. • Parents should be able to decline to receive IFs of their child. • In case of IFs that indicate urgent and serious implications for a child's health, the results must be returned regardless of any preferences of the child and parents. • It is ethically acceptable, but not required, to search for IFs that are not relevant to the clinical indication for sequencing.
US, 2017	• ACMG setup a new process for accepting and evaluating nominations for updates to the secondary findings list. • Based on the previous secondary findings list, 4 genes have been added and one gene been removed. A new updated secondary findings minimum list includes 59 medically actionable genes recommended for return in clinical genomic sequencing.
Canada, 2003	• Clinical genetics records should be maintained indefinitely except those that have minimal importance to future interaction in genetics with the patient or other family members.

TABLE 2. (Continued)

Guideline	Key points
Canada, 2015	• Avoid the discovery of SFs, and focus on the primary indication of the test. • Genome sequencing should only be considered when proved useful in the evaluation process and a selective filtering process is recommended. • The adult patient should have the right to receive or not to receive the results. • The results of the child must be returned to the parents if ACA criteria are satisfied.
Canada and Europe, 2015	• Targeted tests are recommended. • If treatment or prevention is available during childhood and the variant indicates a serious problem, the IFs should be reported to parents. • When carrier status information is relevant to parents for reproductive choices, they could be offered this information. • Parents may also be offered information regarding unsolicited findings that are severe and clinically actionable relevant to their own health.
UK, 2011	• The possibility of incidental findings should be minimized. Targeted tests or analyses are preferred. • Physicians have no obligation to provide IFs irrelevant with clinical question. • Informed consent is not sufficient to deal with IFs. • Where variants are of unknown significance, the responsibility to investigate might be less clear.
UK, 2014	• National Health Service (NHS) should adopt targeted tests using gene lists, which have greater clinical utility then WGS/WES. • It should minimize the generation, interpretation and disclosure of IFs, because the potential harms are likely to outweigh the potential benefits. • Informed consent should be obtained from patients if it is necessary for WGS/WES, which should include the possible generation of IFs. • Disclosure decisions will be informed by clinical judgement, though patients should have opportunities to express views on disclosure. • Patients should be given the opportunity to opt out of re-contact. • Patients should be informed that the sequencing data would be stored in a secured, comprehensive, and accessible NHS database. • A multidisciplinary committee and many evidence-based studies are needed on the return of IFs.
Denmark, 2012	• Patients should be given a “degree of involvement in deciding whether, and to what extent, they are to receive feedback on any incidental findings.” • Genetic testing should be accompanied by “impartial and comprehensive information as well as counseling, both before and after testing.”
Europe, 2013	• Targeted genetic tests are much preferred because they can avoid incidental findings that cannot be interpreted. • Known genetic variants with limited or no clinical utility should be filtered out. • Patients’ claims to a right not to know about findings do not automatically override professional responsibilities. • Guidelines for testing minors should be established to balance the autonomy and interests of child and the parental rights of not receiving IFs of the child.
Germany, 2013	• The council refutes the idea that the doctor has the right to inform relatives of the patient who might also be affected by the genetic condition, or to recommend them to get genetic counseling. • Prenatal genetic diagnosis should only be conducted if there is an increased risk of a genetic disease. • If the genetic information is irrelevant with the health of the born child, this finding should not be communicated to the pregnant woman.
Australia, 2014	• Genomic testing should have a sound evidence base before prescription. • Targeted testing measures are recommended to avoid or minimize incidental findings. • Clinicians should use standard practices in deciding whether to return IFs given the patient has agreed to it.

Abbreviation: ACA=analytic validity, clinical significance, and actionability; ACMG=American College of Medical Genetics and Genomics; IFs=incidental findings; SFs=secondary findings; WES=whole exome sequencing; WGS=whole genome sequencing; UK=the United Kingdom; US=the United States.

Clinical Guidelines for Adults

US: In 2013, the US Presidential Commission for the Study of Bioethical Issues recognized the necessity for professional organizations to guide the management and disclosure of SFs (*17*). The Commission recommended that patients should be informed of the possibility of SFs, the scope of SFs that will be communicated, and the steps of discovering SFs, and that patient preference not to know SFs should be respected. In response, ACMG published two documents in 2013 (*18*–*19*). One document emphasized that patients should be informed of the

possibility of finding SFs for which there may be interventions to prevent disease or reduce disease severity. The other document was specific to the reporting of SFs, and provided a list of reportable gene-condition pairs. ACMG recommended that listed variants should be reported regardless of the indication for sequencing and regardless of the age of the patient, including to minors. In 2014, ACMG updated its guidelines with two notable modifications: 1) patients should have the right to opt out of SF detection, and 2) once patients consent to the analysis, the entire list should be analyzed (*20*). In 2017 and again in 2021, ACMG updated the guidelines and extended the list of gene-disease pairs to additional SFs (*12*,*21*). ACMG also recognized that reporting SFs may introduce costs, impact individuals and families, and generate medical, legal, social, and economic ramifications that need to be assessed.

Canada: In 2015, the Canadian College of Medical Geneticists (CCMG) published guidelines that recommended a cautious approach towards the return of SFs to patients (*13*). Recognizing that reporting SFs is controversial, CCMG recommended focusing on the primary indication of the test, avoiding the discovery of SFs as much as possible. However, CCMG recommended that patients have the option to request and receive SFs.

EU: In 2013, the European Society of Human Genetics (ESHG) published guidelines recommending that SFs that are not interpretable or medically actionable should be avoided (*22*). However, if an SF indicates a serious health problem and is medically actionable, it should be reported to the patient, overriding the patient's desire not to know.

UK: In 2014, the PHG Foundation published recommendations suggesting minimizing the generation, interpretation, and disclosure of SFs (*23*). In the same year, the Association of Genetic Nurses and Counsellors (AGNC) published a position paper stating that patients always have the right to opt-out of receiving SFs and that physicians should only disclose SFs if patients choose to receive them (*24*).

Germany: The German Ethical Council recognized the possibility of SFs with genome sequencing and recommended that the discovery of SFs should be avoided due to a lack of evidence on its benefits (*25*). The patient's right not to know was emphasized.

Australia: In 2014, the Royal College of Pathologists of Australasia (RCPA) published guidelines and recommended that patients should be informed of the types of SFs that may be generated and reported, and have the option of not receiving SFs (*26*). Without a specific list, RCPA suggested that the return of SFs should be limited to variants that are pathogenic and deemed reportable.

Clinical Guidelines for Children

US: ACMG recommended the same policy for children as for adults. That is, once consent is obtained, SFs identified according to the ACMG SF list should be returned to the parents. Parents should have the option of opting out of the analysis for their child. In 2015, the American Society of Human Genetics (ASHG) published a specific position statement for children and adolescents, recommending that physicians should disclose SFs with clinical utility for the child and/or family members if the parents choose to receive them. If the SFs indicate a serious health problem for the child, disclosure should override parental preference.

Canada: CCMG recommended that physicians only return SFs to parents that indicate childhood-onset conditions with high penetrance and medical actionability. Variants that are associated with adult-onset conditions should not be reported, unless the parents want to receive them or disclosure could prevent serious harm to family members' health.

EU: ESHG stated that benefits to the family members should be considered in a decision to disclose a child's SF. In 2015, several professional organizations published a joint statement specific to newborn screening programs, recommending use of targeted sequencing to avoid irrelevant findings and focusing on the primary indications for testing (*27*).

UK: AGNC recommended that detection of children's SFs associated with adult-onset conditions should be avoided.

Similarities and Differences in Guidelines

Table 3 shows similarities and differences between guidelines from the different countries. In terms of general attitude, the US guidelines take a more positive stance compared with other countries. For example, in the US, physicians have the right to search SFs with patient consent and they should return SFs to patients if the findings are on the ACMG SF list. Guidelines from other countries do not support physicians' right to search SFs. Instead, they prioritize patients' right to know or not to know any genomic findings. For children, the US uses the same guidelines used for adults, while the ESHG provides separate

TABLE 3. Comparison of guidelines on returning SFs in clinical setting.

Category	US	Canada	UK	Australia	Denmark	Germany	EU
General attitude							
Positive attitude	√						
Negative attitude		√	√	√		√	√
Minimization of SFs			√				
No Harm principle						√	
For adults							
ACA criteria		√					
Partial ACA criteria	√						
Informed consent	√			√			
Right to know		√			√		
Right not to know	√	√	√		√		
All-or-none policy	√						
For clinicians							
Must-return regardless of preference	√						
Obligation to disclose		√					
No obligation to disclose			√				
Right to search	√						
No obligation to search	√						
Case-by-case determination							√
Decision by physicians			√				√
For children							
Specific guidelines for children							√
Policy for children same as for adults	√						
For genomic data							
Data protection		√	√				
Confidentiality		√	√				

Abbreviation: ACA=analytic validity, clinical significance, and actionability; SFs=secondary findings; All-or-none policy=patients could choose to receive all SFs or none of them; UK=the United Kingdom; US=the United States.

recommendations for children.

Lack of Evidence

The studied guidelines are discordant, reflecting three key differences. First, there is insufficient clinical evidence concerning the range of SFs that should be returned to patients. The ACMG guidelines recommend that only SFs associated with monogenic disorders be returned, and that SFs associated with disorders caused by structural variants, repeat expansions, or copy-number variations are insufficiently understood to be listed. Second, the health benefits of returning SFs are not clear. The CCMG guidelines recommend a cautious approach because the benefits of disclosure are not well established. The AGNC statement indicated that robust evidence for the benefits of SFs is needed. Third, there is a lack of evidence for the impact of disclosure on patients, physicians, and the healthcare system. For example, returning SFs that indicate disease risk will probably lead to confirmatory testing. If the disclosure becomes a routine practice for every patient, the downstream costs may become a financial burden for the healthcare system.

DISCUSSION

This study reviewed clinical guidelines of several countries concerning disclosure of SFs derived from genome sequencing. The review identified discordances between guidelines, as some countries take an open attitude towards disclosure, while others take a more cautious attitude. All guidelines value patient autonomy and the potential benefits of

disclosing SFs with high penetrance and medical actionability. Generating new evidence for updating SF management guidelines is warranted.

Concordant Global Guidelines are Needed

SFs represent an important source of genomic data and are critically important for genomic research and precision medicine (*28*). Since the generation of valid evidence on the clinical implications of variants requires much larger datasets than do other medical research areas, it is necessary to collate clinical genome data internationally, including the retrieval of SFs. For example, recent studies usually employ genome data from nearly 300,000 participants (*29*). Ideally, international genome data should originate from multi-center, multidisciplinary, large-scale studies on a worldwide scale. Therefore, international collaboration on genome data is required.

Considering the significant role of SFs in the accumulated genomic data, globally concordant guidelines on detecting and disclosing SFs would greatly benefit the merging of genome data across countries and support large-scale international collaborations (*11*). Advances in genomic data accumulation may boost progress in genomic research and precision medicine, and the whole of society may be able to fully harness the benefits of genome sequencing.

Patient and Physician Preferences for SF Disclosure

Current guidelines recognize that some patients may want SFs returned and some patients may not. Understanding psychological motivations of wanting or not wanting to know SFs may provide important evidence for updating current guidelines. Methods such as discrete choice experiments (DCE) (*30–31*) and best-worst scaling (BWS) (*32–33*) would be appropriate tools to investigate psychological motivation (*5*,*34*).

Physician preferences on SFs disclosure are also fundamental for clinical guidelines. If physician views are not incorporated, the guidelines may lack consensus and generate much debate among physicians (*35*). Updated guidelines should consider the circumstances under which physicians decide to return SFs, irrespective of patient preference. It would be valuable to identify factors behind physicians' decisions and simulate the effect of the factors (*5*). Regier et al. (2015) and Jiang et al. (2020) utilized DCE to elicit patient and physician preferences towards the return of SFs in Canada (*5*,*36*). Generation of more evidence on preferences for disclosure is warranted.

A Research Agenda to Inform Guidelines for China

Genomics-based precision medicine is increasingly being studied and used in China to advance healthcare technologies (*37*). For example, the China Precision Medicine Initiative (CPMI) is accelerating genomic research (*38*). The lack of guidelines on SF disclosure, however, indicates that precision medicine is at an early stage in China. Physicians and patients have no recommendations to follow when SFs are identified. Professional guidelines are needed to provide support and guidance to SF detection and disclosure in China. This review provides stakeholders in China with a landscape of international guidelines and their similarities and differences that can contribute to the development of guidelines in China.

Cost-effectiveness analysis (CEA) of disclosing SFs is important evidence supporting guideline development. CEA is an established method to inform decision-makers about the value for money of different healthcare technologies, interventions, or policies (*39–40*). However, CEAs that examine the value of returning SFs face methodological challenges due to the long-term impact of sequencing on quality-of-life and numerous downstream interventions after sequencing (*41*). Implementation of CEAs on returning SFs in China faces additional challenges, including measurement of quality-of-life, long-term financial impact, the use of modelling techniques to capture the impact of downstream interventions, and appropriate reimbursement thresholds (*39*,*42–43*). Researchers may need to overcome methodological difficulties to determine whether disclosing SFs is cost-effective in China. Such economic evidence is of critical importance for decision-makers developing guidelines on SF disclosure.

CONCLUSIONS

This study identified differences and similarities between several countries' clinical guidelines on return of secondary genomic findings to patients. Evidence should be established on which SFs to return, the health benefits of disclosure, and the impact of disclosure on patients, physicians, and the healthcare

system.

This study brings attention to the differences between clinical guidelines and supports calls for greater harmonization of guidelines across countries. Concordant guidelines would promote broader international collaboration on genomics and thus may help fully harness the benefits of genome sequencing for all.

This study provides a landscape of international guidelines for stakeholders to use as a reference for developing local guidelines on SF disclosure in China. More economic evaluations on the cost-effectiveness of returning SFs to patients are needed to facilitate the establishment of SF management and disclosure guidelines in China.

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Review

Ethical, Legal, and Social Implications of Genomics in China: A Scoping Review and Implications for Precision Public Health

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ABSTRACT

We conducted a scoping review of Chinese language studies on the ethical, legal, and social implications of genomics and identified four broad themes: ethical considerations, regulatory framework, perceptions of genomics and precision medicine, and future directions of genomics. Ethical, legal, and social implications of genomics are growing in importance and are highly relevant to public health in China.

China is one of the six countries involved in the Human Genome Project and is a critically important player in human genome research globally. China's regulatory requirements for genomics research and practices are evolving, and after the birth of the world's first genetically edited babies (*1*), there has been a renewed interest in assessing the ethical, legal, and social implications (ELSI) of genomics in China.

Applications of genomics lead to Precision Medicine, which tailors treatments to individuals (*2*), with potentially revolutionary changes in three areas: disease classification, clinical research paradigms, and clinical evidence (*3–4*). A subsequent concept is Precision Public Health, which is described as "an emerging multidisciplinary field that uses genomics, big data, and machine learning/artificial intelligence to predict health risks and outcomes and to improve health at the population level." (*5*) Demand for precision medicine and precision public health will continue to grow after the coronavirus disease 2019 (COVID-19) pandemic subsides, and it is therefore critical to examine the ELSI of genomics for public health (*6*). We conducted a scoping review of the landscape of ELSI of genomics research in the Chinese scientific literature and explored its public health implications, including for capacity building and policy development.

METHODS

Our intent was to survey the landscape of ELSI of genomics research and practices in China. We identified studies through a systematic literature search in the three major Chinese citation databases: China National Knowledge Infrastructure (CNKI), Wanfang Database, and Beida Fabao (PKULaw). To be included, articles must be in Chinese and published between January 1, 2000, and December 31, 2020. Two groups of keywords (in Chinese characters) were used in our search*. Reflecting our dual foci on genomics and ELSI, we restricted our scoping review to studies described by one or more keywords from group 1 and one or more keywords from group 2.

We excluded studies related to non-human genome research, such as studies of genetically modified organisms; editorials, news, comments, and conference report collections; studies in settings other than the mainland of China; and articles not in Chinese.

Two reviewers (JX and LJ) independently screened titles and abstracts for eligibility. Inconsistent decisions were resolved through discussion and, when unable to be resolved, were reviewed and decided by the Principal Investigator (ZC).

RESULTS

The initial search yielded 657 articles; there were 37 duplicate records that were excluded. Title and abstract review excluded another 134 records because of wrong publication type (n=36), lack of relevance to human genetics (n=88), or non-Chinese language (n=10). Among the remaining 486 full-text articles, 420 were excluded because of lack of relevance to genomics (n=330), lack of relevance to ELSI (n=70), non-

* Group (1) 基因组学=genomics, 基因测序=genetic testing, 遗传学=genetics, 精准医学=precision medicine, 克隆=clone, and 基因图谱=genetic mapping; and Group (2) 经济学=economics, 伦理=ethics, 法律=law/legal, and 社会=society/social.

Chinese study population (n=17), and wrong outcome (n=3). We identified 23 additional articles by reviewing reference lists and conducting a manual search. In all, 89 studies were included for review and narrative synthesis (Figure 1). A complete list of the studies is in the Supplementary Material (available in http://weekly.chinacdc.cn).

Four themes emerged from our review: ethical considerations, regulatory framework, perceptions of genetic testing and genetic counseling among physicians and the general public, and future directions for genomics.

Ethical Considerations

Qiu and Zhai outlined ELSI issues related to China's precision medicine strategy, including informed consent, independent ethics review, privacy protection, and equity in the use of precision medicine research (*7*). Chen et al. summarized ethical issues related to clinical genetics in China in seven settings — diagnosing hereditary genetic conditions, prenatal diagnosis, newborn screening, making prognoses with genetic information, identifying carriers of pathogenic variants, preimplantation genetic diagnosis, and whole-genome sequencing — and advocated for ethical considerations during genetic testing (*8*). Tao and Wang cautioned against discrimination in employment, marriage, education, and inclusion based on genetic information, and advocated for desensitization and deidentification of biomedical big data (*9*).

Likely spurred by the 1996 cloning of Dolly the

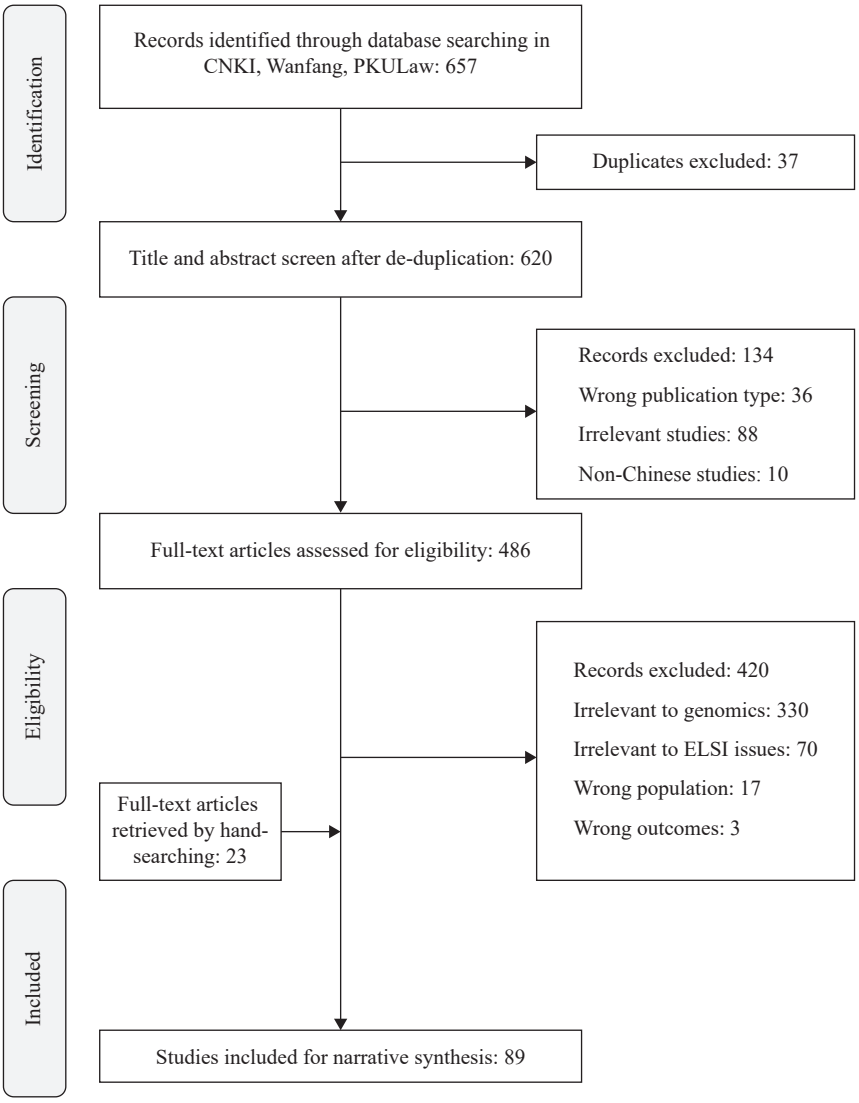

FIGURE 1. Flow chart for literature search of ethical, legal, and social implications of genomics in China.
Abbreviation: ELSI=ethical, legal, and social implications; CNKI=China National Knowledge Infrastructure.

sheep, 50 studies had "cloning" in their titles, with additional papers discussing cloning as a component of genomics research. An emerging consensus is a ban on reproductive cloning while allowing the exploration of cloning for research and therapeutics (*10*).

Regulatory Framework

Research interests in ELSI of genomics in China have grown after the revelation of genetically edited babies (*1*), with particular attention to informed consent and privacy protection (*9*,*11*–*12*). Other areas of interest include gene patents and over-the-counter genetic testing (GT) (*12*–*14*). Recent literature cautions against discrimination based on genetic information (*12*). Such issues require legal or regulatory oversight and warrant additional discussions.

Wang and colleagues used text analysis to outline key issues on ethical oversight related to GT, including data security and sharing, privacy protection, standard operating procedures, and regulations for clinical use of GT and genetic counseling (GC). Seven regulations require informed consent, and two require informed consent on data reuse. These seven regulations stress protection of patient privacy, but provide limited practical guidance. The article by Wang et al. provides a detailed list of the regulations, and recommends strengthening the existing legal and regulatory framework on ethical issues related to GT, stressing the adaptability, agility, and sensitivity of ethics governance; and providing ethics training for precision medicine practitioners. The "Rule on Human Genetic Resources Management, People's Republic of China" outlines regulations on collection, preservation, use, provision, services, governance, and legal responsibilities concerning human genetic resources. (*9*,*11*)

Perceptions of GT/GC among Physicians and the General Public

A new line of research examines perceptions of GT/GC among physicians and the general public (*15*–*20*). Niu and colleagues conducted a stratified random sample survey of Changsha city residents during June–July, 2012 and found positive attitudes toward GT/GC (73.4% of the 399 respondents) but a low level of understanding of GC (*19*). They found married people and college educated people were more likely to have positive attitudes toward GT. Xu and Zhang assessed public perception and attitude toward GT in Guangzhou City and found limited knowledge of GT among respondents (*20*). They predicted higher demand for GT but expressed caution about uncertainties related to wide adoption of GT, given limited familiarity with GT/GC and existing concerns over ethics and privacy protection (*20*). Cao and colleagues presented quantitative analyses of survey data on the perception of precision medicine and its applications in Shanghai Municipality and Lanzhou City from November 2018 to April 2019 (*21*). The authors surveyed 2,250 residents and found that residents were attentive to privacy protections, informed consent, and pricing of precision medicine treatment (*21*). Li et al. found limited knowledge of GT (78.2% of the respondents reported either "never heard of GT" or "just heard about the term GT") among 1,647 households in Xiacheng District, Hangzhou City (*17*). Family history, age, and knowledge and attitude toward GT were strongly associated with demand for GT services (*17*).

Cui and colleagues assessed the perception, attitude, and adoption of precision medicine among 434 clinicians in 48 hospitals across 12 provincial-level administrative divisions (PLADs) (*15*). Consistent with prior studies, they found limited knowledge of precision medicine among the clinicians. However, 92.6% of the clinicians surveyed believed that precision medicine has clinical utility, and 90.3% would recommend GT to patients who would benefit (*15*). Bai et al. surveyed 45 physicians in nine public hospitals on knowledge and attitudes toward GT and bioethics (*18*). They found that young, junior, male physicians tended to have positive views of GT and genetic therapy (*18*).

Future Directions

The development of ELSI of genomics research can be summarized by the three principles of ethics development for precision medicine that were proposed by Tao and Wang — privacy protection, database development and sharing, and shared responsibility and governance (*9*). Tao and Wang had four recommendations for future directions: developing ethical principles and rules for precision medicine, providing training on precision medicine ethics, strengthening ethics review for precision medicine research, and developing legal and regulatory framework governing precision medicine.

Guan pointed to a lack of governance on market entry, GC, and licensing and accreditation of genetic counselors in China, as the existing legal requirements and regulations have primarily focused on technology

and laboratory oversight (*13*). Wu highlighted challenges for clinical guidelines in the era of precision medicine (*22*).

DISCUSSION AND PUBLIC HEALTH IMPLICATIONS

Our scoping review leads to five critical assessments. First, Chinese researchers have increasingly attended to the key ELSI issues in genomics research and practices, as evidenced by the expanding body of literature on this topic (Figure 2). Second, empirical investigation of ELSI of genomics remains scant. Studies have surveyed attitudes and preferences toward GT/GC among physicians, patients, and the public, with a heavy representation of populations in the south and east of China and in one city (Lanzhou), but no national survey exists. Third, China's regulatory framework over genomics research and precision medicine has been responsive to the growing demand, but with varying pace. Currently, no regulations on over-the-counter GT/GC exist in China (*13*). Fourth, there has been no research on reimbursement for GT/GC services. Fifth, GC is an emerging field that requires coordinated effort for capacity building and regulatory oversight in China (*13*).

Conventional wisdom has it that genomics and precision medicine occur at the individual level, and therefore there is no clearly defined role for public health (*23*). However, genomics and precision medicine involve multiple levels of interventions, including patient-provider relationships, families, communities, and reimbursement policies (*23*). Precision public health was a key tool in the COVID-19 response by helping to provide the right interventions for the right populations and by helping to reduce health disparities (*24*). With predictive analytics, genomics extends its reach from precision medicine to precision public health (*25*). The Evaluation of Genomic Applications in Practice and Prevention Initiative provides an example of precision public health practice (*26*). Our review offers important implications for the emerging field of precision public health in China by assessing the landscape of ELSI of genomics in China.

Our review has two important limitations. First, we limited our search to studies published in Chinese. While this was by design to identify studies more relevant to the genomics research and practice in China, we may have missed important literature on ELSI of genomics published in other languages by Chinese authors. Second, we did not assess study quality because most retrieved studies were qualitative in nature. As the literature on ELSI of genomics in China continues to expand, we will revisit this topic

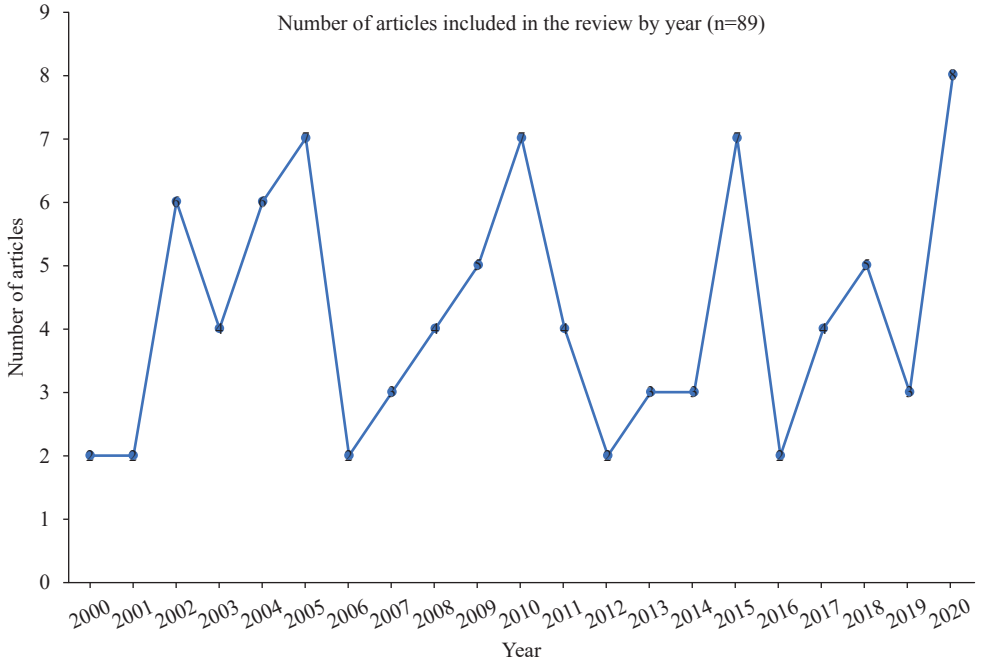

FIGURE 2. Number of publications on ethical, legal, and social implications of genomics in Chinese language included in our review by year of publication.

and update our review.

CONCLUSIONS

We conducted a scoping review of studies on ELSI of genomics in the Chinese language and identified four broad themes of the literature — ethical considerations, regulatory framework, perceptions of genomics and precision medicine, and future directions. We conclude that ELSI of genomics is a growing field and is highly relevant to public health in China.

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SUPPLEMENTARY MATERIALS

LIST OF STUDIES

Ethical Considerations (50)

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Perspectives

Using Genetic Testing at Cancer Diagnosis for Breast Cancer Control

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BACKGROUND

Breast cancer (BC) is the most common cancer among women globally. The WHO estimates 416,000 women are diagnosed to have BC annually in China, and the numbers of BC cases and deaths in China are predicted to rise by 16% and 48%, respectively, over the next 20 years (*1*). BC can be hereditary, and the most common cause of hereditary BC is an inherited pathogenic or likely pathogenic variant (henceforth called 'pathogenic variant' or 'PV') in the *BRCA1* or *BRCA2* genes. *BRCA1/BRCA2* PV carriers have a 17%–44% risk of developing ovarian cancer (OC) and a 69%–72% risk of developing BC up to the age of 80 (*2*). *PALB2* is a more recently established, high-penetrance BC gene: testing for which is now more widely advocated. *PALB2* carriers have a 53% risk of BC up to the age of 80 (*3*). In addition, *PALB2* has recently been shown to be a moderate-risk OC gene with a 5% lifetime risk of OC (*3*). PV in these three genes accounts for around 4% of BC. Most of these cancers are preventable or can be better mitigated if they are detected earlier.

International Clinical Guidelines on Genetic Testing

The use of genetic testing in women with BC has expanded significantly over the past decades because of the increasing number of laboratories offering testing with lower costs, the increasing public awareness and acceptability of testing, and the growing evidence base of clinical benefit for precision prevention. The current guidelines in the US and UK recommend offering genetic testing to people who fulfill recognized or established family history (FH)-based clinical criteria. These criteria are surrogates for *BRCA* probability, with genetic testing usually offered when someone has approximately a 10% probability threshold of being a *BRCA* carrier. However, people with PV in cancer-susceptibility-genes (CSGs) do not always have a strong FH, and these criteria miss a large proportion (approximately 50%) of PV carriers (*4*–*5*). An alternative option is to offer unselected *BRCA1/BRCA2/PALB2* genetic testing for all BC patients to identify more PV carriers. Unselected, multi-gene testing of BC patients has several benefits for PV carrier patients themselves and also enables genetic testing (cascade testing) to identify relatives of all BC patients carrying the familial PV. These relatives can then benefit from early diagnosis and precision prevention.

Benefits for patients: There are several effective and available risk management options for BC patients with high-risk PVs. For patients that have already been diagnosed with unilateral BC (cancer in one breast), PV carriers can choose contralateral, prophylactic mastectomy (CPM) (preventative mastectomy on the other breast) to reduce their risk of developing contralateral BC. Cancer-affected carriers may become eligible for treatment with novel drugs [like poly ADP ribose polymerase (PARP)] inhibitors] and newer, precision medicine-based therapeutics through clinical trials. They can also undergo surgical prevention for OC as they are at increased risk of OC. Therefore, knowing CSG variant status is important for BC clinical management and overall prognosis.

Benefits for relatives: To reduce BC risk, relatives found to be *BRCA1/BRCA2/PALB2* PV carriers can be offered enhanced MRI/mammography screening, risk-reducing mastectomy (RRM) (*6*), or chemoprevention with selective estrogen-receptor-modulators (*7*). To reduce OC risk, *BRCA1/BRCA2* PV carriers can opt for risk-reducing salpingo-oophorectomy (RRSO) (*8*). RRSO is now also recommended for *PALB2* PV carriers (*9*).

Cost-effectiveness: A study was conducted to estimate the health benefits and costs of multigene testing for all BC-patients compared with the current practice of genetic-testing (*BRCA*) based on FH/clinical criteria in the US and UK settings. We obtained data from 11,836 patients in population-based BC cohorts recruited to four large research studies, showing that unselected *BRCA1/BRCA2/*

PALB2 multigene testing approach for all BC patients is cost-effective compared with *BRCA* testing based on FH/clinical criteria — with incremental cost-effectiveness ratios well below UK and US cost-effectiveness thresholds (*10*). One year's unselected panel genetic testing could prevent 2,101 cases of BC or OC and 633 deaths in the UK, and 9,733 cases of BC or OC and 2,406 deaths in the US (*10*). These findings support changing the current policy to expand genetic testing to all women with BC. This is now recommended by the American Society of Breast Surgeons (*11*). Studies in Spain, the US, and Norway have also shown evidence for the cost-effectiveness of testing women with *BRCA*-related cancers and the cascade testing of relatives of the index cases (*5*,*12*–*13*).

UPTAKE OF RISK-REDUCING STRATEGIES

RRM reduces the risk of developing BC in PV carriers with no history of BC by 91%–95% (*6*). However, significant differences have been seen in the uptake of risk-reducing strategies for *BRCA* carriers across countries. The average RRM uptake is 27.8% based on data from a cohort of 3,413 unaffected women with *BRCA1/BRCA2* PV from ten countries (*14*), with the highest in the US (49.9%) and the lowest in Poland (4.5%). The mean age at RRM is 41.8 years (40.7 years for *BRCA1* carriers and 42.4 years for *BRCA2* carriers), and 3.4% of the mastectomies are done at age 60 and above. Globally, there has been an increasing trend in RRM, with uptake rates of 30.3% post-2009 versus 26.9% pre-2009. However, some countries have persistently low rates (Poland) or decreased rates (from 39.1% to 35.9% in Canada). The RRM uptake among unaffected PV carriers was 37.5% in China, though this was based on a small sample of 30 patients (*14*).

Although growing evidence has shown that RRM is safe and provides significant benefits from an oncological perspective, decision-making to undergo RRM remains complex and difficult for many. Reconstruction procedures can be complicated and are associated with a not-insignificant morbidity rate. Many women may have associated psychosocial, body image, or sexual concerns and require psychological support. In recent years, modified surgical options, including nipple-sparing mastectomy in which the nipple-areolar complex is preserved, have become available. This has been shown to improve cosmesis, with patients reporting better psychosocial and sexual well-being (*14*).

RRSO reduces OC risk among *BRCA1/BRCA2* PV carriers by 96% (*8*). The RRSO uptake rates can also vary across countries. Uptake rates increase with time and have been reported to be approximately 64.7% among *BRCA* carriers. The mean age at RRSO is 45.6 years (44.7 years for *BRCA1* carriers and 47.7 for *BRCA2* carriers). China was reported to have a low RRSO uptake rate of 36.7% in comparison to a broader cohort of 6,233 *BRCA* PV carriers from ten countries (*14*). There may be many reasons for such differences in uptake rates, including differences in patient preferences, cultural attitudes, health system differences, out-of-pocket costs, counselling, and extent of follow-up.

Other BC prevention options include chemoprevention and breast screening for PV carriers without a history of BC. The uptake rate of chemoprevention ranged from 2% to 15% across countries. As per the National Institute for Health and Care Excellence (NICE) guidelines for familial BC in the UK, annual mammographic surveillance is offered to women aged 40–69 years with a known *BRCA1/BRCA2* PV, and annual MRI surveillance is recommended at even younger ages (30–49 years). The BC screening guideline in China recommends *BRCA1/BRCA2* PV carriers aged 25–75 years undergo breast ultrasound screening every six to twelve months and conduct a breast MRI annually; *BRCA1/BRCA2* PV carriers aged 30–75 years undergo additional mammography annually.

BREAST CANCER GENETIC TESTING IN CHINA

Patient and disease characteristics in Chinese women are different from those in women from western countries. Chinese women's mean age of BC diagnosis is between 45 and 55: about ten years younger than most Caucasian women (*15*). Young BC patients tend to have a higher CSG prevalence. The prevalence of *BRCA* and *PALB2* PV-carriers appears to be higher in Chinese women with BC than in Caucasian women. Therefore, offering genetic testing to all BC patients would likely greatly benefit Chinese women with BC and their families, preventing many more cancer cases and deaths in China. The one-child policy followed by China for many decades (which has now been changed) has also led to smaller family sizes and a

smaller number of female relatives, making the FH-based testing approach potentially even more likely to miss PV carriers and thus overlook huge opportunities for precision prevention in China. As such, the potential impact and benefit of unselected genetic testing at BC diagnosis in China could be even greater than in other Western populations.

In China, there is currently only limited genetic testing available for BC cases. Even FH/criteria-based testing is not uniformly/systematically available as this is not part of the standard state-funded health package. Most patients have no access to genetic testing. Moving to even a FH/clinical-criteria based testing approach is better than the currently-predominant, no-testing approach. However, an alternative would be to move straight to offering testing for all BC cases and cascade testing relatives of index cases. This would have a much greater impact. The cost-effectiveness of these approaches has been evaluated in another research study by the authors (*16*). We examined the incremental lifetime effects, costs, and cost-effectiveness of multigene-testing all BC patients compared with FH/clinical-criteria based genetic (*BRCA*)-testing and no genetic-testing. The findings of this study suggest that unselected, high-risk, multigene-testing for all Chinese BC patients is cost-effective compared with FH/clinical-criteria testing and no genetic-testing in China. Testing all BC patients at diagnosis can identify many more PV carriers for screening/prevention in China, saving many more lives. One year's unselected multigene testing could prevent 7,868 BC or OC cases and 5,164 deaths in China (*16*).

IMPLEMENTATION OF BC GENETIC TESTING

It is important for research evidence to be transitioned to clinical and public health practice for patient/public benefit. In China, there have been some concerns about the current state of genetic testing implementation and oversight. Although unselected, multigene testing for BC patients has been shown to be cost-effective and the price of genetic testing is falling, there remain a number of challenges to overcome in implementing a policy supporting unselected multigene testing for all BC patients.

In China, genetic testing is mainly performed in laboratories at major hospitals affiliated with top-ranked universities or large commercial companies, while many local laboratories are not capable of undertaking/delivering genetic tests. The current laboratory infrastructure lacks the resources and capacity to deliver unselected genetic-testing for all BC patients given the large numbers diagnosed annually. The pool of trained counsellors or clinicians to deliver genetic counselling is also limited. With more genetic-testing conducted, many more PVs and variants of uncertain significance (VUS) carriers will be diagnosed. In addition to expanding laboratory infrastructure, clinicians will need to be trained to increase their understanding of genetics and ability to counsel patients about genetic-testing and its implications for management including that of VUS. Genetic-counselling services should be improved and implementation could be supported by a process of training and education for healthcare professionals to enhance the genetic-counselling workforce. Newer context-specific delivery models will be needed for implementing this approach. 'Mainstreaming' genetic-counselling and testing, which has been successfully implemented across OC treatment pathways, can be an option for successful, large-scale implementation of testing at BC diagnosis too (*11*). There is also a need to expand resources/infrastructure and clinical manpower for downstream management pathways, including screening and prevention. The outcomes of genetic-testing implementation pathways for BC patients need to be evaluated through real-world studies.

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Methods and Applications

Demand for Direct-to-Consumer Genetic Testing Services in China and Its Implications for Precision Public Health — China, 2021

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ABSTRACT

Introduction: In China, the direct-to-consumer genetic testing (DTC-GT) industry has been undergoing exponential growth during the past few years. This study intends to assess characteristics of DTC-GT users in China, estimate the price elasticity of demand, quantify monetary values of DTC-GT features, and discuss its implications to the development of precision public health.

Methods: A total of 629 participants with an average age of 28.8 years were collected from an online survey conducted in November 2021. A discrete choice experiment and a mixed logit modelling approach were used to elucidate consumer preferences to DTC-GT services and evaluate monetary values of certain features.

Results: DTC-GT users were found to have a higher level of income on average. The price elasticity of DTC-GT services was estimated to be −0.72 (95% CI −0.73 to −0.70). The willingness-to-pay for genetic testing features of physical traits, personality, and dietary recommendation were estimated to be 90, 107, and 220 CNY, respectively.

Discussion: The nature of big genomic data makes DTC-GT have the potential to aid in the advancement of precision public health through more precise disease prevention and control strategies. The study also notes the need for addressing potential drawbacks of DTC-GT and protecting genetic privacy.

INTRODUCTION

Precision public health aims to more precisely describe and analyze individuals and their environment over their life course, tailor preventive interventions for at-risk groups, and eventually improve the overall health of the population by applying technologies from novel genomic big data (*1*–*2*). The genetic data collected by direct-to-consumer databases have the potential to aid in the advancement of precision public health (*3*–*5*). In China, the direct-to-consumer genetic testing (DTC-GT)* industry has also been undergoing exponential growth in the past five years. According to a recent report by Frost & Sullivan, in the mainland of China, the accumulated number of DTC-GT consumers has reached 12.1 million in 2020 and the market is projected to reach 72 million US dollars in 2021. Leading DTC-GT providers in China, such as WeGene and 23mofang, now offer different types of DTC-GT products to consumers in which the results can be easily accessed on a mobile phone without the need for an intermediary medical professional. Table 1 lists testing prices and features of selected DTC-GT products from major providers of China.† This expanding volume of East Asian users in China's DTC-GT market could become helpful for the research and development of precision public health in China (*6*–*7*).

Despite a considerable amount of research that has already utilized individual-level genetic data, little is known about what consumers know and how they respond to DTC-GT services in China. This article serves as the first study to assess characteristics of current DTC-GT users in China, estimate the price elasticity of demand, and quantify monetary values of major features provided by DTC-GT services.

* Different from clinical genetic testing, DTC-GT is marketed publicly via Internet, social media, or television advertisements, and the products can be bought online or in stores directly by consumers. DTC-GT provides consumers access to their genetic information at a relatively lower price, without necessarily involving a healthcare provider or an intermediary medical professional in the process.

† There are two major testing methods with different levels of thoroughness used by DTC-GT products available in China's market. Most DTC-GT products use the SNP-chip genotyping method, which checks for the presence or absence of specific variants, such as particular single nucleotide polymorphisms (SNPs), across the genome at a relatively lower price. Another testing method used by a few high-end DTC-GT products is the whole genome sequencing (WGS) method, which sequences almost the entire genome and identify the variants present within it at a higher price.

METHODS

Sample Collection

The survey was conducted by the China Center for Genoeconomic Studies at China Agricultural University. After providing informed consent, 667 participants took our online survey in November 2021. The survey collected information on participants' demographic and socioeconomic characteristics as well as their experience of using genetic testing services. Excluding participants who did not complete the survey, our analytical sample totaled 629 observations. As reported in Table 2, the average respondent in our sample was 28.8 years old, completed 16.1 years of education, and earned about 105,000 CNY annually.

Design of the Discrete Choice Experiment

To evaluate consumer preferences in DTC-GT services and estimate monetary values of certain features, we integrated a discrete choice experiment (DCE) in the survey. The discrete choice experiment is an advanced research design that can reliably elicit consumers' true preferences and choice intentions by

TABLE 1. Selected DTC-GT products from major providers in China.

Testing method	Company	Product	Feature					Price per kit (CNY)
			Ancestry	Physical traits	Health	Personality	Lifestyle recommendation	
SNP-chip genotyping	WeGene	Basic kit	Yes	Yes	Yes	Yes	Yes	799
	23mofang	Health/ancestry kit	Yes	Yes	Yes	Yes	Yes	699
	23mofang	Ancestry kit	Yes	Yes	No	Yes	No	499
	Gese	Basic kit	Yes	Yes	Yes	Yes	Yes	699
	Genebox	Discovery kit	Yes	Yes	No	No	No	199
	Genebox	Expert kit	Yes	Yes	Yes	No	No	699
WGS	WeGene	WGS regular kit	Yes	Yes	Yes	Yes	Yes	3,999
	WeGene	WGS youth kit	Yes	Yes	Yes	Yes	Yes	2,499

Note: The data were collected (as of February 2022) from websites: WeGene, https://www.wegene.com/shop/ (last accessed February 11, 2022); 23mofang, https://www.23mofang.com/ (last accessed February 11, 2022); Gese, https://www.gesedna.com/ (last accessed February 11, 2022); Genebox, https://genebox.cn/ (last accessed February 11, 2022).
Abbreviation: DTC-GT=direct-to-consumer genetic testing; SNP=single nucleotide polymorphisms; WGS=whole genome sequencing.

TABLE 2. Summarized characteristics by consumers' experience with the usage of DTC-GT services from an internet-based survey (N=629).

Variable	Pooled		DTC-GT user		Non-DTC-GT user	
	Mean	SD	Mean	SD	Mean	SD
Demographic and socioeconomic characteristics						
Male	40.1%	–	44.5%	–	39.1%	–
Age (years)	28.8	7.8	29.0	6.3	28.7	8.0
Ethnic minority	4.6%	–	3.6%	–	4.8%	–
Full-time students	22.6%	–	15.5%	–	24.1%	–
Party member	22.4%	–	34.5%	–	19.8%	–
Years of schooling	16.1	2.1	16.2	2.3	16.1	2.0
Annual income in 10,000 CNY	10.5	13.2	13.9	18.6	9.8	11.7
Knowledge, experience, and perception to DTC-GT						
Knowing DTC-GT very well	23.5%	–	69.1%	–	13.9%	–
Knowing DTC-GT a little	64.9%	–	30.9%	–	72.1%	–
Having used DTC-GT before	17.5%	–	–	–	–	–
Friends or relatives have used DTC-GT before	24.6%	–	71.8%	–	14.6%	–
No. of respondents	629		110		519	

Note: "–" means not applicable.
Abbreviation: SD=standard deviation; DTC-GT=direct-to-consumer genetic testing.

replicating real-life situations (*8*). Then, we identified possible attributes associated with consumers' preferences/purchase decisions of DTC-GT products. To ensure feasibility and respondents' understanding of the choice tasks, we restrained the choice experiment to including four key attributes with various levels: (a) price (levels: 300/600/900/2,500 CNY per testing kit), (b) features of genetic testing results provided (levels: health and ancestry/physical traits/personality/dietary recommendation), (c) research collaboration status (levels: no external collaboration/collaborating with research institutes/having published research articles), and (d) types of interpretation for testing results provided [levels: by words/by artificial intelligence (AI)/by staff]. We applied the D-optimal procedure to generate a total of 8 choice tasks by using JMP (Version 13, SAS Institute Inc., Cary, NC, USA). Each choice task included three DTC-GT alternatives and an opt-out option. In the survey, respondents were asked to choose their most preferred option in each choice task, and an example choice task is presented in Table 3.

Statistical Analyses

This research used the mixed logit model that allowed for random parameters and heterogeneous preferences to estimate attribute coefficients, price elasticity of demand, as well as willingness-to-pay (WTP) for different features in DTC-GT services. Price elasticity was used to evaluate the responsiveness of demands to changes in the price of DTC-GT services. WTP measured the maximum price a consumer is willing to pay for a specific feature of DTC-GT services. All statistical analyses were performed using Stata/MP (Version 14, StataCorp, College Station, TX, USA).

RESULTS

Chinese Consumers' Knowledge, Experience, and Perception of DTC-GT Services

As reported in Table 2, 88.4% of respondents were aware of DTC-GT services, 24.6% respondents reported that their friends or relatives had used DTC-GT services before, and 17.5% respondents (N=110) had actually used or purchased DTC-GT services by themselves. Compared to respondents who have not taken DTC-GT services before (column 3), there was a higher proportion of Han Chinese males and party members among prior users of DTC-GT services (column 2). DTC-GT users on average earn 42,000 CNY more than non-DTC-GT users annually. Overall, 69.1% of DTC-GT users reported knowing DTC-GT services very well, compared to only 13.9% of non-DTC-GT users; 71.8% of DTC-GT users have at least one friend or relative who also has taken DTC-GT services, and the proportion is much lower among non-DTC-GT users (14.6%), which is consistent with the classic theory of diffusion of innovation (*9*).

TABLE 3. An example of a choice task offered to respondents.

Option (A)	Option (B)
Price: 600 CNY	Price: 300 CNY
Ancestry analysis (e.g. the proportion of Northern Han Chinese in the ancestry component)	Ancestry analysis (e.g. the proportion of Northern Han Chinese in the ancestry component)
Health analysis (e.g. the risk of Type 2 diabetes)	Health analysis (e.g. the risk of Type 2 diabetes)
Physical traits (e.g. the genetic height)	
Research collaboration: collaborating with several research universities/institutes	Research collaboration: collaborating with several research universities/institutes
Interpretation for testing results: by detailed text explanation	Interpretation for testing results: by detailed text explanation
Option (C)	**Option (D)**
Price: 900 CNY	
Ancestry analysis (e.g. the proportion of Northern Han Chinese in the ancestry component)	
Health analysis (e.g. the risk of Type 2 diabetes)	(None of the above)
Dietary recommendation (e.g. alcohol drinking advice)	
Research collaboration: having published several research articles	
Interpretation for testing results: by Artificial Intelligence	

Consumer Preferences, Price Elasticity of Demand, and Willingness-to-Pay for DTC-GT Services in China

Parameter estimates (available upon request) demonstrate that respondents prefer to have a DTC-GT service with a lower price and external research collaborations. They prefer additional genetic testing features of dietary recommendation over personality and physical traits. In terms of result interpretation, respondents have a slightly higher preference for having the information by words rather than by staff or AI. The price elasticity of DTC-GT services was estimated to be −0.72 [95% confidence interval (CI): −0.73 to −0.70], indicating that a 10% increase in prices of DTC-GT services would result in a 7.2% decrease in consumer demand. This finding is in line with existing literature that has reported inelastic or nonresponsive demand to a price change of healthcare services in China and across the world (*10*–*11*). Besides basic health and ancestry reports by a DTC-GT product, the mean willingness-to-pay for additional genetic testing features like dietary recommendation, personality, and physical traits was estimated to be 220, 107, and 90 CNY, respectively, illustrating a potential demand for personalized nutrition among Chinese consumers.

DISCUSSION

The nature of big genomic data makes DTC-GT a promising way to improve the health of sub-groups within the population who are more predisposed to certain health conditions and ailments (*7*,*12*–*13*). As illustrated in Figure 1, aligned with the aims of Healthy China 2030, health equity could be advanced through targeted interventions on the basis of both longitudinal behavioral records and genetic data obtained from DTC-GT of subpopulations in the future.

This study was subject to some limitations. First, the current study was based on a sample of 629 participants collected from an online survey, which might lead to a lack of statistical power due to the relatively small sample size. Second, the sample was not nationally representative and more studies are needed to generalize our findings.

Nonetheless, a couple of potential drawbacks of DTC-GT should be noted and avoided. From the perspective of consumers, there could be adverse psychological effects when knowing the potentiality of severe diseases from testing results, and consumers may make irrational decisions that could damage their health based on non-deterministic DTC-GT results (*14*). DTC-GT companies are thus responsible for ensuring the transparency of information and informing consumers to avoid any misinterpretation. In addition, genetic privacy and data protection are a primary legal concern associated with DTC-GT in China (*15*). On April 15, 2021, the Biosecurity Law of the People's Republic of China enacted stricter controls on the use of individual genetic data,

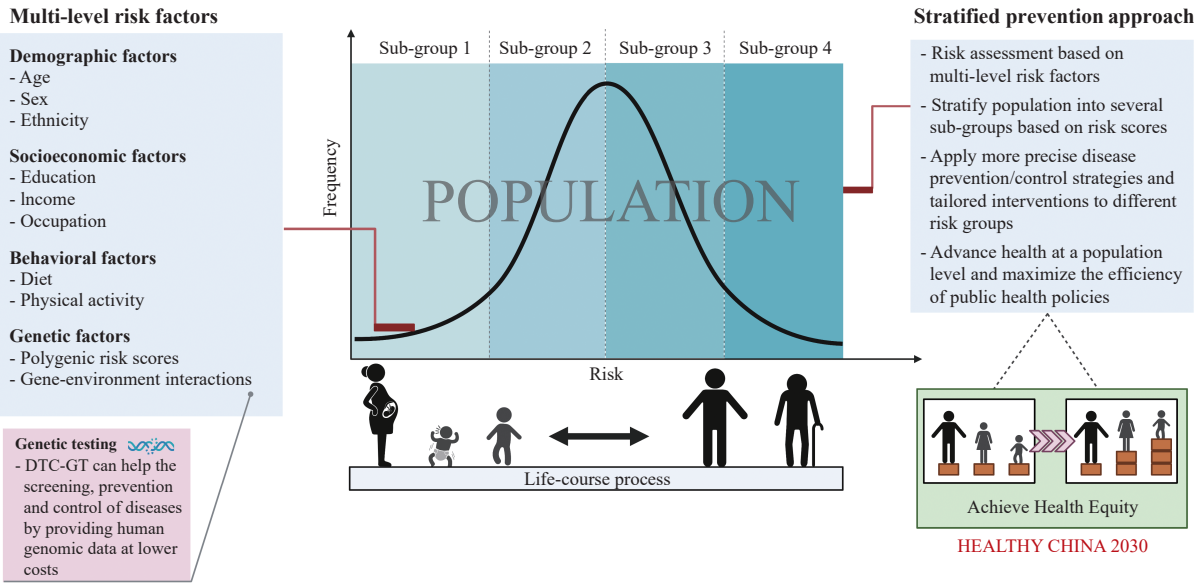

FIGURE 1. A precision public health framework to stratify the population and provide tailored interventions.
Abbreviation: DTC-GT=direct-to-consumer genetic testing.

warranting Chinese consumers with enhanced genetic data and privacy protections. Still, developing a comprehensive legal framework to regulate genetic data and the rapidly evolving DTC-GT market will be a challenge to the government in China.

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