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Human Phenome Research Progress Report 2020

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Background introduction

Definition of human phenome

Genes and the environment interact to determine the traits of the human body, and these traits are known as the phenotype. The phenome was initially defined as the sum of all the traits of an organism. Following deepened research of the human phenotype, the phenome is now defined as the biological, physical and chemical characteristics – they include the morphological characteristics, functions, behaviors, and the rule of molecular composition - of an organism, from its embryonic development to birth, growth, aging, and death.

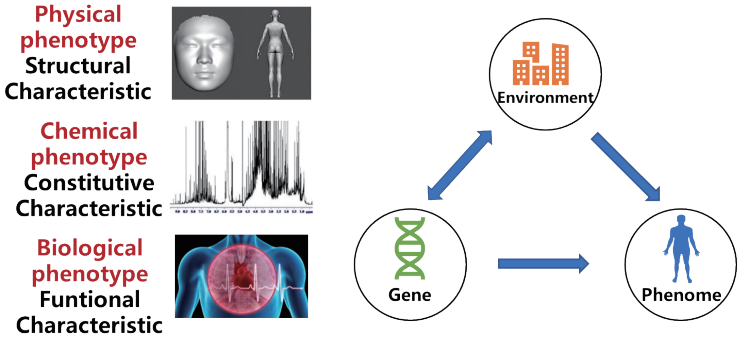

Illustration 1-Concepts of phenotype and phenome

Strategic new height in the post-genomics era

Many experts have forecast that the human phenome will take over the human genome to become the next strategic height in the post-genomics era. The precise measurement of the human phenotype and comprehensive analysis of the human phenome will systematically deconstruct the strong relationship between phenotypes, construct a phenotype network, open up multi-dimensional and cross-scale correlations between the macro and micro phenotypes, and clarify the cross-scale correlation among phenotypes. These important clues to decode the life sciences shall serve to enhance precise health management. The multi-dimensional, cross-scale, high-precision and comprehensive measurement of the

human body will draw a "navigation map" of life sciences in the era of big data, explore the universe of the human body, and safeguard human health.

Accelerated deployment of human phenome research

The United States, the United Kingdom and Germany have accelerated their scientific research support for human phenome research, with the number of related research projects constantly rising in recent years.

The American Human Phenome Research Program kicked off such efforts at an earlier stage - in 2006, the MIND Institute at the University of California, Davis, launched the Autism Phenome Project[1]. Since then, the National Cancer Institute (NCI) has established the Clinical Proteomic Tumor Analysis Consortium (CPTAC)[2]. The comprehensive protein-genomic analysis further explained the gene mutations that drive the disease phenotype and clarified the tumor pathophysiology to explore personalized and precise clinical treatments.

In its 2015 fiscal year budget, the National Science Foundation (NSF) Directorate for Biological Sciences (BIO)[3] identified the "prediction of individual traits (genome to phenome) based on DNA sequence" as one of the key projects to support. The National Heart, Lung, and Blood Institute (NHLBI) also launched the Trans-Omics (TOPMed) project[4], which collects whole-genome sequencing and other omics data, and combines them with molecular, behavioral, imaging, environmental and clinical data to improve the prevention and treatment of heart, lung, blood diseases and sleeping disorders. Meanwhile, the US NIH launched the TGAC pilot project[5], using project databases such as that of the ExAC to study the influence of genes and gene mutations on phenotypes. The NSF, in

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[1] Autism Phenome Project. Available from: https://health.ucdavis.edu/mindinstitute/research/autism-phenome-project/index.html.

[2] National Cancer Institute's Clinical Proteomic Tumor Analysis Consortium (CPTAC) Available from: https://proteomics.cancer.gov/programs/cptac.

[3] 2015 fiscal year budget Available from: https://www.nsf.gov/about/congress/reports/nsf13079.pdf

[4] Trans-Omics for Precision Medicine Program. Available from: https://www.nhlbi.nih.gov/science/trans-omics-precision-medicine-topmed-program.

[5] NIH pilot project will match researchers to genes, gene variants of interest.; Available from: https://www.nih.gov/news-events/news-releases/nih-pilot-project-will-match-researchers-genes-gene-variants-interest

partnership with the Simons Foundation[6], also launched four new centers to bring mathematical perspectives to biological research in its search for the rules of life. The latest precision health research project[7] established by the National Human Genome Research Center (NHGRI) under the NIH focuses on using "Reverse Phenotyping" to perform reverse engineering of genomic data. In this process, phenotypes are refined based on genetic marker data in order to analyze genetic big data. Reverse Phenotyping uses cutting-edge genomes and computing tools to develop and evaluate next-generation health care methods in order to make improvements to disease diagnosis, treatment and prevention.

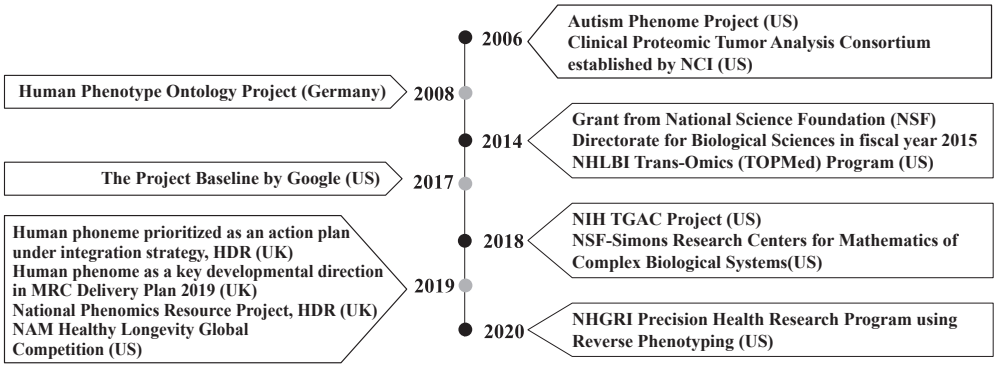

Illustration 2-Human phenome-related research projects in developed countries

Phenotype-related health research projects have also been rolled out in recent years. For example, Google launched a large-scale health project in 2017 titled Project Baseline[8]. The project used a variety of new health tools to collect massive volumes of health data by continuously tracking volunteers' conditions of gut microbiota, sleep, exercise, and mental state in multiple dimensions, so as to create a "standardized human health map" and offer clues

[6] NSF-Simons centers to search for the Rules of Life.
Available from:
https://www.nsf.gov/news/news_summ.jsp?cntn_id=245523&org=NSF&from=news
[7] NHGRI Precision Health Research Program Using Reverse Phenotyping to Better Understand Genomics. Available from:
https://www.genomeweb.com/researchfunding/nhgri-precision-health-research-program-using-reverse-phenotyping-betterunderstand#.X5puLEfitPZ.
[8] Project Baseline. Available from: https://www.projectbaseline.com/

for disease prediction. The National Academy of Medicine also launched the Healthy Longevity Global Competition[9] in 2019 as part of its efforts to achieve breakthrough innovations that would extend human health and improve bodily functions of the elderly.

Europe has also successively introduced scientific research projects related to the human phenotype. Charite-Universitatsmedizin in Berlin, Germany launched the Human Phenotype Ontology (HPO) project[10] in 2008. The team used ontology engineering and computer science to structurally summarize the phenotypic information from medical literature, provide standard vocabulary for phenotypic abnormalities in human diseases, and establish tiers for phenotype-related vocabulary.

As the first country to build a human phenome research platform, the United Kingdom has also made human phenotype research a priority funding project. In April 2019, Health Data Research UK published an integration strategy and the 2019-2020 annual plan[11], in which the human phenome was prioritized as an action plan, and commenced a national human phenome resource project[12]. The MRC 2019 annual plan[13] also identified the human phenome plan as a key developmental direction.

China has taken the lead in launching the human phenome plan and has systematically deployed its research. In 2015, the Ministry of Science and Technology conducted a fundamental research titled "Survey on Physical Conditions of Various Ethnic Groups in China Through the Lens of Phenotype", which laid out the foundation for collecting physical phenotypic characteristics of 56 ethnic groups. In May that same year, the CPC Shanghai Municipal

[9] National Academy of Medicine Launches Global Competition Seeking Solutions for Improving Healthy Longevity. Available from: https://nam.edu/national-academy-of-medicine-launches-global-competition-seeking-solutions-for-improving-healthy-longevity/

[10] Human Phenotype Ontology(HPO). Available from: www.humanphenotypeontology.org

[11] HDR UK. Available from: https://www.hdruk.ac.uk/

[12] National Phenomics Resource Project. Available from: https://www.hdruk.ac.uk/projects/national-phenomics-resource/

[13] MRC Delivery Plan 2019. Available from: https://www.ukri.org/files/about/dps/mrcdp-2019/.

Committee and the Shanghai Municipal Government issued the "Opinions on Accelerating the Construction of a Science and Technology Innovation Center with Global Influence", which positioned "international human phenome" at the frontier of major science and technology breakthroughs.

In April 2016, the State Council issued "The Plan of Shanghai to Systematically Promote the Pilot Program of Comprehensive Innovation and Reform and Accelerate the Building of a Globally Influential Center for Scientific and Technological Innovation", in which the International Human Phenome Project was listed under major science projects that required deployment. In the same month, the Shanghai Zhangjiang High-tech Park launched the Molecular Phenome International Joint Center project and became an important part of the Zhangjiang Comprehensive National Science Center. In June that same year, the Shanghai Science and Technology Commission launched a major project titled "Research on Cross-scale Associations of Human Phenotypes and Their Genetic Mechanisms", which focused on the gene-environment-phenotype interaction mechanism and systematically measured the phenotypic characteristics of the Chinese natural population, characterizing the phenotypic traits of the healthy and the sick population, clarifying the genetic mechanism of the cross-scale correlation of human phenotypes, and promoting humanity in an all-round manner. In August 2016, the "13th Five-Year" plan for scientific and technological innovation in Shanghai listed the "international human phenome" as a strategic direction in the promotion of major breakthroughs in indigenous innovation.

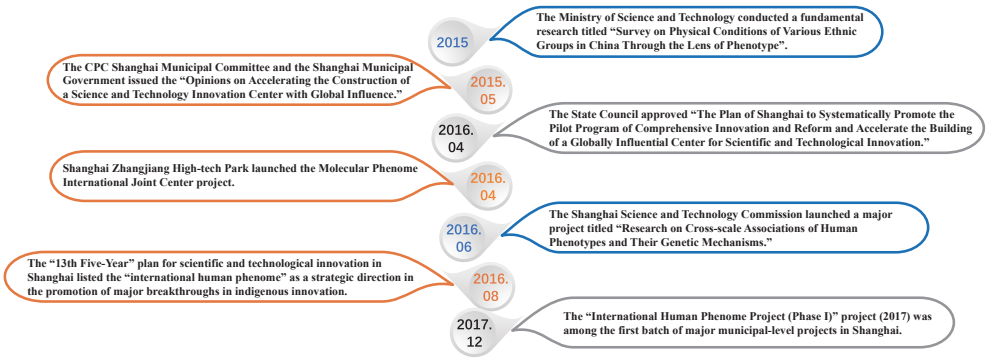

Illustration 3-Deployment of human phenome research projects in China

In December 2017, the "International Human Phenome Project (Phase I)" project undertaken by Fudan University in partnership with the Shanghai Institutes for Biological Sciences of the Chinese Academy of Sciences, Shanghai Jiao Tong University, and Shanghai Institute of Metrology and Testing Technology gained approval to become the first batch of major municipal-level projects in Shanghai to receive special funding.

"Human Phenome " International big science Project

While focusing on national and regional deployment, a team of scientists led by academician Jin Li of Fudan University has been actively working on the "Human Phenome " International big science Project. Backed by the funding allocated for the first batch of major science and technology projects in Shanghai, the phenotypic measurement of natural populations using 20,000 test indicators has officially commenced. The project is expected to achieve a comprehensive examination of 1,000 people in Shanghai and 10,000 people for application demonstration. In the future, we expect to precisely examine 50,000 people on a global scale and 500,000 people for application demonstration. We hope to draw the "navigation map" of the human phenome under the same technical standard and distributed international big science model featuring shared data resources.

Leading a new round of life science and bioindustry revolution

As a new paradigm of life science research, human phenome research is set to lead a new round of life science and bioindustry revolution by instigating original innovation, supporting precision medicine, leading international cooperation, and fostering industrial transformation.

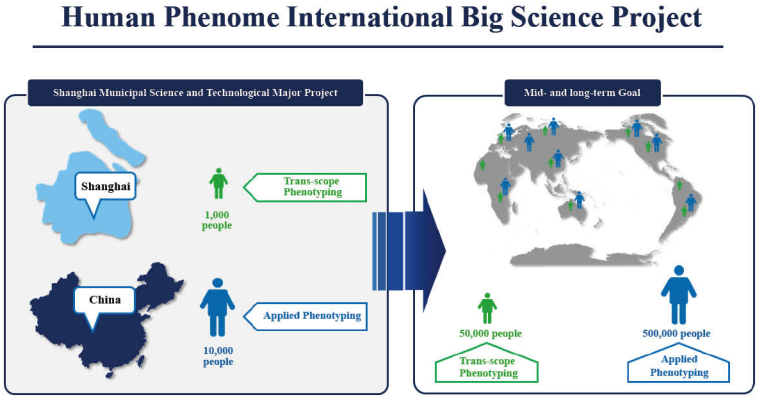

Illustration 4-Human Phenome International Big Science Project

Part I Human Phenome Research at a breaking point

Human Phenome research at a fast-development phase

Human phenome research has entered a period of rapid development in the past ten years. The number of papers on human phenomics and the popularity of human phenomics research increased significantly in 2020. Take the reports submitted to the American Society of Human Genetics Annual Meeting as an example. There were only 15 reports with the themes of "phenome", "genome-phenome", and "PheWAS" in 2017. In 2019, there were 59. The integration of multi-omics methods of phenomics and genomics to comprehensively analyze diseases and the development of personalized treatments are now trending topics.

Phenome project a consensus among the academia

In 2003, Nelson Freimer and Chiara Sabatti published an article in *Nature Genetics*, hence initiating the Human Phenome Project (HPP)[14] to gather a more powerful, standardized and diverse human phenotype database and integrate a series of science disciplines. At the same time, the initiative will promote cooperation between public institutions such as the National Institutes of Health (NIH) and the Wellcome Trust of the United Kingdom (Wellcome Trust) and non-profit organizations, biopharmaceutical companies, and other industries. Since the human phenome project was put forward, its importance has gradually become recognized by the entire academic community.

On the 125th anniversary of *Science* journal in 2005[15], the magazine published a list containing what it called the 125 most challenging scientific

[14] Freimer, N. and C. Sabatti, The human phenome project. Nat Genet, 2003. 34(1): p. 15-21.
[15] Kennedy, D. and C. Norman, What don't we know? Science, 2005. 309(5731): p. 75.

problems of the contemporary era. Topping the list were genetic and development-related questions such as "To What Extent Are Genetic Variation and Personal Health Linked?", "Why Do Humans Have So Few Genes?", and "What Genetic Changes Made Us Uniquely Human?". The bottleneck of these issues lies in the failure to interrelate genes, environmental factors and the phenotype. In 2010, the British *New Scientist* journal listed 50 ideas[16] that could change the course of future science, among which the phenome was ranked 13th. The article argues that the phenome is one of the most important scientific research priorities at the current stage, and is poised to bring tremendous breakthroughs. In 2013, *Nature*[17] reviewed the necessity of omics, which was experiencing rapid development. Phenomes are perceived to be able to systematically sort out disease-related phenotypic information, which may hold the key to unlocking medical and health big data. In 2016, the NSF published an article[18] in Science which laid out the blueprint for the development of NSF in the next few decades and proposed six research frontiers and three suggestions for reform. Among them, "understanding the rules of life (i.e. predicting phenotypes from genotypes)" was ranked 3rd. In 2018, in *Nature* journal's Technology Outlook section, "linking genotype and phenotype" was listed as one of the technology fields that can change life science research. In 2019, *Science* journal published a special edition[19] titled "Genotype to Phenotype", which analyzed and summarized the relationship between genotype and phenotype. In 2020, *Nature Review Genetics* magazine published a review article titled "The Future of Genetics and Genomics". Aravinda Chakravarti, a member of the National Academy of Sciences, the National Academy of Medicine, and the Indian National Science Academy, listed "decoding multifactorial phenotypes" as

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[16] Fifty ideas that will change science forever, in New Scientist. 2010: UK. p. 18.
[17] Baker, M., Big biology: The 'omes puzzle. Nature, 2013. 494(7438): p. 416-9. Available from: https://www.nature.com/articles/494416a
[18] Mervis, J., SCIENCE POLICY. NSF director unveils big ideas. Science, 2016. 352(6287): p. 755-6.
Powell, K., Technology to watch in 2018. Nature, 2018. 553(7689): p. 531-534.
[19] McGuire, A.L., et al., The road ahead in genetics and genomics. Nat Rev Genet, 2020. 21(10): p. 581-596.

one of the future research directions.

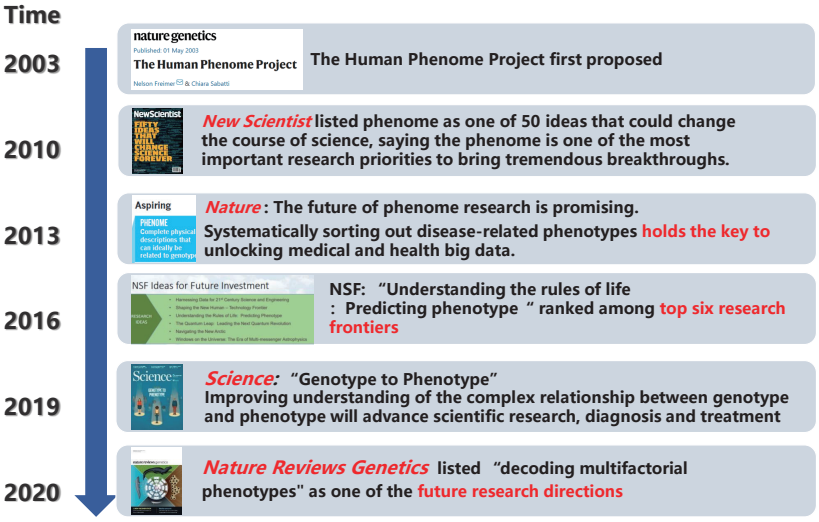

Illustration 5: Some commentaries by the academic community

In addition to the above academic reviews, various disciplines have also realized the importance of phenome research. In 2012, the American Society of Human Genetics (ASHG) annual meeting, which is the world's largest human genetics conference, held the 2012 Forum of the Human Variome Project[20] themed "Getting Ready for the Human Phenome Project", which clarified the necessity and feasibility of establishing a human phenome project. Since then, the research based on phenomics, genome-phenome and Phenome-wide Association Studies (PheWAS) has increased yearly. In 2019, Nature[21] published a brief historical review of human disease genetics, systematically reviewing the milestones in the development of human disease genetics, and pointed out the following: to fully realize the potential of genomics, continuous collaborative efforts in multiple aspects are required to create a more comprehensive genotype-phenotype map so that a thorough understanding of the disease can be established to provide basis and targets for future clinical treatment.

[20] Oetting, W.S., et al., Getting ready for the Human Phenome Project: the 2012 forum of the Human Variome Project. Hum Mutat, 2013. 34(4): p. 661-6.
[21] Claussnitzer, M., et al., A brief history of human disease genetics. Nature, 2020. 577(7789): p. 179-189. BOX 1

In 2020, the top cardiovascular journal *Circulation* published expert opinions[22] suggesting that epidemiology can only moderately predict the risk of cardiovascular disease. However, the study of the phenome through imaging can systematically determine its risk, and phenotype measurement is more meaningful for cardiovascular disease risk prediction.

At the end of 2020, the American Association for Dental Research adopted "Science for the Next Century: Deep Phenotyping" as the theme for its annual conference. In the lecture on deep phenotyping, dental experts introduced the progress and highlights of dental caries, periodontal disease, dental microbiome, and craniofacial anomalies. The content was published in the *Journal of Dental Research*[23].

Countries accelerating investment in human phenome research facilities

In 1996, Europe initiated the construction of the Orpha knowledge base for rare diseases and related drugs and created standard terminologies for 1,000 to 2,000 rare disease phenotypes. Orpha.net[24], which was launched in 2000, has become the preferred information provider and partner for patients, hospitals, major research institutions and pharmaceutical companies for its detailed and authoritative rare disease data.

The United Kingdom had an early start in phenotype research. It had as early as 1999 proposed the building of the UK Biobank[25], which was eventually launched in 2007. The biobank provides researchers with materials including human phenotype and is one of the largest health research projects in the UK.

In 2012, the Medical Research Council (MRC), in cooperation with the National Institute for Health Research (NIHR), announced the establishment of the MRC-NIHR Phenome Centre[26] (MRC-NIHR Phenome Centre) in the

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[22] Wierzbicki, A.S., Phenomics, Not Genomics, for Cardiovascular Risk Assessment. Circulation, 2020. 142(9): p. 821-823.

[23] WRIGHT, J. T. & HERZBERG, M. C. 2021. Science for the Next Century: Deep Phenotyping. J Dent Res, 220345211001850.

[24] orpha.net. Available from: https://www.orpha.net.

[25] UK Biobank. Available from: https://www.ukbiobank.ac.uk/

[26] Payne, T., London 2012 anti-doping laboratory to be developed into the world's first Phenome Center. Bioanalysis, 2012. 4(16): p. 1975-1975.

UK. This is the world's first phenome center. The center used the 2012 London Olympics drug metabolism testing laboratory facilities to create conducive conditions for researchers to explore disease characteristics and develop new drugs and treatment options. The National Phenotypic Screening Center[27] (NPSC) for human, animal and plant phenotype screening provides biologists with an opportunity to verify phenotype analysis.

In November 2012, the National Center for Biotechnology Information (NCBI) under the National Institutes of Health (NIH) in the United States announced the launch of a public free database called ClinVar[28] that would support research on the relationship between human genotypes and medically important phenotypes.

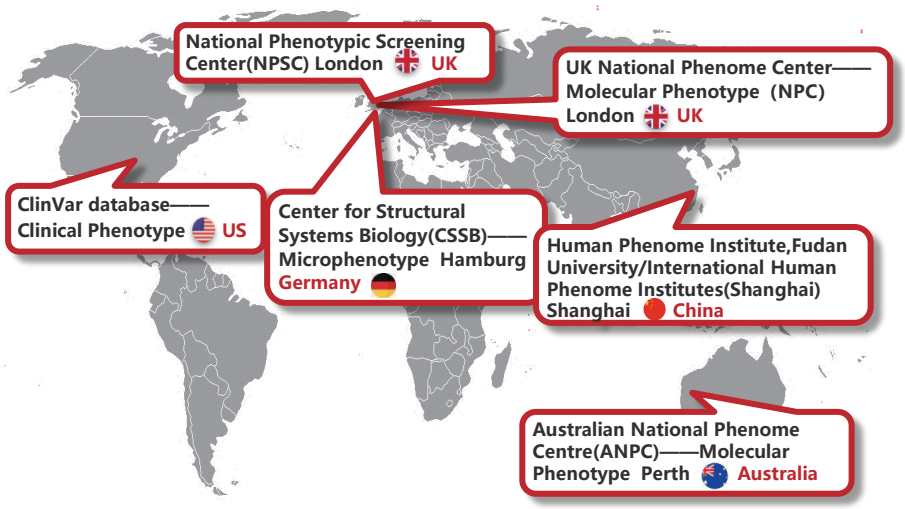

Illustration 6 An overview of human phenome research platforms across the globe

In 2014, Germany established the Center for Structural Systems Biology[29] (CSSB), which uses "super microscopes" such as the X-ray radiation source PETRA III (PETRA III) for electron storage rings and the X-ray free-electron laser (XFEL) to study the microscopic phenotype of biological samples and

[27] National phenotypic screening center. Available from: https://npsc.ac.uk/.
[28] Landrum, M.J., et al., ClinVar: public archive of relationships among sequence variation and human phenotype. Nucleic Acids Research, 2014. 42(D1): p. D980-D985.
[29] Centre for Structural Systems Biology. Available from: https://www.cssb-hamburg.de/about_us/index_eng.html.

analyze the phenotype and molecular basis of diseases.

Australia also set up the Murdoch University-led Australian National Phenome Center (ANPC) in 2019 to study the complex interactions and effects of genes, environment and lifestyle on human and animal health.

Countries stepping up efforts on "large cohort" as a strategic foundation

The large cohort is the basis for the human phenome study. At present, collecting human phenotype data based on the large cohort research system and studying the occurrence and development of human diseases under the combined action of the environment and genes have been widely accepted by the academic community. In the past ten years, countries around the world have attached great importance to large cohort research, and many countries have invested large sums of money and treated it as an important direction in strategic scientific research. The precision medicine programs in the United Kingdom and the United States have made large cohorts the main recipient of funding. China's cohort research started relatively early. Established in 2007, the Taizhou cohort[30], which has a size of 200,000 people, is one of the largest of its kind in China. It has been carried out for 13 years and 1.5 million biological samples have been collected during the phenome studies.

Progress 1 Remarkable achievements made through large cohort researches

The UK's large-scale prospective cohort study, the UK Biobank (UKB), was launched in March 2006. It is the world's largest human information resource bank and has collected health data and biological samples of 500,000 people. The UKB started collecting data on participants in 2010 and carried out biomarker analysis, medical imaging research and large-scale gene sequencing projects from 2016-2017, all of which have made significant progress. As of 2020, the results based on the cohort database have been remarkable. More than 1,500 scientific papers have been published, of which 131 can be found in top scientific journals. In terms of population health monitoring, the "UK Biobank Cancer

[30] Taizhou Cohort. Available from: http://fdtzihs.org.cn/sy

Numbers Summary Report", "UK Biobank Malignant Cancer Summary Report" and "UK Biobank Death Summary Report" have been published based on UKB data, and data analysis has been used to provide several policy recommendations for public health in the UK.

The Taizhou Cohort is a large-scale natural population cohort constructed based on a population of 5 million residents in China's Taizhou City. It aims to study the relationship between genetic factors, environmental factors and their interactions with major chronic diseases. The cohort research has involved the participation of multiple disciplines, taking into account the basic elements of epidemiology, systematically collecting biological samples, and focusing on the collection of various clinical phenotype data. As of 2020, the baseline population of the Taizhou cohort was 200,000, and 1.5 million biological samples had been collected from the population after monitoring the group for 13 years. More than 1,000 phenotypes and hundreds of exposure data were also collected from each participant. As the largest single-regional biobank in China, the Taizhou cohort has accumulated PB-level health and medical big data resources and is a world-leading population resource of high-quality and high-standard. A study[31] based on the Taizhou cohort found that for five common malignancies such as colorectal cancer, esophageal cancer, liver cancer, lung cancer and gastric cancer, early cancer signals - trace tumor methylation - can be detected non-invasively before reaching the current clinical diagnosis gold standard, or even before patients exhibit symptoms. A systematically designed sub-cohort under the framework of the "Taizhou Cohort" called the "Taizhou Imaging Study" has been carried out in rural communities in recent years. Disease status and risk factors of asymptomatic cerebral small vessel disease (CSVD) and their correlation with cognitive impairment, abnormal gait, and other disease phenotype have provided clinical intervention strategies for related diseases. Based on a cohort survey[32] of

[31] Jiang, Y., et al., Lifestyle, multi-omics features, and preclinical dementia among Chinese: The Taizhou Imaging Study. Alzheimers Dement, 2020.

[32] SUO, C., YANG, Y., YUAN, Z., ZHANG, T., YANG, X., QING, T., GAO, P., SHI, L., FAN, M., CHENG, H., LU, M., JIN, L., CHEN, X. & YE, W. 2019. Alcohol Intake Interacts with Functional Genetic Polymorphisms of Aldehyde Dehydrogenase (ALDH2) and Alcohol Dehydrogenase (ADH) to Increase Esophageal Squamous Cell Cancer Risk. J Thorac Oncol, 14, 712-725.

the Taizhou population, the association mechanism between drinking and high risk of esophageal squamous cell carcinoma was clarified, and it was confirmed that the elderly, females, non-smokers and non-drinkers who have poor oral hygiene indicators are susceptible to esophageal squamous cell carcinoma[33].

Progress 2 Systems medicine with deep phenotyping as a new healthcare paradigm

As modern medicine improves, the spectrum of diseases has undergone tremendous changes. Globally, chronic diseases lead to a heavy burden on the healthcare system because of increased deaths, disabilities, and a poorer quality of life. Leroy Hood, co-founder of the Institute for Systems Biology (ISB), and his team have proposed a new discipline[34] known as P4 medicine that is centered on the principles of predictive, personalized, preventive, and participatory, as well as the concepts of "demystifying disease, democratizing healthcare". Many experts have called for the use of systems medicine with deep phenotyping as a new healthcare model that would treat the body as a multi-layered network[35] and use a holistic approach to decipher the complex factors behind human health and diseases. The systems medicine that disrupts the original paradigm leverages big data to analyze human phenotypes in an in-depth, intensive, and dynamic manner, providing the scientific basis to identify individual health conditions. Deep phenotyping and systems medicine are now used in areas such as gastrointestinal tumors, multiple myeloma, prevention of metabolic syndrome in newborns and maternal type 2 diabetes in women, and personal health management. [36]

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[33] EKHEDEN, I., YANG, X., CHEN, H., CHEN, X., YUAN, Z., JIN, L., LU, M. & YE, W. 2020. Associations Between Gastric Atrophy and Its Interaction With Poor Oral Health and the Risk for Esophageal Squamous Cell Carcinoma in a High-Risk Region of China: A Population-Based Case-Control Study. Am J Epidemiol, 189, 931-941.

[34] Sagner, M., et al. (2017). "The P4 Health Spectrum - A Predictive, Preventive, Personalized and Participatory Continuum for Promoting Healthspan." Prog Cardiovasc Dis 59(5): 506-521.

[35] Trachana, K., et al. (2018). "Taking Systems Medicine to Heart." Circ Res 122(9): 1276-1289.

[36] Yurkovich, J.T., et al., A systems approach to clinical oncology uses deep phenotyping to deliver personalized care. Nat Rev Clin Oncol, 2020. 17(3): p. 183-194.

Progress 3 Omics profiling in personalized healthcare and health management

The dynamic iPOP (Integrated Personal Omics Profiling) study, which was proposed by Michael Snyder of Stanford University[37], is focused on genomics, transcriptomics, proteomics, metabolomics and autoantibodies, and is aimed at accurately understanding the molecular and physiological profiles of humans. There are extensive and dynamic changes in various molecular components and biological pathways when people are in good health or suffering from illness. iPOP can help explain the states of health and illness, accurately diagnose and analyze individuals, and foster precision medicine. Portable biosensors play an active role in managing health and diagnosing and analyzing diseases while eliminating the geographic restrictions associated with conventional community-based health services. Over the past decade, the use of iPOP has been explored in multiple fields including pregnancy, diabetes, space travel health risks[38], and personal health management. It has also been proven to be highly valuable to personalized health management[39], disease prevention, and early-stage diagnosis.

Long-term tracking of phenotypic and multi-omics data using a big data approach, together with gene sequencing, can help us promptly make clinically actionable health-related discoveries[40]. In 2019, Michael Snyder and his team published an article in the *Nature Medicine* journal[41], identifying clinically relevant molecular pathways in a prospective longitudinal cohort (n=109) with deep molecular and physiological profiling. The cohort underwent integrative personalized omics profiling for 2 to 8 years, and the team discovered over 67 clinically actionable health discoveries and identified multiple molecular

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[37] Chen, R., et al., Personal omics profiling reveals dynamic molecular and medical phenotypes. Cell, 2012. 148(6): p. 1293-307.
[38] GARRETT-BAKELMAN, F. E., SNYDER, M. P. & TUREK, F. W. 2019. The NASA Twins Study: A multidimensional analysis of a year-long human spaceflight. Science, 364.
[39] PIENING, B. D.,., WEINSTOCK, G. M. & SNYDER, M. P. 2018. Integrative Personal Omics Profiles during Periods of Weight Gain and Loss. Cell Syst, 6, 157-170.e8.
[40] SCHüSSLER-FIORENZA ROSE, S. M., HADDAD, F. & SNYDER, M. P. 2019. A longitudinal big data approach for precision health. Nat Med, 25, 792-804.
[41] Schussler-Fiorenza Rose, S.M., et al., A longitudinal big data approach for precision health. Nat Med, 2019. 25(5): p. 792-804

pathways associated with metabolic, cardiovascular, infectious, inflammatory, and oncologic pathophysiology, offering suggestions that would help individuals treat or control their health problems. The study proved that long-term collection and multi-omics analysis of phenotypic data can help reveal health problems and improve health conditions in a more comprehensive and timely manner compared to the annual health check recommended under the current healthcare system.

Part II Human phenome project advances rapidly

China took the initiative in launching the human phenome research project while simultaneously building the human phenome research platform[42]. In 2017, under the International Human Phenome Project (Phase 1), the 4,000-square-meter Human Phenome Institute (HuPI) of Fudan University was set up at its Zhangjiang campus. As of today, Fudan University has established the world's first cross-scale and multi-dimensional phenotyping platform for deep phenotyping and data analysis, covering 20,000 phenotypes in 15 categories. The platform has world-leading analysis functions for proteomes and metabolomes and is equipped with 3D imaging and fMRI facilities to help profile the physique, structure and functions, providing a one-stop solution to the measurement of human phenotypes at both macro and molecular levels. Meanwhile, the Chinese Academy of Sciences-Max Planck Partner Institute for Computational Biology has established a series of computational analysis platforms that integrate functional omics data and biological network analysis, providing data integration, disease-related network analysis, and data prediction and inference to foster phenome research. The International Human Phenome Institute (Shanghai) has also been developing a proprietary cloud platform for the sharing and processing of phenotypic data. The platform has passed a preliminary assessment and will be soon open to the global scientific community on a trial basis.

While building the platform, Chinese scientists have also been committed to advancing the International Human Phenome big science Project. In May 2015, Academician Jin Li of Fudan University initiated and organized the

[42] Multi-dimensional Phenotyping platform. Available from: https://hupi.fudan.edu.cn/en/content.jsp?urltype=news.NewsContentUrl&wbtreeid=1041&wbnewsid=1121

Xiangshan Science Conference on International Human Phenome Research and proposed the establishment of the International Human Phenome Project. In May 2016, with the support of the International Center for Genetic Engineering and Biotechnology (ICGEB), Fudan University held the 2016 International Symposium of Genetics and Human Phenomics in Shanghai, during which Academician Jin Li of Fudan University, Academician Leroy Hood of the Institute for Systems Biology, and Academician Jeremy Nicholson of Imperial College London unveiled the initiative of launching the International Human Phenome Research Project, thus laying the foundation to bolster China's discourse in global human phenome research. In October 2018, the Human Phenome Consortium of China (HPCC) and the International Human Phenome Consortium (IHPC) were set up at the Second International Symposium of Human Phenomics hosted by Fudan University, making a preliminary clarification of the roadmap, cooperation mechanism and organizational structure of the international big science project of human phenomes. This marked a crucial step in the official launch of the International Human Phenome big science Project on a global scale. In December 2018, the Working Group of Standards and Technical Specifications under the China Human Phenome Research Collaborative Group was established at Fudan University. Twenty-three experts in metrology and standardization from Fudan University, the National Institute of Metrology of China, China Electronics Standardization Institute, Shanghai Institute of Measurement and Testing Technology and China Electronics Corporation served as members of the working group. The working group has since been advancing the establishment of the China Chapter of the international Massive Analysis and Quality Control (MAQC) Society and has applied to the International Standardization Organization (ISO) for the establishment of the Human Phenome Technical Committee. On November 1, 2018, Fudan University received approval from the Shanghai Science and Technology Commission to launch the Belt and Road International Joint Lab Project. The Silk Road Anthropology International Joint Lab helped lay the foundation for the International Human Phenome big science Project. At the 1st General Assembly of the BRICS Universities League in 2019, Academician Jin

Li delivered a keynote speech and advocated the establishment of the BRICS human health community via global cooperation on human phenomes, thus marking a new milestone in the International Human Phenome big science Project.

The International Human Phenome Institute (Shanghai), a new research and development institution initiated by Fudan University in 2019, plays a strategic role in contributing strong scientific research capabilities, coordinating with research institutions from home and abroad, and facilitating the transformation of high-quality achievements under the International Human Phenome big science Project.

Illustration 7 The 2016 International Symposium of Genetics and Human Phenomics

Illustration 8 The 2018 International Symposium of Human Phenomics

At present, the HPCC has 77 members, including 26 Academicians, and works with 33 Chinese universities and research institutes, 22 top-tier hospitals and 5 leading Chinese companies. The IHPC engages top experts in related fields from 21 research institutions in 17 countries, and its council members include 10 Academicians from various countries.

Between October 24 and 26, 2020, the third International Symposium of

Human Phenomics themed "Phenomics and Human Health" was held by Fudan University, the Phenomics Academic Subgroup of Biophysical Society of China, and the International Human Phenome Institutes (Shanghai). Many Chinese and foreign academicians, experts and other well-known researchers were invited to attend the symposium where they delivered speeches. At the plenary meeting of the International Human Phenome Research Collaborative Group, the participating scientists reached an important consensus that the human phenome big science project should focus on three near-term priorities - phenomics research of new coronary pneumonia and other major diseases, technology system and research infrastructure for phenome research, and standard operating procedures (SOPs) in phenomics research - in order to advance human phenome research.

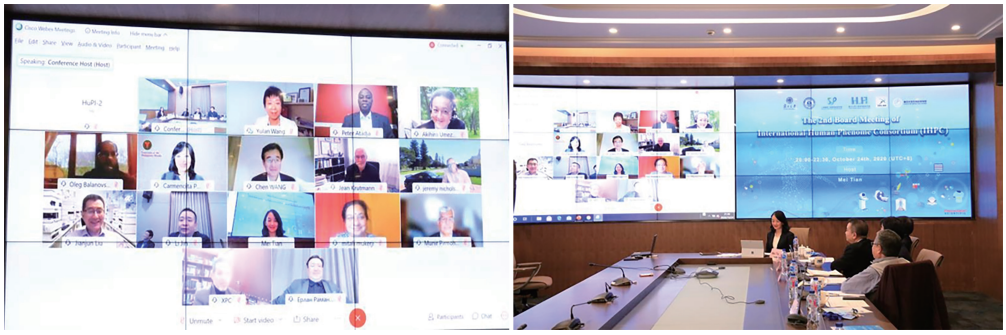

Illustration 9: IHPC Council meeting on October 24, 2020

Part III Key contributions to the battle against the Covid-19 pandemic

Revealing the clinical features of the new coronary pneumonia

On January 24, 2020, when the COVID-19 epidemic was still in its early stage, Professor Wang Chen (a member of the Chinese Academy of Engineering), Professor Gao Fu (a member of the Chinese Academy of Science) and other researchers jointly published an online commentary[43] on *The Lancet* which summarized the progress of the epidemic and identified the potential areas of focus for future clinical and basic research. On February 15, 2020, the team comprising Professor Cao Bin and Professor Wang Jianwei published an article in The Lancet about the first batch of 41 patients who were transferred to Wuhan's designated hospital (Wuhan Jinyintan Hospital) due to 2019-nCoV infection. The article revealed clinical features (clinical phenotypes) of these patients, providing valuable first-hand clinical data[44] from the epidemic. In February 2020, Zhong Nanshan (a member of the Chinese Academy of Engineering) and his team published an original article[45] online in *the New England Journal of Medicine* that revealed the clinical characteristics of the new coronary pneumonia based on the research of a large sample of patients. The article also analyzed variables such as age distribution, symptoms, virus transmission routes, protection methods, treatments and mortality, and pointed out that the enforcement of epidemiological measures in a strict and timely manner is essential to curbing the rapid spread of the virus. On February 12, 2020, Zhang Yuanzhen and Hou

[43] Wang, C., et al., A novel coronavirus outbreak of global health concern. Lancet,2020. 395(10223): p. 470-473.
[44] Huang, C., et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet, 2020. 395(10223): p. 497-506.
[45] Guan, W.J., et al., Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med, 2020. 382(18): p. 1708-1720.

Wei of Wuhan University and Yang Huixia of Peking University published an article[46] in The Lancet about the clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in pregnant women. The retrospective review was based on the studies of 9 pregnant women who were infected with COVID-19, and included epidemiological characteristics, clinical performances, multiple laboratory and imaging findings, maternal and fetal complications and pregnancy outcomes, thus providing the earliest clinical data for the treatment of pregnant women and fetuses during the epidemic.

Several academic papers published in top medical journals have identified the imaging phenotypes of COVID-19. On January 24, Professor Cao Bin of the China-Japan Friendship Hospital and his team reported the imaging phenotypes and laboratory test results of COVID-19 cases. On January 25, 2020, China's COVID-19 research team published a brief report in *the New England Journal of Medicine* about a case with a previously unknown Betacoronavirus in Wuhan and the patient's imaging phenotype[47]. Due to the efforts of multiple clinical and research teams, the phenotypic characteristics of COVID-19 cases such as early-stage thin ground-glass opacities[48] and progressive-stage diffuse ground-glass opacities in the lungs, were quickly reported to help detect carriers of the virus and monitor disease progression.

On February 17, 2020, Wang Fusheng (a member of the Chinese Academy of Sciences) and his team published an article in *The Lancet Respiratory Medicine*[49] about the pathological findings of COVID-19 associated with acute respiratory distress syndrome. The results of the pathological phenotype

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[46] Chen, H., et al., Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet, 2020. 395(10226): p. 809-815.

[47] Zhu, N., et al., A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med, 2020. 382(8): p. 727-733 Figure 1

[48] CHEN, H., GUO, J., WANG, C., LUO, F., YU, X., ZHANG, W., LI, J., ZHAO, D., XU, D., GONG, Q., LIAO, J., YANG, H., HOU, W. & ZHANG, Y. 2020. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet, 395, 809-815.

[49] Xu, Z., et al., Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med, 2020. 8(4): p. 420-422

of pulmonary edema and hyaline membrane formation laid the foundation for exploring the pathogenesis of COVID-19 and timely respiratory support for severely ill patients. On April 28, 2020, Bian Xiuwu (a member of the Chinese Academy of Sciences) and his team further unraveled the pathological phenotypes of patients with COVID-19 infection[50]. In addition to pathological changes in the lungs, the microscopic pathological phenotypes also demonstrated the presence of the virus in the lungs, suggesting that patients need to be placed under extended quarantine while elderly patients with underlying diseases need to undergo follow-up medical testing. The pathological phenotypes of patients with COVID-19 infection effectively paved the way for medical support, improved treatments, and better prediction of illness severity.

Multi-scale phenotyping reveals disease progression and predicts clinical outcome

The research team of the Human Phenome Institute of Fudan University identified the molecular markers in the peripheral blood and plasma samples of 66 COVID-19 patients whose conditions varied in severity, as well as 17 healthy controls based on transcriptomics, proteomics, and metabolomics. The team conducted a full-period, cross-scale phenotypic study on the serum of patients and healthy controls, and found that gene expression, proteins, metabolites, and extracellular RNA (exRNAs) demonstrated a strong correlation with multiple clinical parameters[51]. In addition, it was found that multiple tissue-specific proteins and exRNAs vary significantly between people with mild and severe COVID-19 infection, indicating that COVID-19 causes multiple tissue damage. The significant differences in the immunophenotype and molecular phenotypes

[50] YAO, X. H., HE, Z. C., LI, T. Y., ZHANG, H. R., WANG, Y., MOU, H., GUO, Q., YU, S. C., DING, Y., LIU, X., PING, Y. F. & BIAN, X. W. 2020. Pathological evidence for residual SARS-CoV-2 in pulmonary tissues of a ready-for-discharge patient. Cell Res, 30, 541-543.

[51] CHEN, Y. M., ZHENG, Y., YU, Y., WANG, Y., HUANG, Q., QIAN, F., SUN, L., SONG, Z. G., CHEN, Z., FENG, J., AN, Y., YANG, J., SU, Z., SUN, S., DAI, F., CHEN, Q., LU, Q., LI, P., LING, Y., YANG, Z., TANG, H., SHI, L., JIN, L., HOLMES, E. C., DING, C., ZHU, T. Y. & ZHANG, Y. Z. 2020. Blood molecular markers associated with COVID-19 immunopathology and multi-organ damage. Embo j, 39, e105896.

of patients with mild and severe COVID-19 infection verified that metabolic and immune disorders, indicative genes, proteins and exRNAs can be used as potential biomarkers to predict the prognosis of SARS-CoV-2 infection. The team proposed a protein biomarker that could potentially predict patients' clinical outcomes and further improve the understanding of the pathophysiology and clinical progress in the field of COVID-19.

Related technologies support diagnosis of COVID-19 cases

In April 2020, the Macau University of Science and Technology, Sichuan University, Tsinghua University, and Sun Yat-sen University worked together to develop an AI system[52] that could diagnose COVID-19 cases and distinguish them from common pneumonia and normal controls by using a large-scale computer tomography (CT) database covering 4,154 patients. The system, which can accurately predict the clinical prognosis and help clinicians identify early clinical treatments and allocate resources appropriately, was then shared with the world to assist doctors in the global response to COVID-19. During the epidemic, the Australian National Phenome Center offered recommendations[53] regarding the handling of blood samples amid rising demand for nuclear magnetic resonance spectroscopy. These suggestions have proved effective in the storage of samples for clinical and molecular phenotyping and subsequent laboratory testing. The center and other phenome research teams proposed that phenome research[54] can effectively address the weakness of nucleic acid testing in major public health emergencies and quickly screen patients with COVID-19. Wearable biosensors that dynamically measure related phenotypes have also played a key role in the fight against the COVID-19 epidemic, as frequent

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[52] Zhang, K., et al., Clinically Applicable AI System for Accurate Diagnosis,Quantitative Measurements, and Prognosis of COVID-19 Pneumonia Using Computed Tomography. Cell, 2020. 182(5): p. 1360.

[53] Kimhofer, T., et al., Integrative Modeling of Quantitative Plasma Lipoprotein, Metabolic, and Amino Acid Data Reveals a Multiorgan Pathological Signature of SARS-CoV-2 Infection. J Proteome Res, 2020. 19(11): p. 4442-4454.

[54] Wong, C.K., et al., Artificial intelligence mobile health platform for early detection of COVID-19 in quarantine subjects using a wearable biosensor: protocol for a randomised controlled trial. BMJ Open, 2020. 10(7): p. e038555.

remote measurement of physiological data makes it possible to monitor high-risk populations under quarantine and enables diagnosis to be performed at a very early stage.

Outlook: New paradigm drives new transformation

As a new paradigm for life science, human phenome research fosters a raft of basic research programs and related technological innovation, and accelerates industrial transformation. The proposal and advancement of the Human Phenome Project will help bolster global collaboration and allow research and collaborative achievements to benefit human health.

Create an atlas to drive original innovation

China has a large multi-ethnic population, giving it a unique advantage in human genetic resources. With the aid of fast-developing precision human body measurement technology, human phenome research can help identify cross-scale relations and associations between genome, phenome and the environment, as well as between micro-phenomes and macro-phenomes. This will help create a multi-dimensional, cross-scale and full-cycle atlas of the human phenome in relevant populations, and draw a new map following the Human Genome Project that would help us navigate the complex life processes.

Support precision medicine and improve human health

Human phenome research can help clarify the pathogenic factors and evolving pedigrees of various diseases, fundamentally improve the efficiency and accuracy of medical diagnosis, and support the development of precision medicine. It will enable precision sub-typing, classification, diagnosis and treatment, improve the medical security system and bring benefits to human health.

Gather innovative elements to create a highland of collaboration

As China yields more scientific achievements, its contribution and influence on the global stage has been growing steadily. The Human Phenome Project

will make full of its leading advantages in scientific concepts, research facilities, organizational modes, standards/systems, targets/plans, public product supply, and transformation applications to help improve China's experience in driving international cooperation in the life sciences and attract top international talent and high-level institutions to carry out scientific and technological cooperation and exchanges with China. The project will help gather innovative elements to contribute to China's dual circulation strategy.

Accelerate industrial transformation and drive innovation and development

Human phenome research will help discover a batch of brand-new phenotypic markers and identify new drug targets and mechanisms on a large scale, thus providing a huge impetus to the research and development of new diagnostic reagents and products, next-generation original drugs, personalized health devices, and smart medical devices and equipment. The project will help form a high precision library of biological and health big data which would help foster and develop the big health industry focused on "phenome + big data" and "phenome + artificial intelligence." The scientific results delivered by the human phenotype project will provide China with an innovation prowess that allows it to lead the global biomedical industry in transforming and cultivating growth drivers for the big health industry. The human phenome project has a significant socio-economic value in effectively driving the development of pharmaceutical manufacturing and health industries.