Rare Diseases Research in China:

Yesterday, Today, and Tomorrow

Shuyang Zhang, M.D.

Peking Union Medical College Hospital

NRDRS

中国国家罕见病注册体系

NATIONAL RARE DISEASES REGISTRY SYSTEM OF CHINA

北京协和医院

PEKING UNION MEDICAL COLLEGE HOSPITAL

Rare Diseases: Global Challenges

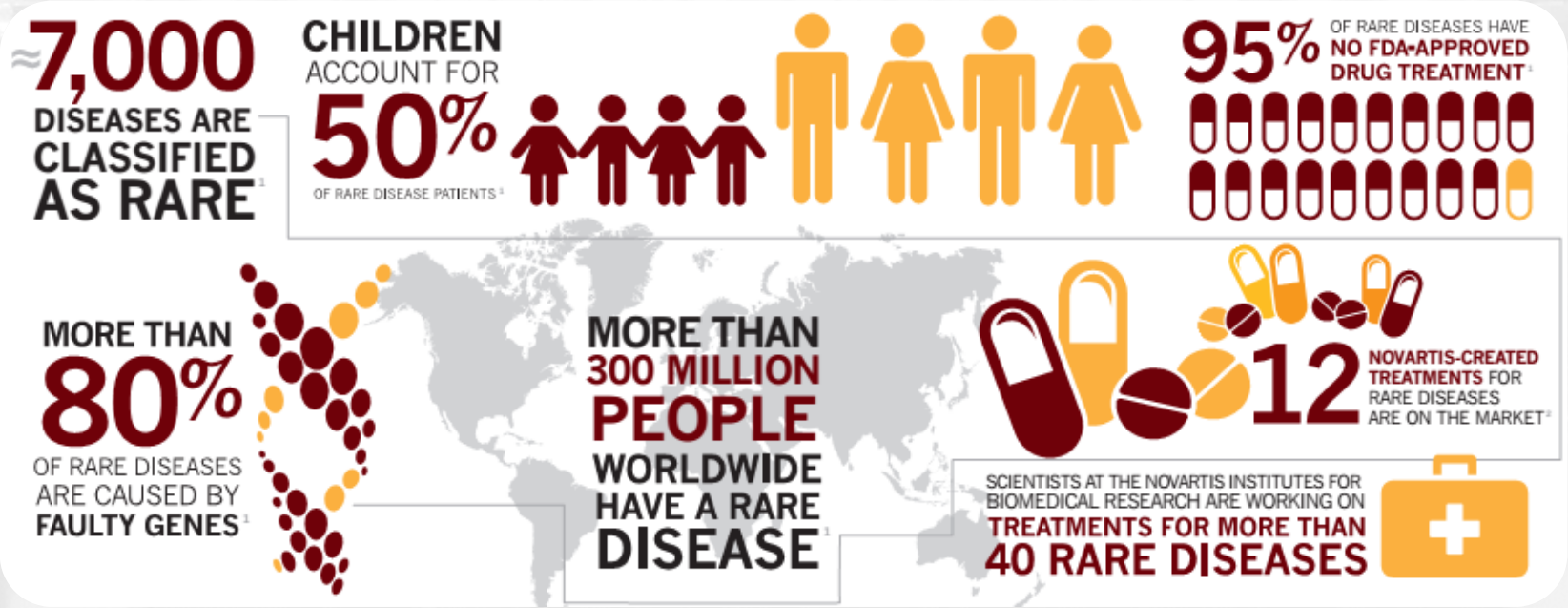
Low frequency of single disease, with high overall prevalence

Difficulties

- Research
- Diagnosis
- Treatment

Values

- Society
- Science



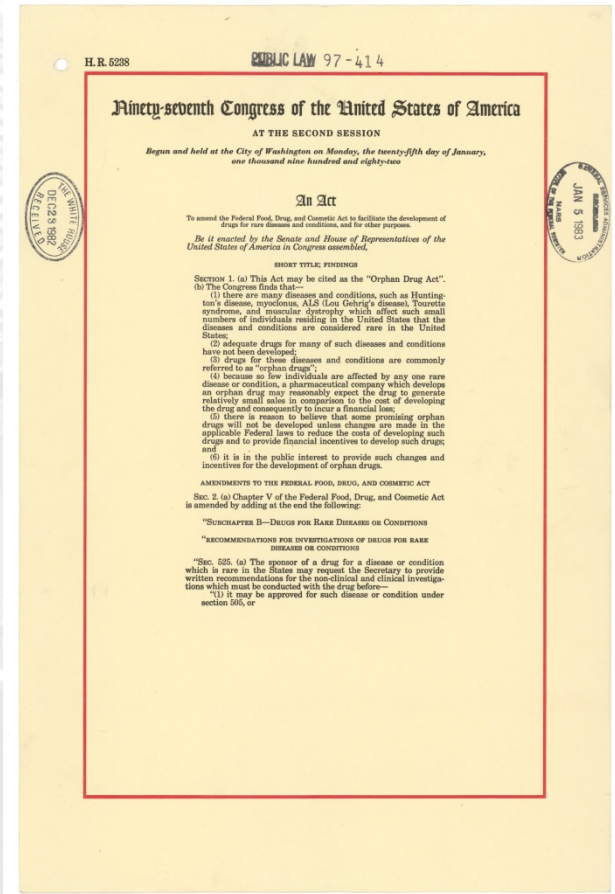
https://www.novartis.com/stories/medicines/rare-diseases-more-common-you-think

Legislation for Rare Diseases

Orphan Drug Act in 1983, US

The Pharmaceutical Affairs Law, Japan, in 1993, including regulation on orphan drugs

Regulation on Orphan Medicinal Products, European Parliament, in 1999



H.R. 5238 PUBLIC LAW 97-414

Ninety-seventh Congress of the United States of America

AT THE SECOND SESSION

Begun and held at the City of Washington on Monday, the twenty-fifth day of January, one thousand nine hundred and eighty-two

An Act

To amend the Federal Food, Drug, and Cosmetic Act to facilitate the development of drugs for rare diseases and conditions, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SHORT TITLE; FINDINGS

SECTION 1. (a) This Act may be cited as the "Orphan Drug Act".
(b) The Congress finds that—
(1) there are many diseases and conditions, such as Huntington's disease, myoclonus, ALS (Lou Gehrig's disease), Tourette syndrome, and muscular dystrophy which affect such small numbers of individuals residing in the United States that the diseases and conditions are considered rare in the United States;
(2) adequate drugs for many of such diseases and conditions have not been developed;
(3) drugs for these diseases and conditions are commonly referred to as "orphan drugs";
(4) because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss;
(5) there is reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs; and
(6) it is in the public interest to provide such changes and incentives for the development of orphan drugs.

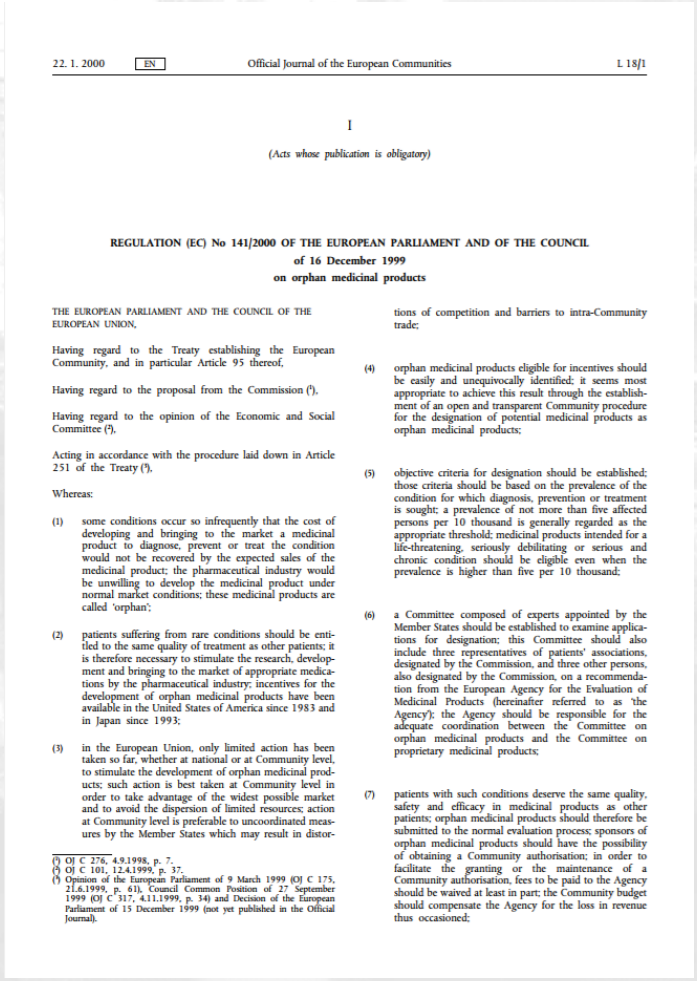
AMENDMENTS TO THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

SEC. 2. (a) Chapter V of the Federal Food, Drug, and Cosmetic Act is amended by adding at the end the following:

"SUBCHAPTER B—DRUGS FOR RARE DISEASES OR CONDITIONS

"RECOMMENDATIONS FOR INVESTIGATIONS OF DRUGS FOR RARE DISEASES OR CONDITIONS

"SEC. 525. (a) The sponsor of a drug for a disease or condition which is rare in the States may request the Secretary to provide written recommendations for the non-clinical and clinical investigations which must be conducted with the drug before—
"(1) it may be approved for such disease or condition under section 505, or



22. 1. 2000 EN Official Journal of the European Communities L 18/1

I

(Acts whose publication is obligatory)

REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 16 December 1999
on orphan medicinal products

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission (1),

Having regard to the opinion of the Economic and Social Committee (2),

Acting in accordance with the procedure laid down in Article 251 of the Treaty (3),

Whereas:

(1) some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the medicinal product; the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions; these medicinal products are called 'orphan';

(2) patients suffering from rare conditions should be entitled to the same quality of treatment as other patients; it is therefore necessary to stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry; incentives for the development of orphan medicinal products have been available in the United States of America since 1983 and in Japan since 1993;

(3) in the European Union, only limited action has been taken so far, whether at national or at Community level, to stimulate the development of orphan medicinal products; such action is best taken at Community level in order to take advantage of the widest possible market and to avoid the dispersion of limited resources; action at Community level is preferable to uncoordinated measures by the Member States which may result in distortions of competition and barriers to intra-Community trade;

(4) orphan medicinal products eligible for incentives should be easily and unequivocally identified; it seems most appropriate to achieve this result through the establishment of an open and transparent Community procedure for the designation of potential medicinal products as orphan medicinal products;

(5) objective criteria for designation should be established; those criteria should be based on the prevalence of the condition for which diagnosis, prevention or treatment is sought; a prevalence of not more than five affected persons per 10 thousand is generally regarded as the appropriate threshold; medicinal products intended for a life-threatening, seriously debilitating or serious and chronic condition should be eligible even when the prevalence is higher than five per 10 thousand;

(6) a Committee composed of experts appointed by the Member States should be established to examine applications for designation; this Committee should also include three representatives of patients' associations, designated by the Commission, and three other persons, also designated by the Commission, on a recommendation from the European Agency for the Evaluation of Medicinal Products (hereinafter referred to as 'the Agency'); the Agency should be responsible for the adequate coordination between the Committee on orphan medicinal products and the Committee on proprietary medicinal products;

(7) patients with such conditions deserve the same quality, safety and efficacy in medicinal products as other patients; orphan medicinal products should therefore be submitted to the normal evaluation process; sponsors of orphan medicinal products should have the possibility of obtaining a Community authorisation; in order to facilitate the granting or the maintenance of a Community authorisation, fees to be paid to the Agency should be waived at least in part; the Community budget should compensate the Agency for the loss in revenue thus occasioned;

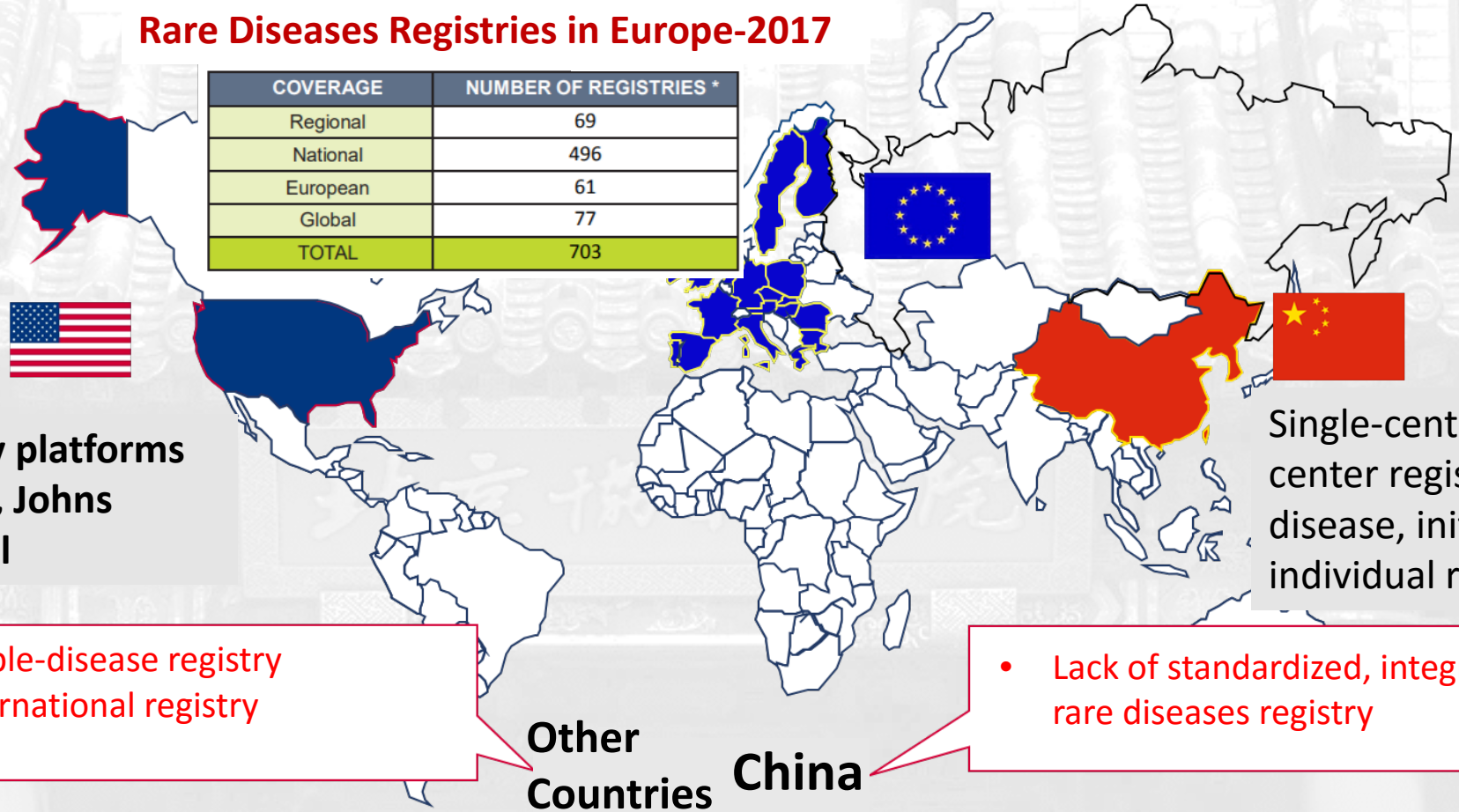
(1) OJ C 276, 4.9.1998, p. 7.
(2) OJ C 101, 12.4.1999, p. 37.
(3) Opinion of the European Parliament of 9 March 1999 (OJ C 175, 21.6.1999, p. 61), Council Common Position of 27 September 1999 (OJ C 317, 4.11.1999, p. 34) and Decision of the European Parliament of 15 December 1999 (not yet published in the Official Journal).

https://ec.europa.eu/health/human-use/orphan-medicines/developments_en https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/OOPDNewsArchive/ucm333527.htm

Rare Diseases Research: Patient Registries - Fundamental Infrastructure

Rare Diseases Registries in Europe-2017

COVERAGE	NUMBER OF REGISTRIES *
Regional	69
National	496
European	61
Global	77
TOTAL	703



Multiple registry platforms by NIH, Harvard, Johns Hopkins Hospital

- Single or multiple-disease registry
- National & international registry
- Sustainable

Other Countries

China

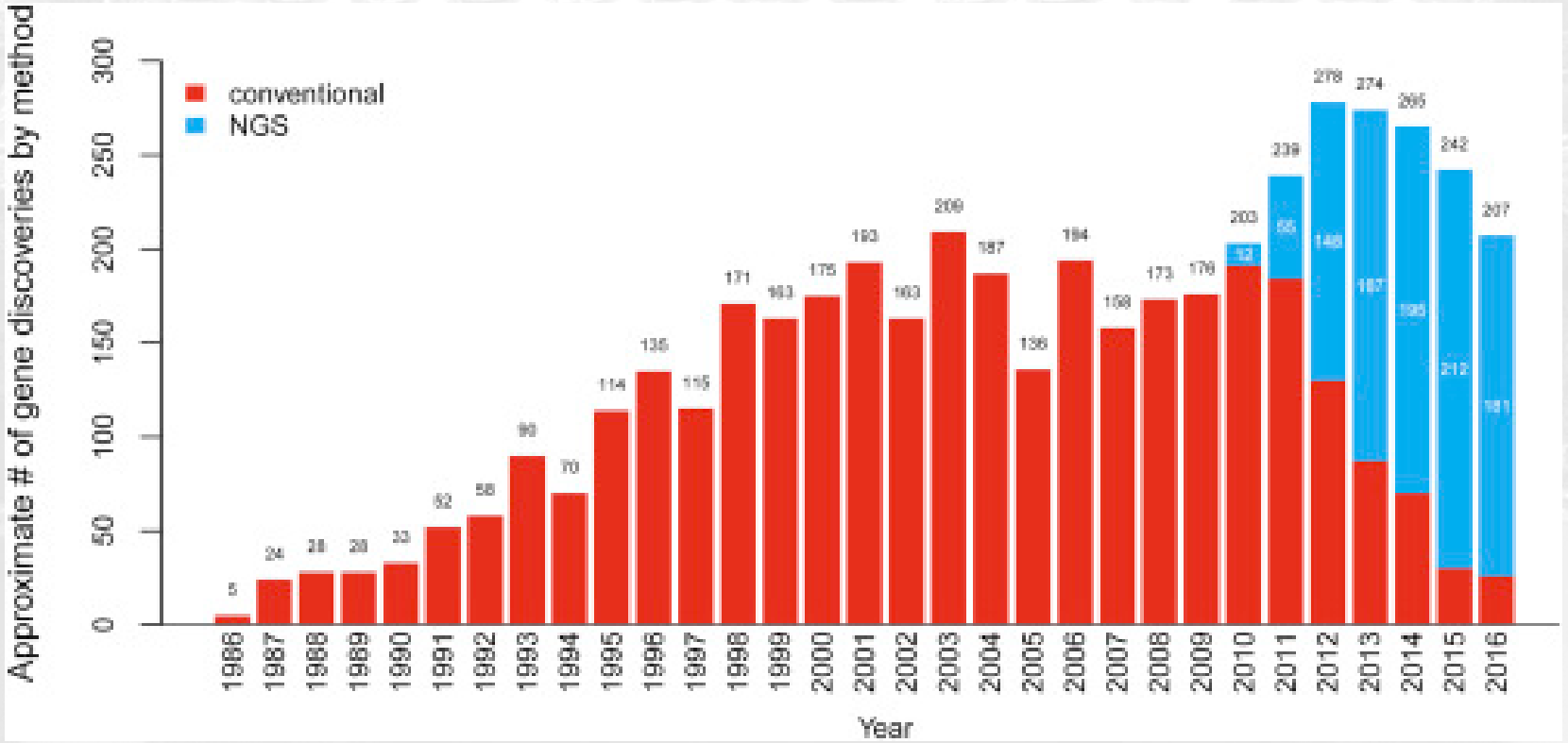
Single-center or multi-center registries on single disease, initiated by individual researcher

- Lack of standardized, integrated rare diseases registry

http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf

Rare Diseases Research: Technical Advances

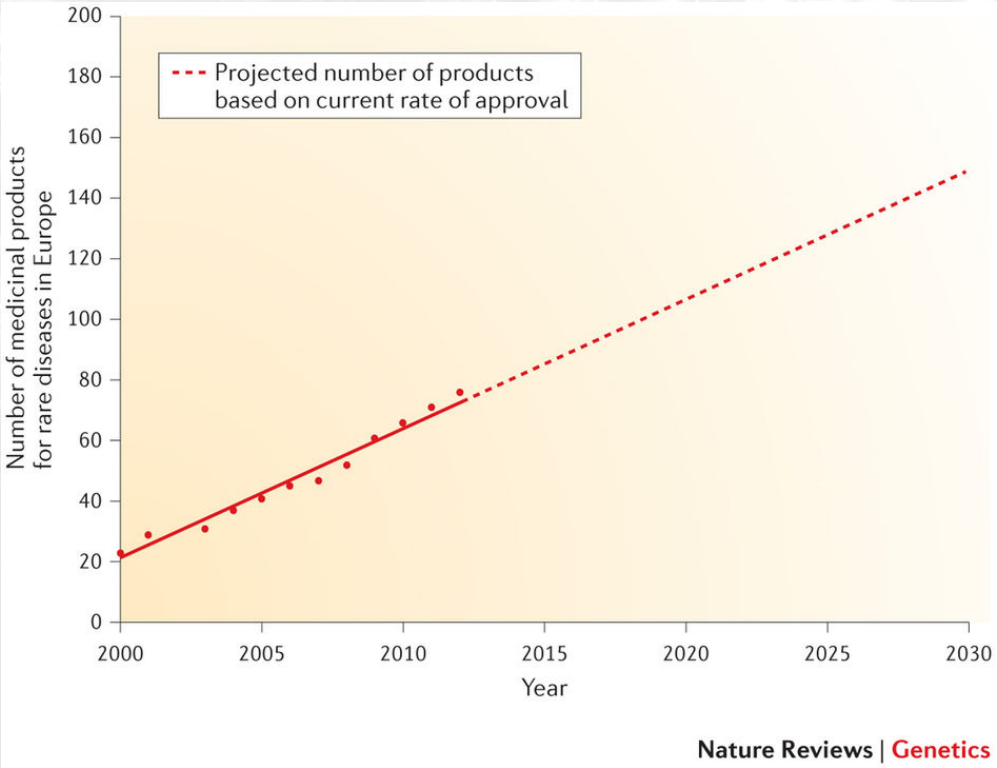
Number of novel pathological genes and contribution of NGS



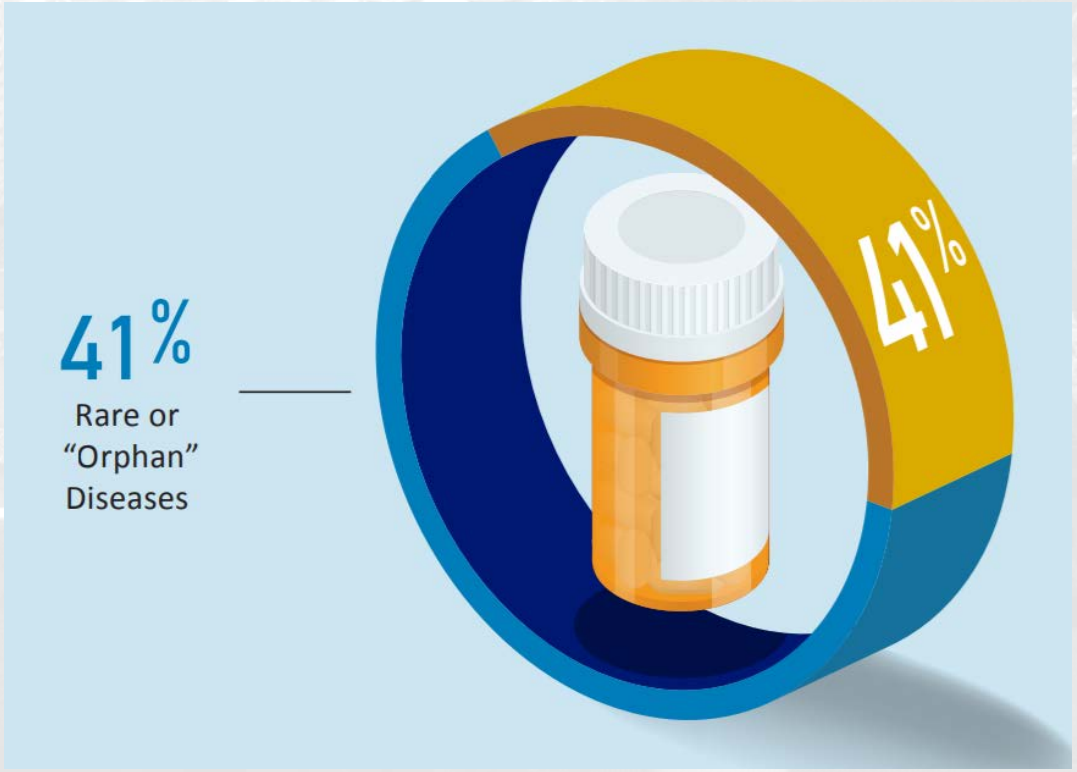
Boycott KM, Rath A, Chong JX, et al. International Cooperation to Enable the Diagnosis of All Rare Genetic Diseases. American journal of human genetics 2017;100:695-705.

Rare Diseases Research: Drug Development

Number of rare diseases medical products approved each year



41% of FDA approvals belongs to rare or "orphan" disease drugs in 2015

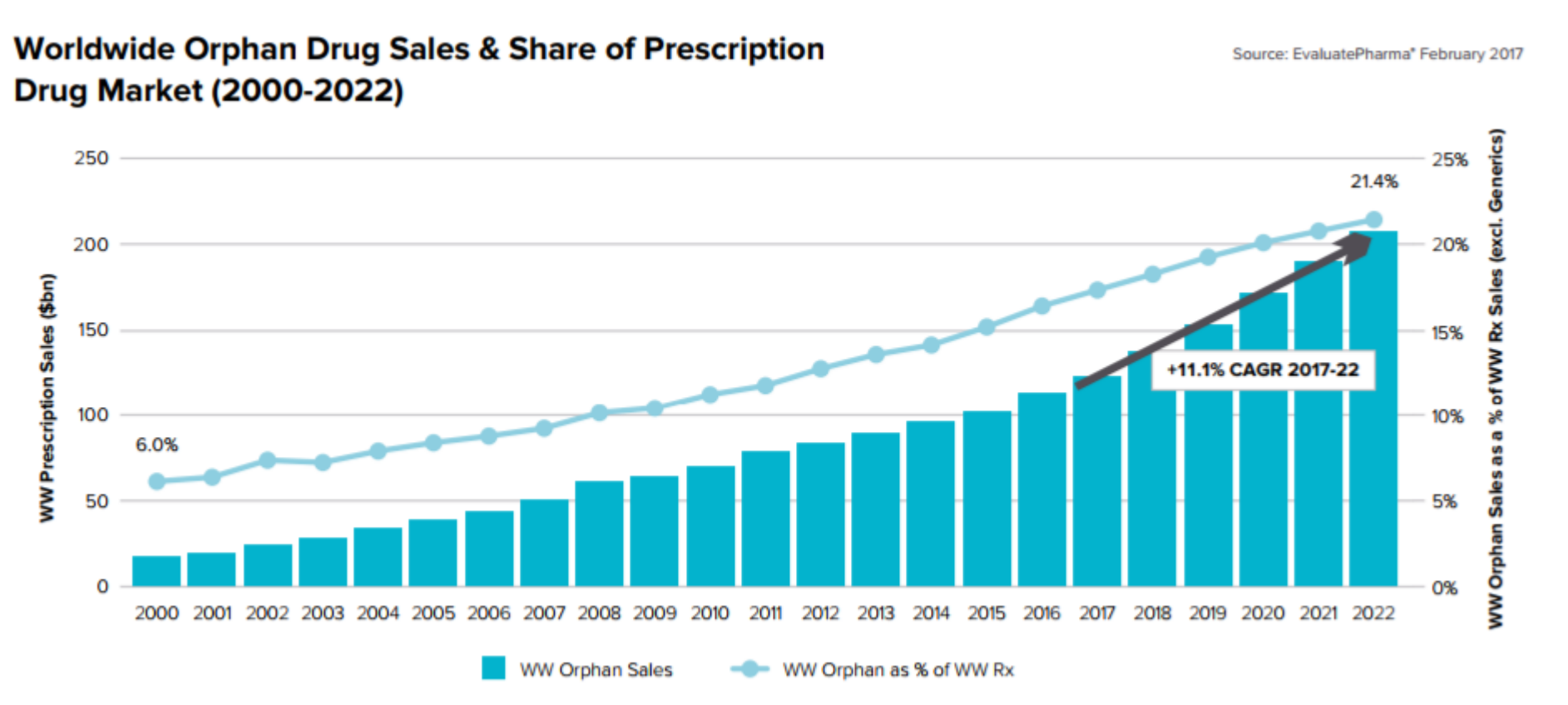


Boycott KM, Vanstone MR, Bulman DE, MacKenzie AE. Rare-disease genetics in the era of next-generation sequencing: discovery to translation. Nat Rev Genet 2013;14:681-91.

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM536693.pdf

Rare Diseases Research: Orphan Drug Market

Booming of Global Orphan Drug Market



EvaluatePharma. Orphan Drug Report 2017. available on:http://info.evaluategroup.com/rs/607-YGS-364/images/EPOD17.pdf

Rare Diseases Research in China

Yesterday

- Rare Diseases Society
- Advocacy Groups
- Academic Works
- Challenges

Regional Rare Diseases Research Associations

北京医学会罕见病分会
Rare disease branch of the Beijing Medical Association

Beijing City

2012.12

山东省罕见疾病防治协会

Shandong Province

2010.10

浙江省医学会
Zhejiang Medical Association

Zhejiang Province

2016.2

2011.3

上海市医学会
ShangHai Medical Association

Shanghai City

2013.6

廣東省醫學會
GUANGDONG MEDICAL ASSOCIATION

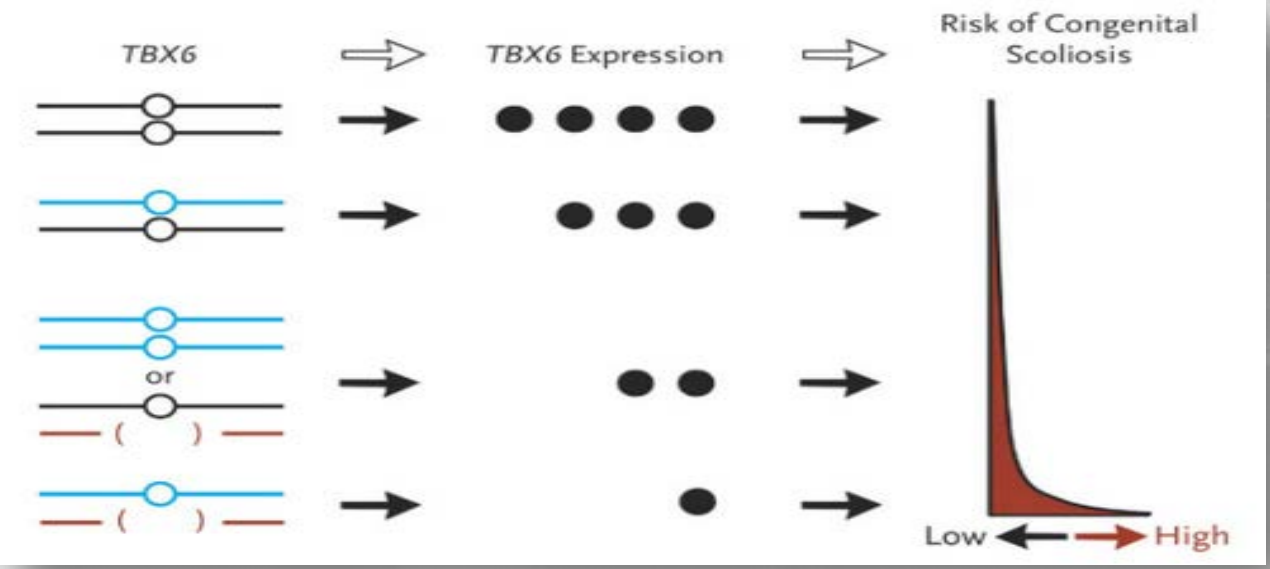
Guangdong Province

Academic Works: Congenital Scoliosis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

TBX6 Null Variants and a Common Hypomorphic Allele in Congenital Scoliosis



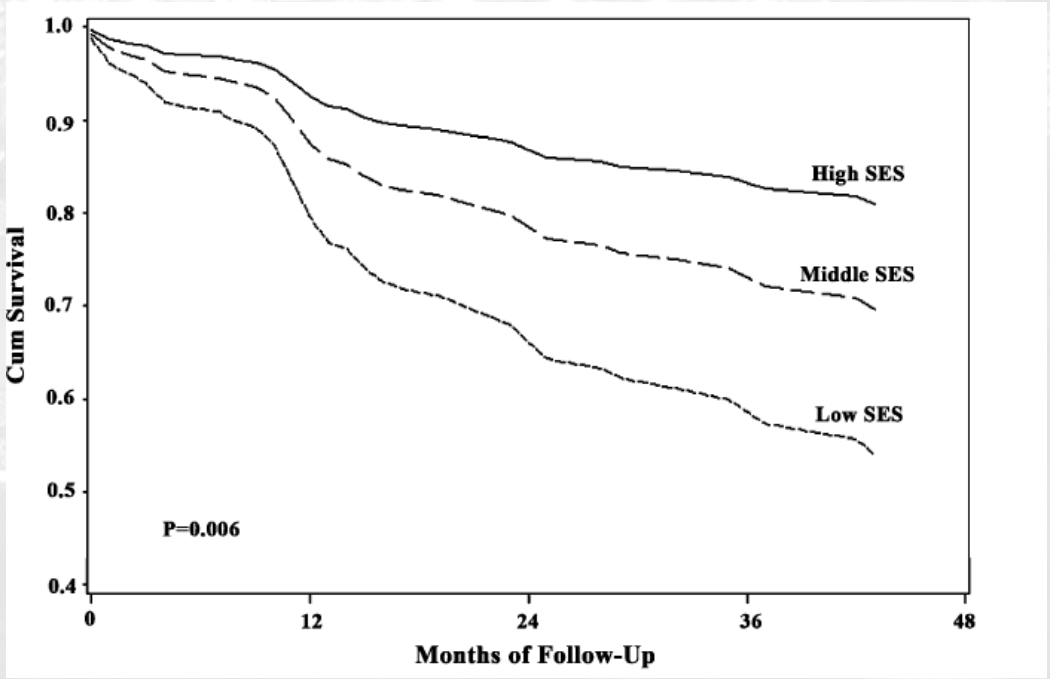
The Department of Orthopedics Surgery, PUMCH: Locate pathological compound variation of *TBX6* gene in congenital scoliosis for the first time.

Wu N, Ming X, Xiao J, et al. TBX6 Null Variants and a Common Hypomorphic Allele in Congenital Scoliosis. New England Journal of Medicine 2015;372:341-50.

Academic Works: Pulmonary Arterial Hypertension

Lower Socioeconomic Status Is Associated with Worse Outcomes in Pulmonary Arterial Hypertension

Wen-Hui Wu[1*], Lu Yang[1*†] Fu-Hua Peng[1*], Jing Yao[1], Li-Ling Zou[2], Dong Liu[1], Xin Jiang[1], Jue Li[2], Lan Gao[3], Jie-Ming Qu[4,5], Steven M. Kawut[6,7], and Zhi-Cheng Jing[1]



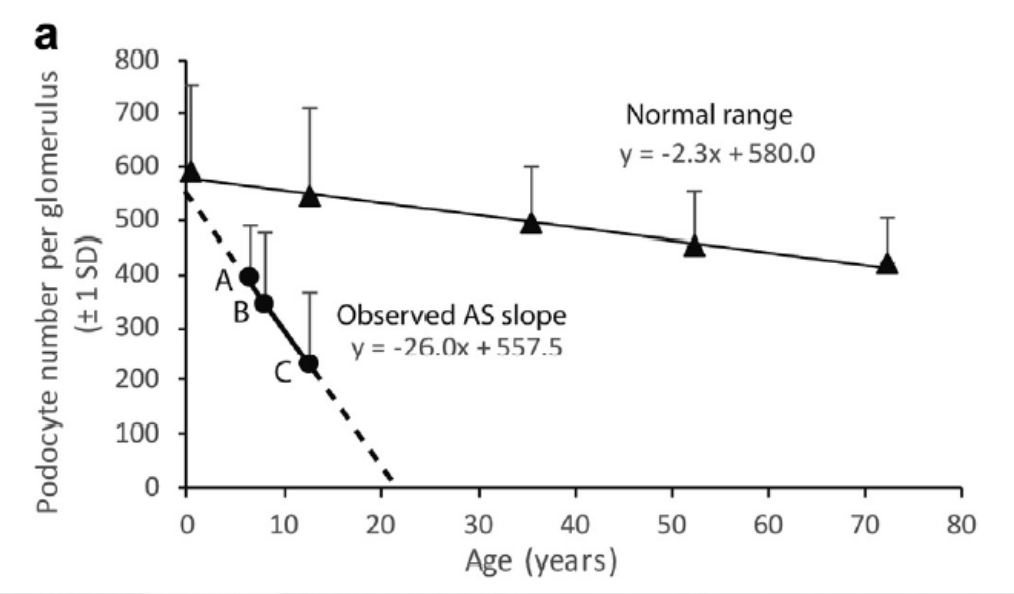
Wu WH, Yang L, Peng FH, et al. Lower socioeconomic status is associated with worse outcomes in pulmonary arterial hypertension. Am J Respir Crit Care Med 2013;187:303-10.

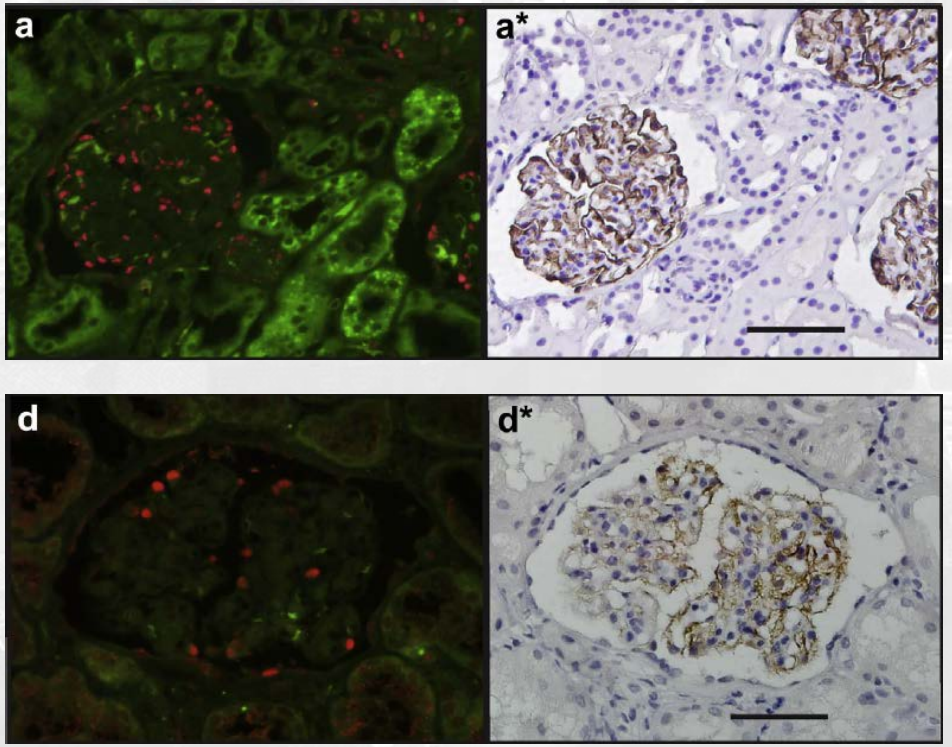
Academic Works: Alport Syndrome

www.kidney-international.org clinical investigation

Accelerated podocyte detachment and progressive podocyte loss from glomeruli with age in Alport Syndrome

Fangrui Ding[1,5], Larysa Wickman[2,5], Su Q. Wang[3], Yanqin Zhang[1], Fang Wang[1], Farsad Afshinnia[3], Jeffrey Hodgin[4], Jie Ding[1,6] and Roger C. Wiggins[3,6]





Ding F, Wickman L, Wang SQ, et al. Accelerated podocyte detachment and progressive podocyte loss from glomeruli with age in Alport Syndrome. Kidney Int 2017.

Rare Diseases Advocacy Groups

中国罕见病
Rare Disease in China

中国罕见病参考名录（修订版）| 关注

2017-02-27 罕见病发展中心 中国罕见病

美儿SMA关爱中心
Meier Advocacy & Support Center for SMA

China MPS

TSC 蝴蝶结结节性硬化症罕见病关爱中心
TSC China Alliance

LAM-CHINA
NONPROFIT ORGANIZATION
蓝梅淋巴管肌瘤罕见病关爱中心

CMT 关爱之家

硬皮病关爱之家
Chinese Organization for Scleroderma

朗格罕天使之家

特纳之家

自助 助人 温暖 希望
Pseudomyxoma Peritonei (PMP) Support Alliace

Challenges of Rare Diseases in China

- Lack of legislation
- Absence of definition for rare diseases
- Lack of social security system
- Shortage of support in research
- Difficulties in long-term follow-up

Laws and regulations relating to rare diseases worldwide*

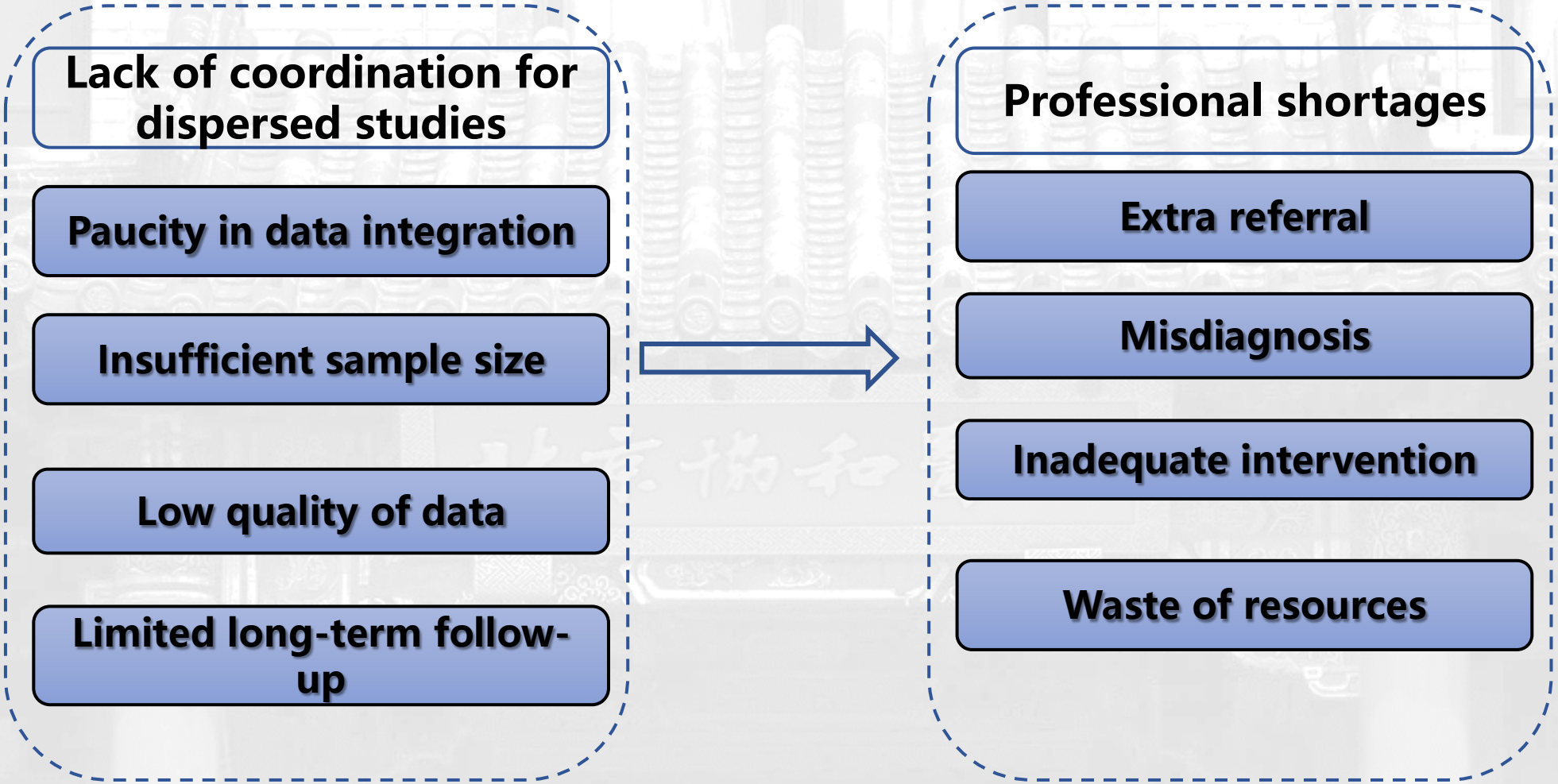
	USA	EU	JAPAN	TAIWAN	CHINA
Disease prevalence	0.75‰	0.5‰	0.4‰	0.1‰	N/A
Estimated affected population	>20 million	25–30 million	<50,000	>2000	10 million
Government officials involved	FDA/OOPD	EMA/COMP	MHLW	DOH	CFDA
Legal framework	Orphan Drug Act (1983) Rare Diseases Act of 2002 (2002)	Regulation (EC) No. 141/2000 (1999)	Revised orphan drug regulation (1993)	Rare Disease Control and Orphan Drug Act (2000)	N/A
Drug fast-track approval	Yes	Yes (centralized application)	Yes	Yes	Yes
Protocol assistance in clinical trial	Yes	Yes	Yes	Yes	N/A
Tax benefits	Up to 50% for clinical expenses	Managed by member countries	15% tax credits Up to 14% corporate tax reduction	N/A	N/A
Market exclusivity	7 years	10 years	10 years	10 years	N/A

*Adapted from Song *et al* (2012)[4], Hall & Carlson (2014)[8], Liu *et al* (2010)[10] and Montoya (2011)[11]
CFDA: China Food and Drug Administration, COMP: Committee of Orphan Medicinal Products, DOH: Department of Health, EMA: European Medicines Agency, FDA: Food and Drug Administration, MHLW: Ministry of Health, Labour and Welfare, N/A: not available, OOPD: Office of Orphan Products and Development

Table 1

http://comradis.biz/media/1007/rare-diseases-in-china-comradis.pdf

Challenges of Rare Diseases in China



Challenges of Rare Diseases in China

- Absence of social support
- Shortage of patient organizations
- Limited diseases covered
- Public ignorance
- Disadvantages in daily life

NORD: 250+ member organizations

Japan Patient Association : over 90% of 89 members are rare diseases patient organizations

EURORDIS: over 700 member organizations

China: 70 patient organizations covering 59 diseases[1]

1、 肖磊. 患者组织在罕见病和孤儿药研发中的作用. 国际药学研究杂志 2017:209-14.

Rare Diseases Research in China:
Today

National Strategy

Government Support

Policy

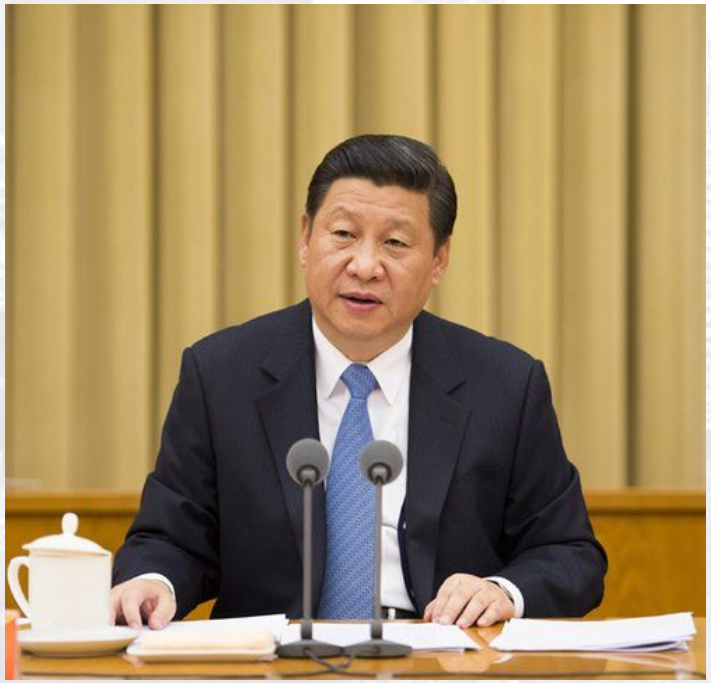
NRDRS

Collaboration & Partnership

Social Recognition

Rare Diseases Society

Rare Diseases Research in China: National Strategy



There will be no overall well-off society without **overall health**.
——Jinping Xi

….Need to build drug supplement system by supporting **orphan drugs.**
——Keqiang Li

"**Overall health** is the primary aim of building Healthy China."——*Outline of "Healthy China 2030" Program*

http://www.gov.cn/xinwen/2016-10/25/content_5124174.htm

Rare Diseases Research in China: Policy

二、**支持罕见病治疗药物和医疗器械研发。**由卫生计生部门公布罕见病目录，建立罕见病患者注册登记制度。罕见病治疗药物和医疗器械申请人可提出减免临床试验申请，加快罕见病用药医疗器械审评审批。对于国外已批准上市的罕见病治疗药物和医疗器械，可有条件批准上市，上市后在规定时间内补做相关研究。

Support the development of rare diseases drugs and medical devices, by accelerating processes, exempting clinical trials, or allow clinical trials after approval.

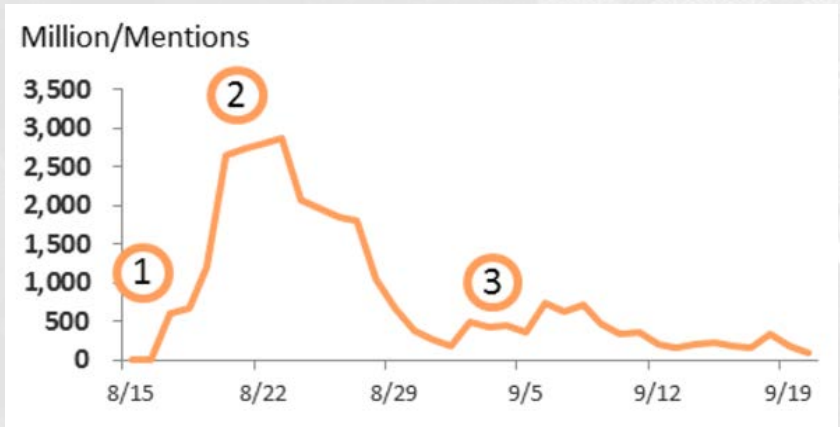
http://www.sda.gov.cn/WS01/CL0087/172567.html

Rare Diseases Research in China: Social Recognition

ALS ASSOCIATION

every drop adds up™

冰桶挑战——微博讨论趋势



冰桶挑战——关键词分析

http://www.seeisee.com/index.php/2014/09/26/p8040

Rare Diseases Research in China: Government Support

国家卫生计生委医政医管局

主站首页 | 首页 | 最新信息 | 政策文件 | 工作动态 | 关于我们 | 图片集锦 | 专题专栏

通告公告

您现在所在位置： 首页 > 最新信息 > 医疗与护理 > 通告公告

国家卫生计生委办公厅关于增补并调整部分罕见病诊疗与保障专家委员会成员的通知

发布时间：2017-05-04

国卫办医函〔2017〕419号

各省、自治区、直辖市卫生计生委，新疆生产建设兵团卫生局：

为进一步加强罕见病管理，促进罕见病规范化诊疗，保障罕见病用药基本需求，维护罕见病患者健康权益，根据国家卫生计生委罕见病诊疗与保障专家委员会（以下简称委员会）建议，经研究，决定增补并调整部分成员如下：

一、增补北京协和医院赵玉沛院士、解放军总医院陈香美院士、中国科学院上海生命科学研究院杨胜利院士等3人为顾问。

二、增补北京协和医院副院长张抒扬为副主任委员，调整原委员会委员上海交通大学医学院附属新华医院李定国为副主任委员。

三、增补复旦大学附属儿科医院副院长王艺、四川大学华西医院罕见病诊治中心副主任商慧芳、浙江省医学会罕见病分会副主任委员谢俊明等3人为委员。

四、在北京协和医院设立委员会办公室，负责委员会日常工作。北京协和医院副院长张抒扬兼任办公室主任。

国家卫生计生委办公厅

2017年4月28日

Expert Committee on diagnosis and treatment of rare diseases of China National Health and Family Planning Commission:

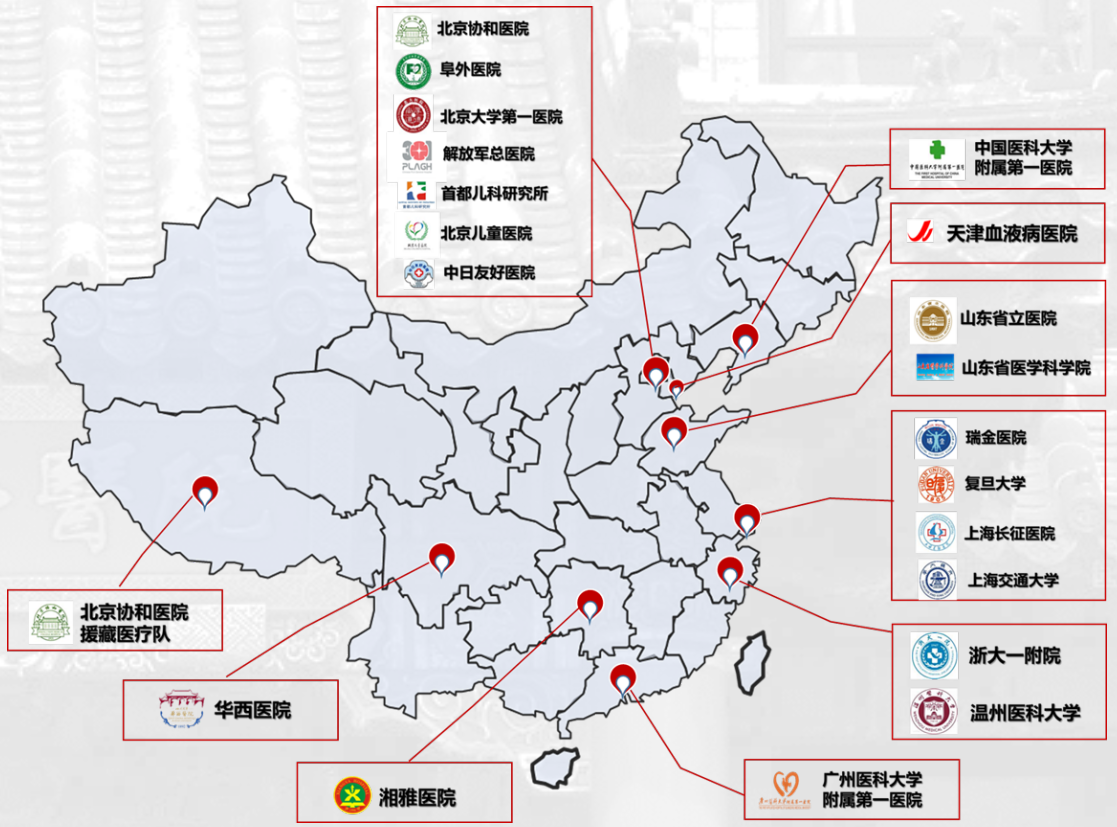
Set up **Commission office** in Peking Union Medical College Hospital

http://www.nhfpc.gov.cn/yzygj/s7659/201705/d209552a6ca04f1c8011f0d9e0f16392.shtml

National Rare Diseases Registry System of China

NRDRS 中国国家罕见病注册系统
NATIONAL RARE DISEASES REGISTRY SYSTEM OF CHINA

- 20 top medical institutions and hospitals in China
- 50,000 cases covering more than 50 diseases
- Multi-omics database and multi-center biological bank



National Rare Diseases Registry System of China

NRDRS 中国国家罕见病注册系统
NATIONAL RARE DISEASES REGISTRY SYSTEM OF CHINA

- Introduction of ChinaHPO (CHPO)
- Team member holding position in SNOMED CT
- Participation in translation and construction of Chinese knowledge base

SNOMED International
Leading healthcare terminology, worldwide

Rare Diseases Society of Chinese Research Hospital Association

中国研究型医院学会
CHINESE RESEARCH HOSPITAL ASSOCIATION

Led by Peking Union Medical College Hospital, Rare Diseases Society of Chinese Research Hospital Association was fund in December 2016.

Rare Diseases Research in China: Collaboration and Partnership

- Sequencing
- Prenatal Diagnosis
- Big Data
- Phenotyping

神州医疗
Digital China Health

VeritasGenetics

CNGB China National GeneBank 国家基因库

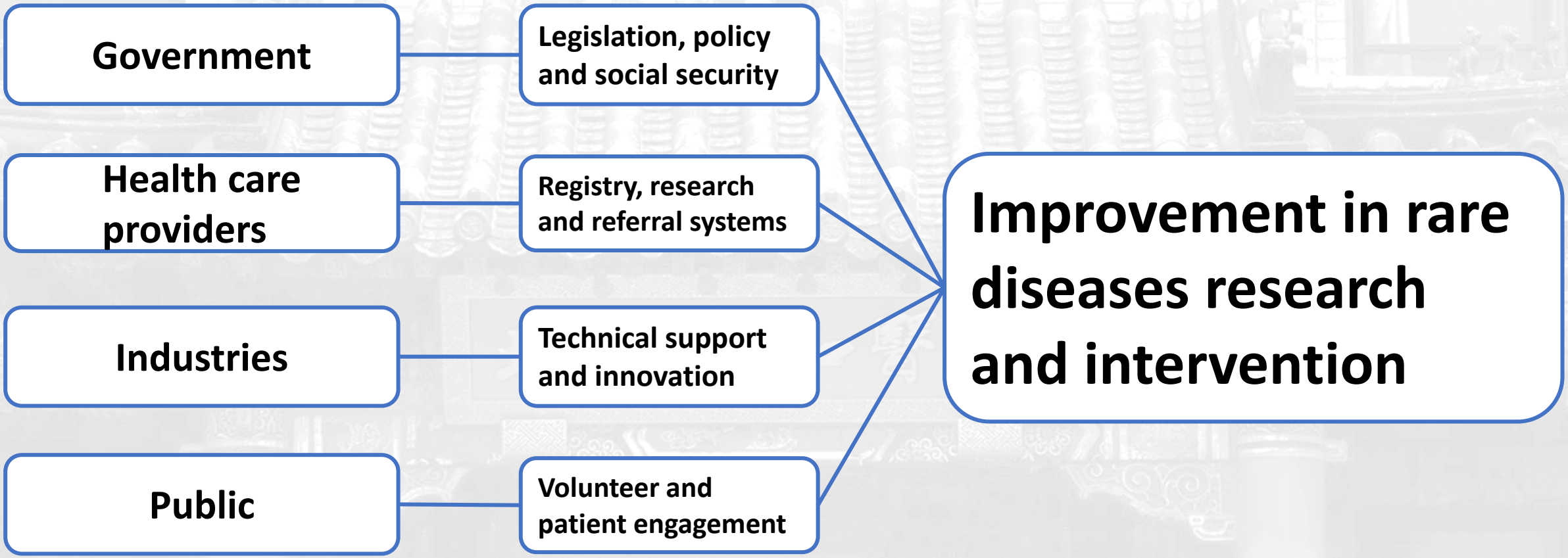
药明康德
WuXi AppTec

Rare Diseases Research in China

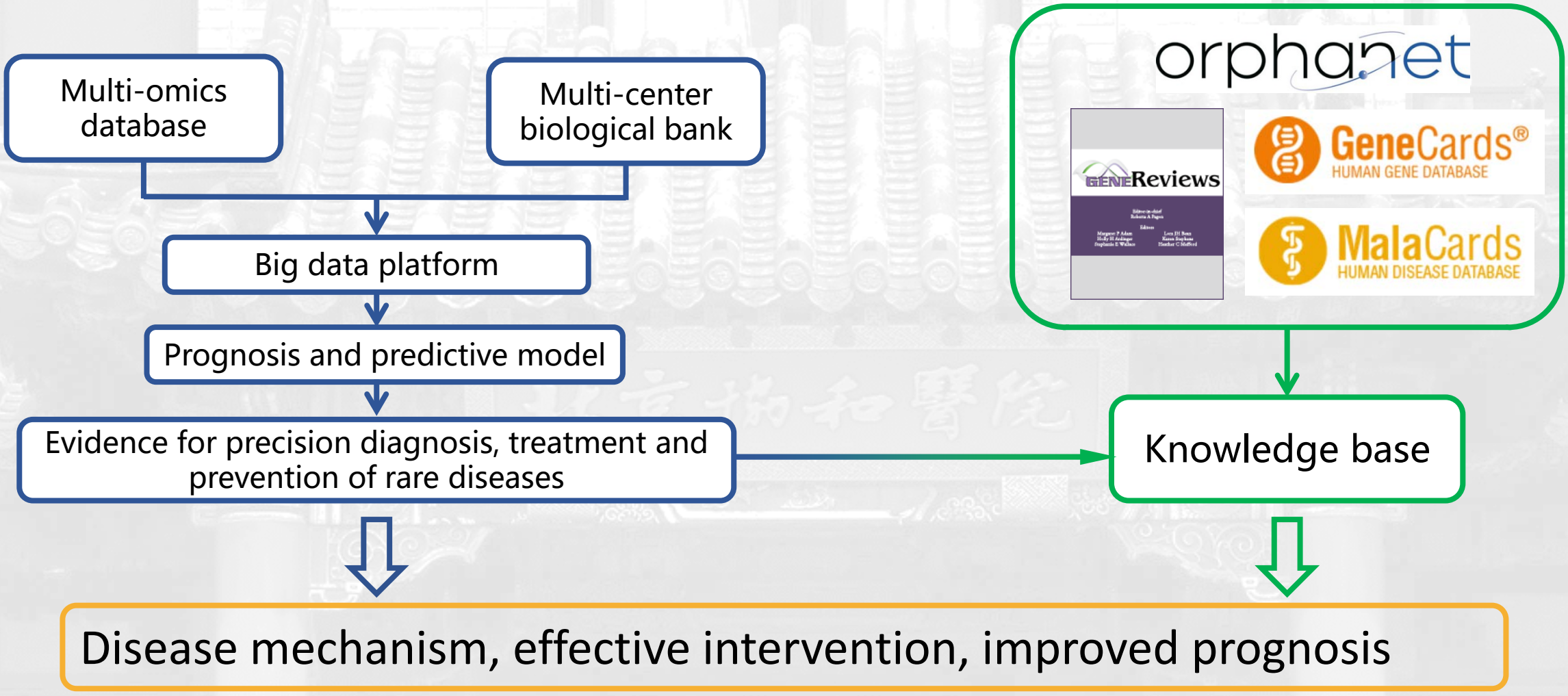
Future

Collaboration & Innovation

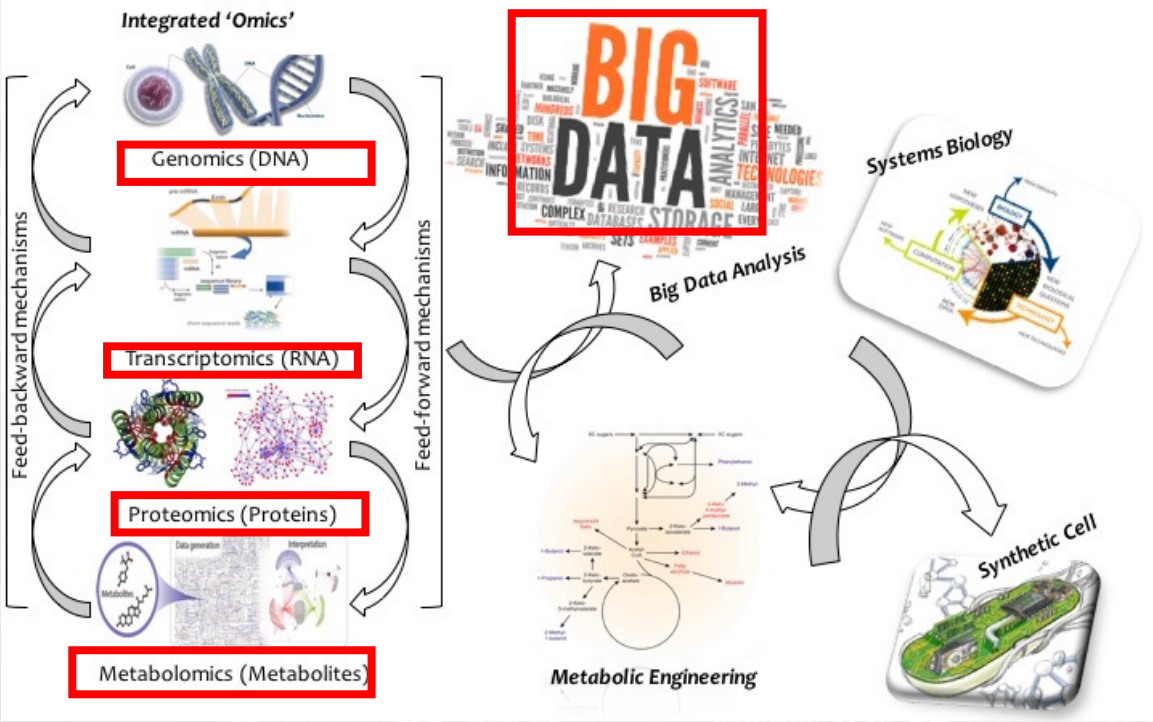
Establishment of Collaboration and Innovation Network



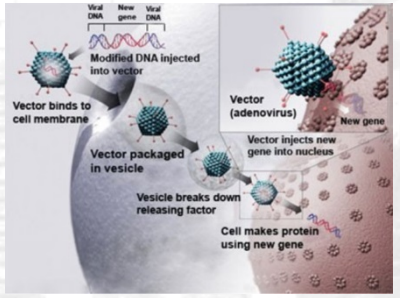
National Database and Rare Diseases Knowledge Base in Chinese



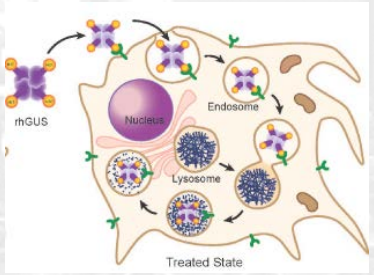
Accelerating Exploration and Innovation



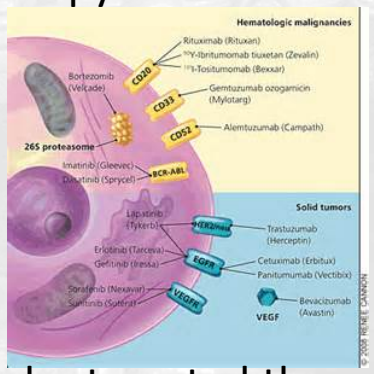
Promoting research



Gene therapy



ERT

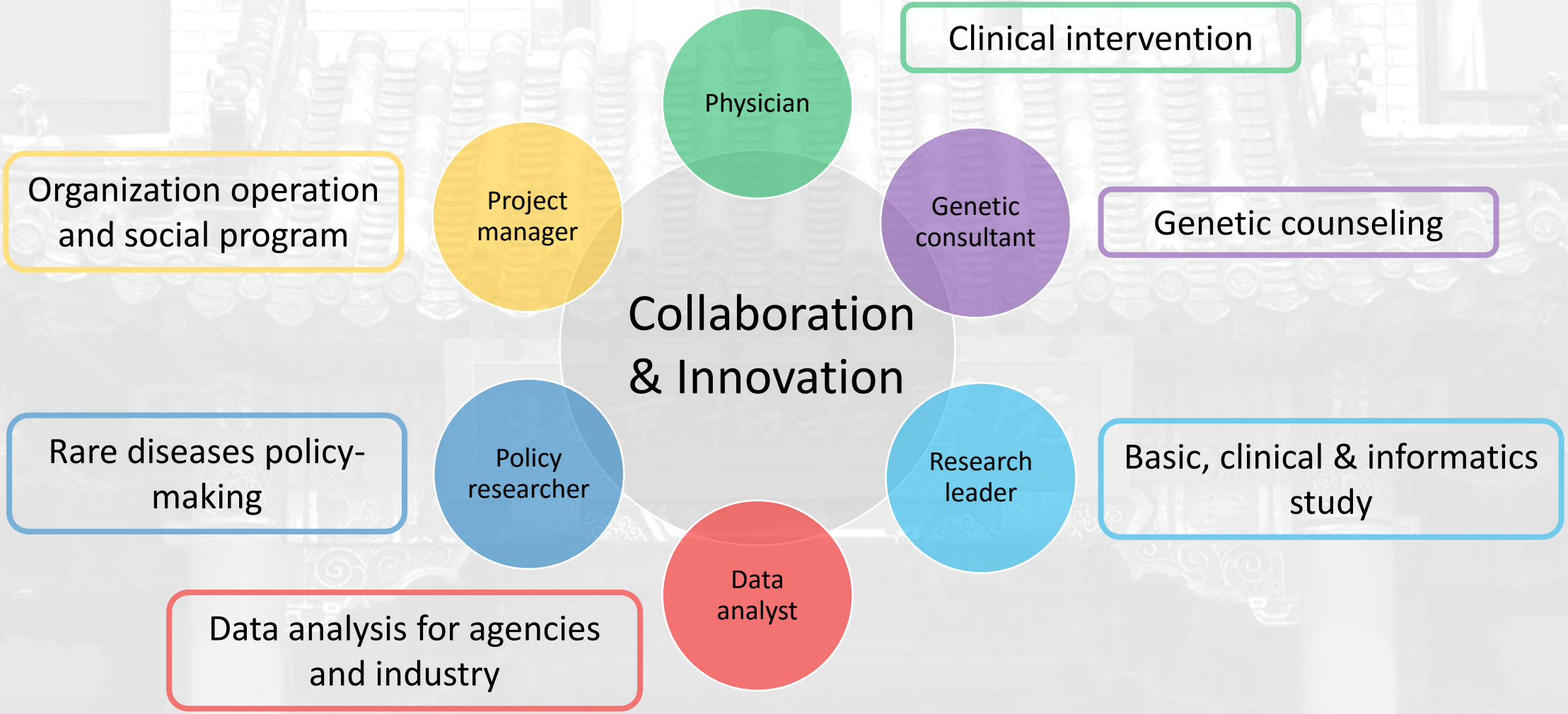


Molecular targeted therapy

Promoting therapy

NRDRS 中国国家罕见病注册系统
NATIONAL RARE DISEASES REGISTRY SYSTEM OF CHINA

Medical Education and Specialty Training



Promoting Patient Care and Outcomes

Better disease management
& Higher life quality

Patient-physician relationship	Patient education	Psychological intervention	Social security
Building trust, involving decision-making and keeping follow-up	Encouraging participation of registry	helping communication and providing support	assisting in education, employment and medical insurance

Joining the Leadership of International Cooperation

orphanet

NRDRS 中国国家罕见病注册系统
NATIONAL RARE DISEASES REGISTRY SYSTEM OF CHINA

首页 知识库 数据共享 项目动态 关于我们

ICORD
International Conference on Rare Diseases & Orphan Drugs

GeneCards® HUMAN GENE DATABASE

MalaCards HUMAN DISEASE DATABASE

GENEReviews

CHPO

Rare Diseases: Global Challenge and China's Roles

Multiparty coordination

&

Constructive innovation

THANK YOU

National Rare Diseases Registry System of China
www.nrdrs.org

NRDRS
中国国家罕见病注册体系
NATIONAL RARE DISEASES REGISTRY SYSTEM OF CHINA

北京协和医院
PEKING UNION MEDICAL COLLEGE HOSPITAL