Value of rare disease therapies for developing healthcare systems

Moderator

Prof Gordon G Liu

Peking University National School of Development

Panel

Dr Thomas Butt

Fellow, Peking University China Center for Health Economic Research

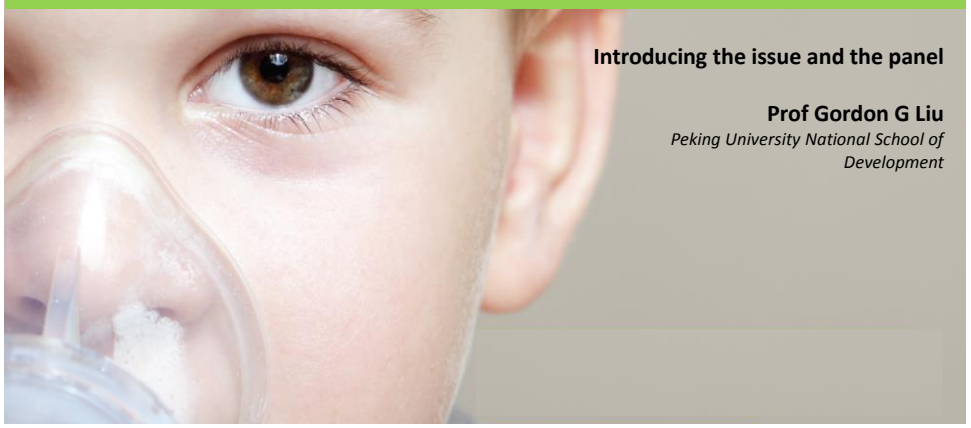
Kevin Huang

President, Chinese Organization for Rare Disorders

Ran Geng

Biotech Venture Capital Investor

Value of rare disease therapies for developing healthcare systems



Introducing the issue and the panel

Prof Gordon G Liu

Peking University National School of Development

Background to rare disease in China

7000 rare diseases	80% genetic diseases	10 million patients*	282 drugs approved by CFDA	<40% diagnosis rate**	5-year diagnosis period**

Without public reimbursement, most rare disease therapies are unaffordable to patients in developing countries due to high prices

- Treatment for one rare disease therapy in China was estimated to result in health expenditure equivalent to 69 years of income for an urban resident.[3]

[1] Wang J-B, Guo JJ, Yang L, Zhang Y-D, Sun Z-Q, Zhang Y-J. Rare diseases and legislation in China. The Lancet.375(9716):708-9. [2] Dunoyer M. Accelerating access to treatments for rare diseases. Nature Reviews Drug Discovery. 2011;10:475. [3] Xin XX, Guan XD, Shi LW. Catastrophic expenditure and impoverishment of patients affected by 7 rare diseases in China. Orphanet journal of rare diseases. 2016;11(1):74.

Topical

Imatinib (Gleevec, Novartis) for Chronic Myeloid Leukemia

Issue

Rare diseases create a substantial unmet medical and social need, which is particularly acute for **patients** in developing countries.

Companies need to recoup their investment in R&D across a small number of patients so rare disease therapies are often priced highly

Developing **health care systems** have multiple competing priorities for limited health resources and must provide "the greatest good to the greatest number".

How should developing health care systems evaluate and prioritise therapies for rare diseases?

Multi-stakeholder problem

Companies

Providers

Government

Patient organizations

Investors

Payers

Intro to panelists

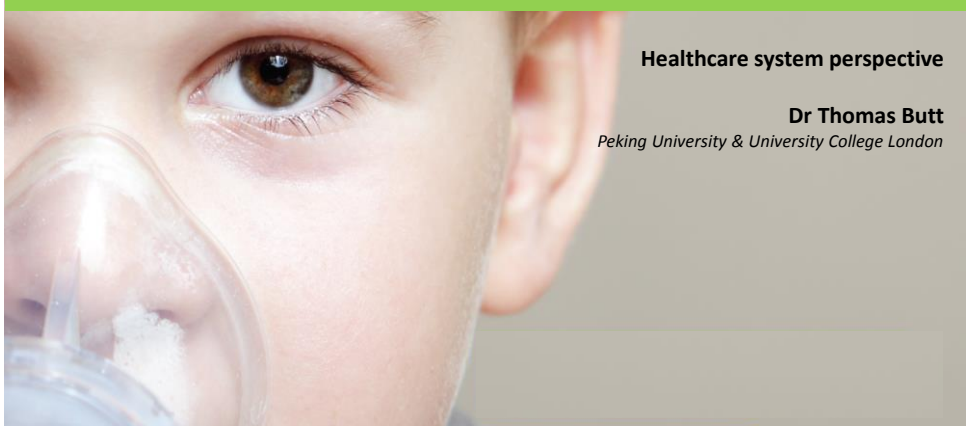
Moderator
Prof Gordon G Liu
Professor of Economics, Peking University

Healthcare system perspective
Dr Thomas Butt
Fellow in Health Economics, Peking University & Visiting Principal Research Associate, University College London

Patient perspective
Kevin Huang
President, Chinese Organization for Rare Disorders

Industry and investor perspective
Ran Geng
Biotech Venture Capital Investor
Board Observer, Adlai Nortye Biopharma

Value of rare disease therapies for developing healthcare systems



Healthcare system perspective

Dr Thomas Butt
Peking University & University College London

Conflicts of interest

- Views are my own

- Have participated in advisory boards for Roche and hold stock in BioMarin Pharmaceutical

There are good reasons that rare disease therapies deserve special consideration by the healthcare system

1. Equity — Rare disease patients are often disadvantaged in terms of **access** to high quality care

2. Additional (unmeasured) value to society — The public may attach greater value to treatments that address **unmet need, severe pediatric and terminal diseases**, etc.

3. Innovation — Public policy aims to encourage innovation. Rare disease therapies are **often highly specialised** (e.g. gene therapy)

4. Evidence development — Rarity means these therapies **cannot reach the same levels of evidence** as more common therapies and often must rely on smaller single arm studies with associated uncertainty

5. Budget impact — While these therapies have a high cost per patient, the overall budget impact to the healthcare system is often small - **low risk**

Example from an established HTA system that gives extra value to rare disease therapy

The National Institute for Health and Care Excellence (NICE) Highly Specialised Technology Appraisal (HST) process in England

- **special methods** to deal with the challenges of evaluation and uncertainty

1. Evaluation

Extra value of rare disease therapy: specific methods with wider scope and, since 2017, QALY modifiers

Incremental QALYs gained	Weight vs. GBP100k per QALY
≤10	1
11-29	1-3
≥30	3

NICE Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes May 2017

Patient access schemes and managed access agreements are becoming essential

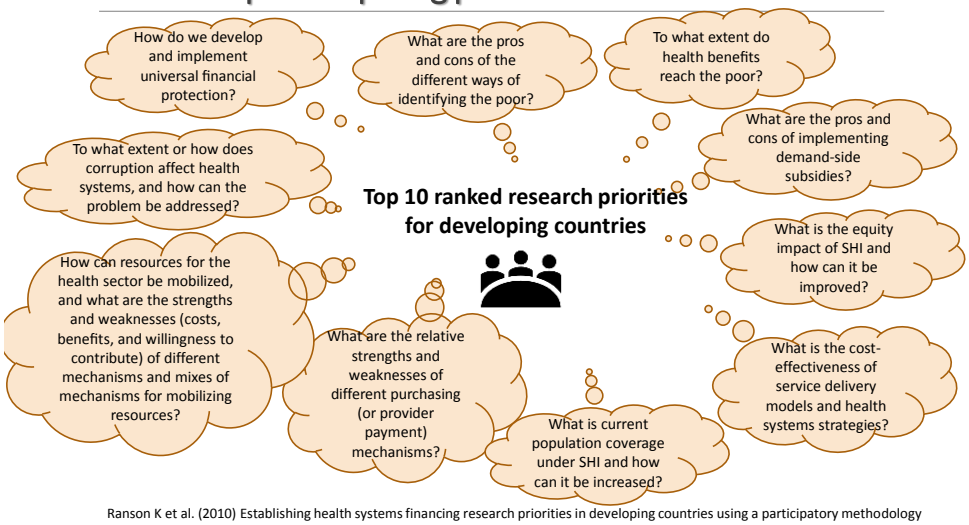
2. Implementation

Access with evidence development (patient access schemes/ PAS or managed access agreements/MAA)

Disease	Drug	Cost (patient/year)	NICE recommendation
aHUS	Eculizumab	GBP340,200	Yes with PAS
MPS IVa	Elosulfase alfa	GBP394,680	Yes with managed access agreement and PAS
DMD	Ataluren	GBP220,256	Yes with managed access agreement and PAS
Fabry	Migalastat	GBP210,000	Yes with PAS

Adapted from Raftery J. (2017) NICE's proposed new QALY modifier for appraising highly specialised technologies. BMJ

However, developing healthcare systems are faced with multiple competing priorities



Ranson K et al. (2010) Establishing health systems financing research priorities in developing countries using a participatory methodology Social Science & Medicine 70 1933-1942

There are specific challenges for developing healthcare systems to provide access to rare disease therapies

1. Evaluation challenges	
Methods	Often still refining methods: the core appraisal methods must be optimised before making adjustments for special cases
Adaptation of evidence base	Often limited evidence generated in other (developed) countries increasing uncertainty
Real-world evaluation and re-assessment	Do developing countries have the infrastructure and resources to implement methods such as managed access agreements?

There are specific challenges for developing healthcare systems to provide access to rare disease therapies

2. Implementation challenges	
Diagnosis	Uncertainty in the number of patients is a concern when budget impact arguments are key
Treatment guidelines and medical expertise	What is the comparator? Basic care and appropriate use of current health technology may do as much good as a high cost drug

And, companies must use the definition of rare disease responsibly: Imatinib (Gleevec, Novartis) for Chronic Myeloid Leukemia

- Initial price USD26,000/year in 2001. At the time, price was described as "high but fair" by Novartis CEO Daniel Vasella.
- Since then, the price and number of indications has steadily increased reaching USD146,000/year with global sales of patented imatinib approx. USD4.7bn in 2015

	Generic Name	FDA ODD Date/MA Date	Indication
1	Imatinib	01.31.01/05.10.01	Chronic Myeloid Leukemia (CML)
2a	Imatinib Mesylate	11.01.01/02.01.02	Kit-positive Unresectable and/or Metastatic Malignant Gastrointestinal Stromal Tumors (GIST)
2b	Imatinib Mesylate	11.01.01/12.19.08	Adjuvant Treatment Following Complete Resection Kit-Positive GIST
3	Imatinib Mesylate	08.25.05/10.19.06	Hypereosinophilic Syndrome and/or Chronic Eosinophilic Leukemia
4	Imatinib Mesylate	09.09.05/10.19.06	Aggressive Mastocytosis without D816V c-kit mutation
5	Imatinib Mesylate	10.05.05/10.19.06	Myelodysplastic /Myeloproliferative Diseases
6a	Imatinib	10.11.05/10.19.06	Relapsed or Refractory Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ALL)
6b	Imatinib	10.11.05/01.25.13	Newly Diagnosed Ph+ALL with Chemotherapy
7	Imatinib Mesylate	12.19.05/10.19.06	Dermatofibrosarcoma Protuberans (DFSP)

http://www.ascopost.com/issues/may-25-2016/the-arrival-of-generic-imatinib-into-the-us-market-an-educational-event/

Developing methods takes time

Budget impact approach (short-term fix)

Target high budget impact therapies for 'full assessment' to reduce burden on new HTA systems. Need robust horizon scanning…

Value-based assessment approach (long-term solution)

Develop specific methods to evaluate rare disease therapies that account for the additional value of rarity, burden of disease, innovation, etc.

Concluding statement

- **Rare disease therapies have specific features that mean they should be subject to a different evaluation process that accounts for these**
- In developing countries, establishing these methods can take time
- **Targeting of HTA at higher budget impact therapies may be a short term solution while capacity is developed so as not to disadvantage rare disease patients**
- Rare disease therapies still need to be priced responsibly and should go through an appropriate process that ensures the public are obtaining value for money

*In the context of high **patient need** and **un-measured value**, developing healthcare systems should assess rare disease therapies using a **modified value assessment framework alongside sensible consideration of the budget impact***

Value of rare disease therapies for developing healthcare systems

Patient perspective

Kevin Huang
President, Chinese Organization for Rare Disorders

The progress of rare disease in China

Kevin HUANG

罕见病发展中心
Chinese Organization for Rare Disorders

In the past decade, PAGs have made significant impact on policies, patient finding and public awareness

2008-2018

Advocacy

- Before 2008, rare to see the term ‘rare disease’ or ‘orphan drug’
- In 2009, **International Rare Disease Day** was introduced into China
- In 2014, the **Ice Bucket Challenge** came to China; the topic reached 3.6B views
- In the past decade, influenced over **150 million people**

罕见病发展中心
Chinese Organization for Rare Disorders

The development of PAGs in China

2008-2018

PAGs

- Around 80 PAGs developed in the past 10 years, covering 60 rare diseases, 60% in Beijing & Shanghai
- CORD support PAGs through an Incubation Program and Small-grants Program benefitting around 20 PAGs per year
- Patient management – launched patient survey covering 5000+ patients (ongoing)

罕见病发展中心
Chinese Organization for Rare Disorders

The development of PAGs in China

2008-2018

Dx & Tx

- Initiated **medical education programs for patients** to help them better understand their diseases: online & offline
- Established diagnosis and treatment network:
  - Improved local physicians' capability to diagnose and treat rare diseases through specialist training
  - Helped establish rare disease-specific outpatient sites
  - Helped establish MDT practice

罕见病发展中心 Chinese Organization for Rare Disorders

The past decade of rare disease in China

2008-2018

Policy

- In 2016, CORD published a **Rare Disease List** of 147 diseases, which translates into the publication of the first official National Rare Disease List in 2018
- PAG plays a crucial role in
  - The development of **priority review** process for rare disease therapies
  - The **insurance coverage decisions** for rare disease therapies

罕见病发展中心 Chinese Organization for Rare Disorders

In 2014, CORD launched a patient survey that generated valuable insights for policy makers and drug manufacturers

Design

- Distributed to physicians, patient groups, and online
- 2014 – 2018, survey is ongoing

Patient characteristics

- 5,321 valid responses
- 159 distinct rare diseases
- From 30 of 31 provinces

Top diseases:

- 1-5: CAH, SMA, Hemophilia, DMD, PNH
- 6-10: Methylmalonic acidemia, AHC, Spinocerebellar ataxia, Peutz-Jeghers syndrome, Prader-Willi syndrome
- 11-15: Langerhans cell histiocytosis, Gaucher's, Multiple sclerosis, Neurofibromatosis, Neuromyelitis
- 16-18: Niemann-Pick's, ALS, PKU

Source: CORD 2014-2018 Chinese Rare Disease Patient Registry

罕见病发展中心
Chinese Organization for Rare Disorders

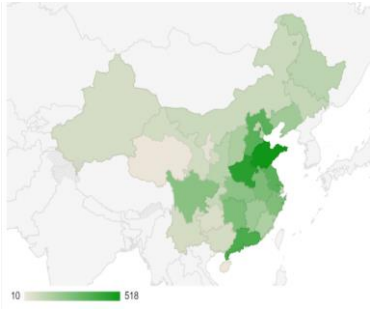
Key Results

- **Young: 56.6%** are under 18; Mean age of 17.75 (SD=16.59)
- **Unemployed: 56%** of working-age patients are not employed
- **High medical cost paid OOP:**
  - Median cost of treatment other than medication: USD $3,152-7,880
  - Median cost of medication: $1,576-3,152
  - **76.7%** of patients' primary payment method is out-of-pocket
- **High unmet medical need**
  - **Visit hospital frequently: 28%** have 10+ hospital visits / yr
  - **Majority have disability: 53.6%**

Source: CORD 2014-2018 Chinese Rare Disease Patient Registry

Still, majority of these diagnoses are made in three economic centres

- Province of residence



Province of diagnosis

- **3 provinces are key for diagnosis:**
  - **More than half** of patients are diagnosed in Beijing, Shanghai or Guangdong (vs. around 10% are residents)

Source: CORD 2014-2018 Chinese Rare Disease Patient Registry

The profitability of developing rare disease therapies is controversial

"Across a range of financial indicators, rare disease companies do not perform as well as their industry peers"[1]:

However, "*Publicly listed pharmaceutical companies that are orphan drug market authorization holders are associated with higher market value and greater profits than companies not producing treatments for rare diseases*"[2]

1. Morel T et al. (2014) Market watch: Are orphan drug companies the pick of the pharmaceutical industry? Nat Rev Drug Discov. 2014 Jan;13(1):10. doi: 10.1038/nrd4205 2. Hughes DA, Poletti-Hughes J (2016) Profitability and Market Value of Orphan Drug Companies: A Retrospective, Propensity-Matched Case-Control Study. PLoS ONE 11(10): e0164681. https://doi.org/10.1371/journal.pone.0164681

Newly approved therapies are rarely available in China. Do they have commercial value at all?

Rare Disease Therapies

Top 5 Brands	Indication(s)	US Sales 2016	Approved in China
COPAXONE® (glatiramer acetate injection)	Multiple Sclerosis	$3.3B	X
AVONEX® (interferón beta-1a)	Multiple Sclerosis	$1.7B	X
Sensipar® (cinacalcet) Tablets	Hyperparathyroidism	$1.2B	X
XYREM® (sodium oxybate) oral solution	EDS	$1.1B	X
SOLIRIS® (eculizumab)	aHUS, PNS, Myasthenia Gravis	$1.1B	X

Source: Evaluate 2017, Orphan Drug Report 2017

How big is their commercial value?

Oncology Therapies

Brands with Matching Sales	Indication(s)	US Sales 2016	Sales in China
Rituxan Rituximab	NHL, RA	$4.0B	$166M
Herceptin trastuzumab	Breast Cancer	$2.5B	$159M
gleevec imatinib mesylate	Acute Lymphocytic Leukemia	$1.2B	$101M
ALIMTA	Lung Cancer, Mesothelioma	$1.1B	$37M
VELCADE (bortezomib)	Multiple Myeloma	$1.0B	$41M

Source: IMS Health, Statisca.

Western orphan drug developers lack the capital or existing presence to launch the business in China

Top 5 rare disease Tx are developed by…

Rising biotech stars or regional players

$14B

Median Market Cap

Lack of presence in China

Oncology Tx of same revenue are developed by

$213B

Median Market Cap

Established business in China

In the past 3 years, the policies have made rare diseases a more attractive therapeutic area for drug makers

- In 2015, the State Council announced a directive that suggested accelerating the approval of rare disease drugs
- **Designated regulatory committee:** In 2016, NHFPC, following the directive, set up the Rare Disease Dx Tx and Care Advisory Committee
- **Insurance coverage:** In Jul. 2017, 36 drugs are added to the national reimbursement list; 2 of which are for rare diseases (hemophilia and MS)
- **Accelerated approval:** In Oct. 2017, CFDA set up priority review and conditional approval designations for drugs with high unmet need, including rare diseases therapies
  - As Jul. 2018, 25 rare disease therapies have been granted priority review for NDA or clinical trials

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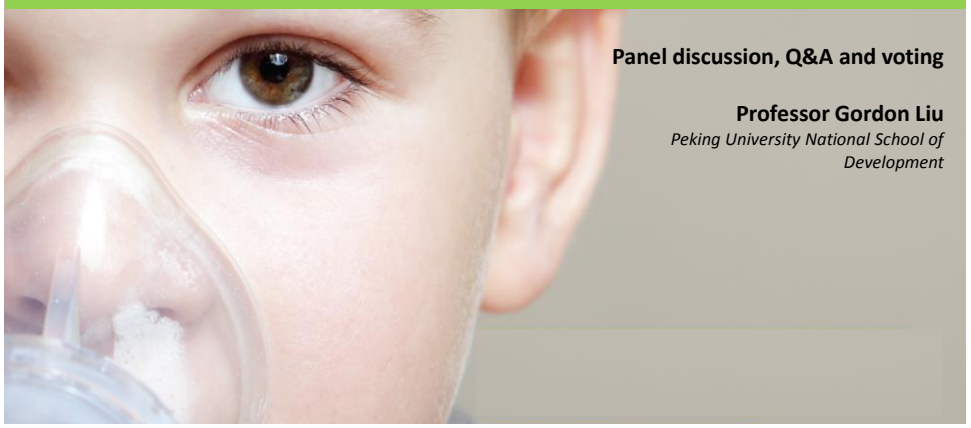

Panel discussion, Q&A and voting

Professor Gordon Liu
Peking University National School of Development

Audience poll

Developing health care systems should evaluate rare disease therapies using:

A	the **same** value framework as other treatments
B	a **different** framework to other treatments
C	should **not be evaluated** due to low budget impact
D	I don't know!

Vote now *using the URL or QR code*

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vote at raredisease.participoll.com

Results

Developing health care systems should evaluate rare disease therapies using:

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A B C D 0

vote at raredisease.participoll.com

Thank you!