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


Topical

Imatinib (Gleevec, Novartis) for Chronic Myeloid Leukemia

After seven days, "Dying To Survive" is already China's 14th-highest-grossing film

Box office takings

- 5.7 billion yuan
- "Wolf Warrior II"
- 3.6
- "Operation Red Sea"
- 3.4
- "The Mermaid"
- "The Fate of the Furious"
- 2.7
- "Monster Hunt II"
- 2.4
- "Journey to the West"
- 2.2
- "Detective Cone: Age of Extinction"
- 2.0
- "The Ex-File 3: The Return of the Ex"
- 1.9
- "Kung Fu Yoga"
- 1.6
- "Dying to Survive"
- 1.7
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

<table>
<thead>
<tr>
<th>Incremental QALYs gained</th>
<th>Weight vs. GBP100k per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10</td>
<td>1</td>
</tr>
<tr>
<td>11–29</td>
<td>1.3</td>
</tr>
<tr>
<td>≥30</td>
<td>3</td>
</tr>
</tbody>
</table>

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

2. Implementation

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

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

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

- How do we develop and implement universal financial protection?
- What are the pros and cons of the different purchasing mechanisms?
- To what extent do health benefits reach the poor?
- What is the equity impact of SHI and how can it be improved?
- How do we develop and implement universal financial protection?
- What are the relative strengths and weaknesses of different purchasing (or provider payment) mechanisms?
- What is the cost-effectiveness of service delivery models and health systems strategies?
- What are the pros and cons of implementing demand-side subsidies?
- To what extent or how does corruption affect health systems, and how can the problem be addressed?
- What is current population coverage under SHI and how can it be increased?
- How can resources for the health sector be mobilized, and what are the strengths and weaknesses (costs, benefits, and willingness to contribute) of different mechanisms and mixes of mechanisms for mobilizing resources?

**Top 10 ranked research priorities for developing countries**

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

### 1. Evaluation challenges

<table>
<thead>
<tr>
<th>Methods</th>
<th>Often still refining methods: the core appraisal methods must be optimised before making adjustments for special cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptation of evidence base</td>
<td>Often limited evidence generated in other (developed) countries increasing uncertainty</td>
</tr>
<tr>
<td>Real-world evaluation and reassessment</td>
<td>Do developing countries have the infrastructure and resources to implement methods such as managed access agreements?</td>
</tr>
</tbody>
</table>
There are specific challenges for developing healthcare systems to provide access to rare disease therapies.

2. Implementation challenges

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment guidelines and medical expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertainty in the number of patients is a concern when budget impact arguments are key</td>
<td>What is the comparator? Basic care and appropriate use of current health technology may do as much good as a high cost drug</td>
</tr>
</tbody>
</table>

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

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

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.

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

- 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

The development of PAGs in China

- 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)
The development of PAGs in China

- 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

The past decade of rare disease in China

- 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
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

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**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%

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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

Value of rare disease therapies for developing healthcare systems

Investor and manufacturer perspective

Ran Geng
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”\(^2\)

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

<table>
<thead>
<tr>
<th>Top 5 Brands</th>
<th>Indication(s)</th>
<th>US Sales 2016</th>
<th>Approved in China</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COPAXONE</strong> (glatiramer acetate injection)</td>
<td>Multiple Sclerosis</td>
<td>$3.3B</td>
<td>X</td>
</tr>
<tr>
<td><strong>AVONEX</strong> (interferon beta-1a)</td>
<td>Multiple Sclerosis</td>
<td>$1.7B</td>
<td>X</td>
</tr>
<tr>
<td><strong>Sensipar</strong> (calcium supplement)</td>
<td>Hyperparathyroidism</td>
<td>$1.2B</td>
<td>X</td>
</tr>
<tr>
<td><strong>XYREM</strong> (sodium oxybate oral solution)</td>
<td>EDS</td>
<td>$1.1B</td>
<td>X</td>
</tr>
<tr>
<td><strong>SOLIRIS</strong> (eculizumab)</td>
<td>aHUS, PNS, Myasthenia Gravis</td>
<td>$1.1B</td>
<td>X</td>
</tr>
</tbody>
</table>

Source: Evaluate 2017, Orphan Drug Report 2017
**How big is their commercial value?**

### Oncology Therapies

<table>
<thead>
<tr>
<th>Brands with Matching Sales</th>
<th>Indication(s)</th>
<th>US Sales 2016</th>
<th>Sales in China</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rituxan</strong></td>
<td>NHL, RA</td>
<td>$4.0B</td>
<td>$166M</td>
</tr>
<tr>
<td><strong>Herceptin</strong></td>
<td>Breast Cancer</td>
<td>$2.5B</td>
<td>$159M</td>
</tr>
<tr>
<td><strong>Gleevec</strong></td>
<td>Acute Lymphocytic Leukemia</td>
<td>$1.2B</td>
<td>$101M</td>
</tr>
<tr>
<td><strong>ALIMTA</strong></td>
<td>Lung Cancer, Mesothelioma</td>
<td>$1.1B</td>
<td>$37M</td>
</tr>
<tr>
<td><strong>VELCADE</strong></td>
<td>Multiple Myeloma</td>
<td>$1.0B</td>
<td>$41M</td>
</tr>
</tbody>
</table>

Source: IMS Health, Statista.

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**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

- **Oncology Tx of same revenue are developed by**
  - Established business in China
  - $213B Median Market Cap

Lack of presence 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

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:

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<table>
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<tbody>
<tr>
<td>A</td>
<td>the same value framework as other treatments</td>
</tr>
<tr>
<td>B</td>
<td>a different framework to other treatments</td>
</tr>
<tr>
<td>C</td>
<td>should not be evaluated due to low budget impact</td>
</tr>
<tr>
<td>D</td>
<td>I don’t know!</td>
</tr>
</tbody>
</table>

Vote now using the URL or QR code

raredisease.participoll.com

Results

Developing health care systems should evaluate rare disease therapies using:

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Thank you!