Orchard therapeutics

Should gene therapies be exempt from HTA scrutiny? An Industry Perspective

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ISPOR, November 2019

Global Fully Integrated Biotech Dedicated to Transforming the Lives of Patients with Rare Diseases Through Innovative Gene Therapies

Singular focus on *ex-vivo* autologous HSC gene therapy for rare diseases

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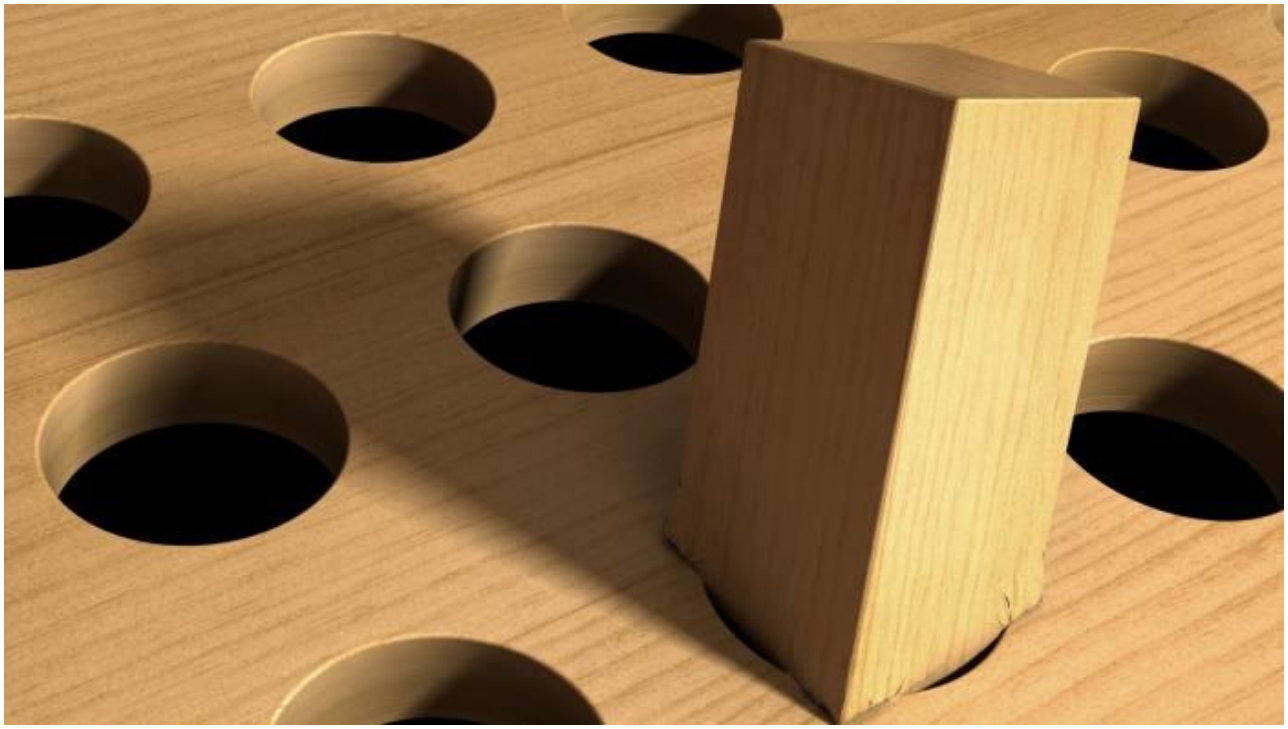
Over 150 Patients Treated with Orchard's Autologous *Ex Vivo* HSC Gene Therapies

Function	Program	Patients treated[1]	Longest patient follow-up (years)
Primary Immune Deficiencies	**Strimvelis®** (ADA-SCID)	24	18
	OTL-101 (ADA-SCID)	62	6
	OTL-103 (WAS)	16	8
	OTL-102 (X-CGD)	10	3
Neurometabolic Disorders	**OTL-200** (MLD)	33	8
	OTL-203 (MPS-I)	4	~1
Hemoglobinopathies	**OTL-300** (TDT)	9	3

Persistent, long-term effects across five indications with follow-up out to 8 years

[1] Patients treated in the development phase, including in clinical trials and under pre-approval access (defined as any form of pre-approval treatment outside of a company-sponsored clinical trial, including, but not limited to, compassionate use, early access, hospital exemption or special license). Data based on the most recent public data presentation for each program
Data include all patients treated with CD34+ hematopoietic stem cells transduced *ex vivo* with vector of interest.



"My" Industry Perspective:

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1. **Clinical evaluation of gene-therapies through HTA is critical (need to centralise)**
2. HTA systems are not currently able to accommodate the unique gene therapy challenges
3. There is no one-size fits all approach in gene-therapies HTA: flexibility and affordability are key

Today, all therapies go through the same 2 step process: a centralised regulatory review followed by national / regional cost-benefit assessments

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Clinical evaluation 1

Regulatory Approval occurs at national (US, AUS, CAN, JP) or EU level

Regulatory Agencies (FDA, EMA, TGA)

Performs clinical **risk benefit assessments** (safety/efficacy)

FDA

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

Health Canada

TGA Health Safety Regulation

This is followed by national (regional) price / reimbursement assessments

HTAs (e.g. NICE, CADTH, G-BA, SMC, AIFA, HAS)

- Perform **cost benefit assessments**
- New product is **compared to standard of care**
  - No improvement typically = no price premium
  - With clinical improvement, methods vary to determine the price premium
  - Is it meaningful? Can it be proven / supported?

HAS HAUTE AUTORITÉ DE SANTÉ

Gemeinsamer Bundesausschuss

NICE

Agenzia Italiana del Farmaco AIFA

There are already a number of examples focusing on centralised clinical and HTA reviews aiming at a streamlined process

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Clinical evaluation 1

eunethta EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

*"**EUnetHTA Joint Assessments (JA) are health technology assessments jointly produced by at least four EUnetHTA partners in different European countries**.*

EUnetHTA processes, guidelines and the HTA Core Model® are used for the production of assessments that are subject to extensive review procedures in order to ensure high quality."

Beneluxa Initiative on Pharmaceutical Policy

*"We cooperate in Health Technology Assessments. By using expertise acquired in the European Network on Health Technology Assesment (EUnetHTA), **we have a strong base for performing joint assessments**."*

VALLETTA DECLARATION

- ***Joint clinical assessment and health economic evaluation***
- *Joint pricing negotiations for medicines that have not yet received a marketing authorisation or are at an early stage of marketing authorisation*
- ***Information exchange on particular drugs or drug classes that have significant therapeutic value and a substantial budget impact***

Non-exhaustive list of activities, based on descriptions of each body

Also the EU is working towards a new HTA system building upon already existing initiatives and valid across all member states

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Clinical evaluation 1

- EC initiative to strengthen EU-level cooperation among Member States for assessing health technologies
- Objective to boost innovation and improve competitiveness of the European healthcare sector
- Builds on HTA Network and the EUnetHTA Joint Action

Commission Proposal: four focus areas

Joint clinical assessments for the most **innovative** health technologies with **greatest impact for patients**	**Joint scientific consultations,** whereby industry can seek advice from HTA authorities	**Horizon scanning,** with a view to identifying promising health technologies at an early stage	Continuing voluntary cooperation on other aspects of HTA

This proposal could provide an opportunity to develop a review framework suitable for the assessment of gene-therapies in Europe

It is unlikely that the Regulation will be agreed upon before 2020/21

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EU countries currently use different HTA frameworks to assess medicines

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HTA systems not currently fit 2

HTA frameworks in the EU

HTA Agency	HTA method	HTA perspective (economic analysis)	Value judgement			Acceptability of extrapolation	Uncertainty analysis
			Clinical benefit	Cost-effectiveness analysis	Budget impact		
HAS (TC, CEESP)	Mixed model	Payer (collective perspective)	++++	++++*/1	+++++1	+	+
IQWiG, G-BA	Clinical model	Payer (only drug budget impact)	++++	+1	+	+	+
AIFA, regions	Mixed model	Payer	++++	+	+++	+	+
AETS, regions	Mixed model	Payer	++++	+	++++	+	+
TLV	Health economic model	Societal	+++	++++*	++2	++++	+++
NICE (England), SMC (Scotland)	Health economic model	National health insurance	+++	++++	++++ (NHS England)	++++	+++
ZIN	Health economic model	Societal	+++	++++	++++	++	++
Danish health authority	Mixed model	Societal	++++	++++	+++	+	+

*No formal threshold;
[1] only in certain cases/products.
[2] Low at national level and High for county councils Mixed model means clinical and health economic model

High: Critical driver in HTA decision	Moderate: Secondary /complementary drivers in HTA decisions	Low: Marginal impact in HTA decision

Adapted from ARM, Sept 2018

Different EU countries also have very different approval rates of gene therapies

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HTA systems not currently fit 2

	France	Germany	UK	Italy	Spain	Sweden
Glybera®	Not recommended*	Non-quantifiable added benefit*	NA	NA	NA	NA
Imlygic®	NA	No added benefit	Recommended with restriction	List Cnn, not reimbursed	NA	NA
Strimvelis®	NA	NA	Recommended	List H	NA	NA
Kymriah®	Recommended	Non-quantifiable added benefit	Funded via CDF with CED scheme	NA	NA	**
Yescarta®	Recommended	Non-quantifiable added benefit	Funded via CDF with CED scheme	NA	NA	***
Luxturna®	Recommended	Ongoing G-BA assessment	Ongoing NICE HST assessment	NA	NA	NA
Provenge®	NA	Non-quantifiable added benefit*	Not recommended*	NA	NA	NA
Zalmoxis®	Not recommended	Non-quantifiable added benefit	NA	List H	NA	NA
Alofisel®	Recommended	Non-quantifiable added benefit*	Not recommended	NA	NA	NA
Chondrocelect®	Not recommended*	Not eligible to early benefit assessment	Recommended	NA	Recommended	NA
MACI®	NA			NA	NA	NA
Holoclar®	Recommended with restriction		Recommended with restriction	List H	NA	NA
Spherox®	NA	NA	Recommended	NA	NA	-

Adapted from ARM "Getting Ready: Recommendations for timely access to ATMPs in Europe - 2019

Many groups are calling for more appropriate methods to evaluate gene therapies, focusing on a number of common factors

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HTA systems not currently fit 2

Alliance for Regenerative Medicine

GENETIC ALLIANCE UK

EUCOPE
European Confederation of Pharmaceutical Entrepreneurs AISBL

- **Review of current evidence standards** required for HTA analysis
- Special allowances for **gene-therapies in areas without current SoC**
- Consider wider implementation of **conditional approval and reimbursement**
- Increase use of **real world evidence** for data collection
- Mitigation strategies for **data uncertainty**
- Ensure affordability

It is now recognised that the economic analyses of gene-therapies have to be different to the evaluation of mainstream therapeutics

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HTA systems not currently fit 2

Challenges in assessing gene-therapies

- × Variable epidemiology and heterogeneous patient population
- × Impact of disease severity and impact on caregivers
- × Endpoint selection
- × Wide benefit range: stopping disease progression to cure
- × How to value a gene-therapy?
- × Dealing with data uncertainty and durability

Proposed gene-therapy check list

Characteristics of the gene-therapy

- ✓ Effectiveness
- ✓ Unmet need
- ✓ Trial design and use of surrogate endpoints
- ✓ Transferability of trial results

Valuation of gene-therapy

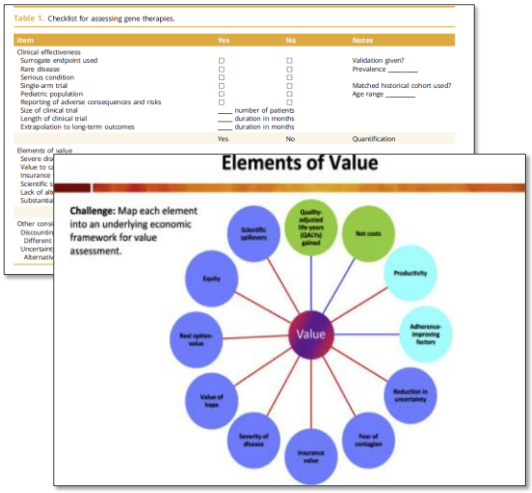
- ✓ Related to its benefit range (e.g. is it a cure?)
- ✓ Impact on caregiver burden, societal benefit

Additional considerations:

- ✓ Discounting
- ✓ Handling of uncertainty
- ✓ Economic approach taken and factors considered in formal analysis

Drummond et al. 2019

Framework based on Drummond et al, 2019



Also HTA bodies are reviewing their methodology, ICER and NICE have overlapping considerations in their consultation documents

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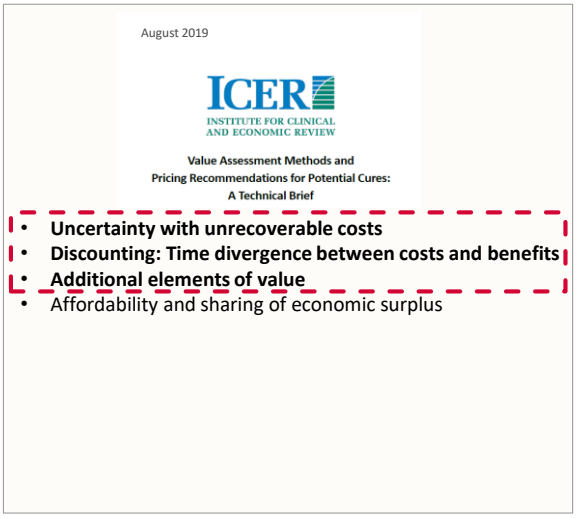
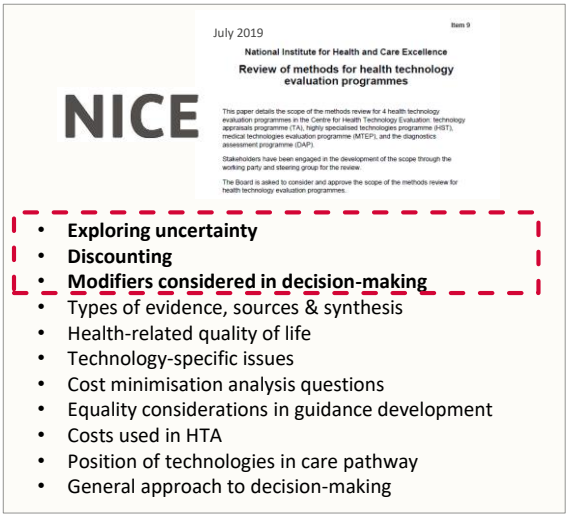
HTA systems not currently fit 2



- **Uncertainty with unrecoverable costs**
- **Discounting: Time divergence between costs and benefits**
- **Additional elements of value**
- Affordability and sharing of economic surplus



- **Exploring uncertainty**
- **Discounting**
- **Modifiers considered in decision-making**
- Types of evidence, sources & synthesis
- Health-related quality of life
- Technology-specific issues
- Cost minimisation analysis questions
- Equality considerations in guidance development
- Costs used in HTA
- Position of technologies in care pathway
- General approach to decision-making

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Not all gene-therapies have the same budget impact / affordability

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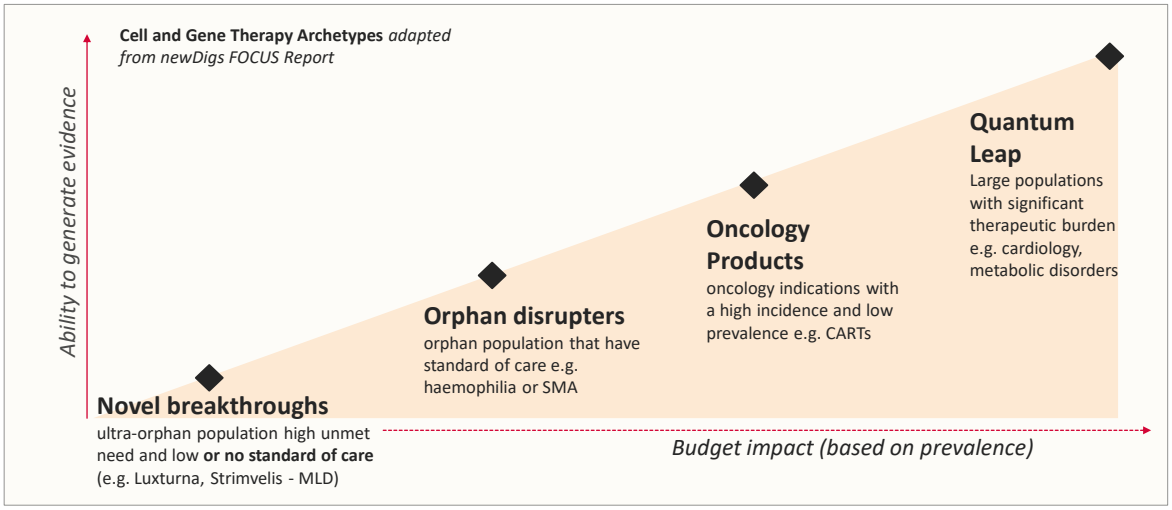
Flexibility and affordability 3



https://newdigs.mit.edu/sites/default/files/NEWDIGS%20FoCUS%20Frameworks%2020180823.pdf

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Not all gene-therapies are the same, different archetypes require different forms of HTA assessment to clearly validate their potential

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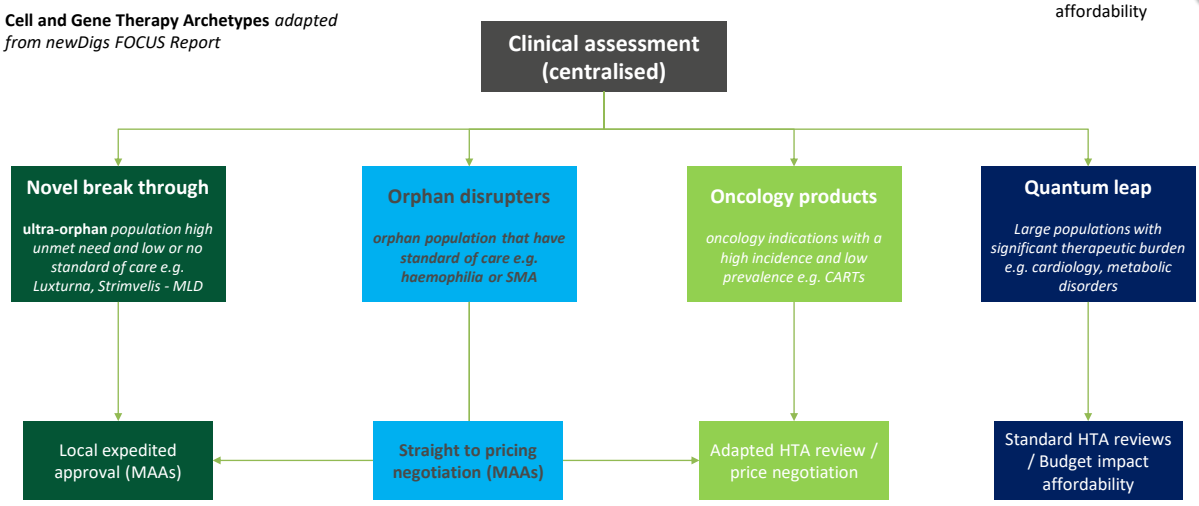
Flexibility and affordability 3

Cell and Gene Therapy Archetypes *adapted from newDigs FOCUS Report*



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England's HST is an example for an *adapted HTA review*

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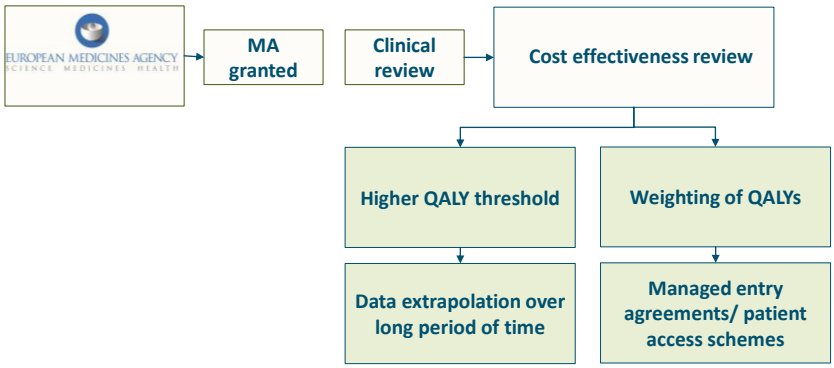
Flexibility and affordability 3

HST requirements

- ✓ Treatment will be concentrated in very few centres
- ✓ Distinct pt group for clinical reasons
- ✓ Chronic and severely disabling condition
- ✓ The technology is expected to be used exclusively in the context of a highly specialised service
- ✓ The technology is likely to have a very high acquisition cost
- ✓ The technology has the potential for life long use
- ✓ The need for national commissioning of the technology is significant



In Scotland ultra-rare therapies benefit from a dedicated pathway similar to a *local tailored review*

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Flexibility and affordability 3

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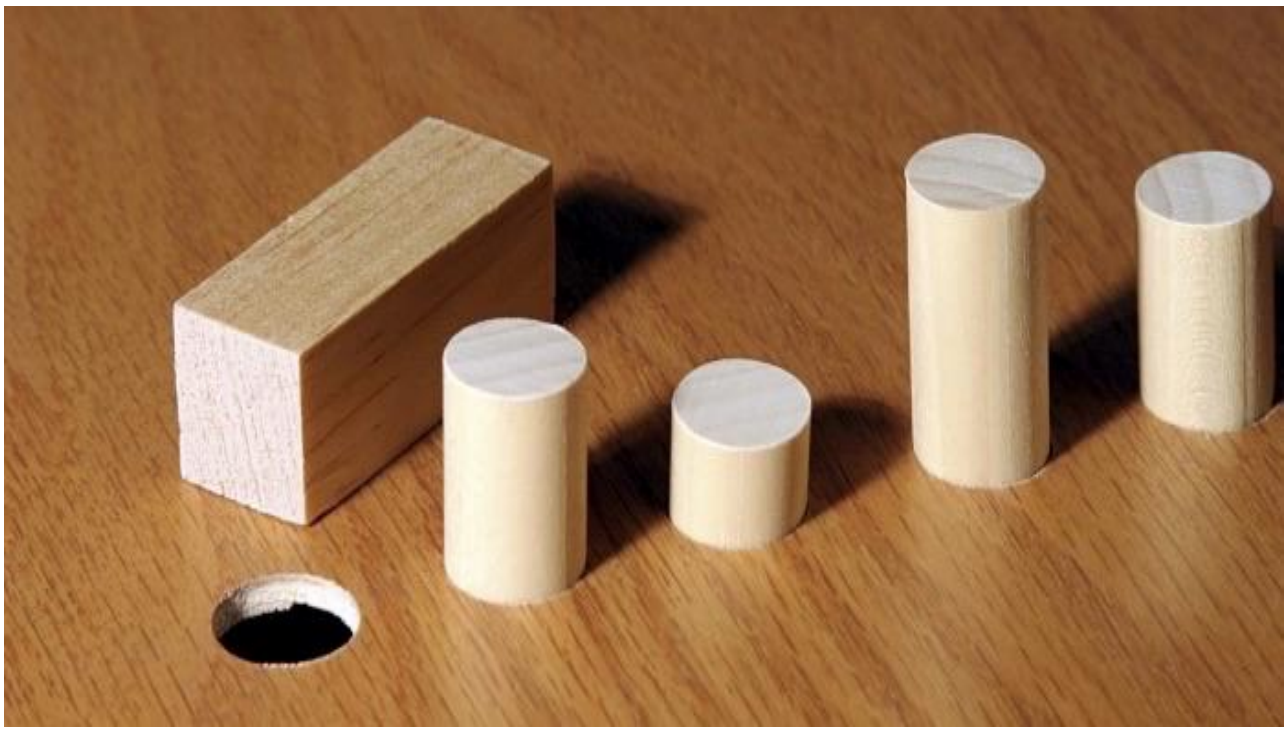

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