The challenges of patient stratification studies and personalised treatments for health technology assessment

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Senior Researcher
Belgian Healthcare Knowledge Centre, KCE
• Semi-governmental institution
  • Operational 2004

• 50 researchers
  • medicine, economics
  • statistics, sociology, law

• Studies (n>300)
  • Clinical practice guidelines
  • Health services research (HSR)
  • Health technology assessment (HTA) + KCE Trials (started in 2016)

• Policy recommendations, no decisions
“Personalized medicine” refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.” — President’s Council of Advisors on Science and Technology 2008

Defining PM - Targeted Therapy
Oh no!

Challenges are Data Explosion and Cognitive Overload

- Diagnostic Imaging: Functional and Anatomical
- Proteomics and other effector molecules
- Functional Genetics: Gene expression profiles
- Structural Genetics: e.g., SNPs, haplotypes
- Decisions by Clinical Symptoms

Human Cognitive Capacity

Facts per Decision

- 1M proteins
- 25K genes

Graph showing exponential growth from 1990 to 2020.
What is innovation in healthcare?

Technical innovator

New pathway

Technical breakthrough

Clinical Development

The evidence gap

HTA

Patient benefit

Routine practice

MIND THE GAP
The split in governance and the evidence gap

One government?

Regulator

- EMA/national regulator
  - Drug efficacy/safety

Notified bodies/national regulator
  - Device performance/safety

HTA/payer

- National/regional
- Added therapeutic benefit versus standard of care
- Value for money
Adaptive pathways

- **Aim:** clinical development from 12 to 4y.
- In parallel: real-life data capture.
- Bad track record of pharma to meet post-marketing commitments.
- Patients deserve to be protected as in a phase 3 setting: discontinuation of development versus withdrawal of product from the market.
- Observational data are no surrogate for RCT.
How aligned are the perspectives of EU regulators and HTA bodies? A comparative analysis of regulatory-HTA parallel scientific advice

Figure 3
Level of agreement for each domain: Health Technology Assessment bodies (HTABs) vs. regulators (based on 31 procedures). $n$ represents the total number of HTABs expressing an opinion for each domain. ■ full agreement ■ partial agreement ■ disagreement

How to fill the evidence gap?

- Align evidentiary requirements of regulators and payers
  - Where possible, require pre-market at least one RCT versus standard of care with patient relevant outcome
    - in line with Helsinki declaration
    - for evaluation of added therapeutic value

- Perform the missing comparative trial
  - Post-marketing: industry support is unlikely
  - Publicly-funded, role of payers
Randomised trials balance for the unknown
Real-world data are not sufficient - the case of renal denervation

- EU HTA report:
  - “renal denervation using the Symplicity® system appears to decrease blood pressure, whereas the effects of other systems on blood pressure are uncertain.”
  - Reimbursed in 13 countries in Europe, and in most cases regardless of the type of device.

- The same day: RCT for FDA: NO EFFICACY, all trials put on hold.
Propensity score

- **Major concern**: no good estimate of treatment effect → misinformation

Source: Dahabreh, JAMA, 2014
For your information

- EUneHTA guideline “Internal validity of non-randomised studies (NRS) on interventions”

1st recommendation:

As the inclusion of non-randomised studies (NRS) in an HTA report requires large efforts (but often fails to increase the validity of the report’s conclusion), the decision to do so should be made only after careful consideration of all advantages and disadvantages.

The inclusion of NRS evidence might mislead researchers into the false belief that RCTs are not worthwhile to perform. Thus, HTA might act as a barrier in finding out the ‘true’ effect of an intervention.

In the assessment of safety, however, non-comparative studies may play a greater role (37).
Comparative Effectiveness

Comparator

- best
- active
- placebo
- none

Endpoints
- Quality of Life (EQ-5D)
- Survival

Study population

pragmatic practice-oriented trial

placebo-controlled trial

narrow (efficacy)

broad (effectiveness)
Registry-based RCT, towards EHR-based RCTs

R-RCT vs. RCT

STEMI Thrombectomy Story

TASTE (R-RCT) vs. TOTAL (taditionell RCT)

500,000 € vs. 15,000,000 €

1st patient: June 2010
30 centers
33 months to full enrollment
7,244 patients

1st patient: August 2010
87 centers
48 months to full enrollment
10,732 patients

NEXT GENERATION SEQUENCING GENE PANELS FOR TARGETED THERAPY IN ONCOLOGY AND HAEMATO-ONCOLOGY

MARC VAN DEN BULCKE, LORENA SAN MIGUEL, ROBERTO SALGADO, ELS DE QUECKER, HARLINDE DE SCHUTTER, ANOUK WAEYTENS, PETER VAN DEN BERGHE, SABINE TEJPAR, JEROEN VAN HOUDT, STEVEN VAN LAERE, BRIGITTE MAES, FRANK HULSTAERT

March 2015
The increase in new cancer drug costs

Peter B. Bach, MD, MSKC
LYG, QoL & QALY gained

<table>
<thead>
<tr>
<th>Perfect health</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>QoL</td>
<td>0.5</td>
</tr>
<tr>
<td>Death</td>
<td>0.0</td>
</tr>
</tbody>
</table>

With new health technology

Without new health technology

Start intervention

Life years
Incremental Cost-Effectiveness Ratio (ICER)

More Costs

More Effective (LY, QALY)

IV
Less effective
More costs

I
More effective
More costs

III
Less effective
Less costs

II
More effective
Less costs
How to estimate an ICER?

Future

Model

Data

Assumptions
Test specificity of companion diagnostic impacts ICER

% false positives = 1 - specificity

Cost per test € 341
Overall incr. cost crizotinib/mo. €8 767
True positive treated gains 0,863 LYG
False positive treated gains 0 LYG
Test sensitivity 100%

Herceptin (trastuzumab) in early breast cancer

Xalkori (crizotinib) in NSCLC
ICER for treatment targeting 5% of the patient population

Cost per test: € 100 or € 500
Incr. cost per treatment: € 25000
True positive treated gains 1 QALY
False positive treated loses 0,1 QALY
Test sensitivity: 100%

Specificity of test for target population:

- 500€ test
- 100€ test
“Frankly sir, we’re tired of being on the cutting edge of technology.”