The health systems perspective

Biomarkers, Health Technology Assessment and sustainability of healthcare systems

Annie Pannelay, PharmD, MBA
Agency for Innovators AFIN
September 2018
Annie Pannelay

Hands-on experience across the health ecosystem, with a focus on evidence based medicine and value-based healthcare
Agenda

• Growth of healthcare budgets is faster than economic growth
• Areas of focus include hospital and the cost of medicines
• Research on biomarkers has increased in the past 20 years
• Challenges to reconcile for HTA pathways to be suited to biomarkers
  – Geographical alignment challenges
  – Views on robust clinical evidence
  – Apprehension about costs
• Thoughts for the future: How to make sure industry is coming up with the right products
Healthcare budget growth outpace economic growth

Spending on healthcare as % GDP

- France
- Germany
- Italy
- Russia
- Sweden
- United Kingdom

OECD Average 9.1%

Economic growth, health spending and pharma trends

- Real GDP
- Healthcare spending
- Pharma sales growth

2006 to 2016, Local currency Units, % change

Source: OECD
This is driven by population ageing – but not only

Ageing population: forecast

<table>
<thead>
<tr>
<th>% 65 and Over: 2015</th>
<th>% 65 and Over: 2050</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>2050</td>
</tr>
</tbody>
</table>

The population of people older than 65 years represented ~ 7% in 2015. By 2050, this proportion of the population will more than double, reaching 15.6%.

Sources: U.S. Census Bureau, 2013, 2014; International Data Base, U.S. population projects
Payers focus is on high contributors to health spending

- Across Europe, inpatient care represents the largest contributor to health spending.
- In the sample, the expected growth for spending on medicines is over 5% from 2017-2020.

<table>
<thead>
<tr>
<th>Country</th>
<th>Inpatient</th>
<th>Outpatient, home based and day care</th>
<th>Long term care</th>
<th>Medicines Blue: OTC</th>
<th>Exp growth 17-20</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>33.6</td>
<td>25.9</td>
<td>14.9</td>
<td>9.5</td>
<td>2.6</td>
<td>5.5%</td>
</tr>
<tr>
<td>Belgium</td>
<td>28.0</td>
<td>21.3</td>
<td>24.5</td>
<td>12.0</td>
<td>1.8</td>
<td>4.8%</td>
</tr>
<tr>
<td>France</td>
<td>29.3</td>
<td>25.0</td>
<td>12.0</td>
<td>12.6</td>
<td>1.8</td>
<td>5.9%</td>
</tr>
<tr>
<td>Germany</td>
<td>27.6</td>
<td>24.0</td>
<td>16.0</td>
<td>12.8</td>
<td>1.5</td>
<td>6.6%</td>
</tr>
<tr>
<td>Hungary</td>
<td>26.9</td>
<td>25.6</td>
<td>4.3</td>
<td>28.9</td>
<td>8.4%</td>
<td>14.5%</td>
</tr>
<tr>
<td>Italy</td>
<td>28.6</td>
<td>26.9</td>
<td>10.3</td>
<td>16.9</td>
<td>4.6%</td>
<td>17.4%</td>
</tr>
<tr>
<td>Netherlands</td>
<td>19.4</td>
<td>30.8</td>
<td>26.8</td>
<td>7.6</td>
<td>5.9%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Poland</td>
<td>33.8</td>
<td>26.5</td>
<td>5.7</td>
<td>10.3</td>
<td>6.1%</td>
<td>12.9%</td>
</tr>
<tr>
<td>Romania</td>
<td>36.4</td>
<td>13.6</td>
<td>1.8</td>
<td>26.5</td>
<td>14.3%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Slovakia</td>
<td>27.4</td>
<td>23.4</td>
<td>0.3</td>
<td>27.0</td>
<td>7.6%</td>
<td>21.9%</td>
</tr>
<tr>
<td>Spain</td>
<td>24.0</td>
<td>34.8</td>
<td>9.2</td>
<td>11.9</td>
<td>6.8%</td>
<td>14.9%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>23.5</td>
<td>32.2</td>
<td>18.3</td>
<td>12.1</td>
<td>4.4%</td>
<td>14.0%</td>
</tr>
</tbody>
</table>

Source: Eurostat, 2014
Research on biomarkers has grown – adoption remains low

- There is no separate framework for qualification of novel technologies unless medical device/medicine
- Pharmacoeconomics require whole of pathway approach
- There are no value-based pricing guidelines for innovative diagnostics in any of the EU member states
- The outcome of underdeveloped pricing system might limit access of patients to novel “therapy-test” products

What are the gaps to be filled to facilitate adoption of biomarkers?

Pubmed hits on "biomarkers"
Thousand hits, retrieved Sept 2018

2.5 times increase from 2005 to 2017
The HTA perspective

### Global evidence, local decisions

<table>
<thead>
<tr>
<th>Cancer medicines</th>
<th>Cancer diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>National</td>
<td>CMS, Large private</td>
</tr>
<tr>
<td>Regional</td>
<td>CMS, Large private</td>
</tr>
<tr>
<td>Local</td>
<td>CMS, Large private</td>
</tr>
</tbody>
</table>

- Coverage for Diagnostics is decided at local and regional level
- Innovators are often SMEs with low resources struggling to supply information to each organisation
- Harmonisation and design of good practice even more challenging than for medicines

### Apprehension about costs and lack of clinical evidence

- Testing large @risk populations who may benefit might prove costly
- Tests for cancer diagnostic available for self pay market aren’t supported by robust clinical evidence

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internet search on biomarkers available self pay in Germany</td>
<td>11</td>
</tr>
<tr>
<td>No RCT identified for patient relevant outcomes</td>
<td>10</td>
</tr>
<tr>
<td>RCT with the outcome of interest</td>
<td>1</td>
</tr>
<tr>
<td>RCT showing strong evidence of reduction of mortality</td>
<td>0</td>
</tr>
</tbody>
</table>

Snapshot adapted from the Luzak study


Markus B.; Brüggenjürgen, B.; Stefan, W. Personalised Medicine in Europe—Enhancing Patient Access to Pharmaceutical Drug-Diagnostic Companion Products.

What could support the development of HTA processes suited to biomarkers?

Early HTA definition

Early HTA includes all methods used to inform:
- industry
- other stakeholders

About the potential value of new medical products in development,
- including methods to quantify and manage uncertainty

Methods are varied

They include:
- Economic modelling – Markov models not always suited to complexity and effect of implementation of biomarkers on care pathways -> Systems modelling to address time dependent behaviors
- MCDA/stakeholders preferences (MCDA: Multi Criteria Decision Analysis)
- Headroom analysis – Applicable for industry only

Izjerman, 2017
What could support the development of HTA processes suited to biomarkers? (2)

The EFLM TE-WG 14 item checklist

1. Identify unmet need
   - What is the clinical management problem and desired outcome?
     - What is the health condition and clinical management problem?
     - What is the target group?
     - What is current practice?
     - What are the limitations of current practice?
     - What are the desired outcomes?

2. Verify unmet need
   - Is there an existing solution?
     - Could the problem be solved by optimising current practice?
     - Could these solutions be effective?
     - Could these solutions be cost effective?
     - Are there any barriers for these solutions?

3. Validate intended use
   - Would the biomarker contribute to the solution?
     - How would the biomarker alter and improve current practice?
     - What are the expected outcomes of test results?
     - How do these outcomes compare to the desired outcomes defined in STEP 1

4. Assess feasibility
   - Is the biomarker solution feasible in practice?
     - Under what conditions would the new biomarkers be feasible?
     - Commercially?
     - Economically?
     - Technically?
     - Organisationally?
     - Are there any other barriers?
<table>
<thead>
<tr>
<th>Title</th>
<th>Author</th>
<th>Year</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation of Biomarkers: Application in Urological Cancers</td>
<td>Moniek Martine Vedder</td>
<td>2016</td>
<td>Thesis, Erasmus MC, University Medical Center Rotterdam</td>
</tr>
<tr>
<td>Diagnostic Test” Co-Development in Europe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methods of Early Health Technology Assessment in Precision Medicine</td>
<td>Janet Boutell</td>
<td>2018</td>
<td>Glasgow molecular pathology node, poster</td>
</tr>
<tr>
<td>Health Technology Assessment of Drugs With Companion Diagnostics at</td>
<td>CADTH</td>
<td>2017</td>
<td>Health Technology Assessment of Drugs With Companion</td>
</tr>
<tr>
<td>CADTH</td>
<td></td>
<td></td>
<td>Diagnostics at CADTH</td>
</tr>
<tr>
<td>Emerging Use of Early Health Technology Assessment in Medical</td>
<td>IJzerma</td>
<td>2017</td>
<td>PharmacoEconomics</td>
</tr>
<tr>
<td>Product Development: A Scoping Review of the Literature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedural guidance for the systematic evaluation of biomarker tests</td>
<td></td>
<td>2014</td>
<td>Ludwig Boltzmann institute</td>
</tr>
<tr>
<td>Clinical effectiveness of cancer screening biomarker tests offered as</td>
<td>Luzak</td>
<td>2016</td>
<td>The European Journal of Public Health</td>
</tr>
<tr>
<td>self-pay health service: a systematic review</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systematic review of frameworks for staged evaluation of predictive</td>
<td>Malottki</td>
<td>2015</td>
<td></td>
</tr>
<tr>
<td>biomarkers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Practical guide for identifying unmet clinical needs for biomarkers</td>
<td>Monaghan</td>
<td>2018</td>
<td>The Journal of the International Federation of Clinical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemistry and laboratory medicines</td>
</tr>
<tr>
<td>Targeting biomarker development in response to unmet clinical needs</td>
<td>Monaghan</td>
<td>2014</td>
<td>for the Test Evaluation Working Group of the European</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Federation of Clinical Chemistry and Laboratory Medicine</td>
</tr>
<tr>
<td>Early Stage Health Technology Assessment for Precision Biomarkers in</td>
<td>Steuten</td>
<td>2016</td>
<td>Journal of Integrative Biology</td>
</tr>
<tr>
<td>Oral Health and Systems Medicine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precision Medicine in Oncology and Immuno-Oncology: Where We</td>
<td>Scheuenpflug</td>
<td>2017</td>
<td>Biomed Hub 2017,2(suppl 1):18-18</td>
</tr>
<tr>
<td>Stand and Where We’re Headed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Technology Assessment of Companion Diagnostic Biomarkers as</td>
<td></td>
<td>2013</td>
<td>Value in Health</td>
</tr>
<tr>
<td>Spinner Gatekeepers for Personalized Medicine Market Access</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attracting Investors: the value of HTA.</td>
<td>Tolley</td>
<td>2018</td>
<td></td>
</tr>
</tbody>
</table>
Annex: Categories of biomarkers

- **Susceptibility/Risk biomarker** - A biomarker that indicates the risk for developing a disease or sensitivity to an exposure in an individual without clinically apparent disease.

- **Diagnostic biomarker** - A biomarker used to identify individuals with the disease or condition of interest or to define a subset of the disease.

- **Monitoring biomarker** - A biomarker used to detect a change, over time, in the degree or extent of disease, safety indicator, or exposure.

- **Prognostic biomarker** - A biomarker used to identify likelihood of a clinical event, disease recurrence or progression.

- **Predictive biomarker** - A biomarker used to identify individuals who are likely to experience a favorable or unfavorable effect from a specific intervention or exposure.

- **Pharmacodynamic biomarker** - A biomarker used to show that a biological response has occurred in an individual who has received an intervention or exposure.

- **Safety biomarker** - A biomarker used to monitor toxicity.
The journey to market is designed for medicines

Review of...

- Safety
- Manufacturing and clinical production standards
- Clinical performance
- Correlation between clinical performance and potential price
- Price negotiation with manufacturers
- Medicines procured as efficiently as possible (tenders) and providers are reimbursed

Flow of information

- Is there a need?
- Is the product deemed safe in this indication?
- Should it be included in treatment guidelines?
- Should we pay for this?
- Any price adjustment?
- Nominated tariffs and usage monitoring

Biomarkers

- No separate framework for qualification of novel technologies unless medical device/medicine
- Evidence standards to be defined
- Need whole of pathway approach – see next slide
- Unclear and challenging timelines for reimbursement frameworks
- Effort needed to connect clinical diagnostic labs to where outcomes benefits can be seen
## Current trends in healthcare and challenges for biomarkers

<table>
<thead>
<tr>
<th>Current trends</th>
<th>Biomarkers development</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>• Focus on outcomes that matter to the patients: survival, degree of health</td>
<td>• Focused on surrogate endpoints/intermediary outcomes</td>
</tr>
<tr>
<td><strong>Value demonstration</strong></td>
<td></td>
</tr>
<tr>
<td>• Need to demonstrate the impact and effectiveness</td>
<td>• Patients benefit from pathway improvement, not from the test</td>
</tr>
<tr>
<td><strong>Data</strong></td>
<td></td>
</tr>
<tr>
<td>• Adoption of VBHC incentivises the harmonisation of data and processes</td>
<td>• Need for custom data domains – data managed separately in trials</td>
</tr>
<tr>
<td><strong>Evidence standards</strong></td>
<td></td>
</tr>
<tr>
<td>• Strong need for evidence base and clinical utility measure</td>
<td>• Quicker discovery pace, lack of standards to qualify novel biomarkers</td>
</tr>
</tbody>
</table>
Demonstrating the value of tests: NICE approach

- META-Tool was developed as a light version of the NICE scientific advice suited to medtech companies
- Process includes a review of:
  - Product information
  - Regulatory and HTA requirements
  - Questions for economic evaluation
  - Value proposition
  - Clinical treatment pathway
  - PICO statement
  - Measuring clinical effectiveness
  - Economic data collection
  - Funding and commissioning
  - Adoption and impact

**NICE Cost effectiveness framework**

- Higher cost
- Lower effectiveness
- Likely to be rejected

- Lower cost
- Lower effectiveness
- May be acceptable

- Lower cost
- Higher effectiveness
- Likely to be acceptable

- Higher cost
- Higher effectiveness
- Likely to be acceptable

Adapted from NICE