Health economics for stratified medicine

Friday 16 September 2016, Academy of Medical Sciences
Key issues in the health economics of stratified medicine

Adrian Towse
Director of the Office of Health Economics
Visiting Professor London School of Economics

Academy of Medical Sciences Forum:
Health economics for stratified medicine
5th October 2016
Agenda: Three big issues

• New elements of value come into play
  • The value of knowing and related elements
• Paying for value
  • Fair shares for diagnostics, drugs, payers and patients – the dynamic perspective
• Standards of evidence have to be different
  • Not that different – clinical utility evidence
The Economics of Personalized Medicine: A Model of Incentives for Value Creation and Capture

Personalized medicine is a concept promoted as a new paradigm for health care delivery, with particular emphasis on more tightly linking genomics-based diagnostics and therapeutic. Previous analyses focused on the pharmaceutical market; this analysis also addresses the incentives to develop linked genomics-based diagnostics and the broader public policy implications. Using a standard economic framework of an insurer-payer negotiating reimbursement with manufacturers of an innovative, targeted diagnostic and a companion patented therapeutic, several illustrative hypothetical scenarios are developed. The relative importance of the key economic factors is examined, including whether the reimbursement system is value or cost based, whether the therapeutic is already marketed, the strength of diagnostic intellectual property, and a current year versus longer time frame. The results suggest that health systems reforms that promote value-based, flexible reimbursement for innovative, patent-protected diagnostic and therapeutic products are critical to create stronger economic incentives for the development of personalized medicine.

Total Value Created by Tx with and without Dx

**Base Case: Tx with no Dx**

100 patients receive Tx
20% respond
Willingness to pay (WTP): $1000 per patient
Total value generated:
  - (100 x $1000) = $100,000

**Tx with perfect Dx**

100 patients are tested
20 receive Tx
Willingness to pay (WTP): $6000 per patient
Total value generated:
  - (100 x .2 x $6000) = $120,000

Therefore, a Dx test has the potential to generate an additional $20,000.
Sources of value from PGx

Value

1. Reducing drug adverse effects
2. Reducing time delays in selecting optimal Tx
3. Increasing adherence or willingness to start Tx
4. Enabling Tx effective in a small fraction to be made available
5. Reducing uncertainty about value

Can and Should Value Based Pricing Be Applied to Molecular Diagnostics?

Martina Garau, Adrian Towse, Louis Garrison, Laura Housman and Diego Ossa

April 2012
The Value of Knowing and Knowing the Value:
Improving the Health Technology Assessment of Complementary Diagnostics

Phase I: Complementary Diagnostics: A Literature Review on the Value of Knowing

Phase II: Landscape Review of Complementary Diagnostics in Europe
Garrison et al. (2016) EPEMED Report

Health economics for stratified medicine, 5th October 2016
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  • Not that different – clinical utility evidence
UK Academy of Medical Sciences Reports
(December 2007 and July 2013)

The Academy of Medical Sciences | FORUM

Optimizing stratified medicines R&D:
addressing scientific and economic issues
Report of a meeting organised by the Academy of Medical Sciences,
Roche and GE Healthcare.

December 2007

Realising the potential of stratified medicine

July 2013

Health economics for stratified medicine, 5th October 2016
Flexible, value-based pricing and reimbursement

**Recommendation 14**

To incentivise the development of stratified medicine products appropriately, we recommend that a pricing and reimbursement system is developed that (a) enables prices to be adjusted over time to reflect increases and decreases in value, and (b) can manage two diagnostic scenarios: companion tests of one biomarker and large platform tests of multiple biomarkers. This system should consider the impact on projected cost per quality-adjusted life years gained, the cost-offsets compared with existing practice, the value of greater certainty of response and the value of improved adherence and uptake in the population.
A possible way to split the value between Rx and Dx

Recommendation 15

To incentivise stratification, at least in the short term, we recommend that health technology assessment bodies develop a model to separate the value between the drug and companion diagnostic. The medicine should be considered as the primary source of the health gain in responders. The diagnostic should be valued in terms of the cost savings and improvements in quality and length of life from reduced adverse drug reactions in non-responders, and in terms of increased certainty of response. Better patient adherence and greater overall appropriate use may also result, and this value could be divided similarly.
Agenda: Three big issues

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<table>
<thead>
<tr>
<th>Techology</th>
<th>Economic and testing features</th>
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</thead>
<tbody>
<tr>
<td>HER2 testing for breast cancer</td>
<td>A low-cost immunohistochemistry (IHC) (approx. $100–$200) test for human epidermal growth factor receptor 2 (HER2)-positivity was used in the initial clinical trial program and was provided by diagnostic companies. Subsequently, a higher cost and more accurate test ($300–$500) was developed (called 'FISH') and is in use. Approximately 80% of initial testing is done with IHC, with FISH retesting for patient with equivocal results. The drug manufacturer receives nearly all of the economic value created by the combination from the drug trastuzumab (Herceptin®, Roche)</td>
</tr>
<tr>
<td>BCR-ABL testing for chronic myelogenous leukemia (CML)</td>
<td>An example of an ex ante test (breakpoint cluster region-Abelson (BCR-ABL) gene) closely tied to the development of the drug: large majority of value capture by the drug imatinib (Gleevec®, Novartis). A second, BCR-ABL test is used to monitor for resistance and assignment to second-line therapies</td>
</tr>
<tr>
<td>Oncotype Dx® (Genomic Health) for breast cancer recurrence</td>
<td>An example of a relatively high-cost, value-capturing test aimed at avoiding unproductive chemotherapy</td>
</tr>
<tr>
<td>EGFR mutation testing in nonsmall-cell lung cancer (NSCLC)</td>
<td>An example where the stratifying mutation (epidermal growth factor receptor (EGFR)) was identified in trials that also included test-negative patients</td>
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<tr>
<td>HLA-B*5701 allele testing for abacavir in HIV</td>
<td>Example of a test to identify patients who are more likely to suffer a severe adverse reaction to the HIV drug abacavir (Ziagen®, Viiv Healthcare)</td>
</tr>
<tr>
<td>KRAS testing in colorectal cancer</td>
<td>The KRAS mutation predicts which patients will not respond to two different monoclonal antibody treatments for colorectal cancer. The biomarker was identified after the products were on the market</td>
</tr>
<tr>
<td>PreDx® (Tethys Biosciences) diabetes risk test</td>
<td>This multimarker test identifies which prediabetic patients are at high risk of progressing to Type 2 diabetes: it indicates whether to begin prophylactic treatment with metformin</td>
</tr>
<tr>
<td>ALK mutation testing in NSCLC</td>
<td>Example of the drug crizotinib (Xalkori®, Pfizer) that targets a small subset (approximately 4%) of patients in disease condition with significant unmet medical need. It offers substantial survival gains in the subset, but with high testing cost per identified responder that must be factored in</td>
</tr>
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## Evidence from the 9 case-studies

- Predominant funders are the drug developers (as part of the Rx development) and public research bodies
- Less clear role from Dx manufacturer

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>n</th>
<th>Case studies</th>
<th>Main study design</th>
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<tr>
<td>Drug Developer</td>
<td>6</td>
<td>Her2-BCa; EGFR-NSCLC; KRAS-CRC; BCR-ABL-CML; HIV, and Hep-C</td>
<td>RCT</td>
</tr>
<tr>
<td>Public Research</td>
<td>5</td>
<td>GenProfiling-Bca; KRAS-CRC; CYP2C19; Hep-C, and PreDx DRS</td>
<td>RCT</td>
</tr>
<tr>
<td>Dx Developer</td>
<td>2</td>
<td>GenProfiling-Bca; CYP2C19, and PreDx DRS</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Payer</td>
<td>1</td>
<td>CYP2C19</td>
<td>Prospective observational</td>
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</table>
Reasonable evidence requirements for companion Dx

**Recommendation 16**

We recommend that health technology assessment bodies, payers and regulators adopt a flexible approach to the generation of clinical utility evidence required for diagnostic tests.

- A double randomisation model for the development of combination stratified medicine and diagnostic should not become a requirement.
- The delivery of a prototype diagnostic test for use in phase III development should not call for significant investment in advance of being in a position to recognise the efficacy or otherwise of the drug itself in phase II.
- Clinical utility of combination stratified medicine and diagnostic could be assessed in small randomised studies (if not built into phase III of drug development), which can lead to conditional reimbursement approval plus real-world data collection after launch.
Barriers to diagnostic innovation

Economic Incentives for Evidence Generation: Promoting an Efficient Path to Personalized Medicine

Adrian Tourae, MA, MPH\(^a\), Louis P. Garlino, Jr., PhD\(^b\)

\(^a\)Office of Health Economics, London, UK; \(^b\)University of Washington, Seattle, WA, USA

**Abstract**

The preceding articles in this volume have identified and discussed a wide range of methodological and practical issues in the development of personalized medicine. This concluding article uses the resulting insights to identify implications for the economic incentives for evidence generation. It argues that promoting an efficient path to personalized medicine is going to require appropriate incentives for evidence generation including: 1) a greater willingness on the part of payers to accept prices that reflect value; 2) consideration of some form of intellectual property protection (e.g., data exclusivity) for diagnostics to incentivize generation of evidence of clinical utility; 3) realistic expectations around the standards for evidence; and 4) public investment in evidence collection to complement the efforts of payers and manufacturers. It concludes that such incentives could build and maintain a balance among: 1) realistic thresholds for evidence and the need for payers to have confidence in the clinical utility of the drugs and tests they use; 2) payment for value, with prices that ensure cost-effectiveness for health systems; and 3) levels of intellectual property protection for evidence generation that provide a return for those financing research and development, while encouraging competition to produce both better and more efficient tests.

**Keywords:** economic incentives, personalized medicine, pharmacoeconomics, stratified medicine.

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Barriers to diagnostic innovation

Challenges:

• Lack of value-based pricing for diagnostics
• Difficulty of collecting evidence
• Limited ability to protect intellectual property
• Need for competition – first Dx is not necessarily the best
Consider intellectual property protection for companion Dx

**Recommendation 17**

We recommend that the problem of rewarding evidence generation for diagnostics used in combination with stratified medicines is addressed urgently. In determining the reward for a new stratifying diagnostic, pricing and reimbursement systems must consider the costs of evidence generation and not simply the costs of production. To incentivise the generation of evidence about analytical and clinical performance and clinical utility successfully, consideration should be given to promotion of commercially approved diagnostic tests unless an ‘in-house’ test has evidence of equivalent or improved quality.
Factors:
- Economies of scale in HTA review of Tx & Dx
- Economies of scope—evaluation expertise and disease area
- Complementary/tied products
- Consistency across health sector
References (i)

- Academy of Medical Sciences. (2013) Realizing the Potential of Stratified Medicine, London, UK.


THANK YOU FOR YOUR ATTENTION

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Modelling the cost-effectiveness of stratified medicines

Katherine Payne
Health Economics for Stratified Medicine
Academy of Medical Sciences & Pharmacogenetics and Stratified Medicine Network
5th October 2016
Towards effective use of healthcare budgets

Economic evaluations

INPUTS

Resources:
Drugs
monitoring
Clinic visits
In-patient stays

Process of health care

OUTPUTS

Alternatives:
1) Drug A
2) Drug B

Outcomes:
Clinical effectiveness (CEA)
Quality adjusted life year (CUA)

Study perspective
Study time horizon
Vehicle for CEA

• Trial-based CEA
  – Accurate patient-level resource use data
  – Robust internal validity but limited generalisability
  – Short follow-up
  – need to extrapolate outcomes (life-years & QALYs)

• Decision analytic model-based CEA
  – Structured framework to collate all available data
  – Key role for early economic evaluation
  – Vital to capture relevant diagnostic and care pathways
  – Still needs robust data to populate the model
  – Recommended by NICE
A pragmatic randomized controlled trial of thiopurine methyltransferase genotyping prior to azathioprine treatment: the TARGET study

- 167 TMPT test & 166 current practice starting azathioprine
- Rate of severe neutropaenia: 1.3%
- No difference in stopping azathioprine due to ADR (p = 0.59)
- TPMT variant homozygotes should avoid standard azathioprine doses to prevent severe neutropaenia
- TPMT did not predict all cases of neutropaenia (10%)
The Cost-Effectiveness of a Pharmacogenetic Test: A Trial-Based Evaluation of TPMT Genotyping for Azathioprine

Alexander J. Thompson, MSc¹, William G. Newman, FRCP, PhD², Rachel A. Elliott, PhD, BPharm, MRPharmS³, Stephen A. Roberts, PhD, BSc¹, Karen Tricker, PhD, MPM², Katherine Payne, PhD, MSc, BPharm, MRPharmS¹,*

- Individual patient-level data (n=333 patients)
- The UK health service perspective
- Time horizon of 4 months
- Resource-use: inpatient, outpatient, day-case, prescribed medication, monitoring, management of neutropenia, GP visits
- Health status data: EQ-5D-3L at baseline and 4-months
Result: The cost effectiveness plane

Fig. 2 – Cost-effectiveness plane of TPMT genotyping and treatment versus no-genotyping and current practice.
UGT1A1 testing & Irinotecan

- reduce the incidence of severe (NCI Common Toxicity Criteria grade 3 or 4) neutropaenia from irinotecan in advanced colorectal cancer

- UGT1A1 test stratifies patient population into three neutropaenia risk groups

- Cost of the test
  - No published UK price list: £29 to £117 charge (NHS labs)
  - Invader molecular assay® Third Wave Technologies: US$250 to US$500
Key Model Data Requirements

- Current treatment pathways advanced CRC
- Irinotecan-based chemotherapy regimen(s) used
- Prevalence of irinotecan-related neutropaenia
- Costs of managing patients on irinotecan-based chemotherapy
- Cost of managing irinotecan-related neutropaenia
- Utility data for the health states
- Need to characterise uncertainty
Potential Data Sources

- Randomised control trial
- Systematic reviews +/- meta-analysis
- Observational (cohort) data
- Retrospective extraction from medical records
- Expert elicitation
The clinical effectiveness and cost-effectiveness of genotyping for CYP2D6 for the management of women with breast cancer treated with tamoxifen: a systematic review

DOI 10.1007/s40273-013-0033-x

A Systematic Review of Utility Values for Chemotherapy-Related Adverse Events
Do health economic evaluations using observational data provide reliable assessment of treatment effects?

Dimitrios Rovithis

- Identifying and measuring causal effect
- Interface between econometrics and economic evaluation
- Approaches: matching, regression analysis, propensity scores, instrumental variables, difference-in-differences
- Develop methods how observational data should be analysed
Reporting Guidelines for the Use of Expert Judgement in Model-Based Economic Evaluations

Cynthia P. Iglesias¹ · Alexander Thompson² · Wolf H. Rogowski³,⁴ · Katherine Payne²

Key Points for Decision Makers

Expert judgement has a role in model-based economic evaluations (EEs) of healthcare interventions

A two-round online Delphi process identified guidelines for reporting two types of study design to use expert judgement in model-based EE: (i) an expert elicitation study requiring 16 reporting criteria; and (ii) a Delphi study to collate expert opinion requiring 11 reporting criteria.
Expert Judgement

- Expert Opinion
  - Judgement expressed quantitatively
    - Qualitative methods of elicitation (e.g. focus groups, nominal group technique, Delphi survey etc.)
  - Collating Expert Judgement
    - Identify consensus and express this quantitatively
      - Consensus methods (e.g. Delphi survey, nominal group technique etc.)
- Expert Elicitation
  - Judgement expressed quantitatively in an statistical format (i.e. probability density function, pdf)
    - Quantitative methods of elicitation (e.g. roulette, tertile, probability, etc.)
  - Weight views and express pooled/aggregated view quantitatively in an statistical format (i.e. probability density function)
    - Behavioural aggregation (i.e. group elicitation – get experts together and elicit a single distribution)
    - Mathematical aggregation (e.g. elicit distribution for each expert separately)
    - Mixed methods (e.g. nominal group technique + quantitative method of elicitation)
    - Quantitative methods (e.g. linear pooling or multiplicative pooling)
Expert Opinion

The Appropriate Elicitation of Expert Opinion in Economic Models
Making Expert Data Fit for Purpose

William Sullivan¹ and Katherine Payne²

¹ ScHARR, The University of Sheffield, Sheffield, South Yorkshire, UK
² The University of Manchester, Manchester, Greater Manchester, UK

Expert Elicitation

Tony O'Hagan - SHELFL: the Sheffield Elicitation Framework

MATCH Uncertainty Elicitation Tool
Concluding Remarks

• Role for decision-analytic models to produce evidence of relative cost effectiveness for stratified medicines
  • Early economic models with iterative approach
  • Value of diagnostic and treatment component

• Need for robust data

• Lack of RCT data need alternative data sources
  • Observational data: develop statistical methods
  • Expert elicitation: use robust approach
Economics of Genomics and Precision Medicine (CPD workshop)

Workshop overview

Our three-day Economics of Genomics and Precision Medicine CPD workshop will help those involved in the provision, commissioning or evaluation of healthcare services to assess whether genomic technologies and precision medicine offer value for money.
Health economics and drug safety

Professor Dyfrig Hughes  FFRPS FBPhS FLSW
Centre for Health Economics & Medicines Evaluation
Bangor University, Wales

@HughesDyfrig
ADRs not from errors

Errors that cause events that are not ADRs

Errors that don’t cause adverse events

ADRs from errors

ADRs not from errors

ADEs that are not reactions to a medicine

Drug Safety - ADEs incl. ADRs

Aronson J. QJM. 2009;102(8):513-21
Direct cost of ADEs and ADRs

- Patients admitted to hospital with ADEs
  - Range from €702 to €40,273 (n=17 studies)
- Patients experiencing ADEs during hospitalisation
  - Range from €943 to €5,973 (n=9 studies)

Hughes et al. Pharmacogenetics 2004, 14:335–342
Cost of illness

• The annual costs attributable to all ADEs and preventable ADEs for a 700-bed hospital are $5.6m and $2.8m, respectively
  • JAMA 1997; 277(4): 307-11

• The projected annual cost of ADR related admissions to the NHS is £466m
  • BMJ 2004; 329(7456): 15-9
  • £½bn per year ≡ 16,000 QALYs lost
Despite a significant reduction in errors, the findings of this economic analysis suggest that the PINCER intervention produced marginal health gain at slightly reduced overall cost.
Carbamazepine

• Carbemazepine is first-line treatment for epilepsy
• ADRs in 5%
• Macropapular Exanthema (ME)
  • ‘Mild’ rash resolves spontaneously upon discontinuation
• Hypersensitivity syndrome (HSS)
  • Rash, fever, eosinophilia, hepatitis and nephritis
  • 10% mortality

McCormack et al. NEJM. 2011;364(12):1134-43.
SJS / TEN

- Stephen-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) occurs ~1 in 10,000
  - Blistering rash
  - Up to 50% mortality
Carbamazepine pharmacogenetics

- **HLA-B*15:02** allele associated with SJS in Han Chinese, Thai and other Asian populations
  - These individuals should be screened before starting treatment
- **HLA-A*31:01** associated with hypersensitivity reactions to CBZ in populations of European and Japanese descent
  - Presence of allele increases risk of cutaneous ADR from 5% to 26%
  - Absence of allele reduces risk of ADR from 5% to 3.8%

McCormack et al. NEJM. 2011;364(12):1134-43.
Cost-effectiveness of routine testing for HLA-A*31:01 in patients with epilepsy eligible for treatment with carbamazepine

- Cost-effectiveness of routine testing for HLA-A*31:01 in patients with epilepsy eligible for treatment with carbamazepine
- NHS perspective
- Testing consists of an initial screen for HLA-A*31 (£51.71)
- Patients who test positive are assessed for HLA-A*31:01 (£90.40)
- Assumed to receive lamotrigine
Newly diagnosed patient

No testing. Standard treatment with CBZ

+ive treat with LTG

Tested for HLA-A*3101

-ive treat with CBZ

Uncontrolled epilepsy

Remission

Death

No ADR Death CBZ

Mild Rash Death VPA

HSS Death VPA

SJS/TEN Death VPA

No ADR Death LTG

Mild Rash Death VPA

HSS Death VPA

SJS/TEN Death VPA

No ADR Death CBZ

Mild Rash Death VPA

HSS Death VPA

SJS/TEN Death VPA

No ADR Death CBZ

Mild Rash Death VPA

HSS Death VPA

SJS/TEN Death VPA

Remission
Results

- 38 year old male, experiencing 12 seizures per year

<table>
<thead>
<tr>
<th></th>
<th>With test</th>
<th>No testing</th>
<th>Incremental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per patient</td>
<td>£10,808</td>
<td>£10,508</td>
<td>£300</td>
</tr>
<tr>
<td>QALY per patient</td>
<td>15.7744</td>
<td>15.7510</td>
<td>0.0235</td>
</tr>
<tr>
<td>ICER cost per QALY gained</td>
<td></td>
<td></td>
<td>£12,808</td>
</tr>
<tr>
<td>ICER cost per adverse event averted</td>
<td></td>
<td></td>
<td>£37,314</td>
</tr>
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~8 quality-adjusted days
CEAC
Conclusions

- SPC: There are insufficient data supporting a recommendation for *HLA-A*\(^{*31:01}\) screening before starting carbamazepine treatment

- HE analysis: Routine testing for *HLA-A*\(^{*31:01}\) in populations of European descent is likely to represent a cost-effective use of NHS resources
A Systematic Review of Economic Evaluations of Pharmacogenetic Testing for Prevention of Adverse Drug Reactions

Catrin O. Plumpton¹ · Daniel Roberts¹ · Munir Pirmohamed² · Dyfrig A. Hughes¹,²

Identification

Records identified through databases
Medline (n=307)
Embase (n=639)
NHS EED (n=83)

Additional records identified through other sources (n = 7)

Records after duplicates removed (n = 852)

Titles screened (n = 852) → Excluded (n = 611)

Screening

Abstracts screened (n = 241) → Excluded (n = 178)

Full-text articles screened (n = 63) → Excluded (n = 16)

Reasons for exclusion:
- No economic evaluation (n=112)
- Genotype mediates efficacy (n=30)
- Genotype mediates disease risk (n=15)
- Genotype of virus (n=5)
- Comparison of test methods (n=7)
- No genetic test (n=25)

Included

Studies included (n = 47)
- HLA-B*57:01 (prior to abacavir)
- HLA-B*15:02 and HLA-A*31:01 (prior to carbamazepine)
- HLA-B*58:01 (prior to allopurinol)
- CYP2C19 (prior to clopidogrel treatment)

? TPMT (prior to 6-mercaptoputidine, azathioprine and cisplatin therapy)
? CYP2C9 and VKORC1 (to inform genotype-guided dosing of coumarin derivatives)
? MTHFR (prior to methotrexate treatment)
? Factor V Leiden testing (prior to oral contraception)

✗ Testing for A1555G is not cost effective before prescribing aminoglycosides
Magnitude of benefit

- Serious ADRs are rare; alternative Rx may be less effective

- Mean QALY gains are relatively small:
  - warfarin 0.003 QALY
  - abacavir 0.003
  - phenytoin/carbamazepine 0.02-0.03 QALY
  - clopidogrel 0.05 QALY

- In context
  - 0.05 QALY is about 2.5 quality-adjusted weeks, and
  - 0.003 QALY is just 1 day
Economic challenges

• Evidential standards – is there a level playing field?
  • Evidence in the context of rare events
  • What are the comparative effectiveness and costs of alternative courses of action?
• Methodological – NICE reference case
• Equity – “QALY is a QALY is a QALY” – or is it?
  • Should a QALY lost because of iatrogenic harm (SJS) be valued the same as a QALY lost through 2nd degree burns?

Acknowledgements

• Catrin Plumpton, Munir Pirmohamed, Tony Marson, Ana Alfirevic, Vincent Yip

• Health and Care Research Wales, Department of Health, Medical Research Council, National Institute for Health Research (RfPB, i4i)
‘NICE evaluation of stratified medicines’

Dr Sarah Byron
Senior Technical Adviser, Observational Data Unit
5th October 2016
NICE - Aims

- Speed the uptake by the National Health Service (NHS) of interventions that are both clinically effective and cost effective
  
  *Produce evidence-based guidance*

- Encourage better and more rational use of available resources by focussing the provision of health care on the most cost-effective interventions
  
  *Develop quality standards and performance metrics*

- Encourage more equitable access to healthcare (reduce post-code lottery of care)
  
  *Provide a range of information services*

- Encourage the creation of new and innovative technologies.
NICE Process

- Independent Review of evidence
- Evidence submissions
- Stakeholder Perspectives
- Independent decision-making Committee
- Public Consultation
- Decision

Guides efficient allocation of healthcare resources
NICE- Companion Diagnostics evaluation

- Health and Social Care Directorate
- Centre for Clinical Practice
- Centre for Health Technology Evaluation
  - Medical Technologies Evaluation Programme (MTEP)
  - Interventional Procedures
  - PASLU
  - Highly Specialised Technologies
  - Scientific Policy & Research
- Scientific Advice
- Diagnostics Assessment Programme (DAP)
- Technology Appraisals

NICE
Defining Diagnostics

Companion Diagnostics

Stratified/Precision Medicine

‘Identification of sub-populations where treatment is more likely to be effective’

‘Providing information essential for the safe and effective use of a corresponding therapeutic’
**Companion Diagnostics – Potential Impacts**

- **Stratification of patient populations**
  - Improved clinical outcomes
    - Focus on benefits
    - Avoidance of adverse effects
  - Cost savings
    - Avoidance of ineffective treatments

**Improved treatment cost-effectiveness**

- .......dependent on cost of diagnostic testing to identify patient populations
  - Expensive tests required?
  - Only small proportion of patients identified for treatment?
Clinical and Cost-Effectiveness Diagnostics Assessment

LINKED EVIDENCE MODELLING

Diagnostic Accuracy → Impact on Treatment Decisions → Impact on Outcomes

Utilises existing evidence for parts of the care pathway to develop models

Can utilise existing models (directly or with modification)

Topic/clinical expert input into model structure and evidence gaps
Assessing Companion Diagnostics

The ideal situation....

• Co-dependent pharmaceutical & diagnostic that can be considered as a ‘package’ for assessment of clinical & cost-effectiveness
• Health outcomes (length and quality of life) from the treatment may be available from the clinical trials of the treatment
• Companion diagnostic testing costs can be included in the cost effectiveness analysis
• Technology Appraisals Programme

Very similar approaches to assessment of pharmaceuticals without companion diagnostics........
Assessing Companion Diagnostics

Real world scenarios....

- Companion diagnostic test(s) used in clinical trials may not be widely adopted in on-going clinical practice.
- Laboratories providing companion diagnostic testing may prefer to develop an alternative test based on efficiency, skill base or available equipment considerations.
- *Diagnostics Assessment Programme*

*Use of companion diagnostic tests in clinical practice that are different to those used in the clinical trials significantly increases the complexity of companion diagnostic assessment.*
Companion Diagnostics - Alternative Tests

Linking to health outcomes evidence....

• For companion diagnostics not used in treatment clinical trials, developers could:
  ▪ Retrospectively re-analyse clinical trial samples to demonstrate concordance with the test used in clinical trials
  ▪ Use side by side analysis of a sufficient and clinically relevant set of samples to demonstrate concordance with the test used in clinical trials
  ▪ Perform conventional diagnostic accuracy studies
    ✓ Where the marker is well defined
    ✓ There is a “gold standard

Consideration of this type of data could significantly increase the resources and time needed for the HTA of pharmaceuticals with companion diagnostics...........
Companion Diagnostics - Alternative Tests

Assessment options........

1. Assessment of the companion diagnostic used in the clinical trials only, together with general commentary on the potential risks of using alternative companion diagnostic tests
   ○ Technology Appraisal Programme

2. Detailed consideration of the alternative companion diagnostic options used in clinical practice leading to separate cost effectiveness estimates for the drug in combination with each of the alternative companion diagnostic options
   ○ Diagnostics Assessment Programme
Companion Diagnostics Evaluation at NICE

In April 2013, NICE published an updated guide to the methods of technology appraisal. The updated guide includes a new section on companion diagnostics (Section 5.9):

- If companion diagnostic test carried out solely to support the treatment decision for the drug under evaluation, the costs of the test should be incorporated into the assessment of cost effectiveness.

- A sensitivity analysis should be provided without the cost of the companion diagnostic test.

- When appropriate the diagnostic accuracy of the test for the biomarker should be examined and when appropriate incorporated in the economic evaluation.

- When appropriate, the possibility that using alternative tests may affect selection of the patient population for treatment and the cost effectiveness of the treatment will be highlighted in the appraisal guidance.

- Expectation that assessments of multiple companion diagnostic test options will generally be undertaken in the NICE diagnostics assessment programme.
## Companion Diagnostics - Technology Appraisals

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Condition</th>
<th>Marker</th>
<th>NICE technology appraisal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>chronic myeloid leukaemia</td>
<td>Philadelphia chromosome (bcr-abl) Kit (CD 117)</td>
<td>50, 70, 241, 251 86, 196, 209</td>
</tr>
<tr>
<td></td>
<td>GIST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>breast cancer</td>
<td>HER-2 (protein)</td>
<td>107, 257 208</td>
</tr>
<tr>
<td></td>
<td>metastatic gastric cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>breast cancer</td>
<td>HER 2 (protein) (negative)</td>
<td>242, 263</td>
</tr>
<tr>
<td>Cetuximab Panitumumab</td>
<td>metastatic colorectal cancer</td>
<td>KRAS</td>
<td>218, 176, 240, 242</td>
</tr>
<tr>
<td>Gefitinib Erlotinib Afatinib</td>
<td>non-small-cell lung cancer</td>
<td>EGFR TK mutations</td>
<td>192, 258, 310</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>malignant melanoma</td>
<td>BRAF V600 mutation</td>
<td>269</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>non-small-cell lung cancer</td>
<td>anaplastic lymphoma kinase fusion (ALK) genes</td>
<td>296</td>
</tr>
</tbody>
</table>

Mostly using rapid single technology appraisal (STA process)

Consideration of the companion diagnostic to support optimal use of the pharmaceutical but no detailed evaluation of the companion diagnostic and alternative companion diagnostic options
DAP Companion Diagnostics Topics

Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer:


- Existing TA guidance for drugs gefitinib and erlotinib
- Companion Diagnostic testing in place across the NHS; wide variety of tests in use across laboratories providing EGFR-TK mutation testing
- EGFR-TK mutation testing notified to NICE by National Clinical Director for Cancer to identify which tests were capable of supporting the clinical and cost effective use of gefitinib and erlotinib based on available evidence
- Assessment did not revisit the cost effectiveness of gefitinib and erlotinib
- Had relevant outcomes evidence for test used in drug clinical trial and retrospective reanalysis of samples from clinical trials for a further test
- No outcomes evidence and no way to link to outcomes evidence for several tests
- Included a survey of labs providing EGFR-TK testing which provided information on test characteristics and costs and national quality assurance scheme data
NHS RECOMMENDATIONS

• Made by the Diagnostics Advisory Committee (DAC) informed by the diagnostics assessment report
• A number of tests were recommended as options as there was a reasonable evidence base to support their use
• For the other tests the DAC concluded there was insufficient evidence on which to base a recommendation
• The DAC indicated that test validation and competent execution were key issues and stressed the importance of participation in external quality assurance schemes
• The guidance includes a research recommendation to encourage studies directly comparing different EGFR-TK mutation test methods and stipulates that these studies should link to patient outcomes
October 2012, Diagnostics Assessment programme started an evaluation of 9 KRAS mutation testing methods for identifying adults with metastatic colorectal cancer who may benefit from first-line treatment with cetuximab (Erbitux).

Guidance production process paused in November 2013 in anticipation of changes in the marketing authorisation for cetuximab.

Process terminated in September 2014 following confirmation of expected changes.
Thank you very much for your attention!

sarah.byron@nice.org.uk
Health Economics of Stratified Medicines
An Industry Perspective

Gavin Lewis, Global Head of Oncology Market Access, AstraZeneca
Health Economics of Stratified Medicine, London

5th October 2016
Health Economics of Stratified Medicine

Key implications, challenges and opportunities

- Evidence Generation
- Regulatory and HTA evolution
- Flexible Pricing
What is personalised healthcare?

AZ defines *personalised healthcare* (PHC) as the combination of drug and diagnostic test to improve patient outcomes.

- **Our medicines are most effective when matched to patients’ individual characteristics**
- **Diagnostic tests** can identify patients’ characteristics, e.g.
  - **What genes** drive patients’ cancer
  - **Cell types** that predict response in asthma

- **This approach leads to better patient outcomes**
- Targeting medicines to patients who will benefit most
- Minimising trial and error treatment

Other terms are used for this approach:
- Personalised medicine
- Precision medicine
- Tailored therapy
- Stratified medicine
The evolution of genomics in lung cancer diagnosis

**Historical View**
- Adeno-carinoma
- Squamous
- Large-cell

**1987**
- Unknown
- KRAS
- EGFR

**2004**
- Unknown
- KRAS
- EGFR

**2012**
- Unknown
- EGFR
- KRAS
- ROS1
- RET
- PIK3CA

Worldwide, lung cancer is the most common cause of cancer-related death (1.3M deaths). Traditional classification used morphology.

Discovery showed that NSCLC cells can harbor a single specific mutated KRAS oncogene.

AstraZeneca in collaboration with external groups show that clinical response to gefitinib correlates with EGFR mutations.

Global genomics initiatives (e.g., TCGA) identify multiple additional primary genetic “drivers”.
>80% of our clinical pipeline has a PHC approach

Pipeline data correct as of 28 July 2016

1 Includes significant fixed-dose combination projects, and parallel indications that are in a separate therapy area. (See LCM chart for other parallel indications and oncology combination projects)

# Partnered and/or in collaboration; ¶ Registrational P2/3 study
### PHC: Delivering better, safer and more efficacious treatments

#### Conceptually PHC aligns with the goals of Payers

<table>
<thead>
<tr>
<th>Personalized HealthCare</th>
<th>Health Technology Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• To deliver better, safer, more effective treatments</td>
<td>• Better and more predictable clinical outcomes</td>
</tr>
<tr>
<td>• To better understand disease diversity or subtypes</td>
<td>• Improved quantity and quality of life</td>
</tr>
<tr>
<td>• To identify the differences between patients</td>
<td>• Fewer unnecessary treatments / side effects and associated costs</td>
</tr>
<tr>
<td>• To identify the best drug targets</td>
<td>• Better compliance</td>
</tr>
<tr>
<td>• To improve the quality and efficiency of R&amp;D</td>
<td>• Optimized use of resources in healthcare</td>
</tr>
</tbody>
</table>
Evidence Generation

• Adaptive pathways can be defined as a prospectively planned, iterative approach to bringing medicines to market. The iterative development plan will initially target the development to a well-defined group of patients that is likely to benefit most from the treatment. This is followed by iterative phases of evidence gathering and progressive licensing adaptations, concerning both the authorised indication and the potential further therapeutic uses of the medicine, to expand its use to a wider patient population as more data become available.

• What challenges arise when shifting from A to B?

• How should HTA evolve to accommodate earlier license approval and assessment?
Evidence Generation and HTA methods

Health Economics has tools to support evolving regulatory pathways

- Indirect Comparison methods
- Extrapolation and modelling
- Agile re-assessment
- Risk share arrangements
- Flexible pricing
- RWE sources

Single Arm Studies
SurrogateEndpoints
Data Maturity
Multiple Indications / Combos
Large variation in benefit assessments by HTA institutions with opportunity for greater harmonisation and development signals to industry

<table>
<thead>
<tr>
<th>ESMO</th>
<th>ASCO</th>
<th>G-BA</th>
<th>HAS</th>
<th>NICE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Score</strong></td>
<td><strong>ASCO</strong></td>
<td><strong>G-BA</strong></td>
<td><strong>HAS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>(min-max)</strong></td>
<td><strong>(min-max)</strong></td>
<td><strong>1 (less than comparator) to 6 (substantial added benefit)</strong></td>
<td><strong>ASMR: V (none) to I (major)</strong> <strong>SMR: insufficient - substantial</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Afatinib</strong></td>
<td>4</td>
<td>43</td>
<td>Considerable benefit (Del19 subgroup)</td>
<td></td>
</tr>
<tr>
<td><strong>Abiraterone</strong></td>
<td>4</td>
<td>42</td>
<td>Considerable benefit (BSC subgroup)</td>
<td></td>
</tr>
<tr>
<td><strong>Enzalutamide</strong></td>
<td>4</td>
<td>32</td>
<td>Considerable benefit</td>
<td></td>
</tr>
<tr>
<td><strong>Trastuzumab emtansine</strong></td>
<td>5</td>
<td>26</td>
<td>Considerable benefit (subgroup)</td>
<td></td>
</tr>
</tbody>
</table>

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**Notes:**
- **V**: Very high
- **V<sub>a</sub>**: Very high
- **III**: High
- **II**: Moderate

- **✓ a**: Industry signals
- **✓ b**: Industry signals
Payers may recommend more restrictive diagnostic cut-off on grounds of cost effectiveness

- What criteria for cut-off?
  - Not always binary e.g. level of PDL1 expression
- Ex-ante versus ex-post confirmation of eligible population and price impact

Cost-effective below the red line
Multiple indication oncology medicines increasing dramatically with personalised medicine

Near-laurus Oncology Pipeline Assets and Target Indications

- **2014**:
  - Single Indication: 40
  - Multiple Indications: 48

- **2020**: 21

- **Number of Indications**:
  - 2
  - 3
  - >3

Source: IMS MIDAS Q4 2014, IMS Health R&D Focus
Price should correlate to value to enable patient access and drive correct development incentives*

*Numbers are purely for illustration only and not representative of expected prices
Conclusions

Access to stratified medicines can be improved by...

1. Greater integration of clinical evidence requirements between regulators and payers when evaluating benefit of personalised medicines

2. Increased adoption of evidence synthesis, disease modelling and management of uncertainty methods by HTA institutions

3. Healthcare systems ability to implement pricing flexibility to align price and value as evidence evolves and new indications emerge

4. Investment in data sources to track medicine utilisation, outcomes and implement patient access schemes