HERC Health Economics Research Centre
Nuffield Department of Population Health

UNIVERSITY OF OXFORD

3rd UPGx Personalized Medicine Day, Toulouse, France, 17th November 2017

Pharmacogenomics in Oncology: Deciphering the Ethical, Legal and Societal Issues

Economic evaluation in cancer pharmacogenomics

Dr James Buchanan

james.buchanan@dph.ox.ac.uk | @jbuchanan_ox | https://healtheconomicsandgenomics.com

Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, UK

Outline

1. Economic evidence for pharmacogenomic testing in cancer

2. Challenges for health economists evaluating pharmacogenomic tests in cancer

3. Health economic issues related to pre-emptive pharmacogenomic testing

Economic evaluation

- We live in a world of scarce healthcare resources – trade-offs are required
- Economic evaluation: systematic and explicit way of making choices in healthcare
- Definition: "*The comparative analysis of alternative courses of action in terms of both their costs and their consequences*" (Drummond *et al.*, 2005)
- Most common approach: cost-utility analysis
  - Outcomes expressed using quality adjusted life years (QALYs)
  - Final result: cost per QALY gained – compared to threshold (£20-30k in England, $100k in USA)
- Other approaches:
  - Cost-effectiveness analysis (outcomes expressed in natural units)
  - Cost-benefit analysis (outcomes expressed in monetary terms)

Economic evidence for pharmacogenomic testing in cancer

Berm *et al.* (2016)

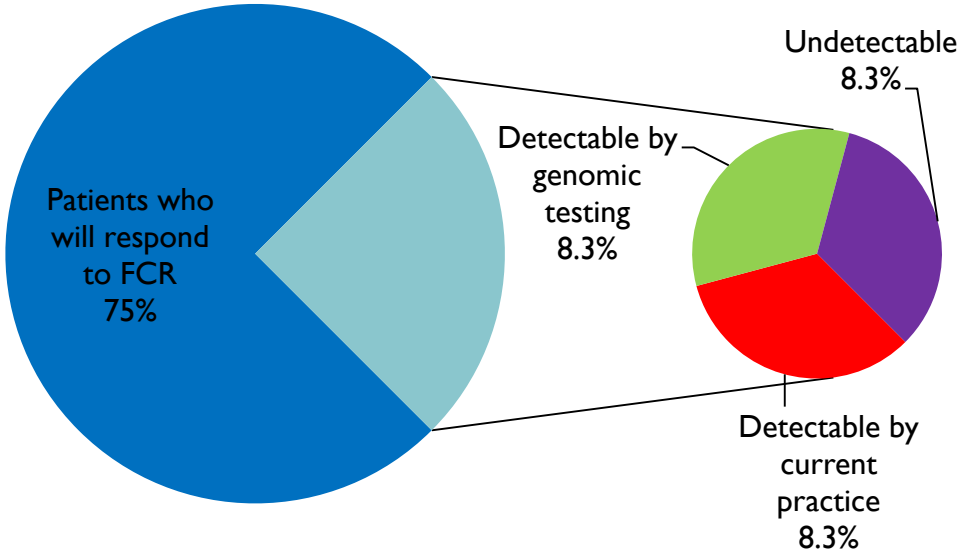
- 80 studies presented cost-effectiveness evidence
  - Mostly (68%) cost-utility analyses
  - Mainly single gene tests / small panels (KRAS, EGFR, 21 gene panel for breast cancer)
- PGx testing cost-effective in most studies
- 26% of studies: PGx offers both clinical benefits + cost savings
- 2010 onwards: 11% of studies reported that PGx testing not cost-effective
- Two concerns:
  - Studies don't assess the inherent value of testing
  - All studies funded by pharmaceutical companies concluded that PGx tests were cost-effective

Verbelen *et al.* (2017)

- Narrower scope than Berm *et al.* - economic evaluations for PGx associations listed in the US FDA Table of Pharmacogenomic Biomarkers in Drug Labelling
- 44 economic evaluations identified between 2000-2015
  - Mostly (68%) cost utility analyses
- 57% of studies: PGx is cost saving or cost-effective
- Economic evaluations identified for only 15% of the drugs on the FDA list
- Few of these drugs have applications in cancer

CLL and genomic testing

- First-line treatment in patients who can tolerate aggressive chemotherapy is combination FCR chemotherapy (rituximab / cyclophosphamide / fludarabine)
- **25%** of these patients will not respond to FCR – characterised by certain genetic mutations
- Current genetic tests (FISH / karyotyping) can identify **1/3** of these patients
- Genomic tests (targeted next generation sequencing) could identify **2/3** of these patients



Summary of comparators

Comparator	Current or future practice?	Pre-treatment genetic or genomic testing?	Ibrutinib used?
A	Current	Genetic testing	No
B	Current	Genetic testing	As refractory treatment for all patients
C	Current	None	No
Intervention 1	Future	Genomic testing	As refractory treatment for likely FCR responders As first-line treatment for likely FCR non-responders
Intervention 2	Future	Genomic testing	As refractory treatment for all patients

Retrospective sample analysis study

	Percentage of patients	
	Genetic testing	**Genomic testing**
Predicted PFS positive at 36 months	7%	17%
True PFS positive (as % of predicted PFS positive)	78%	82%
Residual group	93%	83%
Patients not progressing as % of residual group	69%	75%

Economic evaluation results

Analysis	Comparator	Mean LYs / QALYs per patient	Mean costs per patient	ICER (excluding dominated strategies)	ICER (excluding extendedly dominated strategies)
CEA	C	6.37	£69,704	-	-
	A	6.61	£71,576	£7,903	£7,903
	Int 2	6.65	£91,790	£580,390	EXT.DOM
	B	7.63	£107,703	£16,133	£35,376
	Int 1	7.45	£119,088	DOM	DOM
CUA	C	5.60	£69,704	-	-
	A	5.82	£71,576	£8,565	£8,565
	Int 2	5.93	£91,790	£177,198	EXT.DOM
	B	6.44	£107,703	£31,153	EXT.DOM
	Int 1	6.67	£119,088	£50,559	£55,891

Isolating the value of pharmacogenomic testing

Analysis	Comparator	Mean LYs / QALYs per patient	Mean costs per patient	ICER (excluding dominated strategies)	ICER (excluding extendedly dominated strategies)
CEA	C	6.37	£69,704	-	-
	A	6.61	£71,576	£7,903	£7,903
	Int 2	6.87	£90,876	£74,059	EXT.DOM
	Int 1	7.20	£101,941	£33,905	EXT.DOM
	B	7.63	£107,703	£13,269	£35.376
CUA	C	5.60	£69,704	-	-
	A	5.82	£71,576	£8,565	£8,565
	Int 2	6.14	£90,876	£59,897	EXT.DOM
	Int 1	6.44	£101,941	£37,027	£48,893
	B	6.44	£107,703	£1,497,878	£1,497,878

Economic evidence for WGS & WES

- Schwarze *et al.* (under review in Genetics in Medicine): *Are whole exome and whole genome sequencing approaches cost-effective? A systematic review of the literature*
- Search period: 2005-2016
- Inclusion criteria: economic evaluations, cost studies or outcome studies for WGS or WES
- 36 studies identified
  - Mostly neurological or neurodevelopmental disorders (n=7)
  - Few cancer studies (n=3)
- Cost estimates for a single test (2016 values, PPP adjusted):
  - WES: $555 to $5,169
  - WGS: $1,906 to $24,810
- Only 8 economic evaluations; 1 related to cancer
  - Bennette *et al.* (2015): cost-effectiveness of generating information on incidental findings
  - Colorectal cancer: $118,883 per QALY gained – not cost-effective
- **Health economic evidence base for WES and WGS is very limited**

UNIVERSITY OF OXFORD

Challenges for health economists evaluating pharmacogenomic tests in cancer

Health economic challenges

Issues surrounding the health economic evaluation of genomic technologies

Aim: Genomic interventions could enable improved disease stratification and individually tailored therapies. However, they have had a limited impact on clinical practice to date due to a lack of evidence, particularly economic evidence. This is partly because health economists are yet to reach consensus on whether existing methods are sufficient to evaluate genomic technologies. As different approaches may produce conflicting adoption decisions, clarification is urgently required. This article summarizes the methodological issues associated with conducting economic evaluations of genomic interventions. **Materials & methods:** A structured literature review was conducted to identify references that considered the methodological challenges faced when conducting economic evaluations of genomic interventions. **Results:** Methodological challenges related to the analytical approach included the choice of comparator, perspective and timeframe. Challenges in costing centered around the need to collect a broad range of costs, frequently, in a data-limited environment. Measuring outcomes is problematic as standard measures have limited applicability, however, alternative metrics (e.g., personal utility) are underdeveloped and alternative approaches (e.g., cost–benefit analysis) underused. Effectiveness data quality is weak and challenging to incorporate into standard economic analyses, while little is known about patient and clinician behavior in this context. Comprehensive value of information analyses are likely to be helpful. **Conclusion:** Economic evaluations of genomic technologies present a particular challenge for health economists. New methods may be required to resolve these issues, but the evidence to justify alternative approaches is yet to be produced. This should be the focus of future work in this field.

Original submitted 30 July 2013; Revision submitted 12 September 2013

KEYWORDS: cost–benefit analysis ▪ cost–effectiveness analysis ▪ costs ▪ economic evaluation ▪ effectiveness ▪ extra-welfarism ▪ genetics ▪ genomics ▪ outcomes ▪ review ▪ welfarism

James Buchanan*[1], Sarah Wordsworth[1] & Anna Schuh[2]

Timing of economic evaluations

- The attributes of pharmacogenomic tests (e.g. costs, accuracy) are constantly evolving
- Economic evaluations become outdated rapidly

How much do pharmacogenomic tests cost?

- We generally don't know
  - Limited evidence in the literature
  - No national guidelines
  - Significant variation between laboratories and countries
  - Costs span multiple disorders

What is the correct comparator?

- Difficult to determine in pharmacogenomic testing in cancer
  - e.g. genetic testing in Lynch syndrome
  - Many potential combinations of genetic tests

1. Strategies without genetic testing
   1(1). No testing at all (all diagnosed LS negative)
   2(2). Amsterdam II criteria for diagnosis
2. IHC four-panel test for *MLH1*, *MSH2*, *MSH6* and *PMS2*, followed by mutation testing if IHC result abnormal
3. IHC four-panel test, followed by *BRAF* V600E mutation testing if *MLH1* abnormal and mutation testing if MMR protein other than *MLH1* abnormal or *BRAF* V600E mutation not found
4. MSI testing, followed by mutation testing if MSI found
5. MSI testing, followed by *BRAF* V600E mutation testing if MSI found, followed by mutation testing if *BRAF* V600E mutation not found
6. As Strategy 5 but IHC performed in parallel with mutation testing to aid interpretation (i.e., not used diagnostically)
7. IHC four-panel test followed by mutation testing if IHC result abnormal. If IHC result normal, follow Strategy 5
8. Direct mutation testing.

Genomic data and outcomes

- The evidence base linking genomic data with health and non-health outcomes in cancer is very limited
- Driven by poor quality effectiveness data
  - RCTs for pharmacogenomic tests are large, lengthy and expensive
- Economic evaluations rely on data on surrogate endpoints (e.g. PFS)
- Potentially important aspects of value excluded from our analyses e.g.:
  - Value of possessing pharmacogenomic information
  - Anxiety associated with identification as a drug non-responder.
- Casts doubt on conclusions of economic evaluations

Health economic issues related to pre-emptive pharmacogenomic testing

MEDICINE'S FUTURE?

In an ambitious experiment, a rural U.S. health system is trying to integrate genomic screening into routine care

By **Bijal P. Trivedi**, *in Danville, Pennsylvania*

Two points to note for the UPGx study

1. Cost-effectiveness very sensitive to composition of a gene panel
    - Actions taken based on test results vary between genes
    - May be difficult to definitively conclude that a pre-emptive pharmacogenomic test is cost-effective
2. Important to consider behavioural factors
    - No health benefit to identifying a marker if no action is taken
        - E.g. if individual distrusts a result
    - Negative health or non-health consequences for individuals identified as non-responders?
    - Negative health consequences for individuals identified as good metabolisers?
    - Behavioural factors can significantly impact on cost-effectiveness

Reasons to be optimistic (1)

Genomics england

About Us | 100,000 Genomes Project | Taking Part | For Healthcare Professionals | Research | Industry Partnerships | News & Events

Home › The 100,000 Genomes Project

The 100,000 Genomes Project

The project will sequence 100,000 genomes from around 70,000 people. Participants are NHS patients with a rare disease, plus their families, and patients with cancer.

The aim is to create a new genomic medicine service for the NHS – transforming the way people are cared for. Patients may be offered a diagnosis where there wasn't one before. In time, there is the potential of new and more effective treatments.

The project will also enable new medical research. Combining genomic sequence data with medical records is a ground-breaking resource. Researchers will study how best to use genomics in healthcare and how best to interpret the data to help patients. The causes, diagnosis and treatment of disease will also be investigated. We also aim to kick-start a UK genomics industry. This is currently the largest national sequencing project of its kind in the world.

Useful links

Insurance
Find out how taking part in the Project may affect insurance.

Reasons to be optimistic (2)

Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and *De Novo* Requests, and Inclusion in Decision Summaries and Device Labeling

---

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

Document issued on August 24, 2016.
This document will be in effect as of October 23, 2016.

The draft of this document was issued on May 18, 2015.

For questions about this document regarding CDRH-regulated devices, contact the Office of the Center Director (CDRH) at 301-796-5900 or Anindita Saha at 301-796-2537 (Anindita.Saha@fda.hhs.gov)..

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

Thank you for your attention

Any questions?

Dr James Buchanan

james.buchanan@dph.ox.ac.uk | @jbuchanan_ox | https://healtheconomicsandgenomics.com

Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, UK