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Methodological issues surrounding the health economic evaluation of genomic technologies and a case study of these issues in the research setting

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Literature review (1)

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.

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Literature review (2)

- Aims:
  - Identify references considering methodological challenges in genomics
  - Is genomics exceptional?
- 2772 references identified; 52 met inclusion criteria
- 39 published since 2008
- Issues fell into four categories
  1. Analytical approach
  2. Costs and resource use
  3. Measuring outcomes
  4. Measuring effectiveness

Analytical approach

- Perspective
  - Health service vs. societal
  - Genomic test results can impact on both healthcare and life decisions
- Timing of analysis
  - Test attributes poorly defined for newer tests - evolve over time
  - Patient categorisation also changes over time
- Analytical context
  - Tests have multiple applications in different contexts – cost-effectiveness will differ
    - Oncotype DX in breast cancer / colon cancer
  - Choice of comparator important – standard genomic testing practice does not exist
  - Need to incorporate subsequent therapeutic decisions in analyses

Costs and resource use (1)

- Which costs should be included?
  - Patient recruitment
  - Sample reception
  - Lab testing
  - Data analysis
  - Reporting results
  - Counselling
  - Management of adverse drug reactions
  - Actions taken based on test results
  - Monitoring disease progression and drug response
  - Indirect costs to patients (Oncotype DX in breast cancer)
  - Infrastructure costs

Costs and resource use (2)

- How much do genomic tests cost?
  - Unclear
  - No national guidelines / agreed reimbursement rates
  - Bottom-up microcosting required – generalisable?
- When should cost data be collected?
  - Tumours evolve and acquire mutations – genomic tests need to be repeated over time
  - Data filters are updated over time to reflect new findings – should samples be reanalysed each time?

Measuring outcomes (1)

- Disease-specific and preference-based outcome measures
  - Don't capture value of possessing diagnostic information
  - Don't reflect typical health states after genomic tests
  - Will contribute to genomic interventions appearing very cost-ineffective
- Personal utility
  - Benefits or harms manifested outside of medical contexts
  - Positive effects:
    - Improvements in patient understanding / uptake / adherence
    - Patients given sense of control / reassurance / greater ability to plan
  - Negative effects:
    - Increase in anxiety (test suggests non-response to treatment / incidental findings)
  - These effects are not captured by metrics focussing on clinical utility

Measuring outcomes (2)

- Cost benefit analysis (CBA)
  - One way to overcome problems associated with frequently used outcome measures and incorporate personal utility into analyses
  - How to monetise health outcomes?
    - Discrete choice experiments (DCEs)?
    - Contingent valuation?
    - Best-worst scaling?
  - However, most HTA agencies favour cost-utility analysis using QALYs
    - Exceptions: supplementary analyses (CADTH / PBAC), public health (NICE)

Measuring effectiveness (1)

- Patient and clinician behaviour
  - How will patients and clinicians use these tests?
  - Limited evidence – if testing is not mandated, universal uptake unlikely?
- Effectiveness data quality
  - Often weak
    - Large RCTs required – nobody willing to invest
    - Test performance in research ≠ test performance in clinical practice
    - Test performance varies by lab characteristics
  - Alternatives:
    - Noninferiority trials?
    - Disease registries? Observational / cohort studies? Expert opinion?
    - Practice based evidence generated in post-implementation studies?

Measuring effectiveness (2)

- Data complexity
  - Limited evidence base linking genomic data with health outcomes
  - Genomic testing outcomes are influenced by multiple genes, each genetic mutation can influence multiple outcomes, and the influence of a mutation on a given outcome can vary across individuals
  - Solution: polygenic risk scores?
    - Require lots of data
    - Limited reproducibility

Research prioritisation

- Importance of value of information (VOI) analysis
- Weak effectiveness data + robust data collection methods unavailable
- VOI methods currently infrequently applied

Summary

- Multiple methodological challenges
- Are these challenges individually unique to genomics?
- Is it the breadth of challenges that is unique to genomics?
- *"the 'new genetics' does not pose new problems for health economics, but it highlights aspects of evaluation that have been neglected in previous economic evaluation research" (Jarrett et al. 2006)*
- *"genetic exceptionalism exists and new methods are required to evaluate the outcomes arising from genomic technologies" (Rogowski et al 2010)*

Case study

- Technology Strategy Board / CRUK tumour profiling tests ≤£300
- Oxford Molecular Diagnostics Centre (NHS)
- Main objective: estimate costs using multi-gene cancer panel compared to single-gene testing for cancer diagnostics and treatment
  - Cost questionnaires (Life Technologies PGM, Roche Cobas z480)
  - Costs multiple scenarios (PGM, EGFR, BRAF, KRAS, PIK3CA, ALK, NRAS, no testing)
  - Cost-effectiveness analysis for lung and bowel

Example 1 – advancement

- Rapid technological development (Ion Chef, QIAsymphony) within genomic testing and new mutation kits (NRAS, PIK3CA) – new information arrives during cost collection and analysis

Example 2 – testing guidelines

- UK National Quality Assessment Services Guidelines for molecular pathology
- Current clinical practice – comparators in analysis – does not match quality assessment schemes
  - Lung cancer: EGFR, KRAS, BRAF and PIK3CA (2013)
  - Bowel cancer: KRAS, BRAF, PIK3CA and NRAS (2013)

Example 3 – clinical context

- Platform can be cost-effective but depends on clinical context
- Decision models for multiple strategies followed by treatment (chemo vs targeted)

vs

Lung: PGM most cost effective, measured in LYG and QALY

Bowel: none cost-effective, measured in LYG and QALY

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Transforming patient healthcare, pioneering tomorrow's technology

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