REVIEW STRATEGIES TO INFORM RESEARCH PRIORITIZATION OF BIOMARKERS

AKI-DIAGNOSTICS CASE STUDY

.... A BIT OF A MONSTER ....

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BACKGROUND
WHAT TYPE OF EVIDENCE SYNTHESIS MONSTER?

- Big
- Complicated
- Unpredictable
- Important
METHODS

...THE PLAN

- Identify cost-effective tests with strong clinical and analytical validity
  1. Create a shortlist of AKI diagnostic tests/biomarkers (review 1)
  2. Assess and compare the validity of the selected biomarkers (review 2)
  3. Early economic modelling of the selected biomarkers

- NIHR funded HTA Evidence Synthesis

- Team with expertise in AKI, diagnostic tests, systematic reviewing, meta-analysis, information science, economic modelling
Literature Search for blood/urine/plasma tests for AKI found 4,804 records

Screened 4804 title & abstracts to identify in-development AKI tests

Group 487 studies into 152 unique tests

Rank 152 tests

Top 10 tests
Ranking method developed by team consensus

- Volume of evidence ≥ 6 publications
- Currency of evidence ≤ 5-years old
- Population ≥ 1500 subjects or samples across studies
- Biological / mechanistic plausibility. Four markers:
  - inflammatory marker,
  - functional marker
  - damage marker
  - cell cycle marker

BNP
Cystatin C
IL-6
IL-18
KIM-1
L-FABP
NAG
Nephrocheck®
NGAL
TNF-α
METHODS CHALLENGES EMERGED...

LOTS of studies

Poor reporting

Complex terminology

LOTS of multiple test data

Complexity of including analytical and clinical validity
Maintain methodological rigour
NGAL, Cystatin C and Nephrocheck® biomarkers selected:
- Convergence of evidence
- FDA licensing
QUADAS-2 quality assessment
Meta-analyses of diagnostic accuracy
- Blood serum, blood plasma and urine tests considered separately
- ICU and post-cardiac surgery settings considered separately
Developed a framework for the assessment of measurement

7,967 records (for 10 biomarkers) 4,784 (duplicates removed)

3 biomarkers prioritised

3,260 records to screen:
471 Cystatin-C; 47 Nephrocheck®, 919 NGAL;
1,507 Multi-biomarker; 316 Biomarker unspecified

207 eligible papers

61 included in synthesis

39 NGAL 17 Cystatin C 10 Nephrocheck®
Economic evaluation assessed:

- Nephrocheck®
- Cystatin C in urine
- Cystatin C in plasma
- Cystatin C in serum
- NGAL in urine
- NGAL in plasma
- NGAL in serum

Data required:

- Review 2 results
- AKI early treatments in ICU review
- Model searches for
  - Costs
  - Health Utilities
  - Risks
  - of AKI / CKD / Dialysis / ESRD / Transplant

Value of Information Analysis to inform future research priorities
RESULTS

Research Findings
- Large number of potential biomarkers and diagnostic tests that could improve care for patients at risk from AKI in critical care
- Nephrocheck® performed best
- All 3 tests were found to be cost effective

Future research
- Refine
  - 2 stage review approach for large volume of literature
  - Framework of the assessment of measurement procedures
- Value of information highlighted:
  - Identify current clinical care pathways for patients at risk of AKI
  - Evaluate any changes to the care pathway following positive test
- Encourage better reporting, especially of analytical factors
- Missed promising in-development biomarkers?
  - Prioritisation process had pragmatic focus on objective criteria (e.g. volume of evidence)

- Study took longer and reviewed fewer biomarkers than expected due to
  - Volume of literature following decision to broaden scope to include tests developed outside the critical care setting
  - Volume of multiple test data
  - Complexity of data extraction
  - Poor reporting, makes comprehensive synthesis of test analytical and clinical validity difficult
Large complex biomarkers reviews require a clear plan, commitment to methods and team expertise.

However, the plans and team should be flexible in case a monsters start to lurk…

Further methods development is needed to identify how to do this efficiently and with rigour
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