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

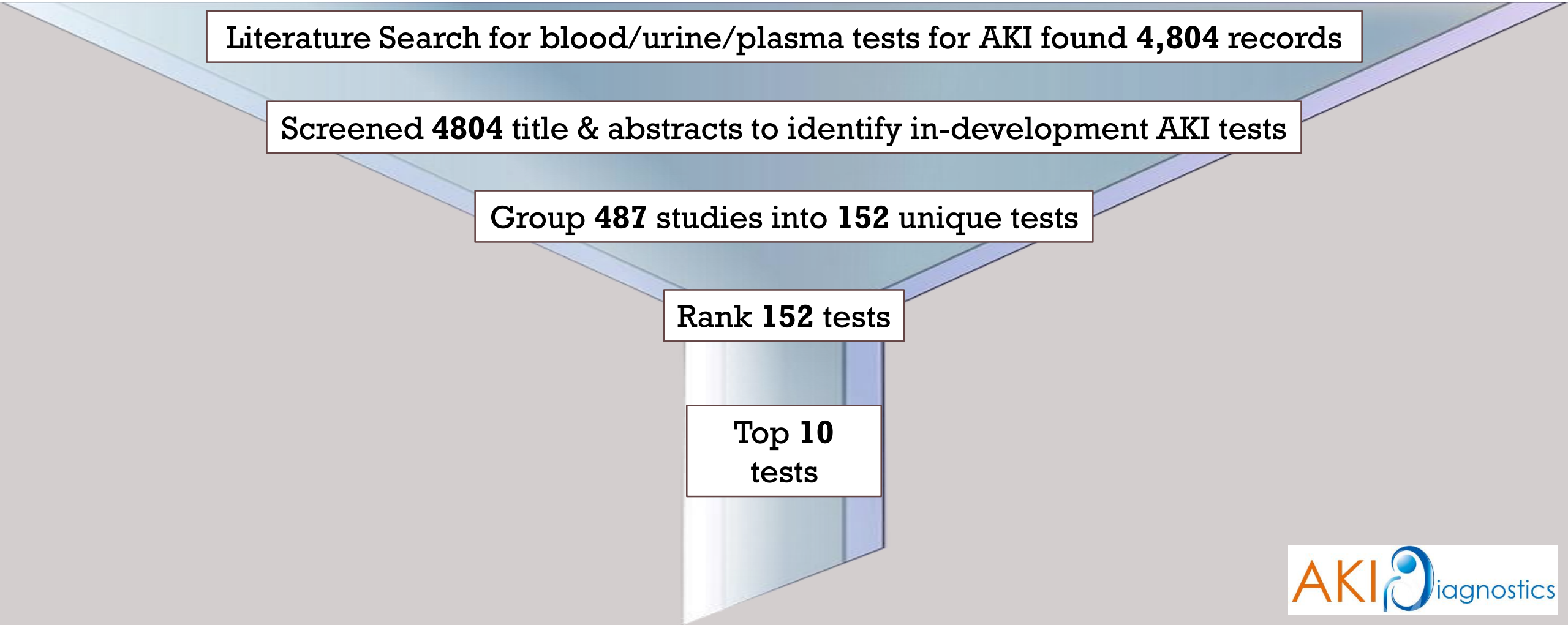
- Identify cost-effective tests with strong clinical and analytical validity

  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

IDENTIFYING AND PRIORITISING BIOMARKERS



AKI Diagnostics

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

BIOMARKER RANKING METHOD

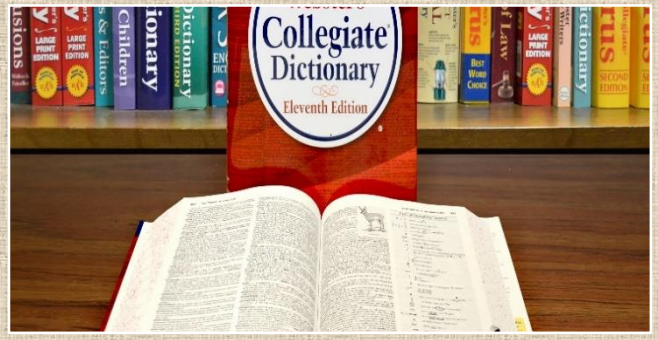
Ranking method developed by team consensus

- 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

METHODS CHALLENGES EMERGED…

LOTS of studies

Poor reporting

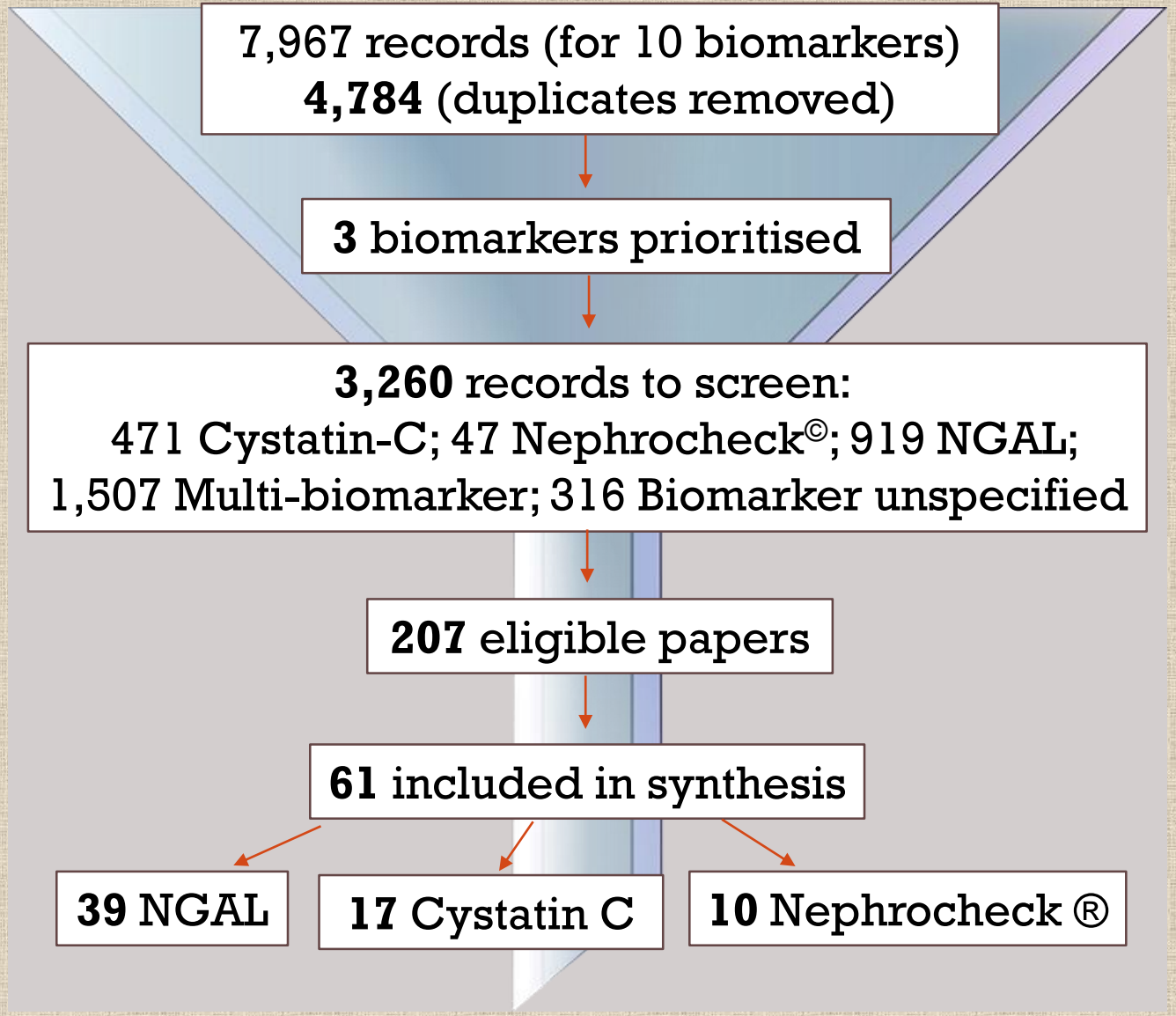


Complex terminology

LOTS of multiple test data

Complexity of including analytical and clinical validity

REVIEW 2
ANALYTICAL AND CLINICAL VALIDITY OF 3 BIOMARKERS



- 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

ECONOMIC EVALUATION

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

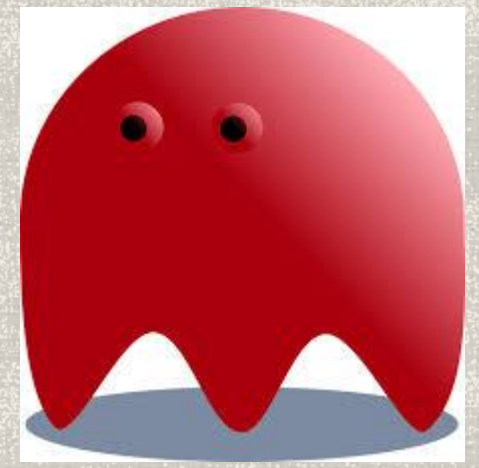
- Large number of potential biomarkers and diagnostic tests that could improve care for patients at risk from AKI in critical care
- Nephrocheck ® performed best
- All 3 tests were found to be cost effective

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

LIMITATIONS

- 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



AKI Diagnostics

BOTTOM LINE

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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AKI Diagnostics

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