SYSTEMATIC REVIEW OF FRAMEWORKS FOR STAGED EVALUATION OF PREDICTIVE BIOMARKERS

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PREDICTIVE BIOMARKERS

- Differential efficacy or toxicity
- Of a particular treatment

- HER2 expression – trastuzumab – breast cancer
- ALK gene rearrangements – crizotinib - NSCLC
Huge increase in biomarker research

number of hits for "biomarker" in Pubmed

year


0 10000 20000 30000 40000 50000 60000

Biomarker Research
BIOMARKER RESEARCH

- Huge increase in biomarker research
- Relatively little impact on clinical practice

- January 2013 – EMA licensing: 37 biomarkers in indications/contraindications of 41 drugs
Biomarker Research

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How to improve this?

Model for phased evaluation of drugs

Could a phased evaluation process exist for predictive biomarkers?
**QUESTIONS**

- What has been published?
- Are there common stages?
- What study designs are used at each stage?
- Are there criteria to move to the next stage?

- When to finalise biomarker evaluation method?
- When to identify the threshold for a continuous biomarker?
METHODS - SYSTEMATIC REVIEW

- Searches: MEDLINE, EMBASE, internet, licensing agencies
- Inclusion: frameworks for staged evaluation of predictive biomarkers
- Data collection: situation, stages, aims, study designs, results, entry and completion criteria
- Comparison of frameworks based on stages and situation to which applicable
Records identified in databases (n = 26,624; MEDLINE n = 11,376, EMBASE n = 15,197)

Other sources (n = 67; internet n = 63, reference checking n = 4)

Records after duplicates removed (n = 16,268)

Records screened (n = 16,268)

Records excluded (n = 15,917)

Full-text articles assessed for eligibility (n = 340)

Full-text articles excluded, with reasons (n = 296)
- 277 no framework
- 19 no predictive biomarker

Papers included in review (n = 31)
- 23 in synthesis
- 8 not analysed
MODEL I: general
3. FDA Drug-Diagnostic Co-Development Concept Paper, 2005

MODEL II: alongside phased drug development

MODEL III : multi-marker classifier (e.g. proteomic signatures)

MODEL IV: predicting safety of a marketed treatment
STAGES OF BIOMARKER DEVELOPMENT (GENERAL MODEL)

- **pre-discovery**
  - Question

- **discovery**
  - Candidate biomarkers

- **analytical validation**
  - Assay performance (e.g. accuracy + precision vs. reference standard*)

- **clinical validation**
  - Outcome prediction

- **clinical utility**
  - Improvement of patient outcomes

- **implementation**
  - Performance in real life
MAIN STUDY DESIGNS
(GENERAL MODEL)

**pre-discovery**  
- none?

**discovery**  
- Knowledge-driven  
  - Data-driven (eg. GWAS)
  - Preclinical models
  - Using patient samples:
    - Case-control
    - Biomarker-outcome correlation

**analytical validation**  
- “Analytic validity studies” (prospective or retrospective)

**clinical validation**  
- Including:
  - Retrospective on stored samples from trials
  - Prospective as secondary outcome
  - Case-control
  - Diagnostic accuracy studies

**clinical utility**  
- RCT:
  - Biomarker-strategy
  - Enrichment
  - Stratified
  - But possible:
    - Case-control
    - Single-arm

**implementation**  
- HTA audit cohort
FOUR MODELS

I. GENERAL

- pre-discovery
- discovery
- analytical validation
- clinical validation
- clinical utility
- implementation

II. ALONGSIDE PHASED DRUG DEVELOPMENT

- pre-clinical
- p. I trial
- p. II trial
- p. III trial
- implementation

III. MULTI-MARKER CLASSIFIER

- pre-discovery
- candidate biomarkers
- predictive model
- internal validation
- external validation
- clinical utility
- implementation

IV. SAFETY BIOMARKER

- surveillance
- discovery
- pre-clinical
- analytical validation
- clinical utility
- implementation
FINALISING THE LABORATORY PROCEDURES
ESTABLISHING A THRESHOLD

- pre-discovery
- discovery
- analytical validation
- clinical validation
- clinical utility
- implementation

1 framework
1 framework
1 framework
CASE STUDY – MODEL II
(ALONGSIDE PHASED DRUG DEVELOPMENT)

HER2 expression: trastuzumab in breast cancer
CONCLUSIONS

- Some general agreement on necessary stages
- Problems with “one-size-fits-all” approach
- Different approach:
  - Biomarker for drug
  - Drug for biomarker
- Little detail or agreement on research designs prior to clinical utility
- No consensus on when a laboratory procedure should be finalised or threshold established