# Field application of the EVIDEM multicriteria decision framework to support coverage decisions for a screening test

EVIDEM

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## Background

- Healthcare decisionmaking is a complex process that involves scientific assessment of available evidence and requires application of value judgment.[1,2]
- There is growing recognition that accessibility to the information on which decisions are based, together with transparent and explicit approaches to decisionmaking are necessary to legitimize and improve decisions.[3-5] This recognition has led to a number of approaches in this direction, including the 6-STEPPPs approach and other multicriteria models.[6-14]
- The EVIDEM framework was developed to integrate assessment of evidence and explicit value judgments using a multicriteria decision analysis (MCDA) approach, with the aim of supporting transparent and efficient healthcare decisionmaking.[15]
- Objective: To field test the EVIDEM framework, initially developed in the Canadian drug formulary context, in the South African context for the assessment of a screening test.

## Methodology

- A collaborative team was established with a private health insurer in South Africa (Discovery Health). Liquid based cytology (LBC) for cervical cancer screening was selected as an intervention requiring a coverage decision which would benefit from an MCDA framework such as EVIDEM.
- Data for each Value Matrix component (intrinsic value) was collected and synthesized using a simplified EVIDEM methodology. Disease impact data was obtained from the public domain. Clinical data, was derived from a CADTH meta-analysis of trials comparing LBC with conventional cytology (CC). Cost-effectiveness and impact on other spending were based on a CADTH economic evaluation of LBC, using selected screening strategies most applicable to the Discovery Health setting. Budget impact data was based on information provided by the insurer.
- Quality of evidence was assessed using the Quality Matrix instruments for two types of evidence (clinical and economic evaluation) and for two criteria of quality ("completeness and consistency or reporting" and "relevance and validity of evidence").
- The intrinsic value of LBC was assessed by the decisionmaking committee by assigning to each value component weights (independent of intervention) and scores based on the synthesized evidence presented in the Value Matrix. Weights and scores were combined using an MCDA linear model to derive a value estimate.
- Components affecting the extrinsic (or system-related) value of LBC in the Discovery Health setting were explored by participants.
- Participants were surveyed on whether value components should be always, sometimes or never considered and outcomes of approach regarding data on intervention, deliberative process and communication of decision.

## Results

### Synthesized evidence For selected Value Matrix components

#### Cluster: Disease impact – example D1

| | | Synthesized evidence available | Score |
|---|---|---|---|
| D2 | Size of population affected by disease | Cervical cancer can affect all women from the age they become sexually active. Invasive cervical cancer is the second most common cause of cancer morbidity and mortality in South African women. Annual incidence and mortality rates of invasive cervical in Southern Africa are the second highest in the world.[4] Through the introduction of pap smear screening programmes, the incidence of cervical cancer has decreased considerably, however the rate of cervical cancer in South Africa remains high.[5] Cervical cancer comprises 18.2% of all cancers reported in 1997.[6] In 2001, the annual cervical cancer incidence was 9/100,000 in white women and 40/100,000 in black women.[7] In 1993 to 1995, the lifetime risk of cervical cancer was 1 in 34 (3.0%) among black women and 1 in 93 (1.1%) among white women.[7] | 0 ☐ Extremely rare disease<br>1 ☐<br>2 ☐<br>3 ☐ Common disease<br>*Scoring example (for information only)*<br>*0: X < 1/100,000*<br>*1: 1/100,000 ≤ X < 1/1,000*<br>*2: 1/1,000 ≤ X < 1/100*<br>*3: X ≥ 1/100* |

#### Cluster: Intervention – example I3

| | | Synthesized evidence available | Score |
|---|---|---|---|
| I3 | Improvement of efficacy/ effectiveness | The difference between LBC and conventional cytology lies in the preparation of the samples, which may lead to a possible improvement in sensitivity (coupled with reduced specificity) and reduction in inadequate specimens. (see below) | 0 ☐ Lower efficacy /effectiveness<br>1 ☐<br>2 ☐<br>3 ☐ Major improvement in efficacy<br>*Scoring example (for information only)*<br>*0: Lower efficacy/effectiveness than comparators*<br>*1: Same as comparators*<br>*2: Some improvement*<br>*3: Major improvement in efficacy/effectiveness, larger eligible population* |

**EFFICACY DATA** [9]

**Standard outcome measures**
**Sensitivity:** The proportion of samples identified by the cytological test as potentially indicating cancer* out of all cases of cancer* confirmed by histology (gold standard) or other means; the higher the sensitivity of a test, the lower the risk of false negative results
**Specificity**: The proportion of samples identified by the cytological test as negative out of all truly negative samples confirmed by histology or other means; the higher the specificity of a test, the lower the risk of false positive results
*cancer or potential cancer precursor: cytology cut-off was low-grade squamous intraepithelial lesion or worse [LSIL+] or atypical squamous cells of undetermined significance or worse [ASCUS+], depending on study; histological reference level was: cervical intraepithelial neoplasia (CIN 1, 2 or 3), depending on study
Note that for diagnostic tests increase in sensitivity is usually paired with decrease in specificity.

**Pivotal clinical trial(s) for intervention**: meta-analysis of 20 studies directly comparing LBC with conventional cytology (pap smear) (up to June 2006) with manual reading of the results (no automated screening system); split sample or two-cohort studies
- **Intervention & comparators**: LBC- Sure Path, LBC-ThinPrep, conventional cytology (pap smear)
- **Patient inclusion and exclusion criteria**: not specified

**Main outcome measure: sensitivity and specificity**

| | LBC n=28,736 | CC n=39,377 | Absolute difference |
|---|---|---|---|
| Sensitivity (95% CI) | 80% (72% to 87%) | 74% (63% to 84%) | 6.4% (-6.5% to 18.8%) |
| Specificity (95% CI) | 82% (69% to 91%) | 87% (74% to 95%) | -4.0% (-19.9% to 10.6%) |

CC: conventional cytology; CI: confidence interval; LBC: liquid-based cytology

Based on these results, the probability that
- LBC is more sensitive than conventional cytology is 83% (+/-37%)
- LBC is less specific than conventional cytology is 72% (+/-45%)

Results did not differ substantially if ThinPrep data (2 studies) was not included in meta-analysis.

**Other outcome: percentage of unsatisfactory samples (requiring patient recall)**

| | LBC | CC | Absolute difference |
|---|---|---|---|
| **ThinPrep (44 studies; n=704,813 [LBC]; n=1,316,318[CC])** | | | |
| Percentage of unsatisfactory samples (95% CI) | 2.2% (1.2% to 3.3%) | 3.0% (1.9% to 4.2%) | -0.8% (-1.9% to 0.2%) |
| **Sure Path (15 studies; n=597,565 [LBC]; n=692,406 [CC])** | | | |
| Percentage of unsatisfactory samples (95% CI) | 0.82% (0.1% to 1.5%) | 3.3% (1.0% to 5.7%) | -2.5% (-4.4% to -0.6%) |

CC: conventional cytology; CI: confidence interval; LBC: liquid-based cytology

#### Cluster: Economics – exampleE3

| | | Synthesized evidence available | Score |
|---|---|---|---|
| E3 | Impact on other spending *(e.g. hospitalization, disability)* | **Impact of intervention on other expenditures (excluding intervention cost, see E1)** Includes colposcopic cost, based on data available in economic evaluation[9] (see E2) (see below) | 0 ☐ Substantial spending<br>1 ☐<br>2 ☐<br>3 ☐ Substantial savings |

**Mean costs per woman (population 15 to 69 years of age) over lifetime horizon**

| | Colposcopy costs (R)* | Incremental colposcopy cost |
|---|---|---|
| LBC | R 19 | R 8 |
| CC | R 11 | |

*Based on an increase in colposcopy rate of 705 per 100,000 women and an average cost of R1,128 (Can$141) per colposcopy, assuming that biopsies are performed during 50% of colposcopies

Data on impact on other spending including treatment of cancer and pre-cancer is not available.

Some savings may be derived from better efficiency in slide examination (reduced interpretation time by pathologist) and potential to more easily perform other tests such as HPV testing without patient recall.[9]

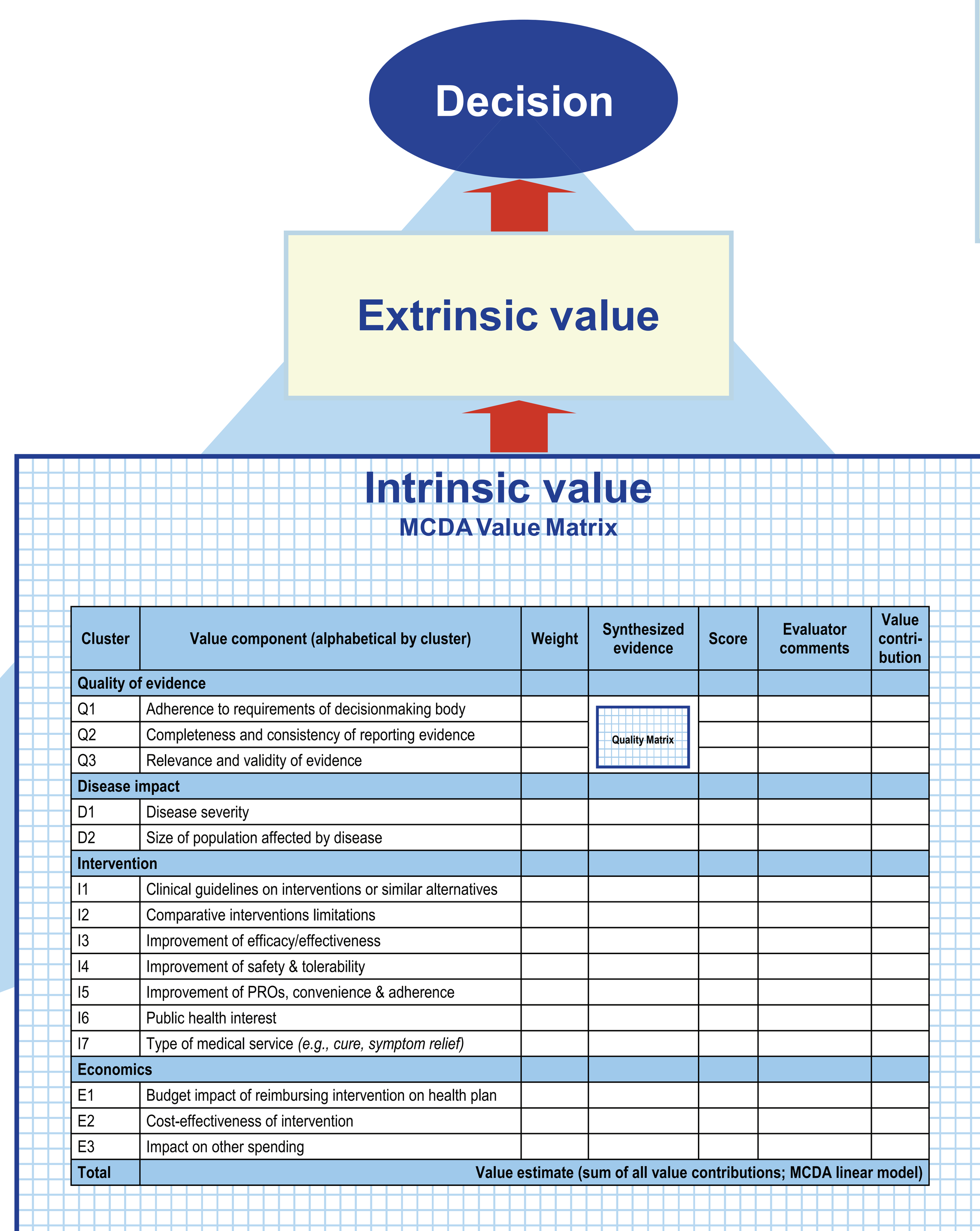
### Decision

### Extrinsic value

| Extrinsic value components* | Should this be considered? Would it impact positively or negatively on value of intervention? |
|---|---|
| Impact on future decisions | Decision to fund LBC coverage although not considered cost-effective will be setting a precedent as LBC technology will be expanded to other cytology tests<br>Considered as negative impact on value |
| Relationship with pathology providers | Ongoing negotiations with the pathology groups in other areas may be impacted<br>Considered as a positive impact on value |
| Impact on screening intervals | Screening interval may be extended to 2 to 3 years than annually<br>Considered as a positive impact on value |
| Patient expectation | Discovery Health members expect that their pap smears will be paid in full and are likely to resist any benefit design which implements a co-payment for a more expensive technology<br>Considered as a negative impact on value |

*Extrinsic value components may include: appropriate use; opportunity cost; organizational structure required; stakeholder pressures; political context; population priorities & access; regulatory status of intervention etc…

### Intrinsic value



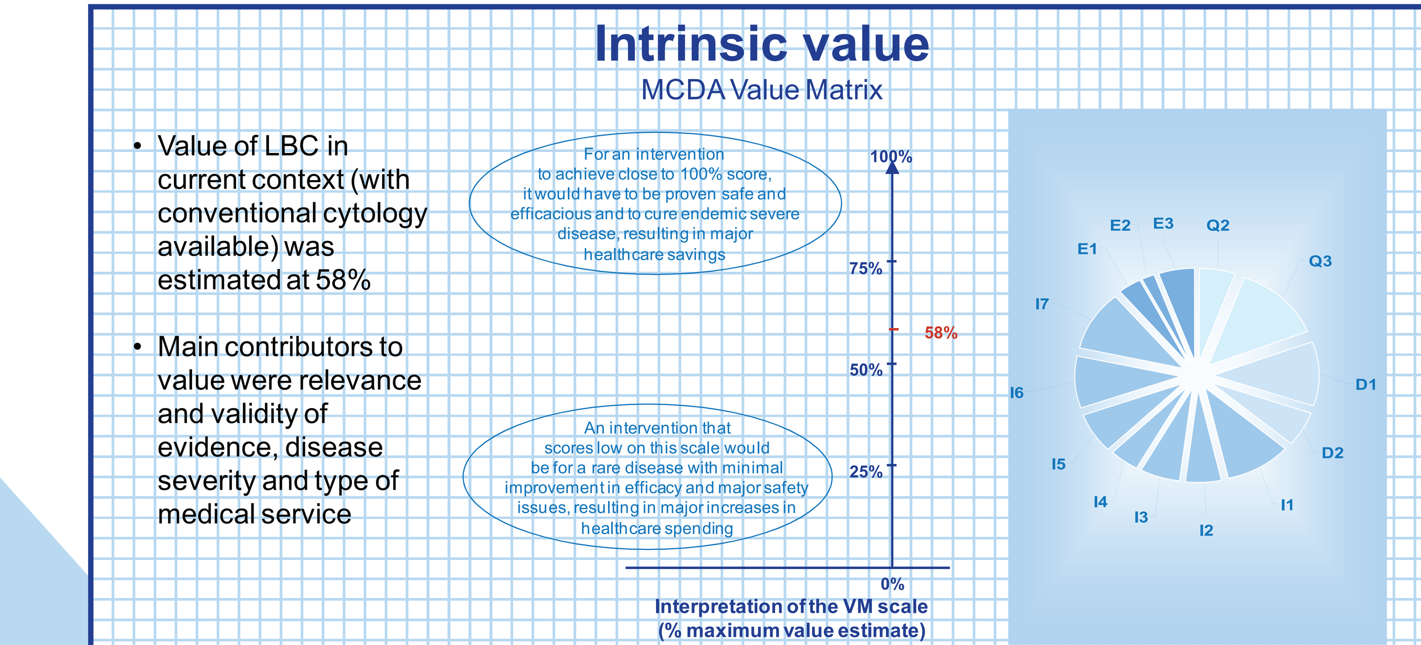
MCDA Value Matrix

| Cluster | Value component (alphabetical by cluster) | Weight | Synthesized evidence | Score | Evaluator comments | Value contri-bution |
|---|---|---|---|---|---|---|
| Quality of evidence | | | | | | |
| Q1 | Adherence to requirements of decisionmaking body | | Quality Matrix | | | |
| Q2 | Completeness and consistency of reporting evidence | | | | | |
| Q3 | Relevance and validity of evidence | | | | | |
| Disease impact | | | | | | |
| D1 | Disease severity | | | | | |
| D2 | Size of population affected by disease | | | | | |
| Intervention | | | | | | |
| I1 | Clinical guidelines on interventions or similar alternatives | | | | | |
| I2 | Comparative interventions limitations | | | | | |
| I3 | Improvement of efficacy/effectiveness | | | | | |
| I4 | Improvement of safety & tolerability | | | | | |
| I5 | Improvement of PROs, convenience & adherence | | | | | |
| I6 | Public health interest | | | | | |
| I7 | Type of medical service *(e.g., cure, symptom relief)* | | | | | |
| Economics | | | | | | |
| E1 | Budget impact of reimbursing intervention on health plan | | | | | |
| E2 | Cost-effectiveness of intervention | | | | | |
| E3 | Impact on other spending | | | | | |
| Total | Value estimate (sum of all value contributions; MCDA linear model) | | | | | |

### Intrinsic value

MCDA Value Matrix

- Value of LBC in current context (with conventional cytology available) was estimated at 58%
- Main contributors to value were relevance and validity of evidence, disease severity and type of medical service




Synthesized Evidence
For each component of the Value Matrix

Targeted health technology assessment report

Quality of Evidence
Quality Matrix

### Quality of evidence

| Type of evidence | Completeness and consistency of reporting (Q2) | Relevance and validity of evidence (Q3) |
|---|---|---|
| Clinical data | 75% | 75% |
| Economic evaluation | 50% | 75% |

#### Full assessment – example Q3-clinical

**Clinical data – relevance and validity of evidence**

**Disease:** Cervical cancer
**Intervention:** Liquid-based cytology
**Setting**: Discovery Health - South Africa

**Study:** Krahn M et al..Meta-analysis of LBC accuracy (sensitivity and specificity). In Liquid-based techniques for cervical cancer screening: systematic review and cost-effectiveness analysis. http://cadth.ca/index.php/en/publication/799 –

| Type of evidence | Question | Comments | Score |
|---|---|---|---|
| Efficacy/safety, effectiveness, or PRO data | Is the study question relevant (choice of comparator, time horizon, patient population, and outcome)? Is the design appropriate (setting & design, sample size, patient allocation, analyses, statistics)? | The study question is relevant with regard to comparator (conventional cytology (CC); however, it does not assess the most relevant outcome, morbidity and mortality due to cervical cancer that would occur with screening programs using these technologies. The design is appropriate for the study question. (*See details below*) | 1 ☐ Low relevance/validity<br>2 ☐<br>3 ☒<br>4 ☐ High relevance/validity |

| | Dimension | Question | Comment |
|---|---|---|---|
| 1 | Target population | Is the target population relevant (age, gender, disease stage, comorbidities, inclusion criteria/exclusion criteria etc)? Does it correspond to the actual population in which the intervention is envisioned to be used? | Target population (sexually active women ≥15 years of age) is relevant. The studies included were carried out in different countries and settings, although most of them were done in Europe and the USA. |
| 2 | Intervention & comparators | Is the intervention in agreement with expected use? Does the choice of comparators reflect standard of care? | Yes, CC is standard of care for screening for cervical cancer in the South African private healthcare sector. |
| 3 | Outcome measures | Are the selected outcomes measures (efficacy, safety and PRO) relevant? Are rationales for outcomes selection valid? Are the instruments/methods/units used to measure outcomes (efficacy, PRO*) valid? | Although the specificity and sensitivity of LBC compared to CC is a relevant primary outcome measure when comparing the technical performance of these two interventions, the most relevant outcome measure would be morbidity and mortality due to cervical cancer (no data available on these outcomes – only modeled in economic evaluation). |
| 4 | Study design | Was the sample size appropriate? Is the design appropriate? For RCTs, this includes: randomization; patient allocation concealment; blinding as appropriate; completeness of follow up; avoidance of carry-over effects. For observational studies (cross-sectional, cohort, or case-control) this includes adequate methods of selection of participants and control of confounding. | Literature search procedure and study inclusion criteria appropriate with regard to scientific standards. Sample size for the 20 studies pooled for the primary outcome analysis was large (28,736 women for LBC and 39,377 for CC). The primary outcome analysis included only studies directly comparing LBC to CC (2-cohort or split-sample studies), which is appropriate. |
| 5 | Adverse events | Are methods for monitoring the occurrence of adverse events and assumptions with regard to which adverse events are related to the intervention(s) relevant and valid in light of previous experience with similar interventions / populations? Are all relevant adverse events reported (deaths, serious, common, discontinuations), both treatment-related and all-cause? | Adverse events not addressed. Since the procedure for obtaining the sample from the patient is the same for both LBC and CC, incidence of adverse events is assumed to be the same. |
| 6 | Time horizon | Is time horizon long enough to capture all meaningful differences in key outcomes between the intervention and comparators? (e.g., Was the study stopped prematurely because of observed benefits or harms?) | Time horizon is not applicable for the outcome measures assessed (comparative accuracy of two screening tests). |
| 7 | Analyses | Are the analyses appropriate and comprehensive with sound and relevant statistics (e.g., intention-to-treat; missing data; control of confounding; subgroup analyses)? | Data analyses appear to be scientifically appropriate and comprehensive with relevant statistics. |
| 8 | Results (precision and strength of effect) | Are differences observed meaningful (clinically and statistically)? Is there evidence of a dose-response relationship? | Observed differences between the two screening methods not statistically significant. |

### Evidence available

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**Liquid based cytology for screening cervical cancer in South Africa**

## Discussion and conclusion

- The EVIDEM framework is applicable to the assessment of value of a screening intervention in the Discovery Health (South African private payer) context and provides a practical tool integrating a targeted HTA report with a MCDA approach to support decisionmaking.
- Available clinical evidence was fairly relevant and valid. Partial reporting of disaggregated data in the published economic evaluation limited its usefulness.
- The Value Matrix scale estimated the intrinsic value of LBC in current context, i.e., relative to existing technology (conventional cytology), reflecting minor improvement at a significant cost, but also captured importance of absolute elements of value such as disease severity, type of medical service and quality of evidence. Non quantifiable extrinsic value elements were also identified and considered.
- Participants indicated that most Value Matrix components should be always considered.
- A majority of participants reported that EVIDEM would improve: understanding of intervention; access to quality of evidence; consideration of key elements of decision; transparency of the decision; and understandability of decision by stakeholders.
- Further field testing and instrument validation is needed to collaboratively advance this framework and contribute to more transparent and efficient healthcare decisionmaking.

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