The Adherent Patients Only Sample Illusion: Why Adherent-Only Results Cannot Generally Inform Real-World Decisions

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EE222

Introduction/Objectives

Adherent Patient Subgroup (APS) cost-effectiveness analyses (CEAs) can appear to provide actionable evidence but generally **cannot inform real-world decisions**, because adherence status is unknown at treatment initiation. Thus, a decision-maker (e.g., physician) cannot directly use APS CEA results to guide treatment selection. Available evidence suggests that physicians are poor predictors of patient adherence.[1,2]

The physician interested in implementing cost-effective treatments faces two choices: (1) prescribe the overall sample's cost-effective (ITT) treatment, or (2) attempt to use APS CEA results.

One may view the physician's assessment of likely adherence as an **imperfect diagnostic test**, with true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN). As in any diagnostic setting, **prevalence of adherence is critical**.

We sought to provide a **necessary decision-analytic framework** for applying APS CEA results to illustrate how APS results must be combined with **non-adherent outcomes and diagnostic uncertainty** to adequately inform decisions.

Methods

We modeled adherence (ADH) as a diagnostic decision problem; Figure 1: comparing two strategies: a **No Test** strategy, in which all patients are assigned the intervention identified as cost-effective in the overall intent-to-treat (ITT) population, and a **Test** strategy, in which patients are classified as testing positive **"ADH"** or negative - non-adherent (**"nADH"**) using an imperfect diagnostic test. The test is characterized by conditional probabilities (its sensitivity (Se) & specificity (Sp)), and adherence prevalence (π). The test generates four classification outcomes: **TP**, **FP**, **TN**, **FN**), with joint probabilities:

TP = π · Se, **FP** = (1−π) · (1−Sp), **TN** = (1−π) · Sp, and **FN** = π · (1−Se)

The joint, marginal, and predictive (conditional) probabilities are summarized in Table 1.

This illustrative example uses base-case values of adherence prevalence (π = 0.54) and diagnostic accuracy (Se = Sp = 0.90). Subgroup Costs (C) and QALYs (Q) for correctly classified (**TP** & **TN**) and misclassified **(FP** & **FN)** patients were derived from the Diabetes Prevention Program (DPP)[3] and a companion analysis (Poster **EE112**; see QR code below for full details).

In our example, treatments (metformin – MET; Lifestyle – LS or Placebo – PBO) are assigned based on cost-effectiveness results within each test-defined group **("ADH" and "nADH").**

Figure 2 is an extended subtree to the top pathway of Figure 1, showing the partial example of the LS treatment option conditional on the "ADH" designation. There is a C and a Q for ADH patient treated with LS intervention: These outcomes(C and Q) are calculated as weighted averages of TP and FP:

$$C_{LS} = P(ADH|"ADH").C_{LS}^{ADH} + P(nADH|"ADH").C_{LS}^{nADH} \quad \text{Eqn 1}$$

$$Q_{LS} = P(ADH|"ADH").Q_{LS}^{ADH} + P(nADH|"ADH").Q_{LS}^{nADH} \quad \text{Eqn 2}$$

Not shown are MET and PBO options (as well as all 3 options for the "nADH" designation). "ADH" patients (both TP & FP) receive the cost-effective intervention for them based on analogous values to C_{LS} and Q_{LS} counterparts. Similarly, "nADH" (TN, FN) receive the cost-effective intervention for them (possibly different).

The marginal probabilities of test designations, **"ADH"** and **"nADH,"** are calculated as:

$$P("ADH") = P("ADH", ADH) + P("ADH", nADH) \quad \text{Eqn 3}$$

$$P("nADH") = P("nADH, ADH + P("nADH" nADH) \quad \text{Eqn 4}$$

$$C_{Test} = P("ADH") \,.\, C_{LS} + P("nADH") \,.\, C_{MET} \quad \text{Eqn 5}$$

$$Q_{Test} = P("ADH") \,.\, Q_{LS} + P("nADH") \,.\, Q_{MET} \quad \text{Eqn 6}$$

Methods (cont.)

The weighted average costs (C) and QALYs (Q) within each test-defined group (Eqns 5 & 6) are then combined to estimate overall outcomes for the Test strategy (Figure 1), which are then compared head-to-head with the No Test strategy.

This framework demonstrates that APS results require specification of adherence prevalence, diagnostic accuracy, **and** outcomes among nADH patients to inform decision making. The analysis is intended to demonstrate the **structure and necessity of this decision framework**, rather than to provide definitive empirical estimates.

Results

These inputs imply the corresponding joint, marginal, and predictive probabilities shown in Table 1, which determine treatment assignment and expected outcomes under the Test strategy.

Using these values, the Test strategy yielded lower expected costs ($6,513) and slightly higher effectiveness (2.0999 QALYs) compared with the No Test strategy ($8,811; 2.099 QALYs), corresponding to an incremental difference of $2,298 and −0.00086 QALYs (Test vs no Test). Test strategy dominates in this specification.

Table 1: Diagnostic Building Blocks (Base Case)

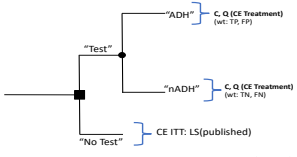
Component	Measure	Definition	Value
P("ADH", ADH)	TP	π . Se	0.486
P("ADH, nADH)	FP	(1−π) . (1−Sp)	0.046
P("nADH", nADH)	TN	(1−π) . Sp	0.414
P("nADH", ADH)	FN	π . (1−Se)	0.054
Marginal	P("ADH")	Se·π + (1−Sp)·(1−π)	0.532
Marginal	P("nADH")	(1−Se)·π + Sp·(1−π)	0.468
Predictive, conditional	PPV	P(ADH | "ADH")	0.914
Predictive, conditional	NPV	P(nADH | "nADH")	0.885

Expected outcomes are derived by weighting subgroup costs and QALYs using PPV and NPV.
π = 0.54, Se = 0.90, Sp = 0.90

Results (cont.)

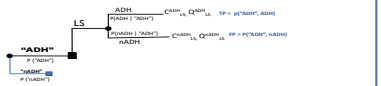
Thus, the Test strategy is dominant (less costly, more effective). At a willingness-to-pay threshold of $50,000/QALY, the Test strategy also produced higher net monetary benefit ($98,480 vs $96,139), confirming its preferred status under base-case assumptions.

Figure 1: Decision Framework: Test vs No test



Outcomes are calculated as weighted averages using predictive values (PPV, NPV).

Figure 2: subtree "ADH" (Test positive) patients. Expected outcomes(C,Q) are calculated as weighted averages of TP and FP under the assigned treatment(e.g., LS). Comparable subtrees across treatments determine the CE intervention for ADH



Conclusions

Adherent-only cost-effectiveness results may appear relevant for decision making; however, they cannot, on their own, inform treatment selection because adherence status is unknown at treatment initiation. Optimal policy requires a framework like we provide and explicit modeling of adherence prevalence, diagnostic misclassification, and outcomes among non-adherent patients.

References

Ref →

Poster EE112 →