

# Model-free predictions in personalized medicine with quantified uncertainty and personalized decisions: A case study on the conversion from MCI to AD

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## 2 ABSTRACT

3 [Luca & Astri, draft]

4 Patients with Mild Cognitive Impairment have an increased risk of Alzheimer's disease. Early  
5 identification of underlying neurodegenerative processes is essential to provide treatment before  
6 the disease is well established in the brain. It is therefore of extreme interest to study how well  
7 several kinds of predictors – from neuropsychological examinations to advanced brain-imaging  
8 techniques – allow us to prognose the onset of the disease.

9 But more is needed for a personalized approach to prognosis, prevention, treatment, than just  
10 the obvious requirement that prognoses be as best as they can be for each patient. Several  
11 situational elements that can be different from patient to patient must be accounted for:

- 12 • the *kinds* of clinical data and evidence available for prognosis;
- 13 • the *outcomes* of the same kind of clinical data and evidence;
- 14 • the kinds of treatment or prevention strategies available, owing to different attitudes toward  
15 life, different family networks and possibilities of familial support, different additional medical  
16 factors such as physical disabilities, different economic means;
- 17 • the advantages and disadvantages, gains and costs of the same kinds of treatment or  
18 prevention strategies; the patient has a major role in the quantification of such gains and  
19 costs;
- 20 • finally, the initial evaluation by the clinician – which often relies on too subtle clues (family  
21 history, regional history, previous case experience) to be considered as measurable data.

22 Statistical decision theory is the normative quantification framework that takes into account these  
23 fundamental differences. Medicine has the distinction of having been one of the first fields to  
24 adopt this framework, exemplified in brilliant old and new textbooks on clinical decision making.

25 Clinical decision making makes allowance for these differences among patients through two  
26 requirements. First, the quantification of prognostic evidence on one side, and of gains and costs  
27 of treatments and prevention strategies on the other, must be clearly separated and handled  
28 in a modular way. Two patients can have the same prognostic evidence, and yet very different  
29 prevention options. Second, the quantification of independent prognostic evidence ought to be in  
30 the form of *likelihoods about the health condition* (or equivalently of likelihood ratios, in a binary  
31 case), that is, of the probabilities of the observed test outcomes given the hypothesized health  
32 conditions. Likelihoods from independent clinical tests and predictors can then be combined  
33 with a simple multiplication; for one patient we could have three kinds of predictor available; for  
34 another, we could have five. The clinician's pre-test assessment is included in the form of a  
35 probability. These patient-dependent probabilities are combined with the patient-dependent costs  
36 and gains of treatment or prevention, to arrive at the best course of action for that patient. The  
37 main result underlying statistical decision theory is that decision making *must* take this particular  
38 mathematical form in order to be optimal and logically consistent.

39 The present work investigates the prognostic power of a set of neuropsychological and Magnetic  
40 Resonance Imaging examinations, demographic data, and genetic information about APOE status,  
41 for the prediction of the onset of Alzheimer's disease in patients defined as mildly cognitively  
42 impaired at a baseline examination. The longitudinal data used come from the ADNI database.

43 The prognostic power of these predictors is quantified in the form of a combined likelihood for  
44 the onset of Alzheimer's disease. As a hypothetical example application of personalized clinical  
45 decision making, three patient cases are considered where a clinician starts with prognostic  
46 uncertainties (possibly coming from other tests) of 50%/50%, 25%/75%, 75%/25%. It is shown  
47 how these pre-test probabilities are changed by the predictors.

48 This quantification also allows us to rank the relative prognostic power of the predictors. It is  
49 found that several neuropsychological examinations have highest prognostic power, much higher  
50 than the genetic and an imaging-derived predictors included in the present set.

51 Several additional advantages of this quantification framework are also exemplified and  
52 discussed in the present work:

- 53 • missing data are automatically handled, and results having partial data are not discarded; this  
54 quantification therefore also accounts for patient-dependent availability of *non-independent*  
55 predictors;
- 56 • no modelling assumptions (e.g. linearity, gaussianity, functional dependence) are made;
- 57 • the prognostic power obtained is intrinsic to the predictors, that is, it is a bound for *any*  
58 prognostic algorithm;
- 59 • variability ranges of the results owing to the finite size of the sample data is automatically  
60 quantified.
- 61 • the values obtained, being probabilities, are more easily interpretable than scores of various  
62 kinds.

63  Maybe we can also add two examples of different clinical decisions, coming from different  
64 gain/cost evaluations?

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## 1 INTRODUCTION

70 [Luca, pieces of text]

71 Personalized diagnosis, prognosis, treatment, and prevention strategies must make allowance for several  
72 fundamental differences among patients:

- 73 • the *kinds* of clinical data and evidence available for diagnosis or prognosis can be different;
- 74 • the *values* of the same kind of clinical data and evidence can be different;
- 75 • the kinds of treatment or prevention options can be different;
- 76 • the advantages and disadvantages, gains and costs of the same kinds of treatment or prevention can be  
77 different;
- 78 • finally, the evaluation of the clinician – which often relies on too subtle clues (family history, regional  
79 history, case experience) to be considered as measurable data – can be different.

80 Is there really a methodological framework that can take all these differences into account? Yes, there  
81 is, and Medicine has the distinction of having been one of the first fields to adopt it (Ledley and Lusted,  
82 1959): Statistical Decision Theory. Its application in Medicine is explained and exemplified in several,  
83 brilliant, old and new textbooks (Weinstein and Fineberg, 1980; Sox et al., 2013; Hunink et al., 2014). This  
84 theory has mathematical and logical foundations and its principles constitute indeed the foundations for the  
85 definition and realization of Artificial Intelligence (Russell and Norvig, 2022) 

86 The basics of clinical decision making  ..basics: each piece of evidence contributes with a likelihood or  
87 odds; they combine together and together with the clinician's pre-data evaluation. Then they are combined  
88 with the different gains/costs of treatments or prevention strategies to find the optimal one. Decision trees  
89 can be necessary (but don't change this framework). Costs & gains are evaluated by clinician & patient  
90 together.

$$\begin{aligned}
 & \overbrace{p(\text{health condition} \mid \text{results of all tests, prior info})}^{\text{post-test probability}} \propto \\
 & \overbrace{p(\text{health condition} \mid \text{prior info})}^{\text{pre-test probability by clinician}} \times \\
 & \text{likelihoods of tests} \left\{ \begin{array}{l} p(\text{result of 1st test} \mid \text{health condition, prior info}) \times \\ p(\text{result of 2nd test} \mid \text{health condition, prior info}) \times \\ \dots \end{array} \right. \quad (1)
 \end{aligned}$$

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