

Model-free prognosis and decision in personalized medicine: A case study on the conversion from Mild Cognitive Impairment to Alzheimer's Disease

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2 ABSTRACT

3 [Luca & Astri, draft]

4 Patients with Mild Cognitive Impairment (MCI) have an increased risk of a trajectory toward
5 Alzheimer's disease (AD). Early identification of patients with a high risk of AD is essential to
6 provide treatment before the disease is well-established in the brain. It is, therefore, of great
7 importance to study how well different kinds of predictors allow us to estimate a trajectory from
8 MCI towards AD in an individual patient.

9 But more is needed for a personalized approach to prognosis, prevention, and treatment, than
10 just 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, and different economic means;
- 17 • the advantages and disadvantages, benefits and costs of the same kinds of treatment or
18 prevention strategies; the patient has a major role in the quantification of such benefits 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 benefits and
27 costs 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;
34 for 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 benefits 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 Mag-
40 netic Resonance Imaging examinations, demographic data, and genetic information about
41 Apolipoprotein-E4 (APOE) status, for the prediction of the onset of Alzheimer's disease in patients
42 defined as mildly cognitively impaired at a baseline examination. The longitudinal data used come
43 from the ADNI database.

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

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

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

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

64 Keywords: keyword, keyword, keyword, keyword, keyword, keyword, keyword, keyword

1 EACH PATIENT IS UNIQUE

65 Meet Olivia, Ariel, Bianca, Curtis.¹ These four persons don't know each other, but they have something in
66 common: they all suffer from a mild form of cognitive impairment, and are afraid that their impairment
67 will turn into Alzheimer's disease within a couple of years. In fact, this is why they recently underwent
68 some clinical analyses and cognitive tests. Today they got the results of their analyses. From these results
69 and other demographic factors their clinician is assessing their risk of developing Alzheimer, and will then
70 decide on possible preventive treatments together with the patients.

71 Besides this shared condition and worry, these patients have other things in common – but also some
72 differences. Let's take Olivia as reference and see the similarities and difference between her and the other
73 three:

- 74 • Olivia and Ariel turn out to have exactly identical clinical results and age. They also have the same
75 preventive-treatment options. Ariel, however, comes from a different geographical region from Olivia,
76 where the conversion rate from Mild Cognitive Impairment to Alzheimer is lower: about 30%, whereas
77 in Olivia's it is around 45% ? Moreover there is no history of Alzheimer in Ariel's family.
- 78 • Olivia and Bianca also have exactly the same clinical results and age. They come from the same
79 geographical region and have very similar family histories. Bianca, however, is soon going to move to
80 another country where a new preventive treatment is available; this option is not open to Olivia.
- 81 • Olivia and Curtis have different clinical results and age – in particular, Olivia has the risky APOE4
82 allele whereas Curtis hasn't, and Curtis is more than 20 years younger. But they otherwise come from
83 the same geographical region, have very similar family histories, and the same preventive options.

84 We can categorize these differences as Figure  **** summarizes the similarity and differences between
85 Olivia and the other three patients. Table  **** reports the clinical results and demographic data common
86 to Olivia, Ariel, Bianca, as well as those of Curtis.

87 We will soon see that despite the many factors in common among these four patients – even despite the
88 identical clinical results for Olivia, Ariel, Bianca – *each patient will be prescribed a different treatment*
89 *option from the other three.*

90 The difference in treatment originates from

¹ Fictive characters; any reference to real persons is purely coincidental

— Luca, old pieces of text —

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

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

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

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

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

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Supplementary Material should be uploaded separately on submission, if there are Supplementary Figures, please include the caption in the same file as the figure. LaTeX Supplementary Material templates can be found in the Frontiers LaTeX folder.

DATA AVAILABILITY STATEMENT

The datasets [GENERATED/ANALYZED] for this study can be found in the [NAME OF REPOSITORY]
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FIGURE CAPTIONS



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