

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

4 Patients with Mild Cognitive Impairment have an increased risk of a trajectory toward Alzheimer's
5 Disease. Early identification of patients with a high risk of Alzheimer's Disease is essential to
6 provide treatment before the disease is well-established in the brain. great importance to study
7 how well different kinds of predictors allow us to prognose a trajectory from Mild Cognitive
8 Impairment towards Alzheimer's Disease 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 additional medical
15 factors such as physical disabilities, different attitudes toward life, different family networks
16 and possibilities of familial support, 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. The present work investigates the prognostic power of a set of neuropsycholo-
42 gical and Magnetic Resonance Imaging examinations, demographic data, and genetic information
43 about Apolipoprotein-E4 (APOE) status, for the prediction of the onset of Alzheimer's Disease in
44 patients defined as mildly cognitively impaired at a baseline examination. The longitudinal data
45 used come from the ADNI database.

46 (APOE) status, for the prediction of the onset of Alzheimer's disease in patients defined as
47 mildly cognitively impaired at a baseline examination. The longitudinal data used come from the
48 ADNI database.

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

54  [rewrite following](#) This quantification also allows us to rank the relative prognostic power of the
55 predictors. It is found that several neuropsychological examinations have the highest prognostic
56 power, much higher than the genetic and imaging-derived predictors included in the present set.

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

- 59 • missing data are automatically handled, and results having partial data are not discarded; this
60 quantification, therefore, also accounts for patient-dependent availability of *non-independent*
61 predictors;
- 62 • no modelling assumptions (e.g., linearity, gaussianity, functional dependence) are made;

- the prognostic power obtained is intrinsic to the predictors, that is, it is a bound for *any* prognostic algorithm;
- variability ranges of the results owing to the finite size of the sample data are automatically quantified.
- the values obtained, being probabilities, are more easily interpretable than scores of various kinds.

Keywords: Clinical decision making, Utility theory, Probability theory, Artificial Intelligence, Machine Learning, Base-rate fallacy

1 EACH PATIENT IS UNIQUE

Meet Olivia, Ariel, Bianca, Curtis.¹ These four persons don't know each other, but they have something in common: they all suffer from a mild form of cognitive impairment, and are afraid that their impairment will turn into Alzheimer's Disease within a couple of years. In fact, this is why they recently underwent some clinical analyses and cognitive tests. Today they received the results of their analyses. From these results, available clinical statistical data, and other relevant information, their clinician will assess their risk of developing Alzheimer. The clinician and each patient will then decide among a set of possible preventive treatments.

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

- Olivia and Ariel turn out to have exactly identical clinical results and age. They would also get similar benefits from the available preventive-treatment options. Ariel, however, comes from a different geographical region from Olivia, where the conversion rate from Mild Cognitive Impairment to Alzheimer is lower: about 30%, whereas in Olivia's it is around 45% (Petersen et al., 1999) Moreover there is no history of Alzheimer's Disease in Ariel's family.
- Olivia and Bianca also have exactly the same clinical results and age. They come from the same geographical region and have very similar family histories. In fact we shall see that they have the same probability of developing Alzheimer's disease. Bianca, however, suffers from several allergies and additional clinical conditions that would render some of the preventive options less beneficial to her.
- Olivia and Curtis have different clinical results – in particular, Olivia has the risky Apolipoprotein-E4 (APOE4) allele (Liu et al., 2013) whereas Curtis hasn't – and age, Olivia being more than 20 years older than Curtis. But they otherwise come from the same geographical region, have very similar family histories, and would get similar benefits from the preventive options.

We can categorize these differences as “difference in auxiliary information” (Olivia and Ariel), “difference in preventive benefits” (Olivia and Bianca), “difference in clinical factors” (Olivia and Curtis). Figure 1 summarizes the similarity and differences between Olivia and the other three patients. Table 1 reports the clinical results and demographic data common to Olivia, Ariel, Bianca, as well as those of Curtis.

Considering the similarities and differences among these patients, which treatments are optimal and should be prescribed to them?

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

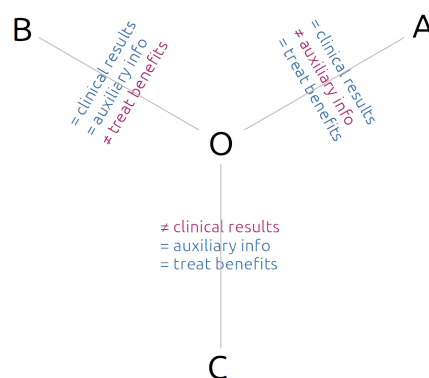


Figure 1. draft, needs better font sizes

Table 1. Clinical results & demographic data

Patient	Age	Sex	HC · 10 ⁻³	APOE4	ANART	CFT	GDS	RAVLT-im	RAVLT-del	RAVLT-rec	TMTA	TMTB
Olivia, Ariel, Bianca	83.5	F	2.77	Y	14	18	0	29	12	3	126.5	117.0
Curtis	61.5	M	4.17	N	6	13	1	16	2	0	24.8	83.4

99 The main purpose of the present work is to illustrate, using the four fictitious patients above as example,
 100 how this clinical decision-making problem can today be solved methodically, exactly, and at low compu-
 101 tational cost, when the available prognostic clinical information involves one-dimensional or categorical
 102 variates such as those listed in table 1. The solution method takes into account and integrates available
 103 clinical statistical data and each patient's unique combination of clinical results, auxiliary information, and
 104 preventive benefits. It is therefore the staple method for personalized prognosis, diagnosis, treatment.

105 In our example we shall find that despite the many factors in common among the four patients – even
 106 despite the identical clinical results for Olivia, Ariel, Bianca, and despite the identical probability of
 107 conversion for Olivia and Bianca – *the optimal treatment option for each patient is different from those*
 108 *for the other three*. This result exemplifies the importance of differences in clinical results, auxiliary
 109 information, or preventive benefits among patients.

110 The method used is none else than decision theory, the combination of probability theory and utility
 111 theory. Medicine has the distinction of having been one of the first fields to adopt it (Ledley and Lusted,
 112 1959). Its medical application is explained and exemplified in old and new brilliant textbooks (Weinstein
 113 and Fineberg, 1980; Sox et al., 2013; Hunink et al., 2014).

114 Decision theory also constitutes the foundation for the construction of an Artificial Intelligence agent
 115 (Russell and Norvig, 2022, ch. IV; Jaynes, 2003, chs 1–2).

— 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.

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

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FUNDING

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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

193 The datasets [GENERATED/ANALYZED] for this study can be found in the [NAME OF REPOSITORY]
194 [LINK].

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FIGURE CAPTIONS

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