

Personalized prognosis & decision: An example study on the conversion from Mild Cognitive Impairment to Alzheimer's Disease

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ABSTRACT

Patients with Mild Cognitive Impairment have an increased risk of a trajectory toward Alzheimer's Disease. Early identification of patients with a high risk of Alzheimer's Disease is essential to provide treatment before the disease is well-established in the brain. great importance to study how well different kinds of predictors allow us to prognose a trajectory from Mild Cognitive Impairment towards Alzheimer's Disease in an individual patient.

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

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

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

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

The present work investigates the prognostic power of a set of neuropsychological and Magnetic Resonance Imaging examinations, demographic data, and genetic information about Apolipoprotein-E4. The present work investigates the prognostic power of a set of neuropsychological and Magnetic Resonance Imaging examinations, demographic data, and genetic information about Apolipoprotein-E4 (APOE) status, for the prediction of the onset of Alzheimer's Disease in patients defined as mildly cognitively impaired at a baseline examination. The longitudinal data used come from the ADNI database.

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

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

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

- missing data are automatically handled, and results having partial data are not discarded; this quantification, therefore, also accounts for patient-dependent availability of *non-independent* predictors;
- 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  *need to explain the variates and refer to (Rye et al., 2022).*

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

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

Table 1. Clinical results & demographic data

Our main purpose in the present work is to illustrate, using the four fictitious patients above as example, how this clinical decision-making problem can today be solved methodically, exactly, and at low computational cost, when the available prognostic clinical information involves one-dimensional or categorical variates such as those listed in table 1. The solution method integrates available clinical statistical data with each new patient's unique combination of clinical results, auxiliary information, and treatment benefits.

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

The method used is none other than decision theory, the combination of probability theory and utility theory (von Neumann and Morgenstern, 1955; Raiffa and Schlaifer, 2000; Raiffa, 1970; Lindley, 1988; Kreps, 1988; Jaynes, 2003, chs 13–14). Medicine has the distinction of having been one of the first fields to adopt it (Ledley and Lusted, 1959), with old and new brilliant textbooks (Weinstein and Fineberg, 1980; Sox et al., 2013; Hunink et al., 2014) that explain and exemplify its application.

Decision theory is also the normative foundation for the construction of an Artificial Intelligence agent capable of rational inference and decision making (Russell and Norvig, 2022, ch. IV; Jaynes, 2003, chs 1–2). The present method can therefore be seen as the application of an *ideal machine-learning algorithm*. “Ideal” in the sense of being free from approximations, special modelling assumptions, and limitations in its informational output; not in the sense of being impracticable. Another important point of the present work, indeed, is to show that *for some kinds of dataset* such ideal machine-learning algorithm is a reality. It is preferable to popular algorithms such as neural networks, random forests, support-vector machines, which are unsuited to clinical decision-making problems owing to their output limitations. We discuss this matter further in § ***.

Add other advantages of this exact approach:

- it does not make assumptions, besides natural assumption of smoothness of full-population frequency distribution
- can be used with partially missing clinical data

- can be used with binary or continuous predictands
- it tells us the maximum predictive power of the predictors
- it quantifies how prediction could change if we had more sample data
- it can be applied on-the-fly to each new patient

and goals, results, and some synopsis

The inferential and decision-making steps are summarized in table 2.

Table 2. Inferential and decision-making steps. Steps in **boldface** represent patient-dependent, personalized steps that cannot be obtained from the learning dataset

1. Infer the full-population frequencies of predictors and predictand, using available datasets.
2. **Assess in respect of which variates the present patient can be considered as belonging to the same population underlying the learning dataset.**
3. **Assess the prior probability of the predictand for the present patient.** This step allows us (a) to consider additional clinical information outside of the dataset's variates, and available for the present patient only; (b) to correct for mismatches between the dataset's underlying population and the patient's one.
4. Calculate the *likelihood* of the predictand for a specific patient, given the patient's predictor values. Combine this likelihood with the prior from step 3, to obtain the final probability for the predictand, for the present patient.
5. **Assess the clinical courses of action available for the present patient, together their benefits and costs.** This step is fundamentally patient-dependent and is the one open to most variability from patient to patient.
6. Choose the course of action having maximal expected benefit for the present patient, given the benefits assessed in step 5 and the final probability assessed in step 4.

2 PRACTICAL EXAMPLE

 It may be optimal to present the steps in reverse order: the last one explains the goal, and makes clear why the preceding steps are necessary.

2.1 Learning

In the learning stage we infer the statistical relationships of a large population of which our future patients can be considered members, at least in some respects. Such relationships will help us in our prognoses. The basic idea is intuitive. If a patient can be considered a member of this population, and if we knew the joint frequencies of all possible combinations of predictor and predictand values in such population – and knew nothing else – then we would say that the probability for the patient to have particular values is equal



Figure 2. Upper-left: Sample data. Upper-right: candidate frequency distribution that fits the data and does not look unnatural. Lower-left: candidate distribution that might look natural but doesn't fit the sample data. Lower-right: candidate distribution that fits the data very well but looks unnatural.

to the population frequency. Pure symmetry considerations lead to this intuitive result (de Finetti, 1930; Dawid, 2013; Bernardo and Smith, 2000, §§ 4.2–4.3).

But it must be emphasized, and it is essential for our method, that it is *not* necessary (and is seldom true) that a future patient be considered as a member of such a population *in all respects*. A patient can be considered a member only *conditionally* on particular variate values. We shall discuss this point with an example in § 2.2.

If the full statistics of such a population were known, our task would just be to “enumerate” rather than to “learn”. Learning comes into play because the full population is not known: we only have a sample from it.

The most we can do is therefore to assign a probability to each possible frequency distribution for the full population. The probability of a specific “candidate” frequency distribution is intuitively determined by two factors: (a) how well it fits the sample data, (b) how biologically or physically reasonable it is. Figure 2 show a fictitious sample data and various candidate frequency distributions

Some more intuition and details about the maths, principles, and characteristics (Dunson and Bhattacharya, 2011; Rossi, 2014; Rasmussen, 1999).



Figure 3. ✎ Examples of a-priori probable candidates of frequency distribution for a variate such as AVDEL30MIN_neuro or AVDELTOT_neuro

The core of our method is the computation of the probabilities of all possible frequency distributions for the full population. From it we obtain the joint probability distribution $p(X, Y, Z, \dots)$ for all variates X, Y, Z, \dots available in the dataset.

This is the maximal amount of information that can be extract from our dataset. From it we can indeed quickly calculate any quantity typically outputted by specific or approximate algorithms. For example:

- *Conditional probability, “discriminative” algorithms:* if we are interested in the probability of Z given X, Y , we calculate $p(Z | X, Y) := p(X, Y, Z) / \sum_Z p(X, Y, Z)$.
- *Conditional probability, “generative” algorithms:* if we are interested in the probability of X, Y given Z , we calculate $p(X, Y | Z) := p(X, Y, Z) / \sum_{X, Y} p(X, Y, Z)$.
- *Regression or classification:* if we are interested in the average value of Z given X, Y , we calculate $E(Z | X, Y) := \sum_Z Z p(Z | X, Y)$. The “noise” around this average value is moreover given by $p(Z - E | X, Y)$.
- *Functional regression:* if Z turns out to be a function f of X, Y , then the probability will be a delta distribution: $p(Z | X, Y) = \delta[Z - f(X, Y)]$. The present ideal machine-learning algorithm thus always recovers a functional relationship if there is one, including its noise distribution.


We will see that no one of these quantities can be used alone to solve our clinical decision problem for all future patients.

The present method moreover has some further advantages and yields additional useful information:

- *Discrete or continuous variates:* the variate to be prognosed can be not only binary or discrete, as in the present case, but also continuous.

- *Partially missing data*: data having missing values for some variates can be fully used, both in the learning dataset and in the prognostic results of new patients.
- *Maximal predictive power of the variates*: from the probability distribution $p(X, Y, Z, \dots)$ we can calculate the mutual information between any two sets of variates, for example between Z and $\{X, Y\}$. This quantity tells us what is the maximal predictive power – which can be measured by accuracy or other metrics – from one set to the other that can be achieved by any inference algorithm (MacKay, 2005; Good and Toulmin, 1968; Cover and Thomas, 2006). Functional dependence is included as a special case; for example, a binary variate Z is a function of $\{X, Y\}$ if and only if their mutual information² equals 1 Sh.
- *Variability owing to limited sample size*: we can calculate how much any of the quantities listed so far – from average values to mutual information – could change if more sample data were added to our dataset.

For readers with an interest in machine learning and artificial intelligence, we briefly discuss the drawbacks of some popular inference algorithms with respect to the present ideal algorithm.

Neural networks and gaussian processes are based on the assumption that there is a functional relationship from predictors to predictand, possibly contaminated by a little noise, typically assumed gaussian. This is a very strong assumption, quite unrealistic for many kinds of variables considered in medicine. It can only be justified in the presence of informationally very rich predictors such as images. In our case the mutual information between predictors and the conversion variate is 0.14 Sh, to be compared with 1 Sh, if conversion were a function of the predictors, and with 0 Sh, if conversion were completely unpredictable. See § *** for further details. An additional deficiency of neural networks is that they do not yield any probabilities, even if there are many efforts to render such an output possible (Pearce et al., 2020; Osband et al., 2021; Back and Keith, 2019). Such an advance, however, would still not solve the final deficiency of neural networks and gaussian processes: they try to infer the predictand from the predictors but cannot be used for the reverse inference.

Random forests also assume a functional relationship from predictors to predictand. This assumption is mitigated when the predictand is a discrete variate; in this case a random forest can output an agreement score from its constituent decision trees. This score can give an idea of the underlying uncertainty, but it is not a probability,³ and therefore cannot be used in the decision-making stage, see § 2.6. It is possible to transform this score into a proper probability (Dyrland et al., 2022), but this possibility does not solve the final deficiency of random forests: like neural networks, they try to infer the predictand from the predictors but cannot be used for the reverse inference.

Parametric models and machine-learning algorithms such as logistic or linear regression, support-vector machines, or generalized linear models make even stronger assumptions than neural networks and random forests. They assume specific functional shapes or frequency distributions. Their use may be justified when we are extremely sure – for instance thanks to underlying physical or biological knowledge – of the validity of their assumptions; or when the computational resources are extremely scarce. But it is otherwise unnecessary to be hampered by their restrictive and often unrealistic assumptions.

An important common deficiency of most inference algorithms mentioned above is that their inference only goes from predictors to predictands. In the next two sections we shall see that this precludes – or makes

² The “shannon” (Sh) is a measurement unit of information, as specified by the ISO (International Organization for Standardization) (2008).

³ It is sometimes called a “non-calibrated probability”, which is akin to a “non-round circle”.

much riskier – the prognostic use of the learning dataset for patients belonging to different populations, such as Ariel.

2.2 Population assessment

Most medicine students learn about the *base-rate fallacy* (Bar-Hillel, 1980; Jenny et al., 2018; Sprenger and Weinberger, 2021; Matthews, 1996). Suppose that in a large set of clinical trials it is found that, among patients having a particular value of some predictors, 71.4% (or 5/7) of them eventually developed a disease, while 28.6% (or 2/7) did not. See upper panel of side figure; each dot may represent 10 000 or one million patients. The fallacy lies in judging that a new real patient from the full population, who has those particular predictor values, also has a 71.4% probability of developing that disease. In fact, *this probability will in general be different*. In our example it is 33.3%, see lower panel.

The discrepancy in the frequencies of predictand given predictors for the trial data and for the full population arises from the fact that the proportion of positive vs negative disease cases in the full population has some value, say 16.7%/83.3% in the side example; but the samples for the trials (indicated by the dashed line in the lower panel) were chosen so as to have a roughly 50%/50% proportion. This sampling procedure is called “class balancing” in machine learning. More generally this discrepancy can appear whenever a population and a sample dataset from it do not have the same frequency distribution for the disease or predictand. In this case cannot rely on probabilities of “predictand given predictors” obtained solely from the sample dataset.

A little counting in the side figure reveals, however, that other probabilities may be relied upon. *In the full population*, among all patients who developed the disease, 83.3% (or 5/6) of them had the particular predictor value, while among those who did not develop the disease, 33.3% (or 1/3) had the particular predictor value. *And these frequencies are the same in the clinical trials*. These frequencies from the clinical trials can therefore be used to make a prognosis using Bayes's theorem:

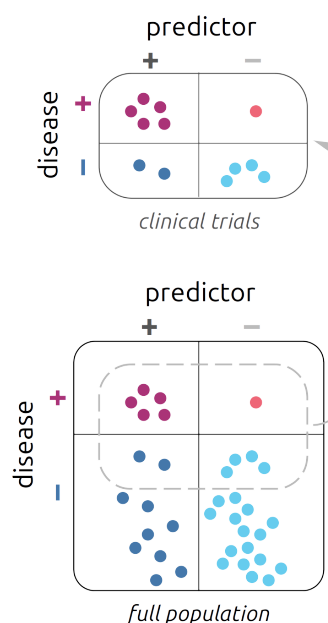
$$p(\text{predictand}|\text{predictors}) = \frac{p(\text{predictors} | \text{predictand, dataset}) \cdot p(\text{predictand} | \text{population})}{\sum_{\text{predictand}} p(\text{predictors} | \text{predictand, dataset}) \cdot p(\text{predictand} | \text{population})} \quad (1)$$

In our example we find

$$p(\text{disease+} | \text{predictor+}) = \frac{p(\text{predictor+} | \text{disease+, trials}) \cdot p(\text{disease+} | \text{population})}{\left[p(\text{predictor+} | \text{disease+, trials}) \cdot p(\text{disease+} | \text{population}) + p(\text{predictor+} | \text{disease-, trials}) \cdot p(\text{disease-} | \text{population}) \right]} \quad (2)$$

$$\approx \frac{0.833 \cdot 0.167}{0.833 \cdot 0.167 + 0.333 \cdot 0.833} = 0.33$$

which is indeed the correct full-population frequency.



If the patients for the clinical trials had been chosen with the same frequencies as the full population (no “class balancing”), then the use of the probability

$$p(\text{predictand} \mid \text{predictors, dataset}) \quad (3)$$


from the dataset would be correct. But the probabilities

$$p(\text{predictors} \mid \text{predictand, dataset}) \quad (4)$$

together with Bayes's theorem as in eq. (1) would also lead to the same result. We thus see that *using the probabilities $p(\text{predictors} \mid \text{predictand})$ from the dataset is generally superior to using $p(\text{predictand} \mid \text{predictors})$* . The former give the same results as the latter when use of the latter is correct, and they allow us to apply corrections when use of latter is incorrect.

 **Illustration of this by training on dataset with a proportion of cAD/sMCI and application to a separate dataset with a different proportion.**

The situation discussed above generalizes and becomes more complicated as we consider multiple predictor and predictand variates. In general, of all probabilities $p(\dots \mid \dots)$ obtained from the dataset we should use those having in the conditional “ $\mid \dots$ ” argument any variate we suspect having dataset statistics different from those of the population of interest, obtaining the final desired probabilities from Bayes's theorem.

It may be necessary to use dataset probabilities different from $p(\text{predictand} \mid \text{predictors})$ even when the dataset has statistics identical with the population it is sampled from.  ***

The use of the probabilities $p(\text{predictors} \mid \text{predictand})$ from a dataset is especially important for a personalized, patient-adapted approach to prognosis and treatment. A new patient, such as Ariel, may come from a population with statistical properties different from the available dataset. No prognosis, or an in-principle incorrect prognosis, can be made for Ariel if our inference algorithm only relies on the probabilities $p(\text{predictand} \mid \text{predictors})$.

(Lindley and Novick, 1981; Sprenger and Weinberger, 2021; Bar-Hillel, 1980)

2.3 Prior probability

(Lindley and Novick, 1981; Sprenger and Weinberger, 2021; Bar-Hillel, 1980)

2.4 Likelihood and posterior probability

(Lindley and Novick, 1981; Sprenger and Weinberger, 2021; Bar-Hillel, 1980)

2.5 Benefit assessments

(Sox et al., 2013; Hunink et al., 2014)

2.6 Maximization of expected benefit

(Lindley, 1982)

— 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.

$$\begin{aligned}
 & \overbrace{p(\text{health condition} \mid \text{results of all tests, prior info})}^{\text{post-test probability}} \propto \\
 & \overbrace{p(\text{health condition} \mid \text{prior info})}^{\text{pre-test probability by clinician}} \times \\
 & \text{likelihoods of tests} \left\{ \begin{array}{l} p(\text{result of 1st test} \mid \text{health condition, prior info}) \times \\ p(\text{result of 2nd test} \mid \text{health condition, prior info}) \times \\ \dots \end{array} \right. \quad (5)
 \end{aligned}$$

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The authors were too immersed in the development of the present work to keep a detailed record of who did what.

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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] [LINK].

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