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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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ABSTRACT

[Luca & Astri, draft]

Patients with Mild Cognitive Impairment have an increased risk of Alzheimer's disease. Early identification of underlying neurodegenerative processes is essential to provide treatment before the disease is well established in the brain. maybe move this last part below, after "the present work"? Here we investigate the prognostic power of a set of neuropsychological and Magnetic Resonance Imaging examinations, demographic data, and genetic information about 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.

A personalized approach for prognosis and for treatment and prevention strategies requires, however, that the prognostic power of the predictors listed above be quantified and used in a specific way. It is not enough that prognoses be as best as they can be for each patient (that is an obvious requirement). Allowance must instead be made for several fundamental differences among patients:

- the *kinds* of clinical data and evidence available for prognosis can be different;
- the *outcomes* 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, gains and costs of the same kinds of treatment or prevention can be different; in particular, the patient has a major role in their quantification;

- 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 – can be different.

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

Two main requirements must be met for optimal clinical decision making. First, the quantification of prognostic evidence on one side, and of gains and costs of treatments and prevention strategies on the other, must be clearly separated. 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, 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 present work meets the two requirements above by quantifying the prognostic power of the chosen predictors – neuropsychological examinations, demographic data, Magnetic Resonance Imaging, genetic information – 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 probabilities are changed by the predictors. Maybe we can also add two examples of different clinical decisions, coming from different gain/cost evaluations?

The mutual dependence and relative predictive strength of the mentioned predictors is also quantified. It is found that ...

Possibly add about the quantification of uncertainty coming from the finite sample size?

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1 INTRODUCTION

[Luca, 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, gains 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 gains/costs of treatments or prevention strategies to find the optimal one. Decision trees can be necessary (but don't change this framework). Costs & gains are evaluated by clinician & patient together.

$$\overbrace{\mathrm{p}(\text{health condition} \mid \text{results of all tests},\ \text{prior info})}^{\textit{post-test probability}} \propto \overbrace{\mathrm{p}(\text{health condition} \mid \text{prior info})}^{\textit{pre-test probability by clinician}} \times \textit{likelihoods of tests} \begin{cases} \mathrm{p}(\text{result of 1st test} \mid \text{health condition},\ \text{prior info}) \times \\ \mathrm{p}(\text{result of 2nd test} \mid \text{health condition},\ \text{prior info}) \times \\ \dots \end{cases} \quad (1)$$

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

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