



Scores versus clinical profiles in therapeutic decisions: a positive example from the Italian Medicines Agency (AIFA) decisions in the field of osteoporosis

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Introduction

The attempt to mathematicise the cognitive approach to reality can be traced back to ancient Greek culture. Mathematics is a most powerful cognitive tool, whose potential is evoked by the name itself, as *mathesis* means “learning reality”. Actually, and surprisingly enough, reality reveals a peculiar correspondence between this approach and its intrinsic constitutive mechanisms, and the development of a favorable cultural context has disclosed the operative potential of this approach. The link between science and praxis has changed completely our relationship with reality. Mathematization has been a driving element also in the field of medical care, generating levels of progress that have recently involved also the strict clinical milieu.

An example of this is the contribution to the definition of risk profile for a given patient to develop a given outcome. In Rheumatology, for instance, the use of diagnostic scores is employed to assess the activity profile of the disease in patients with Rheumatoid Arthritis (RA) using the 28-joint Disease Activity Score (DAS28) [1], or to calculate the risk of fragility fractures, using the fracture risk assessment tool (FRAX) [2]. The importance of these tools, however, has generated a tendency deserving careful analysis, as it goes beyond a specific medical field, and that, in our opinion, requires a more general evaluation for the possible problems that may ensue. Indeed, this issue evolves in a totally different way and with very specific implications when the approach is

automatically extrapolated to the domain of therapeutic decision-making.

Scores in therapeutic decisions

Using mathematical scores to define a therapeutic approach raises issues that cannot be underrated. Here are the three main issues.

1. Overestimating the conditions for the indications to treatment. As said, in RA, DAS28 is obtained combining four numeric variables: tender joint count (TJC), swollen joint count (SJC), visual analogue scale (VAS), erythrocyte sedimentation rate (ESR) [1]. DAS28 is used to evaluate the activity of arthritis in clinical trials, but this score is being increasingly proposed as guide to treatment decisions [3]. However, several other rheumatologic conditions may cause overestimation of DAS28 thus confounding its relationship with the clinical profile of arthritis. VAS and TJC, for example, can also be affected by other causes of pain not generated by arthritis, as for example fibromyalgia. In addition, osteoarthritis, for example, can generate pain in the hand and knee joints—conditions also included in the DAS28. The score can be high, and therefore suggestive of active arthritis, for other causes, making it less reliable when dealing with questions as relevant as a therapeutic decision [4].
2. Scores may emphasize statistically significant conditions that are not relevant from a clinical point of view. A recent article analyzed the results of trials comparing the radiological progression of arthritic damage (assessed using the Sharp/van der Heijde score), in patients treated with biotechnological drugs or with methotrexate (MTX) [5]. For instance, the TEMPO study on patients with early RA showed a radiological progression of 3.3 units in two

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years of treatment in patients randomized to MTX, compared to 1.1 units in patients on etanercept, and −0.56 units in patients treated with a combination of MTX and etanercept [6]. The difference was statistically significant, although, a 3.3 units difference is 0.7% of the total number of units in the Sharp/van der Heijde score, where the total score is 448 units. One objection could be that rarely patients develop damage as high as 50% over the highest value, suggesting that a value of 224 be considered as the real value, i.e., 50% of the highest value. Here again, a 3.3 units variation in a two-year period is 1.5% of this value. This change would not be clinically detectable in the single patient, whereas a clinically relevant change (5 to 15 units) would be observable only after several years and would not be of any practical use for patient management [7]. Similar results in patients with early RA have been reported with other biotechnological agents, with statistically significant but not clinically relevant differences vs. MTX in the individual patient [8].

3. Underrated role of the physician. Tendentially, the risk with the use of scores in therapeutic decision-making is that the professional role of the physician is underrated. Using scores strengthens the impression of the physician as a mere drug “dispenser”, whose prescriptions are trapped in score grids. This condition can further induce professionals to disengage from personalized patient care, a cultural shift which many expert observers consider as an unprecedented challenge for our professional life [9].

A positive example

The debate on such complex matters should not neglect a positive – and particularly significant – example. FRAX is a score largely used in the field of osteoporosis [2, 10]. It combines the effect of several clinical risk factors to define an individual’s global fracture risk, which is then expressed as percent probability in a 10-year period. The increasing tendency to mathematization is generating recurrent suggestions to use FRAX not only to identify high-risk subjects, but also to define a threshold to start pharmacological treatment [11–14]. The same Authors of the FRAX underline how this would be inadequate [15]. In fact, the score obtained is determined by the interaction of factors that in most cases are not susceptible of modifications following pharmacological treatment: age, family history of fractures, smoking, alcohol consumption, BMI, all of which only need a non-pharmacological approach to reduce their impact on osteoporotic fracture risk.

These considerations were taken into account in Italy in the discussion on the identification of a threshold to start pharmacological treatment for osteoporosis and the related decisions on drug reimbursement. An alternative solution to the score has been identified. In Italy, treatments are not universally

reimbursed; in fact, the Italian national drug agency (AIFA) defines (by releasing statements called “nota”) the conditions that properly entitle to reimbursement. When evaluating the domain of osteoporosis treatment, AIFA has correctly rejected the use of FRAX or other similar scores in decisions concerning pharmacological treatment. The need to identify a proper (and cost-effective) threshold for drug treatment in osteoporosis has been therefore approached using an alternative option: the description of a series of appropriate clinical profiles (Table 1) [16]. They represent the clinical conditions bearing a fracture risk that makes an intervention cost-effective and which are susceptible of pharmacological treatment. In addition, for each clinical profile, the “nota” lists treatments according to three categories of preferential choice on the basis of the available evidence [16].

Advantages of outlining reference clinical profiles

The choice to favor the use of clinical profiles in therapeutic decision-making may be a useful example to consider. The score is no doubt useful to define the profile of individuals requiring specific clinical attention, but cannot automatically translate into an indication for pharmacological treatment, least of all into an indication to the use of one drug rather than another. Against this background, the use of clinical profiles rather than of scores is undoubtedly mandatory in osteoporosis treatment, but these considerations may apply also to other medical conditions, on the basis of a series of considerations.

1. Outlining appropriate clinical profiles reduces the employment of subjective variables (as TJC, pain, in the mentioned examples), in favor of more verifiable parameters such as fractures, SJC, erosion, steroid use, etc. Similarly, an appropriate combination of objective and verifiable conditions could be outlined for many other medical condition, deriving risk profiles that may justify a given pharmacological treatment based on the available literature. This increases the specificity of the evaluation, allowing a more accurate epidemiological definition of the entity of these conditions.
2. The use of clinical profiles emphasizes the clinical significance. It avoids the risk (as is often the case when using scores) that variations in a factor or combination of factors – “mathematically influential” as they may be – turn out to be not clinically relevant or vice versa. This, along with the considerations listed above, is also relevant in terms of expenditure control – i.e., in defining which individuals are entitled to treatment provided by the health care system. Indeed, the epidemiological impact of objective clinical variables can be more easily described and managed than variations linked to combination of variables in a score.

Table 1 As an example of list of clinical profiles, we report the following “Nota 79”

Prescription covered by the Italian National Health Care System is restricted to the following conditions for osteoporosis fracture risk [16].

Secondary prevention for individuals with a history of osteoporotic fractures

- vertebral or femoral osteoporotic fractures

<i>Condition</i>	<i>First choice treatment</i>	<i>Second choice treatment</i>	<i>Third choice treatment</i>
1–2 fractures	Alendronate (\pm vit.D), Risedronate, Zoledronate	Denosumab, Ibandronate, Raloxifene, Bazedoxifene	Strontium ranelate
≥ 3 fractures OR ≥ 1 fracture + spine or femur T-score ≤ -4 OR ≥ 1 fracture + treatment >12 months with prednisone or equivalent ≥ 5 mg/die OR New vertebral or femoral fracture despite treatment with drugs in Nota 79 for at least one year	Teriparatide	Denosumab, Zoledronate	Alendronate(\pm vit.D), Risedronate, Ibandronate Strontium ranelate
• non-vertebral, non-femoral osteoporotic fractures + spine or femur T-score ≤ -3	Alendronate (\pm vit.D), Risedronate, Zoledronate	Denosumab, Ibandronate, Raloxifene, Bazedoxifene	Strontium ranelate

Primary prevention in menopausal women or men aged ≥ 50 yrs. at high fracture risk due to one of the conditions listed below

<i>Condition</i>	<i>First choice treatment</i>	<i>Second choice treatment</i>	<i>Third choice treatment</i>
Current or expected treatment >3 months, with prednisone or equivalent ≥ 5 mg/die	Alendronate (\pm vit.D), Risedronate, Zoledronate	Denosumab	
Adjuvant hormone blockade in women with breast carcinoma or men with prostate carcinoma	Alendronate (\pm vit.D), Risedronate, Zoledronate, Denosumab		
Spine or femur T-score ≤ -4 OR Spine or femur T-score ≤ -3 + at least one of the following conditions: 1) Family history of vertebral or femoral fractures 2) Comorbidity with increased fracture risk (RA or CTDs, diabetes, COPD, IBD, AIDS, Parkinson, multiple sclerosis, severe motor disability)	Alendronate (\pm vit.D), Risedronate,	Denosumab, Zoledronate, Ibandronate, Raloxifene, Bazedoxifene	Strontium ranelate

3. Clinical profiles value the active role of the physician, who is prompted to identify and appreciate each single risk factor involved and the possible co-morbidities, and to take appropriate action. In fact, in clinical practice there are, on the one hand, conditions that do not require pharmacological treatment but which should nevertheless be recognized and treated without resting on the illusion that only drug treatment confers control of the disease. On the other hand, other circumstances should be considered as, for instance, the case of a patient with RA also affected by osteoarthritis or fibromyalgia: these concomitant conditions cannot be concealed by the use of a score that subtly may indicate in an automatic way a given drug or induce in diagnostic or professional disengagement toward the patient. Every tool that favors the necessary doctor-patient relationship and an adequate management should be encouraged and pursued, especially in deciding the most appropriate pharmacological treatment.

The workplace for health

Taking charge of a patient, considering a patient as a whole, is hailed as an irrevocable need [9, 17]. With the current

awareness of the relevance of personalized medicine, such elements are fundamental when choosing a drug and trying to favor compliance. The list of clinical profiles to employ as paradigm for therapeutic indications seems to comply with this approach. Vice versa, an increasing and indiscriminate use of scores in choosing the appropriate pharmacological treatment could lead to a sort of disengagement of the physician vis-à-vis the patient. This could lead to the feeling that the therapeutic indication can, after all, be handled automatically, subtly suggesting that this could eventually even be an advantage. Instead, the workplace for health is intrinsic in the doctor-patient relationship, unconstrained and responsible. The essence of this relationship is looking at the other as a person. The patient, especially in the current scenario, wants to be “taken in charge”, as would be the case with a relative, and wants to be taken along on his way to bear the disease condition. A similar attitude is universally recognized as appropriate because it corresponds to our own expectations; however, it is demanding, not automatic, nor is it self-sustainable.

Unfortunately, we are fascinated by mathematization: it seems to promise that we will be exempted from the burden of this relationship. And yet, only if we take charge of this relationship, if we consider the other in a familiar way, does

our work become efficient and effective and stands out against the growing dissatisfaction of health care workers [18].

The essential vs. the non-essential: telling the difference

The problem of mathematization imposes a broader critical issue. Math is certainly useful and will be more and more central in our future—and this is not to be feared. The trend will impose a reflection on our profession and make us discern what is essential from what is not and can therefore be deferred. The doctor-patient relationship is by all means essential and the decision and management of therapy remain an essential component of this relationship. And looking as a person at who is in front of us is pivotal. It is important to heed whatever favors this relationship and oppose any obstacle to it [19]. To this regard, it could be useful to discourage the use of scores in therapeutic decisions concerning indication to drug treatment and develop clinical profiles as guide to pharmaceutical treatment whenever possible. This could be considered part of a more general effort aiming at reorganizing care delivery itself around medical conditions and improving expenditure control [20].

Furthermore, the demanding burden of sustaining the doctor-patient relationship suggests the need to implement efforts in the educational field, both in the Continuing Medical Education programs and when training the new generations of physicians. It is of utmost importance to overcome self-referencing and open up the professional domain to the human resources that help bear the burden of our demanding professionalism.

Compliance with ethical standards

Disclosures None.

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