

Title

Logics of the theranostic and diagnostic processes

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Abstract

The theranostic process innovates by relying on mechanistic biomarkers that have combined diagnostic and therapeutic utility; hence the term theranostic. Yet, some have argued that there is nothing substantially different about the theranostic strategy. Theranostics are just more efficient ways of doing what the diagnostic process has always been about: finding the cause of the condition to arrive at the right treatment plan. This may be correct from the point of view of clinical practice. However, it is incorrect from the point of view of clinical epistemology. This paper argues that there is a significant distinction between the diagnostic process and the theranostic process in matters of logic and in terms of the vulnerabilities to clinical errors to which these processes are respectively exposed. I argue that the diagnostic process follows a hypothetico-deductive model of demonstration that calls upon system 1 and system 2 reasoning patterns, which makes this process liable to cognitive diagnostic errors (i.e., errors that stem from failures in the clinician's knowledge and reasoning). In turn, the theranostic process takes the form of a deductive-nomological explanation that eliminates the need to appeal to System 2 reasoning, which makes this process liable to system-related diagnostic errors.

Keywords

Theranostic; Logic of science; Clinical reasoning; Diagnostic error; Precision Medicine

1. INTRODUCTION

Diagnosis is central to contemporary biomedical practice. In common usage, the term *diagnosis* tends to mean one of two things (Jutel, 2009). One tends to speak of a diagnosis either as a *thing* or as a *process*. As a thing, the diagnosis is a category label or description found in a diagnostic nosology (e.g., the International Classification of Diseases). The diagnostic thing has various explicit functions that are not always directly related to the patient's affliction (e.g., billing and reimbursement). In this sense, the diagnosis is a complex, multi-faceted social object with different meanings and effects for different people, leading to different processes (e.g., predicting course and prescribing treatment, but also providing a path to self-understanding (Gómez-Carrillo & Kirmayer, 2023) and to claiming insurance). As a process, diagnosis involves a chain of reasoning culminating in a medical decision. It has one explicit set of functions related to the medical act of improving patients' health. Here, I am only interested in diagnosis as a process.

Recently, proponents of precision medicine have suggested that the process of diagnosis can be refined or complemented by identifying biomarkers that predict positive and negative responses to specific treatments, an approach termed *theranosis*. The availability of theranoses would make the medical diagnostic process more accurate, effective, and efficient. In these discussions, there is sometimes the assumption that the diagnostic component of the theranostic process will perform the same work as a conventional diagnosis in non-precision medicine, and that precision medicine may not be so different than conventional medicine (Guchet, 2017; Pokorska-Bocci et al., 2014; Wiesing, 2018, 2019). While this may be correct from the point of view of medical practice — as a set of institutionally defined acts aimed at making people well when they seek help — I will argue that this equivalence is incorrect from the point of view of clinical epistemology, the theory of what it means to know and reason in medicine.

Aim and claim

My aim is to show how the processes of diagnosing and theranosing differ logically; to offer a logic of the diagnostic process and of the theranostic process. By logic, I mean *logic of science* (e.g., (Popper, 2005)), a concept well known in the philosophy of science that I suggest can help understand the distinction between the medical acts of diagnosing and theranosing. My claim (figure 1) is that, from a logical point of view, the diagnostic process is not an explanation of the observed symptoms. It is a demonstration through which the clinician corroborates a cause by falsifying alternative causes in a differential diagnosis (§2).

In turn, the theranostic process enables the clinician to explain, in a logical sense, observed signs and symptoms by subsuming them under an explanans. This distinction discloses an important aspect of the logic of the theranostic, which is that it *turns on its head* the logic of medical diagnosis. Whereas the logic of the medical diagnosis involves reasoning from effect to cause to demonstrate a diagnosis, the logic of the theranostic process involves reasoning from cause to effect to explain the effect, using the biomarker as the basis of a ‘nomological’ statement – see section §3 for details. Effectively, the logic of the theranostic changes the *rational direction* (Feinstein, 1973b) of diagnostic reasoning.

Interestingly, the above distinction tells us something important about the inner workings of clinical reasoning as sometimes depicted using dual-process theory. Whereas the diagnostic process often requires slow, analytic, and counterfactual cognition akin to a careful process of demonstration (i.e., system 2 thinking), the theranostic process asks the clinician to rely mostly on fast system 1 thinking to generate robust explanations. I will argue that understanding the logical distinction between the diagnostic process and the theranostic process, along with the distinction between these two regimes in matters of clinical reasoning is relevant for understanding the kind of diagnostic errors to which each process is liable (§4).

Clarification on the scope of this paper

Projects on the logic of science have not traditionally been engaged in the description of psychological processes, but rather in the description of fictional ‘rational reconstructions’ (Reichenbach, 2006/1938). In stating the task of philosophy of science (or epistemology), Reichenbach explained that

“...[e]pistemology does not regard the processes of thinking in their actual occurrence; this task is entirely left to psychology. What epistemology intends is to construct thinking processes in a way in which they ought to occur if they are to be ranged in a consistent system” (Reichenbach, 2006/1938, p. 5).

This is the basis of the distinction in the philosophy of science between the study of the *context of justification* and the study of the *context of discovery* of scientific knowledge; the study of the context of justification concerning the rational reconstructions of science and the study of the context of discovery concerning the way scientists’ psychology influences the production of knowledge. Of course, there are significant overlaps between the two, especially in a discipline like — the philosophy of — medicine. This is evident from works on the logic of medical diagnosis (e.g., Croskerry, 2009) combining psychological considerations (e.g., appeal to intuition of the medical professional) with logical ones to support claims on the working of logical steps (e.g., Stanley, 2019). Despite this, one can broadly split research on diagnostic reasoning into two orientations that reflect the context of justification and the context of discovery: (1) research on the formal structure of diagnostic reasoning aimed at implementation using computational methods (e.g., Ledley & Lusted, 1959), with implication for how the process of medical diagnosis can be implemented in artificial intelligence systems — for a recent discussion see (Pietarinen & Stanley, 2025) — and (2) research on the psychology of diagnostic reasoning relevant for issues related to diagnostic errors.

Because my argument leans on basic moves belonging to the domain of rational reconstruction while aiming at contributing to the reflection on the psychology of the medical diagnostic and theranostic processes, it should be viewed as a hybrid between these two broad orientations. My goal is to make distinctions where there may be lacking given the little engagement that philosophers of science have had with the issue of theranosis in precision medicine, and to see how well these distinctions align with the reality of medical reasoning *ranged in a consistent system*, and whether doing this could help us in framing the psychological source of theranostic errors.

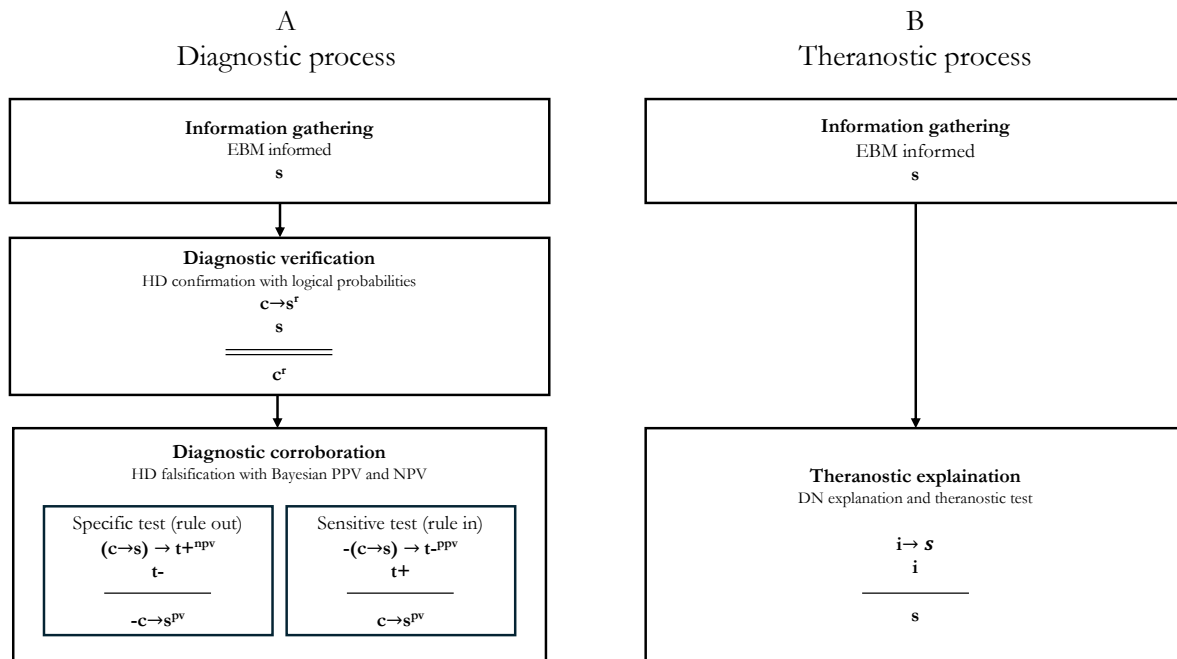


Fig. 1. A. Flowchart of the logic of the diagnostic process. An evidence-based (evidence-based medicine, EBM) information gathering step is applied to detect relevant symptoms (s). Diagnostic verification is used to induce possible causes (c) of s with a level of probabilistic support (r) using a hypothetico-deductive (HD) model of confirmation. The causes forming a differential diagnosis are eliminated or pruned using a HD model of falsification and results of Bayesian diagnostic testing (t) -- t^+ positive, t^- negative – of the hypothesized causes, or diseases (d) -- d^+ present, d^- not present. Falsification based on specific tests allows ruling out c or d with a degree of support equivalent to the negative predictive value (npv), whereas falsification based on sensitive tests allows ruling in c or d with a degree of support equivalent to the positive predictive value (ppv). **B.** Flowchart of the logic of the theranostic process. An EBM information gathering step is applied to detect relevant symptoms (s). This step is

immediately followed by a step of diagnostic testing whereby, upon the detection of a theranostic biomarker, the individual is classified as having the diseases, thereby explaining s as a consequence of initial conditions (i).

2 DIAGNOSTIC LOGIC

In its 2015 report, The Committee on Diagnostic Error in Health Care of the US National Academies of Science presented the diagnostic process that can be summarized in 6 phases (The National Academies of Sciences Engineering, and Medicine et al., 2015). After experiencing a health problem (phase 1) , a patient may engage the health care system (phase 2), triggering an iterative process in three steps (phase 3):

(step 3.1) an information-gathering step centered on the clinical interview, the review of the patient's file (e.g., patient's history), and a physical exam (if relevant);

(step 3.2) an integration and interpretation step centered on diagnostic testing;

(step 3.3) a working diagnosis step, which may be a differential diagnosis or a single diagnosis, or referring the patient to another clinician (e.g., a specialist).

Steps 3.1 to 3.3 iterate until the clinician achieves enough certainty to communicate the working diagnosis to the patient (phase 4) and to suggest a treatment plan if applicable (phase 5), which may itself provide additional diagnostic information (e.g., if the treatment triggers a new health problem). Based on the treatment outcome, the clinician can then assess the diagnosis and identify diagnostic errors that may explain negative outcomes (phase 6).

Studies on diagnostic logic in the medical literature detail these six phases, with a focus on phase 3. For instance, Stanley (Stanley, 2019) breaks down the diagnostic process in three

steps: (1) “[h]ypothesis-generation, based predominantly on sensory input [...]: patient-history, physical examination, testing” (Stanley, 2019, pp. 437–438); (2) “[h]ypothesis-selection judged by probabilities/prevalence for the population incidence of disease”(Stanley, 2019, p. 438); (3) “[t]esting hypotheses by judicious use of test-results and clinical observation”(Stanley, 2019, p. 438). Stanley’s approach reflects a standard in the literature on the logic of diagnostic reasoning: the seminal paper by Robert Ledley and Lee Lusted titled *Reasoning Foundations of Medical Diagnosis* (Ledley & Lusted, 1959). The paper advances 3 foundations of medical diagnosis. The first foundation is what the authors call the logical concept. The second is the probabilistic concept, and the third is the value concept. The first concept of Ledley and Lee Lusted describes the way a diagnostician combines medical knowledge with symptom presentation to arrive at possible diagnoses and is formalised using propositional logic. The second concept describes how the diagnostician reduces their uncertainty with respect to possible diagnoses and is formalised using Bayesian probabilities. The third describes how the diagnostician makes decisions as to the appropriate intervention given social, ethical, and economic constraints and is formalised using game theory. Thus, each of the concepts describes a step in a medical diagnostic procedure that can be viewed as mapping onto one of the steps described by the Committee on Diagnostic Error in Health Care’s. The logical and probabilistic concepts map onto steps 3.2 and 3.3 of phase 3, and the value concept maps on phase 5.

Diagnosing being an irreducibly uncertain process, each of the steps presented by the Committee on Diagnostic Error, Stanley, or Ledley and Lusted can be presented as strategies to reduce various sources of uncertainty in diagnostic decision making; uncertainty in the identification of the applicable diagnosis based on evidence; uncertainty in the application of a diagnosis to a specific patient given information such as false positive and negative rates; and uncertainty in the relevance of the diagnostic act given constraints in resources utilization (cf. Bhise et al., 2018). Arguably, these uncertainties all trace back to the fact that the *rational direction* of travel of the diagnostic process is from observation to cause; tracing back to the fundamental Humean problem of induction.

In this section, I will describe how the logical and probabilistic concepts feed from the information-gathering step understood as a moment of evidence gathering (e.g., clinical interview), whereby the clinician obtains medically relevant information; how they connect to the integration and interpretation step whereby the clinician constitutes a *refined working diagnosis*; and how they are reflected in the working diagnosis step, whereby the clinician prunes down a differential diagnosis using the results of a diagnostic test. The different logical strategies that we will discuss next can all be viewed as strategies to minimize the impact of the fundamental problem of irreducible uncertainty at the core of diagnostic decision making.

Information gathering

The information gathering step starts with the interview, as the clinician inquires about the patient's history. Sometimes, direct observations from the patient assessment, accompanied by standard pattern recognition based on an implicitly or explicitly considered category of a diagnostic classification manual may be sufficient to arrive at the working diagnosis (e.g., a dermatological condition). In such cases of "direct" diagnosis, a diagnostic test is not required, as the cause of the observation does not need to be inferred. As Alvan Feinstein observed (Feinstein, 1973a), signs and symptoms often come to the clinician's attention not as pure data but already as medically qualified facts, and sometimes already as diagnoses. In cases where pattern recognition is not sufficient to reach a working diagnosis, the clinician will have to engage in a process of probabilistic and logical inference to produce an *indirect* diagnosis. This will involve a particular way of sampling information, signs, and symptoms amenable to establishing a differential that will then be verified and corroborated, as I will discuss next.

For a mere fact to enter the domain of medicine, there must be evidence that the fact has clinical utility, such as diagnostic utility. If the cause is not directly observable, the medically relevant fact will be the fact that suggests a cause for which there exists a reliable test. A stabbing sensation in the chest is medically relevant because it may indicate a condition

involving the swelling of the lining of the lungs that can be tested for with blood tests or scans. In more generic terms, if a patient presents with symptoms $s1$ and $s2$, which are respectively related to conditions $c1$ and $c2$, and if there exists high-quality evidence for the sensitivity and specificity of tests for $c1$ — we will return to these notions later — but only very poor evidence for the sensitivity and specificity of tests for $c2$, then the clinician may pay more attention to $s1$ than to $s2$.

Evidence frameworks further tune the clinician's attention towards signs and symptoms that may have diagnostic utility. The hierarchy of evidence in evidence-based medicine (EBM) (Evidence-Based Medicine Working Group, 1992) is a common evidence framework, used to rank the evidence available to support clinicians' medical acts. The consensus in matters of diagnosis is that evidence for diagnostic tests from randomized controlled trials (RCTs) and meta-analyses should be ranked higher than evidence from observational and case-series studies, which are ranked above expert judgment or clinical expertise studies — although this may vary depending on the jurisdiction of application and the quality of the research (e.g., a poorly designed RCT may be at the same level as a cohort study, (Burns et al., 2011)). There exists a literature on the logic of EBM wherein a common view is that the process of arriving at an empirical conclusion follows a falsificationist logic (Djulfegovic et al., 2009; Senn, 1991). The logic of EBM is a logic of medical research, which would be relevant for a more general project on the logic of medicine as a whole. Here however I want to focus on diagnostic logic, in the context of clinical reasoning.

Diagnostic verification and the logical concept

I argue that the logical concept relates to the process of refinement of a differential called *diagnostic verification* (Kassirer, 2010), which involves verifying whether the causes listed in a differential match the patient's signs, symptoms, and situation (e.g., risk factors). Diagnostic verification happens prior to diagnostic testing, as it enables the clinician to ensure that only the most useful tests are commissioned relative to their risk level and cost. I distinguish the phase of diagnostic verification from what I call *diagnostic corroboration*,

which relates to the probabilistic concept of Ledley and Lusted. The differential diagnosis includes the most probable testable causes of observed signs and symptoms. Building the list of these causes corresponds to verifying the differential, which means ensuring that the listed causes are worth testing for. Here, I argue that the verification of the differential diagnosis takes the form of a hypothetico-deductive (HD) confirmation based on logical probabilities. The HD model is a common model in the philosophy of science used to account for the logic of scientific demonstration by way of confirmation or falsification. The HD model defines logical relations between a hypothesis H and evidence E , in a way that allows deducing or inducing H from E . The HD model matches the underlying idea of the formalism used to describe the logical concept according to Ledley and Lusted, when one treats the observed symptoms as E and the disease of cause as H .

According to Ledley and Lusted, the first source of information considered under the logical concept is the nosological knowledge E of the relation between symptoms S and causes C . The second source of knowledge is the patient presentation, which relates the patient to S . The logical montage described by Ledley and Lusted takes the form, implicitly, of an HD confirmation, where the hypothesis H is implemented as the nosological knowledge E that maps S and C ($E[s(1), \dots, s(n), c(1), \dots, c(n)]$), where the evidence E is implemented as the presentation G ($G[s(1), \dots, s(n)]$), and where the conclusion of the HD confirmation is the diagnosis implemented as F ($F[c(1), \dots, c(n)]$). Assuming that the statements S , C and F are related using the logical operators of propositional logic, one can infer the diagnosis by computing the function F upon computing the function G as it relates to F ; hence according to Ledley and Lusted “... [t]he logical aspect of the medical diagnosis problem is to determine the disease F such that if medical knowledge E is known, then: if the patient presents symptoms G , he has diseases F ” (Ledley & Lusted, 1959, p. 11).

Put simply, the logical problem is to find the F that follows from E being true (i.e., known) and G being true (i.e., known). Considering the simplest scenario where E is $cI \rightarrow sI$, where $\rightarrow$ is a material implication, and assuming that G is sI , then, finding the condition or disease in F will involve inferring cI from observing the evidence or presentation sI . Of course, this

is not a valid deduction. This is a simple induction. And as we will see later this approach has fundamental limitations. However, it seems sufficient to describe what is going on when building a differential diagnosis at the stage of diagnostic verification, especially if we supplement it with a probabilistic interpretation.

The logical interpretation of probabilities (e.g., Carnap, 1950) derives from the classical interpretation of probabilities, where the probability of an outcome is the ratio of that outcome (i.e., favorable cases) to the number of possible outcomes of the same class (i.e., possible cases), provided we have no good reason to believe the outcomes are not equally probable (a.k.a., Laplace's principle of indifference). The logical interpretation of probabilities builds on the classical interpretation to provide a degree of support r for the confirmation of a hypothesis H based on evidence E . For instance, if 9 out of 10 patients with respiratory diseases present with rales, the probability of sampling at random a patient with respiratory diseases being accompanied with rales is 90%. According to the logical probability interpretation, this should bring support to the hypothesis that respiratory diseases cause rales to a degree r of 90%, such that:

$$\frac{H \rightarrow E^{r=90\%}}{E} = \frac{H^{r=90\%}}{H^{r=90\%}} \quad \text{eq1.}$$

In eq. 1, the conclusion that H is not deductively valid, but it is *partially entailed* or logically supported to a degree r of 90%. I suggest that diagnosticians arrive at the listed causes in the *differential diagnosis* in this way, by weighing and filtering in which hypotheses are best partially entailed by the observed evidence, or symptoms. This is of course not how diagnosticians arrive at the *working diagnosis*. It simply characterizes the way they build the list of possible causes that may be worth testing for.

The approach I present here is different from the diagnostic logic of abductive reasoning proposed by Stanley (Stanley, 2019; Stanley & Campos, 2013). According to Stanley and Campos, diagnostic verification rests on a process of Peircean habitual abduction whereby

the clinician, based on already known rules (e.g., a nosology), establishes possible explanations for the observed facts (e.g., signs and symptoms). The abduction works like this: Given that I observe the symptom S , and given that C causes S , it must be the case that C is the best explanation for the observed S ; hence, for instance

“... physician may observe that a patient has rales (crackling auscultatory sounds) [and reason] that if the patient had pulmonary congestion, then rales would be a predictable consequence [and finally conjecture] that the patient may have pulmonary congestion” (Stanley & Campos, 2013, p. 307).

The reader will notice that this is very close to the HD model of logical probabilities above. Both abduction and the simple induction that underwrites the HD model are ampliative (Douven, 2021), as their conclusions presuppose more than what is logically contained in their premises (e.g., the *surprising* aspect of the fact, or the uniformity of nature), and therefore have non-essential consequences. However, abduction presupposes the comparison of hypotheses. Induction does not. This is an important distinction in the context of medical diagnosis. In the example of pulmonary congestion, there is no need to appeal to alternative explanations to start building the differential. One can simply infer that the condition may apply if the signs that are known to correlate with the condition also apply. Additionally, because diagnostic verification involves listing the most probable causes of the observed symptoms and ranking them in order of relevance for testing, one must appeal to some form of quantitative assessment of the ranked hypotheses or diseases. Based on knowledge of physiology and the probabilities that the signs may be observed under the hypothesized condition, one knows that rales are a symptom of respiratory diseases and that respiratory diseases can cause rales with a certain degree of probability P , or partial entailment, such that *respiratory diseases* $C \rightarrow$ *rales* S with support r . Upon the observation of rales S , one concludes that a respiratory disease should be included in the differential. Whether abductive reasoning can be probabilistic remains an open debate.

That said, there may be more than one useful logic of diagnostic reasoning. A possibility is that both HD confirmation and abduction are used sequentially in diagnostic verification; the HD confirmation with logical probabilities being used as the process of hypothesis generation (i.e., establishing a list $C1, C2, \dots, Cn$ with probabilities $p(C1), p(C2), \dots, p(Cn)$ based on nosological knowledge and observed signs and symptoms, and abductive reasoning being applied to the list to further reason about the generated hypotheses (e.g., ‘If $C1$ were true, S would be a matter of course, but not so much if $C2$ were true’). The list of possible causes C here does not need to form a distribution since the probabilities are based on degrees of support r for the causes C taken independently. Rather, the list C captures the *naïve* list of causes that an experienced clinician would reduce to the final diagnostic space using more patient specific information, likely using abduction.

Diagnostic corroboration and the probabilistic concept

Stanley suggests that the second step of the diagnostic process, after abduction, which I suggested could be supplemented by a HD confirmation with logical probabilities, is the deduction of testable consequences (e.g., if it is a respiratory disease, I should hear peculiar chest sounds) that can be demonstrated (e.g., with detailed auscultation). Stanley describes this as the step of hypothesis selection, which ought to be followed by a step of hypothesis testing. Stanley provides several additional options for hypothesis selection (e.g., probabilistic assessment, inference to the best explanation, and pattern recognition), and provides an account of diagnostic testing as the basis of the hypothesis testing phase. Here I suggest interpreting these two steps – selection and testing -- as a single step of *diagnostic corroboration*: the process of seeking falsifiers for the causes listed in the verified differential diagnosis using Bayesian diagnostic testing (figure 2) and pruning down the differential using falsificationist logic.

One can find commonalities between diagnostic corroboration such as defined here and Ledley and Lusted’s work. For Ledley and Lusted, the probabilistic concept of medical diagnosis is used to tackle the *probabilistic problem* of diagnosis, which they define as the

problem of finding “... *which of the disease [...] given by the logical diagnosis function F is the patient most likely to have*” (Ledley & Lusted, 1959, p. 14). The probabilistic problem is the problem of finding the most likely diagnosis when considering patient specific information. Ledley and Lusted use Bayesian probabilities to show how knowledge of the patient and medical knowledge can be combined to find the probability of diseases. This is typically done within the context of diagnostic testing.

Running a diagnostic test allows the clinician to reduce their uncertainty over the differential diagnosis. At a high level, there are 3 notions of relevance to understand Bayes rule and diagnostic testing: (1) the pre-test probability or prior — the probability of the cause before testing for it — which is established based on the clinical assessment (e.g., does the patient’s history indicate that they belong to a high-risk group?), or based on the prevalence in the population of people having the disease being tested for; (2) the post-test probability, or posterior probability of the patient having the disease, that is, the probability after considering the test results at the light of the pre-test probabilities; (3) the test accuracy defined by the tests sensitivity and specificity and associated false positive and false negative rates (figure 2).

Diagnostic testing helps diagnosticians to reduce their uncertainty about the causes in the differential diagnosis. This however requires additional reasoning. One might think that a useful diagnostic test is an accurate test that will identify the presence of the disease when positive and will identify the absence of the disease when negative. But there are two problems with this. First, an accurate test alone, or even taken in combination with prevalence rates, might not be adequate to characterize the patient's situation. The diagnostic test should factor in as much patient-specific information as possible into the prior probabilities, as nothing guarantees that the patient will fall into the average of its prevalence class; hence the clinician should carefully conduct her interview and incorporate a variety of information coming from the patient’s history (Kennedy, 2021) in the information gathering phase. Second, even though this might sound counterintuitive, in and of themselves, positive results of highly sensitive tests — tests that get it right when the person has the disease — are not

so helpful, and the negative results that come from highly specific tests — tests that get it right when the person does not have the disease — are equally not so helpful. Diagnostic testing alone cannot ground diagnostic decision-making, at least not through a logic of confirmation. It must be coupled with a falsificationist logic.

Consider this example by Johnson (Johnson, 2018). D-dimer tests have high sensitivity for deep venous thrombosis (DVT) (i.e., when d^+ , then returns t^+ 99% of the time) while having low specificity for DVT (i.e., when d^- , then returns t^- only 40% of the time) (Stein et al., 2004) — and something like a lung auscultation for respiratory diseases has 37% sensitivity and 89% specificity for common respiratory pathologies (Arts et al., 2020). Considering this, one might expect the positive and negative results of such tests respectively to provide useful information. But they aren't, at least no more than the next black raven is. As illustrated by Johnson, imagine the following situation. Following an interview with a patient presenting with shortness of breath, the clinician adds DVT to their differential, even though they conclude that the patient has low risk factors for DVT. The test is positive, and the post-test probability of the patient having the condition increases — albeit still somewhat low. But despite the low risk factors, the clinician gives credence to the test results, since they know that D-dimer tests have very good sensitivity. The clinician decides to order an angiogram, and the results are interpreted as showing an emboli. The patient is put on anticoagulants, and suffers an intracerebral bleed. The next crow was white. How could this happen?

Knowing the sensitivity of the test, the clinician should have suspected that a positive D-dimer would probably be a false positive in a patient with low risk factors. The lesson here is that a test with high sensitivity (high probability of t^+ when d^+) will not be useful if it is positive (especially in a low-risk patient). The positive test result t^+ is not the helpful result of the test since logically, the induction of d^+ from t^+ is fully uncertain. This is nothing more than a statistically sophisticated tale of what Hempel was already illustrating in his discussion of confirmation based on Semmelweis' struggles with finding the cause of puerperal fever (Hempel, 1966).

The helpful result is the negative test result when dealing with a highly sensitive test, and a positive test result when dealing with a highly specific test. High sensitivity provides a good basis for postulating the relation of implication between d^+ and t^+ ($d^+ \rightarrow t^+$), thereby allowing for a good falsification (d^-) to rule out a cause in the differential. Similarly, the value of a high specificity test ($d^- \rightarrow t^-$) comes from its positive results (t^+), which can falsify the assumption of the test, which is that $d^- \rightarrow t^-$ and thereby allow to rule in the cause. In the context of medicine, this allows one to prune down the differential diagnosis. Some have argued that the logic of ruling out diseases in a differential diagnosis was that of the disjunct syllogism, whereby one can deduce the truth of one of the disjuncts by negating the other (e.g., A or B, not A, therefore B) (Federspil & Vettor, 2001). However, this would suggest that the real cause is always contained in the differential, which in practice, is not always the case (Price & Vlahcevic, 1971). Rather, the pruned down differential should be viewed as a corroborated set of causes or hypotheses awaiting to be rejected. Positive and negative predictive values can be calculated to increase certainty about the falsification; the positive predictive value establishing the likelihood that a positive test t^+ detects the presence of the disease d^+ based on prior patient information, and the negative predictive value establishing the likelihood that a negative test t^- detects the absence of a disease d^- , also based on prior information.

In sum, diagnostic corroboration – the second step in diagnostic logic as I present it here – involves pruning down the differential diagnosis built during the step of diagnostic verification by looking for falsifiers; the falsifier when dealing with a sensitive test postulating that $t^+ \rightarrow d^+$ being t^- , and the falsifier when dealing with a test postulating that $t^- \rightarrow d^-$ being d^+ . In the former case, the reasoning is that *if the patient had the disease, their test should have returned positive; it returned negative with a probability equal to the negative predictive value, therefore they may rule out the disease with support equivalent to the negative predictive value*. In the latter case, the reasoning is that *if the patient did not have the disease, their test should have returned negative; it returned positive with a probability equal to the positive predictive value, therefore we may consider ruling in the disease, with support equivalent to the positive predictive value*. Here, one can imagine that

the predictive value has a function analogous to the degree of support r under the HD model of confirmation with logical probabilities.

A Pre-test probabilities $P(D)$		B Test accuracy $P(T D)$		C Post-test probabilities $P(D T) = [P(D)P(T D)]/P(T)$	
d+	d-	d+	d-	d+	d-
p	1-p	Sensitivity	False positive	PPV	$t+ d-$
		False negative	Specificity	$t- d+$	NPV

Fig. 2. Pre-test, test, and post-test probabilities in diagnostic testing. (1) The prior or pre-test probability $P(D)$, where $P(d+)$ is the proportion of people having the disease, and where $P(d-)$ is the proportion of people not having the disease. (2) The likelihood or accuracy matrix $P(T|D)$ of the test expressed as $P(T|D)$, where $P(t+ | d+)$ is the probability of a positive test in the presence of the disease (a.k.a. sensitivity, or true positives), where $P(t+ | d-)$ is the probability of a positive test in the absence of the disease (a.k.a. false positive rate), where $P(t- | d+)$ is the probability of a negative test in the presence of the disease (a.k.a. false negative rate), and where $P(t- | d-)$ is the probability of a negative test in the absence of the disease (a.k.a. specificity, or true negatives). (3) The posterior probability for a positive or negative test $P(D|T)$, where, $P(d+ | t+)$ is the probability that the positive tests ($t+$) predicts the presence of the disease ($d+$) after taking the prevalence into account, and where $P(d- | t-)$ is the probability that the negative tests ($t-$) predicts the absence of the disease ($d-$) after taking the prevalence into account.

3 THERANOSTIC LOGIC

In a 2019 critical review on the meaning of theranosis, Urban Wiesing (Wiesing, 2019) provided two different definitions of theranoses. The first is a broad definition that frames theranosis as a combination of the diagnostic and the therapeutic processes. Some present the theranostic process as a treatment strategy first, instead of as a diagnostic strategy with treatment implications (Pene et al., 2009). That said, even under that view, the theranostic

process remains a matter of merging the diagnostic and the therapeutic processes. The second is a narrow definition that frames theranosis as a diagnostic technology with therapeutic effects (e.g., tracking with a gamma camera the spread of thyroid cancer cells while treating the thyroid cancer with I-131 radiotherapy). Effectively, a theranostic technology implements the process of combining diagnostics and therapeutics. Thus, there is a close connection between the two definitions. Here I will focus on the logic involved in producing theranostic knowledge, that is, diagnostic knowledge with treatment implication using theranostic technologies, and argue against the claim that there is no fundamental logical distinction between the theranostic process and diagnostic process.

The strategy behind the theranostic process starts by the identification of disease-specific biomarkers constituting targetable mechanisms of disease. But not all biomarkers are theranostic biomarkers in that sense (for a taxonomy of the levels of biomarkers, see (Constant, 2024, 2025; Tabb & Lemoine, 2021). The American Food and Drug Administration (FDA) defined biomarkers as:

“[a] defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions [and] is not a measure of how an individual feels, functions, or survives” (FDA-NIH Biomarker Working Group, 2025, p. 47).

The FDA identifies several clinical utilities for biomarkers – e.g., susceptibility/risk biomarker, diagnostic biomarker, monitoring biomarker, prognostic/predictive biomarker, and response biomarker. They explain that:

“[d]iagnostic biomarkers are used for the critical determination of whether a patient has a particular medical condition for which treatment may be indicated [and that] various genetic markers, for example, can predict the likelihood of breast cancer recurrence after surgical tumor removal, i.e., they are prognostic biomarkers [and

that] pathophysiologic markers, such as decreased or preserved ejection fraction in heart failure, can predict who will respond to specific treatments; i.e., it is a predictive biomarker” (FDA-NIH Biomarker Working Group, 2025, p. 5).

In short, a biomarker is a biological variation that allows clinicians and researchers to carry their work, which involves acts such as identifying the presence of a disease (diagnosis), predicting the course of a disease with and without treatment (prediction/prognosis), intervening on the disease (therapy), and classifying diseases (nosology).

The FDA further explains that some “*diagnostic biomarkers [...] identify disease subtypes [and] thus often play critical roles when the results of diagnostic classification can be used as prognostic biomarkers and predictive biomarkers*” (FDA-NIH Biomarker Working Group, 2025, p. 5). Such biomarkers cumulating diagnostic, therapeutic, prognostic/predictive, and to some extent nosological utility are the kind of biomarkers that form the basis of the theranostic strategy. They constitute treatment targets that provide more fine-grained classification of subpopulations, or *strata*, and carry actionable therapeutic information (Weber et al., 2023). For instance, *HER2 breast cancer* refers to the breast cancer characterized by the amplification of HER2/neu genes (i.e., too many copies) making HER2 protein receptors that control cell growth, leading to HER2 protein overexpression and subsequent uncontrollable growth. HER2 breast cancer has associated targeted treatment, trastuzumab, which binds to tumor cells to reduce cell signaling, which leads to cell-cycle arrest and apoptosis in HER2 overexpressing cells (Baselga et al., 2001).

According to Weising (Wiesing, 2019), the theranostic process would be nothing more than a diagnostic strategy that any good practitioner should adopt. It is nothing above and beyond the careful selection of the treatment that should correspond to the patient’s situation. For Weising, the term theranosis in its broad definition simply summarizes what has always been the goal of medicine, the term “epitomizing” the inseparability of diagnosis and therapy (Baum & Kulkarni, 2012). The only difference between the diagnostic process and the theranostic process would be the level of description sought after (e.g., symptoms level vs.

biomarker level). I think that this is wrong. It is true that in practice, the goal of a diagnosis is to account for the patient's condition to reach an effective treatment plan, with the gold standard for diagnoses being a causal explanation (Maung, 2017).

However, as I will show in the next subsection, when looking at the logic of the theranostic process, there is something quite distinctive, namely, the fact that it turns the diagnostic logic of corroboration on its head, into a logic of explanation. As Feinstein (Feinstein, 1973b) stressed it, the 'rational direction' of diagnostic reasoning is opposite to that of pathogenetic reasoning, which goes from cause to effect, and not from effect to cause. Logically, reasoning from cause to effect means positing the antecedent cause to explain the effect, instead of trying to induce the cause from the observed effect. Theranostic reasoning is pathogenic reasoning based on biomarkers. Diagnostic reasoning is not. Diagnostic reasoning involves moving from an observed effect to a demonstrated hypothesised cause. I propose that contrary to diagnostic reasoning, theranostic reasoning involves 'explaining' the observed effect as a logical consequence of the detection of a pathological mechanism: the theranostic biomarker.

Theranoses as explanations

The theranostic process flips the diagnostic process on its head, shifting from pruning a differential using diagnostic corroboration to zeroing in on the cause of the symptoms through an explanatory inference (cf. Hey & Kesselheim, 2016), much in the sense intended by Hempel and Oppenheim's deductive-nomological model (DN) (Hempel & Oppenheim, 1948). The DN model, much like the HD model, is a montage of propositions describing their logical relation, and based on which one performs a logical inference. It involves deriving an explanandum (i.e., the proposition to explain) from an explanans (i.e., the propositions that explain). The logical montage of the DN model of theranoses is as follows: The explanandum is the symptom *S* (e.g., headaches, nausea, and facial numbness in cases where HER2 breast cancer has spread to the brain), and the explanans is a combination of the identification of the mechanistic biomarker (e.g., HER2 overexpression) through theranostic testing

functioning as an initial condition I coupled with a mechanism M (e.g., HER2/neu gene amplification leads to HER2 protein overexpression, which leads to the spread of cancer cells) that predicts that the symptoms S will occur under I , thereby functioning as a nomological statement. A theranostic DN model could be:

Explanans

eq.2

M predicts that $I \rightarrow S$

The theranostic test identifies I

Explanandum

Therefore S

I see three possible issues with the logic that eq.2 seeks to capture. First, one might argue that what is at stake here is what Hempel calls an *inductive statistical* (IS) explanation and not a DN explanation. Second, clarification might be needed on why the first premise should be considered a nomological statement. Third, one might wonder why I am discussing DN explanations at all in 21st-century philosophy of medicine, as the DN model is largely considered outdated, and philosophy has since moved on to more compelling models of explanations.

First, under the IS model, the explanandum must be reasonably expected (Hempel 1970), whereas under the DN model, one considers the explanandum to occur definitely. I won't firmly claim which, between the DN or IS model, best describes the logic of theranosis, as this entirely depends on whether we consider that biomedical approaches in medicine establish law-like relations or only strong correlations. Those who advocate for theranostic biomarkers likely view them as working like law-like relations, hence my appeal to the DN view to account for the logic of the activity that they are engaged in. Theranostic biomarkers seek, by definition, to be more than mere statistical correlations — biomarkers associated with a positive treatment response based solely on correlation studies are called *statistical* biomarkers and are unsatisfactory for theranoses (Tabb & Lemoine, 2021). The theranostic process isn't designed to be about John Jones situations. Here, the implication relation in the explanan is not between a disease (e.g., John Jones suffering from a *Streptococcus* infection)

and a therapy (e.g., penicillin), allowing us to explain through confirmation why John is getting better. The move is about affirming the antecedent of an implication relation between conditions established via theranostic testing (e.g., HER2 overexpression) and symptoms that mechanistically occur under tested conditions given our knowledge of the disease's pathophysiology.

Second, the type of statement derived from a mechanistic biomarker closely resembles a nomological statement. A nomological statement, for the purpose of the DN model, is a universal, empirically grounded statement that can be presented as a law if proven true. It is of the conditional form *if X then Y* (e.g., if HER2/neu amplification, then spread of cancer cells). It isn't a specific statement *X is Y* or a generalized statement such as *all Xs are Y* (e.g., all cases of HER2/neu amplification have led to the spread of cancer cells), or a statement limited by contingencies, such as *all X given C are Y* (e.g., all cancers with HER2/neu amplification spread). Nomological statements must have explanatory power, allowed by the 'if then' structure, and not by the generalized character of the statement, and therefore remain true in counterfactual scenarios. In other words, there must be something about X that makes it such that Y is the case, beyond the mere fact that all instances of X have been Y — all this may be better expressed as *for every x, if x is a_phi then x is a_psy*. A biomarker is a mechanism that predicts symptoms, and this prediction stems from a mechanistic explanation of why that is the case. The truthfulness of HER2/neu gene amplification ultimately leading to uncontrollable cell growth and the spread of breast cancer and associated symptoms isn't true because it's the case in all stage IV HER2 breast cancer instances. There can always be cases of remission. Rather, that statement is true due to the underlying mechanism of gene amplification, overexpression, and the travel of cancer cells through the bloodstream and lymphatic system. So why not simply opting for a mechanistic model of explanation?

While defending against the second issue, I go beyond what is strictly required from the DN model by appealing to mechanisms and implicitly to a notion of the direction of causality -- fatally missing in the DN model. And so, it might appear as if I'm abandoning the DN model altogether and solely focusing on more recent accounts of causal theories of explanation,

which might seem more reasonable. But I am not. My aim here is to describe the *logic* of the theranostic process. I am not trying to find the best description of how theranostic technologies work. I am after a description of the logic of using them. As a technology, a theranosis may indeed be better framed as a causal explanation, providing the causal history for the explanandum (e.g., the sequence of encounters between causal processes modifying each other's structures as per a causal-mechanical model (Salmon, 1984) of HER2/neu gene amplification). But such a description doesn't need to appeal to something like theranostic testing (although it can refer to it), which, in turn, is a key component of theranostic as a process carried out by clinicians.

4 DIAGNOSTIC AND THERANOSTIC REASONING

In medicine, clinical reasoning is not always presented in logical terms as understood in the philosophy of science. It tends to be framed in psychological terms or as a mix of both (for a review see (Croskerry, 2009)), with an emphasis on psychological considerations (e.g., ethical, social, and economic considerations). One popular mixed approach to diagnostic reasoning is the dual process theory of decision making, based on the distinction between system 1 and system 2 processes (Kahneman, 2011; Sloman, 1996). The dual-process theory applied to the diagnostic process delineates the information gathering and interpretation phases into system 1 and system 2 processes (The National Academies of Sciences Engineering, and Medicine et al., 2015). According to this perspective, information gathering involves sampling and comparing data with existing knowledge through system 1 pattern matching. System 1, being stimulus-driven, excels in predictable environments (e.g., consulting a diagnostic manual for a prototypical patient), relying on pattern recognition of well-learned associations (e.g., automatically associating *pleuritic pain* to hearing *stabbing sensation in the chest*). However, system 1 may prove insufficient for reaching a diagnosis in cases of uncertainty regarding symptom causation; for instance, when pattern matching yields associations with different diseases, prompting the clinician to formulate a differential diagnosis, or when the clinician lacks experience or knowledge in the problem domain (Evans & Stanovich, 2013). In such scenarios syllogistic reasoning is engaged under system

2 (The National Academies of Sciences Engineering, and Medicine et al., 2015). System 2, driven by deliberate reasoning, necessitates the construction of a mental model to anticipate outcomes under various circumstances, such as performing a lung auscultation to rule out respiratory diseases. This mental model -- or the logic of its operation -- is essentially what we discussed in section 2.

System 1 and system 2 in theranostic reasoning

The logical interpretation of the dual-process theory of diagnostic reasoning would posit that HD confirmation and logical probabilities are employed to construct the differential under system 1, while HD falsification and Bayesian diagnostic testing are used to refine the differential through system 2 counterfactual thinking. But how are system 1 and system 2 thinking utilized in the theranostic process? And is there a difference in their application compared to the diagnostic process? The distinction lies in the minimal, if any, involvement of system 2 thinking in the theranostic process. Effective diagnostic thinking aims to match symptoms with their corresponding causes to formulate potential treatment plans. The focus here is on achieving a symptom-cause match, with the diagnosis being a precursor to devising treatment plans. Conversely, in theranostics, the objective is to match the *right patient* with the *right treatment* at the *right time*. The unit of interest shifts to a biomarker-treatment match rather than a symptom-cause match. While theranostics presupposes the correct treatment, it does not presuppose the identification of the right patient. Therefore, the challenge lies not in identifying the cause for treatment but in ensuring that the patient with the treatable cause is identified.

This shift reduces the reliance on system 2 thinking, emphasizing instead the importance of optimizing resources in the medical system to ensure accurate diagnostic testing and appropriate treatment allocation. While this approach offers advantages such as reducing -- certain kinds of -- diagnostic errors and facilitating rapid decision-making in high-certainty environments, it also carries a significant drawback of depersonalizing the treatment process, potentially compromising patient-centered care, particularly in specialties like psychiatry

where biomarkers may be challenging to obtain and not great at characterizing the disease process (Gómez-Carrillo et al., 2018, 2023).

Diagnostic errors in the diagnostic and the theranostic processes

Broadly speaking, a medical error refers to “... *an event that results in unintended harm to the patient by an act of commission or omission rather than by the underlying disease or condition of the patient*” (Patient Safety, 2004, p. 201). Medical errors typically arise from a failure of execution, when a planned action is not carried out as intended, a planning failure, when the wrong plan is formulated, or a failure by omission, when an action that did not require planning but that nonetheless had to be performed is overlooked (The National Academies of Sciences Engineering, and Medicine et al., 2015). Specifically, the failure within the diagnostic process will result in an incorrect diagnosis, a missed diagnosis, or a delayed diagnosis (Schiff et al., 2009) that will be the source of the harm. Failures within the diagnostic process can also manifest as *near misses* (e.g., a radiologist overlooking a significant finding on a chest X-ray, later identified by the attending clinician during image review) (Newman-Toker, 2014). Errors in the diagnostic process leading to unintended harm are deemed *no-fault errors* when caused by factors beyond the clinician's control (e.g., an atypical disease presentation or misleading patient-provided information) (The National Academies of Sciences Engineering, and Medicine et al., 2015). Those resulting in patient harm are classified as *system-related errors* when stemming from medical team miscommunication, care coordination issues, organizational inefficiencies, or technical equipment failures (The National Academies of Sciences Engineering, and Medicine et al., 2015), and as *cognitive errors* when arising from the clinician's inadequate knowledge or poor critical thinking skills (e.g., difficulties in data gathering and interpretation) (Kassirer & Kopelman, 1989).

The diagnostic process heavily relies on system 2 thinking, rendering it particularly susceptible to cognitive errors (e.g., treating DVT diagnostic test results as confirmations in low-risk patients); hence the attention paid to preventing diagnostic errors by making

clinicians' aware of the logical and probabilistic foundations of diagnosis (e.g., discerning when to employ confirmation and when not to). The theranostic process, in turn, mitigates the risk of cognitive errors by reducing the demand for system 2 thinking. However, it is vulnerable to system-related errors due to its heavy reliance on identifying the correct patient-marker match through theranostic testing and screening. If we agree that the theranostic process involves minimal system 2 thinking, it follows that errors in this process are more likely to stem from system-related failures than cognitive ones. Such failures may pertain to the patient and institutional costs associated with screening, which may not always align with patient well-being (e.g., unintended harm such as distress and unnecessary interventions like biopsies in breast cancer screening with high false positive and false negative rates) (Bond et al., 2013; Nelson et al., 2016). Ensuring a correct understanding of the logic of the diagnostic and theranostic processes may help in mitigating and preventing errors by elucidating these processes' vulnerabilities to the various sources of diagnostic errors.

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