DIAGNOSIS FROM A CLINICIAN’S POINT OF VIEW

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Diagnosis is an interpretation of a patient’s illness sufficient for medical decisions and treatment targeting. Therefore, depending on the severity of the disease and the treatment needed, the diagnosis can be less or more precise (e.g., of common cold, or of an hematological cancer). Reaching a diagnosis involves a *first stage* of gathering clinical information about the patient and generating one or more diagnostic hypotheses, and a *second stage*, in which the best founded hypotheses surviving the first stage are verified by laboratory tests, imaging or other investigations. This presentation is aimed at reviewing frequent error sources and teaching diagnostic reasoning. It is splitted into the following 4 sections.

1. First stage: from information about a patient to the diagnosis or diagnostic hypothesis/es;
2. Second stage: updating the initial diagnosis or hypothesis/es;
3. Diagnostic errors;
4. Evidence-based diagnosis (EBD);
5. Learning diagnostic competence.

1. **First stage: from information about a patient to the diagnosis or diagnostic hypothesis/es**

   The process of diagnosis starts with gathering clinical information about a patient, and connecting this information with the physician’s memorized clinical knowledge. The connection activates a mental process that may result in a diagnosis or one or more diagnostic hypotheses. In routine cases, expert physicians tend to use *forward inductive reasoning*, i.e., they use short-cut mechanisms (*heuristics*) to go from the data gathered to the rapid *categorization* of the patient’s case into a nosographic class. In more difficult cases, they use a *backward, hypotetico-deductive reasoning*, i.e., they generate one or more hypotheses specifying which findings should
be present (and which absent) if the patient had a given disease, and go ahead to search for them (1-3). However, this is an oversimplified account, because:

- **forward inductive reasoning** from the patient’s earliest findings is needed to start the diagnostic process, even when an **hypotetico-deductive reasoning** follows, and
- even in routine cases resolved by **forward reasoning**, the final diagnostic decision must be preceded by a fast, often semi-conscious **hypothetico-deductive** moment to discard the most implausible hypotheses.

The first stage of the diagnostic process can be split into the following 4 overlapping components.

a. gathering clinical data about the patient;
b. using the clinical data to reach a diagnosis, or generate one or more diagnostic hypotheses
c. *forward, inductive vs hypothetico-deductive reasoning.*

Each of these components deserves a short comment.

a. gathering clinical data about the patient

*“Much of the art of medicine lies in gathering this information”* (4). Symptoms and physical signs may be manifest and easy to notice, or they may be subtle and difficult to elicit or find out, or imperfectly known by the physician. Collecting a meaningful clinical evidence requires (5, 6):

- to know the existence and the clinical features of the diseases compatible with the patient’s clinical presentation;
- to know which clinical evidence to look for, and how to detect it;
- to be receptive of the verbal and non verbal communication from the patient, and to perceive any cues from his physical appearance;
- to generate early hypotheses and to use them to guide the interview and physical examination, but……
- … to escape the bias of preferentially seeing what’s in agreement with the hypothesis (7), and to be alert to cues of alternative disorders.

Gathering clinical evidence is a sequential process, in which the collection of data very early becomes selective: *“first, we look at the patient. We notice their age, sex, dress, expression, posture, tremor, gait. We hear their tone of voice in telling their story. We may even smell something—*
alcohol, cigarette smoke, body odour. We see, hear, feel, and smell the physical evidence. Second, we focus on particular features, especially those referred to in the history. We do not continue as detached observers. We select some components to attend to, and filter out or disregard others.” (5).

b. from the clinical data to diagnostic hypotheses, or diagnosis

Gathering clinical evidence is closely intertwined with the generation of hypotheses in a circular process of data → hypothesis → hypothesis-driven collection of new data, and so on. Diagnostic expertise needs ability in collecting clinical evidence, and the cognitive connection of this evidence with a rich and well organized medical knowledge and experience in a domain (8): clinical reasoning and medical knowledge are interdependent, and cannot be taught separately. The organization of knowledge in the long-term memory may be conceived (9) as a number of nodes representing bits of information, interconnected by links in an intricaded network (semantic network). The role of the amount and (even more) of the mental organization of knowledge in the diagnostic process is clearly illustrated by the two following citations: “Disease knowledge can be represented as a (sub)network of biomedical and clinical concepts, interconnected by links. Diagnosing a patient is equivalent to find a path in the network from signs, symptoms, complaints, and patient-background factors, to the node representing the diagnostic category-label” (9); and: “With experience, new concepts and concrete examples are added to the [sub]network, and new, stronger, richer connections are made between existing concepts and examples” (10). An expert in a domain with a large amount of knowledge and experience has a better diagnostic efficiency in that domain in comparison with a non-expert. However, the diagnostic efficiency in a domain is not automatically transferred to other domains, and the domain-limited knowledge of the specialists can represent a bias in diagnosing cases outside their specialty as being within that specialty (11). The mental sub-network activated by a clinical finding can be represented by a plot called mind (or concept) map, although in an oversimplified form (12). Constructing mind maps starting from one important clinical finding can be of use as an help to represent a diagnostic mental process (13).
c. forward, inductive vs hypothetico-deductive reasoning

“Imagine that 3 individuals encounter a 4-legged beast in the street. The first, Pat Wreck, says: it looks like Lassie. It’s a dog (14)”.

This statement is an example of pattern recognition. As the dog is immediately recognized in the street, there are diseases that can be instantly diagnosed on perceptual appearance (pattern recognition), such as Down syndrome, Parkinson’s disease, overt hyperthyroidism. Pattern recognition is fast, automatic, and very often accurate (15).

In other patients presenting with clinical features characteristic of a disease, eg “typical” anginal chest pain, or ascites, hard liver and splenomegaly, the expert physician uses forward reasoning and rapidly makes a diagnosis of coronary artery disease or cirrhosis. In such situations, they use mental short-cuts (heuristics) (16) from their experience and knowledge to the case at hand, and make a direct diagnosis (categorization): “For the expert, the solution of a problem within his or her domain of expertise is often straightforward or obvious…….More often than not, an expert is not solving problems but remembering solutions” (9).

The hypothetico-deductive reasoning takes place in more difficult cases, or when the doctor is unfamiliar with the patient’s pathology. It begins with the generation of one or more hypotheses of disease, that guide the search of selective information for confirmation or dismission (1): “The context [given by the hypotheses] helps formulate appropriate questions as the physician takes a history of the present illness, directs certain specific aspects of the physical examination, and identifies tests that might provide additional relevant clinical data” (3, pag. 9).

2. Second stage: updating the initial diagnosis or hypothesis/es

Reaching a diagnosis involves updating the initial hypothesis/es with an imperfect information (2), and interpreting the test results in agreement with the bayesian principles. This procedure needs to know the accuracy of tests, an information lacking or imperfect for new, evolving investigations; furthermore, picking up the true diagnosis among competing hypotheses needs a strategy for a differential diagnosis. Accordingly, this section is splitted into 3 components:
a. from pre- to post-test probability, using tests of well known accuracy;
b. new investigations
c. differential diagnosis

a. from pre- to post-test probability, using tests of well known accuracy

The measures of accuracy of many common tests (ie true-positive and false-positive, false-negative and true-negative rates) are generally known, and allow the application of the bayesian principles. The simplest and now recommended procedure is of connecting the test likelihood ratios (LR) with the pre-test probability in the Fagan’s nomogram to obtain the post-test probability of diagnosis (17, pag. 127-32 and 486-515) (LR of a positive test: the ratio between true-positive and false-positive rates; LR of a negative test: the ratio between false-negative and true-negative rates). Both the concepts of pre-test probability and of the LR and other measures of accuracy of the tests deserve a comment from a clinical point of view.

• The pre-test probability is the probability of a disease estimated from the clinical examination during the first stage of the diagnostic process. However, the estimate of the pre-test probability does not enter into the clinical reasoning in this stage, and becomes of interest in the second stage, to assess the effect of the tests in updating the diagnostic hypotheses. Not surprisingly, experimental studies show that the clinicians’ estimate of pre-test probability is poorly reproducible and inaccurate (18-21) In fact, the pre-test probability depends on two components that in most cases can only be roughly guessed, ie the disease prevalence in the patient population with a clinical presentation, and the similarity between the patient’s clinical features and those of a disease stored in the physician’s memory (22). An empirical but practical solution is giving semiquantitative estimates of the pre-test probability, categorized as low, intermediate and high as in several examples of the literature (23, 24), and analysing how different numerical estimates modify the post-test probability of disease.

• Common sense is needed to use LR or other measures of test accuracy in the practice with individual patients (25). Physicians must take into account that the true-positive rate is low in the initial stage and less severe forms of disease (spectrum bias, [26]), ie when the early diagnosis might allow a more effective treatment, and that in differential diagnosis the
false-positive rate is different across the competing diseases in differential diagnosis. With tests giving scalar results, the ROC curve is the appropriate statistical tool for identifying the best cut-offs along the test results (27); however, it is very rarely used in practice (28), and is of no help when different levels of the test results point towards different diagnoses (eg: ALT< 300 IU suggests chronic liver disease, > 500 IU acute hepatitis from any cause [29]). Eventually, an abnormal test result may be due to comorbidity and entirely unrelated with the present problem, particularly in the elderly (30).

b. new investigations

New investigations of increasing diagnostic importance are mostly in imaging (eg advanced computed tomography, magnetic resonance imaging and positron emission tomography) and in molecular biology. Some imaging investigations (eg MRI, PET) are now proposed as a first-line or single modality for whole-body tumor staging (31); the genomic medicine has revolutioned the taxonomy of several disease (eg, in hematological oncology [32]), and is needed for identifying and targeting the treatment of some tumors (e.g; gastrointestinal stromal tumors [33]. The assessment of these investigations is incomplete or lacking, and their application by clinicians is very often non-evidence-based.

c. differential diagnosis

Differential diagnosis is needed when more than one diagnostic hypotheses are compatible with a clinical presentation. After rejecton of the least plausible hypotheses, the leading hypothesis and each of the competing hypotheses are taken two at a time, and compared for their ability to explain the patient’s findings (34). The clinicians tend to compare first the more likely hypotheses, and those of diseases more serious if undetected or more responsive to a treatment (35). There are error sources in differential diagnosis, dealt with in the next section.

3. Diagnostic errors

Diagnostic errors involve the risk of inappropriate, delayed or omitted treatment. Errors in potentially fatal diseases are best detected by autopsy studies, that show a present median rate of 23% of unsuspected or wrong
clinical diagnoses, decreasing over time (36). Overall, the incidence of diagnostic errors is believed to be high (37), and can be due to a large number of biases or sources (37-40), among which the most frequent are reported in the following list.

- Inability in eliciting information from the interview, or perceiving physical abnormal findings;
- Failure to generate a diagnostic hypothesis. It can be due to a clerk-like passive annotation of findings in the interview or physical exam, to lacking knowledge, or to cognitive inability to connect the patient’s information with the knowledge in memory. This is the first source error among a list of the top-ten more frequent error sources alleged by physicians (38);
- Base-rate neglecting, ie the tendency to disregard the relative prevalence of two competing diseases with similar clinical presentation;
- Anchoring, conservatism, confirmation bias. The tendency to stick in the leading hypothesis and requiring redundant evidence for its confirmation, not searching or undervaluing data in favor of a competing diagnosis;
- Neglecting to consider how accurate are the tests (ie false-negative and false-positive rates), and what’s the pre-test probability;
- Failing to consider the severity and stage of the patient’s disease in the interpretation of false negative results of a test.

4. Evidence-based diagnosis (EBD)

Evidence-based Medicine (EBM) has prompted the physicians to search and appraise medical paper-based and online literature as an help for their practice. To appraise therapeutic studies EBM Working Group recommends systematic reviews and controlled randomised trials, identified since many years as the best designs to appraise a new treatment (41, 42), and mostly used in the published research. In contrast, the criteria recommended by EBM to appraise studies on diagnostic tests seem to be unfrequently used (in the 18.9% of the studies in top medical journals in a recent survey [43]), and the criteria recommended by EBM (44) to appraise descriptive clinical studies are vague and unclear. So, not surprisingly the guidebook by Sackett & al (the “bible” of EBM [45]) includes 50 pages on therapy and 28 pages on the appraisal of diagnostic tests, disregarding clinical studies; in the 2003
issues of ACP Journal Club there are 122 abstracts of therapeutic and 11 of
diagnostic studies (8 on tests). What’s most important, there are no sources
of diagnostic information of practical use similar to those of therapeutic
information, such as the Cochrane Database of Systematic Reviews (CDSR)
or Clinical Evidence, a pre-filtered, easy to consult compendium.

The relatively few EBM-related publications providing diagnostic
information applicable in practice (24, 46 and some articles in the series on

The Rational Clinical Examination in JAMA) may help for updating
hypotheses and in the differential diagnosis. However, they (and the Pubmed
Clinical Queries [47]) very rarely assist to answer questions such as “what
is the cause of the symptom X?”, and: What is the cause of the physical finding
X”? (48, 49), ie in the generation of diagnostic hypotheses. This is probably
because the interpretation of clinical findings not only requires to know
whether they are present or not, but also their severity, type of onset and
course, clustering, and other patient’s features, including comorbidity. In
summary, particularly with regard to the hypothesis generation, the statement
that evidence-based medicine follows when a correct diagnosis has been
made (50) may be shared.

5. Learning diagnostic competence

“To study the phenomenon of disease without books is to sail an
uncharted sea, while to study books without patients is not to go to
sea at all” W. Osler, as reported by Golden RL, JAMA 1999; 282:
2252-8

The diagnostic process can be stopped at the level sufficient for
decision making and targeting the treatment. Diagnostic competence has 5
components (51-54).

a. Skill in eliciting and perceiving clinical data from and about a patient;
b. Extensive and structured memorized disease knowledge;
c. Connecting the information about the patient with the memorized
knowledge to develop diagnostic hypotheses;
d. Knowledge of and compliance with methodological principles;
e. Feedback verification of the true diagnosis.
a. Skill in eliciting and perceiving clinical data from and about a patient

Acquiring this ability needs experience with real patients. For educational efficiency, experience must be extensive, to involve patients with different diseases, be independent and active, just supervised by a teacher. The teacher must be respected as a competent and knowledgeable clinician, and open to discussion and reflection.

b. Extensive and structured memorized disease knowledge

Clinical descriptions in textbooks and medical literature are organized by diseases (e.g., pneumonia, or cirrhosis), whereas in the real patients the physician starts from symptoms and signs to infer a diagnosis, and then goes from the disease to symptoms, signs and tests to verify the diagnosis. Therefore, the learner must memorize both the knowledge directions, i.e., from symptoms and signs à disease and from disease à symptoms and signs. An important help for the memorization and retrieval of the clinical knowledge is provided by its mental organization in semantic networks (9, 54), and possibly by the translation of the networks in concept maps (12, 13).

c. Connecting the information about the patient with the memorized knowledge to develop diagnostic hypotheses

This is a key recommendation, because the early generation of hypotheses is recognized as an essential component of the diagnostic ability (3). An efficient way for educating learners to the early generation of hypotheses is presenting a very little information about a patient (e.g., sex, age, reason for seeking medical help), and stimulating each of them to ask questions to get further information, explaining why the question was posed. The process goes on with the interpretation of the answers, disclosure of sequential chunks of data, further questions and interpretation, until reaching a diagnosis (53). The efficiency of the procedure is shown by the increasing attitude to the early and increasingly appropriate hypotheses generation along the duration of a teaching course.

d. Knowledge of and compliance with methodological principles

There are reasons to believe that the exact, numerical application of
methodological principles is exposed to frequent, serious fallacies and rarely used by physicians (28). However, knowledge of and compliance with these principles are essential in diagnostic reasoning (51). They cannot be taught in isolation, and should be taught, learned and applied as a referral framework of clinical knowledge and experience (8, 9).

e. Feedback verification of the true diagnosis

In order to learn from experience, the learner must know whether his/her clinical decision was correct or wrong. Therefore, the conclusion of each case presented must be disclosed to the learners, alongside with information about the contribution of the clinical findings and investigations to the diagnosis.

References
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