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Point of view

# Science of performing diagnostic tests

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ABSTRACT

Advances in diagnostic technologies have revolutionized the field of neurology. There is no doubt that such technologies in clinical practice can hold great promise to improve the diagnosis of movement disorders. However, our concern in the era of diagnostic tests is that clinicians become too dependent on the tests without proper consideration of the clinical context. No matter how excellent a diagnostic test itself is, it is a different matter in clinical practice whether the test enhances the diagnostic accuracy or provides added value beyond the information that is already available. In this article, we explain why clinical evaluation continues to have a central role in the diagnosis of diseases.

Advances in diagnostic technologies have revolutionized the field of neurology. The development of imaging techniques is changing our traditional way of practice based on clinical history and examination whether we like it or not. The discovery of autoantibodies is rapidly expanding the area of autoimmune neurology. Genomics have changed the way we make differential diagnoses of genetic and infectious diseases. There is no doubt that such technologies in clinical practice can hold great promise to improve the diagnosis of movement disorders. However, our concern in the era of diagnostic tests is that clinicians become too dependent on the tests without proper consideration of the clinical context. No matter how excellent a diagnostic test itself is, it is a different matter in clinical practice whether the test enhances the diagnostic accuracy or provides added value beyond the information that is already available. Herein, we will explain why clinical evaluation continues to have a central role in the diagnosis of diseases.

Bayesian reasoning, in which further information changes the probability of the presence of a condition, is used when clinicians consider the accuracy of diagnostic tests in clinical decisions [1]. It starts with the probability that a patient has a disease before a test (that is the pre-test probability) and can be combined with the sensitivity and specificity of the test to estimate the probability that the patient has the disease after the test (that is the post-test probability). Most studies on diagnostic tests describe how well they identify patients with a disease by presenting the post-test probability. However, the post-test probability can change according to the pre-test probability. Furthermore, the value of a diagnostic test is another issue. Its value cannot be simply measured by either the pre-test probability or the post-test probability.

Before discussing the accuracy and value of diagnostic tests in detail, it is important to briefly review the concepts of sensitivity, specificity, and predictive values (Table 1). Sensitivity α is the proportion of individuals with the disease who have a positive result ($A_1$/A), whereas specificity β is the proportion of individuals without the disease who have a negative result ($B_2$/B). The positive predictive value (PPV) and negative predictive value (NPV), which refer to the post-test probabilities, are defined as the proportion of individuals with a positive test result who have the disease ($A_1/(A_1+B_1)$ or $\alpha A/[\alpha A+(1-\beta)B]$) and the proportion of individuals with a negative test result who do not have the disease ($B_2/(A_2+B_2)$ or $\beta B/[(1-\alpha)A+\beta B]$), respectively. The predictive values are influenced by the prevalence in the population being tested, which equates to the pre-test probability in a clinical situation. If prevalence A/(A + B) is expressed as þ, the PPV and NPV are $\alpha þ/[\alpha þ+(1-\beta)(1-þ)]$ and $\beta(1-þ)/[(1-\alpha)þ+\beta(1-þ)]$, respectively. The derivation of these formulae is described in detail in the Supplement.

According to Bayesian reasoning, a positive test result is more informative when the pre-test probability is higher [2]. We will apply this concept to the clinical use of dopamine transporter (DAT) imaging in the diagnosis of Parkinson's disease (PD). DAT imaging enables *in vivo* detection of presynaptic striatal dopaminergic function. This test can be of great assistance in differentiating Parkinson's disease (PD) from essential tremor, dystonic tremor, and drug-induced parkinsonism [3]. A previous study showed that a DAT scan has a sensitivity of 97% and a specificity of 98% to differentiate between PD and non-PD [4]. Thus, the PPV of the DAT scan is $0.97þ/(0.95þ+0.02)$, which can be expressed graphically shown in Fig. 1A. Let us suppose that a 70-year-old man (Patient 1) visited our clinic due to a concern about PD because his brother was recently diagnosed with PD. He has only mild postural tremor in both hands. Additionally, he does not have non-motor symptoms such as hyposmia or REM sleep behavior disorder. If his DAT

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**Table 1**
The two-by-two table showing the population distribution by test and disease.

| | Disease (+) | Disease (−) |
|---|---|---|
| Test (+) | $A_1$ (True Positive) | $B_1$ (False Positive) |
| Test (−) | $A_2$ (False Negative) | $B_2$ (True Negative) |
| Total | **A** | **B** |

**Sensitivity α** = $A_1/A$, **Specificity β** = $B_2/B$, **Prevalence þ** = $A/(A + B)$.
**PPV** = $A_1/(A_1+B_1)$ or $\alpha A/[\alpha A+(1-\beta)B]$ or $\alpha þ/[\alpha þ+(1-\beta)(1-þ)]$.
**NPV** = $B_2/(A_2+B_2)$ or $\beta B/[(1-\alpha)A+\beta B]$ or $\beta(1-þ)/[(1-\alpha)þ+\beta(1-þ)]$.

scan is positive, does he have PD? He had no definite parkinsonian symptoms and signs, indicating that his pre-test probability is very low. Thus, even though the DAT scan has a high sensitivity and specificity, a positive test result does not mean that he has PD (Discussion on pre-clinical or prodromal PD is a different issue in this case.). In fact, a negative test result is more meaningful in such a low pre-test probability situation (Fig. 1A). In contrast, suppose that a 70-year-old man (Patient 2) visited our clinic due to a 6-month history of progressive aggravation of tremor. He had unilateral resting tremor, bradykinesia and rigidity. These symptoms were improved with levodopa. If the DAT scan is positive, the probability of true PD is high because the pre-test probability is very high (Fig. 1A). These examples clearly show that the accuracy of the test depends on the pre-test probability.

However, a higher post-test probability does not indicate a more valuable test result. We believe that the value of a diagnostic test lies in its ability to provide additional diagnostic certainty beyond that obtained from the clinical encounter. In this context, the value depends on how much the test result can increase the probability of a condition compared to the pre-test level. It is a valuable diagnostic test if the test result has a high post-test probability when the pre-test probability is low. The value of positivity in diagnostic tests, which is called the ΔPPV in this article, is (post-test probability – pre-test probability) which is equal to (PPV – disease prevalence). Thus, the ΔPPV can be expressed as $\{\alpha þ/[\alpha þ+(1-\beta)(1-þ)]\}-þ$. The ΔPPV of a DAT scan for a diagnosis of PD is expressed as $[0.95þ(1-þ)]/(0.95þ+0.02)$ (Fig. 1B). In the case of Patient 2, he has a very high PPV; however, the ΔPPV is low meaning that the DAT scan did not add much to the diagnostic certainty because the diagnosis was already almost certain on clinical grounds only. In this regard, we need to consider whether a patient really needs DAT imaging.

Here is another example regarding the ΔPPV. Progressive supranuclear palsy (PSP) is an atypical parkinsonian disorder characterized by tau pathology. There are studies reporting that tau imaging is useful for the differentiation of tauopathy from non-tauopathy such as PD [5,6]. One of the studies showed that tau imaging separated PSP patients from PD patients with a sensitivity and specificity of 84.8% and 92.3%, respectively [6]. Accordingly, the ΔPPV of tau imaging for a diagnosis of PSP can be expressed as $[0.771þ(1-þ)]/(0.771þ+0.077)$ (Fig. 2). Suppose that a 50-year-old woman (Patient 3) presents to our clinic complaining of postural instability that had progressed over a 1-year period. She also had vertical supranuclear gaze palsy, and her brain magnetic resonance imaging revealed prominent midbrain atrophy. In this case, does she also need tau imaging? Based on the information already available, the pre-test probability of the patient is high enough without an additional diagnostic test. Thus, the ΔPPV in this case will be low (Fig. 2). Of course, tau imaging may be necessary for the confirmation of PSP or for the exclusion of non-PSP at the early stage especially in a research setting. However, we need to weigh and consider how much the test will help in our routine practice. Such unnecessary diagnostic tests waste precious resources and may do more harm than good in clinical practice [7].

The clinical usefulness of Bayesian reasoning requires an accurate estimate of pre-test probability. However, the estimate of pre-test probability may be difficult to establish, particularly in complex diagnostic cases. Therefore, weighing clinical information is essential in diagnostic evaluation. Suppose that a patient with suspected corticobasal syndrome shows rapidly progressive myoclonus. This “rapidly progressive” feature strongly suggest Creutzfeldt-Jakob disease [8]. Conversely, if the patient presents with slowly progressive myoclonus, it is more likely to consider corticobasal degeneration or Alzheimer's disease pathology [9]. These specificities may, in turn, influence the interpretation of diagnostic tests performed early or late in the disease course.

When applying research findings on diagnostic accuracy to real clinical settings, clinicians should be aware of whether the study population for that test reflects the true prevalence of the disease. The difference between presumed prevalence ($þ_1$) and true prevalence ($þ_2$) results in the PPV gap, which is (presumed PPV – true PPV). The PPV

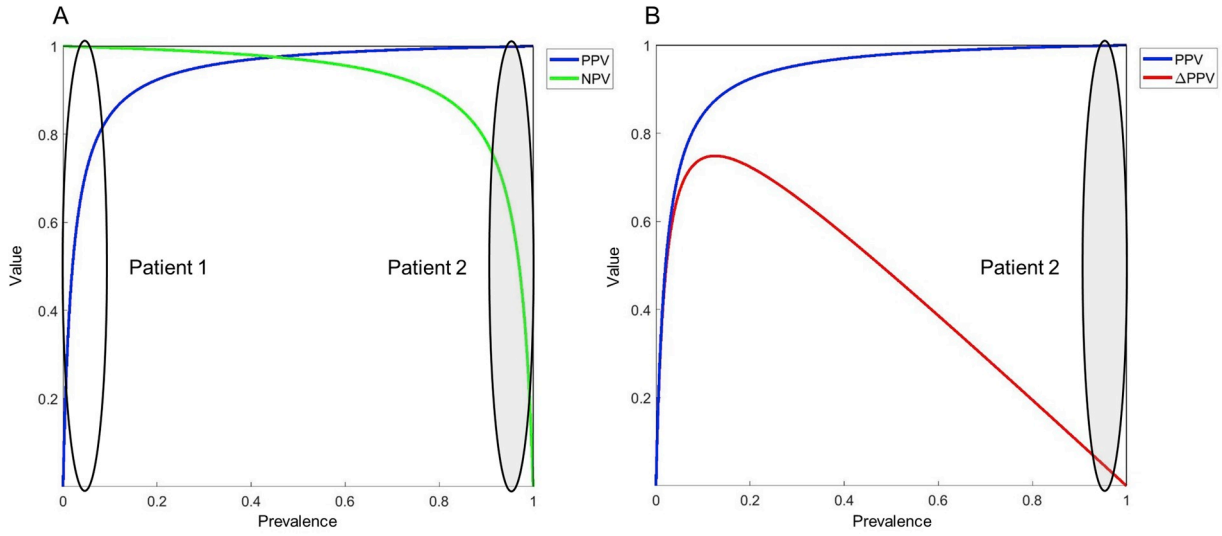


**Fig. 1. Positive and negative predictive values (PPV and NPV) and ΔPPV of dopamine transporter imaging by prevalence of Parkinson's disease**
Sensitivity α = 97%, Specificity β = 98%, þ = Prevalence.
PPV = $\alpha þ/[\alpha þ+(1-\beta)(1-þ)] = 0.97þ/(0.95þ+0.02)$.
NPV = $\beta(1-þ)/[(1-\alpha)þ+\beta(1-þ)] = 0.98(1-þ)/(0.98-0.95þ)$.
ΔPPV = $\alpha þ/[\alpha þ+(1-\beta)(1-þ)]\}-þ = [0.95þ(1-þ)]/(0.95þ+0.02)$.

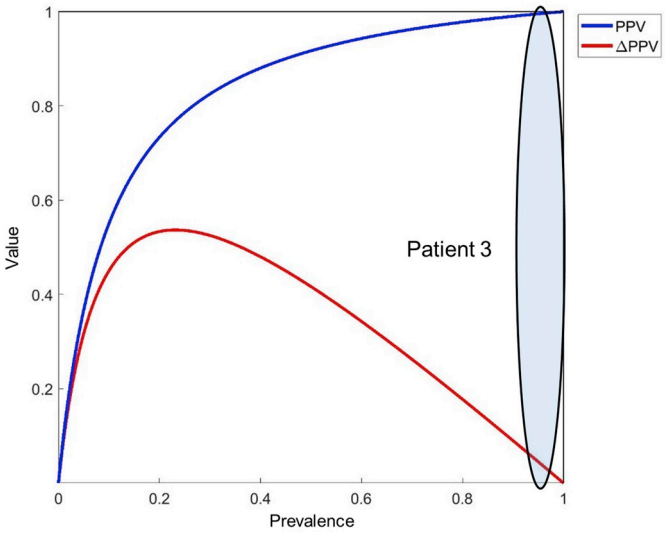


**Fig. 2. Positive predictive value (PPV) and ΔPPV of tau imaging by prevalence of progressive supranuclear palsy**.
Sensitivity α = 84.8%, Specificity β = 92.3%, þ = Prevalence.
PPV = αþ/[αþ + (1–β)(1–þ)] = 0.848þ/(0.771þ + 0.077).
ΔPPV = αþ/[αþ + (1–β)(1–þ)]}–þ = [0.771þ(1–þ)]/(0.771þ + 0.077).

gap can be calculated by the formula: $\alpha þ_2/[\alpha þ_2 + (1-\beta)(1-þ_2)] - \alpha þ_1/[\alpha þ_1 + (1-\beta)(1-þ_1)]$. For example, the revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB) has been recently established, in which a reduced striatal DAT uptake is included as one of the indicative biomarkers [10]. The relevant study showed that the use of DAT imaging in distinguishing DLB from other types of dementia has a sensitivity of 77.7%, a specificity of 90.4%, and a PPV of 82.4% [11]. However, in that study, approximately 50% of the included patients were DLB, when the typical prevalence in clinical practice is around 10% only among demented patients. Even though the study claimed that the PPV is 82.4%, the PPV in a real clinical setting will be 47.3%, and the PPV gap is approximately 35%. This 35% is the error of judging the post-test probability or of the confidence in the test result.

Because resources are not infinite and will be limited, there is bound to be a gap between needs and resources. Therefore, it is essential to use medical resources properly and refrain from providing unnecessary treatment. To accomplish this, clinicians should 1) appreciate the pre-test probability correctly and understand what the test result will mean based on the pre-test probability and 2) avoid the uninformed overuse of a test. We would like to emphasize that the clinical utility of diagnostic tests relies on the competence of the clinician.

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## Authors' contributions

Dr. R Kim did the literature search and wrote the first draft of the manuscript.

Dr. BS Jeon designed the research, and made critical revisions to the manuscript.

## Declaration of competing interest

No conflicting relationship exists for the authors.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.10.003.

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