# Use of Bayesian statistical approach in diagnosing secondary hypertension

#### **Bayesian analysis**

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**Abstract**: Bayes's theorem is predominantly used in diagnosing based on the results of various diagnostic tests. This statistical approach is intuitive in differential diagnosis as it explicitly takes into consideration data from medical history, physical examination, laboratory findings and imaging. Bayes's theorem states that the probability of disease occurrence (or occurrence of other outcome) after new information is obtained, called *a posteriori* probability, depends directly on an *a priori* probability and the value of likelihood ratio associated with a given test result. This paper describes basic Bayesian analysis in relation to the diagnosis of two types of secondary hypertension; primary aldosteronism and pheochromocytoma. This choice is based on two facts; primary aldosteronism is believed to be the most common and the most commonly detected cause of symptomatic hypertension and pheochromocytoma is thought to have rapid progress and stormy clinical course. This article aims to draw physicians' attention to and increase the knowledge of Bayesian analysis, and to describe its use in everyday clinical decision making. On the basis of this theorem's foundations, the discussion in relation to the issue of differential diagnosis between physicians, their patients, and medical students should also improve. When used in practice, one should be aware, however, of Bayesian analysis limitations concerning the diagnostic test application and limited knowledge of diagnostic test accuracy, and insecure or faulty *a priori* probability estimates.

**Key words**: Bayesian theorem, clinical decision making diagnostic test, evidence-based medicine, statistical analysis

# INTRODUCTION

The probability is the measure of the expectation extent, of a certain event or phenomenon [1]. In the biostatistical reasoning the probability is examined by two separate trends. Foundations of the more recent one better known among physicians and more frequently used at present have been created by Fisher and Pearson in the twenties of the previous century (known in English literature as the "frequentist statistics") [2,3]. In its investigations, this movement employs such a well known cause-effect relationship measures as the odds ratio, relative risk or correlation coefficient, and the statistical theorem is based mainly on the interpretation of the result analysis,

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which tests the posed hypotheses, considering a given "p" value, identical with statistical significance level. Another statistical approach was introduced over 200 years ago by Thomas Bayes and, named after the author, is known as the "Bayesian theorem/analysis", which from the mathematical perspective is a conditional probability theorem [4]. Although older, it is rarely employed in current medical studies. The overview of the topic literature reveals, however, a growing interest in this type of statistical analysis, and increasingly more frequent attempts of using it, not only in theoretical investigations but also in evidence based medicine (EBM) [5-12]. The Bayes's theorem is intentionally or unintentionally used by physicians in everyday medical practice rather intuitively, while the traditional statistical analysis often brings numerous problems, also considering the interpretation of results [13]. Moreover, while classical statistical hypotheses testing and determining the precision of information is applicable mainly in determining the magnitude and values of the relationships of differences between groups, the Bayes's theorem will first of all assess the information associated with an individual patient.

The Bayes's analysis is most frequently used in the process of diagnosing where decisions are made based on results of

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Definition					
The percentage of patients with a positive result of the test diagnosing a certain disease (clinical condition). It is a measure of the diagnostic test's capacity for disease detection. The probability of a positive test result in genuinely ill patients. A/A + C					
The percentage of healthy individuals with a negative result of the test diagnosing a certain disease (clinical condition). It is a measure of the diagnostic test's capacity for disease absence confirmation.					
The probability of a negative test result in genuinely healthy individuals. D/B + D					
The percentage of people with a positive diagnostic test result who suffer from a given disease.					
The probability of an individual genuinely suffering from a given disease with a positive result of the test diagnosing this disease.					
A/A + B					
The percentage of individuals with a negative test result who do not suffer from a given disease.					
The probability of an individual not suffering from a given disease with a negative result of the test diagnosing this disease.					
D/C+ D					
The probability of obtaining a genuinely positive diagnostic test result in a patient, to the probability of obtaining a falsely positive result in a healthy individual, ratio.					
Sensitivity/ (1 – Specificity)					
The probability of obtaining a falsely negative diagnostic test result in a patient, to the probability of a negative result in a healthy individual, ratio.					
	Definition         The percentage of pati (clinical condition). If         The probability of a point of the probability of a point of the percentage of head disease (clinical condition). If the percentage of head disease (clinical condition) absence confirmation.         The percentage of head disease (clinical condition). If the percentage of head disease.         The percentage of peoint disease.         The percentage of peoint disease.         The percentage of individual disease.         The percentage of individual disease.         The probability of an intest diagnosing this is         D/C + D         The probability of obtain is         Sensitivity/ (1 - Spector)         The probability of obtain	Definition         The percentage of patients with a positive re (clinical condition). It is a measure of the di         The probability of a positive test result in gen         A/A + C         The percentage of healthy individuals with a disease (clinical condition). It is a measure absence confirmation.         The probability of a negative test result in gen         D/B + D         The percentage of people with a positive diag disease.         The probability of an individual genuinely suff of the test diagnosing this disease.         A/A + B         The percentage of individuals with a negative disease.         D/A + B         The percentage of individuals with a negative disease.         D/C + D         The probability of an individual not suffering fittest diagnosing this disease.         D/C + D         The probability of obtaining a genuinely positive re Sensitivity/ (1 – Specificity)         The probability of obtaining a falsely negative	Definition         The percentage of patients with a positive result of the test diagnosing (clinical condition). It is a measure of the diagnostic test's capacity for the probability of a positive test result in genuinely ill patients.         A/A + C         The percentage of healthy individuals with a negative result of the test disease (clinical condition). It is a measure of the diagnostic test's crabsence confirmation.         The probability of a negative test result in genuinely healthy individuals         D/B + D         The percentage of people with a positive diagnostic test result who su disease.         The probability of an individual genuinely suffering from a given disease of the test diagnosing this disease.         A/A + B         The percentage of individuals with a negative test result who do not su disease.         D/C + D         The probability of an individual not suffering from a given disease with test diagnosing this disease.         D/C + D         The probability of obtaining a genuinely positive diagnostic test result probability of obtaining a falsely positive result in a healthy individual sensitivity/ (1 – Specificity)         The probability of obtaining a falsely negative diagnostic test result in a healthy individual sensitivity of obtaining a falsely negative diagnostic test result in the probability of obtaining a falsely negative diagnostic test result in test diagnostic test result in the probability of obtaining a falsely negative diagnostic test result in the probability of obtaining a falsely negative diagnostic test result in tesult in tesult in the negative diagnostic test result		

#### Fig. 1. Diagnostic test accuracy

various diagnostic tests. In a broader sense, it is not only the laboratory, imaging or pathomorphologic findings, but also the patient medical history, physical examination and questionnaire, which are regarded as diagnostic tools [14-16]. In the diagnostic test interpretation, the researcher would most frequently use the concept of sensitivity, specificity and prediction values (positive and negative) [12,14]. For a better understanding of the Bayes's theorem, the familiarity with the term "likelihood ratio" (LR), is essential, which in the Polish literature is often translated as the credibility index (Fig. 1) [12,14]. From viewpoint of the Bayes's analysis, the following question is important: "What is the probability of a certain individual

being ill if we are dealing with results of diagnostic tests which have not been ordered incidentally?".

According to the Bayes's theorem, the probability of disease incidence (or of a study end point), called the a posteriori probability, is directly and proportionally dependent on the value of the initial *a priori* probability and the LR (Appendix A) [5-8,10-12]. The LR value, as easily noticeable, depends in turn on the diagnostic test effectiveness (its sensitivity and specificity). Obviously, the higher the *a priori* probability and the LR, for a positive test result in a given clinical situation, the higher the probability of diagnosing the disease, as the *a pos*teriori probability approximates 100% (de facto, it will never reach it; disregarding of course, extremely striking diagnostic cases, i.e.; it is hard not to diagnose diabetes, with a glycemia of 750 mg/dl when it is not a matter of a measuring error). On the contrary, the smaller, the *a priori* probability and the LR value for a negative test result, the more the *a posteriori* probability approximates 0%. In order for a correct diagnosis in the differential diagnostic procedure, one has to reach the situation when part of the possible causes for symptoms occurrence will with great likelihood be eliminated; this is when one can give up performing further tests and treatment (the "test threshold" is reached, usually at the  $\sim$ 5–15% probability), and the probability for the occurrence of other reasons of the examined condition reaches the level when one can give up further tests and introduce the appropriate treatment (the "treatment threshold" is being reached, probability usually  $\sim 85-95\%$ ). It is believed that if after diagnostic tests, none of the thresholds has been reached, it is necessary to perform additional diagnostic tests [6,7]. These concepts have been presented in Figure 2. With the results of the ordered tests being independent of each other, then each time, the *a posteriori* probability becomes the *a priori* probability with the use of a new test, and the final result then depends on the accuracy of tests previously performed and on the result of the new test itself. Those interested in the mathematic description of the process, will find the Bayes's formula in its basic mathematic comprehension in the conclusion part of the present article (Appendix A). For readers who intend to employ the transformed form of the formula, the LR indexes have been included. Moreover, for all Readers who would like to make use of the Bayes's theorem in day-to-day contact with their patients and for whom applying the breakneck calculations with the use of included formulas is too time-consuming, I would like to recommend a simplified version of the analysis in the form of a clear normogram which aids in the calculation of the *a posteriori* probability on the basis of the *a priori* probability and the likelihood ratio value (Appendix B).

The aim of this article is to introduce the terms and depict the basic Bayes's analysis in the diagnosis of two secondary types of arterial hypertension, primary aldosteronism and pheochromocytoma. A selection of this kind is not an incidental one; hyperaldosteronism is the most common and increasingly more commonly diagnosed cause of endocrine, symptomatic hypertension, while arterial hypertension, secondary



Fig. 2. Test threshold and treatment threshold of the outcome on the basis of Bayesian analysis (from: *Szczeklik A, eds. Choroby wewnętrzne. Podręcznik multimedialny oparty na zasadach EMB. T. 2, Kraków, Medycyna Praktyczna, 2006: 2333,* modified)

to pheochromocytoma, is one of the most dangerous. This article is meant to be mainly didactic, to draw one's attention to certain terms and the vocabulary employed in this analysis, to broaden its knowledge among physicians, and facilitate a conscious and rational diagnostic decision making, in day to day medical practice. Any deliberations and remarks regarding various aspects of arterial hypertension are secondary in this context.

#### Heads or tails, that is, some mathematics

For a better understanding of the Bayes's approach, the theorem about conditional probability, let us analyze a few examples. Let a given random event be a coin toss. As its result, obtaining heads or tails is considered (we disregard other events i.e. the coin standing on its edge). Let us pose the question: "What is the probability of obtaining heads?". The answer: 1/2, because we may obtain two results (here: the number of possible events, the fraction denominator), but the only advantageous result is obtaining heads (here: numerator). It is obvious that the reasoning is just the same with the result being tails! The Probability of acquiring heads or tails is the same. Let us now pose the next question: "What is the probability of drawing a white ball out of a top hat in which there are five white balls and ten black ones?". The answer: 5/15 that is 1/3. Now, a more difficult example: "There are two top hats. In the first one there are five white balls and ten black ones and in the second one, eight white balls and 12 black ones. Let us toss the coin; with heads obtained, let us draw one ball out of the first top hat, with tails obtained, let us draw one ball out of the second top hat. What is the probability of obtaining a white ball?". The immediate association is simple: "It depends..."! On what? Of course it depends on which side of the coin we obtain with the toss! Whichever side we obtain, we win; we are going to draw a ball. However, the probability of its obtaining depends conditionally on the result of the toss. In this case the answer is; before the toss 1/6, if in the toss we obtain heads and 1/5 if we obtain tails in the toss. (In or-

With the toss of a symmetrical dice, what is the probability of obtaining a number of dots greater than 3, if the obtained number of dots is even?

Solution:

$$\begin{split} &\Omega - \text{elemental events space,} \\ &B - \text{obtaining an even number of dots event,} \\ &A \cap B - \text{obtaining an even, greater than 3, number of dots event} \\ &\Omega = \{1; 2; 3; 4; 5; 6\} \\ &B = \{2; 4; 6\} \\ &A \cap B = \{4; 6\} \\ &P(A | B) = P(A \cap B) / P(B) \rightarrow P(A | B) = 2/6 : 3/6 = 2/3 \\ &\text{Answer: The probability of obtaining a number of dots greater than 3, when obtaining an even number of dots is 2/3. \end{split}$$

Fig. 3. The example of Bayesian analysis

der to make it clear, let us add that the overall probability of obtaining a white ball before the coin toss, is 1/6 + 1/5, that is 11/30). We just performed a mathematic analysis according to Bayes's theorem; an initial condition appeared in the reasoning. In order to answer the question "With the toss of a symmetrical dice, what is the probability of obtaining a number of dots greater than three if the obtained number of dots was even?", refer to Figure 3. There may be numerous textbook examples of conditional probability. For the inquisitive Reader I recommend the abundant literature on the topic.

### Symptomatical arterial hypertension diagnosis

Arterial hypertension, secondary to endocrine disorders, occurs most often with a sudden onset, with a periodical, particularly an unstable character and with "typical" primary spontaneous hypertension risk factors being absent (i.e. excessive body mass, significant family history, inappropriate lifestyle), the physical examination (and/or other supplementary exams) demonstrate irregularities (i.e. hypokalemia, hypernatremia), lastly, the hypertension is resistant to pharmacological treatment [17,18]. The diagnosis of the described secondary hypertension involves three stages [17-20]:

- 1) patient's history and physical examination stage
- 2) biochemical findings stage
- 3) imaging stage.

The same scheme will be employed to present the Bayesain analysis.

### Primary aldosteronism

By definition, primary aldosteronism occurs in a hypertensive patient with increased plasma aldosterone levels or aldosterone urinary excretion, a decreased plasma renin activity or with an increased ARR index (proportion of aldosterone concentration to plasma renin activity), and in consequence hypokalemia and metabolic alkalosis develop [17,19]. The reason for this clinical condition is an increased autonomous aldosterone secretion. An increasing trend of this type of arterial hypertension prevalence is observed, secondarily to reported increased morbidity as result of more frequently performed biochemical tests, including screening tests. It is now accepted that it may concern 5-15% of arterial hypertensive patients [17,19].

The physician starts thinking of the disease with the patient entering the consulting room. According to the Bayesian analysis, the physician estimates the probability of disease occurrence *a priori* on the basis of the patient's history and physical examination. This is the area of highest risk in the Bayesian analysis and the most criticized one by skeptics [5-8,10]. The probability for aldosteronism is different (greater) when the patient is a 48-year-old female, with a history of a 3-month headache, with coexisting tinnitus, frequent nose bleeds, muscular weakness with periodical paresthesias and myospasm, and is reporting polyuria. It occurs that the blood pressure value is much above the reference values and the ionogram ordered "by the way" (because after all, the patient has been unwell for several weeks) demonstrates hypokalemia. A different probability (smaller) is assigned when the patient is a 45-year-old man, whose mother and father have been suffering from hypertension "ever since", and his body mass index (BMI) is 31 kg/m<sup>2</sup>, and in addition he is a smoker. We also are aware that a slight hypokalemia attracts attention, in the check up ionogram. Moreover, in an abdominal ultrasound exam performed additionally the physician noticed a difficult to interpret, hyperechogenic region within the right kidney/adrenal gland, which raised diagnostic alertness. The taken blood pressure occurred higher than the normal value range, with the patient taking two hipotensive drugs including the diuretic. Each physician; performing a Bayesian analysis must subjectively determine (and does it, even if completely subconsciously, without being aware of the existence of the Bayesian analysis concept) the initial probability of primary hyperaldosteronizm being the reason for the patient's hypertension. However, for many clinical issues there is a lack of "standardized" probability tables of certain diseases occurrence, which are estimated on basis of the patient's history and physical examination. The employment of the Bayesian analysis in the diagnosis of arterial hypertension secondary, to primary hyperaldosteronizm, is shown in Figure 4. Let us assume in our investigations that considering the patient's history and physical examination, the subjectively estimated probability for disease occurrence is 70% in the first instance and 5% in the second. This value is the "first" a priori probability. In order to disentangle our doubts, according to present standards [17,19] and so, in order to involve the least possible costs, we order obtaining the ARR index and the diagnosis is going to be made on the basis of this test's result. In order to determine the *a posteriori* probability, the knowledge of the sensitivity and specificity of the employed diagnostic test is essential. Of help will be the laboratory analysis, or the literature evidence survey. The test result occurred positive in the first case, and negative in the second. The sensitivity and specificity of this method are 90% and 70%, respectively [20].

Fig. 4. Bayesian analysis in diagnosing primary aldosteronism

<b>Patient 1.</b> A 48-year-old female, with a 3-month history of headache; accompanying tinnitus, frequent nose bleeds, muscular weakness, periodical paresthesias, myospasm and polyuria. Arterial blood pressure: 176/102 mmHg. Serum Potassium: 2.8 mM/I.	Patient 2. A 45-year-old male, BMI 31 kg/m <sup>2</sup> , smoker, with family history of arterial hypertension (mother and father), taking two hypotensive drugs, including a diuretic. Blood pressure; 152/94 mmHg. Serum Potassium P: 3.3 mM/l. Abdominal ultrasound examination: hyperechogenic image of right kidney/adrenal gland (?) – difficult to interpret.
1. The a priori probability I: 70%	1. The a posteriori probability I: 5%
2. Diagnostic test I:	2. Diagnostic test I:
obtaining the aldosterone/ plasma renin activity ratio	deriving the aldosterone level to plasma renin activity ratio
Test result: positive Sensitivity: 90% Specificity: 70%	Test result: negative Sensitivity: 90% Specificity: 70%
3. The a posteriori probability I: 81%	3. The a posteriori probability I: 0.8%
$(0.9 \times 0.7) / [(0.9 \times 0.7) + (0.3 \times 0.5)] = 0.808$	$(0.1 \times 0.05) / [(0.1 \times 0.05) + (0.7 \times 0.95)] = 0.0075$
(a priori II for the next test)	(a priori II for the next test)
4. Diagnostic test II:	4. Diagnostic test II:
computed tomography of adrenal glands	computed tomography of adrenal glands
Test result: positive Sensitivity: 90% Specificity: 90%	Test result: negative Sensitivity: 90% Specificity: 90%
5. The a posteriori probability II: 97%	5. The a posteriori probability II: 0.08%
$(0.9 \times 0.81) / [(0.9 \times 0.81) + (0.1 \times 0.19)] = 0.97$	$(0.1 \times 0.0075) / [(0.1 \times 0.0075) + (0.9 \times 0.9925)] = 0.0008$
↓ ↓	$\downarrow$
PROBABILITY OF PRIMARY ALDOSTERONISM OCCURRENCE	PROBABILITY OF PRIMARY ALDOSTERONISM OCCURRENCE

The likelihood ratio for a positive and negative test result is 3.0 and 0.143, respectively. Therefore, the estimated a posteriori probability is now 81% in the first instance and 0.8% in the second. The next examination ordered with the aim of determining the localization and the type of the alteration, is the computed tomography (CT) scan of the adrenal gland. Despite exceeding the "test threshold" (0.8%), for clinical reasons, the examination is being performed in the second patient, given an abnormal ultrasound exam result. Our a posteriori probability, having done the first test becomes now the "second", a priori probability. Also here, the test's result is positive only in the first instance; a single alteration has been demonstrated within the left adrenal gland ( $25 \times 15$  mm), with no enhancement after the contrast medium being administered, identical with adenoma. As the sensitivity and specificity of the CT adrenal gland tumors diagnosis are on the average respectively: 90% and 90% [19], therefore the LR for a positive and negative result are 9.0 and 0.11, and the "new" a posteriori probability is now 97.4% in the first instance and 0.08% in the second. With over 97% probability we can now say that arterial hypertension in our patient is a symptom of primary aldosteronism and is the result of an adrenal gland tumor (we can

see that the disease "treatment threshold" has been exceeded for this disease), on the other hand we excluded this disease (with over 99% probability) as the reason for hypertension in the second patient (the "test threshold" has been reached). It is worth mentioning that the value of the obtained *a posteriori* probability for a single patient is in a way, the equivalent of the "p" value obtained with the "traditional" statistical analysis for a group of similar patients. The higher is the probability, the lower the statistical significance value and vice versa.

#### Pheochromocytoma

Pheochromocytoma is a neoplasm which develops from the chromaffin cells, localized usually in the adrenal glands, the symptoms of which are associated with excess production and release of catecholamines [17,21]. The adrenergic receptor stimulation by catecholamines results in permanent or periodic arterial hypertension. It is true that the prevalence of this disease in patients with arterial hypertension does not exceed 1%, with the annual morbidity of 2–8 cases/1,000,000, however a correct diagnosis and treatment protect the patient from clinically malignant symptoms and life-threatening cardiovas-

Pat wit acc ski a " any	tient 1. A 23-year-old male, BMI 28 kg/m <sup>2</sup> , h periodical strong headaches, with companying anxiety, heart palpitations and n paleness. The history of him ever acquiring serious disease" is negative, he does not use of drugs. Arteria blood pressure: 166/96 mmHg.	Pathis dis dis of the of the pash (include)	tient 2. A 50-year-old female, with a positive tory of arterial hypertension, ischemic heart ease and paroxysmal atrial fibrillation (all eases diagnosed one year ago). A history a 5-month, increasing paroxysmal headache, en with a nosebleed, paleness and coldness fingers, frequent anxiety onsets during the st year and hidrosis, especially at night. spite taking three hypotensive drugs, cluding a diuretic), arterial blood pressure: 8/96 mmHg.
1.	The a priori probability I: 50%	1.	The <i>a priori</i> probability I: 20%
2.	Diagnostic test I:	2.	Diagnostic test I:
	Plasma free urinary metanephrine level assessment		Plasma free urinary metanephrine level assessment
	Test result: positive Sensitivity: 99% Specificity: 89%		Test result: negative Sensitivity: 99% Specificity: 89%
3.	The a posteriori probability I: 90%	3.	The a posteriori probabiliy I:
	$(0.99 \times 0.5) / [(0.99 \times 0.5) + (0.11 \times 0.5)] = 0.9$		0.3% (0.01 $\times$ 0.2) / [(0.01 $\times$ 0.2) + (0.89 $\times$ 0.8)] = 0.003
	(a priori II for the next test)		
4.	Diagnostic test II:		
	Adrenal gland magnetic resonance imaging		
	Test result: positive Sensitivity: 99.9% Specificity: 67%		
5.	The a posteriori probability II:		
	96.4% (0.999 $\times$ 0.9) / [(0.999 $\times$ 0.9) + (0.33 $\times$ 0.1)] = 0.964		
	$\downarrow$		$\downarrow$
	PROBABILITY OF PHEOCHROMOCYTOMA OCCURRENCE		PROBABILITY OF PHEOCHROMOCYTOMA OCCURRENCE

Fig. 5. Bayesian analysis in diagnosing pheochromocytoma

cular complications [17,21]. It is necessary to mention that about 10% of tumors are malignant based on histopathologic examination [17,21].

Similarly to the previous case, let us take two examples (Fig. 5). A 23-year-old patient reports to the consulting room, BMI 28 kg/m<sup>2</sup>, he complains of periodical strong headaches, with anxiety, palpitations and skin paleness. In a routine check-up elevated arterial blood pressure has accidentally been reported. The patient reports not ever being "seriously ill", or taking any drugs. Another patient is a 50-year-old woman with a history of arterial hypertension, ischemic heart disease and paroxysmal atrial fibrillation (all diseases discovered a year before), who reported a recently increasing paroxysmal headache, which was often accompanied with epistaxis, paleness and coldness of the fingers. During the last year she noticed frequent anxiety onsets and hidrosis, especially at night. Despite taking three hypotensive drugs (including a diuretic), the patient's arterial blood pressure was elevated. What could therefore be the *a priori* probability that the reason for the arterial hypertension in these patients is pheochromocytoma? Let us subjectively admit that 50% in the first instance and 20% in the second.

The first stage of the pheochromocytoma diagnosis is according to guidelines [17,21] to obtain a level of methylated derivatives of catecholamines in the plasma, or in 24-hour urine. As the urinary metanephrines could not be measured (patient refusal and no approval for hospitalization), the assessment of plasma free metanephrines was ordered. In the first instance the obtained test result was positive and in the second instance it was negative. Keeping in mind the mean sensitivity and specificity test values (99% and 89%) [17], the likelihood ratio was derived for the positive and negative test results, 9.0 and 0.01, respectively. The assessed a posteriori probabilities are therefore 90% and 0.3%. It is highly improbable in the second instance that arterial hypertension is caused by pheochromocytoma (since the "test threshold" was reached), therefore further diagnostic evaluation is going to be done for the first patient only. The next step is to perform the imaging examination, CT

or magnetic resonance (MR). With regard to the patient young age and the possibility of extraadrenal tumor localization, the MR was performed. This test is almost 100% sensitive (let us admit 99.9%) in pheochromocytoma diagnosing and localizing, and 67% specific [17], therefore the LR for a positive test result is 3.1, and 0.0001 for a negative result. Being aware of a positive test result and left adrenal gland pheochromocytoma manifestation, and taking the previous a posteriori probability value as the present a priori value, it can be stated that the probability of diagnosing pheochromocytoma in this young patient is 96.4%. Despite exceeding the "treatment threshold", in order to fulfill the clinical criteria, another diagnostic test should be considered in this patient; 123 I-meta-iodobenzylguanidine scintigraphy. Such management, however, aims at diagnosing potential multiple tumors and the extra adrenal ones and not at diagnosing the disease according to the Bayesian analysis comprehension. Let us, however, leave further diagnostic evaluation to clinical practitioners...

# DISCUSSION

Statistically speaking, differential diagnosis is a process of testing the hypotheses, based on available information. From the Bayesian point of view the researcher is keen on the estimated probability of a certain clinical condition occurrence in a given patient being as close as possible to the "0" value (0%; there is a high chance of this clinical condition not occurring; reaching the "test threshold") or "1" (100%; there is a high chance of this clinical condition the "treatment threshold"). It is obvious that knowing the *a priori* probability, physicians will order further tests to increase/decrease the *a posteriori* probability of the disease occurrence, until one of the mentioned "threshold" values is reached [7,10].

# The *a priori* probability, that is the degree of suspicion of certain disease occurrence

It has been considered that experts, physicians experienced in a given specialty, and results of reliable studies concerning a given discipline (preferably systematic surveys and metaanalyses concerning various prognostic traits) [22], may possibly be the source of knowledge on the *a priori* probability. The a priori probability is then determined, for example, on basis of the familiarity with the statistical significance of linear regression indexes, and logistic odds ratios, approved risk factors which occur in a given individual (taken from available evidence of traditional statistic analysis) [10]. There are however some shortcomings of a procedure of this kind, because an erroneously low a priori probability coerces in consequence the employment of an excess of diagnostic tests before confirming the diagnosis and thus a delay in the appropriate therapy commencement, while the opposite situation (adopting too high an *a priori* probability) may conduce performing an unnecessarily high number of tests before the disease exclusion,

or even introducing needless treatment in a de facto, healthy individual [23].

The *a priori* probability represents a strong mechanism which controls factors potentially disturbing the theorem (just as the analyses are meant to do it; stratification or more variables), for the physician intuitively assigns each patient "his own" probability [10] (i.e. he assigns a greater risk of ischemic heart disease occurrence, with symptoms of a strong, burning, chest pain to a 50-year-old, smoking, obese man, than to a 25-year-old, non-smoking woman with no additional risk factors, with the same symptoms, thus "controlling" in a way the influence of gender, age, obesity and smoking addiction, on the results of his observation). In the literature, the necessity of developing better methods of a priori probability estimation for the occurrence of those diseases, with which the physician deals most often in day to day practice, and of training physicians in the proper a priori probability assessment based on the results of the patient's history and physical examination. Procedure of this kind should increase precision in therapeutic decision making and utilize more efficiently available diagnostic tests. This is important from the economic viewpoint and it may also improve the patients' care quality [23].

# Diagnostic test

It is rare for one test to be sufficient to diagnose or exclude a disease. The choice of a diagnostic strategy with the use of reliable tests depends on the degree of difficulty of a given case, on the familiarity with the issue, and on available alternatives [24].

According to epidemiologic standards, the diagnostic test interpretation is based on the familiarity with indexes which describe its accuracy (Fig. 1). The advantage of the LR is the possibility to omit the necessity of calculating the sensitivity, for assessment of which it is necessary to demonstrate the results in a dichotomous form; a relative lack of impact of disease prevalence on its value; and interpretation facility [6,12,25]. Some may believe, the presentation of results with the use of the LR rarely employed in the literature is misleading, however, there is evidence that the majority of physicians interpret its significance correctly as the ability for a certain test result to increase or decrease the probability of disease occurrence [26].

# **Reasoning limitations**

The final therapeutic decision should depend on the probability of disease occurrence (estimated on basis of patient's history and physical examination and the power of pieces of evidence, brought by the diagnostic tests results), as well as on the current knowledge and interpretation of the topic literature, on physician's experience and his beliefs. The conclusions of the Bayesian analysis may however be erroneous, considering the possibility of a faulty assessment of the *a priori* probability, and unsatisfactory diagnostic tests accuracy. The chances of an erroneous *a priori* probability estimation are associated most frequently with the issue of the prevalence of a given disease (the probability of a particularly rare disease is usually overestimated, whereas the probability of "popular" diseases, encountered by physicians every day, is usually underestimated) and with the accordance (quantitative and qualitative) of presented symptoms with those of the "textbook" (what as we know is not always so obvious), as well as with physician's experience and other factors disturbing the theorem (a typical source of error in statistical reasoning) [26].

It has been demonstrated that even experienced physicians assign different *a priori* probabilities to identical clinical cases [23]. Nevertheless, the whole diagnostic scheme describes the differential diagnosis process with the use of the Bayesian analysis specific terminology, well known to each physician.

Moreover, the employment of the Bayesian analysis may be associated with an overestimation of the probability of the total possibility of "being ill". Let us imagine a situation where a patient reports to the consulting room with a chest pain. With the differential diagnosis it is important to first of all consider: ischemic heart disease, aortic dissecting aneurysm, gastroesophageal reflux disease, pulmonary embolism, psychological disorders and several others... One need not forget that the total probability of these diseases occurrence may not exceed 100% (when diagnosing we "cut" successive pieces from the whole cake)! It has been demonstrated that an overestimation may concern over half the cases in the *a priori* probability estimation, and the probability of "being ill" may reach even 290% [27].

Another source of errors is associated with the diagnostic test *per se* and its methodological correctness. Nowadays those who evaluate the diagnostic tests are required to take account of all those elements in their testing which may influence the results credibility, and have been discussed in the studies of the working groups of the STARD and QUADAS initiatives [28,29].

### The employment of theory in practice

Let us pose the question: "Who is the addressee of this article?" It seems that any physician, be it a theoretician, or a practitioner. One must not forget that a person utilizing EBM recommendations is more inclined to utilize the Bayes's theorem consciously, and with conviction [26], and primary care physicians and internists who for the most part must rely on a frequently difficult patient's history and physical examination, not yet knowing the supplementary examinations results, are especially familiar with the differential diagnostic problems. Moreover, there is a multitude of symptoms corresponding with many clinical entities and usually they are "the first line" to contact the patient, also the one ignoring or exacerbating his ailments [9]. Let us, however, not forget about physicians of other specialties, for whom information contained in this article may seem worth considering in the day to day diagnostic process.

# SUMMARY

Although the proficiency in solving diagnostic issues differs among individual physicians and depends greatly on the clinical experience and knowledge acquired in a given discipline (that is on intuitive knowledge acquisition, on the possibility of an initial assessment of the disease depending on the clinical condition and on the LR depending on test result), it is worthwhile attempting to knowingly employ the Bayesian analysis in practice, especially in teaching. With the use of the information conveyed by patient's history, physical examination and supplementary test results: laboratory findings and imaging, it takes account of the intuitive approach to the issue of estimation of the final diagnosis. Employing this type of reasoning, the physician should, however, be aware of its limitations. In summary, I am convinced that observations presented in this article, illustrating the use of the Bayesian statistical reasoning in the diagnosis of secondary arterial hypertension, remind us of the purposefulness and usefulness of this approach which is consciously or unconsciously used by all of us in everyday diagnostic and therapeutic decision making.

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#### Appendix A. Bayes's theorem

The theorem on conditional probability (Bayesian theorem)

I. <u>Mathematical form:</u> If  $\Omega$  is a set of elemental events, B is a random event such, that B belongs in a set of elemental events  $\Omega$  and P(B) > 0, then for each elemental event A the conditional probability of A occurrence, under the condition, of event B taking place, we call the number

 $P(A | B) = P(A \cap B) / P(B)$ 

where P (A $\cap$ B) is the probability of the product of events A and B.

II. The form utilized in the diagnostic process:

1. For a positive diagnostic test result:

P(D = 1 | T = 1) = P(T = 1 | D = 1)P(D = 1) / [P(T = 1 | D = 1)P(D = 1) + P(T = 1 | D = 0)P(D = 0)]

2. For a negative diagnostic test result:

P(D = 1 | T = 0) = P(T = 0 | D = 1)P(D = 1) / [P(T = 0 | D = 1)P(D = 1) + P(T = 0 | D = 0)P(D = 0)]Where: D is the presence (D = 1) or absence (D = 0) of the disease, T is the diagnostic test result: positive (T = 1) or negative (T = 0).

In this situation:

P(D = 1 | T = 1) is probability of disease occurrence, with a positive test result (a posteriori probability),

P(D = 1 | T = 0) is probability of disease occurrence, with a negative test result (a posteriori probability),

P(T = 1 | D = 1) is the probability for a positive test result in an ill individual (probability for a genuinely positive result = test sensitivity),

P(T = 0 | D = 1) is the probability for a negative test result in an ill individual (probability for a falsely negative result = 1 - sensitivity),

P(T = 0 | D = 0) is the probability for a negative test result in a healthy individual (probability for a genuinely negative result = test specificity),

P(T = 1 | D = 0) is the probability for a positive test result in a healthy individual (probability for a falsely positive result = 1 - specificity),

P(D = 1) is the probability of disease occurrence (a priori probability),

P(D = 0) is the probability for disease absence (1 - a priori probability).

Based on the information mentioned above, the Bayes's theorem takes the form:

1. for the positive diagnostic test result:

$$P_{a \text{ posteriori}} = \frac{\text{sensitivity} \times P_{a \text{ priori}}}{[\text{sensitivity} \times P_{a \text{ priori}} + (1 - \text{specificity}) \times (1 - P_{a \text{ priori}})]}$$

2. for the negative diagnostic test result:

$$P_{a \text{ posteriori}} = \frac{(1 - \text{sensitivity}) \times P_{a \text{ priori}}}{[(1 - \text{sensitivity}) \times P_{a \text{ priori}} + \text{specificity} \times (1 - P_{a \text{ priori}})]}$$

III. With the "likelihood ratio" being employed, the Bayesian reasoning will follow the stages (a longer but more intuitive method);
 1. We change the *a priori* probability (percentage) to the disease occurrence chance:

% of patients in the population chance: (numerator/denominator – numerator)

10% (1/10)	1:9 (1/9)
25% (1/4)	1:3 (1/3)
50% (1/2)	1:1 (1)
75% (3/4)	3:1 (3)
90% (9/10)	9:1 (9)
2. We calculate positive or negative "likelihood ratio	o" (depending on test result):

LR(+) = sensitivity / 1 - specificity LR(-) = 1 - sensitivity/specificity

3. We multiply the a priori chance of disease occurrence by the "likelihood ratio" obtaining a fraction numerator/denominator):

 $P'_{a \text{ posteriori}} = (numerator/denominator - numerator) \times LR (+/-) = numerator/denominator$ 

4. We calculate the *a posteriori* probability changing the chance to percentage this time:

 $P_{a \text{ nosteriori}} = (numerator/numerator + denominator) \times 100\%$ 

**Appendix B.** Normogram for *a posteriori* probability estimation on the basis of *a priori* probability and likelihood ratio values (based on: *Fagan TJ. Letter: normogram for Bayes theorem. N Engl J Med. 1975; 293: 257*)



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