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The uncertainty of false-positive test results

>> In our commentary, we point out errors in reporting that can lead to inaccurate scientific and political conclusions. There are two ways to describe the frequency of events: **prevalence and incidence**.

Prevalence describes the proportion of individuals within a defined population at a given time who meet a defined condition, such as suffering from a particular disease. Prevalence is reported to provide a snapshot of a condition in comparable populations.

Incidence describes the number of new events that occurred within a defined time period, usually based on 100,000 individuals in a defined population. The scatter of the incidence value increases the smaller the population and/or the observation period is chosen. Depending on the question to be answered, it may be useful to calculate changes in daily and annual intervals.

Both results, prevalence and incidence, are based on test results that may be **positive or negative** and, moreover, **true or false**.

When reporting the prevalence or incidence of deaths, **false-positive results** can be disregarded because false-positive deaths rarely occur. This statement does not apply to the determination of cause of death or to the confirmation of an existing disease or infection. Causes of death, disease, and infection can only be confirmed with detailed additional information because tests performed for this purpose are by no means free of false results and, with few exceptions, a medical diagnosis cannot be proven by a single sign, symptom, or test. Neither a positive PCR test nor a positive mammogram can prove the suspected disease without additional information, because false-positive results can only be distinguished from **true-positive results by comparison with a gold standard**. In medicine, a gold standard refers to a condition that is closest to the currently accepted truth. Others refer to „a proven, useful reference condition" as the so-called gold standard.

Two frequently cited statistical analyses confirm that false-positive results of mammography (1) and ferritin measurement in the diagnosis of iron deficiency anemia occur in about 10% of the tests (2). It is problematic for the informative value of a test that in almost all tests „false-positive" results are found significantly more frequently (5 to 274 times) than „false-negative" results. It is also problematic that the „false-positive" test results represent a higher risk of misinterpretation of a test result than the „false-negative" results.

A **„false-negative"** test result is when a test subject is found to meet a condition (e.g., breast cancer or SARS-CoV-2) even though the test did not detect that condition. In practice, „false-negative" results can be easily explained because it is quite easy to see what the test did not detect by looking at the subsequent clinical course. Here is an example: If, two weeks after an mammogram without pathological findings, a woman palpates a new sign – e.g., a new lump in the breast, which is then detectable on repeat mammography and can also be detected by sonography and confirmed as a malignant tumor by histological examination – the result of the first (negative) mammogram will retrospectively classified as „false-negative."

It is not important to emphasize that in many cases, the initially undetected tumor can be identified in both images by comparing the two mammograms in retrospect. However, it is not necessarily possible to deduce from this that the tumor was overlooked during the first diagnosis because additional preliminary information was already available before the second diagnosis of the first X-ray image. In technical jargon, this difference is referred to as different „pre-test probabilities" in the first and second findings. This argument of different **pre-test probabilities** becomes clear when the scenarios of „false-negative" and „false-positive" test results are applied to the example of the PCR test.

Basically, a **„false-positive"** result occurs when a test indicates the presence of a condition (e.g., breast cancer or SARS-Cov-2) even though that condition is very unlikely to be present, i.e., cannot be confirmed by all other available methods to date. Therefore, expected „false-positive" test results may be easily detected (because a condition cannot be detected) but are not easily explained. Example: If a mammography test indicates a district suspicious for tumor that cannot be confirmed by ultrasound examination and possibly additionally by histopathologic examination (gold standard), the positive mammography finding will ultimately be classified as a „false positive." Accordingly, the following applies: **the result of a test is called „false-positive" if there is a positive test result that is not confirmed by the gold standard.**

This comparison confirms that in the case of a **„false-negative"** result, the initially undetected finding can be corrected by an additional piece of information - in our example, the newly appeared nodule - in the further clinical course. From a scientific perspective, the probability that it could be a „false-positive" result of a mammography can be increased by another non-invasive procedure, e.g., an ultrasound examination, and, if the suspicion of malignant disease persists, it can be classified with sufficient probability as a „false-positive" result without evidence of a substrate by an additional negative histopathological examination.

In the case of a PCR test, however, the differentiation of a „true-positive" from a „false-positive" test is more difficult than in the case of mammography, because in the case of mammography other methods (ultrasound, histology) are available in addition to X-ray technology to invalidate the suspicion of a „true-positive" finding. In the case of a „false-positive" PCR test, on the other hand, there is as yet no further method with which the distinction between „true-positive" and „false-positive" PCR tests can be corroborated.

The **„ignorance of the unknown"** that is evident here describes an

evidentiary emergency that physicians must constantly contend with by using additional testing methods. Experienced clinicians can solve this problem with little effort, while novice clinicians incur significant diagnostic costs. Whether PCR tests are suitable for diagnostics because of this evidence emergency is debated differently by different scientists. Legal clarification will be needed because of the derivation of not insignificant restrictions by regulations and laws.

The time until the decision could be used to catch up on the documentation already suggested by different scientists of the need for care. For this purpose, the need for care must be documented for all tested individuals together with their positive or negative test result in one or more defined cohorts, in addition to the PCR test result. The test results are available to the test centers and the need for care can be obtained from the affected individuals (no care or inpatient or intensive care within three months of the PCR test). These data should be collected for ethical, medical, epidemiological, and economic reasons.

However, responsible scientists could preempt political will by reporting, from defined samples of a cohort to be determined, all test results (positive and negative) within a defined test period, **along with actual inpatient care needs** (general or intensive care) within the first three months since the test was performed. This simple correlation could verify a not insignificant contribution to the evaluation of the suitability of the PCR test as a diagnostic tool. The additional effort is certainly justified. <<

Citation

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Literature

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