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European Patent Application 20764639.9
THERAPY GUIDANCE AND/OR THERAPY MONITORING FOR TREATMENT OF SHOCK
4TEEN4 Pharmaceuticals GmbH

This refers to the communication dated March 14, 2025:

The Examining Division regards the feature „a predetermined threshold, that is between 25 and 150 ng/ml for plasma DPP3“ as unclear.

We would like to reply thereto in written prior to Oral proceedings to enable the Examining Division to take our arguments into account as early as possible. We are of course prepared to present the same during Oral Proceedings.

A person skilled in the art, who is Statistician in the medical field, i.e a biostatistician, interprets the feature „a predetermined threshold, that is between 25 and 150 ng/ml for plasma DPP3“ as follows:

The predetermined threshold can have a value between 25 and 150 ng/ml for plasma DPP3, i.e. the predetermined threshold could be for example 30 ng/ml or 40 ng/ml or 50 ng/ml or 140 ng/ml. All these thresholds are meaningful for a medical practitioner. The actual determined DPP3 level in a blood sample of a patient may have a value above or below said predetermined threshold. If said actual determined DPP3 level in a blood sample of a patient is above said predetermined threshold then the medical practitioner would consider this patient as being in shock or as predicted to run into shock.

Having a look at the declaration of Dr. Oliver Hartmann, exemplary calculations were made for cut-offs of

1) 45 ng/ml
2) 50 ng/ml
3) 55 ng/ml

Each of these above-mentioned exemplary cut-offs is a value between 25 and 150 ng/ml for plasma DPP3.
We will explain the meaning of the claim for the threshold 45 ng/ml and threshold 55 ng/ml in the following.

Case 1: threshold 45 ng/ml

Let's assume the medical practitioner would choose the first cut-off that is a value between 25 and 150 ng/ml for plasma DPP3 and that is 45 ng/ml.

The medical practitioner would then take blood draws from patients and would obtain plasma therefrom and would then determine the respective DPP3 concentration in the obtained patient's plasma sample.

A patient having a determined DPP3 concentration of 48 ng/ml would then be „above the predetermined threshold" and the medical practitioner would consider this patient as being very likely in shock or very likely running into shock.

If another patient had a determined DPP3 concentration of 40 ng/ml the determined DPP3 value would be "below the predetermined threshold" and the medical practitioner would consider this patient as being very likely NOT in shock or very likely NOT running into shock.

Case 2: threshold 55 ng/ml

Let's assume the medical practitioner would choose another cut-off that is a value between 25 and 150 ng/ml for plasma DPP3 and that is 55 ng/ml.

The medical practitioner would then take blood draws from the same patients and would obtain plasma therefrom and would then determine the respective DPP3 concentration in the obtained patient's plasma sample.

A patient having a determined DPP3 concentration of 48 ng/ml would then be „below the predetermined threshold“ and the medical practitioner would consider this patient NOT as being very likely in shock or NOT very likely running into shock.

If the other patient had a determined DPP3 concentration of 40 ng/ml the determined DPP3 value would be also with this threshold “below the predetermined threshold“ and the medical practitioner would consider also this patient as being very likely NOT in shock or very likely NOT running into shock.

Please, consider the following technical terms and the possible cases in diagnostic methods:

> False positive: The patient is healthy, but the test incorrectly classified them as sick.
> True positive: The patient is sick, and the test correctly indicated this.
> True negative: The patient is healthy, and the test correctly indicated this.
> False negative: The patient is sick, but the test incorrectly classified them as healthy.

For the sake of our exercise - Let us now assume that the patient having a determined DPP3 concentration of 48 ng/ml actually runs into shock.

Under this assumption the chosen threshold of 55 ng/ml led to a false negative conclusion, whereas the threshold of 45 ng/ml led in this case for this patient to a true positive conclusion.

This does not mean that any of both thresholds would be wrong per se! It was wrong for this one patient in one case, but statistically for most of the patients the classification would have been correct, nevertheless. We are talking here about statistics and probabilities!

Further note, that for each and every threshold within the threshold range there will be false positives, false negatives, true positives and true negatives.

There is no diagnostic test in this world and no threshold in any diagnostic method that would allow only true negatives and true positives. For any diagnostic method and any chosen threshold, you will have a certain number of false negatives and false positives even though statistically every of the possible threshold is meaningful.

In the following we copied some helpful explanations from Wikipedia:
https://en.wikipedia.org/wiki/Sensitivity_and_specificity:

“The occurrence of false negatives and false positives, true negatives and true positives for a given method and threshold can be expressed mathematically.

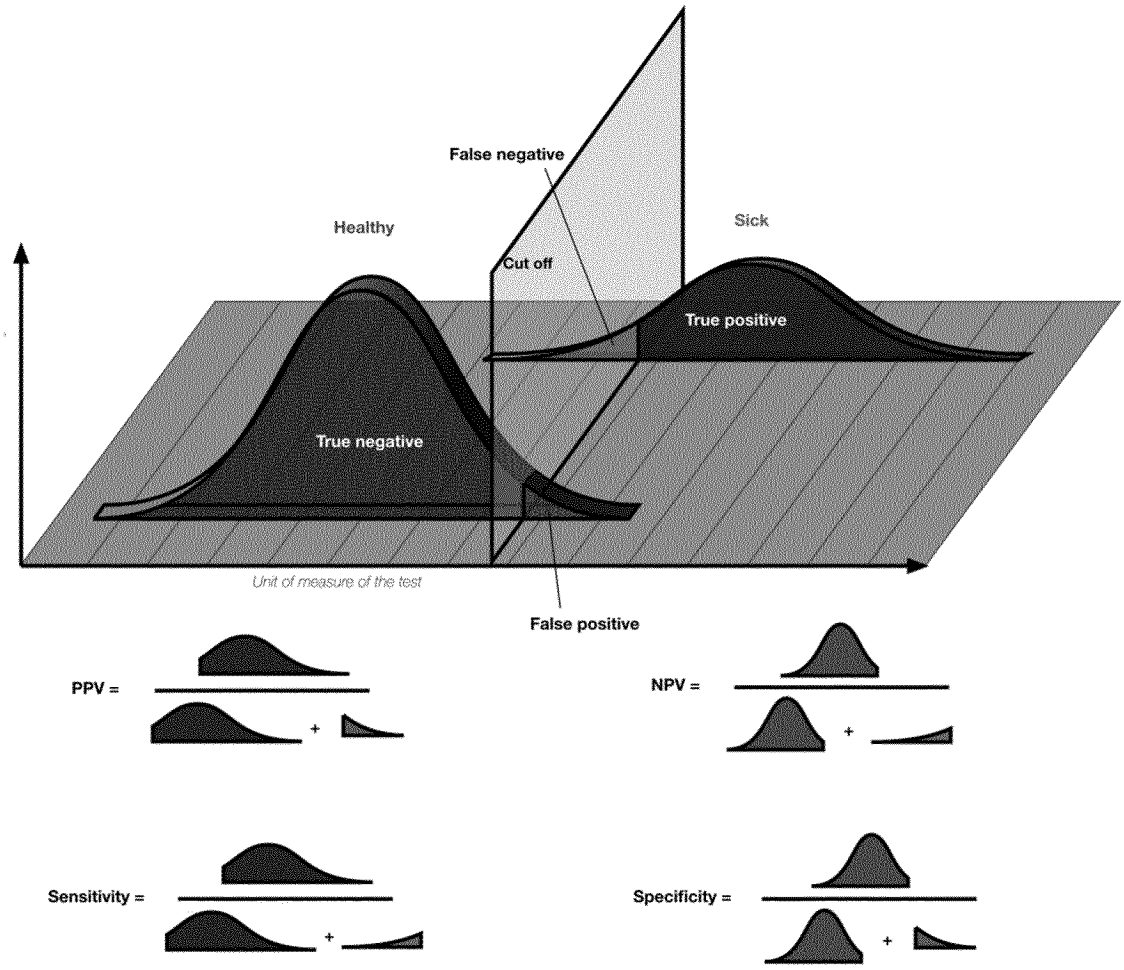
In medicine and statistics, sensitivity and specificity mathematically describe the accuracy of a test that reports the presence or absence of a medical condition. If individuals who have the condition are considered "positive" and those who do not are considered "negative", then sensitivity is a measure of how well a test can identify true positives and specificity is a measure of how well a test can identify true negatives:

- **Sensitivity** (true positive rate) is the probability of a positive test result conditioned on the individual truly being positive.
- **Specificity** (true negative rate) is the probability of a negative test result, conditioned on the individual truly being negative.

For all testing, both diagnoses and screening, there is usually a trade-off between sensitivity and specificity, such that higher sensitivities will mean lower specificities and vice versa.

A test which reliably detects the presence of a condition, resulting in a high number of true positives and low number of false negatives, will have a high sensitivity. This is especially important when the consequence of failing to treat the condition is serious and/or the treatment is very effective and has minimal side effects.

A test which reliably excludes individuals who do not have the condition, resulting in a high number of true negatives and low number of false positives, will have a high specificity. This is especially important when people who are identified as having a condition may be subjected to more testing, expense, stigma, anxiety, etc.



Sensitivity and specificity

The terms "sensitivity" and "specificity" were introduced by American biostatistician Jacob Yerushalmy in 1947."

What does this mean for our example?

A medical practitioner who is in addition to the Statistician in the medical field, a biostatistician, the person skilled in the art is very well aware of the above contexts. He will choose a threshold that is between 25 and 150 ng/ml for plasma DPP3 depending on whether he finds it more acceptable to have more false positive or more false negative conclusions.

For instance, the medical practitioner could measure plasma DPP3 for deciding which patient should obtain fluid administration. In this case, he would probably choose a lower threshold between 25 and 150 ng/ml for plasma DPP3, maybe 25 or 30 ng/ml. In this case he would probably overtreat more patients as if he chooses a higher threshold, but this may be acceptable as the treatment of fluid administration is safe and no harm is done.

In another instance the medical practitioner may measure plasma DPP3 for deciding which patient shall obtain a treatment having probably higher adverse effects. For this decision, he would probably choose a higher threshold between 25 and 150 ng/ml for plasma DPP3, maybe 70 or 90 ng/ml, thereby minimizing treating healthy patients, but he will miss some sick patients because the threshold is quite high and there are sick patients below said higher threshold.

This also means that the shifting of the threshold within the predetermined range as mentioned in the claims just changes the sensitivity and the specificity of the diagnostic method. Both statistic measures are counteracting, if you improve the sensitivity, you will worsen the specificity of the test and vice versa.

In his declaration, Dr. Hartmann has nicely explained the above said. In table A you can see that despite choosing different thresholds, in our case 45 ng/ml, 50 ng/ml or 55 ng/ml, the performance measures are essentially equivalent.

Therefore, all that the person skilled in the art needs to know is that he must choose a threshold that is between 25 and 150 ng/ml for plasma DPP3.

The above-explained consequences are clear to person skilled in the art.

Applicants once again kindly ask for including an expert in this field into the Examining Division, which is a Statistician in the medical field, a biostatistician. We are convinced that the wording of the claims is clear to person skilled in the art.

Further, the Examining Division asked to include a comparison step to DPP3 values of healthy persons.
It may be true that a threshold range is calculated statistically by some statistical comparison to DPP3 values of healthy persons. But once this has been done, once the threshold range has been determined (as this was done by the inventors of the present application) the medical practitioner will not compare an actual determined DPP3 value of a patient to DPP3 values of healthy persons, but he will compare said determined DPP3 value of a patient blood sample to said predetermined threshold. This is exactly reflected and encompassed by the actual wording of the claims. If we introduced that the

predetermined threshold value is obtained by measuring DPP3 levels in samples from "normal" healthy subjects or derived therefrom we would introduce a step or a feature into the claims that will not be performed when the inventive method is infringed or when the inventive method is induced to be infringed. It would render the claims useless and unenforceable.

Also, there is no constant shifting of the scope of the claims. The claims are clear and concise and clearly understood by a person skilled in the art. It is also not missing in the claims how threshold values are determined. The "art" of how thresholds are determined is basic knowledge of a person skilled in the art which is a Statistician in the medical field. It is described in textbooks; it is described in the description of the present application. The claims are in accordance with Art. 84 EPC.

We kindly ask the Examining Division to reconsider its conclusion in view of the above arguments and clarifications and furthermore, since numerous Examining Divisions were of the same opinion and granted patent claims with the exact same wording.

Applicants again respectfully requests that the presently pending claims are granted without Oral Proceedings.

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