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Datasheet for the decision of 28 October 2014

Case Number: T 2207/09 - 3.3.08

Application Number: 03700338.1

Publication Number: 1463839

IPC: C12Q1/68, C12Q1/70

Language of the proceedings: EN

Title of invention:
Method for detecting human papilloma virus mRNA

Patent Proprietor:
Norchip A/S

Opponent:
Quiagen GmbH

Headword:
Papilloma virus/NORCHIP

Relevant legal provisions:
EPC Art. 100(c), 100(a), 56

Keyword:
Basis in the application as filed - (yes)
Inventive step - (yes)

Decisions cited:
T 0165/00

Catchword:

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Case Number: T 2207/09 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 28 October 2014

Appellant: (Opponent)	QIAGEN GmbH Qiagen Str. 1 40724 Hilden (DE)
Representative:	Kilger, Christian A. Fanelli Haag Kilger PLLC Fasanenstrasse 29 10719 Berlin (DE)
Respondent: (Patent Proprietor)	Norchip A/S Industriveien 8 3490 Klokkarstua (NO)
Representative:	White, Nina Louise Boult Wade Tennant Verulam Gardens 70 Gray's Inn Road London WC1X 8BT (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 17 September 2009 rejecting the opposition filed against European patent No. 1463839 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	M. Wieser
Members:	M. R. Vega Laso
	J. Geschwind

Summary of Facts and Submissions

I. The appeal of the opponent (appellant) lies from the decision of an opposition division of the European Patent Office, posted on 17 September 2009, by which the opposition to the grant of European patent No. 1 463 839 with the title "Method for detecting human papillomavirus mRNA" was rejected under Article 101(2) EPC. The patent originates from European patent application No. 03700338.1, published as WO 03/057914 (in the following "the application as filed").

II. The patent was granted with 6 claims. Claim 1 reads as follows:

"1. An in vitro method of screening human subjects to assess their risk of developing cervical carcinoma, which method comprises screening the subject for expression of mRNA transcripts of the E6 gene from each and only HPV types 16,18,31,33 and 45 using an amplification technique and sorting the subject into one of two categories of risk for development of cervical carcinoma based on expression of E6 mRNA from at least one of said HPV types, wherein individuals positive for expression of said E6 mRNA from at least one of said HPV types are scored as carrying integrated HPV and are therefore classified as high risk for development of cervical carcinoma, whereas individuals negative for expression of all E6 mRNA are scored as not carrying integrated HPV and are therefore classified as no detectable risk for development of cervical carcinoma."

Dependent claims 2 to 6 specify variants of the method according to claim 1.

III. The patent had been opposed under Article 100(a) and (c) EPC, in particular on the grounds that the claimed subject-matter lacks novelty (Article 54 EPC), does not involve an inventive step (Article 56 EPC), and extends beyond the content of the application as filed.

IV. In the decision under appeal, the opposition division found that none of these grounds for opposition prejudiced the maintenance of the patent in the granted form. Various objections raised by the opponent under Article 100(c) EPC were dismissed. In particular, the opposition division acknowledged that the feature "*each and only HPV types 16, 18, 31, 33 and 45*" in claim 1 had a basis in the passage on page 19, lines 14 to 17 and in claim 10 of the application as filed, which included a reference to claim 6.

With regard to Article 100(a) EPC, the opposition division held that the claimed subject-matter was novel (Article 54 EPC) and involved an inventive step (Article 56 EPC). In particular, the opposition division regarded document (8) as the closest state of the art for the assessment of inventive step (see point 2.7 of the decision under appeal). Starting from that document, the technical problem to be solved was formulated as "... the provision of a screening method with increased coverage of the HPVs [i.e. human papilloma viruses] found in cancers" (see point 2.8). This problem was considered to be solved by the claimed screening method. The opposition division held that the notional skilled person, being cautious and conservative by nature, would not have departed from the screening method described in document (8). Even if the skilled person had nevertheless considered testing other combinations of HPV types, the specific

combination of five HPV types defined in claim 1 would not have been obvious and the skilled person would not have had a clear expectation of success.

V. In the statement setting out the grounds of appeal, the appellant contested the findings of the opposition division on Article 100(c) and Article 100(a) in conjunction with Article 56 EPC. In support of its objection of lack of inventive step, the appellant filed new evidence.

VI. The respondent (patent proprietor) replied to the statement of grounds of appeal and filed further evidence in support of its arguments on inventive step, in particular two scientific publications and a summary of clinical studies.

VII. As a subsidiary request, both parties requested oral proceedings.

VIII. The parties were summoned to oral proceedings. In a communication under Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) attached to the summons, the board commented on the admissibility of the evidence submitted in appeal proceedings, and expressed a provisional opinion on some of the substantive issues to be discussed during the oral proceedings.

IX. The respondent replied to the board's communication and filed a set of amended claims as an auxiliary request, the claims of the patent as granted being maintained as the main request.

X. The appellant submitted additional arguments and evidence in reply to the communication by the board.

XI. During the oral proceedings, which were held on 28 October 2014, the respondent withdrew the set of claims according to the auxiliary request.

XII. The following documents are referred to in the present decision:

(5): F. X. Bosch et al., 7 June 1995, Journal of the National Cancer Institute, Vol. 87, No. 11, pages 796 to 802;

(8): WO 94/26934, published on 24 November 1994

(16):N. Muñoz, Journal of Clinical Virology, 2000, Vol. 19, pages 1 to 5;

(17):A. Schneider et al., 28 September 2001, Deutsches Ärzteblatt, Vol. 98, No. 39, pages A2517 to 2521.

XIII. The submissions made by the appellant were essentially as follows:

Article 100(c) EPC

The feature "each and only HPV types 16, 18, 31, 33 and 45" in claim 1 had no basis in the application as filed. There was no direct and unambiguous disclosure of a defined set of HPV types as specified in claim 1 in the application as filed. The passage on page 19, lines 14 to 17 of the application as filed could not serve as a basis for claim 1 either, because this passage related to the target gene and did not limit the HPV types. In claim 10 of the application as filed, to which the opposition division referred in its

decision, the wording "at least one" – not "each and only" - was used.

Articles 100(a) and 56 EPC – Inventive step

It had been correctly decided by the opposition division that document (8) represented the closest state of the art, because it disclosed all the features of claim 1 of the patent in suit, with the sole difference that HPV type 35 was replaced by HPV type 45. In this document, HPV types 16 and 18 were described as the most relevant variants for risk determination, and it was suggested to expand an HPV test to additional variants, for instance types 31, 33 and 35.

For the assessment of inventive step, the notional person skilled in the art was a molecular biologist, or a clinician in a diagnostic company which had an extensive background in molecular biology, specifically virus detection. The skilled person was aware of the fact that various HPV types existed and that they could be divided into various risk types.

Starting from document (8), the technical problem to be solved was to provide a screening method with a broader geographic coverage for the HPV types found in patients at risk of developing cancer. The solution proposed in claim 1 was obvious in view of document (5), a worldwide HPV study of the regional and global distribution of HPV types, showing that the five most prevalent HPV types were types 16, 18, 31, 33 and 45, which provided an 80% global coverage. In view of document (5), the skilled person would have become aware of the low prevalence of type 35, and would have replaced it for type 45 which has a higher prevalence.

This particular selection of HPV types to be tested was confirmed by document (16).

The selection of the five HPV types 16, 18, 31, 33 and 45 was to be seen as an arbitrary selection among equal alternatives, because it did not achieve a technical effect going beyond the sum of the respective individual effects known from document (5). The purported technical effect that nearly 90% of the cervical carcinoma samples were related to one of the HPV types 16, 18, 31, 33 and 45 was to be considered a "bonus effect". The examples in the patent in suit focused on the HPV types 16, 18, 31 and 33 and did not describe a test for HPV 45. Nor was HPV type 45 mentioned in paragraph [0171], the table in paragraph [0132] or the passage on page 39, line 4 of the patent.

The reasoning of the opposition division that the use of five, rather than any other number of HPV types, was an indicator of inventive step was flawed. Even though the skilled person, starting from document (8), could have added further HPV types, he/she would not have done so. The skilled person knew that an assay becomes more and more error-prone the more HPV types are tested simultaneously. The choice of five HPV types was a compromise between sensitivity, specificity and cost. Thus, the subject-matter of claim 1 did not involve an inventive step.

XIV. The submissions made by the respondent may be summarized as follows:

Article 100(c) EPC

The passage on page 19, lines 14 to 17 of the application as filed provided a clear basis for the feature "each and only HPV types 16, 18, 31, 33 and 45".

Articles 100(a) and 56 EPC – Inventive step

Document (10) would be a more appropriate choice for the closest state of the art. However, even if document (8) were chosen as the starting point for assessing inventive step, the claimed subject-matter was not obvious to a person skilled in the art.

Document (8) described methodology for detection of E6/E7 mRNA transcripts. The methodology was exemplified by testing ability to amplify E6/E7 mRNA from HPV types 16 and 18 in cell cultures. There was no data relating to detection of E6/E7 mRNA transcripts in actual clinical samples. On page 14, lines 3 to 12, it was suggested that the principle of co-amplification used with HPV types 16 and 18 could be applied to a plurality of HPV types. There was no clear teaching in this passage that one should use a "closed" group of five types, namely 16, 18, 31, 33 and 35. Moreover, document (8) failed to disclose any suitable primers for amplification of any HPV types other than 16 or 18.

The formulation of the technical problem proposed by the opposition division over-stated the technical teaching of document (8), because this document provided no data to establish that the assay described therein actually worked on clinical samples from subjects with cervical cancer, or cervical pre-cancer, let alone what the coverage rate might be. Against this

background, the suggestion that a person of ordinary skill in the art would deduce from document (8) that the selection of HPV types needed to be modified in some way to "improve" coverage seemed flawed. Document (8) did not even teach whether the method should be used diagnostically (e.g. to confirm cases of invasive carcinoma in situ) or to assess risk of developing cervical cancer. Hence, a more appropriate formulation of the problem to be solved would be production of an assay which enabled "high risk" subjects to be identified at an early stage, i.e. before development of carcinoma in situ, based on E6 mRNA expression.

HPV prevalence data based on DNA genotyping in patients with confirmed invasive cervical cancer was not the basis on which the skilled person would have selected HPV types for inclusion in an HPV assay, particularly not an mRNA-based assay. In any event, the global prevalence data did not identify a "big five" set of HPV types.

With the use of the HPV types specified in claim 1, an unexpected technical effect was achieved. While based on the prevalence data in document (5) one would have expected that 80% of all cervical cancers could be identified, the mRNA-based assay of the invention detected nearly 90% of confirmed cancer cases.

Since nothing in the available prior art would have prompted a person of ordinary skill to design an mRNA-based assay capable of detecting a combination of only five HPV types, particularly when the DNA-based assays already available in the art were designed to detect a minimum of 13 HPV types, the subject-matter of claim 1 involved an inventive step.

XV. The appellant (opponent) requested that the decision under appeal be set aside and that the patent be revoked.

XVI. The respondent (patent proprietor) requested that the appeal be dismissed.

Reasons for the Decision

Article 100(c) EPC

1. Among the various objections under Article 100(c) EPC dismissed by the opposition division in the decision under appeal (see section 2.3 of the decision), solely the opposition division's findings concerning the feature "*each and only HPV types 16, 18, 31, 33 and 45*" were contested by the appellant in its statement of grounds of appeal (see section IV above). In its reply to the board's communication under Article 15(1) RPBA, the appellant referred to the arguments set out in the notice of opposition. However, it did not put forward any reasons why the opposition division's findings on further objections under Article 100(c) EPC were not correct.

2. According to the jurisprudence of the Boards of Appeal, a reference to submissions before the first-instance department cannot normally replace an explicit account of the party's legal and factual reasons in appeal proceedings (see e.g. decision T 165/00 of 30 November 2000). In the present case, the board sees no special circumstances that justify taking a decision on issues which were not properly raised and substantiated in appeal proceedings.

3. In the decision under appeal, the opposition division held that the feature "*each and only HPV types 16, 18, 31, 33 and 45*" of the method of claim 1 had a basis in the passage on page 19, lines 14 to 17 of the application as filed. This passage reads:

"*In the methods based on detection of E6 mRNA alone it is preferred to detect at least types HPV 16, 18, 31, 33 and 45, and in a preferred embodiment the assay may detect* ***only*** *these HPV types*" (emphasis added by the board).

4. While the wording "each" present in claim 1 is not found in this passage of the application as filed, the board holds that this wording does not add anything which goes beyond what a skilled reader understands from the passage quoted above, namely that each of the five HPV types mentioned therein is detected.

5. Additionally, the passage on page 21, lines 5 to 30 of the application as filed, to which the opponent (the present appellant) referred in its notice of opposition, describes as a most preferred embodiment a method that involves "*... screening for E6 mRNA using a technique which is able to detect E6 mRNA from HPV types 16, 18, 31 and 33, and preferably also 45*". Contrary to the appellant's view, the fact that in this passage the detection of HPV type 45 in addition to types 16, 18, 31 and 33 is disclosed only as a preferred embodiment, or that other methods involving detection of E6 mRNA from additional HPV types are described in the application as filed, neither weakens nor eliminates the clear and unambiguous disclosure of a screening method with the features specified in claim 1. Also the fact that, in the examples of the

application, primers for HPV types other than 16, 18, 31, 33 and 45 are described is of no detriment to the specific disclosure of the claimed method in the general part of the description.

6. Thus, the opposition division's finding that Article 100(c) EPC does not prejudice the maintenance of the patent as granted is, in the board's judgement, correct.

Articles 100(a) and 54 EPC – Novelty

7. The appellant expressly acknowledged the novelty of the claimed subject-matter with regard to document (8), and the board does not see any reason to differ from the opposition division's findings in section 2.4 of the decision under appeal.

Article 56 EPC – Inventive step

The closest state of the art

8. Both the opposition division and the appellant regarded document (8) as the closest state of the art for the assessment of inventive step. So does the board.

9. Document (8) describes a specific assay for HPV infections associated with cervical dysplasia and cellular transformation to malignancy, relying on the amplification of mRNA expressed from oncogene regions (E6/E7 genes) of HPV types implicated in malignant or pre-malignant cervical lesions. The assay restricts detection to malignant and pre-malignant HPV types, and distinguishes actual oncogene expression from mere passenger presence of virus (see page 2, lines 23 to 31).

10. The amplification method described in document (8) is exemplified only for HPV types 16 and 18. However, the following is stated on page 14, lines 4 to 8:

"*Co-amplification. Once primers have been selected for both HPV 16 and HPV 18 a co-amplification of both targets is required for clinical use. Co-amplification is required because only a single specimen is obtained. This can be done not only for HPV 16 or HPV 18, but also can be applied to a plurality of HPV types including but not limited to HPV 31, 33, and 35, as well as any other types that prove to be oncogenic.*"

11. The board interprets this passage as a hint to the skilled person to include in the co-amplification assay not only the HPV types specifically mentioned but also any further HPV types associated with carcinoma, in particular cervical carcinoma. Contrary to the appellant's view, the board does not see in this passage a suggestion that only **five** HPV types need to be co-amplified. While in fact only five HPV types (16, 18, 31, 33 and 35) are specifically suggested, it is clear from the wording "*including but not limited to*" and "*as well as any other types*" that any **further** HPV types that prove to be oncogenic can be included.

12. The board also disagrees with the appellant's argument that a combination of HPV types 16 and 18 with any HPV types other than HPV types 31, 33, and 35 that prove to be oncogenic is suggested in the passage quoted above. The appellant's interpretation of the relevant statements in document (8) disregards the wording "*including ... HPV 31, 33, and 35*", which clearly indicates that these three HPV types are to be co-amplified with types 16 and 18.

The technical problem to be solved

13. The difference between the assay suggested in the passage on page 14, lines 4 to 8 document (8) and the screening method according to claim 1 lies in the set of HPV types to be amplified. In particular, claim 1 requires that E6 mRNA from **each and only** HPV types 16, 18, 31, 33 and 45 be amplified. The board construes the wording "*each and only*" as meaning that, in the claimed method, E6 mRNA from every one of these HPV types but from no more than these five specific types is amplified.

14. The board therefore shares the view of the opposition division that, starting from document (8), the problem to be solved can be formulated as the provision of an assay with improved coverage of the HPV types associated with cancer, in particular cervical carcinoma.

15. It was not disputed by the appellant that this problem is solved by the method according to claims 1 to 6 of the patent as granted, which comprise screening samples for E6 mRNA from each and only HPV types 16, 18, 31, 33 and 45. The appellant's argument that the examples in the patent do not include HPV type 45 is not valid in view of Table 14 of the patent, showing an amplification assay with primers directed to HPV types 16, 18, 31, 33 and 45.

Is the solution proposed in claim 1 obvious?

16. As stated above, the only suggestion that a person skilled in the art derives from the passage of document (8) quoted in paragraph 10 above is that,

besides HPV types 16, 18, 31, 33 and 35, further HPV types which prove to be oncogenic can be included in the assay. Contrary to the appellant's view, there is no suggestion to limit the assay to five HPV types, let alone to replace HPV type 35 with HPV type 45.

17. The board takes the view that a person skilled in the art confronted with the problem of providing an improved assay would not have found in the further documents cited in the appeal proceedings any information that would make obvious the solution proposed in claim 1.

18. In document (5), on which the appellant strongly relied, the results of worldwide epidemiological studies on the prevalence of human papilloma virus in cervical cancer are reported. According to this document, there are more than 20 different cancer-associated HPV types. Table 2, in which the prevalence of individual HPV types by geographic region is provided, shows that types 16, 18, 31, 33 and 45 are the most prevalent types at the global level, and in Figure 1 HPV distribution for types 16, 18, 45, 31 and 33 in different regions is shown.

19. The board holds that, having regard to the information provided in document (5) as a whole, the choice of HPV types 16, 18, 31, 33 and 45 for a screening assay to assess the risk of a subject developing cervical carcinoma can only be made with hindsight. Even though types 16, 18, 31, 33 and 45 are, in fact, shown to be the most prevalent types, the skilled person would not have disregarded further HPV types with fairly high prevalence. For instance, there was, in the board's view, no reason for a person skilled in the art to include HPV type 33 in the assay, but to exclude

type 52, which according to the results in Table 2 of document (5) has nearly the same prevalence (25% as opposed to 26%).

20. Document (5) does not expressly suggest including in the assay only the five most prevalent types. Rather, it is stated in the final discussion that:

"*Diagnostic, therapeutic, and vaccination strategies must consider the complexity posed by the existence of at least 20 different cancer-associated HPVs. Further efforts are necessary to determine whether less prevalent types [often termed "intermediate risk" (50)] confer cancer risks to an individual that are equivalent to those posed by infection with the most common types (e.g., HPVs 16 and 18, which are termed "high-risk"). Although our understanding of cervical cancer has been enlightened by defining the role of HPV, it may be complicated by the intricacies of this diverse group of viruses (6).*" (see page 801, paragraph bridging the left- and right-hand columns)

21. Hence, the board judges that the solution proposed in claim 1 was not obvious to a skilled person in view of document (8) in combination with document (5).

22. The same applies to a combination of document (8) with either document (16) or document (17), or any other document cited in the appeal proceedings. While it is stated in document (16) (a summary of studies carried out on HPV and cervical cancer) that HPV types 16, 18, 45, 31 and 33 are the most prevalent in the general population, it is also stated that, in addition to HPV 16 and 18, HPV 31, 33, 35, 45, 51, 52, 58 and 59 can be considered as carcinogenic (see abstract). It is not apparent to the board why a person skilled in the

art seeking to improve the assay described in document (8) would have restricted the assay to only five types, in particular types 16, 18, 31, 33 and 45, and omitted the further carcinogenic types mentioned in document (16).

23. Similarly, it is stated in document (17) that cervical cancer is primarily caused by the "high-risk" types of human papilloma virus (HR-HPV), HPV types 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70 und 73 being regarded as carcinogenic (see page A2517, left-hand column, first paragraph). Even though it is stated in lines 13 to 16 of the right-hand column on the same page that 80% of all cervical carcinomas can be identified by assaying HPV types 16, 18, 31, 33 and 45, a person skilled in the art, having in mind the suggestion in document (8) to include not only type 35 but also any other types that prove to be carcinogenic (see paragraph 10 above), would have no reason to restrict the coverage of an assay to assess the risk of developing cervical carcinoma to HPV types that account for only 80% of all cervical carcinomas, thus omitting other HPV types mentioned in document (17) that may cause at least part of the remaining 20% potentially life-threatening carcinomas.

24. The appellant argued that the selection of the five HPV types 16, 18, 31, 33 and 45 was to be seen as an arbitrary selection with no particular technical effect. The board disagrees. It has not been disputed by the appellant that, by restricting the assay to the detection of only five HPV types, it becomes less costly and also less prone to false negatives than assays detecting more HPV types. Nor has the appellant contested that, by including HPV type 45 in addition to types 16, 18, 31 and 33 in the assay, nearly 90% of the

cervical carcinomas are detected (see page 8, lines 48 to 50 of the patent), which is a substantially higher coverage than that indicated in document (17) or calculated from the prevalence data in document (5).

25. Since a screening method to assess the risk of a human subject developing cervical carcinoma based on the detection of each and only HPV types 16, 18, 31, 33 and 45 was not obvious to a person skilled in the art seeking to improve the assay described in document (8), the board does not need to judge whether or not the skilled person had a reasonable expectation of success.

Conclusion

26. None of the grounds for opposition under Article 100(a) and (c) EPC brought forward by the appellant prejudices maintenance of the patent in the granted form. Thus, the opposition division's decision rejecting the opposition is upheld.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated