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**Datasheet for the decision of 14 August 2025**

**Case Number:** T 1798/23 - 3.3.08

**Application Number:** 16751551.9

**Publication Number:** 3332028

**IPC:** C12Q1/689, G16B15/00, G16B20/00, G16B30/00, G16B40/00

**Language of the proceedings:** EN

**Title of invention:**
Genetic resistance prediction against antimicrobial drugs in microorganism using structural changes in the genome

**Patent Proprietor:**
bioMérieux

**Opponent:**
Norens Patentbyrå AB

**Headword:**
Method of genetic resistance prediction/BIOMÉRIEUX

**Relevant legal provisions:**
EPC Art. 56
EPC R. 76(2)(b)
RPBA 2020 Art. 13(2)

**Keyword:**
Admissibility of opposition - (yes)
Auxiliary requests 2 to 12 - lack of inventive step - (yes)
Admissibility of late filed arguments - (no)

**Decisions cited:**
T 1178/04, T 1179/16, T 1518/20

**Catchword:**

Europäisches Patentamt
European Patent Office
Office européen des brevets

**Beschwerdekammern**

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**Case Number: T 1798/23 - 3.3.08**

# D E C I S I O N
# of Technical Board of Appeal 3.3.08
# of 14 August 2025

| | |
|---|---|
| **Appellant:** (Opponent) | Norens Patentbyrå AB<br>Box 101 98<br>100 55 Stockholm (SE) |
| **Representative:** | A. Bratt<br>Noréns Patentbyrå AB<br>Box 10198<br>100 55 Stockholm (SE) |
| **Respondent:** (Patent Proprietor) | bioMérieux<br>Chemin de l'Orme<br>69280 Marcy - l'Etoile (FR) |
| **Representative:** | W. Thomann and T. Wilk<br>Schnappauf, Georg<br>ZSP Patentanwälte PartG mbB<br>Hansastraße 32<br>80686 München (DE) |
| **Decision under appeal:** | **Interlocutory decision of the Opposition Division of the European Patent Office posted on 8 September 2023 concerning maintenance of the European Patent No. 3332028 in amended form** |

**Composition of the Board:**

| | |
|---|---|
| **Chair** | T. Sommerfeld |
| **Members:** | M. Montrone |
| | A. Bacchin |

## Summary of Facts and Submissions

I. European patent No. 3 332 028 B1 ("the patent") was granted for European patent application No. 16 751 551.9 which has been filed as International patent application published as WO 2017/021529.

II. An opposition was filed against the granted patent. The patent was opposed in its entirety under Article 100(a) EPC (in conjunction with Articles 53(c) and 56 EPC), 100(b) and 100(c) EPC.

III. The present appeal has been filed by the opponent (appellant) against the interlocutory decision of an opposition division, according to which the patent could be maintained in amended form on the basis of the set of claims of auxiliary request 1 filed at the oral proceedings on 22 June 2023.

IV. In reply to the appellant's appeal, the patent proprietor (respondent) requested that the appeal be dismissed (meaning that the patent be maintained on the basis of auxiliary request 1 found allowable by the opposition division) or, alternatively, that the patent be maintained on the basis of the sets of claims of auxiliary requests 2 to 12. At the oral proceedings before the board, the respondent withdrew auxiliary request 1.

V. Claim 1 of auxiliary request 2 reads:

"1. A computer implemented method of determining structural variations in a genome of a microorganism, particularly a bacterial microorganism, comprising:

obtaining or providing a first data set of gene sequences of a plurality of clinical isolates of the microorganism, wherein optionally at least a part of the gene sequences of the first data set are assembled; analyzing the gene sequences of the first data set for structural variations of the genome to obtain a third data set of structural variants, wherein a structural variation of the genome is where at least two adjacent bases in a gene sequence are changed, and wherein the structural variations are detected alignment-free; providing a second data set of antimicrobial drug, e.g. antibiotic, resistance and/or susceptibility of the plurality of clinical isolates of the microorganism;

correlating the third data set with the second data set and statistically analyzing the correlation; and determining the structural variations in the genome of the microorganism associated with antimicrobial drug, e.g. antibiotic, resistance".

VI. Claim 1 of auxiliary request 3 differs from claim 1 of auxiliary request 2 in that the feature "*particularly a bacterial microorganism*" has been replaced in the preamble by "*selected from the group consisting of Acinetobacter, Escherichia, Enterobacter, Klebsiella, Proteus, Pseudomonas, Salmonella, Serratia, Shigella and Staphylococcus*" and in that the feature "*or annotated to a pan-genome*" has been added.

VII. Claim 1 of auxiliary request 4 is based on claim 4 of auxiliary request 2 and reads:

"1. A diagnostic method of determining an infection of a patient with a microorganism, particularly a bacterial microorganism potentially resistant to antimicrobial drug treatment, comprising the steps of:

a) determining, in a sample obtained or provided from the patient, the presence of at least one structural variation in at least one genetic sequence of the microorganism, particularly bacterial microorganism contained in the sample,
wherein the structural variation of the genome is where at least two adjacent bases in a gene sequence are changed, and wherein the structural variations are detected alignment-free or annotated to a pan-genome, and
b) determining whether the at least one structural variation is associated with antimicrobial drug, e.g., antibiotic, resistance by correlating the at least one structural variation with a data set of antimicrobial drug, e.g., antibiotic, resistance and/or susceptibility of a plurality of clinical isolates of the microorganism and statistically analyzing the correlation, wherein the presence of said at least one structural variation associated with antimicrobial drug, e.g., antibiotic, resistance is indicative of an infection with an antimicrobial drug resistant microorganism in said patient".

VIII. Claim 1 of auxiliary request 5 differs from claim 1 of auxiliary request 2 in that the feature "*particularly a bacterial microorganism*" has been replaced in the preamble by "*selected from the group consisting of Acinetobacter, Escherichia, Enterobacter, Klebsiella, Proteus, Pseudomonas, Salmonella, Serratia, Shigella and Staphylococcus*".

IX. Claim 1 of auxiliary request 6 differs from claim 1 of auxiliary request 4 in that in step a) the feature "*or annotated to a pan-genome*" has been deleted.

X. Claim 1 of auxiliary request 7 differs from claim 1 of auxiliary request 6 in that the feature "*particularly a bacterial microorganism*" has been replaced in the preamble by "*selected from the group consisting of Acinetobacter, Escherichia, Enterobacter, Klebsiella, Proteus, Pseudomonas, Salmonella, Serratia, Shigella and Staphylococcus*" and in that in step (a) the feature "*particularly a bacterial microorganism*" has been deleted.

XI. Claim 1 of auxiliary request 8 differs from claim 1 of auxiliary request 2 in that the feature "*detected alignment-free*" has been replaced by "*annotated to a pan-genome*".

XII. Claim 1 of auxiliary request 9 differs from claim 1 of auxiliary request 8 in that the feature "*particularly a bacterial microorganism*" has been replaced in the preamble by "*selected from the group consisting of Acinetobacter, Escherichia, Enterobacter, Klebsiella, Proteus, Pseudomonas, Salmonella, Serratia, Shigella and Staphylococcus*".

XIII. Claim 1 of auxiliary request 10 differs from claim 1 of auxiliary request 4 in that in step a) the feature "*detected alignment-free*" has been deleted.

XIV. Claim 1 of auxiliary request 11 differs from claim 1 of auxiliary request 10 in that the feature "*particularly a bacterial microorganism*" has been replaced in the preamble by "*selected from the group consisting of Acinetobacter, Escherichia, Enterobacter, Klebsiella, Proteus, Pseudomonas, Salmonella, Serratia, Shigella and Staphylococcus*" and in that in step (a) the feature "*particularly a bacterial microorganism*" has been deleted.

XV. Claim 1 of auxiliary request 12 differs from claim 1 of auxiliary request 11 in that the feature "*detected alignment-free*" has been added.

XVI. In a further submission, the appellant submitted additional arguments.

XVII. In a communication pursuant to Article 15(1) RPBA, the board provided its preliminary assessment on some of the issues including claim construction and inventive step of all auxiliary requests on file.

XVIII. In reply thereto, the appellant submitted further arguments.

XIX. The following documents are referred to in this decision:

D2: Wozniak M. *et al.*, BMC Genomics, 2012, Vol. 13 (Suppl. 7), S23, 1-17

D13: Iqbal Z. *et al.*, Nature Genetics, 2012, Vol. 44(2), 226-232

D14: Tettelin H. *et al.*, PNAS, 2005, Vol. 102(39), 13950-13955

D15: Nguyen N. *et al.*, J. Computational Biology, 2015, Vol. 22(5), 387-401

D18: Vinga S., Briefings in Bioinformatics, 2013, Vol. 15(3), 376-389

XX. The arguments of the parties relevant for the decision are dealt with in the Reasons for the Decision.

XXI. The requests of the parties being relevant for the decision are the following (for the complete list of the parties' requests, see the minutes of the oral proceedings, page 2):

(a) The appellant requested:
- that the decision under appeal be set aside and that the patent be revoked,
- that the opposition be held admissible,
- that the respondent's new line of argument under inventive step first raised at the oral proceedings before the board not be admitted/considered.

(b) The respondent requested:
- that the opposition be held inadmissible,
- that the patent be maintained on the basis of auxiliary requests 2 to 12 filed in reply to the appeal
- that a new line of argument under inventive step first raised at the oral proceedings before the board be admitted/considered.

## Reasons for the Decision

*Admissibility of the opposition*

1. With their reply to the appellant's grounds of appeal, the respondent maintained their objection, already raised at opposition proceedings, to the admissibility of the opposition, due to a lack of the necessary information allowing the unambiguous identification of the opposed patent in the notice of opposition.

1.1 It was submitted that while the notice of opposition indicated the correct European patent application No. 16 751 551. 9, the publication number was wrong with regard to the last digit (it indicates EP 3 332 02**3**, whereas the publication number for the patent in suit is EP 3 332 02**8**), as well as the title of the invention reading "*Genetic testing for alignment-free predicting resistance of microorganisms against the antimicrobial agents*" (this being the title of EP 3 332 023), instead of "*Genetic resistance prediction against antimicrobial drugs in microorganism using structural changes in the genome*" (this being the title of the patent EP 3 332 028).

1.2 The two publication numbers identified thus two patents, both belonging to Ares Genetics GmbH, with the two titles of the inventions as indicated above.

2. According to Rule 76(2)(b) EPC the notice of opposition must contain, *inter alia*, the number of the European patent against which opposition is filed, the name of the proprietor of the patent and the title of the invention. The opposition is rejected as inadmissible if the notice of opposition does not sufficiently identify the patent, unless the deficiency has been remedied before expiry of the opposition period (Rule 77(1) EPC).

2.1 The admissibility of an opposition must be assessed *ex officio* in every phase of the opposition and ensuing appeal proceedings (e.g. T 1178/04 and also Case Law of the Boards of Appeal of the EPO, 11th edition, 2025 (hereafter "Case Law"), IV.C.2.3.1).

2.2 Since the mention of the grant of the patent was published in the European Patent Bulletin on 6 January 2021, the opposition period expired on 6 October 2021.

2.3 The notice of opposition filed on 29 September 2021 and the accompanying letter, Form 1038, correctly indicated the publication number of the patent as EP 3 332 028.

2.4 With submissions dated 30 September 2021, the notice of opposition was filed anew with the corrected title ("Genetic resistance prediction against antimicrobial drugs in microorganism using structural changes in the genome"). The letter also contained the name of the patent owner (Ares Genetics GmbH), the European patent application No. 16751551. 9 and the patent's publication number EP 3 332 028, all as correctly indicated before in the first notice of opposition.

2.5 From the European Patent Register it can be derived that on 5 October 2021, the EPO issued a communication (Form 2302) indicating deficiencies under Rule 76(2)(b) EPC in the notice of opposition of 29 September 2021. The deficiency was due to a difference in the title of the invention subject of the patent from the title indicated in the Register and the opponent was invited to remedy the deficiency within a period of two months from notification of the communication.

2.6 Irrespective of whether the submissions of 30 September 2021 were actually in reply to the EPO's communication of 5 October 2021, due to the opponent becoming aware of the deficiency in advance of the date indicated in that communication, or were filed by the opponent on its own motion, it is evident that the errors were corrected before expiry of the opposition period, as required by Rule 77(1) EPC.

2.7 In addition, the board also finds that since the publication numbers indicated in the notice of opposition on 29 September and on 30 September 2021 correspond to one patent while the different titles correspond to two patents owned by Ares Genetics GmbH could not have caused any ambiguity as to the identification of the opposed patent. In fact, the notice of opposition filed on 29 September and the accompanying Form 1038 mentioned the European patent application No. 16 751 551. 9 and the publication number EP 3 332 028 which are both identical to that indicated in the corrected notice of opposition filed on 30 September. The information provided in the submissions of 30 September 2021 thus clearly and consistently indicates the number of the opposed patent, the name of the proprietor and the title of the invention.

2.8 The board thus concludes that before expiry of the opposition period, namely on 30 September 2021, the notice of opposition sufficiently identified the patent with the information required by Rule 76(2)(b) EPC.

3. The opposition is therefore admissible.

*Auxiliary request 2*

*Claim construction - claim 1*

4. Claim 1 concerns a computer implemented method of determining structural variations in a microbial genome which comprises the following steps:

- "*obtaining or providing a first data set of gene sequences of a plurality of clinical isolates of the microorganism*" (emphasis added),

- analysing said first data set for structural genomic variations "*where at least two adjacent bases in a gene sequence are changed*" which "*are detected alignment-free*" to "*obtain a third data set of structural variants*" (emphasis added),
- "*providing a second data set of antimicrobial drug [...] resistance and/or susceptibility of the plurality*" of microbial clinical isolates (emphasis added),
- "*correlating the third data set with the second data set*" and "*statistically analyzing the correlation*", and
- "*determining the structural variations in the genome of the microorganism associated with antimicrobial drug [...] resistance*".

5. Thus claim 1 relates to a computer-based method which statistically correlates microbial genomic sequence variations of at least two consecutive bases in clinical isolates detected by alignment-free methods with an antimicrobial drug resistance of these isolates for determining an association between these sequence variations and the microbial drug resistance.

6. Claim 1 specifies that the first data set of gene sequences is obtained from a plurality of clinical isolates. The term "*plurality*" according to its ordinary meaning in the art relates to at least two such clinical samples.

7. Since the change of "*at least two adjacent bases in a gene sequence*" is not further specified, claim 1 encompasses any change of at least two consecutive nucleotides compared to a reference sequence, including insertions and deletions (i.e. "indels") of gene fragments or whole genes.

8. Nor is the "*alignment-free*" detection of sequence variations mentioned in claim 1 further specified. This term thus encompasses any such method suitable for detecting at least 2 consecutive nucleotide changes in a sequence compared to a reference sequence. Alignment-free methods for comparing and analysing sequences as alternative to alignment-based methods were commonly known to the skilled person at the relevant filing date of the patent (e.g. document D13, abstract, "*de Bruin graphs*" and document D18, abstract and page 377, right column, third paragraph).

*Admission/consideration of a new line of argument under inventive step*

9. At the oral proceedings before the board, the respondent for the first time in the proceedings argued that there were more distinguishing features between the claimed method and that of document D2 and reformulated the technical problem in view of these distinguishing features (see Minutes of oral proceedings, page 4).

10. The appellant objected to these submissions as being late filed and requested that they be not admitted/ considered in appeal.

11. The issue to be assessed as regards the admission of the respondent's new line of argument is thus whether this submission represents an amendment of the respondent's case and if yes, whether exceptional circumstances existed that could be justified by cogent reasons (Article 13(2) RPBA).

12. The respondent did not dispute that this line of argument had not been presented during the opposition proceedings, or in the written phase of the appeal proceedings. However, the respondent contested that the submission of this line of argument only at the oral proceedings before the board amounted to an amendment of their case. In particular, since their argumentation was based on the method of claim 1 and its construction, their argumentation contained no new facts. Consequently the finding of an additional distinguishing feature between the claimed method and that of document D2, the presence of a technical effect ascribable thereto and the formulation of a technical problem based thereon was not new, but merely expanded and refined their initial arguments on inventive step. Consequently, this line of argument should be admitted into the proceedings.

13. The board does not agree. At the oral proceedings before the opposition division all parties agreed that the sole difference between the claimed method and that of document D2 resided in the issue of how a structural variation in a sequence was to be determined (decision under appeal, Reasons 6.1.1 and 6.1.2). Although the appellant maintained this line of argument in their grounds of appeal, the respondent in reply thereto did not submit that there was a further difference between the two methods, let alone that the obtained sequence variations represented intra-strain variations from clinical samples only. Nor did the respondent submit that there was a technical effect ascribable to that difference. A technical problem based thereon was not formulated either.

13.1 In view of this course of events, the submission of this new line of arguments by the respondent only at

the oral proceedings before the board introduces new facts, namely the presence of a further distinguishing feature in claim 1, the presence of a technical effect ascribable thereto and the formulation of a more ambitious technical problem based thereon. Consequently, the respondent has amended their case.

13.2 As regards the exceptional circumstances justified by cogent reasons, the respondent has not submitted any. Instead the respondent argued that the new line of argument represented merely a refinement of their previous submissions. For the reasons set out above this is not convincing. The consideration of a new distinguishing feature in claim 1 entails a complete re-evaluation of the claimed method requiring a new discussion of inventive step.

13.3 According to Article 12(3) RPBA, the respondent's reply to the appeal has to contain their complete case. It was the respondent's choice of not bringing forward this new line of argument in their reply. The submission of this new line of argument for the first time at the oral proceedings before the board runs thus counter the need for procedural economy and the principle of procedural fairness.

13.4 In view of these considerations, the board does not admit this new line of argumentation into the proceedings (Article 13(2) RPBA).

*Inventive step*

*Distinguishing feature, technical effect and technical problem to be solved*

14. It is uncontested that document D2 represents the closest prior art for the method of claim 1. The board has no reason to come to a different conclusion.

15. Document D2 discloses a method for identifying drug resistance-associated variations in the genome of *Staphylococcus aureus* (*S. aureus*) by associating a genomic "*gene gain/loss*" (i.e. indels) and "*amino acid point mutations*" of 100 fully sequenced *S. aureus* strains with drug resistance phenotypes mediated by a comparative analysis (page 3, left column, penultimate paragraph). Document D2 reports that many *S. aureus* isolates are methicillin resistant (MRSA) which represents a major health problem (title, abstract, page 1, right column, first paragraph, page 2, right column, second paragraph, page 3, left column, second to fifth paragraph and page 13, left column, sixth paragraph). The different *S. aureus* strains sequenced are at least in part obtained from clinical isolates (page 3, right column, fourth paragraph, strains "*MRSA252 and MSSA476 [29]*", "*CF-Marseille [42]*" and "*ECT-R_2 [46]*"). The method aims at the identification of "*genetic variations which are likely to be associated with drug resistance*" (page 4, left column, eight paragraph) which includes the identification of new and known drug resistance gene variations (page 6, right column, second and third paragraph, page 11, left column, second paragraph and page 13, right column, second and third paragraph). Document D2 thus describes an alignment-based detection of genomic gene variations in *S. aureus* which are compared to drug resistant phenotypes followed by a statistical analysis to predict an association of these variants with antimicrobial drug resistance.

16. In agreement with the conclusions of the opposition division, the method of claim 1 differs from that of document D2 solely in that the structural variations are *inter alia* detected "*alignment-free*" (decision under appeal, Reason 6.1.1). It is apparent from this section of the appealed decision too that both parties agreed with these conclusions of the opposition division. Only at the oral proceedings before the board did the respondent argue that there were more distinguishing features. However, for the reasons set out above (points 9, 12, 13 and 13.1 to 13.4), this new line of argument was not admitted into the proceedings.

16.1 Comparative data are not on file which disclose potential advantages of an alignment-free detection of structural variants compared to the alignment-based detection method reported in document D2.

16.2 Accordingly the technical problem to be solved resides in the provision of "*an alternative method for detecting structural variants associated with antimicrobial resistance*" (decision under appeal, Reason 6.1.2).

*Obviousness*

17. Starting from the method disclosed in document D2, the skilled person looking for a mere alternative to alignment-based methods for detecting structural variations of at least 2 consecutive nucleotides would have looked at the relevant art in this technical field. Document D18 is a review article about information theory applications for biological sequence analysis (title). Its teaching can thus be regarded as belonging to the common general knowledge of the skilled person. This document reports that alignment-

free methods "*have grown in the past decades as powerful approaches to compare and analyze biological sequences, constituting alternatives to alignment-based techniques*" (D18, page 377, right column, third paragraph, emphasis added). These methods are also used for analysing bacterial genomic sequences and show at least for certain applications a "*higher performance*" than "*BLAST*", i.e an alignment-based method (D18, page 381, left column, third paragraph). Alignment-free methods for detecting structural variations are thus common alternatives to alignment-based methods. By combining the teaching of documents D2 and D18, the skilled person would have thus arrived at the method of claim 1 in an obvious manner.

18. The respondent argued that the skilled person in the field of the claimed method was a microbiologist who would not have consulted the teaching of document D18 because its content was rather theoretical and directed to persons working in the field of informatics.

19. The board however concurs with the appellant that the skilled person in the field of the claimed invention represents a team encompassing a microbiologist and a person familiar with bioinformatics. This is due to the fact that the invention is directed to a "*computer implemented method*" based on sequence comparisons and statistical correlations of sequence-based data with microbial phenotypes of antimicrobial drug resistance and/or drug susceptibility. Accordingly, such a team in seek of an alternative for an alignment-based sequence analysis approach would turn to documents dealing with common alternative methods in this field, such as for example, those reported in document D18.

20. The opposition division held that the claimed method was inventive since document D2 contained no pointers for the skilled person in looking for an alignment-free detection of structural variations of a change in 2 or more adjacent nucleotides as an alternative to an alignment-based method. Moreover document D2 disclosed no motivation for the skilled person in changing the alignment-based method to an alignment-free method that did not rely on a reference sequence (decision under appeal, point 6.1.4.4). The respondent shared that view.

21. The board cannot agree thereto. It is established case law that the question of whether a skilled person would consider a modification of the prior art critically depends on the problem to be solved by the alleged invention. If the only contribution of the invention is to propose something different from the prior art (i.e. the provision of an alternative as in the present case), then it is usually appropriate to consider that the skilled person would take into account any common alternative known in the respective technical field (unless the closest prior art teaches away from it). In such cases it might not even be required to justify the selection of a particular solution, because it was assumed that an invention based on incorporating known features for the sole purpose of establishing novelty must be rendered obvious by a corresponding step of selecting any alternative known in the art (Case Law, I.D.4.5, in particular T 1179/16, Reasons 3.4.4 and T 1518/20, Reasons 1.5.4).

22. In the present case document D2 does not teach away from using methods other than alignment-based ones for the detection of sequence variations. Nor has this been argued by the opposition division or the respondent. In

these circumstances, the board agrees with the appellant that the skilled person looking for an alternative method for detecting sequence variants does not need a motivation or pointer in document D2 for modifying the method disclosed therein. Even more so since for the reasons provided above under claim construction (point 8), alignment-free methods for analysing sequence variations were commonly used alternatives to alignment-based methods at the relevant filing date of the patent (e.g. document D18, page 377, right column, third paragraph, page 381, left column fourth paragraph and page 385, left column, first bullet point in the box entitled "*Key Points*").

23. Also the fact that document D18 is silent on studying sequence variations and their potential involvement in the specific context of microbial drug resistance as argued by the respondent and the opposition division is irrelevant since this is already disclosed in document D2. There are also no indications derivable from document D18 that alignment-free methods are unsuitable for studying the claimed microbial sequence variations. Nor has this been argued by the respondent.

24. The method of claim 1 lacks thus an inventive step and auxiliary request 2 contravenes Article 56 EPC.

*Auxiliary requests 3 and 5*

25. As set out above in sections VI and VIII, the alignment-free detection method of claims 1 of auxiliary requests 3 and 5 has been limited compared to claim 1 of auxiliary request 2 in that the microorganism has been selected from a group which *inter alia* consists of "*Staphylococcus*". As set out above (point 15) too, document D2 uses for its method

isolates of *S. aureus*, i.e. a "*Staphylococcus*" strain. Hence the objections under lack of inventive step raised above against the method of claim 1 of auxiliary request 2 apply likewise to the method of claims 1 of auxiliary requests 3 and 5 (Article 56 EPC).

*Auxiliary request 4*

26. In auxiliary request 4, claims 1 to 3 and 6 of auxiliary request 2 have been deleted, so that claim 1 of this request is based on claim 4 of auxiliary request 2. For the exact wording of claim 1 see section VII.

*Claim construction - claim 1*

27. Claim 1 relates to a "*diagnostic method of determining an infection of a patient with a microorganism*". This method comprises process steps a) and b).

27.1 Step a) requires that in a patient sample "*the presence of at least one structural variation in at least one*" microbial sequence is determined wherein the variation is a change "*of at least two adjacent bases*" that is detected "*alignment-free*" or *"annotated to a pan-genome"*.

27.2 Step b) requires further that it has to be determined whether this "*at least one structural variation is associated with antimicrobial drug [...] resistance*". This is achieved "*by correlating*" the structural variation "*with a data set of antimicrobial drug [...] resistance and/or susceptibility of a plurality of clinical isolates of the microorganism*" and by "*statistically analysing the correlation*", "*wherein the presence of said at least one structural variation*"

that is associated with an antimicrobial drug resistance "*is indicative of an infection*" of the patient with a drug resistant microorganism.

27.3 The use of further process steps is not excluded from claim 1 due to the use of the "comprising" language.

28. Claim 1 therefore relates to a diagnostic method of determining an infection of a drug resistant microorganism in a patient. This is achieved by a statistical correlation between a specified claimed genomic variation in a sampled microorganism detected by an alignment-free method or by annotation to a pan-genome. The association of this variation with a drug resistant/susceptible data set of clinical isolates indicates then the patient's infection with a drug resistant microbial strain. Claim 1 encompasses two embodiments as regards the determination of genomic variants, (1) "*alignment-free*" and (2) *"annotated to a pan-genome".*

*Inventive step*

*Distinguishing feature, technical effect and technical problem to be solved*

29. Document D2 remains the closest prior art. It is contentious between the parties whether or not document D2 discloses a diagnostic method of determining an infection of a drug resistant microorganism in a patient.

29.1 The respondent submitted for the first time at the oral proceedings before the board that document D2 did not disclose such a diagnostic method. It is derivable from the decision under appeal (Reason 6.2.2), that there

was an agreement between the parties that the sole distinguishing feature between the method of claim 4 of auxiliary request 1 (i.e. claim 1 of auxiliary request 4) was the type of method used for detecting genomic variations, namely an alignment-free detection or an annotation to a pan-genome versus an alignment-based one. Nor did the respondent identify in their reply to the appeal further differences.

30. Irrespective of the issue of admitting the respondent's new line of argument, the board is not convinced by the respondent's arguments and agrees with the appellant that document D2 discloses a diagnostic method since this document reports that "*we can use the determinants to predict drug resistance*" (page 6, right column, third paragraph and point 15 above).

31. The respondent in addition repeated its new line of argument submitted for the first time in appeal as regards the further difference between the claimed method and that of document D2, namely that the structural variations were identified in the claimed method by comparing bacterial sequences within the clinical samples which provided a data set of intra-strain sequence variations that did not rely on a comparison with data already stored in a database. The board has already decided in the context of auxiliary request 2 that this line of arguments is not considered in appeal (points 9 and 13.4 above). Accordingly, this line of arguments is disregarded for the issue of inventive step of auxiliary request 4 as well.

32. The sole difference between the claimed method and that of document D2 remains thus in the determination of the claimed sequence variations. Since claim 1 comprises two alternative embodiments for detecting sequence

variations (point 28 above), the following assessment will be limited to the embodiment of an alignment-free detection method vis-a-vis the alignment-based detection disclosed in document D2.

33. Since no beneficial technical effect can be ascribed to the claimed embodiment under consideration, the technical problem to be solved resides in the provision of an alternative diagnostic method of determining an infection of a drug resistant microorganism in a patient.

*Obviousness*

34. Since an alignment-free detection of structural variations is a commonly used alternative to alignment-based methods (point 17 above), the issue to be assessed under obviousness remains the same as that set out above for claim 1 of auxiliary request 2, including the arguments and facts assessed by combining document D2's teaching with that of document D18. Consequently, the reasons indicated above under lack of inventive step for claim 1 of auxiliary request 2 apply to the diagnostic method of claim 1 of auxiliary request 4 too (Article 56 EPC).

*Auxiliary requests 6, 7 and 12*

35. The methods of claim 1 of auxiliary requests 6, 7 and 12 differ from claim 1 of auxiliary request 4 in that the feature "*annotated to a pan-genome*" has been deleted (auxiliary requests 6 and 7 only) for detecting structural variations, and in that the microorganism to be diagnosed has been further specified as being "*selected from the group consisting of Acinetobacter, Escherichia, Enterobacter, Klebsiella, Proteus,*

*Pseudomonas, Salmonella, Serratia, Shigella and Staphylococcus*" (auxiliary requests 7 and 12 only).

*Inventive step*

36. The embodiment concerning an "*alignment-free*" detection of structural variations in claim 1 of auxiliary request 6 is identical to that of claim 1 of auxiliary request 4. Accordingly, the same reasons as regards the lack of inventive step of the diagnostic method of claim 1 of auxiliary request 4 apply to claim 1 of auxiliary request 6 (Article 56 EPC).

37. Moreover, as set out above under points 15 and 25, document D2 discloses the use of a specific *Staphylococcus* strain (*S. aureus*) for its method, i.e. a strain likewise mentioned in claims 1 of auxiliary requests 7 and 12. Since otherwise the diagnostic method of claim 1 of auxiliary requests 7 and 12 for the "alignment-free" embodiment is identical to that of claim 1 of auxiliary request 4, the reasons set out above for lack of inventive step for auxiliary request 4 apply likewise for auxiliary requests 7 and 12 (Article 56 EPC).

*Auxiliary requests 8 to 11*

38. The diagnostic method of claim 4 of auxiliary requests 8 and 9 and of claim 1 of auxiliary requests 10 and 11 differs from that of claim 1 of auxiliary request 4 in that the embodiment "*detected alignment-free*" has been deleted. The claimed diagnostic methods have thus been limited to a detection of structure variations by an annotation "*to a pan-genome*". Furthermore in claim 4 of auxiliary request 9 and in claim 1 of auxiliary request 11 the microorganism to be diagnosed has been further

specified as being "*selected from the group consisting of Acinetobacter, Escherichia, Enterobacter, Klebsiella, Proteus, Pseudomonas, Salmonella, Serratia, Shigella and Staphylococcus*".

*Claim construction*

39. The term "*pan-genome*" in claim 4 of auxiliary requests 8 and 9 and in claim 1 of auxiliary requests 10 and 11 is not further specified. Nor is the feature "*annotated*" in the context of a pan-genome in these claims specified. Thus claims 1 and 4 of the respective auxiliary requests encompass any ordinary means of annotation, including alignment-based annotations.

39.1 A pan-genome according to its ordinary meaning concerns the entire genomic repertoire of strains within a phylogenetic clade, i.e. within a monophyletic group of organisms composed of a common ancestor and its lineal descendants. In other words, a pan-genome includes a core genome containing genes present in all strains of this group and a dispensable genome composed of genes absent from one or more strains and genes that are unique to each strain (i.e. indels, e.g. document D14, abstract and page 13950, right column, first paragraph; document D15, abstract and page 399, last paragraph to page 400, first paragraph).

39.2 Moreover the use of such a pan-genome as an alternative to "*current reference genomes*" (document D15, page 400, first paragraph) has been known to the skilled person at the relevant filing date of the patent as well.

*Inventive step*

*Distinguishing feature, technical effect and technical problem to be solved*

40. It is uncontested that document D2 remains the closest prior art for the diagnostic methods of claims 1 or 4 of auxiliary requests 8 to 11. The sole distinguishing feature between claim 4 of auxiliary requests 8 and 9 and claim 1 of auxiliary requests 10 and 11 and the method of D2 remains in the type of method used for determining the claimed sequence variation, i.e. by being "*annotated to a pan-genome*" vis-a-vis a comparative analysis of gene families in a reconstructed consensus phylogenetic tree in whole-genome sequences of *S. aureus* (D2, page 3, right column, third paragraph). Since for the reasons indicated above (point 39), claims 1 and 4 respectively of these auxiliary requests encompass an alignment-based annotation to a pan-genome, this embodiment will be considered in the following for the assessment of inventive step.

41. Comparative data are not on file which disclose potential advantages of detecting structural variants by the embodiment under consideration compared to the method disclosed in document D2. In the absence of such data, the board agrees with the appellant and the opposition division that no advantageous technical effects are ascribable to this distinguishing feature.

42. Consequently, in agreement with the opposition division (decision under appeal, Reasons 6.1.2) and the appellant too, the objective technical problem to be solved resides in the provision of an alternative method for detecting genomic sequence variants associated with microbial drug resistance. The respondent has not argued differently.

*Obviousness*

43. The board agrees with the appellant that by combining the teaching of document D2 with that of document D14 the skilled person would have arrived in an obvious manner at the claimed methods.

44. Starting from the method disclosed in document D2, the skilled person looking for an alternative method for determining the claimed structural variations would have looked at the relevant common art in this technical field.

45. Document D14 discloses a genome sequencing of multiple strains of Group B Staphylococcus ("GBS") and a comparison of their sequences for making a pan-genome. Document D14 observes that after sequencing multiple strains of GBS, sequence information of eight genomes is not enough for identifying all genes present in the bacterial species and that, in particular, traits pertained to the dispensable genome (i.e. indels, points 7 and 39.1 above), are linked to pathogenesis (virulence), antibiotic resistance, vaccine design, evolution and the concept of species (page 13954, right column, third paragraph to page 13955, left column, second paragraph).

46. As set out above (point 39.2), the use of annotations to a pan-genome for determining sequence variations was known in the art at the relevant filing date of the patent.

47. The board agrees with the respondent insofar that document D14 is silent on the use of pan-genomes in detecting structural variations that are associated

with antimicrobial drug resistance. However, for the reasons set out above (point 23) in the context of document D18, this is irrelevant since document D2 already discloses the use of alignment-based methods for this particular purpose. There is also no need for pointers in document D2 for using an alternative detection method for determining sequence variations, or for a particular motivation to do so. Rather the important issue is, as likewise indicated above (point 21), whether documents D2 and/or D14 contain a disclosure that would have taught the skilled person away from applying a detection method based on an alignment-based annotation to a pan-genome. This, however, is not the case and has also not been argued by the respondent.

48. Thus the reasons indicated under lack of inventive step above for claims 1 of auxiliary requests 2 and 6 apply for the method of claim 4 of auxiliary requests 8 and 9 and for the method of claim 1 of auxiliary requests 10 and 11 as well (Article 56 EPC).

**Order**

**For these reasons it is decided that:**

1. The appealed decision is set aside.

2. The opposition is admissible.

3. The patent is revoked.

The Registrar: The Chair:

C. Rodríguez Rodríguez T. Sommerfeld

Decision electronically authenticated