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Datasheet for the decision of 27 June 2023

Case Number: T 1680/20 - 3.3.08

Application Number: 13757943.9

Publication Number: 2823062

IPC: C12Q1/68

Language of the proceedings: EN

Title of invention:
Size-based analysis of fetal DNA fraction in maternal plasma

Patent Proprietor:
The Chinese University of Hong Kong

Opponent:
James Poole Limited

Headword:
Analysis of clinicallly-relevant DNA in plasma/THE CHINESE UNIVERSITY OF HONG KONG

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
Novelty - (yes)
Inventive step - (yes)

Decisions cited:
T 0247/20

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 1680/20 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 27 June 2023

Appellant: (Patent Proprietor)	The Chinese University of Hong Kong Knowledge Transfer Office Shatin New Territories Hong Kong, SAR (CN)
Representative:	Uexküll & Stolberg Partnerschaft von Patent- und Rechtsanwälten mbB Beselerstraße 4 22607 Hamburg (DE)
Respondent: (Opponent)	James Poole Limited One Southampton Row London WC1B 5HA (GB)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 29 May 2020 concerning maintenance of the European Patent No. 2823062 in amended form**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	R. Morawetz
	A. Bacchin

Summary of Facts and Submissions

I. European patent No. 2 823 062 ("the patent") is based on European patent application No. 13 757 943.9, which was filed as an international application published as WO 2013/132305 ("the application"). The patent is entitled "*Size-based analysis of fetal DNA fraction in maternal plasma*".

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

D11 WO 2012/071621

D12 US 2011/0171741

D15 Lo Y.M.D. et al., Science Translational Medicine 2, 2010, 1-13

D15a Supplementary materials for D15, 1-57

D17 WO 2011/090556

III. One opposition to the granted patent was filed. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), and under Article 100(b) and (c) EPC.

IV. By way of an interlocutory decision, the opposition division decided that the patent in amended form on the basis of auxiliary request 2, and the invention to which it relates, met the requirements of the EPC. The opposition division also held that the invention as defined in claim 1 of the main request was not

disclosed in a manner sufficiently clear and complete for it to be carried out (Article 83 EPC) and that the set of claims of auxiliary request 1, submitted during the hearing before the opposition division and being identical to auxiliary request 22 submitted with letter dated 26 April 2019, met the requirements of Rule 80 EPC and Articles 123(2), 123(3), 83, 84 EPC but that claim 1 lacked novelty over document D11 (Article 54(3) EPC) and document D12 (Article 54(2) EPC).

V. The patent proprietor (appellant) filed an appeal against the opposition division's decision.

VI. In its statement setting out the grounds of appeal, the appellant maintained the set of claims of the main request and auxiliary request 1 considered in the decision under appeal. The appellant argued, *inter alia,* that the impugned decision was unsubstantiated as regards the lack of novelty of claim 1 of auxiliary request 1 over document D11, that claim 1 was novel over document D11 and document D12 and involved an inventive step when document D12 was considered to represent the closest prior art.

VII. In reply to the statement of grounds of appeal, the opponent (respondent) provided, *inter alia,* its arguments with respect to the lack of novelty of claim 1 of auxiliary request 1 over documents D11 and D12 and lack of inventive step when document D17 was considered to represent the closest prior art.

VIII. The board scheduled oral proceedings, in accordance with the parties' requests, and subsequently issued a communication under Article 15(1) RPBA, in which it indicated its preliminary opinion with respect to,

inter alia, substantiation of the impugned decision. The board noted that it considered itself to be in a position to decide the issue of novelty over document D11 on appeal.

IX. The respondent made no further substantive submissions, withdrew by letter dated 23 June 2023 its request for oral proceedings and announced that it would not attend the oral proceedings.

X. The oral proceedings before the board took place as scheduled. During the oral proceedings, the appellant withdrew its main request. At the end of the oral proceedings, the Chairwoman announced the board's decision.

XI. The wording of claim 1 of auxiliary request 1, the sole claim request dealt with in this decision, is set out in the reasons for the decision, below.

XII. The parties' submissions, insofar as they are relevant to the decision, are discussed in the reasons for the decision, below.

XIII. The appellant requested that the decision under appeal be set aside and the patent be maintained in amended form on the basis of the set of claims of auxiliary request 1 submitted during the hearing before the opposition division and being identical to auxiliary request 22 that had been submitted by letter dated 26 April 2019.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

Auxiliary request 1 - claim 1

Claim construction - the claimed invention

1. Claim 1 of auxiliary request 1 reads as follows (for ease of reference and in accordance with the feature structure applied in the decision under appeal, labels (a), (a1), (b), (c), (c1), (c2), (d) and (e) have been added by the board to indicate the individual feature groups of claim 1):

"A method of estimating a fractional concentration of clinically-relevant DNA in a plasma sample, the plasma sample including the clinically-relevant DNA and other DNA, the method comprising:

(a) for each size of a plurality of sizes:
(a1) measuring an amount of a plurality of DNA fragments from the plasma sample corresponding to the size;
(b) calculating, with a computer system, a first value of a first parameter based on the amounts of DNA fragments at multiple sizes, the first parameter providing a statistical measure of a size profile of DNA fragments in the plasma sample;
(c) obtaining one or more first calibration data points,
(c1) wherein each first calibration data point specifies a fractional concentration of clinically-relevant DNA corresponding to a calibration value of the first parameter, and
(c2) wherein the one or more first calibration data points are determined from a plurality of calibration samples;

(d) comparing the first value to a calibration value of at least one first calibration data point; and
(e) estimating the fractional concentration of the clinically-relevant DNA in the plasma sample based on the comparison."

2. The board adopts the overall claim construction used in the decision under appeal and followed by the parties on appeal. Accordingly, feature group (a) is understood to apply to feature group (a1) of claim 1 only.

3. The board follows the normal rules of claim construction, in which the terms used in the claims are given their broadest technically sensible meaning in the overall context in which they appear (see also Case Law of the Boards of Appeal, 10th edition 2022 - "Case Law", II.A.6.1).

4. In agreement with the respondent, the board considers that the term "*fractional concentration*" implies a quantitative value which reflects the proportion of "*clinically-relevant DNA*" in the plasma sample. In other words, the fractional concentration is not merely whether a sample has a concentration of clinically-relevant DNA which lies above or below that of the calibration sample.

5. The board considers that the broadest technically sensible meaning of the expression *"calibration value of the first parameter"* is that it is a single number. This corresponds to the normal meaning of the term "*value*". The board has not been presented with any evidence which would point to a different, generally accepted understanding of the term "*value*" in the art.

6. For the following reasons, the respondent's argument that nothing in the patent suggests that the "*calibration value of the first parameter*" must be a single number rather than being a multidimensional parameter or an array is not found persuasive.

7. Firstly, none of the passages of the patent referred to in this context by the respondent, i.e. paragraphs [0034], [0061] and [0062], relates to the expression "*a calibration value of the first parameter*" let alone provides a definition of it.

8. Secondly, contrary to the respondent's submissions, paragraph [0034] of the patent does not state that the first parameter can be a histogram. It states that "*the first parameter provides a statistical measure of a size profile (e.g., a histogram) of DNA fragments in the biological sample*." The board agrees with the appellant that the "*histogram*" refers to the "*size profile*" but not the first parameter because the reference to "*e.g., histogram*" in paragraph [0034] is included after "*size profile*" and not after "*parameter*".

9. Thirdly, paragraph [0062] of the patent does not relate to a size parameter as defined in feature (b) of claim 1, i.e. a parameter that provides *"a statistical measure of a size profile of DNA fragments in the plasma sample"* and it does not state that a first parameter as defined in claim 1 can be a histogram either.

10. Finally, paragraph [0061] of the patent provides five examples of parameters used to quantify the relative abundance of short DNA in maternal plasma. In these examples, proportions or ratios of size distributions

are used as parameters. The calculated values of these parameters would, however, not be size distributions as such but single numbers.

Novelty

The decision under appeal

11. The opposition division held that claim 1 of auxiliary request 1 lacked novelty over document D11. By way of justification, the opposition division summarised the relevant disclosure of document D11 and then addressed the appellant's counter-arguments as regards disclosure of feature groups (a1), (c1) and (c2) of claim 1 in document D11.

12. The opposition division did not, however, explicitly correlate the disclosure in document D11 to each and every feature group of claim 1 or provide a logic chain of reasoning as to why and where all the technical features of the claimed invention are disclosed in combination in document D11. Such a correlation cannot be inferred from the decision under appeal either. It is also not apparent from the impugned decision that the disclosure of feature groups other than (a1), (c1) and (c2) was uncontested.

13. As a consequence, the board agrees with the appellant that the conclusions reached by the opposition division as regards lack of novelty over the disclosure in document D11 are not duly supported by the reasons given for the decision, i.e. the decision is not reasoned, contrary to the requirements of Rule 111(2) EPC.

14. However, the appellant did not argue that there was a violation of Rule 111(2) EPC which amounted to a procedural violation of a substantial nature requiring that the decision under appeal be set aside and remitted to the department of first instance (Article 11 RPBA). Neither does the board consider the present violation of Rule 111(2) EPC as a procedural violation of a substantial nature, for the reason that the outcome of the proceedings would not have been different, had the violation not occurred (see Case Law V.11.6.2). This is because claim 1 of auxiliary request 1 was also found to lack novelty over document D12, so that a causal link is missing between the procedural violation and the filing of the appeal. Remittal of the case to the opposition division was also not requested by the respondent.

15. Since the board, on account of the appealed decision and the parties' submissions on appeal, was in a position to decide the issue of novelty over document D11 on appeal, the board refrained from remitting the case to the opposition division.

Document D11

16. As set out above (see point 13.), the impugned decision is not reasoned within the meaning of Rule 111(2) EPC as regards lack of novelty over document D11. It is therefore erroneous for that reason alone.

17. Consequently, the appellant did not have to prove on appeal that the impugned decision is also incorrect on the merits as regards lack of novelty over document D11. Instead, the burden of proving that the objection regarding lack of novelty over document D11 is substantiated remained with the respondent (see also

Case Law, III.G.5.2.3).

18. The respondent submitted that all of the steps in claim 1 were disclosed in paragraphs [0176] to [0184] of document D11, except for the explicit use of a computer system for calculating the parameters but that anyone reading document D11 would immediately understand that the relevant calculations would implicitly be performed by computer.

19. Document D11 discloses that "[t]*he degree of the change in the circulating DNA size profile can also be used for determining the fractional concentration. In one implementation, the exact size distribution of plasma DNA derived from both tumor and non-tumor tissues can be determined, and then the measured size distribution falling between the two known distributions can provide the fractional concentration (e.g. using a linear model between the two statistical values of the size distributions of the tumor and non-tumor tissues).*" (paragraph [0184], page 46, lines 26 to 31).

20. With respect to feature group (b) of claim 1, the respondent submitted that the "*first parameter based on the amounts of DNA fragments at multiple sizes*" was not a single value and was the same as "*the circulating DNA size profile*" disclosed in paragraph [0184] of document D11 which was "*used for determining the fractional concentration*".

21. However, feature group (b) of claim 1 refers not only to the "*first parameter*" but also requires that "*a first value of a first parameter*" be calculated while paragraph [0184] of D11 is silent with respect to the calculation of any value based on the circulating DNA size profile (see point 19. above). The board

furthermore agrees with the appellant that the value of the parameter is not a size distribution as such. Disclosure of "*the circulating DNA size profile*" in paragraph [0184] of document D11 therefore does not anticipate feature group (b) of claim 1.

22. With respect to feature groups (c), (c1) and (c2) of claim 1, the respondent submitted that the "*calibration value of the first parameter*" did not need to be a single number and that the size distributions which were determined for *"plasma DNA derived from both tumor and non-tumor tissues"* were the *"one or more first calibration data points ... determined from a plurality of calibration samples"* in claim 1.

23. This line of argument fails in view of the claim construction adopted by the board (see point 5. above). The board agrees with the appellant that the "*size distribution of plasma DNA derived from both tumor and non-tumor tissues*" disclosed in paragraph [0184] of document D11 represents a set of values and not calibration data points that specify "*a fractional concentration of clinically—relevant DNA*" in the sense of claim 1. Disclosure of "*size distribution of plasma DNA derived from both tumor and non-tumor tissues*" in paragraph [0184] of document D11 therefore does not anticipate feature groups (c), (c1), and (c2) of claim 1.

24. In this context, the board does not share the respondent's view that the appellant's submission that a "*distribution does not represent a value or a point*" should be rejected under Article 12(2) RPBA. This submission directly addresses the interpretation of paragraph [0184] of document D11 in the decision under appeal and does not go beyond the factual and legal

framework of the opposition proceedings. It thus cannot be considered as an amendment of the appellant's appeal case vis-à-vis the first instance proceedings in the sense of Article 12(2) and (4) RPBA (see e.g. T 247/20, Reasons 1.3).

25. With respect to feature group (d) of claim 1, the respondent submitted that the step in which the "*measured size distribution falling between the two known distributions*" was determined in paragraph [0184] of document D11, for instance by "*using a linear model between the two statistical values of the size distributions of the tumor and non-tumor tissues*" was the step of "*comparing the first value to a calibration value of at least one first calibration data point*" in claim 1 for two reasons: (a) the "*calibration value of the first parameter*" in claim 1 did not need to be a single number, rather than being a multidimensional parameter or an array and (b) lines 30 to 31 of paragraph [0184] referred to interpolating between two "*values*", so there was no difference anyway.

26. The respondent's main line of argument as to why document D11 also discloses feature group (d) of claim 1 fails in view of the claim construction adopted by the board (see point 5. above).

27. The respondent's further line of argument is not found persuasive for the following reasons. The mere reference to the statement *"e.g. using a linear model between the two statistical values of the size distributions of the tumor and non-tumor tissues"* (paragraph [0184], lines 30 to 31) fails to explain how the "*size distributions of the tumor and non-tumor tissues*" are converted into a calibration value of at least one first data point and compared with the first

value of the first parameter in the sense of feature group (d) of claim 1. The step wherein the "*measured size distribution falling between the two known distributions*" is determined in paragraph [0184] of document D11 therefore does not anticipate feature group (d) of claim 1.

28. The board concludes from the above observations that claim 1 is novel over document D11.

Document D12

29. The opposition division held that claim 1 lacked novelty over the disclosure in document D12 because paragraph [0058] and claim 12 of document D12 disclosed reference standards that corresponded to the calibration data points of claim 1. This is disputed by the appellant.

30. Document D12 concerns methods for determining a size distribution of DNA molecules in a sample and calculating a single molecule DNA integrity index (smDI) which quantifies the ratio of large to small DNA molecules in the sample (see paragraph [0039]). In paragraph [0058], document D12 discloses that in one aspect, the method can be used for determining if a subject is likely to have a cancer. To this end, the smDI of DNA molecules in a sample from the subject (e.g. a cell free body fluid) is determined and compared to a predetermined cut-off value. An smDI of at least about 0.04, 0.06, ... 0.8 or 0.9 indicates that the subject is likely to have cancer.

31. As correctly noted by the appellant, paragraph [0058] of document D12 does not mention any reference standards, it mentions cut-off values for smDIs. The

board furthermore agrees with the appellant that a size distribution of DNA molecules in a sample merely provides information as to the presence or relative presence of DNA molecules of different sizes in a sample, which does not directly provide an estimate of the fractional concentration of a clinically—relevant DNA. The cut-off values mentioned in paragraph [0058] of document D12 are therefore not calibration data points in the sense of claim 1.

32. Claim 12 of document D12 relates to a method for determining the tumor load in a subject compared to one or more reference standards, wherein the smDI of DNA molecules in a sample from the subject is determined and compared to a positive and/or negative reference standard, wherein the negative and positive reference standards are representative of defined amounts of tumor load.

33. According to paragraph [0090] of document D12, "'[t]*umor load*' ... *refers to the number of cancer cells, the size of a tumor, or the amount of cancer in the body*". As set out above (see point 4.) a "*fractional concentration*" is understood to imply a quantitative value which reflects the proportion of clinically-relevant DNA in the total population. The board agrees with the appellant that none of the definitions of tumor load in paragraph [0090] of document D12 correspond to the fractional concentration of tumor DNA within the meaning of claim 1 of auxiliary request 1.

34. The board furthermore agrees with the appellant that the reference standards which are mentioned in claim 12 of document D12 are not calibration data points in the sense of claim 1 as they do not represent a fractional

concentration of tumor DNA in a sample. Document D12 discloses that the "*negative reference standard is representative of the tumor load in a subject that does not have the cancer*" and "*the positive reference standard is representative of the tumor load in a subject that has the cancer*" (see claim 13). Comparison of the smDI of the DNA molecules in the sample with the reference standards therefore results in a classification of the subject analysed, i.e. whether he/she has cancer or not (claim 13 of document D12), the stage of the cancer (claims 14 and 15 of document D12), the progress or prognosis of cancer (claim 17) and whether cancer treatment is efficacious (see claim 18 of document D12). It does not, however, result in any quantitative information regarding the fractional concentration of tumor DNA in the sample in the sense of claim 1.

35. The board's understanding of the disclosure in claim 12 of document D12 (see points 32. to 34.) is not changed by the respondent's assertion that it cannot see any difference between the measure of "*tumor load*" in claim 12 of document D12 and the "*fractional concentration*" in claim 1. The respondent failed to cite any part of document D12 that would support the conclusion that a method of determining tumor load is the same or at least includes a method for determining a fractional concentration of tumor DNA in a plasma sample in the sense of claim 1 of auxiliary request 1.

36. The respondent's further assertion that it would be clear from at least claims 13, 17 and 18 that the method of claim 12 of document D12 can be used for determining the fractional concentration of tumor-derived DNA is likewise not persuasive in view of the type of the reference standards used in claim 12 of

document D12 (see point 34. above).

37. Finally, the respondent's assertion that the negative reference standard specified in claim 13 of D12 is a "*calibration data point*" within the meaning of the claim also fails. As correctly pointed out by the appellant, the "*negative reference standard*" of document D12 is representative of a person who does not have cancer and the use of such a negative reference standard can only provide information on whether a tumor is present or absent, but can provide no information on the "*fractional concentration*" of the tumor DNA in a plasma sample comprising both the tumor DNA and other DNA, as required by claim 1.

38. The board concludes from the above observations that document D12 does not disclose calibration data points which specify a fractional concentration of clinically-relevant DNA in the sense of claim 1. Claim 1 is novel over document D12.

Inventive step

Closest prior art

39. Having held claim 1 to lack novelty, the opposition division did not decide on inventive step of claim 1 of auxiliary request 1.

40. As set out above, claim 1 concerns a method of estimating a fractional concentration of clinically-relevant DNA in a plasma sample, the plasma sample including the clinically-relevant DNA and other DNA.

41. The board concurs with the respondent that document D17, which discloses a method for measuring

fractional concentration of fetal DNA circulating in maternal plasma, is a suitable starting point for the assessment of inventive step as it relates to the same purpose as claim 1 of auxiliary request 1.

42. Document D17 relates to methods for determining the fraction of fetal nucleic acids in a maternal sample comprising a mixture of fetal and maternal genomic DNA (paragraph [0008]). These methods comprise at least three method steps, namely (a) amplifying a plurality of polymorphic target nucleic acids in the mixture of fetal and maternal genomic DNA; (b) performing massively parallel sequencing of at least a portion of the amplified product obtained in (a), and (c), based on the sequencing, determining the fraction (paragraph [0009], claim 1). The methods of document D17 are based on the use of polymorphic sequences to distinguish between nucleic acids of fetal and maternal origin in the sample (paragraphs [0056], [0062] and [0063]).

Objective technical problem to be solved

43. According to the respondent, the method in claim 1 of auxiliary request 1 differs from the disclosure in document D17 in that the estimate of fractional concentration is based on the plasma DNA's size distribution rather than on specific polymorphic markers.

44. The board agrees with the respondent that the technical effect of this difference is the provision of a simpler method because there is no need to identify specific markers exclusive to the fetal DNA and further that the objective technical problem to be solved vis-à-vis document D17 therefore resides in providing a simpler method to estimate fractional concentration of

circulating fetal DNA.

Obviousness of the claimed solution

45. The question to be answered in assessing obviousness is whether the skilled person starting from the disclosure of a method involving markers exclusive to the fetal DNA in document D17 and seeking to solve the objective technical problem formulated above would have modified the method disclosed in document D17 to arrive at the claimed solution.

46. The respondent submitted that the skilled person starting from document D17, and seeking a simpler way to estimate fractional concentration of circulating fetal DNA, would have been led to the claimed solution in an obvious way based on the teaching in document D15.

47. Document D15 studies the size distribution of fetal DNA circulating in maternal plasma and it discloses that fetal DNA shows a reduction in a 166-base pair (bp) peak relative to a 143-bp peak (abstract, Fig. 2C, page 10, right hand column) which is seen for each chromosome (document D15a, Figure S3).

48. Document D15 thus discloses that maternally-derived DNA and fetal DNA on average have a different size. Document D15 does not, however, teach how the differences in size distribution could be used to determine a fractional concentration of fetal DNA.

49. For the following reasons, the respondent's arguments that a skilled person would see from document D15 that the difference in size distribution can be used to distinguish fetally-derived and maternally-derived

circulating DNA in plasma and that they would understand that this parameter could be used as an alternative parameter to calibrate the method of document D17 are not found persuasive.

50. Firstly, the board agrees with the appellant that the size of a single DNA fragment as disclosed in D15 cannot be used to identify the same as a fragment of fetal or maternal origin in a manner that would be similar to the analysis used in document D17 which is based on known polymorphic specific sequences (see point 42. above). The skilled person had thus no reason to understand, based on the teaching in document D15, that the size of the DNA fragments circulating in maternal plasma could be used or how it could be used to distinguish fetally-derived and maternally-derived DNA in plasma without having recourse to specific polymorphic markers.

51. Secondly, the respondent has not explained which aspect of document D17 would represent feature group (c), (c1) and (c2) of claim 1 and it would instead appear that the method of document D17 does not use a calibration step at all (see point 42. above) and nor does the method of document D15 (see point 47. above). The board therefore also agrees with the appellant that it is unclear why the skilled person should use a specific calibration step - feature group (c), (c1) and (c2) of claim 1 - when combining two prior art methods which do not use a respective calibration step. The respondent also did not submit that the calibration step was disclosed in a different prior art document or belonged to the common general knowledge.

52. Contrary to the respondent's submission, a skilled person starting from document D17, and seeking a

simpler way to estimate fractional concentration of fetal DNA in maternal plasma, would therefore not have arrived at the claimed method, even if they would have combined the disclosure of document D17 with the teaching of document D15.

53. The board concludes from the above observations that the subject-matter of claim 1 of auxiliary request 1 meets the requirements of Article 56 EPC.

Conclusions

54. Claim 1 of auxiliary request 1 meets the requirements of Articles 54 and 56 EPC. No other objections were raised by the respondent against the set of claims of auxiliary request 1. The opposition division had held that the set of claims of auxiliary request 1 meets the requirements of Rule 80 EPC and Articles 123(2), 123(3), 83, 84 EPC (see section IV. above). The patent can therefore be maintained in amended form on the basis of the set of claims of auxiliary request 1.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in amended form on the basis of claims 1 to 15 of auxiliary request 1, filed during the hearing before the opposition division and being identical to auxiliary request 22 submitted with letter dated 26 April 2019, and a description and drawings to be adapted thereto, if necessary.

The Registrar: The Chairwoman:

L. Malécot-Grob T. Sommerfeld

Decision electronically authenticated