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# Datasheet for the decision of 12 September 2023

**Case Number:** T 1514/21 - 3.3.08

**Application Number:** 15761889.3

**Publication Number:** 3117012

**IPC:** C12Q1/6883

**Language of the proceedings:** EN

**Title of invention:**
METHODS OF MONITORING IMMUNOSUPPRESSIVE THERAPIES IN A TRANSPLANT RECIPIENT

**Patent Proprietor:**
CareDx, Inc.

**Opponents:**
Regimbeau Sarl
J A Kemp LLP

**Headword:**
Monitoring immunosuppressive therapies in a transplant recipient/CAREDX

**Relevant legal provisions:**
RPBA 2020 Art. 12(4)
EPC Art. 113(1), 83, 56

**Keyword:**
Sufficiency of disclosure - (yes)
Inventive step - main request (yes)
Amendment to case - admitted (no)

**Decisions cited:**

**Catchword:**

Europäisches Patentamt
European Patent Office
Office européen des brevets

**Beschwerdekammern**

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**Case Number: T 1514/21 - 3.3.08**

# D E C I S I O N
# of Technical Board of Appeal 3.3.08
# of 12 September 2023

| | |
|---|---|
| **Appellant:** (Patent Proprietor) | CareDx, Inc.<br>3260 Bayshore Boulevard<br>Brisbane CA 94005 (US) |
| **Representative:** | Marshall, Cameron<br>Howat, Suzy<br>Carpmaels & Ransford LLP<br>One Southampton Row<br>London WC1B 5HA (GB) |
| **Appellant:** (Opponent 1) | Regimbeau Sarl<br>20, rue de Chazelles<br>75017 Paris (FR) |
| **Representative:** | Regimbeau<br>20, rue de Chazelles<br>75847 Paris Cedex 17 (FR) |
| **Party as of right:** (Opponent 2) | J A Kemp LLP<br>80 Turnmill Street<br>London Greater London EC1M 5QU (GB) |
| **Representative:** | J A Kemp LLP<br>80 Turnmill Street<br>London EC1M 5QU (GB) |
| **Decision under appeal:** | **Interlocutory decision of the Opposition Division of the European Patent Office posted on 14 July 2021 concerning maintenance of the European Patent No. 3117012 in amended form** |

**Composition of the Board:**

| | |
|---|---|
| **Chairwoman** | T. Sommerfeld |
| **Members:** | D. Pilat |
| | A. Bacchin |

## Summary of Facts and Submissions

I. European patent No. 3 117 012 is based on European patent application No. 15 761 889.3, filed as an international application published as WO 2015/138997. Two oppositions were filed against the granted patent, on the grounds of Article 100(a), in conjunction with Articles 54 and 56 EP, (b) and (c) EPC. The opposition division considered that the claims as granted (main request) lacked novelty, that the claims of auxiliary request 1 lacked clarity, whereas the claims of auxiliary request 2 fulfilled the requirements of the EPC.

II. Both the patent proprietor and opponent 1 lodged an appeal against the decision of the opposition division.

III. The parties were summoned to oral proceedings. In a communication pursuant to Article 15(1) RPBA, the parties were informed of the board's provisional, non-binding opinion on some of the legal and substantive matters of the case.

IV. Both opponents announced that they would not attend the oral proceedings.

V. Oral proceedings were held in the presence of the patent proprietor only.

VI. At the end of the oral proceedings, the patent proprietor withdrew its appeal, so that opponent 1 became the sole appellant.

VII. The claim set of the main request is identical to the claim set which the opposition division found

allowable. Claims 1 to 3 of the main request read as follows:

"1. A method of monitoring the status of a transplanted organ in a subject, the method comprising:

a) providing cell-free DNA from a sample obtained from a subject who is the recipient of an organ transplant from a donor;

b) sequencing a panel of single nucleotide polymorphisms (SNPs) from the cell-free DNA, wherein the panel of SNPs is suitable for differentiating between donor-derived cell-free DNA and recipient-derived cell-free DNA, and wherein the panel of SNPs comprises SNPs that have an overall population minor allele frequency of >0.4, a target population minor allele frequency of >0.4, the lowest polymerase error rate of the 6 potential allele transitions or transversions, and the genomic distance between each independent SNP is >500kb;

c) assaying variance in SNP allele distribution patterns in the panel as compared to expected homozygous or heterozygous distribution patterns to determine the level of donor-derived cell-free DNA, wherein individual genotyping of the donor and the recipient to determine which allele of the SNP belongs to the donor and to the recipient is not performed; and

d) diagnosing the status of the transplanted organ in the subject, wherein a change in levels of the donor-derived cell-free DNA over a time interval is indicative of the status of the transplanted organ.

2. A method of monitoring immunosuppressive therapy in a subject, the method comprising:

a) providing cell-free DNA from a sample obtained from a subject who is the recipient of an organ transplant from a donor;
b) sequencing a panel of single nucleotide polymorphisms (SNPs) from the cell-free DNA, wherein the panel of SNPs is suitable for differentiating between donor-derived cell-free DNA and recipient-derived cell-free DNA, and wherein the panel of SNPs comprises SNPs that have an overall population minor allele frequency of >0.4, a target population minor allele frequency of >0.4, the lowest polymerase error rate of the 6 potential allele transitions or transversions, and the genomic distance between each independent SNP is >500kb;
c) assaying variance in SNP allele distribution patterns in the panel as compared to expected homozygous or heterozygous distribution patterns to determine the level of donor-derived cell-free DNA, wherein individual genotyping of the donor and the recipient to determine which allele of the SNP belongs to the donor and to the recipient is not performed; and
d) diagnosing the status of the transplanted organ in the subject, wherein a change in levels of the donor-derived cell-free DNA over a time interval is indicative of transplanted organ status and a basis for adjusting immunosuppressive therapy.

3. A method of adjusting an immunosuppressive therapy in a subject, the method comprising:
a) providing cell-free DNA from a sample obtained from a subject who is the recipient of an organ transplant from a donor;
b) sequencing a panel of single nucleotide polymorphisms (SNPs) from the cell-free DNA,

wherein the panel of SNPs is suitable for differentiating between donor-derived cell-free DNA and recipient-derived cell-free DNA, and wherein the panel of SNPs comprises SNPs that have an overall population minor allele frequency of >0.4, a target population minor allele frequency of >0.4, the lowest polymerase error rate of the 6 potential allele transitions or transversions, and the genomic distance between each independent SNP is >500kb;

c) assaying variance in SNP allele distribution patterns in the panel as compared to expected homozygous or heterozygous distribution patterns to determine the level of donor-derived cell-free DNA, wherein individual genotyping of the donor and the recipient to determine which allele of the SNP belongs to the donor and to the recipient is not performed;

d) diagnosing the status of the transplanted organ in the subject, wherein a change in levels of the donor-derived cell-free DNA over a time interval is indicative of transplanted organ status; and

e) adjusting immunosuppressive therapy being administered to the subject."

Dependent claims 4 to 15 define specific embodiments of the methods of claims 1 to 3.

VIII. The documents cited in this decision include the following:

D3 Beck J. *et al.*, Clinical Chemistry, vol. 59, issue 12, pages 1732 to 1741, (2013);

D6 Pakstis A.J. *et al.*, Human Genetics vol. 127 pages 315 to 324 (2010);

D16 WO 2012/019200 A2;

D22 Brodin J. *et al.*, PLOS ONE, vol. 8, issue 7, e70388, pages 1 to 7, (2013)

IX. The parties' arguments relevant for this decision are discussed in the Reasons below.

X. The final requests of the parties relevant for this decision were as follows:

The appellant (opponent 1) requested in writing that the decision under appeal be set aside and that the patent be revoked and that documents A23 to A28 be admitted.

The respondent (patent proprietor) requested that the appeal be dismissed (main request). It further requested that documents A23 to A28 not be admitted into the proceedings or, if admitted, that document A35 be admitted into the proceedings.

The party as of right, opponent 2, requested in writing that documents A29 to A33 not be admitted.

## Reasons for the Decision

*1.* By their decision not to attend the oral proceedings and not to file substantive arguments in reply to the issues raised in the board's communication pursuant to Article 15(1) RPBA, the opponents (appellant and party as of right) waived their opportunity to comment on the board's provisional opinion, either in writing or at the oral proceedings, although this opinion was to

their disadvantage. According to Article 15(3) RPBA, the board is not obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral proceedings of any party duly summoned who may then be treated as relying on their written case.

*Admittance of documents A23 to A35 (Article 12(4) RPBA)*

2. A number of documents were submitted in appeal, which have been renumbered A23 to A35 by the board. With the grounds of appeal, the appellant submitted documents A23 to A28 (originally designated D23, D24, D25A, D25B, D26 and D27). With their appeal, then withdrawn, the respondent submitted documents A29 to A33 (originally designated D23 to D27). With the reply to the patent proprietor's appeal, the appellant further filed document A34 (originally designated D33).

3. In its communication according to Article 15(1) RPBA, the board indicated its preliminary opinion that none of the documents A23 to A35 were to be admitted in appeal. Neither the appellant nor the party as of right replied to the board's communication nor did they attend oral proceedings, while the respondent mostly relied on their written submissions. Under these circumstances the board saw no reason to deviate from its preliminary opinion, and decided not to admit any of documents A23 to A35 into the appeal proceedings as well as any arguments based thereon (Article 12(4) RPBA), for the reasons given below.

4. As argued by the respondent in their reply to the appeal (in particular item 2.4), the appellant has not provided any arguments as to why documents A23 to A28 could not have been filed already with the opposition

division. Appellant's arguments that the filing of these documents was rendered necessary by the decision of the opposition division and that these documents could only be found after extensive search do not explain why they could not have been filed earlier. According to the appellant, these documents were filed to "technically sustain and emphasize the technical information of D3" (grounds of appeal page 4, first full paragraph). The technical information of document D3 was however discussed throughout the opposition proceedings and thus the appellant should have filed then any further evidence that it considered necessary to address this issue. Similar arguments apply to A34's admission, which was filed with the reply to the patent proprietor's appeal, without any justification being given for its submission at all. As to document A35, this was filed by the respondent with the reply to the appeal and the respondent requested that it be admitted if documents A23 to A28 were to be admitted. Since none of A23 to A28 were admitted, there was no reason to admit A35 either.

*Sufficiency of disclosure - Article 83 EPC*

5. Article 83 EPC stipulates that the application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by the person skilled in the art. With respect to the invention as defined in claims 1 to 3 of the main request, this means that the skilled person must be able to monitor the status of a transplanted organ in a subject, and to monitor and adjust an immunosuppressive therapy in a subject by using the methods as claimed. The board agrees with the opposition division and the respondent that this requirement is fulfilled.

6. The appellant argued that the conclusions of the opposition division in points 9.6.16 to 9.6.18 were incorrect because they were based on the wrong assumption that "the mere presence of a non-working embodiment is not necessarily sufficient to already conclude that a patent lacks sufficiency of disclosure" (point 9.6.19). In agreement with the Guidelines (F.III.5.1), the opposition division should have at least requested that clinical cases which cannot be assessed according to the claimed method be clearly excluded from the scope of the claims. The appellant moreover disagreed with the statements in points 9.6.20 to 9.6.22 of the appealed decision, according to which (i) a high percentage of donor derived cell free DNA was observed only during the first days after an organ transplant, and that (ii) the application did not incite the skilled person to implement the claimed method at this time point. Further, the appellant argued that the patent did not provide information regarding the minimum number of SNPs to be used for constituting a "suitable panel". In view of the teachings in document D6, it was doubtful that the claimed method would work with a panel of SNPs comprising only 20 independent SNPs.

7. As correctly observed in the decision under appeal (reasons 9.6.17), during the first days following transplantation, donor derived cell free DNA (dd-cfDNA) may be present in substantial amounts and can represent levels exceeding 90% of the total cell free DNA (cfDNA) in the recipient's blood stream (document D3, Figures 3 and 5A; page 1735, right-hand column, last paragraph). About a week after transplantation, the amount of dd-cfDNA then decreases sharply and reaches a steady-state at low levels, so that at day 8 the amount of recipient-derived DNA represents the major DNA and the

donor-derived DNA represents the minor DNA. The board agrees with the conclusions of the opposition division that, although the method can allegedly not achieve its purpose during such an early phase after transplantation, this non-working embodiment is insufficient to establish a lack of sufficiency of disclosure of the claimed method for the following reasons.

8. The claimed methods are directed to monitoring the status of a transplanted organ (claim 1) or to monitoring and adjusting immunosuppressive therapy (claims 2 and 3), wherein the status of the transplanted organ is diagnosed by determining a change in levels of the dd-cfDNA over a time interval. There is no requirement to put the invention into effect in the first few hours or days post-transplant but also no obligation not to do so: in any case, the levels of dd-cfDNA have to be determined over a time interval; a change in these levels over this time interval is indicative of the transplanted organ status. No evidence has been presented that the changes in dd-cfDNA levels over time, as required in the claim, would not allow monitoring the status of a transplanted organ, even in the early stages after transplantation, regardless of whether dd-cfDNA is present at levels greater than 50% or not. Even if the patent specification does not provide any detailed information on the "change in levels ... " nor on the "time interval", the board was not presented any tangible evidence which would cast serious doubt that the claimed methods could be carried out.

9. As regards the alleged lack of information in the patent concerning the minimum number of SNPs needed for a suitable panel, the board notes that again there is

no convincing evidence that the claimed methods cannot be implemented when a number of SNPs as defined in the claims is used. This applies all the more so given that the examples in the present application already provide such a suitable panel. As argued by the respondent, the skilled person would understand that the likelihood of a panel being generally useful increases as the number of relevant SNPs increases, but this does not prevent them from using panels with a small number of SNPs. Even if the examples in the patent may use 92 SNPs (Example 1) or 266 (Examples 2 to 7) and also the prior art document D6 disclosed a "very restricted" SNP panel composed of 45 unlinked SNPs, there is no evidence on file that a panel with at least 20 independent SNPs would not work in the context of the claimed methods.

10. For the sake of completeness, it is noted that opponent 2 also disagreed with the conclusions of the opposition division that the claims were sufficiently disclosed. Opponent 2 however only stated in this context that they maintained the arguments presented in their opposition (reply, section 7.1 on page 21). As indicated in the preliminary opinion of the board pursuant to Article 15(1) RPBA, it is not for the board to identify the issues that may still be a matter of dispute among those raised in each and every submission in the previous proceedings, nor to identify the arguments as to why the impugned decision is incorrect, but for the parties to bring forward in the statement of grounds of appeal and in the reply their line(s) of argument and all the facts and evidence on which they rely in appeal proceedings; this is not fulfilled by a passing reference to the facts and evidence put forward in opposition proceedings ("Case Law of the Boards of Appeal of the EPO", 10th edition 2022, V.A.2.6.5). Opponent 2 has not reacted to these observations of the

board. Hence, opponent 2's objections under Article 83 EPC are considered unsubstantiated.

11. In view of the arguments above, the claimed methods fulfil the requirements of Article 83 EPC.

*Inventive step - Article 56 EPC*

12. The patent discloses methods of monitoring the status of an allograft in a transplant recipient, as well as methods of monitoring and adjusting immunosuppressive therapies being administered to the transplant recipient (patent, paragraphs [0001], [0005] and [0017]). The methods as claimed are based on the premise that transplant rejection is associated with the death of cells in the transplanted (donor) organ or tissue, which will release donor-derived DNA from the dying donor cells, thus releasing donor-derived cell-free DNA (dd-cfDNA) into the bloodstream of the recipient. To assay the status of the allograft in the recipient, cell-free DNA can be extracted from a sample from the recipient, such as a bodily fluid, and various polymorphic markers, such as single nucleotide polymorphism (SNP) loci, can be sequenced, where the panel of polymorphic markers, such as a panel of SNPs, is suitable for differentiating between donor-derived cell-free DNA and recipient-derived cell-free DNA (rd-cfDNA). The specific polymorphic markers selected to be on the panel include those that are identified as having low probabilities of being identical in any two individuals, thus making them appropriate for differentiating between rd-cfDNA and dd-cfDNA. The number of polymorphic markers on the panel such as, for example, the number of SNPs on the panel, will be sufficient to discriminate between recipient and donor

alleles even in related individuals, excepting identical twins (patent, paragraph [0018]).

*Closest prior art, difference and objective technical problem*

13. The opponents agreed with the opposition division that document D16 is the closest prior art in the assessment of inventive step. The board also agrees that document D16 is a suitable starting point for the discussion of inventive step. Document D16 discloses assay systems for determination of source contribution in a sample (Title). Although mostly in the context of prenatal diagnosis by methods involving the detection of cfDNA from a fetus in the plasma of the pregnant mother, document D16 also teaches methods suitable for monitoring solid organ transplant recipients by following the levels of cfDNA from the transplanted organ (donor-derived) in a sample from the recipient (document D16, paragraphs [0211], [0220]).

14. The parties agreed that the claimed methods according to claims 1 to 3 differ from that disclosed in document D16 in that the panel comprises SNPs that have: (a) an overall population minor allele frequency of >0.4; (b) a target population minor allele frequency of >0.4; (c) the lowest polymerase error rate of the 6 potential allele transitions or transversions, and (d) the genomic distance between each independent SNP is >500kb.

15. According to the respondent, SNPs having an overall population minor allele frequency of >0.4 and a target population minor allele frequency of >0.4 ensure that the SNPs are randomly distributed throughout a population. The lowest polymerase error rate of the 6 potential allele transitions or transversions minimises

experimental noise in the assay using SNPs. Finally, the genomic distance between each independent SNP being >500kb ensures that there is essentially no genetic linkage between two SNPs, maximising the informative data that can be obtained from the panel. All these effects increase the SNP panel's ability to differentiate between donor and recipient DNA. In agreement with the appealed decision (reasons 8.7), and not disputed by the appellant, the respondent argues that the technical effect associated with these differences is an increased chance of finding SNPs that permit donor and recipient differentiation. The board has no reasons to disagree.

16. On this basis, the board agrees with the appellant that the objective technical problem to be solved in the patent is the provision of appropriate means for a proper donor and recipient cfDNA differentiation. Since document D16 does not provide any specific disclosure regarding the SNPs to be used, but only refers to SNPs in general, the board considers that it is not possible to establish that there is an improvement by selecting the claimed SNPs; therefore the board adheres to the technical problem as formulated by the appellant.

17. The solution to the above technical problem lies in the use of "appropriate means" consisting of the panel of SNPs presenting the features identified above to quantify the donor-derived cfDNA present in the sample obtained from the recipient, as set out in paragraphs [0046] to [0049] of the patent. Hence the board considers that the claimed subject-matter solves the technical problem.

18. The appellant disagreed that the technical problem is solved over the whole scope of the claim, arguing that

in paragraphs [0046] to [0049] of the patent the quantification carried out is based on the assumption that the majority of the cfDNA in the sample from the transplant recipient originates from the recipient endogenous DNA, and therefore that the donor-derived cfDNA is in minority (paragraph [0048]). However, if the majority of the cfDNA in the sample were from the donor and not from the recipient it would be questionable whether the claimed methods achieved the technical effect across the entire scope of the claims, regardless of the group of SNPs used in the methods. The board however notes that, even if the majority of the cfDNA did not come from the recipient and the patent's assumption was no longer valid, the method still requires step d) "diagnosing the status of the transplanted organ in the subject, wherein a change in levels of the donor-derived cell-free DNA over a time interval is indicative of the status of the transplanted organ" (emphasis added by the board). A one-time and singular evaluation of the SNPs levels cannot cast serious doubts that the claimed methods achieve the technical effect across the entire scope of the claims, regardless of the group of SNPs used in the methods. The appellant moreover reiterated the arguments based on document D3, already discussed in the context of Article 83 EPC, that the proportion of graft-derived cfDNA (GcfDNA) in document D3 (i.e., dd cfDNA) is of more than 90% at day 1, and reaches about 30% during the fourth day after a liver transplantation for two patients (Figure 5A). As already noted in the context of Article 83 EPC, the variance in the pattern of the GcfDNA steadily decreases over time in all cases after transplantation. Thus there is no evidence in document D3 showing that the distinguishing features used in the claims cannot solve the objective technical

problem of providing appropriate means for a proper donor and recipient cfDNA differentiation.

*Obviousness*

19. In the assessment of obviousness, the question to be answered is whether or not the skilled person starting with the teaching of document D16 and faced with the technical problem defined above (point 16. of the reasons) would have solved the technical problem by modifying the method of document D16 to arrive at the methods as claimed.

20. The board considers that starting from document D16, which does not disclose a panel of SNPs or even SNPs for determining the level of dd-cfDNA in a donor/ recipient sample, and given the technical problem identified above, the skilled person had no indication on how to select the SNPs in the panel to determine the level of dd-cfDNA in a sample for a proper donor and recipient cfDNA differentiation. Although each of the distinguishing features may be known from prior art documents such as D3, D22 and D6 (see below), it is not apparent why the skilled person would turn to these documents and/or why it would combine them with document D16 to arrive at the claimed methods in an obvious way. Accordingly, the board disagrees with the appellant that, starting from document D16 and faced with the above technical problem, the skilled person would have included SNPs with the characteristics as claimed.

21. It is true that the distinguishing features were all disclosed in the prior art and/or were common knowledge of the skilled person at the time the application was filed. Document D3 discloses the features "overall

population minor allele frequency >0.4" and "target population minor allele frequency> 0.4" and their associated technical effects. Document D22 provides informative data regarding polymerase error rate (abstract). Furthermore, although the feature "wherein the genomic distance between each independent SNP is >500kb" is not taught in the prior art, the skilled person understands that a genomic distance superior to 500 kb between SNPs corresponds to a low genetic linkage between each of the SNPs, so that they have a low chance of being inherited together after meiosis when they are on the same chromosome (e.g. document D6, abstract).

22. However, although document D3 teaches the use of a panel of SNPs which can have a minor allele frequency of greater than 0.4, this choice was made in relation to a method that requires the donor and recipient to be genotyped and uses an informative set of SNPs that is specific to each patient (Figure 3). The board notes, however, that since individual genotyping of the donor and the recipient is precluded in the claimed methods and the method in document D3 is not based on a comparison with expected homozygous or heterozygous distribution patterns either, as the identity of each SNP was determined by genotyping, the skilled person would not have turned to this document, let alone isolated this particular feature from it.

23. The board finds therefore that the skilled person looking for appropriate means for a proper donor and recipient cfDNA differentiation could not derive any motivation from documents D16 or D3 to select a panel of SNPs with the claimed characteristics having an increased chance of differentiating between donor and recipient DNA, let alone to use SNPs that have a minor

allele frequency of greater than 0.4 but without performing a genotyping step.

24. Document D22, on the other hand, provides general information regarding polymerase error rates, but does not provide any other aspects of the distinguishing features (decision under appeal reasons 8.23). In the light of this teaching, the board considers that neither document D16 nor D22 indicate that the lowest polymerase error rate of the 6 potential allele transitions or transversions would help to solve the above technical problem and increase the chances of differentiating between donor and recipient DNA.

25. Finally, document D6 may teach the advantages of having low genetic linkage in the panel, but document D6 is in a different field from the invention (forensics, sample tracking and paternity testing; see abstract) and uses a method involving genotyping.

26. The board thus considers that the skilled person would not arrive at the claimed subject-matter in an obvious way. The claims of the main request therefore involve an inventive step.

## Order

## For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

C. Rodríguez Rodríguez T. Sommerfeld

Decision electronically authenticated