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**Datasheet for the decision  
of 2 May 2016**

**Case Number:** T 0644/12 - 3.3.02

**Application Number:** 99918188.6

**Publication Number:** 1076824

**IPC:** G01N33/68, A61B8/08

**Language of the proceedings:** EN

**Title of invention:**

ANTENATAL SCREENING FOR DOWN'S SYNDROME

**Patent Proprietor:**

Wald, Nicholas John

**Opponents:**

PerkinElmer, Inc.

Maternal Fetal Medicine Foundation (opposition withdrawn)

Bauer, Wulf

Media Innovations Limited

**Headword:**

Antenatal screening/WALD

**Relevant legal provisions:**

EPC R. 115(2)

EPC Art. 113(1), 56

**Keyword:**

Inventive step - (no)

**Decisions cited:**

T 0057/09

**Catchword:**



**Beschwerdekammern**  
**Boards of Appeal**  
**Chambres de recours**

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Case Number: T 0644/12 - 3.3.02

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.02**  
**of 2 May 2016**

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**Decision under appeal:** **Interlocutory decision of the Opposition  
Division of the European Patent Office posted on  
3 January 2012 concerning maintenance of the  
European Patent No. 1076824 in amended form.**

**Composition of the Board:**

**Chairman** U. Oswald  
**Members:** T. Sommerfeld  
D. Prietzel-Funk

## Summary of Facts and Submissions

- I. European patent No. 1076824, based on European patent application No. 99918188.6, which was filed as an international patent application published as WO 1999/056132, was granted with 20 claims.
- II. The patent was opposed by four parties, all opponents requesting revocation of the patent in its entirety on the grounds of lack of novelty and inventive step (Articles 54(2) and 56 EPC and Article 100(a) EPC); moreover, Article 53(a) EPC in conjunction with Article 100(a) EPC, Article 100(b) EPC and Article 100(c) EPC were also filed as grounds of opposition by opponents 1, 2 and 4.
- III. The documents cited during the proceedings before the opposition division and the board of appeal include the following:
- E1 Kadir and Economides, *Ultrasound Obstet. Gynecol.* 9:244-247, 1997
  - E2 Thilaganathan et al., *Ultrasound Obstet. Gynecol.* 10:261-264, 1997
  - E3 EP 0800085
  - E6 Wald and Hackshaw, *Prenatal Diagnosis* 17(9): 821-829, 1997
  - E7 Cuckle, *Ultrasound Obstet. Gynecol.* 7:236-238, 1996
  - E9 Wald et al., *J. Med. Screening* 4:181-246, 1997
  - E37 EP 0701131
  - E56 Wald et al., *New Engl. J. Medic.* 341:461-476, 1999
  - E58 Hyett and Thilaganathan, *Current Opinion in Obstetrics and Gynecology* 11:563-569, 1999

- E59 Nicolaides et al., Ballière's Clinical Obstetrics and Gynaecology 14(4):581-594, 2000
- E60 Campogrande et al., J. Med. Screen. 8:163-164, 2001
- E61 Gilbert et al., BMJ 323:1-6, 2001
- E62 Letters to the editor, The New Engl. J. Medic. 341:1935-1937,1999
- E63 "Integrated Test", DSNEWS 7(2):28-29, 2000
- E64 ACOG Practice Bulletin, Clinical Management Guidelines for Obstetrician-Gynecologists, 2007
- E65 "Antenatal care", National Collaborating Centre for Women's and Children's Health, 2003

IV. The patent in suit was revoked by an earlier decision of the opposition division which was set aside with the decision T 57/09 of 13 April 2010. The board remitted the case to the department of first instance for further prosecution on the basis of the third auxiliary request filed during the oral proceedings on the 13 April 2010, having decided that this request complied with Article 123(2) EPC, Article 84 EPC and was novel over document E3.

V. The opposition division concluded that the same third auxiliary request complied with all requirements of the EPC in dispute, namely: Article 54 EPC, Article 56 EPC, Article 53(c) EPC, Article 52(2) (a) (c) and (3) EPC, Article 53(a) EPC and Article 83 EPC, and thus decided, by an interlocutory decision announced at oral proceedings, to maintain the patent in amended form on the basis of said request (Articles 101(3) (a) and 106(2) EPC).

VI. Opponent 1 (appellant) lodged an appeal against that decision. With the statement of the grounds of appeal,

the appellant requested that the decision be set aside and the patent revoked in its entirety.

- VII. The patent proprietor (respondent) filed a response to the appellant's grounds of appeal, and requested that the appeal be dismissed.
- VIII. Opponent 2 withdrew its opposition already before the commencement of appeal proceedings and is thus no longer a party to the proceedings. Opponents 3 and 4, parties as of right, did not make any submissions during the whole appeal proceedings.
- IX. Summons for oral proceedings before the board were issued. In the accompanying communication, the board provided a preliminary opinion concerning admissibility of newly filed documents and novelty.
- X. By letter dated 1 April 2016, the appellant submitted a reply to the issues raised by the board in its official communication.
- XI. Oral proceedings before the board took place as scheduled, in the absence of the duly summoned parties as of right (opponents 3 and 4).

At the end of the oral proceedings, the chairman announced the decision of the board.

- XII. Claim 1 of the sole claim set on file (so called "third auxiliary request") reads as follows:

"1. A method of determining whether a pregnant woman is at an increased risk of having a fetus with Down's syndrome, the method comprising the steps of:

measuring the level of at least one screening marker from a first trimester of pregnancy by:

(i) assaying a sample obtained from the pregnant woman at said first trimester of pregnancy for at least one biochemical screening marker; and/or

(ii) measuring at least one ultrasound screening marker from an ultrasound scan taken at said first trimester of pregnancy;

measuring the level of at least one screening marker from a second trimester of pregnancy by:

(i) assaying a sample obtained from the pregnant woman at said second trimester of pregnancy for at least one biochemical screening marker;

wherein the screening markers from the first and second trimesters consist of one of the following combinations:

1) the at least one screening marker from the first trimester of pregnancy consists of PAPP-A, and the at least one screening marker from the second trimester of pregnancy consists of AFP, uE3, total hCG and inhibin-A;

2) the at least one screening marker from the first trimester of pregnancy consists of PAPP-A and free  $\beta$ -hCG, and the at least one screening marker from the second trimester of pregnancy consists of AFP, uE3 and inhibin-A;

3) the at least one screening marker from the first trimester of pregnancy consists of NT and PAPP-A, and the at least one screening marker from the second trimester of pregnancy consists of AFP, uE3, total hCG and inhibin-A;

4) the at least one screening marker from the first trimester of pregnancy consists of NT, PAPP-A and free  $\beta$ -hCG, and the at least one screening marker from the second trimester of pregnancy consists of AFP, uE3 and inhibin-A;



5) the at least one screening marker from the first trimester of pregnancy consists of PAPP-A, and the at least one screening marker from the second trimester of pregnancy consists of AFP, uE3 and total hCG;

6) the at least one screening marker from the first trimester of pregnancy consists of PAPP-A and free  $\beta$ -hCG, and the at least one screening marker from the second trimester of pregnancy consists of AFP and uE3;

7) the at least one screening marker from the first trimester of pregnancy consists of NT and PAPP-A, and the at least one screening marker from the second trimester of pregnancy consists of AFP, uE3 and total hCG;

8) the at least one screening marker from the first trimester of pregnancy consists of NT, PAPP-A and free  $\beta$ -hCG, and the at least one screening marker from the second trimester of pregnancy consists of AFP and uE3;

9) the at least one screening marker from the first trimester of pregnancy consists of PAPP-A, and the at least one screening marker from the second trimester of pregnancy consists of AFP, uE3 and inhibin-A; and

determining, using a computer program executed on a computer, a quantitative estimate of the risk of Down's syndrome by comparing the measured levels of both the at least one screening marker from the first trimester of pregnancy and the at least one screening marker from the second trimester of pregnancy with observed relative frequency distributions of marker levels in Down's syndrome pregnancies and in unaffected pregnancies."

XIII. Appellant's submissions, in so far as relevant to the present decision, may be summarised as follows:

Document E1 could be considered the closest prior art. The method disclosed in E1 differed from the claimed

one in that it did not use a computer program and did not disclose the specific marker combinations. However, the use of an integrated risk calculation from both the first and the second trimesters was already disclosed in the prior art, namely in E3, as had been decided in T 57/09, therefore being *res judicata*. Moreover, the mathematical calculations for such marker combinations were well-known from the prior art: E6, pages 824 and 825, showing that curves for three different markers can be combined, the effect being better for non-correlated variables. The authors of E1 had suggested as alternative to provide the results of both trimesters in a single combined estimate risk: E1, page 246 right column, last paragraph. To combine results obtained with different markers to provide one single risk estimate was well-known from the prior art, e.g. E9 (page 185, right column, first full paragraph; page 186, right column last paragraph). The advantage alleged by the patent proprietor was certainly not present in the "sequential" embodiment of the method, wherein the population also changed, as in E1. In fact it would not even be possible to perform the test as claimed if in the "sequential embodiment" the patient decided for abortion after the results of the first trimester. The marker combinations could not contribute for inventive step either, as the markers were all well known in the context of screening of Down's syndrome. From the data of E64 (Table 1) it was apparent that the "serum integrated test" according to the first embodiment of claim 1 was not better than the prior art combination of NT measurement together with other first trimester markers (a combination which was suggested by E1, even if no results were provided); the same was also apparent from E65 (Table 9.2). All post-published documents related to the "integrated test" and not to the "sequential integrated test". Moreover the patent

did not provide results for some of the marker combinations. Thus the problem as formulated by the opposition division had not been solved, and should be reformulated as the provision of an alternative method, the solution being nevertheless still obvious.

XIV. The respondent's arguments may be summarised as follows:

The key features of claim 1 were that markers from both the first and the second trimesters were used, which were different for each trimester and which were all used to derive an estimated risk. The concept was not known from the prior art, and was also not disclosed in E3: T 57/09 had only concluded that one single embodiment, namely an embodiment where the same marker was used both in the first and in the second trimester, was disclosed in E3. E1 disclosed sequential screening, wherein the population had changed from the first to the second trimester; non-sequential screening was not disclosed anywhere in the prior art and provided a more accurate risk estimate. In the method according to the invention, the risk estimate was calculated exactly in the same way whether sequential testing or non-sequential testing was performed; this was not obvious in view of the fact that the population had changed and that E1 suggested to do a risk adjustment instead (E1 page 246, left column, last sentence of first paragraph, and right column, penultimate paragraph). The last paragraph of E1 should not be read in isolation; it suggested to derive a risk estimate at 10 to 13 weeks (first trimester) but not to combine the results of the first and the second trimesters. This would be counter-intuitive. The reaction of the medical community to the invention (as disclosed in E56) was first negative and sceptical (E59, page 588, lines 2 to

3; E62; E63) and then its importance was recognised and the test was widely accepted and even recommended in both the US and the UK (E64, E65). When E1 used the term "combined" or "in conjunction" it actually meant to combine the screening tests, i.e. both tests made. The technical problem in view of E1 should be formulated as to improve efficacy of screening test; E1 did not present comparable results - due to the small population size - but the post-published papers (e.g. E64, Table 1) showed that the claimed method was indeed better; in fact, E1 was not even enabling for adjusting the risk.

- XV. The appellant requested that the decision be set aside and the patent revoked.

The respondent requested that the appeal be dismissed.

### **Reasons for the Decision**

1. The appeal is admissible.
2. The oral proceedings before the board took place in the absence of opponents 3 and 4, parties as of right to the present proceedings (Article 107 EPC), who were duly summoned but decided not to attend.

According to Rule 115(2) EPC if a party duly summoned to oral proceedings does not appear as summoned, the proceedings may continue without that party.

In the present case the parties as of right (opponents 3 and 4) have not filed any submissions or requests in writing during appeal proceedings. The provisions of Article 113(1) EPC which govern the right to be heard

have been fulfilled also in respect of opponents 3 and 4, since it was the parties' own choice to remain silent during the whole appeal proceedings.

3. T 57/09 - Res judicata

The present claims have already been the subject of a decision by a technical board of appeal: in decision T 57/09 of 13 April 2010, Board 3.3.08 decided that these claims fulfilled the requirements of Rule 80 and Article 123(2)(3) EPC, of Article 84 EPC, and that they were novel over E3. Thus, as regards these claims, these issues are *res judicata*. Moreover, the further findings in said decision as regards the higher-ranking requests are also *res judicata* in so far as they might have a bearing for the examination of the outstanding issues.

4. Novelty

In its statement of grounds of appeal, the appellant raised an objection of lack of novelty over document E37 (Article 54(2) EPC). In its communication accompanying the summons to oral proceedings, the board expressed its preliminary, non-binding opinion, that E37 did not appear to be novelty-destroying for the claimed subject-matter. The issue was not further discussed at oral proceedings and, in view of the conclusions reached for inventive step (see below), there is no need to elaborate on novelty in the present decision.

5. Inventive step

5.1 The patent aims at providing methods for antenatal screening for Down's syndrome, wherein "a single risk

estimate is derived from measurements of marker levels carried out on biochemical samples (eg. serum or plasma or urine or cells) and/or ultrasound images which are obtained sequentially at two or more different stages of pregnancy" (patent, paragraph [0019]). The patent further states that the individual measurements (of the markers) are obtained by using known methods (paragraphs [0018] and [0019]). As to the markers used, the patent states that "One or more screening markers from each of the stages of pregnancy may be used" and, in fact, "Any markers which are effective at each particular stage may be selected" (paragraph [0019], third and fourth sentence). Claim 1 of the sole request is restricted to a method encompassing measurement of the level of specifically defined screening markers (biochemical and/or ultrasound) from the first trimester of pregnancy followed by measurement of specifically defined biochemical screening markers from the second trimester of pregnancy, and then determining a quantitative estimate of the risk of Down's syndrome. For the exact wording of the claim see section XII.

- 5.2 The board considers that E1 is a suitable starting point for the discussion of inventive step. E1 also discloses antenatal screening for Down's syndrome by a method which involves nuchal translucency (NT) measurement during the first trimester, followed by mid-trimester (second trimester) biochemical screening of  $\alpha$ -fetoprotein (AFP) and free  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG): E1, page 244, right column, last paragraph to page 245, left column, line 2. The difference to the claimed subject-matter is that none of the specific marker combinations of claim 1 is disclosed, nor is the last step of the claimed method, namely the step of "determining, using a computer program executed on a computer, a quantitative estimate

of the risk of Down's syndrome by comparing the measured levels of both the at least one screening marker from the first trimester of pregnancy and the at least one screening marker from the second trimester of pregnancy with observed relative frequency distributions of marker levels in Down's syndrome pregnancies and in unaffected pregnancies".

- 5.3 The patent provides data which allow to conclude that, in comparison to single-trimester screening methods of the prior art, the method according to the invention has a better discriminatory power, i.e. a better detection ratio for the same false positive rate or, conversely, a lower false positive rate for the same detection rate, at least for marker combinations (1) to (4), (5), (7) and (9): see Tables 2a to 3b (methods of the prior art) and Tables 4a to 5b, and Figure 1 (methods of the invention). There is however no data in the patent (nor in the post-published documents) comparing the results of a screening method according to the closest prior art E1 with those of a method according to the invention. Nevertheless, the board considers that it is plausible that the claimed method may have a better discriminatory power than the method of E1. This conclusion relies on the observation that the method of E1 made use of only 3 markers in total while all marker combinations used according to the alleged invention have 4, 5 or 6 markers: it thus appears reasonable that a method making use of more markers, provided that they are independent, leads to an improved discriminatory power of the method. The technical problem can thus be formulated as the provision of an improved method for antenatal screening of Down's syndrome, and the board is satisfied that the claimed solution solves this problem.

- 5.4 It thus has to be assessed whether the claimed solution involves an inventive step.
- 5.5 As regards the first distinguishing feature, namely the specific marker combinations, it is undisputed that, as noted above, all markers mentioned were routinely used in the prior art for the screening of Down's syndrome, and in the same combinations as listed in the claim for each trimester. For example, combinations (1) and (5) consist of measurement of pregnancy-associated plasma protein A (PAPP-A) in the first trimester combined, respectively, with the "quadruple test" or with the "triple test" (both known from document E9, page 181, right column, lines 11 to 13) in the second trimester; combination (7) consists of measurement of PAPP-A and nuchal translucency (NT) in the first semester combined with the "triple test" in the second trimester; combinations (2) and (6) consist of measurement of PAPP-A and free  $\beta$ -hCG in the first semester combined with a variation of, respectively, the "quadruple test" or the "triple test" in the second trimester, the variation consisting of omission of total hCG because of the expected high correlation with free  $\beta$ -hCG (paragraphs [0019] and [0023] of the patent). It should be noted that PAPP-A, NT and free  $\beta$ -hCG were all known as markers for the first trimester, and their use in combination had also already been disclosed (E6: "combined test", page 821, right column, lines 6 to 9; E1, page 246, right column, second sentence of the last paragraph). Notably, also the patent confirms that "Any markers which are effective at each particular stage may be selected" (paragraph [0019], fourth sentence). Thus the specific combinations of markers used for each trimester cannot per se justify an inventive step.



5.6 As regards the further distinguishing feature, namely the step of calculating, with a computer program, a quantitative estimate of the risk of Down's syndrome, the board notes that two aspects of this step are distinct from the method disclosed in E1: the first aspect is the calculation method itself for estimating a combined risk based on measurements of a plurality of non-correlated markers, which is not further defined in E1; and the second aspect is the use, for said calculation, of the results obtained for the markers of both trimesters. The first aspect, while not explicitly disclosed in E1, was well-known in the art. In fact, it was common general knowledge in the field, at the priority date, to provide a combined estimated risk based on measurements of a plurality of non-correlated markers; moreover, the calculation methods were known and readily available to the skilled person, a medical doctor and scientist with knowledge of biostatistics: see e.g. E6, E7 and E9, discussing the calculation of risk based on measurements of multiple markers from the first trimester (E6, E7) and from the second trimester (E9). This was not disputed by the respondent and, in fact, also the patent states that "The estimation of risk is conducted using standard statistical techniques" (paragraph [0018]) and refers, by way of example, to documents of the prior art. Hence, it is considered that this feature cannot per se justify acknowledgement of an inventive step either.

5.7 The second aspect, namely the estimation of a combined risk for markers of both the first and the second trimesters, has not in fact been performed in the available prior art but was suggested in E1, as concluded below.

5.8 In its introductory part, E1 provides an overview of what was common practice (at least in the United Kingdom) in the antenatal screening for Down's syndrome: "Screening for Down's syndrome in the UK has usually been performed during the second trimester by maternal serum biochemistry. However, during the last 4 years, nuchal translucency measurement in the first trimester has been proposed as an alternative" (page 244, left column, lines 1 to 5 of the Introduction). The purpose of E1's study is then defined as being "to assess the effect of introducing nuchal translucency measurement on second-trimester biochemical screening for Down's syndrome in a low-risk population" (page 244, right column, lines 4 to 7). It is thus apparent that E1 proposes to depart from a single-trimester screening of the prior art (i.e. either second or first trimester screening) to a screening wherein measurements in both trimesters are taken into account. In fact, the method of E1 comprises first-trimester screening (nuchal translucency measurement) of all pregnant women followed by second-trimester biochemical screening for those pregnant women who have had a negative test in the first trimester (page 244, right column, last paragraph).

5.9 The results of E1's study are then discussed in the Discussion section, starting on page 245, right column, and culminating with the two last paragraphs of the article.

In the *penultimate paragraph*, the authors of E1 state that "The effect of introducing nuchal translucency measurement on the second-trimester biochemical screening of trisomy 21 has not been assessed before. As nuchal translucency thickness and maternal serum  $\alpha$ -fetoprotein and free  $\beta$ -hCG are independent variables

(...), it is possible to combine these in estimating an individual risk for each pregnancy and keeping the false-positive rate to a minimum. Using both tests in conjunction may increase the overall detection rate". The authors then state that "In this pilot study, there was an increase in the number of invasive procedures performed for screen-positive patients with no increase in the detection rate, because the biochemical results were not adjusted by the nuchal translucency measurements. Therefore, the interpretation of biochemical screening was suboptimal. The other potential problem of sequential screening includes difficulties with counselling when faced with conflicting results."

In the *last paragraph*, it is then stated that "First-trimester biochemical screening has been shown to be as effective as second-trimester testing<sup>18,19</sup>. Recent studies have shown that an improved estimate of risk for fetal trisomies at 10-13 weeks' gestation can be achieved by combining data on maternal age, nuchal translucency measurement, maternal serum total or free  $\beta$ -hCG or pregnancy-associated placental protein A<sup>20-22</sup>. The optimal way of delivering screening for Down's syndrome is by providing the patient with a single individual risk by a combination of nuchal translucency measurement and maternal serum screening."

5.10 As regards the above-cited *penultimate paragraph*, the board notes that it clearly enumerates markers from both trimesters (namely nuchal translucency thickness as first trimester marker, and maternal serum  $\alpha$ -fetoprotein and free  $\beta$ -hCG as second trimester markers) and suggests to combine them "in estimating an individual risk for each pregnancy and keeping the false-positive rate to a minimum", while at the same

time improving the overall detection rate. The board cannot envisage any other interpretation than that the mentioned markers from both trimesters are to be taken together to estimate a combined risk, and this with the same purpose as the invention, i.e. to improve detection rate while keeping the false-positive rate to a minimum. So already this passage alone is considered to provide the suggestion for estimating a combined risk for markers of both the first and the second trimesters.

It is also of relevance that this paragraph further identifies as a problem arising from sequential screening (as performed in E1) the fact that counselling may become difficult when faced with conflicting results. This statement strengthens the above interpretation of combining the independent variables in estimating one - single - individual risk.

- 5.11 The *last paragraph* of E1 then states that biochemical screening is as effective in the first as in the second trimester, and reports that studies have shown that an improved risk estimate can be achieved during the first trimester by combining nuchal translucency measurement and biochemical markers: this first part thus clearly relates to the first trimester only. However, the authors then go on to state that the optimal way of providing screening for Down's syndrome is to provide "a single individual risk by a combination of nuchal translucency measurement and maternal serum screening". While it is not explicitly stated to which trimester the "maternal serum screening" is related, the board considers that, again, the only sensible interpretation in the context of the paragraph is that it relates to both trimesters. Since the paragraph itself clearly states that an improved estimation of risk based on the

results of nuchal translucency measurement and biochemical markers of the first trimester has already been achieved ("studies have shown"), it would not make sense to suggest to perform what was acknowledged as having already been done. Moreover this is also the interpretation which makes more sense within the context of the whole document, which is certainly not restricted to screening in the first trimester but rather to the effect of the first-trimester screening on the second-trimester screening.

5.12 Hence the board comes to the conclusion that, contrary to the respondent's arguments, there was in fact a suggestion in the prior art (and in particular in the closest prior art E1) to provide a combined, single, risk estimate based on the measurements performed in both the first and the second trimesters, with the aim of improving the detection rate without increasing the false positive rate. Thus the skilled person, motivated to provide improved methods for antenatal screening for Down's syndrome, would follow the suggestion of E1 and would arrive at the claimed subject-matter without the need for an inventive skill. It should be noted that to put into practice E1's suggestion would only require to use the available markers and marker combinations to calculate a risk estimate based on measurements of more than one marker, for which purpose mathematical models were well known (e.g. E6).

5.13 The board cannot agree with the respondent's arguments that it would not be obvious, and even counter-intuitive, to calculate a combined risk estimate from measurements of different markers from both the first and the second trimesters. According to the respondent, even more counter-intuitive and associated with even better efficacy of the method was to perform the method

in a non-sequential way, i.e to retain the results of the first trimester until they could be combined with those of the second trimester.

- 5.14 As discussed above, E1 had in fact already made the suggestion to combine results from both trimesters, and it had even stressed the possible problems of sequential testing - thus rendering it apparent that testing should be made in the "non-sequential" way. To calculate a combined estimate risk from a number of different markers had been extensively used in the prior art, and it was clear that the use of two or more - independent - markers provided a more efficient method (in terms of rate of detection versus false positive rate) than the use of one sole marker (E6, page 821, right column, lines 6 to 9; E7, page 236, right column, lines 13 to 16; E9, page 185, right column, lines 3 to 25). There would be no reason to doubt that these conclusions would be valid when using markers from different trimesters rather than from the same trimester, as long as the markers were in fact independent.

The argument that the skilled person would derive from E1 that a risk adjustment had to be made in order to accommodate the change in population which occurred between the first and second trimester is not convincing for the following reasons: first, E1 mentions an eventual need for a risk adjustment when discussing its own results, wherein no combined risk has been calculated, but does not do so when suggesting later on in the paper to provide a combined risk; second, such a risk adjustment, if present, would be a detail of the calculating method, which is not per se part of the claim: in fact, the claim - or the patent - does not provide any details on how the frequencies for

each marker are to be calculated, and it is not even excluded that a risk adjustment may take place. Finally, according to the method as claimed, at least when performed in the non-sequential way, there is a *priori* no change in the population, because all pregnant women are required to undergo testing at both trimesters, without being separately informed of the results of the first trimester. As such, the calculation of the combined risk for the two trimesters according to the invention is identical to that of the combined risk for one single trimester.

- 5.15 For the sake of completeness, it is noted that what might have been considered controversial (rather than counter-intuitive) in the method as claimed was not whether a combined risk estimate could be obtained from the two trimesters but rather whether it would be ethical not to inform the pregnant woman of a positive first-trimester result in order to be able to test again in the second trimester. This view is confirmed by the comments in the post-published literature (e.g. E58, page 565, right column, fourth paragraph). In fact, such a controversy could only be solved in the sequential embodiment of the invention, but as soon as the pregnant woman decides to go through a diagnostic procedure after a positive first-trimester testing then she is no longer being screened according to the method of the invention but instead according to the well-known methods of the prior art.
- 5.16 Claim 1 thus lacks inventive step (Article 56 EPC). Hence the sole request on file is not allowable.

**Order**

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

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:



L. Malécot-Grob

U. Oswald

Decision electronically authenticated