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Body: **Provincial Court**

Location: **Barcelona**

Section: **15**

Date: **01/27/2025**

Appeal No.: **378/2023**

Decision No.: **155/2025**

Procedure: **Appeal**

Presiding Judge: **MARTA CERVERA MARTINEZ**

Type of Decision: **Judgment**

Resolutions in the case: **SJM B 1425/2023,**  
**AAJM B 1458/2023,**  
**AAJM B 1791/2023,**  
**SAP B 582/2025**

**Section No. 15 of the Provincial Court of Barcelona. Civil Calle**

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**Appeal 378/2023 -1**

Subject: Ordinary trial

**Body of origin: Commercial Court No. 01 of Barcelona**

**Original proceedings: Ordinary proceedings (Commercial matter, art. 249.1.4) 1481/2018**

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Appellant/Applicant: GENOMIC HEALTH INC. Attorney:

Angel Quemada Cuatrecasas Lawyer: MIQUEL

MONTAÑA MORA

Respondent: NANOSTRING TECHNOLOGIES SPAIN, S.L., IZASA SCIENTIFIC, S.L.U., ONCOGENOMICS S.L., NANOSTRING TECHNOLOGIES, INC., BRUKER SPATIAL BIOLOGY, INC. (formerly NANOSTRING TECHNOLOGIES, INC.)

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**Issues: Industrial property. Patent infringement.**

**JUDGMENT No. 155/2025**

**Composition of the court:**

JOSE MARIA RIBELLES

ARELLANO LUIS RODRÍGUEZ

VEGA

MARTA CERVERA MARTINEZ

In Barcelona, on January 27, 2025.

**Appellant:** GENOMIC HEALTH, INC.

**Respondents:** NANOSTRING TECHNOLOGIES, INC. (currently BRUKER SPATIAL BIOLOGY, INC), NANOSTRING TECHNOLOGIES SPAIN, S.L., IZASA SCIENTIFIC, S.L.U. and ONCOGENOMICS S.L.

**Appealed decision:** Judgment **Date:** May

19, 2023 **Plaintiff:** GENOMIC HEALTH,

INC.

**Defendant:** NANOSTRING TECHNOLOGIES, INC. (currently BRUKER SPATIAL BIOLOGY, INC), NANOSTRING TECHNOLOGIES SPAIN, S.L., IZASA SCIENTIFIC, S.L.U. and ONCOGENOMICS S.L.

## BACKGROUND

**FIRST.** The wording of the appealed judgment is as follows:

*"The lawsuit filed by GENOMIC HEALTH, INC. against NANOSTRING TECHNOLOGIES, INC., NANOSTRING TECHNOLOGIES SPAIN, S.L., IZASA SCIENTIFIC, S.L.U., and ONCOGENOMICS is dismissed.*

*S.L., acquitting the defendants of the plaintiff's claims. The plaintiff is*

*ordered to pay the costs of the proceedings."*

**SECOND.** An appeal was lodged against the above ruling by the plaintiff's legal representative. The appeal was forwarded to the defendant, who filed a statement of opposition.

**THIRD.** Once the original documents had been received and the corresponding case file had been compiled in the Chamber, a date was set for voting and ruling, and a telematic hearing was held on January 23, 2025.

The rapporteur is Marta Cervera Martínez.

## LEGAL GROUNDS

**FIRST. Terms in which the conflict appears to be determined in this instance.**

1. The entity GENOMIC HEALTH, INC. (hereinafter, GENOMIC HEALTH) brought proceedings against NANOSTRING TECHNOLOGIES, INC., NANOSTRING TECHNOLOGIES SPAIN, S.L., IZASA SCIENTIFIC, S.L.U. and ONCOGENOMICS S.L. an infringement action against the exclusive rights granted by patent ES 2,433,992 (ES992), validation of European patent EP 2,258,872 (hereinafter, EP872), applied for on March 12, 2003, and which expired on March 12, 2023.

The lawsuit filed by GENOMIC HEALTH, INC. alleges that the PROSIGNA® test marketed in Spain by NANOSTRING and its subsidiaries, infringes patent ES'992. This patent protects a method for predicting the probability of survival of breast cancer patients without recurrence, based on the analysis of the level of expression of BAG1 gene RNA in tumor samples.

According to the lawsuit, PROSIGNA® analyzes a panel of 50 genes, including BAG1, which constitutes a direct infringement of patent ES'992. Although NANOSTRING uses a different technology (*nCounter*) and expands the number of genes analyzed, GENOMIC HEALTH maintains that the use of the BAG1 gene still infringes on the scope of protection of its patent. It asserts that any method using BAG1 analysis to predict the recurrence-free survival of breast cancer patients is protected by its patent, regardless of technical differences in the procedure.



2. The defendant, for its part, opposed the claim, requesting its dismissal and arguing that the patent was invalid due to insufficient description, addition of subject matter, and lack of inventive step. As for the non-existence of infringement, it is argued that the method implemented by the PROSIGNA® test differs substantially from that described in Claim 1 (R1) of the patent in question. In particular, the PROSIGNA® test determines the risk of recurrence by comparing the expression profile of 50 genes in the patient with four previously established subtypes of breast cancer. Although the BAG1 gene is part of the set of genes used in this process, its function is limited to contributing to the assignment of the patient to one of the cancer subtypes. However, the BAG1 gene does not have a direct correlation with the risk of recurrence, nor does it constitute a determining explanatory variable within the algorithm used by PROSIGNA®.

3. The trial court dismissed the main claim on the grounds that the PROSIGNA® test does not reproduce all the characteristics of the patent in question. It considers that the PROSIGNA® test uses an algorithm and an analysis of the expression of multiple genes, including BAG1, but that the BAG1 gene does not play the central role claimed in the patent.

**4. GENOMIC HEALTH filed an appeal against the lower court ruling, alleging error in the assessment of the evidence and in the conclusions reached by the judge. The main grounds for the appeal are as follows:**

1) **Incorrect interpretation of the scope of patent protection:** It is argued that the judgment violates Article 69 of the European Patent Convention (EPC) and its Interpretative Protocol by unduly restricting the scope of the patent. In particular, it is argued that the term "comprises" in the claims allows for the inclusion of additional features, an issue that the court did not adequately consider. The judgment relied on the Examples in the patent to limit its scope of protection, which contravenes the interpretation criteria established by the EPC and applicable case law.

2) **Inadequate assessment of expert evidence:** It is alleged that the court based its decision exclusively on the opinion of the NANOSTRING expert (Dr. Pedro Antonio), omitting a critical analysis of the evidence presented by GENOMIC HEALTH and the testimony given during the trial.

3) **Improper addition of features to the claims:** The ruling interprets that the patent requires the correlation between BAG1 gene expression and survival probability to be "direct," a feature not mentioned in the claims or in the patent description. This interpretation unjustifiably restricts the scope of protection, contradicting the literal text of the patent.

4) **Implicit acknowledgment of infringement by NANOSTRING:** It should be noted that NANOSTRING filed an opposition with the European Patent Office (EPO) against the granting of the patent with the aim of having it revoked, which demonstrates its acknowledgment of the possible infringement.

5) **New evidence of infringement:** GENOMIC HEALTH has provided additional studies published after the ruling (such as the article by *BUUS et al.*), which confirm that the PROSIGNA® test infringes the scope of protection of patent ES'992.

5. For their part, the defendants NANOSTRING, ONCOGENOMICS, and IZASA oppose the appeal, requesting its dismissal and confirmation of the first instance judgment. Firstly, they question the introduction of the article by *BUUS et al.*, published after the trial, arguing that its presentation on appeal violates the principles of preclusion and mutation of the subject matter of the proceedings (*mutatio libelli*). They maintain that the article does not prove the existence of an infringement or undermine the evidence presented during the proceedings, emphasizing that the appellant had sufficient time to incorporate this document before the trial.

As for the merits of the case, they reiterate that there has been no infringement, arguing that the PROSIGNA® test does not infringe the patent, as it is not based exclusively on the BAG1 gene for breast cancer prognosis but on a broader set of genetic factors and independent algorithms. They emphasize that the PROSIGNA® algorithm uses four genetic centroids (and not five, as in *Parker's* article) and that BAG1 is not the central focus of the analysis. The defendants argue that the appealed judgment correctly interpreted the scope of protection of the patent, limiting it to methods that use BAG1 directly and exclusively for prognosis, which is not the case with PROSIGNA®. They **also** warn that accepting the broad interpretation proposed by the appellant would constitute an abuse of patent rights, extending its monopoly to unlimited combinations of genes not covered by the original description. Finally, they insist on the invalidity of the patent due to insufficient description, addition of subject matter, and lack of inventive step, emphasizing that the patent does not provide sufficient information to reproduce the invention in all gene combinations, which invalidates its scope.

**SECOND. Background information necessary for contextualizing the dispute.**



6. The appealed decision considers the following facts to be undisputed, as they have been accepted by all parties, and relevant to the resolution of the present lawsuit:

"1.- The evidence presented results in the following account of proven facts:

**From the plaintiff:**

2.- GENOMIC HEALTH INC is the owner of European patent EP 2,258,872 (hereinafter, EP '872), validated in Spain under number ES 2,433,992 (hereinafter ES'992), which expired on March 12, 2023, and which protects a method for predicting the probability of disease-free survival in breast cancer patients based on the level of expression of the BAG1 gene in a tumor sample.

**From the defendants:**

3.- The US company NANOSTRING TECHNOLOGIES, INC. is the developer of the PROSIGNA® test, which it markets in Spain, and has offered it for sale in stores.

4.- NANOSTRING SPAIN is a Spanish subsidiary incorporated on November 17, 2017, wholly owned by the parent company NANOSTRING INTERNATIONAL INC, a US company belonging to the NANOSTRING group, whose corporate purpose is "sales, marketing, and other support services provided by the subsidiary to the parent company." The company NANOSTRING SPAIN markets the PROSIGNA® test in Spain.

5.- IZASA SCIENTIFIC SLU, a member of the Werfen Life group, distributes medical technology products in the Iberian Peninsula. It is listed as the "Global Distributor" in Spain and Portugal for NANOSTRING, the company that developed the PROSIGNA® test, and offers and markets the PROSIGNA® test in Spain. It also offers and markets the reagents necessary for PROSIGNA® gene expression analysis through the so-called "PROSIGNA® Kits," through which doctors are provided with the consumables necessary for the collection and delivery of samples for subsequent analysis using the "nCounter Dx" equipment. It supplies or has supplied the "PROSIGNA® Kits" used to perform the PROSIGNA® test to (i) the Hospital Clínico de Barcelona, (ii) the Complejo Asistencial Universitario de Salamanca, and (iii) the Instituto de Investigación Sanitaria INCLIVA. Among the products offered by IZASA on its website is the "nCounter Dx" analysis equipment, intended for use with the PROSIGNA® test, as its description indicates that it is a "Platform adapted for clinical use with the PROSIGNA® diagnostic test, owned by NanoString, for the analysis of breast cancer."

6.- ONCOGENOMICS is a Spanish company specializing in genetic testing for cancer that markets the PROSIGNA® genomic test in Spain, offers the PROSIGNA® test, and supplies "PROSIGNA® Kits" to third parties.

**From patent ES'992.**

7.- Spanish patent ES'992 is the validation of European patent EP '872, applied for by GENOMIC HEALTH on March 12, 2003, which claims priority from two US patent applications: application US 364890 P, dated March 13, 2002, and application US 412049 P, dated September 18, 2002.

8.- Patent EP '872 is divisional from European patent EP 1,918,386 (the so-called "parent" patent), which in turn is divisional from international application PCT WO2003/078662 ("WO '662," the so-called "grandparent" patent).

9.- Patent ES'992 is entitled "Obtaining gene expression profiles from biopsied tumor tissues," and its purpose is a method that, based on the level of expression of the ribonucleic acid ("RNA") transcript of the BAG1 gene, predicts the probability of long-term survival of a breast cancer patient without recurrence of breast cancer, i.e., without the original tumor reappearing after surgical removal of the primary tumor.

10.- Patent ES'992 comprises five process claims, the first of which is independent and the rest dependent, all of which relate to a method for predicting the long-term survival probability of a breast cancer patient without recurrence of breast cancer after surgical removal of the primary tumor.

11.- The claims have the following wording:

**Claim One (C1):**

"Method for predicting the long-term survival probability of a breast cancer patient without breast cancer recurrence after surgical removal of the primary tumor, comprising determining the level of BAG1 RNA transcript in a breast cancer tissue sample obtained from said patient, normalized against the expression level of all RNA transcripts tested in said sample, or a reference set of RNA transcripts, wherein an increase in the normalized level of the BAG1 RNA transcript compared to the normalized level of the BAG1 RNA transcript in a set of

*Breast cancer tissue reference indicates an increased likelihood of long-term survival without recurrence of breast cancer.*

**Claim 2 (C2):**

*"Method according to claim 1, wherein the breast cancer is invasive breast cancer."*

*It is dependent, protecting the prediction method of Claim 1, with the additional feature that "the breast cancer is invasive breast cancer."*

**Claim Three (C3):**

*"Method according to claim 1 or 2, wherein said RNA is isolated from a wax-embedded breast cancer tissue sample fixed from said patient."*

*It is dependent, protecting the method of predicting the long-term survival probability of a breast cancer patient from any of Claims 1 or 2, with the additional feature that the RNA "is isolated from a wax-embedded breast cancer tissue sample fixed from said patient."*

**Claim Four (C4):**

*"Method according to claim 1, 2, or 3, wherein the level of BAG1 RNA transcript is quantified by RT-PCR."*

*Claim 4 of patent ES'992, dependent on any of the preceding claims, protects the method of predicting the long-term survival probability of a breast cancer patient from any of Claims 1 to 3 in which "the level of the BAG1 RNA transcript is quantified by RT-PCR," i.e., by the reverse transcription polymerase chain reaction technique.*

**Claim Five (C5):**

*"Method according to claim 1, 2, or 3, wherein the level of BAG1 RNA transcript is quantified by alignment."*

*Claim 5 of patent ES'992 protects the method of predicting the long-term survival probability of a breast cancer patient from any of Claims 1 to 3, with the additional feature that "the level of the BAG1 RNA transcript is quantified by alignment."*

**From the patent application**

*12.- Patent EP'872 was granted by the EPO and subsequently confirmed by the EPO Opposition Division.*

*13.- First, the Examination Division issued several communications, both formal and substantive, including the EPO's search and patentability report, which contained objections regarding the addition of subject matter, novelty, and inventive step.*

*14.- During the examination phase, up to two third-party observations were submitted objecting to the patentability of EP '872.*

*15.- The patent holder overcame the objections raised by the EPO Examination Division and by third parties and, after providing the relevant documents and making the necessary amendments, EP '872 was granted.*

*16.- Subsequently, MINTZ LEVIN FERRIS GLOVSKY AND POPEO LLP filed an opposition, raising objections of addition of matter, lack of novelty, lack of inventive step, and insufficiency of the description.*

*17.- Following the oral hearing, by decision of July 25, 2016, the Opposition Division of the EPO, "after careful consideration of the grounds for opposition and the arguments of the parties," rejected the opposition and confirmed the validity of EP '872, without the claims granted by the Examination Division having to be amended.*

**Proceedings in third countries.**

*18.- This Court is not aware of any legal proceedings brought in relation to the patent in question, either challenging its validity or seeking a declaration of infringement by third parties.*

**The ONCOTYPE DX Genomic Test.**

*19.- The plaintiff, GENOMIC HEALTH, markets the ONCOTYPE DX Breast Recurrence Score® ("ONCOTYPE DX®") genomic test in Spain through a distributor, in which:*



- (a) A sample of the tumor surgically removed from a breast cancer patient is analyzed;
- (b) The activity level of a panel of 21 specific genes in that tumor is examined;
- and (c) Based on the expression level of these 21 genes, an algorithm is used to calculate a recurrence score, "Recurrence Score®," between 0 and 100, and predict:
- (i) The risk of recurrence of the malignant tumor after a 10-year period of disease-free survival,
- (ii) The effective benefit that chemotherapy would have on this particular patient.

20.- The panel of 21 genes used by the ONCOTYPE DX® test is composed of 16 genes related to breast cancer and 5 reference genes, all chosen from among the approximately 25,000 genes that make up the human genome.

21.- Among the group of 16 genes related to breast cancer is the BAG1 gene, whose link to breast cancer recurrence is protected by patent ES'992.

**From the PROSIGNA® Genomic Test:**

22.- The defendants offer and/or perform the PROSIGNA® genomic test in Spain, which:

- (a) Analyzes a sample of breast cancer tumor surgically removed from the patient; and estimates the probability of distant recurrence within 10 years.
- (b) It does this by measuring the expression of a panel of 50 genes, including the BAG1 gene, and using an algorithm to calculate a numerical index called "ROR" (Risk of Recurrence), which also uses a scale from 0 to 100.

7. By order dated January 10, 2024, the issue regarding the admission of the documentary evidence submitted together with the appeal brief was resolved, declaring the inadmissibility of the article "Development and validation for research assessment of Oncotype DX® Breast Recurrence Score, EndoPredict® and PROSIGNA®" by BUUS et al., published on February 12, 2021, was declared inadmissible. The court considered that this document was not subsequent to the judgment nor derived from new facts, and therefore should have been submitted during the claim phase. Consequently, the appellant's arguments based on this document should not be taken into consideration in this decision.

**THIRD. Spanish patent ES992: scope of protection.**

8. As we have stated above, the plaintiff is bringing an action for infringement of its Spanish patent ES992. Before examining the infringement it is useful to define its characteristics and scope of protection, as this is necessary for both the infringement analysis and the nullity analysis.

9. We are looking at Spanish patent ES'992 entitled "Obtaining gene expression profiles from biopsied tumor tissues," which describes a method that, based on the level of expression of the ribonucleic acid (RNA) transcript of the BAG1 gene, predicts the probability of long-term survival of a breast cancer patient without recurrence of breast cancer that is, without the original tumor reappearing after surgical removal of the primary tumor.

10. Patent ES'992 comprises five procedural claims, the first of which is independent and the rest dependent, all of which relate to a method for predicting the long-term survival probability of a breast cancer patient without recurrence of breast cancer (reappearance of the tumor) after surgical removal of the primary tumor. Claim One (C1) reads as follows:

*"Method for predicting the long-term survival probability of a breast cancer patient without breast cancer recurrence, following surgical removal of the primary tumor, comprising determining the level of BAG1 RNA transcript in a breast cancer tissue sample obtained from said patient, normalized against the expression level of all RNA transcripts tested in said sample, or a reference set of RNA transcripts, wherein an increase in the normalized level of the BAG1 RNA transcript compared to the normalized level of the BAG1 RNA transcript in a reference set of breast cancer tissues indicates an increase in the probability of long-term survival without breast cancer recurrence."*

11. The procedure is carried out in three stages:

- 1) The level of expression of BAG1 gene RNA is determined in a tumor sample.
- 2) This level is normalized by comparing it with that of other RNA transcripts tested in that sample, or a reference set of RNA transcripts.



3) An assessment is made as to whether an increase in the normalized level of BAG1, compared to the reference set, indicates a higher probability of long-term survival without recurrence.

**12.** BAG1 is an important genetic marker in the progression of breast cancer. The analysis focuses on quantifying BAG1 RNA levels in tumor tissue. Subsequently, normalization allows a reference point to be established that reflects standard or expected biological conditions. Based on a comparison between the patient's expression level and the reference set, conclusions are drawn indicating that BAG1, when expressed at high levels, could have a protective effect against cancer recurrence. The method predicts that higher BAG1 expression is associated with a greater likelihood of the patient remaining disease-free. The main purpose of the patent is the use of the BAG1 gene as a biomarker to assess prognosis in breast cancer patients. The invention is based on the correlation between BAG1 transcript expression and the probability of survival, offering a predictive method with application in clinical practice.

**13.** The central debate concerns the scope of protection of Claim 1 (C1) of the patent, specifically the interpretation of the term "comprises." Both parties, through their experts Dr. Augusto, expert for the plaintiff, and Dr. Pedro Antonio, for the defendant, agree that this term implies that the protected method may include additional steps not explicitly described, provided that they do not alter the technical object of the invention. This interpretation is based on the EPO Examination Guidelines, which state that "comprises" allows the addition of additional features, as long as they do not render the invention impracticable. **Likewise**, EPO case law, in particular Decision T 1023/02, specifies that the added steps must not contradict the technical purpose of the invention. Therefore, the term "comprises" in R1 of patent ES'992 allows for the incorporation of additional elements, provided that they do not impair the functioning of the claimed method.

**14.** The plaintiff argues that the term "comprises" broadens the scope of the protected method, allowing for the analysis of genes other than BAG1. It points out that, on page 3, line 15, the patent states that *"In a particular embodiment, the expression level of one or more prognostic RNA transcripts is determined."* The plaintiff supports its position with the decision of the Opposition Division (OD) of the EPO, dated July 25, 2016, which rejected the restrictive interpretation defended by the defendants. The OD concluded that claim 1 covers the detection of one or more genes, including BAG1, without excluding the presence of other marker genes.

**15.** The defendants, for their part, argue that this interpretation unduly broadens the scope of the patent, granting protection that exceeds the invention described and could render the method impracticable or unfeasible. Therefore, the question to be resolved is whether the technical scope of the invention covers only a prediction method based on the BAG1 gene as a single biomarker or on other combinations of genes.

#### **Assessment by the court**

**16.** Firstly, it follows from the EPO Examination Guidelines and case law (such as decision T 1023/02) that the term "comprises" must be interpreted inclusively, which means that additional elements or steps may be added, provided that they do not conflict with the technical core of the invention. Any addition that affects the central purpose of the invention could be considered an improper addition that would render the patent unworkable or invalid by unjustified extension. This differs from the term "consists of," which establishes a closed list and excludes the addition of features not explicitly mentioned.

**17.** As we have been saying, although "comprises" allows elements to be added, these must not detract from the essential purpose or functioning of the invention. This means that genes other than BAG1 could be analyzed, but the method must remain focused on the analysis of the BAG1 transcript as an essential element for predicting survival, as derived from the wording of R1, which focuses specifically on the analysis of the RNA transcript of the BAG1 gene as a predictive marker of the probability of long-term survival. Therefore, broadly including other genes could contradict the purpose of the patent, as can be inferred from the patent description itself and the examples.

**18.** Analysis of patent ES'992 shows that the methods described for predicting clinical outcomes in breast cancer patients fall into **two main approaches**.

**18.1.** The first approach is based on *prediction from individual genes*, highlighting the BAG1 gene as a relevant marker (Table 4, p. 24; Table 6, p. 26). In example 3 (pp. 23-27), it is shown that certain genes allow us to distinguish between patients with a higher or lower risk of relapse or death. This analysis was carried out using binary models and Cox models, reflected in Tables 4, 6, and 7, showing that high expression of BAG1 has prognostic value and is associated with a higher probability of survival without relapse.



It is stated on p. 24: *"Based on the data presented in Table 4, overexpression of any of the following genes in breast cancer indicates a better prognosis for recurrence-free survival after surgery: Bcl2; CEGP1; GSTM1; PR; BBC3; GATA3; DPYD; GSTM3; ID1; EstR1; p27; XIAP; IGF1R; AK055699; P13KC2A; TGFB3; **BAG1**; pS2; WISP1; HNF3A; NFKBp65."*

**18.2.** The second approach focuses on *prediction based on multiple gene signatures*, integrating up to 10 genes (pp. 27-28). In this case, BAG1 appears in only one of the 42 genetic signatures presented (set "6," line 56, p. 28), and exclusively in patients with estrogen receptor-positive (ER+) breast cancer. In his report (pp. 10-11), expert witness Dr. Pedro Antonio points out that this limitation indicates that, although BAG1 may be part of a multigene signature, its combined predictive value is restricted to specific contexts and cannot be generalized to all patient subgroups.

**19.** Therefore, considering that the patent clearly distinguishes between prediction methods based on single genes, where BAG1 is significant, and multigene genetic signatures, where its relevance is much more limited. This differentiation implies that R1 of the patent is based primarily on the analysis of BAG1 as an individual marker. Therefore, attempting to extend its application to broader genetic signature models would not be supported by the patent description, which underscores the importance of distinguishing between single-gene predictive approaches and those based on multiple genes.

**20.** The patent description reinforces that the approach is exclusively directed at the BAG1 gene as a predictor of survival, and although the possibility of analyzing other genes in other contexts is mentioned, the evaluation of other genes for the same purpose is not explicitly detailed or claimed. Nowhere in the patent description is it stated that the invention would work by combining each of the genes considered in isolation with any combination of any set of genes. Furthermore, the effectiveness of BAG1 in the multigene approach is very limited, as can be seen on p. 28, line 56, of the patent.

**21.** Analysis of the original application WO'662, from which patent ES'992 derives, reveals that the initial protection was intended to cover methods for predicting the risk of recurrence in breast cancer patients based on the expression of "one or more genes" from a closed and specific list. Claim 32 of WO'662 states that the genes used must be selected exclusively from this group, limiting the method to specific combinations and excluding genes not included in that list. R32 of WO'662 reads:

*"32. A method for predicting the long-term survival probability of a breast cancer patient without breast cancer recurrence after surgical removal of the primary tumor, comprising determining the expression level of one or more prognostic RNA transcripts or their products in a breast cancer tissue sample obtained from said patient, normalized against the expression level of all RNA transcripts or their products, wherein the prognostic transcript is the transcript of **one or more** genes selected from the group consisting of: FOXM1, PRAME, Bcl2, STK15, CEGP1, Ki-67, GSTM1, CA9, PR, BBC3, NME1, SURV, GATA3, TFRC, YB-1, 20 DPYD, GSTM3, RPS6KB1, Src, Chk1, ID1, EstR1, p27, CCNB1, XIAP, Chk2, CDC25B, IGF1R, AK055699, PI3KC2A, TGFB3, BAG1, CYP3A4, EpCAM, VEGFC, pS2, hENT1, WISP1, HNF3A, NFKBp65, BRCA2, EGFR, TK1,*

*VDR, Contig51037, pENT1, EPHX1, IF1A, DIABLO, CDH1, HIF1a, IGFBP3, CTSC, and Her2, where overexpression of one or more of FOXM1, PRAME, STK15, Ki-67, CA9, NME1, SURV, TFRC, YB-1, RPS6KB1, Src, Chk1, CCNB1, Chk2, CDC25B, CYP3A4, EpCAM, VEGFC, hENT1, BRCA2, EGFR, TK1, VDR, EPHX1, IF1A, Contig51037, CDH1, HIF1a, IGFBP3, CTSC, Her2, and pENT1 indicates a decreased likelihood of long-term recurrence-free survival from breast cancer, and overexpression of one or more of Bcl2, CEGP1, GSTM1, PR, BBC3, GATA3, DPYD, GSTM3, ID1, EstR1, p27, XIAP, IGF1R, AK055699, PI3KC2A, TGFB3, BAG1, pS2, WISP1, HNF3A, NFKBp65, and DIABLO indicates*

*an increased likelihood of long-term survival without breast cancer recurrence.*

**22.** Insofar as, in the processing of patent ES'992, the owner opted for more restrictive wording, limiting the method to the determination of a single gene, BAG1, instead of "one or more genes," this explains the intention to specifically protect methods that use individual genes, such as BAG1, differing from the original application, which contemplated multiple combinations. Therefore, the possibility of adding previous stages to the patented method—derived from the expression "comprises"—would always result in a prediction of long-term survival probability through the expression of a single gene, BAG1, and not through a combination of genes, which is ruled out.

**23.** We must note that the conclusion reached is not incompatible with the Resolution of the Opposition Division (OD) of the EPO of July 25, 2016, invoked by the plaintiff as the basis for its reasoning. In the section entitled "Reasons for the decision," paragraphs 1.9 to 1.10, the OD responds to the opponent's objection regarding the use of the term "comprises" in R1, page 4 of document No. 3, and states: *"This text provides a valid basis for a claim directed to a method comprising the detection of expression levels of one of the genes listed, in general, regardless of the presence of other marker genes. This appears to be the scope of claim 1."* The OD clarifies that R1 protects a method that analyzes BAG1.



individually, but the use of the term "comprises" allows for the inclusion of other genes in the analysis, provided that BAG1 is part of the process and central to the prediction. This is the sentiment of the resolution if read in its entirety.

24. In the novelty analysis (section 3.5), it is noted that although document D1 mentions the measurement of BAG1 mRNA levels, it does not establish an explicit relationship between these levels and breast cancer prognosis.

24.1. The Resolution states (p. 25 of document 3) *"But most importantly, the D1 method does not describe an essential feature of claim 1, namely the association between BAG1 RNA levels and prognosis. This feature reflects the purpose of the method and, as such, is a limiting feature of any method claim (see Guidelines F-IV, 4.13)."* (emphasis added)

24.2. The D0 considers that the relationship between BAG1 RNA levels and prognosis is a feature of the patented method; in fact, it is crucial to appreciating the novelty. It is noted that, although D1 describes the detection of BAG1, it does not indicate that its levels have predictive value for long-term survival. The claimed patent focuses on this specific association, the correlation between BAG1 RNA levels and prognosis, which is an essential feature that limits the scope of the claim. The Resolution refers to a "limiting feature" as one that defines the technical subject matter of the invention and restricts the scope of protection. Therefore, it is confirmed that the patent claims the direct relationship between BAG1 gene overexpression and survival prediction.

#### FOURTH. About how the PROSIGNA® test works

25. According to the PROSIGNA® test prospectus (doc. 8 of the complaint) and the explanation given by the expert witness Dr. Pedro Antonio (pp. 6 and 7 of the report), the PROSIGNA® test is based on a classification algorithm known as PAM50, which analyzes the expression profile of 50 genes to classify breast tumors into one of four intrinsic subtypes: Luminal A, Luminal B, HER2-enriched,  $\alpha$ Basal.

25.1. The analysis is performed using RNA extracted from formaldehyde-fixed, paraffin-embedded (FFPE) tumor tissue. The computational algorithm compares the normalized expression profile of the patient sample with prototypical profiles of the four subtypes, known as centroids. Each sample is assigned the subtype with the highest Pearson correlation.

25.2. In addition to the classification, the test provides a recurrence risk score (RRS) on a scale of 0 to 100. This score reflects the probability of distant recurrence at 10 years in postmenopausal women with early-stage, hormone receptor-positive breast cancer.

25.3. The ROR calculation is based on a Cox model that uses Pearson's correlation of a subset of 46 genes (out of the 50 initially analyzed), together with the proliferation index and tumor size. The variables obtained are multiplied by the model coefficients to generate the ROR value, which is adjusted to a scale of 0 to 100 using reference values obtained in clinical validation studies.

26. The BAG1 gene is part of the set of genes used both for tumor subtype classification and for determining the risk of recurrence. However, PROSIGNA® does not base its results exclusively on BAG1, but requires the combined analysis of 46 genes. This difference is fundamental with respect to patent ES992, where survival prediction is determined solely on the basis of BAG1 gene expression. Therefore, although BAG1 is included in the PROSIGNA® method, its role is one among many in a comprehensive approach that analyzes multiple genes, which significantly distinguishes it from the method protected by patent ES'992, which focuses exclusively on the evaluation of BAG1. We can therefore conclude that the PROSIGNA® genomic test would not infringe the patent in question, and we must now proceed to analyze each of the characteristics of R1 to verify whether or not they are reproduced in the defendant's test.

#### FIFTH. Regarding the analysis of the infringement.

27. The technical characteristics of R1 of patent ES'992 are as follows:

*"(a) A method for predicting the long-term survival probability of a breast cancer patient without breast cancer recurrence;*

*(b) The method is implemented after surgical removal of the primary tumor,*

*(c) It comprises:*

*(i) Determining the level of RNA transcript of the BAG1 gene in a sample of breast cancer tissue obtained from said patient,*



*(ii) Normalized against the expression level of all RNA transcripts tested in that sample, or against a reference set of RNA transcripts,*

*(iii) whereby an increase in the normalized level of the BAG1 gene RNA transcript relative to the normalized level of the BAG1 gene RNA transcript in a reference set of breast cancer tissues indicates an increased likelihood of long-term survival without breast cancer recurrence.*

28. It is undisputed that the defendant's test reproduces characteristics (a), (b), (c)(i), and (c)(ii).

28.1. (a) *A method for predicting the probability of long-term survival of a breast cancer patient without recurrence of breast cancer;* the PROSIGNA® test is a method designed to predict the probability of long-term survival in breast cancer patients without recurrence. This conclusion is based on the information contained in the test leaflet, specifically in Section 1 on Purpose/Intended Use (doc. 8 of the complaint).

28.2. (b) *The method is implemented after surgical removal of the primary tumor;* the PROSIGNA® test is performed after surgical removal of the primary tumor, as stated in Section 1 on Purpose/Intended Use (doc. 8 of the complaint).

28.3. (c) *It comprises:*

(i) *Determining the level of BAG1 gene RNA transcript in a breast cancer tissue sample obtained from the patient;* the PROSIGNA® test analyzes the level of BAG1 RNA transcript, among the 50 genes analyzed in the test, for both molecular classification and prognosis, as stated in the package insert, sections 1, 2.2, and 11.5 (document no. 8).

(ii) *Normalized against the expression level of all RNA transcripts tested in that sample, or against a reference set of RNA transcripts,* the PROSIGNA® test performs normalization using the nCounter Dx system of gene profiles to determine the prototypical expression profiles of the four intrinsic breast cancer subtypes package insert, section 2 (document no. 8).

29. The feature under discussion is (c)(iii) *In which an increase in the normalized level of the BAG1 gene RNA transcript compared to the normalized level of the BAG1 gene RNA transcript in a reference set of breast cancer tissues indicates an increase in the probability of long-term survival without breast cancer recurrence.*

29.1. The plaintiff argues that the stage of the method described in section (c)(iii) of the claim does not add technical value to the patented method, but rather is an inevitable conclusion that any expert would reach after comparing the levels of BAG1 RNA in a sample with those of the reference. Therefore, it understands that the actual technical steps are the obtaining and normalization of RNA levels (i and ii), while the conclusion about the probability of survival should not be considered an additional technical step.

30. We cannot agree with this conclusion. The EPO's D0 decision recognizes that the relationship between BAG1 RNA levels and prognosis (*feature (c)(iii)*) constitutes an essential feature of the patented method. This relationship limits the scope of the claim, defines the technical subject matter of the invention, and restricts its scope of protection. In this regard, EPO case law, as reflected in decision T 26/86 and in the Examination Guidelines (G-VII, 5.4), establishes that an invention must be assessed as a whole, taking into account both technical and non-technical features. Although the prediction of survival may appear non-technical, in the context of the invention it generates an overall technical effect, as it is based on the expression of the BAG1 gene. Consequently, section (c)(iii) of the claim represents a fundamental technical contribution to the patented method and should be considered a limiting feature that defines the invention, such that only if the PROSIGNA® test reproduces it could we find infringement of the patent.

31. Given the subject matter of the patent, as indicated, and the wording of feature (c)(iii), we must conclude, in line with the appealed judgment, that the PROSIGNA® test does not reproduce this feature and therefore does not infringe the patent.

31.1. As we have explained, the subject matter of patent ES'992 focuses on determining the expression of the BAG1 gene as the sole marker for predicting the probability of long-term survival without recurrence in breast cancer. In contrast, the PROSIGNA® test uses a multigene profile that analyzes the expression of 46 genes.

31.2. While the method claimed in the patent is based on direct comparison of the normalized level of BAG1 RNA transcript in the test sample with a reference set, where an elevated level



level of BAG1 indicates a higher probability of survival. In contrast, the PROSIGNA® test follows a more complex procedure that:

1. uses Pearson correlation coefficients to measure the similarity between the tumor being analyzed and reference tumor subtypes.
2. It applies a correction to these coefficients using a Cox model, adjusting the prediction according to the tumor subtype (Basal, HER2, Luminal A, or Luminal B).

**31.3.** Unlike the claimed method, the PROSIGNA® test does not calculate coefficients for each gene individually or use a direct discrimination analysis based on BAG1. The Cox model corrects the overall coefficients already determined, which improves the accuracy of the final result (ROR, "*Risk of Recurrence*"). This is explained by Dr. Pedro Antonio (pp. 26 and 27), correcting the analysis performed by Dr. Augusto.

**31.4.** The PROSIGNA® algorithm does not evaluate BAG1 in isolation, as Mr. Augusto appears to claim in his report (p. 37), but rather analyzes the overall expression profile of the sample and compares it to prototypical profiles of tumor subtypes. The PROSIGNA® test does not directly compare BAG1 levels with a reference set, but rather evaluates overall gene expression profiles. The final stage of PROSIGNA® involves comparing complete profiles, which differs from the patented method, which is based on a direct correlation of BAG1 with the probability of survival.

**31.5.** Not only is the individual expression of BAG1 irrelevant in the PROSIGNA® analysis, but the analysis includes a total of 46 genes, many of which, such as ACTR32, ANLN, BIRC5, and BLVRA, are not present in claim 32 of WO'662, from which patent ES'992 derives (pages 13 of Dr. Pedro Antonio's report).

**32.** We can conclude that while any method that measures BAG1 under similar conditions could be protected by patent ES'992, in the case of the PROSIGNA® test which involves a broader multigene approach, it would be outside the scope of protection since it does not exclusively evaluate BAG1 or establish a direct relationship between its expression and survival prognosis.

For all the above reasons, we must dismiss the appeal and uphold the judgment of the lower court.

#### **SIXTH. Costs of the appeal.**

**33.** The dismissal of the appeal entails the imposition of costs in the second instance, all in accordance with the provisions of Article 398 LEC in relation to Article 394.2 LEC.

#### **WE DECLARE**

To dismiss the appeal filed by the legal representative of GENOMIC HEALTH, INC. against the judgment of Commercial Court No. 1 of Barcelona dated May 19, 2023, handed down in the proceedings to which this case relates, which we confirm with the imposition of costs for the second instance and forfeiture of the deposit made to appeal.

The parties entitled to do so may lodge an appeal against this ruling before this court within twenty days of its notification, in accordance with the applicable legal and jurisprudential criteria.

The case files shall be returned to the court of origin with a certified copy of this judgment, once it becomes final, for the relevant purposes.

Thus, by this ruling of ours, which shall be certified in the Rollo, we pronounce, order, and sign.