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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte BRUCE K. PATTERSON[1]

Appeal 2016-001355
Application 13/294,101
Technology Center 1600

Before TAWEN CHANG, RACHEL H. TOWNSEND, and DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

CHANG, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to methods of determining the presence of cancerous cervical cells in a sample and of predicting whether a subject has a cervical intraepithelial neoplasia (CIN) lesion that is a CIN2+ lesion. The Examiner rejected the claims as obvious.

We have jurisdiction under 35 U.S.C. § 6(b). We reverse the Examiner's obviousness rejection. Pursuant to 37 C.F.R. § 41.50(b), however, we enter a new ground of rejection under 35 U.S.C. § 101.

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[1] Appellant identifies the Real Party in Interest as IncellDX, Inc. (Appeal Br. 3.)

STATEMENT OF THE CASE

The PAP smear "has been the cornerstone of cervical cancer screening since 1949." (Spec. 1:12–13.) In a PAP smear, "cells from the cervix . . . [are] obtained using a brush, suspended in a fixative solution, and . . . applied to a slide prior to staining." (*Id.* at 1:14–16.) Stained slides are then reviewed for evidence of abnormal cells as indicated by characteristics such as increase in nuclear to cytoplasmic ratio. (*Id.* at 1:16–2:2.)

In addition to the PAP smear, other biomarkers, such as those used for molecular detection of HPV DNA, are also used for cervical screening. (*Id.* at 2:3–5.) The Specification states:

> Clinically, the PAP smear and HPV testing are used together though they are very disparate technologies. The PAP smear has relatively low sensitivity (50%) and relatively high specificity (90%) for high grade cervical lesions (pre-cervical cancer and cervical cancer). Conversely, HPV DNA testing has high sensitivity (>90%) but low specificity (30%) for high grade cervical lesions (pre-cervical cancer and cervical cancer. These performance characteristics have supported the combined use of these tests for effective cervical cancer screening.

(*Id.* at 2:11–17.)

According to the Specification, because a PAP smear requires the use of slides, prior art cervical cancer screening using other biomarkers is generally performed on a separate aliquot of a biological sample using liquid-based cervical cytology (LBC). (*Id.* at 2:3–5.) Further according to the Specification, the invention relates to "[m]ethods of predicting whether a subject has a cervical intraepithelial neoplasia (CIN) lesion," comprising "obtaining morphometric data as well as biomarker data and/or non-specific cell data from a liquid cervical cellular sample by assaying the sample in suspension." (*Id.*at 2:25–3:5.) The Specification states:

> The term "CIN lesion" (also referred to in the art as cervical dysplasia) is used in its conventional sense to refer to the abnormal growth of squamous cells on the surface of the cervix. As is known in the art, CIN lesions may be histologically graded as CIN1, CIN2/3, CIN2 and CIN3. CIN1 lesions are those lesions that are confined to the basal 1/3 of the epithelium, and have the least risk of developing into a cancerous lesion, relative to the other categories of lesions. CIN2 lesions are characterized by moderate dysplasia confined to the basal 2/3 of the epithelium. CIN3 lesions (sometimes referred to by those of skill in the art as cervical carcinoma in situ) are categorized by the presence of severe dysplasia that traverses more than 2/3 of the epithelium. The CIN2/3 category (i.e., CIN2+) collectively refers to both CIN2 and CIN3 lesions.

(*Id.* at 6:25–7:4.)

Claims 1, 3, 4, 6–12, 16–23, 52, 71–81 are on appeal. Claims 1, 23, and 52, which are the only independent claims, are reproduced below:

> 1. A method of predicting whether a subject has a cervical intraepithelial neoplasia (CIN) lesion that is a CIN2+ lesion, the method comprising:
>
> obtaining data from a labeled liquid sample of cervical cells in suspension from the subject, wherein the data are obtained by analyzing the liquid sample with a flow cytometric device and comprise per cell morphometric data and data selected from the group consisting of: per cell biomarker data, per cell DNA content data, and combinations thereof; and
>
> predicting from the per cell morphometric data and from the data selected from the group consisting of: per cell biomarker data, per cell DNA content data, and combinations thereof; whether the subject has a CIN2+ lesion.
>
> 23. A method of predicting whether a subject has a cervical intraepithelial neoplasia (CIN) lesion that is a CIN2+ lesion, the method comprising:
>
> (a) providing a biomarker labeled liquid sample of cervical cells in suspension by a method comprising:

(i) combining an initial cervical cell sample with fixation and permeabilization reagents to fix and permeabilize the cells; and

(ii) contacting the fixed and permeabilized cells with a fluorescently labeled biomarker probe that specifically binds to a cervical cancer biomarker;

(b) obtaining per cell morphometric data and per cell biomarker quantitation data from the liquid sample by flowing the liquid sample past an illumination source and one or more optical detectors in a flow cytometer; and

(c) predicting from both the morphometric data and per cell biomarker quantitation data whether the subject has a CIN2+ lesion.

52. A method of determining the presence of a cancerous cervical cell in sample from a subject, the method comprising:

obtaining data from a labeled liquid sample of cervical cells in suspension from the subject, wherein the data are obtained by analyzing the liquid sample with a flow cytometric device and comprise per cell morphometric data and data selected from the group consisting of: per cell biomarker data, per cell DNA content data, and combinations thereof; and

determining that a cancerous cell is present in the sample when:

(i) a cell of the liquid sample is determined to be abnormal based on the per cell morphometric data; and

(ii) the cell of the liquid sample is determined to be abnormal based on the data selected from the group consisting of: per cell biomarker data, per cell DNA content data, and combinations thereof.

(Appeal Br. 64, 66 (Claims App.).)

The Examiner rejects claims 1, 3, 4, 6–12, 16–23, 52, and 71–81 under 35 U.S.C. § 103 as being unpatentable over Ling[2] and Basiji.[3] (Final Act. 3.)

DISCUSSION

Obviousness Issue

With respect to claims 1 and 52, the Examiner finds that Ling teaches "a method for detecting cervical cancer cells in a liquid sample using biomarker-based flow cytometry wherein cells of interest in the liquid samples are labeled with fluorescent antibodies." (Final Act. 4.) The Examiner finds that Ling teaches "cellular morphological changes in the precursor lesions of cervical carcinoma and that prediction of CIN of a subject can be performed by observation of abnormal cervical cells." (*Id.*) The Examiner finds that Ling also teaches "microscopic imaging of cells on slides" but further teaches that "current slide-based morphological analysis are labor intensive and subjective" and "conventional fluorescence-measuring flow cytometry cannot integrate cell morphometric information in the biomarker detection results which is desired in the clinical diagnosis of cervical cancer." (*Id.*) The Examiner finds that, even though Ling "does not explicitly teach a CIN grade designated as 'CIN2+,'" it "inherently teaches

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[2] Jian Ling et al., *Application of Flow Cytometry for Biomarker-Based Cervical Cancer Cells Detection*, 36 DIAGNOSTIC CYTOPATHOLOGY 76–84 (2008) ("Ling").

[3] David A. Basiji et al., *Cellular Image Analysis and Imaging by Flow Cytometry*, 27 CLINICS IN LAB. MED. 653 (2007) ("Basiji"). The Examiner's citation to Basiji in the Final Office Action appears to refer to the author manuscript, numbered pages 1–16, made available in PubMed® Central (PMC) on September 1, 2008. For purposes of consistency all citations to Basiji in this decision also refers to the author's manuscript.

determination of CIN2+ categories" because the Specification teaches that CIN2+ refers to CIN2 and CIN3 lesions collectively while Ling teaches that "the CIN1, CIN2[,] and CIN3 grades may be determined based on morphology of single cells." (*Id.* at 4–5.)

The Examiner finds that Ling does not teach "collecting both morphometric data and biomarker data from a single labeled liquid sample of cervical cells." (*Id.* at 4.) However, the Examiner finds that Basiji teaches "a commercially available imaging flow cytometer, the ImageStream system, which offers significant potential to enhance diagnostic capabilities by combining [the] antibody based evaluation of expressed tumor-associated markers with morphological analysis in a single technology platform." (*Id.* at 5.) The Examiner finds that Basiji teaches that its system "can precisely track moving cells with a high resolution multispectral imaging system to acquire multiple images of each cell" and also discloses "several working examples in which the ImageStream system was used successfully in analyzing cell populations including normal and abnormal cells by both imaging and biomarker or DNA content analysis." (*Id.*)

The Examiner concludes that

> [i]t would have been prima facie obvious for one of ordinary skill in the art at the time of invention to use the ImageStream system of Basiji in the analysis of a labeled liquid cervical cells sample of Ling to obtain both morphometric data and biomarker expression on the same platform. One would be motivated to do so to automate the cell image analysis. The expectation of success is high because Basiji has provided successful examples using the ImageStream system in the analysis of mammary gland originated epithelial cells suggesting that this system can be used with other epithelial carcinoma cell tests including cervical carcinoma cells.

(*Id.*)

With respect to claim 23, the Examiner finds that "Basiji teaches that cells can be fixed by paraformaldehy[d]e before labeling" and that "[p]ermeabilization of cells is inherently included in immunological staining method for detection of an intracellular protein since the cell membrane must be permeabilized to allow the antibody to enter cells." (*Id.* at 7.)

Appellant contends that "***[t]he Examiner has not demonstrated that Ling and Basiji teach or suggest all of the limitations of the claims***." (Appeal Br. 12–22.) In particular, Appellant contends that the cited combination does not suggest "predicting from *both* per cell morphometric data and data selected from the stated group (i.e., per cell biomarker data, per cell DNA content data, and combinations thereof) whether a subject has a CIN2+ lesion," as evidenced by the fact "*neither Ling nor Basiji teach obtaining morphometric data used for determining CIN grade on a flow cytometer*." (*Id.* at 13–17.)

Appellant further argues that "***Ling teaches away from using cervical cell morphology in cancer assessments***," and Basiji "cannot be considered to . . . provide motivation 'to explore a new cervical lesion screening method' that would incorporate morphology-based characteristics" because Basiji teaches "an inability to discriminate cancerous cells from normal cells based on . . . nuclear-to-cytoplasm ratio." (*Id.* at 22–26.) Finally, for similar reasons, Appellant contends that a skilled artisan would not have had a reasonable expectation of success in modifying the methods of the cited art in the manner proposed by the Examiner. (Appeal Br. 27–31.)

The issue with respect to this rejection is whether a preponderance of evidence of record supports the Examiner's conclusion that the combination of Ling and Basiji renders obvious the claims on appeal.

Findings of Fact

1. Ling teaches that

> [t]he Pap test used for cervical cancer screening is subjective, labor-intensive, and has relatively low sensitivity and specificity for the detection of underlying clinically significant lesions. The objective . . . is to develop a biomarker/flow cytometry-based approach for cervical cancer screening. Immunofluorescence technology to quantify cervical cell expression of two biomarkers $p16^{INK4A}$ and Mcm5 was developed and evaluated by both microcopy and flow cytometry. . . . The results indicate that flow cytometry could detect 0.01% dysplastic cells in a background of normal cervical epithelial cells with the combination of the two biomarkers. . . . The experiment yielded 100% sensitivity and 93% specificity with reference to the liquid-based cervical cytology. This study indicates the promise of using multi-color fluorescence flow cytometry for biomarker-based cervical cancer screening. This molecular-based, potentially high-throughput and automated method is expected to provide an alternative/auxiliary means of cervical cancer screening.

(Ling Abstract (emphasis omitted).)

2. Ling's Figure 1 is reproduced below:

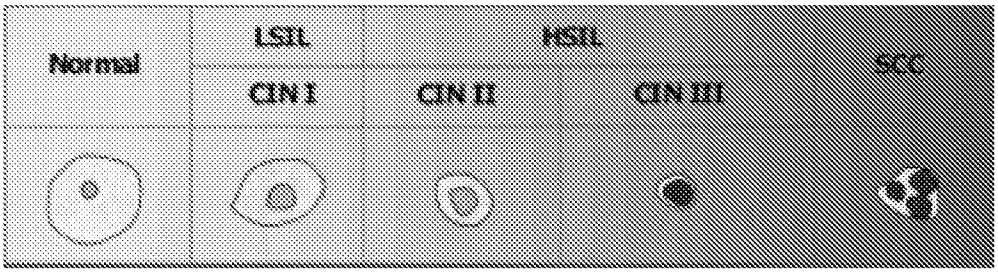

Fig. 1. Morphological changes (the increase of nucleus-to-cytoplasm ratio) of precursor lesions of cervical carcinoma.

As set forth in its caption, Figure 1 of Ling "illustrates the morphological changes that are characteristic of the development of [the] precursor

lesions." (*Id.* at 77, left column.) Ling teaches that "[a] general feature of the high-grade dysplastic cells is that they typically have high nuclear-to-cytoplasmic volume ratios and this ratio increases as the severity of the lesion increases." (*Id.*) Ling further teaches that

> [c]ytologic abnormalities that may reflect underlying cervical dysplasia or squamous cell carcinoma are categorized under the Bethesda 2001 system as atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells suspicious but not diagnostic for a high grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), and squamous cell carcinoma (SCC).

(*Id.* at 76–77.)

3. Ling teaches that

> [a] large number of biomarkers have been identified that are overexpressed in cervical cancer cells. Some of the markers that appear to have potential for cervical cancer screening include $p16^{INK4A}$ (a cyclin-dependent kinase inhibitor protein), Mcm (minichromosome maintenance) proteins, Cdc (cell division cycle) proteins, topoisomerase 2 alpha, PCNA, Ki-67, Cyclin E, p-53, and Rb (retinoblastoma) proteins. . . . In cervical carcinomas, viral DNA integration into the host genome may result in disruption of the E2 open reading frame, resulting in unregulated overexpression of HPV oncogenes E6 and E7, E7-mediated catabolism of pRb, and the reciprocal overexpression of $p16^{INK4A}$. . . . Several studies have demonstrated the successful combination of $p16^{INK4A}$ immunocytochemical assay with the liquid-based Pap test.

(*Id.* at 77, right column (endnotes omitted).)

4. Ling teaches that a study "reported that $p16^{INK4A}$ identified dysplastic squamous and glandular cells of the cervix with a sensitivity of 99.9% and a specificity of 100%." (*Id.* at 78, left column.)

5. Ling teaches that "[f]low cytometry is . . . [the] ideal format for the analysis of single-cell suspensions, quantifying cell structural and molecular features, and for the detection of rare events." (*Id.*)

6. Ling teaches fixing and preserving cervical cancer-derived HeLa cell line, which overexpresses both $p16^{INK4A}$ and Mcm5 and is used as positive control, with methanol-based fixative PreservCyt®. Ling teaches that PreservCyt® "will preserve both cell morphology and cellular molecular markers for at least 30 days" and is also "known to permeabilize cells so that fluorochromes-labeled antibodies can penetrate cells." (*Id.* at 78, bridging paragraph.) Ling likewise teaches obtaining "[r]esidual cervical cytology specimens from PreservCyt® vials" for its study. (*Id.* at 78, right column.)

7. Ling teaches staining a sample with monoclonal antibodies to $p16^{INK4A}$ and Mcm5 conjugated with PE and APC fluorochromes. (*Id.*)

8. Ling suggests that "biomarker overexpressed cells are rare-events, which is similar to the morphology-based detection" and also suggests that "the overexpression of both the $p16^{INK4A}$ and Mcm5 biomarkers is closely related to the abnormality of cell morphology." (*Id.* at 80–81, bridging paragraph.)

9. Ling teaches that "it is possible to use flow cytometry to detect as low as 0.01% cancer cells among a large number of normal cervical cells," which "exceeded the expectation of detecting less than 0.1% abnormal cells among normal cells, which is considered by pathologists as being an acceptable limit for a cervical cancer screening method." (*Id.* at 81, left column.)

10. Ling teaches that, in a flow cytometry experiment, "the HSIL specimen has significantly more cells with high intensities in both PE and

APC bands than the negative specimen," where "[t]he high intensity in the PE and APC bands indicates that both biomarkers $p16^{INK4A}$ and Mcm5 are overexpressed." (*Id.* at 81, bridging paragraph.)

11. Ling teaches that its study

> demonstrated the feasibility of (1) using multiplex detection of $p16^{INK4A}$ and Mcm5 to detect dysplastic cervical cells by immunofluorescence, (2) using multiparameter flow cytometry to detect rare-event dysplastic cells from large background of normal cells, and (3) using multiparameter flow cytometry to identify positive cervical specimens. . . . The method developed for cervical cancer screening in this study can be extended to the diagnosis of other nonhematological cancer.

(*Id.* at 83, left column.)

12. Basiji teaches "[i]maging flow cytometry" that "combines the statistical power and fluorescence sensitivity of standard flow cytometry with the spatial resolution and quantitative morphology of digital microscopy." (Basiji Abstract; *see also id.* at 8.)

13. Basiji teaches that "cellular morphology analysis is an effective means of cancer screening" and that "[d]ysplastic morphology is . . . the primary diagnostic criterion in Pap smears, where microscope-based automated morphological analysis has been shown to be effective and approved by the FDA for primary screening." (*Id.* at 4.)

14. Basiji teaches that "[t]he ImageStream system offers significant potential to enhance diagnostic capabilities by combining antibody based evaluation of expressed tumor-associated markers with morphological analysis in a single technology platform." (*Id.* at 5; *see also id.* at 8.)

15. Basiji teaches an example of using its ImageStream system to discriminate "cancerous from normal mammary epithelial cells." (*Id.* at Abstract.) In particular, Basiji teaches harvesting and washing normal and

neoplastic mammary epithelial cells, staining the normal mammary epithelial cells with fluorescein-conjugated monoclonal antibody to Class I HLA for identification, separately fixing the normal and pooled carcinoma cells in 1% paraformaldehyde prior to mixing the cells, and adding DRAQ5, a DNA binding dye that allows analysis of DNA content and nuclear morphology features. (*Id.* at 5.)

16. Basiji teaches that "[n]ormal cells were noted to have higher scatter intensity and heterogeneity, were generally larger, and had lower nuclear intensity." (*Id.*)

17. Basiji teaches an example where normal and carcinoma cells were able to be discriminated based on scatter intensity scatter texture, morphology, nuclear intensity, and nuclear texture. (*Id.* at 6.) However, Basiji notes that "the nuclear/cellular area ratio was not discriminatory." (*Id.*) Cellular area is the sum of the nuclear area and cytoplasmic area. (*Id.*)

18. Basiji concludes that

> [t]he multispectral/multimodal imagery collected by the ImageStream and analyzed using the IDEAS software package in this engineered experiment revealed a number of significant differences in darkfield characteristics, cellular morphology, DNA content, and nuclear morphology between normal epithelial and epithelial carcinoma cells. While it is well-recognized that cells adapted to tissue culture have undergone a selection process that may have altered their cellular characteristics, these data demonstrate that it is feasible to build an automated classifier that uses the morphometric and photometric features identified and described above to separate normal from transformed epithelial cells and possibly other cell types. The use of tumor-associated antibody based markers could possibly synergize with the morphological analysis to provide a greater depth of understanding of dysplastic changes

> and neoplastic transformations as well as a more accurate staging of these pathologies.

(*Id.*)

Analysis

On balance, we find Appellant has the better argument.

Independent claims 1, 23, and 52 recite methods of predicting whether a subject has a CIN2+ lesion or determining the presence of a cancerous cervical cell in a sample based in part on cell morphometric data obtained through flow cytometry. The Examiner relies on Ling for teaching that cell morphological data, in particular an increase in the nucleus-to-cytoplasm ratio, may be used to distinguish between different categories of CIN lesions. (Final Act. 4; FF2.) However, Basiji, which the Examiner relies on for teaching use of flow cytometry to obtain cell morphometric data, indicates that although the cytoplasmic area was significantly lower in the carcinoma cells, the flow cytometry system was not able to discriminate between normal and carcinoma cells based on the nuclear/cellular area ratio.[4] (FF17.) Thus, while Ling indicates that an increase in the nucleus-to-cytoplasm ratio can be used to distinguish CIN lesions, Basiji indicates that flow cytometry cannot accomplish such a distinction. Accordingly the Examiner has not established that the prior art methods would have provided the claimed means to distinguish cancerous cervical cells from normal cells.

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[4] Cytoplasmic area is the difference of cellular and nuclear area. (FF17.) We note that Basiji states that its system was not able to discriminate between normal and carcinoma cells based on nuclear/***cellular area*** ratio (*id.*), whereas Ling teaches increasing nuclear/***cytoplasm*** with increasing severity of a lesion. However, the Examiner does not argue that there is a meaningful difference between these two ratios.

Therefore, we agree that the Examiner has not established a prima facie case that a skilled artisan would have a reasonable expectation of success in predicting or determining the presence of a particular type of CIN lesion or a cancerous cervical cell using morphometric data obtained through flow cytometry.

The Examiner finds that Basiji generally teaches that its system can obtain measurement of cell morphology information and discriminate between normal and carcinoma cells by morphometric data such as size of cytoplasm and nucleus, even if the system cannot discriminate between normal and carcinoma cells of mammary origin by the particular morphometric characteristic of nucleus-to-cytoplasm ratio. (Ans. 26.) We are not persuaded: The Examiner has not cited evidence that these other types of morphometric data are known to predict the presence of a particular type of CIN lesion or a cancerous cervical cell.

The Examiner further argues that

> [the] reasons for the inability [of Basiji's system] to discriminate the normal and carcinoma cells of mammary origin by the nucleus-to-cytoplasm ratio are that (1) the nuclear area of the carcinoma cell lines was smaller than the normal cells, but to a degree proportional to the difference in cellular area, and (2) it is well recognized that cells adapted to tissue culture have undergone a selection process that may have altered their cellular characteristics.

(Ans. 27.) The Examiner contends that,

> [t]herefore, one of ordinary skill in the art would not have been lead away from . . . [using Basiji's system to predict presence of a particular type of CIN lesion or cancerous cervical cancer] since . . . the inability to discriminate the normal and carcinoma cells by the nucleus-to-cytoplasm ratio disclosed in the experiment of Basiji is intrinsic to the cells used (i.e. the proportional difference in areas of nucleus and the cytoplasm as

> well as tissue culture adaptation). On the other hand, the cells in the patient's cervical sample are not tissue culture adapted and have been clearly shown not to have proportional difference in areas of nucleus and the cytoplasm among normal cells and cells of different cancer development stages. See e.g. Figure 1 of Ling.

(*Id.*)

We are again unpersuaded. The Examiner has not cited evidence supporting the assertion that "the inability to discriminate the normal and carcinoma cells by the nucleus-to-cytoplasm ratio . . . is intrinsic to the [mammary epithelial] cells used." (*Id.*) In particular, while the Examiner contends that Figure 1 of Ling clearly shows that cells in a patient's cervical sample do not have "proportional difference in areas of nucleus and the cytoplasm among normal cells and cells of different cancer development stages"—i.e., normal and pre-cancer/cancer cells have different nuclear/cytoplasm ratios—this also appeared to be true for mammary epithelial cells in vivo. (Appeal Br. 30 (citing B. Arora et al., *Diagnostic Application of Mean Nuclear Area (MNA) Measured by Computerized Interactive Morphometry in Breast Cancer*, 5 INTERNET J. OF PATHOLOGY 1–8 (2006)); Ans. 30 (withdrawing statement that "nucleus-to-cytoplasm ratios are not known to be used in the field to distinguish normal and carcinoma mammary cells").) Likewise, while Basiji does teach that "it is well-recognized that cells adapted to tissue culture have undergone a selection process that may have altered their cellular characteristics" (FF18), the Examiner has not cited to evidence in Basiji or elsewhere that Basiji's inability to discriminate between normal and carcinoma cells using nuclear/cellular area ratio results from such selection and/or alteration.

Accordingly, we reverse the Examiner's rejection of independent claims 1, 23, and 52 as obvious over Ling and Basiji. We also reverse the Examiner's rejection of claims 3, 4, 6–12, 16–22, and 71–81, which depend directly or indirectly from claims 1 or 52. *Hartness Int'l, Inc. v. Simplimatic Eng'g Co.*, 819 F.2d 1100, 1108 (Fed. Cir. 1987) (holding dependent claim to be *a fortiori* non-obvious where independent claim was non-obvious).

NEW GROUND OF REJECTION

Under the provisions of 37 C.F.R. § 41.50(b), we enter the following new ground of rejection: Claims 1, 23, and 52 are rejected under 35 U.S.C. § 101 as being directed to non-eligible subject matter.

Findings of Fact

19. The Specification explains that, "[f]ollowing the advent of liquid-based cervical cytology (LBC), cells from the cervix were obtained using a brush, suspended in a fixative solution, and then applied to a slide prior to staining." (Spec. 1:14–16.)

Principles of Law

> In *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. [66], 132 S.Ct. 1289 . . . (2012), the Supreme Court set forth a framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts. First, we determine whether the claims at issue are directed to a patent-ineligible concept. *Id.* at 1297. If the answer is yes, then we next consider the elements of each claim both individually and "as an ordered combination" to determine whether additional elements "transform the nature of the claim" into a patent-eligible application. *Id.* at 1298. The Supreme Court has described the second step of this analysis as

> a search for an "inventive concept"—i.e., an element or combination of elements that is "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself." *Id.* at 1294.

Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1375 (Fed. Cir. 2015) (second bracket in original).

Analysis

Claim 1

We follow the analytical framework set forth by the Supreme Court in *Mayo* and applied by our reviewing court in *Ariosa*. We begin our analysis at *Mayo* step one: "whether the claims at issue are directed to a patent-ineligible concept." *Ariosa*, 788 F.3d at 1375. We find that the claims are directed to a patent-ineligible law of nature.

In *Mayo*, the claimed invention was a "method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder" comprising administering a certain class of drug and then determining the level of 6-thioguanine (6-TG) in a patient, where a level of 6-TG below or above certain amounts indicated a need to increase or decrease, respectively, the drug dosage. *Mayo*, 566 U.S. at 74–75.

Claim 1 of the instant application is similar, in that it is directed to a method of predicting whether a subject has a CIN2+ lesion by determining the morphometric and biomarker data from a subject's sample of cervical cells. The *Mayo* Court concluded that the claims at issue in that case "set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm." *Id.* at 77. Similarly, claim 1 on appeal sets forth a law of nature—namely, the relationship

between cell morphometric and biomarker data of a subject's cervical cell sample and the likelihood that a subject has a CIN2+ lesion.

In light of our determination that the claims at issue are directed to a natural law, we move to the second step of the *Mayo* analysis: whether additional elements "transform the nature of the claim" into a patent-eligible application. *Ariosa*, 788 F.3d at 1375 (internal quotations and citation omitted).

The claims in *Mayo* included an "administering" step, a "determining" step, and a "wherein" clause. *Mayo*, 566 U.S. 74–75. The Court concluded that "[t]he upshot is that the three steps simply tell doctors to gather data from which they may draw an inference in light of the correlations." *Id.* at 79. In other words,

> the claims inform a relevant audience about certain laws of nature; any additional steps consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately.

Id. at 79–80. The Court concluded that "the steps are not sufficient to transform unpatentable natural correlations into patentable applications of those regularities." *Id.* at 80.

Like the claims in *Mayo*, the manipulative steps of claim 1 on appeal "consist of well-understood, routine, conventional activity," as shown by Ling and Basiji. *Id.* at 79–80. Obtaining biomarker data and morphometric data from a labeled liquid sample of cells in suspension from the subject is routine and conventional. (FF19 (describing suspending cervical cells in fixative solution); FF6 & FF7 (cervical cytology specimens in PreservCyt® vials and staining sample with antibodies conjugated to fluorochromes).)

Likewise, analyzing the sample with flow cytometry to obtain cell morphometric data and biomarker and/or DNA content data is an activity already engaged in by the scientific community. (FF12–FF18.) Finally, the last clause of claim 1 simply requires assessing the cell morphometric data and cell biomarker and/or DNA content data to predict whether a subject has a CIN2+ lesion. That is, the clause simply states the natural law (i.e., the relationship between cell morphology, DNA content, and presence of biomarkers known to indicate cancer on the one hand and likelihood of CIN2+ lesion on the other), with the instruction to "apply it."

Neither does considering the above steps as an ordered combination add anything new to the law of nature that is not already present when the steps are considered separately. In this respect, we note that our conclusion that the Examiner has not shown claim 1 to be obvious over Ling and Basiji does not change our conclusion that claim 1 is directed to an abstract idea without sufficiently more to transform the claim into a patent-eligible application. As discussed above with respect to the obviousness rejection, the Examiner has not shown that a skilled artisan would have had a reasonable expectation that morphometric data obtained via flow cytometry would be able to predict whether a subject has a CIN2+ lesion. A finding of non-obviousness, however, does not necessarily lead to the conclusion that subject matter is patentable eligible. "Groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry." *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2117 (2013). Here, Basiji shows that obtaining cell morphometric data via flow cytometry (and using such data to identify mammary carcinoma cells, even though not being able to use the morphometric data of nuclear/cellular area ratio) is

something routinely engaged in by the scientific community. (FF12–FF18.) The fact that such data can also be used to predict the presence of a CIN2+ lesion, despite lack of a reasonable expectation of success in using the morphometric data of nuclear/cellular area ratio to do so, does not transform the claim into a patent-eligible application of the natural correlation between cell morphometric data generally (as the claim requires) and cell biomarker or cell DNA content data and presence of a particular type of cervical lesion.[5]

In summary, as with *Mayo*, the manipulative steps in claim 1 "simply tell . . . [the relevant audience] to gather data from which they draw an inference in light of the correlations." *Mayo*, 566 U.S. at 79. Put another way, claim 1 "inform[s] a relevant audience about certain laws of nature; any additional steps consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately." *Id.* at 79–80. Accordingly, we find that claim 1 is directed to patent-ineligible subject matter.

Claim 23

Claim 23 is similar to claim 1, except that claim 23 further requires providing a biomarker-labeled liquid sample of cervical cells in suspension by "(i) combining an initial cervical cell sample with fixation and permeabilization reagents to fix and permeabilize the cells; and

[5] Claim 1 does not recite a new method of performing flow cytometry; nor has Appellant argued that the flow cytometer of the claim is structurally distinguishable from Basiji's imaging flow cytometer.

(ii) contacting the fixed and permeabilized cells with a fluorescently labeled biomarker probe that specifically binds to a cervical cancer biomarker." (Appeal Br. 66 (Claims App.).)

We find claim 23 to be directed to a patent-ineligible natural law for the same reasons discussed above with respect to claim 1. We further find that these additional limitations of claim 23 do not transform the claim into a patent-eligible application of the natural law. In particular, as described in Ling and Basiji, fixing and permeabilizing the cells through reagents and labeling cells by contacting cells with a fluorescently labeled biomarker probe are routine and conventional methods used in the art. (FF6 (fixing and permeabilizing cells with methanol-based fixative PreservCyt®); FF7 (staining sample with $p16^{INK4A}$ and Mcm5 antibodies conjugated with fluorochromes); FF15 (fixing cells in paraformaldehyde).) Neither do these additional limitations add anything, when considered as an ordered combination with the rest of claim 23, that is not already present when the steps of the claim are considered separately.

Accordingly, we find that claim 23 is directed to patent-ineligible subject matter.

Claim 52

Claim 52 is similar to claim 1, except that claim 52 relates to determining the presence of a cancerous cervical cell in a sample rather than predicting whether a subject has CIN2+ lesions, and further recites the step of

> determining that a cancerous cell is present in the sample when: (i) a cell of the liquid sample is determined to be abnormal based on the per cell morphometric data; and (ii) the cell of the liquid sample is determined to be abnormal based on the data selected from the group

consisting of: per cell biomarker data, per cell DNA content data, and combinations thereof.

(Appeal Br. 66 (Claims App.).)

For the same reasons discussed above with respect to claim 1, we find that claim 52 is directed to a patent-ineligible natural law, namely, the relationship between cell morphometric and biomarker data of a cervical cell sample and the presence of a cancerous cell. Likewise, claim 52's "determining" clause simply tells the relevant audience about the natural law. *Mayo*, 566 U.S. at 78 (explaining that clauses such as "wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject" "simply tell a doctor about the relevant natural laws, at most adding a suggestion that he should take those laws into account when treating his patient").

Accordingly, we find that claim 52 is directed to patent-ineligible subject matter.

SUMMARY

For the reasons above, we reverse the Examiner's decision rejecting claims 1, 3, 4, 6–12, 16–23, 52, and 71–81 as obvious over Ling and Basiji.

In a new ground of rejection, we reject claims 1, 23, and 52 under 35 U.S.C. § 101 as directed to patent-ineligible subject matter. We have not entered new rejections of the dependent claims, but in the event of further prosecution (see below), the Examiner should consider whether any of the dependent claims should also be rejected under 35 U.S.C. § 101 as directed to patent-ineligible subject matter.

TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b). Section 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review." Section 41.50(b) also provides:

> When the Board enters such a non-final decision, the appellant, within two months from the date of the decision, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:
>
> (1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new Evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the prosecution will be remanded to the examiner. The new ground of rejection is binding upon the examiner unless an amendment or new Evidence not previously of Record is made which, in the opinion of the examiner, overcomes the new ground of rejection designated in the decision. Should the examiner reject the claims, appellant may again appeal to the Board pursuant to this subpart.
>
> (2) *Request rehearing*. Request that the proceeding be reheard under §41.52 by the Board upon the same Record. The request for rehearing must address any new ground of rejection and state with particularity the points believed to have been misapprehended or overlooked in entering the new ground of rejection and also state all other grounds upon which rehearing is sought.

Further guidance on responding to a new ground of rejection can be found in the MANUAL OF PATENT EXAMINING PROCEDURE § 1214.01.

REVERSED; 37 C.F.R. § 41.50(b)