



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/252,078	10/03/2011	Colin Craig McCulloch	250530-4/120718-00504	6421
6147	7590	11/02/2018	EXAMINER	
GENERAL ELECTRIC COMPANY			HARWARD, SOREN T	
GPO/GLOBAL RESEARCH			ART UNIT	
901 Main Avenue			PAPER NUMBER	
3rd Floor			1631	
Norwalk, CT 06851			NOTIFICATION DATE	
			DELIVERY MODE	
			11/02/2018	
			ELECTRONIC	

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

haeckl@ge.com
gpo.mail@ge.com
Lori.e.rooney@ge.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte COLIN CRAIG McCULLOCH

Appeal 2017-002258
Application 13/252,078¹
Technology Center 1600

Before DONALD E. ADAMS, MICHAEL J. FITZPATRICK, and
RACHEL H. TOWNSEND, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of analyzing tissue features, which have been rejected as being directed to patent ineligible subject matter and as obvious.² We have jurisdiction under 35 U.S.C. § 6(b).

¹ Appellant identifies the real party in interest as the General Electric Company. (Appeal Br. 2.)

² We note that the subject matter of this application is similar to that of Application 13/252,069, which is the subject of Appeal No. 2017-008682 and of Application 13/252,072, which was the subject of Appeal No. 2016-001180. In Appeal No. 2016-001180, the Board affirmed the Examiner's rejection of the claims as being both directed to patent ineligible subject matter and as obvious. In a decision issued simultaneously herewith, we affirm the rejection of the claims on appeal in Appeal No. 2017-008682, as being directed to patent ineligible subject matter.

We affirm.

STATEMENT OF THE CASE

Studying tissue specimens using labelled antibodies or antibody surrogates as biomarkers is well known, including testing “for the expression of numerous biomarkers.” (Spec. ¶¶ 3, 5.) “The techniques of tissue treatment and examination have been refined so that the level of expression of a given biomarker in a particular cell or even a compartment of the given cell such as the nucleus, cytoplasm or membrane can be quantitatively determined.” (*Id.* ¶ 4.) “Commonly the treated tissue is examined with digital imaging and the level of different signals emanating from different biomarkers can consequently be readily quantified.” (*Id.*) Appellant’s Specification explains that

[t]he invention relates generally to analyzing and visualizing the expression of biomarkers in individual cells, wherein the cells are examined in situ in their tissue of origin, to identify and understand patterns of expression that have an association with a diagnosis, a prognosis, or a response to treatment of a condition or a disease.

(Spec. ¶ 2.)

Claims 1–13, 15, 18–33, 35, 38–44, and 47 are on appeal. Claim 1 is representative and reads as follows:

1. A method of analyzing tissue features based on multiplexed biometric image data comprising:
 - storing a data set using a storage device, the data set comprising cell profile data comprising multiplexed biometric images capturing the expression of a plurality of biomarkers with respect to a plurality of fields of view, wherein said plurality of biomarkers comprises a plurality of morphological biomarkers and a plurality of non-morphological biomarkers, and in which individual cells are delineated and segmented into compartments, wherein

the cell profile data is generated from a plurality of tissue samples drawn from a cohort of patients having a commonality; and

the data set further comprising an association of the cell profile data with at least one piece of meta-information including a field of view level assessment or a patient-level assessment related to the commonality;

calculating using a processor at least one cell feature based on the cell's expression of each of the plurality of biomarkers, wherein the at least one cell feature comprises a ratio based on a respective concentration level of each biomarker between cell compartments for a respective cell;

calculating using the processor a first and second moment for each of the plurality of fields of view from each of the at least one cell feature wherein the first moment is mean and wherein the second moment is standard deviation;

grouping using the processor the field of view level assessments and examining the plurality of combinations of attributes for an association with the grouped field of view level assessment related to the commonality;

examining using the processor a plurality of combinations of attributes comprising the calculated first and second moments for an association with the at least one piece of meta-information including the field of view level assessment or the patient-level assessment related to the commonality;

ordering the plurality of attributes according to a variable importance of the plurality of attributes;

selecting using the processor one of the plurality of combinations of attributes comprising a predictive combination of attributes based on a comparison of the performance of at least one model of the plurality of combinations of attributes and the variable importance of the plurality of attributes, wherein the predictive combination eliminates a portion of the plurality of attributes based on the variable importance and the at least one piece of meta-information including a field of view level assessment or a patient-level assessment related to the

cohort of patients based on a performance metric of a pre-defined threshold; and

providing an indication of^{f³¹} related to the tissue samples.

(Appeal Br. 16–17.)

The following grounds of rejection by the Examiner are before us on review:

Claims 1–13, 15, 18–33, 35, 38–44, and 47 under 35 U.S.C. § 101 as being directed to non-statutory subject matter.

Claims 1–13, 15, 18–33, 35, 38–44, and 47 under 35 U.S.C. § 103(a) pre-AIA as being unpatentable over Hunter,⁴ Linke,⁵ CRC,⁶ and Pudil.⁷

³ The claim appears to be missing one or more terms. It is not clear what indication is being provided. Nevertheless, it appears that the Examiner treated this last limitation as being directed to providing an indication of a diagnosis, a prognosis, or a response to treatment of a condition or a disease. *See* Final Action 6–7 (noting in the art rejection of the claims that Hunter and Linke are both directed to clinical diagnoses based on tissue sample analyses). We analyze the claims as if this were the limitation.

⁴ Hunter et al., US 2008/0144895 A1, published June 19, 2008.

⁵ Linke et al., US 2006/0275844 A1, published Dec. 7, 2006.

⁶ CRC Press LLC, *Standard Mathematical Tables and Formulae* (Daniel Zwillinger (ed.) 1996).

⁷ P. Pudil et al., *Floating Search Methods In Feature Selection*, *Pattern Recognition Letters*, 1119–25 (1994).

DISCUSSION

I

Patent Ineligible Subject Matter

The Examiner finds that the method of claim 1 and system of claim 21 are claims directed to an abstract idea that fail to meet the standard for statutory eligibility because their central concept is the diagnostic data processing algorithm that correlates cellular features with patient data. (Final Action 3–4.) The Examiner notes that the claims recite using generic structures that perform well-understood, routine, and conventional functions by those of skill in the art prior to the invention. (*Id.*)

We agree with the Examiner’s conclusion that the method of claim 1 and system of claim 21 are patent ineligible abstract ideas.

Section 101 provides that “[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor.” 35 U.S.C. § 101. In *Alice*, the Supreme Court articulated a two-step test for examining patent eligibility under § 101. *Alice Corp. Pty. Ltd. v. CLS Bank Int’l*, 134 S. Ct. 2347 (2014). Step one involves determining whether the claims at issue are directed to a patent ineligible concept, and step two, reached only if the determination in step one is yes, considers 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 2355 (internal quotation marks and citation omitted).

Appellant disagrees with the Examiner’s characterization of the claims, noting that they “are directed to processing of image data of

multiplexed biometric . . . [data]” as opposed to “an algorithm that correlates cellular features with patient data.” (Appeal Br. 9.) Appellant contends that in light of this, the Examiner’s rejection is in error because “image processing claims have been found to be patentable under §101 . . . [and] do no fall within a judicial exception.” (*Id.*) We do not find Appellant’s argument persuasive.

Appellant’s characterization of the claims under step one of *Alice* fails to examine the claims as a whole. *See SAP Am., Inc. v. Investpic, LLC*, 898 F.3d 1161, 1167 (Fed. Cir. 2018). While it is true that Appellant’s claim 1 involves an examination of image data, the steps involved concern manipulating stored data and analyzing it to identify a feature contained within it without more. In particular, the steps require storing the images, using a computer processor to extract information from the stored data concerning cellular features that are within the data set and to correlate the information using mathematical concepts, using the processor to examine the newly correlated information and to group it, and then using the processor to reassess the information using a pre-defined threshold and mathematical modeling, and providing some “indication . . . related to the tissue samples.” The system recited in claim 21 is similar. In addition to reciting a process that performs the data manipulation and analysis noted above, it recites a camera device that captures the multiplexed biometric images that are then stored and a visual display device. As the Examiner explained, when considered as a whole, the method and system both concern a diagnostic data processing algorithm that manipulates stored data for identification purposes.

“The Supreme Court has not ‘delimit[ed] the precise contours of the ‘abstract ideas’ category.’” *Content Extraction & Transmission LLC v. Wells Fargo Bank, Nat’l Ass’n*, 776 F.3d 1343, 1346 (Fed. Cir. 2014) (quoting *Alice*, 134 S. Ct. at 2357). However, our reviewing Court has explained that “[i]nformation as such is an intangible,” and thus, abstract, and “collecting information, including when limited to particular content (which does not change its character as information), [i]s within the realm of abstract ideas.” *Electric Power Group, LLC v. Alstom S.A.*, 830 F.3d 1350, 1353 (Fed. Cir. 2016) (citing cases). So, too, is “analyzing information . . . by mathematical algorithms, without more.” *Id.* at 1354 (citing cases, including *Parker v. Flook*, 437 U.S. 584 (1978), and *Gottschalk v. Benson*, 409 U.S. 63 (1972)). Claim 1 is directed at abstract ideas under those principles.

The system for analyzing tissue features of claim 21 is as well. The focus of claim 21 is not to any improved display device, camera, or storage device, nor is it directed to an improvement in the way computers work. Rather, it, too, is focused on the selection and mathematical analysis of information, which is followed by display of results. Thus, the focus of claim 21 is not on an improvement in computers as tools, but on abstract ideas that use computers as tools. *See SAP*, 898 F.3d at 1167–68 (noting that claims to an improvement in a mathematical technique with no improved display mechanism were abstract as compared to those in *McRO, Inc. v. Bandai Namco Games America Inc.*, 837 F.3d 1299 (Fed. Cir. 2016) which included a “claimed improvement . . . [as] to how the physical display operated (to produce better quality images)” in addition to having

“specificity required to transform a claim from one claiming only a result to one claiming a way of achieving it”).

Appellant’s general argument that image processing claims as a class do not fall within a judicial exception (Appeal Br. 9) is simply incorrect. While it is true that a process involving image analysis via computers was found patent eligible in *Research Corp. Tech. v. Microsoft Corp.*, 627 F.3d 859 (Fed. Cir. 2010), the claims at issue in that case involved an improvement to computer technologies (as compared to the prior art, the “inventive mask produce[d] higher quality halftone images while using less processor power and memory space,” *Research Corp.*, 627 F.3d at 865, and the method, “which required the manipulation of computer data structures (the pixels of a digital image and the mask) and the output of a modified computer data structure (the halftoned image), was dependent upon the computer components required to perform it.” *Bancorp Servs., L.L.C. v. Sun Life Assur. Co. of Canada (U.S.)*, 687 F.3d 1266, 1279 (Fed. Cir. 2012) (distinguishing claims on appeal from those in *Research Corp.*). The claims were not deemed patent eligible simply because they were an improvement in the processing of information (Reply Br. 2), which is what the present claims are alleged to achieve. Collecting and processing information without more is within the realm of abstract ideas, as explained above.

The claims at issue here, while they may improve the processing of the multiplexed images, do not improve computer technologies, *see, e.g.*, *McRO*, 837 F.3d 1299 (improvement in how a physical display operated), *Finjan, Inc. v. Blue Coat Sys., Inc.*, 879 F.3d 1299, 1305 (Fed. Cir. 2018) (claims were directed to employing a new kind of file that enables a computer security system to do things it could not do before), or recite steps

or rules that solve a technological problem in the use of computers in a particular way, *see, e.g., Enfish, LLC v. Microsoft Corp.*, 822 F.3d 1327, 1335–36 (Fed. Cir. 2016); *BASCOM Glob. Internet Servs., Inc. v. AT&T Mobility LLC*, 827 F.3d 1341, 1348–49 (Fed. Cir. 2016)). Rather, as discussed above, they merely use computers as a tool to manipulate stored data and analyze it without more.

Consequently, we agree with the Examiner that the method and system claims at issue are directed to an abstract idea: analyzing collected data using various mathematical concepts, i.e., algorithms, and organizing it into a new form.

We additionally, agree with the Examiner that the limitations of the claim that are in addition to the abstract idea “amount to no more than mere instructions to implement the algorithm on a generic computer (as in claim 1 and its dependents), or generic computer or electronic structures that perform well-understood, routine, and conventional activities.” (Final Action 3.) As explained in Appellant’s Specification “[e]xamination of tissue specimens that have been treated to reveal the expression of biomarkers is a known tool for biological research and clinical studies.” (Spec. ¶ 3.) “Commonly the treated tissue is examined with digital imaging and the level of different signals emanating from different biomarkers” is “readily quantified” including by examining multiple images and to identify patterns. (*Id.* ¶¶ 4–14.) The known prior art processes include using computers to assist in storing collected information about the tissue specimen including the segmentation of “individual cell units and their subcellular compartments (including membrane, cytoplasm and nucleus)” (*Id.* ¶ 9), “grouping . . . cells together which have similar biomarker

expression attributes” (*Id.* ¶¶ 10–11), which grouping “could be examined to identify any cell attribute which is associated with the diagnoses or prognoses of a given condition or disease or with the response to a given therapy for a given condition or disease,” as well as “generat[ing] various expression profiles that are then overlaid on an image of the tissue of interest.” (*Id.* ¶¶ 7, 11.)

In its Appeal Brief, Appellant does not contest this, but rather contends that the Examiner erred by not conducting a “Streamlined Analysis.” (Appeal Br. 9–11.) According to Appellant, if such an analysis had been conducted, it would be seen that “the claims do not tie up an entire judicial exception” because “there is no attempt to tie up an entire algorithm for general use” (Appeal Br. 9–11), as the claims are “within the context of analysis of biological images” (Reply Br. 4

(claims 1 and 21 recite the use of a particular type of data, multiplexed biometric images that capture the expression of biomarkers. The claims at issue are within the context of analysis of biological images and the recited use is clearly defined and limited in scope. As such, there is no attempt to tie up an entire algorithm for general use.)).

We do not find Appellant’s argument persuasive. The question of import under a section 101 analysis is whether the Examiner properly made a determination as to whether the claims were directed to a judicial exception, e.g., an abstract idea, and a determination as to whether there are additional limitations considered individually and together that establish the claims are directed to something significantly more than the judicial exception. We find the Examiner carried out an appropriate analysis of the claims under 35 U.S.C. § 101.

As to Appellant’s argument that the claims are limited to a particular field in which to apply the algorithm, we note that “merely limiting the field of use of the abstract idea to a particular . . . environment does not render the claims any less abstract.” *Affinity Labs of Tex., LLC v. DIRECTV, LLC*, 838 F.3d 1253, 1259 (Fed. Cir. 2016).

Without additional limitations, a process that employs mathematical algorithms to manipulate existing information to generate additional information is not patent eligible. “If a claim is directed essentially to a method of calculating, using a mathematical formula, even if the solution is for a specific purpose, the claimed method is nonstatutory.” *Parker v. Flook*, 437 U.S. 584, 595 . . . (1978) (internal quotations omitted).

Digitech Image Techs., LLC v. Elecs. for Imaging, Inc., 758 F.3d 1344, 1351 (Fed. Cir. 2014). Indeed, “the absence of complete preemption does not demonstrate patent eligibility.” *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1379 (Fed. Cir. 2015). Where a patent’s claims are deemed only to disclose patent ineligible subject matter under the two-step framework, as they are in this case, preemption concerns are fully addressed and made moot. *Id.*; see also *Intellectual Ventures I LLC v. Symantec Corp.*, 838 F.3d 1307, 1321 (Fed. Cir. 2016) (“A narrow claim directed to an abstract idea, however, is not necessarily patent-eligible”); *OIP Techs., Inc. v. Amazon.com, Inc.*, 788 F.3d 1359, 1362–63 (Fed. Cir. 2015) (“[T]hat the claims do not preempt all . . . [inventions in the field] or may be limited to [certain processes in the field] do[es] not make them any less abstract.”). The mere fact that the claims are directed to systems and methods for analysis of biological images, thus, is insufficient to overcome the Examiner’s rejection of the claims on appeal under 35 U.S.C. § 101.

In its Reply Brief, Appellant asserts for the first time, that the claims recite unconventional steps that “confine the claims to a particular useful application” and, thus, “qualify” them as directed to patent eligible subject matter. (Reply Br. 3.) In particular, Appellant states:

none of the cited art of record, as indicated below, appears to teach calculating a first and second moment for each of the at least one cell feature, wherein the first moment is mean and wherein the second moment is standard deviation, and wherein the at least one cell feature comprises a ratio based on a respective concentration level of each biomarker between cell compartments for a respective cell, claims 1 and 21 recite at least limitations other than what is well-understood, routine, conventional activity in the field as well as unconventional steps.

Id. Appellant further argues in the Reply Brief that because claim 21 “recites a particular machine” for capturing multiplexed biometric images that is not simply a generic digital camera, it recites something that “amounts to significantly more and therefore renders this claim eligible under 35 U.S.C. §101.” (*Id.* at 4.) We do not find these arguments persuasive. First, “the reply brief [is not] an opportunity to make arguments that could have been made in the principal brief on appeal to rebut the Examiner’s rejections, but were not.” *Ex parte Borden*, 93 USPQ2d 1473, 1474 (BPAI 2010) (informative). As stated in *Ex parte Borden*, consideration by the Board of new arguments presented for the first time in the Reply Brief that could have been presented earlier would “vitate the force of the requirement in Board Rule 37(c)(1)(vii) that ‘[a]ny arguments or authorities not included in the brief . . . will be refused consideration by the Board, unless good cause is shown.’” *Id.* Appellant has not demonstrated any specific Examiner findings presented for the first time in the Answer

necessitating this specific new argument in rebuttal in the Reply Brief. Nor do we find any substantial differences in the Examiner's initial findings and the Examiner's findings stated in the Answer that would warrant the new arguments presented in the Reply Brief for the first time.

Second, the search for an inventive concept is distinct from demonstrating novelty. *See, e.g., SAP*, 898 F.3d at 1162 (citing *Synopsys, Inc. v. Mentor Graphics Corp.*, 839 F.3d 1138, 1151 (Fed. Cir. 2016) (“[A] claim for a *new* abstract idea is still an abstract idea. The search for a § 101 inventive concept is thus distinct from demonstrating § 102 novelty.”)). Appellant relies on the calculation of a mean, standard deviation, and a ratio as being unconventional steps in the analysis of the tissue. (Reply Br. 3.) However, those steps are simply mathematical calculations which are abstract ideas. An innovation that consists of using particular ineligible subject matter, such as the mathematical calculations that Appellant points to here in organizing the information into a new form, is insufficient to establish that the claims at issue are directed to a patent-eligible application of an abstract idea. *SAP*, 898 F.3d at 1162 (“an advance. . . [that] lies entirely in the realm of abstract ideas, with no plausibly alleged innovation in the non-abstract application realm . . . is ineligible for patenting”); *see also Synopsys*, 839 F.3d at 1152 (“To the extent the Asserted Claims add anything to the abstract idea (i.e., translating a functional description of a logic circuit into a hardware component description of the logic circuit), it is the use of assignment conditions as an intermediate step in the translation process But, given that the claims are for a mental process, assignment conditions, which merely aid in mental translation as opposed to computer

efficacy, are not an inventive concept that takes the Asserted Claims beyond their abstract idea.”).

The fact that claim 21 requires the use of a specialized camera to obtain the multiplexed biometric images is also insufficient to establish that claim is directed to a patent-eligible application of an abstract idea. Irrespective of the camera being a “specialized camera” and not simply any digital camera, the use of such specialized cameras is conventional in obtaining and analyzing cellular data from biomarker stained tissue as explained in Appellant’s Specification. (Spec. ¶¶ 4–14.)

Consequently, for all of the reasons discussed above, we sustain the Examiner’s rejection of claims 1 and 21 under 35 U.S.C. § 101 as being directed to non-statutory subject matter.

Claims 2–13, 15, 18–20, 22–33, 35, 38–44, and 47 have not been argued separately and, therefore, fall with claims 1 and 21, respectively. 37 C.F.R. § 41.37(c)(1)(iv).

II

Obviousness

The Examiner finds that Hunter teaches imaging biological material in multiple optical channels where the plasma membrane and nucleus have been differentially stained and then segmenting the images and calculating various morphological biomarkers from the segmented image and that these markers can be indicative of cancer. (Final Action 6.) The Examiner further finds that Hunter teaches that one such biomarker can be “a ratio of intensities between different compartments of an individual cell.” (*Id.*) The Examiner finds that Hunter teaches that the method can be performed using a computer system that can include a digital camera. (*Id.*)

The Examiner finds that Linke teaches obtaining tissue samples from groups of patients, such as cancer patients, where each group has a common characteristic, such as clinical outcome, or disease group versus control group, and assaying the samples through biomarker analysis of one or more polypeptides that employs imaging and quantifying the amounts of polypeptides, which may be considered non-morphological markers. (*Id.*) The Examiner finds that Linke teaches training a classifier to map selected critical inputs, such as the biomarker quantities, clinicopathological information and histological biomarkers, and outputs such as clinical outcome. (*Id.*) The Examiner notes that Linke teaches that the input data can be pre-processed and transformed, such as by calculation of mean data and covariance matrices. (*Id.* at 6–7.) The Examiner explains that the diagonal entries of the covariance matrix are a “second moment.” (*Id.* at 7.) The Examiner further explains that Linke teaches a subset of features can be selected, based on, e.g., rank order where lowest-ranked features are eliminated, and evaluated, which gives “the best classification results.” (*Id.*) The Examiner notes further, that Linke describes, subsequent to classification, displaying a probability estimate of a clinical diagnosis of a patient. (*Id.*) The Examiner notes that Linke teaches that a computer can be used in performing the methods. (*Id.*)

According to the Examiner, one of ordinary skill in the art would have found it obvious to combine the method of Hunter with Linke in cancer diagnosis as both are concerned with using histological biomarkers in assessing cancer and would readily predict that combination would result in “a method that derives morphological and non-morphological biomarkers from segmented fluorescence microscopy images, selects the best predictive

biomarkers, and classifies the tissue sample based on those features.” (*Id.* at 9.) The Examiner recognizes the combination does not explicitly teach calculating a standard deviation of biomarker data, but that such would have been an obvious statistical measure of the data in the Hunter/Linke combined method of characterizing the distribution of biomarkers (*id.* at 7) as evidenced by the CRC which teaches the mean, standard deviation, and skewness are useful measures for characterizing distributions of variables (*id.* at 9–10).

Appellant contends that the Examiner has failed to establish a prima facie case of obviousness because Hunter does not disclose that the intensity ratio that is measured is a measure taken for each cell rather than a global measure of the tissue, and even if it did, that Hunter does not disclose calculating first and second moments for such a measure. (Appeal Br. 14; Reply Br. 5.) Appellant further argues that the combination of Linke and CRC with Hunter does not disclose “the recited first and second moments of a cell feature including a ratio biomarker expression between compartments” because Linke “discloses determining mean and standard deviation for biomarker expression alone, and not for any cell feature based on a ratio of biomarker expression” and that “the Examiner’s reliance on a general text related to mathematical formulas [for first and second moments] indicates that the relied-upon features of these references are part of a hindsight analysis.” (*Id.*; *see also* Reply Br. 5–7 (noting that Linke “does not disclose any ratio of biomarker expression between compartments”).)

We do not find Appellant’s arguments persuasive. We do not agree with Appellant that Hunter is concerned solely with general identification of membranes in a tissue image. (Appeal Br. 14.) Table 1 of Hunter indicates

that measurement of cell dimensions and cell count are contemplated. This indicates that Hunter is concerned with identification of individual cells. Moreover, we agree with the Examiner (Ans. 6) that Hunter's teaching of using an enhanced membrane mask in combination with CELL IDs to analyze median intensity ratios reasonably conveys to one of ordinary skill in the art that the intensity measure is a per cell measure in cell compartments such as the membrane, cytoplasm, and nucleus. (Hunter ¶ 40 and Table 1.) That is because the enhanced membrane mask segments individual cells, which individual cells have been given a CELL ID. As the Examiner notes, "there would be no purpose to using the membrane mask nor the cell IDs" "if the intensity ratios were 'global measurements'." (Ans. 6.) Thus, even though Hunter does not specifically state that the measure of median intensity ratio is for each respective cell (Reply Br. 6), we agree with the Examiner that such is the import of the disclosure of Hunter (Ans. 6).

Regarding Appellant's argument as to the non-obviousness of determining a first and second moment of a cell feature including a ratio biomarker expression between compartments, we note that Appellant is arguing that neither Hunter nor Linke independently teaches this limitation. However, the rejection was based on what the combination of references would have suggested to one of ordinary skill in the art. "Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [The reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). The Examiner's position is that Hunter teaches determining the claimed ratio and Linke is relied upon for teaching

the obviousness of the statistical analyses of collected data for collected biomarker data in general (Ans. 6) which could also be applied to the ratio that Hunter teaches to collect. The Examiner further relies on the CRC only to explain that means and variances are “useful descriptive statistics of sets of data” that would have been obvious for one of ordinary skill in the art to have used in the Hunter/Linke combination. (*Id.*) We agree with the Examiner’s analysis.

Thus, Appellant has not established error in the Examiner’s rejection of claims 1 and 21 under 35 U.S.C. § 103(a) being unpatentable over Hunter, Linke, CRC, and Pudil.

Claims 2–13, 15, 18–20, 22–33, 35, 38–44, and 47 have not been argued separately and, therefore, fall with claims 1 and 21, respectively. 37 C.F.R. § 41.37(c)(1)(iv).

SUMMARY

We affirm the Examiner’s rejection of claims 1–13, 15, 18–33, 35, 38–44, and 47 under 35 U.S.C. § 101 as being directed to non-statutory subject matter.

We affirm the Examiner’s rejection of claims 1–13, 15, 18–33, 35, 38–44, and 47 under 35 U.S.C. § 103(a) pre-AIA as being unpatentable over Hunter, Linke, CRC, and Pudil.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED