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.
14/805,204	07/21/2015	H. Barton Grossman	4002.001796	9635

23720 7590 06/05/2019

WILLIAMS MORGAN, P.C.
6464 Savoy
Suite 600
HOUSTON, TX 77036

EXAMINER
POHNERT, STEVEN C

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
06/05/2019	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):

nnolan@wmalaw.com
jjohn@wmalaw.com
docketing@wmalaw.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte H. BARTON GROSSMAN, BOGDAN CZERNIAK and SUBRATA SEN[1]

Appeal 2019-000162
Application 14/805,204
Technology Center 1600

Before ULRIKE W. JENKS, TIMOTHY G. MAJORS, and MICHAEL A. VALEK, *Administrative Patent Judges*.

VALEK, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a method for detecting bladder cancer in a patient, which have been rejected as directed to patent-ineligible subject matter and as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

---

[1] Appellants identify the real party in interest as The Board of Regents, The University of Texas System. App. Br. 2. Herein we refer to the Office Action mailed October 13, 2017 ("Non-Final Act."), Appeal Brief filed July 2, 2018 ("App. Br."), Examiner's Answer mailed September 7, 2018 ("Ans."), and Reply Brief filed October 9, 2018 ("Reply").

STATEMENT OF THE CASE

Appellants' "invention relates to a method of detecting bladder cancer in a patient, comprising isolating bladder cells from the patient's urine" and determining "the number of bladder cells in the sample having at least a first threshold number of copies of the aurora kinase A gene." Spec. 4, ll. 12–18. According to the Specification, if "a first threshold percentage of bladder cells have at least the first threshold number of copies of the aurora kinase A gene," the patient may be presumed to have bladder cancer. *Id.* at 7, ll. 8–10. The Specification further explains if the percentage of cells or number of copies exceed a second threshold that is "greater than the first threshold," the patient may be presumed to have aggressive bladder cancer. *Id.* at 7, ll. 14–18.

Claims 1, 3, and 7 are on appeal, and can be found in the Claims Appendix of the Appeal Brief. Claim 1 is the only independent claim and illustrative. It reads as follows:

> 1. A method of detecting bladder cancer in a patient, comprising:
>
> isolating bladder cells from the patient's urine, wherein the patient is a human being;
>
> hybridizing the bladder cells with a labelled DNA probe comprising SEQ ID NO:1, SEQ ID NO:2, a sequence fully complementary to SEQ ID NO:1, or a sequence fully complementary to SEQ ID NO:2, and a first label, to yield a sample of bladder cells in which the aurora kinase A gene is hybridized with the labelled DNA probe;
>
> counting the number of bladder cells in the sample, a number of copies of the aurora kinase A gene in each bladder cell in the sample, and the number of bladder cells in the sample having at least three copies of the aurora kinase A gene;
>
> determining a percentage of the bladder cells having at least three copies of the aurora kinase A gene;

> detecting the bladder cancer in response to greater than or equal to 15% of the bladder cells having at least three copies of the aurora kinase A gene; and
>
> performing on the patient at least one diagnostic or therapeutic method selected from the group consisting of cystoscopy, surgical ablation, Bacillus Calmette-Guerin (BCG) instillation into the bladder, instillation of other chemotherapeutic molecules into the bladder, radiation treatment, and cystectomy, in response to a detection of the bladder cancer.

App. Br. 24. Claims 3 and 7 and further specify a "second threshold" for detecting "aggressive bladder cancer." App. Br. 24–25.

Appellants seek review of the following grounds of rejection made by Examiner:

I. Claims 1, 3, and 7 under 35 U.S.C. § 101 as directed to patent-ineligible subject matter.

II. Claims 1, 3, and 7 under 35 U.S.C. § 103(a) as obvious over Jeong,[2] Steinberg,[3] Spiess,[4] Letessier,[5] GenBank,[6] and Zhou.[7]

---

[2] J. Jeong et al., *Amplification of a Mitotic Kinase Gene as a Marker Bladder Carcinoma*, Annual Meeting of the United States and Canadian Academy of Pathology 2003, Abstract 703, page 155A ("Jeong").

[3] Jordan R. Steinberg et al., *Aurora A as a Potential Biomarker for Bladder Cancer*, Abstract No. 607, XP9113863 (2005) ("Steinberg").

[4] Philippe E. Spiess, *Aurora A Test for Bladder Cancer*, Proc. Amer. Assoc. Cancer Res., Vol. 47, 1061 (2006) ("Spiess").

[5] Anne Letessier et al., *Frequency, Prognostic Impact, and Subtype Association of 8p12, 8q24, 11q13, 12p13, 17q12, and 20q13 Amplifications in Breast Cancers*, BMC Cancer, Vol. 5, 245 (2006) ("Letessier").

[6] GenBank accession BC001280.1 (2006) ("GenBank").

[7] Hongyi Zhou et al., *Tumour Amplified Kinase STK15/BTAK Induces Centrosome Amplification, Aneuploidy and Transformation*, Nature Genetics, Vol. 20, 189–193 (1998) ("Zhou").

ANALYSIS

I. Subject Matter Eligibility

An invention is patent-eligible if it claims a "new and useful process, machine, manufacture, or composition of matter." 35 U.S.C. § 101. However, the Supreme Court has long interpreted 35 U.S.C. § 101 to include implicit judicial exceptions: "[l]aws of nature, natural phenomena, and abstract ideas" are not patentable. *E.g.*, *Alice Corp. v. CLS Bank Int'l*, 573 U.S. 208, 216 (2014).

In determining whether a claim falls within an excluded category, we are guided by the Supreme Court's two-step framework, described in *Alice*. *Id.* at 217–18 (citing *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 75–77 (2012)). In *Alice* step one, we ask whether the claims are directed to an exception to patent eligibility, such as an abstract idea or law of nature. *Alice Corp. Pty. V. CLS Bank Int'l*, 134 S.Ct. 2347, 2355 (2014). In *Alice* step two, we examine the elements of the claims to determine whether they contain an inventive concept sufficient to transform the claimed judicial exception into a patent-eligible application. *Mayo*, 566 U.S. at 71–72 (quoting *Alice*, 134 S.Ct. at 2355).

The Office recently published revised guidance on the application of the Supreme Court's *Alice* analysis. USPTO's January 7, 2019 Memorandum, *2019 Revised Patent Subject Matter Eligibility Guidance,* 84 Fed. Reg. 50–57 ("Guidance"). According to the Guidance, we look to whether the claim recites: (1) a judicial exception, such as a law of nature (Guidance Step 2A, prong 1); and (2) additional elements that integrate the judicial exception into a practical application (Guidance Step 2A, prong 2). Only if the claim recites a judicial exemption and does not integrate that

exception into a practical application, do we then examine whether the claim adds a specific limitation beyond the judicial exception that is not "well-understood, routine, conventional" in the field (Guidance Step 2B). *See* Guidance at 54–56.

Examiner's Findings and Conclusions

Regarding *Alice* step one, Examiner determines that Appellants' claims are directed to a law of nature, specifically the "naturally occurring correlation between the amplification or increased expression of aurora kinase a and detection of bladder cancer." Non-Final Act. 5; Ans. 4. Examiner finds that the isolating and hybridizing steps are "routine and conventional data gathering steps" and that the counting and detecting a percentage of cells steps are themselves merely "abstract ideas, instructions, or mental steps." Non-Final Act. 6. Regarding the "performing on a patient" step, Examiner determines that the Specification evidences that the diagnostic and therapeutic methods recited there are "merely conventional steps for subjects with bladder cancer." *Id.* at 7. Accordingly, Examiner finds that the claims do not "integrate[] the judicial exemptions(s) into a practical application." *Id.* at 8. And at *Alice* step two, Examiner determines "[t]he recited steps [of Appellants' claims] only instruct the user to engage in well-understood, routine and conventional activity." *Id.* at 7.

Appellants' Contentions

Appellants argue that their claims are patent eligible "method of treatment" claims. App. Br. 9–10; Reply 2–4 (citing *Vanda Pharma. Inc. v. West-Ward Pharms.*, 887 F.3d 1117 (Fed. Cir. 2018) and the USPTO's June 7, 2018 Memorandum regarding the *Vanda* decision ("Memorandum")). In particular, Appellants contend that because the last step of claim 1 requires

"performing on the patient at least one diagnostic or therapeutic method . . . in response to a detection of the bladder cancer," the claims are drawn to a practical application of the natural law and therefore patent eligible at *Alice* step one (Guidance Step 2A). App. Br. 9; Reply 4. Appellants do not separately challenge Examiner's finding at *Alice* step two. *See* App. Br. 10 (stating "there is no need to conduct a [Guidance] Step 2B analysis regarding whether claim elements amount to significantly more" because the claims are "eligible subject matter as determined at Step 2A").

Our Review

Applying the Supreme Court's *Alice* framework as explained in the Office's Guidance, we agree with Examiner that Appellants' claims are directed to patent-ineligible subject matter. The Guidance instructs us first to determine whether any judicial exception to patent eligibility is recited in the claim.[8]

Guidance Step 2A, Prong 1

Claim 1 recites the following limitations: (1) "counting the number of bladder cells in the sample, a number of copies of the aurora kinase A gene in each bladder cell in the sample, and the number of bladder cells in the sample having at least three copies of the aurora kinase A gene;" (2) "determining a percentage of the bladder cells having at least three copies of the aurora kinase A gene;" and (3) "detecting the bladder cancer in response to greater than or equal to 15% of the bladder cells having at least three

[8] It is undisputed that Appellants' claims are directed to one of the statutory classes of patentable subject matter, *i.e.*, a method or "process," recited in 35 U.S.C. § 101. Thus, we begin our analysis at Step 2A, prong 1 of the Guidance.

copies of the aurora kinase A gene." These limitations, under their broadest reasonable interpretation, recite a law of nature, namely that the level of aurora kinase A gene amplification in bladder cells isolated from a subject's urine sample indicates that the subject has bladder cancer if that level exceeds a threshold specified in terms of a percentage of cells having a number of copies of that gene.

Claims 3 and 7 each recite a second natural law in addition to that in claim 1. Claim 3 additionally recites the following limitations: (1) "counting the number of bladder cells having at least a second threshold number of copies of the aurora kinase A gene, wherein the second threshold number of copies is five;" and (2) "detecting, in response to greater than or equal to 15% of the bladder cells having at least five copies of the aurora kinase A gene, aggressive bladder cancer." Claim 7 recites the following limitation "if greater than or equal to a second threshold percentage of the bladder cells have at least three copies of the aurora kinase A gene, wherein the second threshold percentage is 20%, detecting aggressive bladder cancer." In both instances, the additional limitations of the dependent claim recite a law of nature, that is, that amplification of the aurora kinase A gene above a somewhat higher threshold than that in claim 1 indicates aggressive bladder cancer.

Guidance Step 2A, Prong 2

Having determined that the claims recite a judicial exception, our analysis now turns to determining whether there are additional elements that integrate the judicial exception into a practical application (Guidance Step 2A, prong 2). "Integration into a practical application" requires that the claim recite an additional element or a combination of elements, that when

considered individually or in combination, "apply, rely on, or use the judicial exception in a manner that imposes a meaningful limit on the judicial exception, such that the claim is more than a drafting effort designed to monopolize the judicial exception." Guidance at 54.

We begin by observing that Appellants' claims are, as a whole, directed to methods for detecting bladder cancer. The preamble of claim 1 states that it is "[a] method of detecting bladder cancer in a patient." The first two steps of "isolating" bladder cells and "hybridizing" them so that aurora kinase A amplification can be calculated are data-gathering steps. The "counting," "determining," and "detecting" steps recite the judicial exception to detect bladder cancer using that data. The last step requires "performing . . . a diagnostic or therapeutic method," but *only* "in response to a detection of the bladder cancer." If the level of aurora kinase A amplification falls below the threshold specified by the natural law, no method of treatment is required.[9] If the level exceeds the threshold, two things happen: (1) bladder cancer is detected; and (2) in response a "diagnostic or therapeutic method" is performed. But only the first of these is informed by the natural law. Nothing in Appellants' claims requires that the level of aurora kinase A amplification and its relationship to bladder cancer be applied, relied upon, or used to perform the diagnostic or therapeutic method that occurs if cancer is detected.

[9] *Cf Ex parte Schulhauser*, Decision on Appeal 2013-007847 at 6–8 (PTAB April 28, 2016) (designated precedential) (explaining that the broadest reasonable interpretation of method reciting steps performed "if" criteria is met encompasses instances where the step is not performed because the criteria is not met).

In all these ways, Appellants' claims are unlike those determined to be patent-eligible in *Vanda* and *Endo*. *See Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117, 1121 (Fed. Cir. 2018); *Endo Pharms. Inc. v. Teva Pharms. USA, Inc.*, 919 F.3d 1347, 1350–51 (Fed. Cir. 2019). The claims in both *Vanda* and *Endo* recited a "method of treating," not merely detecting, a condition. *Id.* Moreover, those claims required the administration of a particular drug with a dosage tailored to the results of testing associated with the law of nature at issue. *Id.* For example, in *Endo* the inventor discovered a natural correlation between the creatinine clearance rate of patients with renal impairment and the AUC of oxymorphone in their bloodstream. 919 F.3d at 1349. Thus, by testing and determining the creatinine clearance rate, one could detect the relative sensitivity of the patient to oxymorphone. *Id.* The claim, however, required more than merely detecting the patient's oxymorphone sensitivity. *See id.* at 1351. It required as a final step, "orally administering to said patient, in dependence on which creatinine clearance rate is found, a lower dosage of the dosage form to provide pain relief." *Id.* This step was not conditional. In all instances, the claims in *Endo* required both the administration of a particular treatment (i.e., oral administration of oxymorphone) and the application of the natural law to tailor the dosage to patient's specific physiology *Id.* at 1349; *see also Vanda*, 887 F.3d at 1121 (claims requiring "internal administering iloperidone" and adjusting dosage based on recited assay results in all instances). As our reviewing court observed, these facts are "material" to patent eligibility because they distinguish the method of treatment claims in *Vanda* and *Endo* from the representative claim in *Mayo*, which "as a whole was not directed to the application of a drug to treat a

particular disease" and did not recite "'a new way of using an existing drug'" such that it could be considered a particular application of the natural law. *Endo* 919 F.3d at 1354 (quoting *Mayo Collaborative Services v. Prometheus Labs., Inc.*, 566 U.S. 66, 87 (2012)).

Indeed, Appellants' claims are more similar to those held ineligible in *Athena Diagnostics, Inc. v. Mayo Collaborative Services, LLC*, 914 F.3d 743, 747 (Fed. Cir. 2019) than they are to those in *Vanda* and *Endo*. The representative claim in *Athena* (claim 9) concerned a method for diagnosing certain disorders based on the presence of an antibody to a particular protein. *Id.* It recited steps such as: (a) "contacting" a sample of body fluid with a specifically-labelled version of the protein; (b) "immunoprecipitating" any complex; and (c) "monitoring" for the label "wherein the presence of the label indicates" the disorder.[10] *Id.* The Federal Circuit held that such steps are not a particular application of the natural law because they "only apply conventional techniques to detect that natural law." 914 F.3d at 751. In doing so, it distinguished claims that require a "new treatment for an ailment, albeit using a natural law" like those in *Vanda* from those that merely "recite a natural law and conventional means for detecting it." *Id.* at 753.

As with the claims in *Athena*, the claims before us here do not recite any "new treatment for an ailment." *See id.* As explained above, no treatment is required if the level of aurora kinase A amplification falls below

[10] These steps are analogous to those of Appellants' claims 1. Step (a) of the *Athena* claim is akin to the "isolating" step in claim 1. Step (b) is similar to the "hybridizing" step. And step (c) is akin to the "counting," "determining," and "detecting" steps of the present claims.

the specified thresholds. And if the natural law is detected, Appellants' claims do not dictate any particular diagnostic or treatment method to be performed. Instead, claim 1 recites a broad Markush group of possible "diagnostic or therapeutic methods" for bladder cancer, including "cystoscopy," surgery (i.e., "surgical ablation" and "cystectomy"), chemotherapy, and "radiation treatment." The Specification does not elaborate on these techniques any more than do Appellants' claims, stating only that "the physician can decide whether [the recited methods] should be performed or considered for performance." Spec. 7. In this sense, Appellants' claims do little more than recite the law of nature while "adding the words 'apply it.'" *Mayo*, 566 U.S. at 72 (quoting *Gottschalk v. Benson*, 409 U.S. 63, 71–72 (1972)). This is very different from the claims in *Vanda* and *Endo* where the natural law was applied to tailor the dosage thereby providing a new treatment for the ailment. In contrast, Appellants' claims merely provide an assay for detecting bladder cancer based on the observation of a natural law with a conditional, post-solution "performing" step that does not involve any particular application of that judicial exception. This raises the "basic underlying concern" of the judicial exceptions to patent eligibility, i.e., that allowing Appellants' claims would "tie up too much future use of" the law of nature itself. *Id.* at 86–87.

For these reasons, we are unpersuaded by Appellants' arguments that the present claims "resemble the claims at issue in *Vanda*" or are otherwise directed to "particular applications" of the natural law App. Br. 9; Reply 4 (citing *Vanda* and the Memorandum). We determine that Appellants' claims do not integrate the judicial exception into a practical application and are therefore directed to the law of nature itself.

Guidance Step 2B

Proceeding to *Alice* step 2 (i.e., Step 2B as provided in the Guidance), we agree with, and incorporate, Examiner's findings that the elements of Appellants' claims, considered both individually and in combination, do not provide an inventive concept beyond the judicial exception itself. Non-Final Act. 6–9. Those findings are supported by the Specification, which indicates that the techniques used to test and determine aurora kinase A amplification as well as the Markush group of diagnostic and therapeutic methods are routine and conventional in the art. *See* Spec. 4 ("Isolating bladder cells . . . from the patient's urine can be performed by any technique known in the art."); 5 ("Hybridizing the bladder cells . . . can be performed by any technique known in the art"); 6 ("Counting the number of bladder cells . . . can be performed by any appropriate technique known to the person of ordinary skill in the art"); and 7 (referring to various conventional diagnostic and therapeutic methods for bladder cancer). Appellants do not challenge any of Examiner's findings at *Alice* step 2. Accordingly, for all of the reasons above, we affirm the rejection.

II. Obviousness

Claims 1, 3, and 7 also stand rejected as obvious over the combination of Jeong, Steinberg, Spiess, Letessier, GenBank, and Zhou. The issue with respect to this rejection is: Does the preponderance of evidence of record support Examiner's conclusion that the cited prior art renders obvious the claimed method?

We begin our analysis with findings of fact regarding the teachings in the cited prior art.

FF1. Jeong teaches that overexpression of aurora kinase A[11] is "associated with aneuoploidy," which in turn is "tightly linked" with clinical prognosis in human bladder cancer. Jeong 155A. Jeong describes results from fluorescence in situ hybridization (FISH) conducted using aurora kinase A DNA probes on both tumor tissue and urine samples from patients with bladder cancer to determine aurora kinase A gene copy numbers for cells in those samples. *Id.* Jeong teaches that tumor samples with "[l]ow levels of [aurora kinase A] amplification (3-4 copies) were diploid or near diploid," whereas tumors "with higher levels . . . (>4 copies) . . . exhibited pronounced aneuploidy." *Id.* Regarding the urine samples, Jeong discloses that "low level of gene amplification (3-4 copies) was ubiquitously present in . . . all patients with bladder cancer" and that a "large portion of cells (>20%) with high gene copy number (4 copies) was identified in . . . patients with a high-grade invasive bladder cancer." *Id.* Based on these results, Jeong concludes that aurora kinase A "gene amplification" is "associated with aneuploidy and aggressive clinical behavior in bladder cancer" and "identification of increased [aurora kinase A] gene copy number could be used as marker for non-invasive detection of bladder cancer." *Id.*

FF2. Steinberg also describes the use of FISH to determine aurora kinase A copy number in cells from urine samples of bladder cancer patients. Steinberg 1. Similar to Jeong, Steinberg reports that "low levels of gene amplification (3-4 copies) were present in the voided urine samples of all patients with bladder cancer" and that "a large proportion of cells (>20%)

[11] Aurora kinase A is also known as STK15 or BTAK. Spec. 3, l. 29. The prior art cited in Examiner's rejection uses these terms interchangeably. For consistency, we use the term "aurora kinase A" in our analysis herein.

with high gene copy number (>4 copies) were identified in . . . patients with high-grade (grade 3) invasive bladder cancer." *Id.* Based on these results, Steinberg teaches that "Aurora A gene amplification is ubiquitous in bladder cancer and is associated with increased chromosome copy number, tumor aneuploidy, and aggressive clinical features." *Id.* Steinberg further teaches that "Aurora A gene copy number could potentially be used as a marker for the detection of bladder cancer." *Id.*

FF3. Spiess reports the use of a "gene-specific FISH probe" to test aurora kinase A copy number in cells from urine samples of patients with bladder cancer. Spiess 1061. Spiess teaches that "tumors with low levels of aurora A amplification (3-4 copies) showed minimal deviation in their chromosome copy number and diploid or near-diploid total nuclear DNA content," whereas "[t]umors with higher levels of Aurora A amplification (>4 copies) had a pronounced increase of chromosome copy number and total nuclear DNA content (aneuploidy)." *Id.* According to Spiess, "[t]he degree of aneuploidy is proportional to [the] degree of amplification/expression" of aurora kinase A in "exfoliated urothelial cells from urine sediments." *Id.*

FF4. Letessier teaches the use of DNA probes to study amplification of several "potential oncogenes," including aurora kinase A (referred to as "AURKA" therein). Letessier 2. Letessier describes the use of FISH was to determine the percentage of tumor cells having a gene copy number over a particular threshold, i.e., greater than 5. *Id.* at 3.

FF5. GenBank discloses the DNA sequence for human Aurora kinase A. GenBank 2–3.

FF6. Zhou teaches "[i]solation of genomic BAC clones and FISH analysis" to determine amplification of aurora kinase A in tumor tissue

samples by hybridization with a DNA probe specific to aurora kinase A. Zhou 192.

Examiner finds that Jeong teaches the isolating, hybridizing, counting and determining steps of claim 1. Non-Final Act. 13. Examiner further determines that Jeong, Steinberg, and Spiess are all drawn to in situ hybridization to detect the number of aurora kinase A genes in the cell's DNA and that GenBank teaches a sequence for that gene that is identical to SEQ ID NO:1. *Id.* at 15–16. Thus, while Jeong, Steinberg, and Spiess do not specifically teach the sequence of the aurora kinase A probes used in their FISH analysis, Examiner determines it would be obvious for the skilled artisan to use a probe comprising a sequence complementary to a known sequence for human aurora kinase A in SEQ ID NO:1. *See id.* 18–19; *see also* Ans. 18–19.

As for the detecting step, Examiner relies on the prior art's teaching that low levels of amplification (3-4 copies) were found in all patients with bladder cancer and that patients with invasive, high-grade bladder cancer had "20% or more cells with greater than 4 copies of aurora kinase A gene." Non-Final Act. 15 (citing Jeong, Steinberg, and Spiess). Examiner acknowledges that these references do not specifically teach "a first threshold percentage [of cells having at least 3 copies] which is 15," but finds that the ranges taught in the prior art overlap with the 15% threshold in claim 1 as well as the second thresholds recited in claims 3 and 7. *Id.*; *see also* Ans. 26–28. Thus, Examiner determines it would be "prima facie obvious" that "samples with less amplification of [a]urora kinase A would be a threshold for less aggressive tumors" and a skilled artisan would be motivated to select such a threshold based on the prior art's teaching that

amplification of aurora kinase A "could be used as a marker for non-invasive detection of bladder cancer." Non-Final Act. 16.

Appellants argue that claim 1 is not obvious because Jeong, Steinberg, and Spiess fail to teach: (a) the claimed sequences for the aurora kinase A DNA probe, and (b) "selection of 15% as the percentage of bladder cells having at least three copies of the aurora kinase A gene as a threshold for detecting bladder cancer in a patient." App. Br. 13. Appellants argue that because Jeong, Steinberg, and Spiess did not include a negative control in their studies (i.e., they did not determine aurora kinase A copy number and cell percentages for urine samples from healthy patients) one of ordinary skill in the art could not determine the claimed threshold of at least three gene copies in 15% or more cells. *Id.* at 13–14. According to Appellants, this threshold was chosen because it "is the lowest value having a false positive rate of 0% while maintaining a low false negative rate" and thus provides both "high sensitivity and high specificity." *Id.* Appellants urge that determining such a threshold requires "the judgment of a person of greater than ordinary skill" to consider tradeoffs between sensitivity and specificity. *Id.* at 17. Finally, Appellants argue that their finding that a "lower bound of 15% [of cells with 3 or more copies] provides a false positive rate of 0% and a false negative rate of only 16%" demonstrates "unexpected results relative to the prior art." *Id.* at 18–19.

We are unpersuaded by Appellants' arguments and generally agree with, and incorporate, Examiner's findings and reasoning in support of the obviousness rejection. *See* Non-Final Act. 12–19. We further address Appellants' arguments in our comments below.

We are not persuaded by Appellants' argument that because Jeong, Steinberg, and Spiess do not teach the particular sequence of the aurora kinase A probes used in their studies it would not be obvious to use a known sequence for aurora kinase A in GenBank. The teachings in Jeong, Steinberg, and Spiess are not limited to a particular sequence for the DNA probe used to observe aurora kinase A amplification. *See* FF1–FF3. Therefore, it would be obvious for a skilled artisan seeking to follow those teachings to detect bladder cancer to use a probe corresponding to a known sequence for aurora kinase A. Appellants do not dispute Examiner's finding that the claimed SEQ ID NO:1 is the same as the sequence for human aurora kinase A in GenBank. Nor is there any evidence to suggest that sequence provides superior or unexpected results as compared to other aurora kinase A probes.[12] Accordingly, we agree with Examiner that this limitation is obvious over the combination of the cited references.

We are also unpersuaded by Appellants' argument that the "greater than or equal to 15% of the bladder cells having at least three copies of the aurora kinase A gene" range in claim 1 is not obvious. Jeong and Steinberg teach that aggressive bladder cancer is associated with a range of aurora kinase A amplification (i.e., >20% of cells with 5 or more copies) that overlaps with and is encompassed by the range recited in claim 1 (i.e., ≥15% of cells with 3 or more copies). *See* FF1–FF2. These references further teach that lower levels of amplification were found in at least some cells (i.e., >0% of cells with 3–4 copies) for all patients with bladder cancer. *Id.*

[12] To the contrary, the Specification states "[t]he labelled DNA probe can comprise any DNA sequence and any detectable moiety, provided the probe recognizes at least a portion of the aurora kinase A gene." Spec. 5.

Given the overlapping ranges in the prior art, we agree that Examiner has presented a sufficient prima facie showing that the claimed range is obvious. *See, e.g.*, *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("[W]e and our predecessor court have consistently held that even a slight overlap in range establishes a prima facie case of obviousness.").

We also agree with Examiner's finding that it would be obvious for the skilled artisan to optimize the prior art range to arrive at the claimed lower threshold for detecting bladder cancer. Jeong and Steinberg both teach that aurora kinase A gene copy number could be used as a marker for the noninvasive detection of bladder cancer. FF1–FF2. Spiess teaches that tumor cells with low levels of amplification showed minimal deviation in their chromosome copy number and that the degree of aneuploidy associated with bladder cancer is proportional to the degree of amplification. FF3. These teachings provide a motivation for the skilled artisan to optimize down from the higher range for "aggressive bladder cancer" reported in Jeong and Steinberg to the lower threshold for detecting bladder cancer generally in claim 1. In doing so, it would be obvious to include a negative control to optimize the lower end of the detection range. *See Peterson*, 315 F.3d at 1330 ("The normal desire of scientists for artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.").

We are not persuaded by Appellants' argument that determining the threshold in claim 1 would require "undue experimentation" and therefore cannot be considered an obvious optimization of the teachings in the prior art. *See* App. Br. 16. The cited prior art demonstrates that techniques for

quantifying the extent of aurora kinase A amplification in bladder cells isolated from urine samples were known to the skilled artisan. *See* FF1–FF3, FF4, and FF6. Such techniques had already been applied to determine such amplification in patients known to have bladder cancer. *See* FF1–FF3. Appellants have not identified any reason why the same techniques could not be used to test samples from healthy subjects to optimize the detection range from those ranges in the prior art.

Appellants next argue that the claimed threshold is non-obvious because "only a person beyond ordinary skill could decide whether a specificity approaching 1 (meaning few, if any, false positives) or a sensitivity approaching 1 (meaning few, if any, false negatives) would be more desirable." App. Br. 16–17. We disagree. As Appellants' argument illustrates, there are a "finite number" of "known options" available to the skilled artisan to use to arrive at an appropriate detection threshold. *See KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). Specifically, one can choose to prioritize specificity (as Appellants say they did in selecting the detection range recited in claim 1) or one can choose to prioritize sensitivity. There is insufficient evidence to indicate that Appellants' choice was any less obvious than choosing the other option. Appellants' arguments that making such a determination is somehow "beyond ordinary skill" or requires "undue experimentation" is merely unsupported attorney argument. *See* App. Br. 16–17.

We further determine that Appellants have not presented sufficient evidence of a teaching away or unexpected results related to the claimed detection range to overcome the evidence of obviousness. *See* App. Br. 18–19. First, the teaching in Jeong, Steinberg, and Spiess that at least some

cells having 3-4 copies of aurora kinase A were found in all the bladder cancer patients they tested does not, as Appellants suggest, teach away from the claimed range. To the contrary, this teaching would motivate the skilled artisan to quantify the percentage of cells in such patients to optimize the detection threshold. Second, one of skill would expect the threshold for detecting bladder cancer generally to be lower than the level of amplification reported for aggressive bladder cancer (i.e., >20% of cells with 5 or more copies) in the prior art. *See* FF1–FF2. Nevertheless, Appellants urge that the claimed range unexpectedly provides a "false positive rate of 0% and a false negative rate of only 16%." App. Br. 16. But Appellants have not identified any evidence to show such rates are sufficiently unexpected to overcome Examiner's prima facie showing of obviousness. *See In re* Geisler, 116 F.3d 1465, 1471 (Fed. Cir. 1997) ("[N]aked attorney argument is 'insufficient to establish unexpected results.'") (quoting *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995)).

Appellants additionally argue that the detection range specified in claim 3 (i.e., 15% or more of cells with at least five copies) for aggressive bladder cancer is non-obvious because one reading Jeong, Steinberg, and Spiess "would draw the straightforward conclusion that 20% of cells having more than 4 copies of the aurora kinase A gene should be the threshold for detecting invasive bladder cancer." App. Br. 20. We disagree. "A person of ordinary skill is . . . a person of ordinary creativity, not an automaton" limited to the specific circumstances and applications recited in the prior art references. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). Here, the prior art teaches that an overlapping range comprising the same number of gene copies in a slightly higher percentage of cells is associated

with aggressive bladder cancer. FF1–FF2. We agree with Examiner that it would be prima facie obvious to optimize down from >20% taught in the prior art to the "greater than or equal to 15%" threshold in claim 3. *See* Non-Final Act 16. This is particularly so because doing so would serve to avoid false negatives, that is, missed diagnoses of aggressive bladder cancer.

Finally, we are unpersuaded by Appellants' additional arguments regarding claim 7. Claim 7 is similar to claim 3, but specifies a somewhat different "second threshold" of 20% or more of cells having 3 or more copies to detect "aggressive bladder cancer." As before, the claimed detection range overlaps with the range that Jeong and Steinberg teach is associated with aggressive bladder cancer (i.e., >20% of cells with 5 or more copies). FF1–FF2. We agree with Examiner that it would be prima facie obvious for the skilled artisan applying those teachings to detect aggressive bladder cancer to optimize the threshold down to the 3 or more copies recited in claim 7. *See Peterson*, 315 F.3d at 1330.

For all of the reasons above, we are unpersuaded by Appellants' arguments regarding Examiner's obviousness rejection. Accordingly, we affirm.

SUMMARY

We affirm the rejection of claims 1, 3, and 7 under 35 U.S.C. § 101 as being directed to patent ineligible subject matter.

We affirm the rejection of claims 1, 3, and 7 under 35 U.S.C. § 103 over Jeong, Steinberg, Spiess, Letessier, GenBank, and Zhou.

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