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Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO.
Row 1: 19/360,756, 10/16/2025, Stephen Yip, 32830/55304E, 2121
Row 2: 4743, 7590, 02/23/2026, MARSHALL, GERSTEIN & BORUN LLP, 233 SOUTH WACKER DRIVE, 6300 WILLIS TOWER, CHICAGO, IL 60606-6357, EXAMINER VARNDELL, ROSS E, ART UNIT 2674, PAPER NUMBER, NOTIFICATION DATE 02/23/2026, DELIVERY MODE 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):

mgbdocket@marshallip.com

Office Action Summary

Application No.

19/360,756

Applicant(s)

Yip et al.

Examiner

Ross Varndell

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AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 16 October 2025.

A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a) This action is **FINAL**.

2b) This action is non-final.

3) An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) Claim(s) 1-20 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) Claim(s) _____ is/are allowed.

7) Claim(s) 1-20 is/are rejected.

8) Claim(s) _____ is/are objected to.

9) Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10) The specification is objected to by the Examiner.

11) The drawing(s) filed on 16 October 2025 is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) All b) Some** c) None of the:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)

3) Interview Summary (PTO-413)

Paper No(s)/Mail Date _____.

2) Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)

4) Other: _____.

Paper No(s)/Mail Date _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Information Disclosure Statement

2. The IDS(s) has/have been considered and placed in the application file.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting

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provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The filing of a terminal disclaimer by itself is not a complete reply to a nonstatutory double patenting (NSDP) rejection. A complete reply requires that the terminal disclaimer be accompanied by a reply requesting reconsideration of the prior Office action. Even where the NSDP rejection is provisional the reply must be complete. See MPEP § 804, subsection I.B.1. For a reply to a non-final Office action, see 37 CFR 1.111(a). For a reply to final Office action, see 37 CFR 1.113(c). A request for reconsideration while not provided for in 37 CFR 1.113(c) may be filed after final for consideration. See MPEP §§ 706.07(e) and 714.13.

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The actual filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/apply/applying-online/eterminal-disclaimer.

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4. Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 10,957,041 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because the '041 patent claims a method for predicting biomarkers (including PD-L1) from digital images of stained tissue slides using a deep learning framework to classify tissue. The instant claims recite a specific implementation of this process, segmenting IHC-stained images into tiles to classify individual cells as PD-L1 positive/negative. This is a routine and obvious application of the predictive biomarker analysis already patented by the same inventive entity.

5. Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 11,610,307 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because the '307 patent claims a computing device configured to identify biomarkers from tiled digital images of stained slides. The instant claims recite the same function steps (tiling, cell/tissue identification, and biomarker metric generation) in the form of a computer-implemented method and CRM. The specific focus on PD-L1 classification does not provide a patentable distinction over the claims previously granted to applicants.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

Whoever 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, subject to the conditions and requirements of this title.

7. Claims 1-20 are rejected under 35 U.S.C. § 101 because the claimed invention is directed

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to an abstract idea without significantly more. The claims recite a method/system/CRM for segmenting a digital image into tiles, identifying cell types within tiles, classifying cells as PD-L 1-positive or PD-L 1-negative, and generating a digital overlay with metrics. Under the broadest reasonable interpretation, these steps encompass mental processes (observations, evaluations, and judgments that a pathologist conventionally performs when reviewing IHC-stained slides for PD-L 1 status) and mathematical concepts (calculating ratios/scores). The additional elements of generic processors and conventional data input/output do not integrate the abstract idea into a practical application and do not amount to significantly more.

INDEPENDENT CLAIMS 1, 19, AND 20 ANALYSIS:

STEP 1: Statutory Category

- Claim 1: Process
- Claim 19: Machine (system with processor+ memory)
- Claim 20: Manufacture (non-transitory CRM)

All claims fall within statutory categories. (Step 1: YES)

STEP 2A, PRONG 1: Judicial Exception?

The claims recite four core steps:

1. Segmenting the digital image into tiles
2. Identifying at least one type of cell within each tile
3. Classifying each cell as PD-L1-positive or PD-L1-negative
4. Generating a digital overlay indicating at least one metric associated with the classifying

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Analysis of each limitation:

Segmenting the digital image into tiles: Under BRI, dividing an image into sub-regions is a process that could be practically performed in the human mind (a pathologist mentally or physically divides a slide into regions for review) or is a mathematical operation (partitioning image data into grids). This falls within the mental process grouping. Identifying at least one type of cell within each tile: Identifying cell types in tissue samples is a core mental task of pathologists - observation, evaluation, and judgment. This is a mental process.

Classifying each cell as PD-L 1-positive or PD-L 1-negative: Pathologists routinely perform this classification visually when reviewing IHC-stained slides - they observe staining intensity/pattern and make a positive/negative determination. This is a mental process. To the extent a trained ML model performs mathematical calculations, the claim does not recite any specific model, algorithm, or mathematical formula - the claim is broad enough to encompass mental evaluation.

Generating a digital overlay indicating at least one metric: Generating an overlay showing a metric (e.g., TPS percentage) encompasses producing a visual summary of classification results. The "metric" could be as simple as a ratio (claim 4 confirms: number positive/ total classified= mathematical calculation). The overlay generation at this high level of generality is a form of data presentation/output.

The claims recite mental processes (observations, evaluations, judgments a pathologist performs) and, to the extent metrics like ratios are computed, mathematical concepts. These are considered together as a single abstract idea.

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(Step 2A, Prong One: **YES**- the claims recite abstract ideas in the mental process and mathematical concept groupings.)

STEP 2A, PRONG 2: Practical Application?

Additional elements beyond the judicial exception:

- "via one or more processors" (claims 1, 19, 20) – generic computer implementation
- "digital image of a slide containing a tissue from a subject, the slide stained by immunohistochemistry (IHC)" – field of use limitation (specifies the type of input data)
- "generating the digital overlay of the digital image" – to the extent this is an additional element, it amounts to outputting results/data presentation

Evaluation under MPEP considerations:

MPEP 2106.05(a)- Improvement to technology: The specification describes improvements in speed and objectivity of PD-L 1 scoring compared to manual pathologist review. However, the claims do not recite any particular technical details of *how* the improvement is achieved- no specific neural network architecture, no specific training methodology, no specific algorithmic technique.

The claims are written at a high level of generality that encompasses any method of segmenting, identifying, classifying, and overlaying. The claims do not reflect the specific improvements discussed in the specification (multiscale deep learning, specific CNN/FCN architectures, specific training techniques).

MPEP 2106.05(b) Particular machine: "One or more processors" is generic. No particular machine.

MPEP 2106.05(c) Transformation: No transformation of a particular article to a different state.

MPEP 2106.05(f) Mere instructions to apply: The recitation of "via one or more processors" amounts to mere instructions to apply the abstract idea on a generic computer. The claims only specify the desired outcome, they do not describe how the processor performs the segmenting, identifying, or classifying.

MPEP 2106.05(g) Insignificant extra-solution activity: Receiving a digital image is pre-solution data gathering. Generating/displaying the overlay is post-solution data output.

MPEP 2106.05(h) Field of use: The limitation to IHC-stained slides, PD-L 1, and tissue from a subject limits the field of use but does not integrate the abstract idea into a practical application.

Key comparison to Example 47 (July 2024 guidance): Like Claim 2 of Example 47 (ineligible), these claims recite detecting/analyzing/classifying using a trained model at a high level without specifying how the detection or classification is accomplished, and without reciting remedial or technical actions that reflect an improvement. Unlike Claim 3 of Example 47 (eligible - which included specific remedial network security actions), these claims stop at generating an overlay showing metrics.

Step 2A, Prong Two: NO, the additional elements do not integrate the judicial exception into a practical application. The claims are directed to the abstract idea.

STEP 2B: Inventive Concept?

Carrying over the additional elements from Prong Two:

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- "Via one or more processors" are mere instructions to apply on generic computer, cannot provide inventive concept. See MPEP 2106.05(f).
- Receiving/processing a digital image of an IHC-stained slide is well-understood, routine, and conventional. The specification acknowledges that IHC staining and digital slide scanning are established techniques (¶¶ [0008]-[0010]).
- Generating a digital overlay. Outputting results in visual form is WURC in the field of computational pathology. Berkheimer evidence: specification, ¶[0011] acknowledges that "some FCNs generate an overlay map to show the location of each classified object in the original image."
- Classifying cells as PD-L 1-positive/negative from IHC slides. The specification acknowledges this is conventionally performed by pathologists.

Even in combination, these additional elements represent applying the abstract idea on a generic computer with conventional data input/output. No inventive concept.

(Step 2B: NO)

DEPENDENT CLAIMS 2-18 ANALYSIS:

Claim	Step 2A, Prong 1	Step 2A, Prong 2	Step 2B	Eligible?
2	YES	NO	NO	Ineligible (adds identifying by tissue/cell class – mental process)
3	YES	NO	NO	Ineligible (adds ratio metric – mathematical calculation)
4	YES	NO	NO	Ineligible (recites ratio calculation – math concept)

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5	YES	NO	NO	Ineligible (adds TPS – conventionally calculated score)
6	YES	NO	NO	Ineligible (TPS as percentage – math)
7	YES	NO	NO	Ineligible (user-defined area – field of use)
8	YES	NO	NO	Ineligible (heat map – data output format)
9	YES	NO	NO	Ineligible (displaying overlay – insignificant extra-solution activity/ WURC)
10	YES	NO	NO	Ineligible (probability map – data visualization)
11	YES	NO	NO	Ineligible (showing classified content per tile – data output)
12	YES	NO	NO	Ineligible (transparency – display formatting)
13	YES	NO	NO	Ineligible (communicating to computing device – WURC data transmission)

14	YES	NO	NO	Ineligible (detecting tumor region then segmenting – mental process)
15	YES	NO	NO	Ineligible (overlay identifies tissue types – data output)
16	YES	NO	NO	Ineligible (overlay identifies cell types – data output)
17	YES	NO	NO	Ineligible, Potentially eligible – adds analyzing "a set of changes in color or brightness between pixels" this is a specific technical implementation tied to pixel-level image analysis that may not be practically performed in the human mind. However, the claim still recites this at a high level. The claim does not specify how the analysis is performed, leaving it broad enough to encompass trivial visual inspection on a digital display.
18	YES	NO	NO	Ineligible (detecting whether cell is colored by IHC stain targeting PD-L1)

				– a pathologist visually does exactly this)
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8. Claims 1-20 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to an abstract idea without significantly more. The claims recite a method/system/CRM for segmenting a digital image into tiles, identifying cell types within tiles, classifying cells as PD-L 1-positive or PD-L 1-negative, and generating a digital overlay with metrics. Under the broadest reasonable interpretation, these steps encompass mental processes (observations, evaluations, and judgments that a pathologist conventionally performs when reviewing IHC-stained slides for PD-L 1 status) and mathematical concepts (calculating ratios/scores). The additional elements of generic processors and conventional data input/output do not integrate the abstract idea into a practical application and do not amount to significantly more.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

10. The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

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2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

12. Claims 1-4, 7, 9, 11, and 13-20 is/are rejected under 35 U.S.C. 103 as being unpatentable over Chukka et al. (US 2016/0042511 A1 – hereinafter “Chukka”) in view of Steele (Measuring multiple parameters of CD8+ tumor-infiltrating lymphocytes in human cancers by image analysis – hereinafter “Steele”).

Claim 1.

Chukka discloses a computer-implemented method for generating a digital overlay of a digital image of a slide containing a tissue from a subject, the slide stained by immunohistochemistry (IHC) (Chukka ¶4: “imaging systems for automatically interpreting and scoring tissue specimen slides, for example, specimens stained with an immunohistochemical (IHC) assay”; IPR2026-00185, EX2, pp. 14-15 & EX1002, p. 31, ¶¶54-55), the computer-implemented method (Chukka ¶7 teaches that the facility may comprise a “computer-readable storage

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medium that can store data ... executed by a computing system,” IPR2026-00185, EX2, p. 48, [0007], see also [0029], [0030], [0031]; EX1002, p. 153, ¶165) comprising:

segmenting, via one or more processors, the digital image into a plurality of tiles (Chukka discloses element [1.B]. EX1002, ¶¶68-71. Chukka discloses “component 112 can use a grid pattern to tile the portion of the slide corresponding to the tissue data” or the “whole slide tissue data,” including using pixel or length dimensions for each tile [0044]; see also id., (“tile-based processing”), [0010], [0039], Fig. 3 (“tile slide” 330); IPR2026-00185, EX2, p. 17-19); for each tile of the plurality of tiles, identifying, via the one or more processors, at least one type of cell within that tile (Chukka’s disclosed system may also “count cells, compute various types of local and global features of these cells, identify the cell types, and perform quantitative analysis” ¶4. IPR2026-00185, EX1002, pp. 26-27, ¶45; “[0044]-[0045] detect stromal regions, cell density, lymphocyte clusters, positively-stained cells, and negatively-stained cells”). IPR2026-00185, EX2, p. 14-15);

for at least a set of cells of the identified at least one type of cell, classifying, via the one or more processors, each cell of the set of cells as PD-L1-positive or PD-L1-negative (Chukka ¶35: “The system invokes the construct classifier component 111 to construct an object classifier model that is used to classify detected objects as, for example, positively-stained nuclear objects, negatively-stained nuclear objects, stromata, or lymphocytes.” IPR2026-00185, EX1002, pp. 35, ¶59); and

generating, via the one or more processors, the digital overlay of the digital image (Chukka ¶4 discloses using this system to analyze the image, or regions of the image, and producing “an overlay image...to label features of interest” in the image. IPR2026-00185, EX1002, p. 32,

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¶¶55, 59, 114-118; Chukka [0010], [0040], [0044], Fig. 3.; IPR2026-00185, EX2, pp. 16, 23, 27), wherein the digital overlay indicates at least one metric (Chukka ¶46 discloses “In block 360, the component generates and stores or displays a score for the slide or one or more regions within the slide by, for example, generating a positivity value (e.g., the ratio of positively-stained nuclear objects to the overall number of positively- and negatively-stained nuclear objects), calculating an H-score, or calculating another metric.”; IPR2026-00185, EX1002, p. 54; Chukka ¶4 discloses using this system to analyze the image, or regions of the image, and producing “an overlay image...to label features of interest” in the image. IPR2026-00185, EX1002, p. 32, ¶¶55, 59, 114-118; Chukka [0010], [0040], [0044], Fig. 3.; IPR2026-00185, EX2, pp. 16, 23, 27) associated with the classifying as ~~PD-L1-positive or PD-L1-negative~~.

Chukka discloses all of the subject matter as described above except for specifically teaching “PD-L1-positive or PD-L1-negative.” However, Steele in the same field of endeavor teaches *PD-L1-positive or PD-L1-negative* (Steele describes and shows digital markups (overlays) where cells are color-coded “The IA software then characterized each cell (c) as true positive (blue), false positive (red), or false negative (orange)” (Fig. 2) based on the metric associated with classification “We then developed and validated a scoring method to enumerate CD8+ TILS in PD-L1–positive and –negative tumor regions in a separate set of dual-stained clinical specimens” (p. 3, right column; IPR2026-00185, EX1002, pp. 17-19, ¶¶30-32).

Therefore, it would have been obvious to one of ordinary skill in the art to combine Chukka and Steele before the effective filing date of the claimed invention. Steele teaches the clinical importance of PD-L1; however, manual pathology scoring is known to be slow, subjective, and prone to variability. Chukka provides an automated image analysis system

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designed to interpret and score tissue specimen slides to “augment the user's own assessment” to make more “reliable and reproducible systems.” The motivation for this combination of references would have been to apply the automated scoring, tiling, and overlay features of Chukka to the specific PD-L1 protocols of Steele to increase the speed, accuracy, and reproducibility of the PD-L1 scoring process.

Claim 2.

The combination of Chukka and Steele teaches the computer-implemented method of claim 1, wherein identifying the at least one type of cell comprises: for each tile of the plurality of tiles, identifying, by tissue class or by cell class, the at least one type of cell within that tile **(Chukka identifies "stroma" (tissue class) and "lymphocytes" (cell class) [¶¶6-7].)**

Claim 3.

The combination of Chukka and Steele teaches the computer-implemented method of claim 1, wherein the at least one metric associated with the classifying comprises a ratio based on a number of cells that were classified as PD-L1-positive **(Chukka ¶46 discloses “In block 360, the component generates and stores or displays a score for the slide or one or more regions within the slide by, for example, generating a positivity value (e.g., the ratio of positively-stained nuclear objects to the overall number of positively- and negatively-stained nuclear objects), calculating an H-score, or calculating another metric.” Steele teaches “PD-L1–positive and –negative” (p. 3, right column). A POSITA would be motivated to apply Chukka’s automated ratio-calculating method to the PD-L1 staining described by Steele to improve the speed and reproducibility of this standard clinical assessment.)**

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Claim 4.

The combination of Chukka and Steele teaches the computer-implemented method of claim 3, further comprising: calculating the ratio as a number of cells classified as PD-L1-positive divided by a total number of cells classified as PD-L1-positive or PD-L1-negative (**Chukka ¶46 discloses “In block 360, the component generates and stores or displays a score for the slide or one or more regions within the slide by, for example, generating a positivity value (e.g., the ratio of positively-stained nuclear objects to the overall number of positively- and negatively-stained nuclear objects), calculating an H-score, or calculating another metric.” Steele teaches “PD-L1–positive and –negative” (p. 3, right column). A POSITA would be motivated to apply Chukka’s automated ratio-calculating method to the PD-L1 staining described by Steele to improve the speed and reproducibility of this standard clinical assessment.)**

Claim 7.

The combination of Chukka and Steele teaches the computer-implemented method of claim 1, wherein the at least one metric is associated with an area defined by a user (**Chukka analyzes regions of interest which can be identified by a user (¶¶ 7, 10, 46).**

Claim 9.

The combination of Chukka and Steele teaches the computer-implemented method of claim 1, further comprising: displaying the digital overlay over the digital image (**Chukka “The computer system 110 displays the images to a user.” (¶ [0027]); “overlay image is produced to label features” (¶ [0004]).**

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Claim 11.

The combination of Chukka and Steele teaches the computer-implemented method of claim 9, wherein displaying the digital overlay over the digital image comprises: displaying, in the digital overlay, a set of tiles over the region of the digital image that depicts a tumor sample tissue **(Chukka discloses “component 112 can use a grid pattern to tile the portion of the slide corresponding to the tissue data” or the “whole slide tissue data,” including using pixel or length dimensions for each tile [0044]; “[0044]-[0045] detect stromal regions, cell density, lymphocyte clusters, positively-stained cells, and negatively-stained cells”).** IPR2026-00185, EX2, p. 14-15); and for each tile of the set of tiles, visually showing classified content of that tile **(Chukka ¶4 discloses using this system to analyze the image, or regions of the image, and producing “an overlay image...to label features of interest” in the image. IPR2026-00185, EX1002, p. 32, ¶¶55, 59, 114-118; Chukka [0010], [0040], [0044], Fig. 3.; IPR2026-00185, EX2, pp. 16, 23, 27).**

Claim 13.

The combination of Chukka and Steele teaches the computer-implemented method of claim 9, wherein displaying the digital overlay over the digital image comprises: communicating, via the one or more processors to a computing device, the digital overlay, wherein a digital display of the computing device displays the digital overlay over the digital image **(Chukka “The computer system 110 displays the images to a user.” (¶ [0027]); “overlay image is produced to label features” (¶ [0004])).**

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Claim 14.

The combination of Chukka and Steele teaches the computer-implemented method of claim 1, wherein segmenting the digital image into the plurality of tiles comprises: detecting, via the one or more processors, a region of the digital image that depicts a tumor sample tissue; and segmenting, via the one or more processors, the region into the plurality of tiles (**Chukka discloses “component 112 can use a grid pattern to tile the portion of the slide corresponding to the tissue data” or the “whole slide tissue data,” including using pixel or length dimensions for each tile [0044]. Chukka teaches the first step of detecting/identifying that specific region (tissue/tumor) before or while segmenting it into tiles rather than tiling the empty glass background. Chukka ¶¶3-4 discloses “manual counting of tumor cells by identifying positively-stained tumor cells ... the system counts positively-stained nuclear objects ... an overlay image is produced to label features of interest in the image of a specimen from a subject.”**).

Claim 15.

The combination of Chukka and Steele teaches the computer-implemented method of claim 1, wherein the digital overlay identifies a plurality of tissue types and indicates, at a set of locations in the digital image within the digital overlay, where each tissue type of the plurality of tissue types is located (**Chukka identifies “stroma” (tissue class) [¶¶6-7]. Chukka “[0044]-[0045] detect stromal regions, cell density, lymphocyte clusters, positively-stained cells, and negatively-stained cells”**. IPR2026-00185, EX2, p. 14-15; Chukka “The computer system 110 displays the images to a user.” (¶ [0027]); “overlay image is produced to label features” (¶

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[0004]). Chukka ¶¶3-4 discloses “manual counting of tumor cells by identifying positively-stained tumor cells ... the system counts positively-stained nuclear objects” By identifying both stroma and tumors, Chukka identifies a plurality of tissue types.).

Claim 16.

The combination of Chukka and Steele teaches the computer-implemented method of claim 1, wherein the digital overlay identifies a plurality of cell types and indicates, at a set of locations in the digital image within the digital overlay, where each cell type of the plurality of cell types is located (Chukka “overlay image is produced to label features of interest” (¶ [0004]).

Chukka ¶35: “The system invokes the construct classifier component 111 to construct an object classifier model that is used to classify detected objects as, for example, positively-stained nuclear objects, negatively-stained nuclear objects, stromata, or lymphocytes.”

The overlay indicates where each cell type “features of interest” are located.).

Claim 17.

The combination of Chukka and Steele teaches the computer-implemented method of claim 1, wherein classifying each cell of the set of cells as PD-L1-positive or PD-L1-negative comprises: for at least the set of cells of the identified at least one type of cell, analyzing, via the one or more processors, a set of changes in color or brightness between pixels within each cell of the set of cells to classify that cell as PD-L1-positive or PD-L1-negative (Chukka ¶3: “percentage of positively-stained (e.g., brown-colored) nuclear objects to the total number of positively-stained and negatively-stained (e.g., blue-colored)”; ¶41: “performing a

thresholding technique ... to identify those portions of the digitized slide data having an intensity value that exceeds a predetermined threshold in the dominant color space ... if the dominant colors are blue and brown, the component can identify those portions having intensity values in the blue or brown color space that exceed a threshold.” Steele describes and shows digital markups (overlays) where cells are color-coded “We then developed and validated a scoring method to enumerate CD8+ TILS in PD-L1–positive and –negative tumor regions in a separate set of dual-stained clinical specimens” (p. 3, right column & p. 8, Fig. 3; IPR2026-00185, EX1002, pp. 17-19, ¶¶30-32).

Claim 18.

The combination of Chukka and Steele teaches the computer-implemented method of claim 1, wherein classifying each cell of the set of cells as PD-L1-positive or PD-L1-negative comprises: for at least the set of cells of the identified at least one type of cell, detecting, via the one or more processors, whether within each cell of the set of cells is colored by IHC stain targeting PD-L1 protein to classify that cell as PD-L1-positive or PD-L1-negative (**Chukka ¶3: “percentage of positively-stained (e.g., brown-colored) nuclear objects to the total number of positively-stained and negatively-stained (e.g., blue-colored)”**; ¶41: **“performing a thresholding technique ... to identify those portions of the digitized slide data having an intensity value that exceeds a predetermined threshold in the dominant color space ... if the dominant colors are blue and brown, the component can identify those portions having intensity values in the blue or brown color space that exceed a threshold.” Steele describes and shows digital markups (overlays) where cells are color-coded “We then developed and validated a scoring method to enumerate CD8+ TILS in PD-L1–positive and –negative tumor**

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regions in a separate set of dual-stained clinical specimens” (p. 3, right column & p. 8; IPR2026-00185, EX1002, pp. 17-19, ¶¶30-32; Steele’s Fig. 3 show dual-stained images (specifically panel D), cells expressing PD-L1 are colored by the IHC stain targeting PD-L1 protien (appearing brown). Cells that are PD-L1 negative appear blue (hematoxylin counterstain) or red (if they are CD8 postive). It would be obvious to use Chukka’s image analysis to distinguish the dual stained images of Steele – brown PD-L1 positive signal from the blue/red negative background.).

Claim 19.

The combination of Chukka and Steele teaches a system for generating a digital overlay of a digital image of a slide containing a tissue from a subject, the slide stained by immunohistochemistry (IHC) (Chukka ¶4: “imaging systems for automatically interpreting and scoring tissue specimen slides, for example, specimens stained with an immunohistochemical (IHC) assay”; IPR2026-00185, EX2, pp. 14-15 & EX1002, p. 31, ¶¶54-55), comprising: a memory storing computer-executable instructions (Chukka ¶7 teaches that the facility may comprise a “computer-readable storage medium that can store data ... executed by a computing system,” IPR2026-00185, EX2, p. 48, [0007], see also [0029], [0030], [0031]; EX1002, p. 153, ¶165); and at least one processor interfaced with the memory and configured to execute the computer-executable instructions to cause the at least one processor to (Chukka ¶7 teaches that the process may be “... executed by a computing system.”) ...

The combination of Chukka and Steele discloses the remaining elements recited in claim 19 for at least the reasons discussed in claim 1 above. The rationale provided for the rejection

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of claim(s) 1 is applicable to claim 19, *mutatis mutandis*. Accordingly, claim 19 is rendered obvious by the combination of Chukka and Steele.

Claim 20.

The combination of Chukka and Steele teaches a non-transitory computer-readable medium storing instructions for generating a digital overlay of a digital image of a slide containing a tissue from a subject, the slide stained by immunohistochemistry (IHC) (**Chukka ¶14**), wherein the instructions (**Chukka ¶17 teaches that the facility may comprise a “computer-readable storage medium that can store data.”**), when executed by one or more processors, cause the one or more processors to (**Chukka ¶17 teaches that the process may be “... executed by a computing system.”**) ...

The combination of Chukka and Steele discloses the remaining elements recited in claim 20 for at least the reasons discussed in claim 1 above. The rationale provided for the rejection of claim(s) 1 is applicable to claim 20, *mutatis mutandis*. Accordingly, claim 20 is rendered obvious by the combination of Chukka and Steele.

13. Claims 5-6 are rejected under 35 U.S.C. 103 as being unpatentable over Chukka in view of Steele as applied to claim 1 above, and further in view of Reck et al. (Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small–Cell Lung Cancer – hereinafter “Reck”).

Claim 5.

The combination of Chukka and Steele teaches the computer-implemented method of claim 1, wherein the at least one metric associated with the classifying (**Chukka ¶146**) comprises a tumor

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positive score (Chukka ¶146 discloses “In block 360, the component generates and stores or displays a score for the slide or one or more regions within the slide by, for example, generating a positivity value (e.g., the ratio of positively-stained nuclear objects to the overall number of positively- and negatively-stained nuclear objects) ~~(TPS)~~ based on the classifying (Chukka ¶135).

Chukka discloses all of the subject matter as described above except for specifically teaching “TPS.” However, Reck in the same field of endeavor teaches *TPS* (p. 1842, ¶1: “Approximately 23 to 28% of patients with advanced non-small-cell lung cancer (NSCLC) have a high level of programmed death ligand 1 (PD-L1) expression, which is defined as membranous PD-L1 expression on at least 50% of tumor cells, regardless of the staining intensity (i.e., a PD-L1 tumor proportion score of 50% or greater”).

Therefore, it would have been obvious to one of ordinary skill in the art to combine Chukka and Reck before the effective filing date of the claimed invention. Chukka provides the capability to count positive and negative cells. Reck describes the KEYNOTE-024 clinical trial, which established the standard of care for non-small-cell lung cancer. Reck provides the clinical motivation to configure Chukka’s automated counting mechanism, specifically to count the PD-L1 positive and negative cells defined by Steele, to output a “tumor proportion score” (TPS), as Reck establishes that this specific metric is required by oncologists to determine if a lung cancer patient is eligible for pembrolizumab therapy.

The instant application uses the term “tumor positive score,” while the art (Reck) uses “tumor proportion score.” In the art, the term “tumor proportion score” is the standard nomenclature because it describes the mathematical nature of the score: it is the *proportion* of

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tumor cells that are positive. The claim term “tumor positive score” is simply a descriptive synonym for the same metric.

Claim 6.

The combination of Chukka, Steele, and Reck teaches the computer-implemented method of claim 5, wherein the tumor positive score (TPS) is expressed as a percentage (**Chukka ¶13 “percentage of positively-stained (e.g., brown-colored) nuclear objects to the total number of positively-stained and negatively-stained (e.g., blue-colored)”**; ¶120).

14. Claim 8, 10, and 12 are rejected under 35 U.S.C. 103 as being unpatentable over Chukka in view of Steele as applied to claim 1 above, and further in view of Saltz et al. (US 2020/0388029 A1 – hereinafter “Saltz”).

Claim 8.

The combination of Chukka and Steele teaches the computer-implemented method of claim 1, wherein generating the digital overlay of the digital image comprises: generating, via the one or more processors, the digital overlay of the digital image as a ~~heat map~~ (**Chukka generates “maps” of intensity (¶125) as an overlay (¶14).**)

Chukka and Steele discloses all of the subject matter as described above except for specifically teaching a “heat map.” However, Saltz in the same field of endeavor teaches a *heat map* (**¶108 and Fig. 7B: “The patch-level predictions for an image are combined and represented to pathologists as a heatmap (for example, as shown in FIG. 7B further described hereinbelow) for review and visual editing for example”**; ¶223: “heatmap overlay on a WSI.”).

Therefore, it would have been obvious to one of ordinary skill in the art to combine Chukka, Steele, and Saltz before the effective filing date of the claimed invention. The motivation for this combination of references would have been to modify the display output of Chukka to overlay the classifications as a color-coded heat map (as taught by Saltz) to allow for faster, more accurate clinical review of the slide.

Claim 10.

The combination of Chukka, Steele, and Saltz teaches the computer-implemented method of claim 9, wherein displaying the digital overlay over the digital image comprises: displaying the digital overlay (**Chukka generates "maps" of intensity (¶25) as an overlay (¶4)**) as a probability map for a cell classification, based on the classifying, over the digital image (**Saltz ¶108 and Fig. 7B: "The patch-level predictions for an image are combined and represented to pathologists as a heatmap (for example, as shown in FIG. 7B further described hereinbelow) for review and visual editing for example"; ¶223: "heatmap overlay on a WSI." A POSITA would understand that the "heatmap" taught by Saltz (which represents combined predictions/classifications) functions as a probability map showing the likelihood or density of the classification (PD-L1) positive cells over the image.**)

Claim 12.

The combination of Chukka, Steele, and Saltz teaches the computer-implemented method of claim 9, wherein displaying the digital overlay over the digital image comprises: displaying the digital overlay over the digital image at a degree of transparency (**Chukka ¶4 discloses using this system to analyze the image, or regions of the image, and producing "an overlay**

image...to label features of interest” in the image. Saltz teaches “heatmap overlay on a WSI ... The TIL-MAP visualization tool displays the TIL-Maps, as polygonal overlays that appear over the H&E image” in ¶223. It is well known and standard in the art of digital image analysis that overlays and heat maps on medical images are displayed with a degree of transparency to allow the user to view the underlying tissue morphology simultaneously with the data.)

Conclusion

15. The prior art made of record but not relied, yet considered pertinent to the applicant’s disclosure, is listed on the PTO-892 form.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ross Varndell whose telephone number is (571)270-1922. The examiner can normally be reached M-F, 9-5 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, O’Neal Mistry can be reached at (313)446-4912. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

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applications is available through Private PAIR only. For more information about the PAIR system, see <https://ppair-my.uspto.gov/pair/PrivatePair>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ross Varndell/
Primary Examiner, Art Unit 2674

WHAT IS CLAIMED:

1. A computer-implemented method for generating a digital overlay of a digital image of a slide containing a tissue from a subject, the slide stained by immunohistochemistry (IHC), the computer-implemented method comprising:
 - segmenting, via one or more processors, the digital image into a plurality of tiles;
 - for each tile of the plurality of tiles, identifying, via the one or more processors, at least one type of cell within that tile;
 - for at least a set of cells of the identified at least one type of cell, classifying, via the one or more processors, each cell of the set of cells as PD-L1-positive or PD-L1-negative; and
 - generating, via the one or more processors, the digital overlay of the digital image, wherein the digital overlay indicates at least one metric associated with the classifying as PD-L1-positive or PD-L1-negative.
2. The computer-implemented method of claim 1, wherein identifying the at least one type of cell comprises:
 - for each tile of the plurality of tiles, identifying, by tissue class or by cell class, the at least one type of cell within that tile.
3. The computer-implemented method of claim 1, wherein the at least one metric associated with the classifying comprises a ratio based on a number of cells that were classified as PD-L1-positive.
4. The computer-implemented method of claim 3, further comprising:
 - calculating the ratio as a number of cells classified as PD-L1-positive divided by a total number of cells classified as PD-L1-positive or PD-L1-negative.
5. The computer-implemented method of claim 1, wherein the at least one metric associated with the classifying comprises a tumor positive score (TPS) based on the classifying.
6. The computer-implemented method of claim 5, wherein the tumor positive score (TPS) is expressed as a percentage.

7. The computer-implemented method of claim 1, wherein the at least one metric is associated with an area defined by a user.
8. The computer-implemented method of claim 1, wherein generating the digital overlay of the digital image comprises:
 - generating, via the one or more processors, the digital overlay of the digital image as a heat map.
9. The computer-implemented method of claim 1, further comprising:
 - displaying the digital overlay over the digital image.
10. The computer-implemented method of claim 9, wherein displaying the digital overlay over the digital image comprises:
 - displaying the digital overlay as a probability map for a cell classification, based on the classifying, over the digital image.
11. The computer-implemented method of claim 9, wherein displaying the digital overlay over the digital image comprises:
 - displaying, in the digital overlay, a set of tiles over the region of the digital image that depicts a tumor sample tissue; and
 - for each tile of the set of tiles, visually showing classified content of that tile.
12. The computer-implemented method of claim 9, wherein displaying the digital overlay over the digital image comprises:
 - displaying the digital overlay over the digital image at a degree of transparency.
13. The computer-implemented method of claim 9, wherein displaying the digital overlay over the digital image comprises:
 - communicating, via the one or more processors to a computing device, the digital overlay, wherein a digital display of the computing device displays the digital overlay over the digital image.
14. The computer-implemented method of claim 1, wherein segmenting the digital image into the plurality of tiles comprises:
 - detecting, via the one or more processors, a region of the digital image that depicts a tumor sample tissue; and
 - segmenting, via the one or more processors, the region into the plurality of tiles.

15. The computer-implemented method of claim 1, wherein the digital overlay identifies a plurality of tissue types and indicates, at a set of locations in the digital image within the digital overlay, where each tissue type of the plurality of tissue types is located.

16. The computer-implemented method of claim 1, wherein the digital overlay identifies a plurality of cell types and indicates, at a set of locations in the digital image within the digital overlay, where each cell type of the plurality of cell types is located.

17. The computer-implemented method of claim 1, wherein classifying each cell of the set of cells as PD-L1-positive or PD-L1-negative comprises:

for at least the set of cells of the identified at least one type of cell, analyzing, via the one or more processors, a set of changes in color or brightness between pixels within each cell of the set of cells to classify that cell as PD-L1-positive or PD-L1-negative.

18. The computer-implemented method of claim 1, wherein classifying each cell of the set of cells as PD-L1-positive or PD-L1-negative comprises:

for at least the set of cells of the identified at least one type of cell, detecting, via the one or more processors, whether within each cell of the set of cells is colored by IHC stain targeting PD-L1 protein to classify that cell as PD-L1-positive or PD-L1-negative.

19. A system for generating a digital overlay of a digital image of a slide containing a tissue from a subject, the slide stained by immunohistochemistry (IHC), comprising:

a memory storing computer-executable instructions; and

at least one processor interfaced with the memory and configured to execute the computer-executable instructions to cause the at least one processor to:

segment the digital image into a plurality of tiles,

for each tile of the plurality of tiles, identify at least one type of cell within that tile,

for at least a set of cells of the identified at least one type of cell, classify each cell of the set of cells as PD-L1-positive or PD-L1-negative, and

generate the digital overlay of the digital image, wherein the digital overlay indicates at least one metric associated with the classifying as PD-L1-positive or PD-L1-negative.

20. A non-transitory computer-readable medium storing instructions for generating a digital overlay of a digital image of a slide containing a tissue from a subject, the slide

stained by immunohistochemistry (IHC), wherein the instructions, when executed by one or more processors, cause the one or more processors to:

segment the digital image into a plurality of tiles;

for each tile of the plurality of tiles, identify at least one type of cell within that tile;

for at least a set of cells of the identified at least one type of cell, classify each cell of the set of cells as PD-L1-positive or PD-L1-negative; and

generate the digital overlay of the digital image, wherein the digital overlay indicates at least one metric associated with the classifying as PD-L1-positive or PD-L1-negative.