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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GUARDANT HEALTH, INC.,
Petitioner,

v.

TEMPUS AI, INC.
Patent Owner.

Case No. IPR2026-00185
Patent No. 10,991,097

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 10,991,097

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LISTING OF CHALLENGED CLAIMS
1. [**PREAMBLE**] A method for creating an overlay map on a digital image of a slide, the method comprising: [**1.A**] receiving the digital image; [**1.B**] separating the digital image into a plurality of tiles, each tile of the plurality of tiles containing a respective portion of the digital image of the slide; and [**1.C**] for each tile of the plurality of tiles: identifying features of the tile; [**1.D**] identifying structural tissue features of a second portion of the digital image of the slide including at least part of one or more other tiles of the plurality of tiles, wherein the second portion is larger than the respective portion of the digital image contained in the tile; and [**1.E**] identifying the majority class of tissue visible within the tile based at least in part on the features of the tile and the structural tissue features of the second portion of the digital image of the slide.
2. The method of claim 1, further comprising: generating a digital overlay drawing of an outer edge of each cell in the image.
3. The method of claim 2, wherein the digital overlay drawing is prepared at the resolution level of an individual pixel.

4. The method of claim 1, wherein the majority class of tissue is selected from the group consisting of epithelium, normal epithelium, immune, stroma, necrosis, blood, and fat.
5. The method of claim 1, wherein the structural tissue features comprises at least one of glands, ducts, vessels, and immune clusters.
6. [**PREAMBLE**] A method for tissue classification of a digital image of a slide, the method comprising: [**6.A**] receiving the digital image; [**6.B**] segmenting the digital image into a plurality of tiles, each tile of the plurality of tiles containing a respective portion of the digital image of the slide; [**6.C**] for each tile of the plurality of tiles: identifying features of the tile; [**6.D**] identifying structural tissue features of a second portion of the digital image of the slide including at least part of one or more other tiles of the plurality of tiles, wherein the second portion is larger than the respective portion of the digital image contained in the tile; and [**6.E**] determining a predicted class for each tile based at least in part on the features of the tile and the structural tissue features of the second portion of the digital image of the slide; [**6.F**] identifying a plurality of cell objects in the digital image;

[**6.G**] determining a predicted class for each of the plurality of cell objects; and [**6.H**] for each of the plurality of tiles that corresponds to one of the plurality of cell objects, assigning the tile the predicted class of the corresponding cell object in place of the predicted class of the tile.
7. The method of claim 6, further comprising: storing, in a first file, for each tile, a tile position and the predicted class of the tile; and storing, in a second file, for each cell object, a polygon outlining the cell object and the predicted class of the cell object.
8. The method of claim 6, further comprising: generating a digital overlay drawing for the digital image, where the digital overlay drawing is a cell mask displaying a polygon around each cell object.
9. The method of claim 6, further comprising: generating a digital overlay drawing for the digital image, where the digital overlay drawing is a histology mask displaying the plurality of tiles and the predict class for each tile.
10. The method of claim 6, further comprising: generating a digital overlay drawing for the digital image; and

displaying, in the digital overlay drawing, the plurality of tiles and the predicted class for each tile that does not correspond to a cell object, and displaying, the plurality of cell objects and the predicted class of each cell object.
11. The method of claim 6, further comprising: generating a digital overlay drawing for the digital image, wherein the digital overlay drawing includes the digital image; and displaying the digital overlay drawing.
12. The method of claim 6, further comprising: generating a digital overlay drawing for the digital image, wherein the digital overlay drawing includes a generated version of the digital image; and displaying the digital overlay drawing.
13. The method of claim 6, further comprising: generating a plurality of digital overlay drawings for the digital image, where each digital overlay drawing corresponds to a different predicted class; and selectively displaying one of the plurality of digital overlay drawings.
14. The method of claim 6, further comprising: generating a digital overlay drawing for the digital image, where the digital overlay drawing comprises percentages of predict classes corresponding to the digital image.

15. The method of claim 6, further comprising: generating a digital overlay drawing for the digital image, where the digital overlay drawing comprises total counts of predict classes corresponding to the digital image.
16. The method of claim 6, wherein the cell objects comprise CD3, CD8, CD20, pancytokeratin, and smooth muscle actin.
17. The method of claim 6, wherein the cell objects include lymphocyte cells and not lymphocyte cells.
18. The method of claim 6, wherein the structural tissue features comprises at least one of glands, ducts, vessels, and immune clusters.

Guardant Health, Inc., ("Petitioner" or "Guardant") hereby requests *inter partes* review of United States Patent No. 10,991,097. This petition demonstrates by a preponderance of the evidence that claims 1-18 of the '097 patent are unpatentable under 35 U.S.C. §102 and §103.

I. INTRODUCTION

The '097 patent generically claims the prior art process of identifying different tissues in a whole slide image ("WSI") by viewing both the features of tissue visible within and surrounding a designated region. In essence, the patent receives a digital image, applies a conventional grid to the image to break it down into sectors (called tiles), and identifies the predominant tissue visible within a tile based at least in part on the features of the tile and its broader context (i.e., the structural tissue features of a larger second portion of the digital image of the slide). Such basic histology analysis of a tissue slide was practiced for many decades previously. Both manual and digital microscopes conventionally applied a grid overlay to assist a pathologist in organized viewing of tissue slides, where the pathologist of course viewed a discrete region in context with the surrounding tissue. Doing it on a computer was nothing new. The claims require nothing more than this conventional approach in prior art digital tissue analysis, and fail to distinguish the prior art.

Indeed, as explained in detail below, Chukka (EX1005), which was never considered by the examiner or disclosed during prosecution, anticipates many challenged claims and evinces obviousness of many others. Chukka specifically teaches identifying different tissue types or classifications in a digital image of tissue based at least in part on the features observed in the tile and informed by structural features in a larger second portion of the digital image. The majority of the challenged claims are thus anticipated by or, at a minimum, obvious over Chukka. For the remaining dependent claims, the additionally recited limitations of those claims were well understood and routine, as the prior art expressly confirms.

Accordingly, the petition should be instituted and the challenged claims cancelled.

II. BACKGROUND

Histology relates to the examination of biological tissues and cells and is often informative to diagnose, evaluate, and monitor diseases. EX1008, 2; *see also* EX1002, ¶24; EX1001, 1:38-53. Basic and conventional techniques include sectioning the tissue, staining the tissue, and mounting the tissue on a slide such that the tissue slide may be viewed under a microscope. *See* EX1008, 1, 2. Hematoxylin and eosin (H&E) and immunohistochemical (IHC) staining are methods of staining tissue and have long been used in the diagnosis of malignancies, including cancers. EX1002, ¶24; EX1008, 2, 3; *see also* EX1001, 2:47-52; EX1009, 65. The viewing of a tissue slide commonly used microscopes with reticles representing a grid pattern, to separate the tissue slide into discrete sections or coordinates. *See* EX1002, ¶25; EX1010, Fig. 6 (depicting simulated reticle as it would appear through eyepiece of microscope):

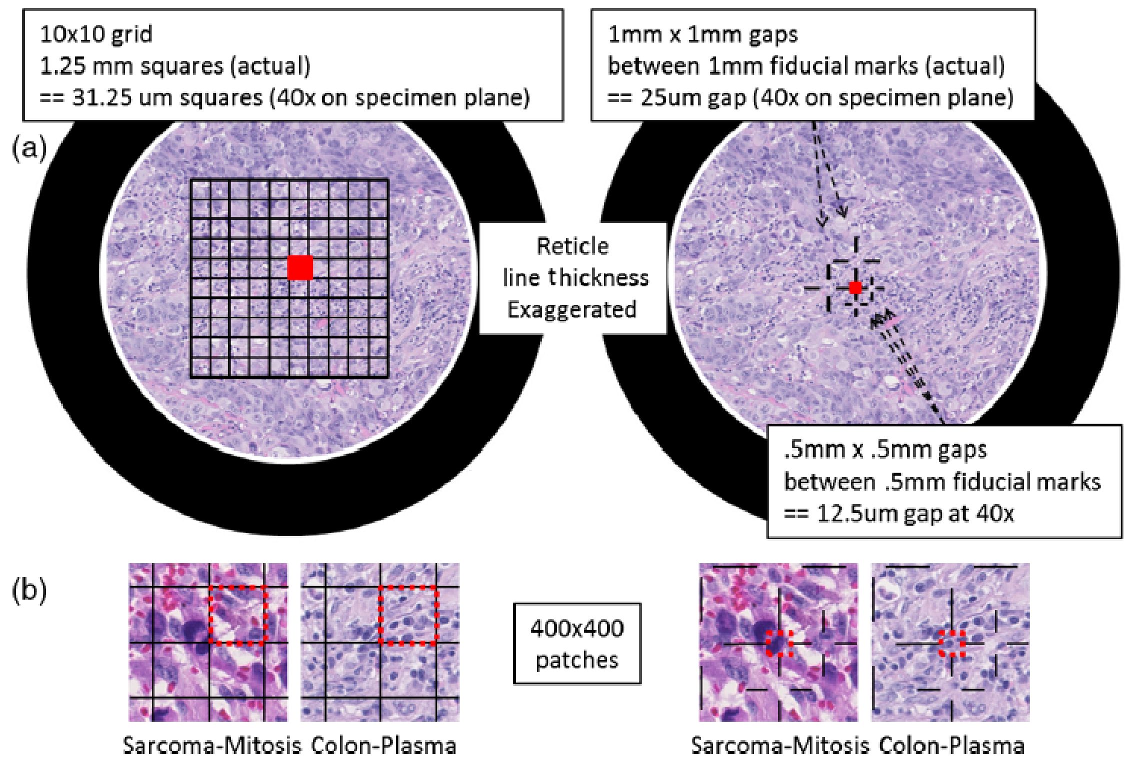


Fig. 6 Reticles (line thicknesses exaggerated) as seen through simulated microscope FOV (a) and 400 × 400 patches as they appear in eeDAP (b). The red squares in the simulated microscope FOVs and the red-dash boundary squares in the 400 × 400 patches indicate the "evaluation" areas. In the 400 × 400 sarcoma patch on the left, a majority of the obvious mitotic figure falls in the grid square to the left of the evaluation square. In the 400 × 400 sarcoma patch on the right, the central cross hairs point to the obvious mitotic figure. In the 400 × 400 colon patch on the left, there are several plasma-cell candidates in the "evaluation" square. In the 400 × 400 colon patch on the right, the cross hairs point to a single plasma-cell candidate to be evaluated.

By the 2010s, analysis of histology slides was routinely digitized and automated. Digital imaging and advances in computer technology enabled computer-implemented tissue classification in stained tissue slides. EX1002, ¶26;

EX1009, 64. Like conventional microscope analysis, digital analysis commonly applied a grid to an image to separate a WSI into discrete image "tiles" for analysis. EX1002, ¶¶26-28; EX1011, 3 (partitioning each histology slide image into multiple non-overlapping image tiles to reduce computational burden); EX1015, Abstract (coarse initial survey of whole slide followed by analysis of tiled regions); EX1005, [0044] ("tile the whole slide tissue data, or a portion thereof"); *see also* EX1015, Fig. 3:

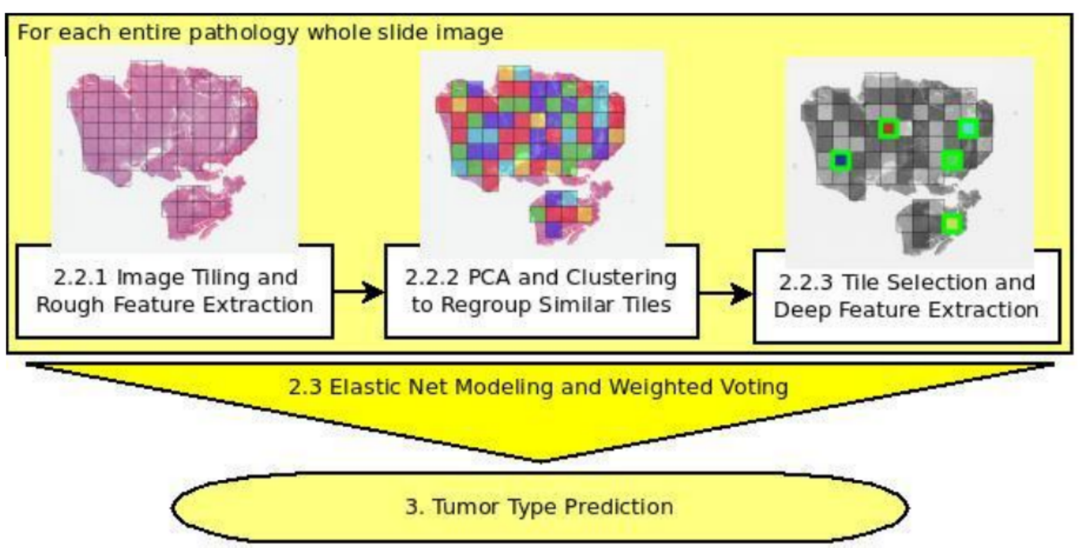


Figure *3*. Pipeline for pathology analysis. Images show a scaled down representative whole-slide image with boxes representing tiles. Unique colors represent clusters.

The detection and identification cells, nuclei, and cell markers was well known to be conventional in histopathology. EX1002, ¶29; EX1016, 2 (automated nucleus detection is fundamental to computer assisted pathology). Automated cell identification (e.g., using segmentation models) was also well-known in the art. EX1002, ¶29; *see also* EX1016, 2; EX1017, 2-3. Additionally, it was common practice to determine and display the boundaries of cells and nuclei as outlines or polygons. *See* EX1017, Fig. 3:

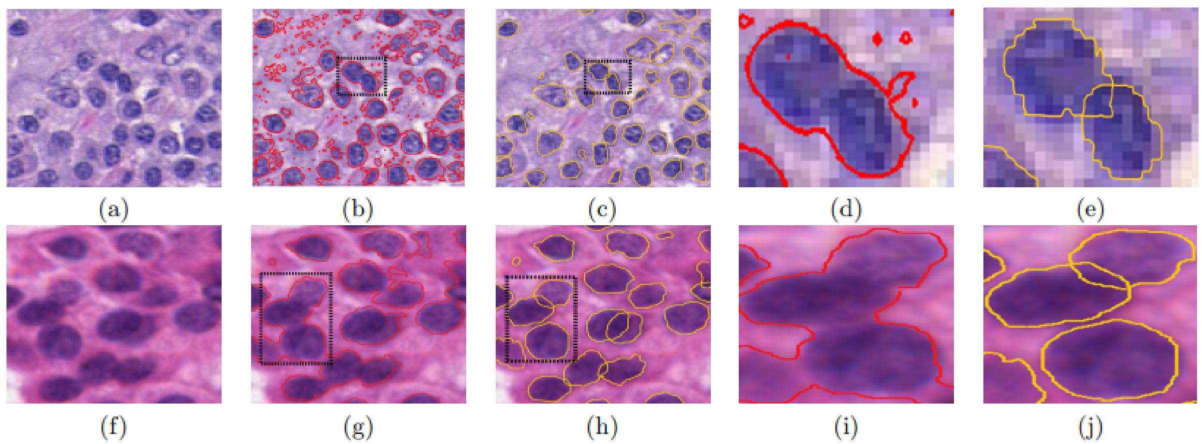


Figure 3. (a), (f) Original histological images corresponding to breast and prostate histology respectively, segmentation results for nuclei and lymphocytes obtained via the (b), (g) Geodesic Active Contour; (c), (h) our integrated AC model; (d), (e) magnified region from (b) and (g); (e), (j) magnified region from (c) and (h).

The prior art literature was filled with teachings to automatically detect, classify, and count cellular objects (including lymphocytes, cell nuclei, and protein biomarkers) on stained tissue slides. EX1002, ¶¶30-32. *See generally* EX1015; EX1018; EX1019; EX1020; EX1023; EX1026.

III. THE ’097 PATENT

The ’097 patent relates to “techniques for analysis of medical images,” especially “images of cancerous tissue.” EX1001, 1:15-17. The ’097 patent acknowledges classification of cancerous tissue was typically determined visually by human analysts.

> Visual inspection can reveal growth patterns of the cancer cells in the tumor in relation to the healthy cells near them and the presence of

> immune cells within the tumor. Pathologists, members of a pathology team, other trained medical professionals, or other human analysts visually analyze thin slices of tumor tissue mounted on glass microscope slides to classify each region of the tissue as one of many tissue classes that are present in a tumor sample.

EX1001, 1:31-39. As the ’097 patent explains, it was routine for pathologists to visually score the slide and “determin[e] characteristics of the cancer tumor in the patient.” EX1001, 1:39-46; *see also id.*, 1:47-50 (listing exemplary tumor characteristics such as “tumor grade, tumor purity, degree of invasiveness of the tumor, degree of immune infiltration into the tumor, cancer stage, and anatomic origin site of the tumor”); *see also* EX1002, ¶33.

The ’097 patent explains that “[m]anually analyzing microscope slides is time consuming” and proposes automating the characterization of tumor tissue with deep learning algorithms. EX1001, 1:56-67. That is, the alleged invention of the ’097 patent is a classic example of taking a human-performed task and doing it on a computer. But skilled artisans already used deep learning to automate analysis of tissue slides as the ’097 patent acknowledges. For example, the ’097 patent explains prior art deep learning algorithms (e.g., convolutional networks) were capable of “analyz[ing] an image and assign[ing] classification labels to each pixel within the image.” EX1001, 2:10-16; *see also* EX1029, 649-651 (describing use of a convolutional network to analyze tissue slide images). The ’097 patent further explains that these same algorithms were capable of "generat[ing] an overlay map to show the location of each classified object in the original image." *Id*.; *see also* EX1029, 651 (showing an overlay map generated with a convolutional network).

In any event, none of the claims require a deep learning algorithm and many claims do not even require computer-aided analysis. For example, independent claim 1 simply requires identification of tissue features by inspection of a digital image—a task which the '097 patent acknowledges human analysts conventionally did. *See* EX1001, 20:48-57 (describing a training set in which "a human analyst has outlined and labeled all relevant tissue classes or labeled each small square tile in each histology slide as non-tissue or as a specific type of cells"). Independent claim 6 requires "classifying" tissues and cells but this too was routine well before the filing date of the '097 patent. EX1002, ¶¶34-41.

A. Prosecution History

The '097 patent was filed as U.S. Application No. 16/732,242 on December 31, 2019, claiming priority to Provisional Application No. 62/787,047 (filed on Dec. 31, 2018). EX1001, cover.

In the only substantive Office action, the Examiner rejected the pending claims as anticipated by, or obvious over, U.S. Patent Appl. Pub. No. 2016/0063724 ("Tunstall," EX1028). EX1004, 670-688 (adding additional references for dependent claim limitations). During an applicant-initiated interview, the discussion focused on “looking outside of a single tile for information about the tiles” (e.g., features “within each tile” and also “in surrounding area” inform tissue classification). EX1004, 821; *see also id.*, 848 (“examining not only features within the tile, but also features outside that tile…typically larger than a tile itself”). Applicant amended the claims accordingly and argued this feature distinguished the asserted art. EX1004, 848-853. The Examiner allowed the claims on the basis that Tunstall fails to disclose “identifying structural features of the second portion of the digital image” larger than the respective portion contained in the tile. EX1004, 860.

As discussed in detail below, Chukka, which was not previously considered by the Office, discloses the alleged missing element and anticipates both independent claims and most dependent claims. Similarly, Gallas describes applying a grid overlay and examining not only features within an evaluation tile but also features in a larger region of neighboring tiles. Additional art including Jones and Sebastiao—neither of which were considered by the Office—render all claims obvious when combined with Chukka or Gallas. Because none of Chukka, Gallas, Jones, and Sebastiao was considered during prosecution, this petition presents new and non-cumulative art and argument. Furthermore, because the Office did not consider these asserted references, this petition also demonstrates material error by the Office in issuing the challenged claims.

B. Level of Skill in the Art

A person of ordinary skill in the art (POSA) as of December 31, 2018, would typically have an M.S. or Ph.D. in computer science, computer engineering, electrical engineering, or biomedical engineering focusing on computer vision[1], image processing, or machine learning, or related discipline, or could have less education but significant professional experience in one or more of these fields. A POSA working in the field would have experience applying computer vision and machine learning to medical image analysis, and as needed, could have consulted a pathologist, oncologist, or literature published by the same regarding specific biomarkers. EX1002, ¶¶51-52.

This petition is supported by the Declaration of Dr. Nikolaos Papanikolopoulos, who is the McKnight Presidential Endowed Professor in Computer Science and the Distinguished McKnight University Professor at the University of Minnesota. EX1002, ¶¶1-8; EX1003. Dr. Papanikolopoulos is well qualified to opine from the perspective of a POSA in this case. *Id.* As Dr. Papanikolopoulos explains, and as addressed in further detail below, the

[1] Computer vision, as used herein, includes methods of acquiring and analyzing digital images to identify and classify objects in the image. EX1002, ¶3.

challenged claims would not have been considered new or non-obvious to a POSA at the relevant time. EX1002, ¶¶9-14.

IV. CITED ART

As explained in detail herein, Chukka alone anticipates most claims and renders obvious the remaining claims when combined with Jones or Sebastiao. In addition, Gallas when combined with Chukka and Jones or Sebastiao renders all claims obvious. None of Chukka, Jones, Sebastiao, and Gallas was previously considered by the Office in connection with the claims of the ’097 patent.

A. Chukka (EX1005)

U.S. Patent Publication No. 2016/0042511 to Chukka et al. (“Chukka,” EX1005) published on February 11, 2016. EX1005, cover. Chukka is prior art to the challenged claims at least under 35 U.S.C. §102(a)(1)-(2), (d)(1)-(2).

Chukka provides a “Tissue Object-Based Machine Learning System for Automated Scoring of Digital Whole Slides. EX1005, Title. Chukka discloses both systems and methods “for providing a learning-based image analysis approach for the automated detection, classification, and counting of objects (e.g., cell nuclei) within digital pathology tissue slides.” EX1005, Abstract; EX1002, ¶¶42-44.

B. Jones (EX1006)

“Voronoi-based segmentation of cells on image manifolds” by Jones et al. (“Jones,” EX1006) published on October 21, 2005, in *International Workshop on*

Computer Vision for Biomedical Image Applications. Jones is prior art to the challenged claims at least under 35 U.S.C. §102(a)(1).

Jones discloses determining cell boundaries in slide images. EX1006, 537, 542; EX1002, ¶¶45-46. For example, Jones discloses generating a digital overlay drawing of an outer edge of each cell in the image, drawing a cell mask displaying a polygon around each cell object and also storing a polygon outlining the cell object and the predicted class of the cell object. EX1006, 535-37, 542.

C. Sebastiao (EX1007)

International Publication No. 2015/124737 to Sebastiao et al. ("Sebastiao," EX1007) published on August 27, 2015. EX1007, cover. Chukka (co-inventor of EX1005) is a co-inventor of Sebastiao. *Id.* Sebastiao is prior art to the challenged claims at least under 35 U.S.C. §102(a)(1)-(2), (d)(1)-(2).

Sebastiao provides "Methods, Kits, and Systems for Scoring the Immune Response to Cancer by Simultaneous Detection of CD3, CD8, CD20, and FoxP3. EX1007, Title. Sebastiao discloses computer-implemented methods for scoring stained tissue slides to identify and classify multiple lymphocyte markers. EX1007, Abstract, [0005]. Sebastiao teaches how to automatically compute immune scores (e.g., CD3, CD8, CD20) for stained slides to identify and classify cells. EX1007, [0014]; EX1002, ¶¶47-48.

D. Gallas (EX1010)

"Evaluation environment for digital and analog pathology: a platform for validation studies" by Brandon D. Gallas, et al. ("Gallas," EX1010) published in November 2014 in the *Journal of Medical Imaging*. Gallas is prior art under §102(a)(1).

Gallas discloses a platform (eeDAP) which allows for viewing and annotating digital histology slides. EX1010, Abstract; EX1002, ¶¶49-50. Gallas's platform includes a computer connected to a monitor that displays digital images. EX1010, Fig. 2 (showing eeDAP hardware), Fig. 4 (screenshot showing display of digital images). Gallas describes separating digital images into tiles with a reticle overlay. Gallas describes the reticles as comprising "fine lines and grids that appear superimposed on the specimen" that allow the user to "narrow tasks to very small regions and individual cells." EX1010, 7. Gallas's reticles separate the digital image into tiles that may be individually and collectively analyzed. *Id.*

V. STATEMENT OF THE PRECISE RELIEF REQUESTED FOR EACH CLAIM CHALLENGED

Petitioner requests review of claims 1-18 of the '097 patent under 35 U.S.C. §311 and AIA §6. The grounds for relief are as follows:

Ground	Claims	Basis
1	1, 4-6, 9-12, 14, 15, 17, and 18	Anticipated under 35 U.S.C. §102 by Chukka

2	2, 3, 7, 8	Obvious under 35 U.S.C. §103 over Chukka and Jones
3	12, 13, 16	Obvious under 35 U.S.C. §103 over Chukka and Sebastiao
4	1, 4-6, 9-12, 14, 15, 17, and 18	Obvious under 35 U.S.C. §103 over Gallas and Chukka
5	2, 3, 7, 8	Obvious under 35 U.S.C. §103 over Gallas, Chukka, and Jones
6	12, 13, 16	Obvious under 35 U.S.C. §103 over Gallas, Chukka, and Sebastiao

VI. CLAIM CONSTRUCTION

Claims are construed to the extent necessary to evaluate patentability in view of the prior art. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017). In mapping the prior art to the claims, Petitioner has applied the plain "meaning that [a] term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). EX1002, ¶53.

VII. DETAILED EXPLANATION FOR GROUNDS OF UNPATENTABILITY

A. [Ground 1] Claims 1, 4-6, 9-12, 14, 15, 17, and 18 Are Anticipated by Chukka

Chukka discloses a classifier that automatically distinguishes features of interest in digitized tissue slides. Chukka also describes producing an overlay image in which features of interest from the classifier are applied as labels onto the digital image of the slide.

Chukka anticipates claims 1, 4-6, 9-12, 14, 15, 17, and 18, as explained in greater detail below. EX1002, ¶¶54-55. Chukka discloses, for example, "imaging systems for automatically interpreting and scoring tissue specimen slides," including IHC slides. EX1005, [0004]. Chukka teaches using the technology to identify, count, and classify cells in the digitized image of the tissue slide, including classifying cells as positively-stained nuclear objects, negatively-stained nuclear objects, stromata, or lymphocytes. EX1005, [0006], [0026]. Chukka specifically teaches producing an "overlay image" to "label features of interest in the image of a specimen from a subject." *Id.*, [0004]. Indeed, Chukka Fig. 3 (reproduced herein), illustrates that the method includes (1) receiving the image, (2) tiling the image, and (3) analyzing the tiles and surrounding area to classify the majority tissue class of each tile. EX1002, ¶56; EX1005, [0039] ("flow diagram illustrating the processing of an analyze slide component **112**"), [0044]

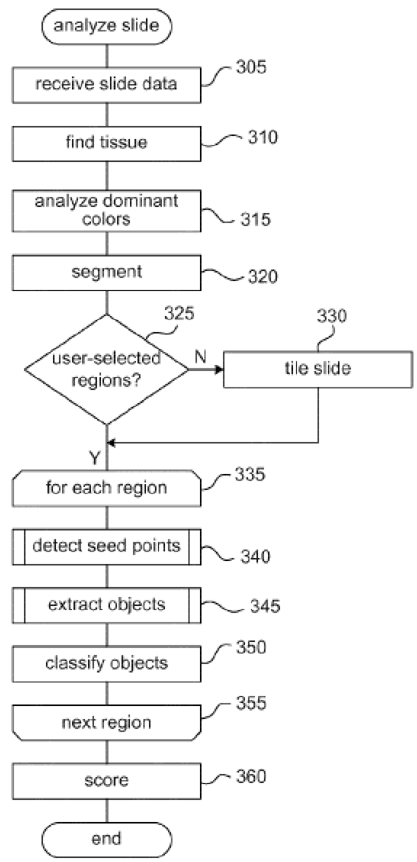


FIG. 3

("tile the whole slide tissue data" and perform a coarse resolution tile-analysis by using "a single tile information from within the tiled region" and also "information from the whole slide context"), [0044]-[0045] (detect stromal regions, cell density, lymphocyte clusters, positively-stained cells, and negatively-stained cells).

Chukka performs a "quantitative analysis" of tissue features in select regions (e.g., tiles) and larger portions of the tissue slide. EX1005, Abstract, [0004]; *see also* EX1002, ¶57. Chukka describes analysis of regions (e.g., tiles) in a digital image as based at least in part on tissue features in regions of the tissue slide other than the select region. *See, e.g.*, EX1005, [0004] ("The system analyzes a region of an image…based at least in part on information and characteristics associated with the whole slide and selects features for quantitative analysis."), *id.* ("The feature computation can use information from not only an annotated region of a slide but also information from the whole slide…"), [0020] ("The disclosed techniques can take advantage of the whole slide context…"), [0044] ("…information from the whole slide context…"), [0045] ("…use of context (e.g., surrounding tiles) provides extra information for classifying…").

As discussed in Section III.A, "looking outside of a single tile for information about the tiles" was erroneously identified as an alleged point of novelty of the '097 patent. This aspect of the challenged claims—and all aspects of the challenged claims—are found in the prior art as illustrated in Chukka. *See* EX1002, ¶¶58-60.

The discussion below cites exemplary prior art disclosure on an element-by-element basis.

1. Claim 1

i. Preamble

> A method for creating an overlay map on a digital image of a slide, the method comprising:

Chukka teaches the preamble. EX1002, ¶¶61-63. Chukka teaches "***imaging systems for automatically interpreting and scoring tissue specimen slides***."[2] EX1005, [0004]. Chukka 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. *Id.*; *see also id*., [0010], [0040], [0044], Fig. 3.

ii. [1.A] Receiving

> receiving the digital image;

Chukka discloses element [1.A]. EX1002, ¶¶64-67. The '097 patent states that "visually detectable basic features" include "lines, patterns of alternating brightness, and obtainable shapes" and "may be combined to create visually

[2] All bold-italic emphasis is added unless otherwise indicated.

detectable complex features including cell size, cell roundness, cell shape, and staining patterns referred to as texture features." EX1001, 10:4-12. Chukka discloses a "learning-based image analysis approach" for analysis of digitized pathology slides that "trains an object classifier" and separates the whole slide into a background region and a tissue region using image segmentation techniques in response to "***receiving a scanned image of a slide containing tissue data***, the facility." EX1005, Abstract; *see also id*., [0008] ("***receiving a digitized image*** of tissue data associated with an input slide"), [0039], Fig. 3 ("receive slide data"), *see also id*., [0004], [0020], [0024].

iii. [1.B] Tiling

> separating the digital image into a plurality of tiles, each tile of the plurality of tiles contains a respective portion of the digital image of the slide;

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. EX1005, [0044]; *see also id*., ("tile-based processing"), [0010], [0039], Fig. 3 ("tile slide" 330).

iv. [1.C] Identify Tile Features

> for each tile of the plurality of tiles: identifying features of the tile;

Chukka discloses element [1.C]. EX1002, ¶¶72-77. Chukka discloses using "analyze slide component 112" to analyze received image data of scanned tissue slides. EX1005, [0039]; *see also id.*, Fig. 3. Chukka further discloses "the component 112 can use a grid pattern to tile the portion of the slide" and exemplifies identified size and dimension features of tiles in such a grid pattern. *E.g.*, EX1005, [0044] (discussing "a fixed or set number of tiles…dimensions for each tile…and so on…" and "the size/shape of each tile and/or the overall number of tiles along each dimension.").

Chukka further describes identifying features of the tiled tissue. For example, Chukka describes classifying tiles "based at least in part on dominant colors" and counting the nuclei for "each tile." EX1005, [0010]. EX1002, ¶¶75-76. Chukka teaches automatically identifying features "based at least in part on one or more selection criteria" such as "***color characteristics, sample morphology … tissue characteristics … spatial parameters … image characteristic parameters***" as well as cellular "***color characteristics," "shape, dimensions, composition, … spatial parameters … image characteristics***, combinations thereof, or the like." *Id.*, [0011]. Chukka "performs a dominant color analysis" to "identify those portions of the digitized slide data having an intensity value that exceeds a predetermined threshold in the dominant color space." *Id.*, [0041].

Chukka describes analyzing the digitized tissue data to identify "glandular and stromal portions based at least in part on, for example, one or more of ***color, texture, a co-occurrence matrix, multi-scale Haar features, filter banks***, and so on." *Id.*, [0042]; EX1002, ¶76. Chukka further discloses extracting "single tile information from within the tiled region" to identify "***coarse texture features***" and the color of stained objects (e.g., "blue-stained cells)." EX1005, [0045]; *see also id.*, [0040]; EX1002, ¶75 (color-based and other image segmentation).

Chukka also explains that "a pathologist" can replace "the automated score …with a manual score (e.g., a score based at least in part on visual inspection)." EX1005, [0005]; EX1002, ¶75. Thus, Chukka disclosure extends to visual features readily identifiable by a pathologist. *See* §II.

v. [1.D] Identify Structural Tissue Features

> identifying structural tissue features of a second portion of the digital image of the slide including at least a part of one or more tiles of the plurality of tile, wherein the second portion is larger than the respective portion of the digital image contained in the tile; and

Chukka discloses element [1.D]. EX1002, ¶¶78-80. As discussed above, Chukka describes identifying features of the tiled slide, including structural tissue features. *E.g.*, EX1005, Abstract, [0010], [0011], [0020]-[0021], [0040]-[0042], [0044]-[0045]. Chukka's analysis is not limited to a single tile region of a tissue slide. *E.g.*, EX1005, [0004] ("The system analyzes a region of an image or an entire image…"), [0007] ("a method for whole-slide interpretation includes identifying portions of a digitized whole slide image corresponding to tissue."), [0010] ("The tissue region is then segmented into tiles and classification and nuclei counting algorithms are performed with respect to each tile that contains tissue.").

In addition to identifying features within each region or tile, Chukka discloses using "information from the whole slide context, which is extracted from different magnifications…." EX1005, [0044]. Chukka further instructs "when examining a particular tile, ***its neighboring tiles*** can be considered in order to provide ***additional context*** and a refined estimate of cell density." EX1005, [0044]; *see also id.*, [0045] ("***use of context (e.g., surrounding tiles)*** provides extra information for classifying, for example, blue-stained cells (tumor nuclei can be discriminated from lymphocytes) based at least in part on their ***relative density and other features***. As a result, ***context analysis*** can be used to perform a wide range of segmentation processes."); EX1002, ¶79.

vi. [1.E] Identify Majority Tissue Class

> identifying the majority class of tissue visible within the tile based at least in part on the features of the tile and the structural tissue features of the second portion of the digital image of the slide.

Chukka discloses element [1.E]. EX1002, ¶¶81-86. Chukka's "analyze slide component 112" classifies tissue slides using a tile-based approach. EX1005,

[0039]-[0044]. Chukka analyzes “single tile image information from within the tiled region and also information from the whole slide context, which is extracted from different magnifications, and image information in the neighbor slides is used.” EX1005, [0044]. Chukka specifically teaches that “additional context” around the tile “can help to discriminate between lymphocytes (generally densely packed) and negative tumor cells.” *Id*.

As discussed above, Chukka expressly discloses classifying and quantifying (e.g., majority visible) tissue, including identified cell objects, of tiles and doing so based at least in part on analysis of features in regions of the slide in addition to a single tile. EX1002, ¶83; EX1005, [0004] (“The feature computation can use information from not only an annotated region of a slide but also information from the whole slide…. The system can automatically count and classify cells and score the image…”), [0010] (“…classification and nuclei counting algorithms are performed with respect to each tile that contains tissue.”), [0036] (“each object can be assigned a probability of belonging to a particular one of tissue, stromal, or lymphatic regions based at least in part on the region segmentation.”), [0041] (“dominant color analysis”), [0045] (“use of context (e.g., surrounding tiles) provides extra information for classifying”).

In one example, Chukka identifies the majority tissue class visible within a tile by, e.g., “distinguish[ing] between ***negative tumor nuclei and lymphocytes***,” via "blue-stained cells (tumor nuclei can be discriminated from lymphocytes)," identifying "***dense lymphocyte clusters***," and identifying "***stromal regions***." EX1005, [0044]-[0045]; EX1002, ¶¶83-85. Tumor, stroma, immune clusters, and lymphocyte (negative or positive) each satisfy the tissue class limitation as described in the specification. EX1001, 6:32-38; EX1002, ¶82.

In view of the foregoing, Chukka anticipates claim 1. EX1002, ¶80.

2. Claim 4

> The method of claim 1, wherein the majority class of tissue is selected from the group consisting of epithelium, normal epithelium, immune, stroma, necrosis, blood, and fat.

Chukka discloses using the classifier to "identify positive and negative nuclei," "***lymphocytes***, and ***stroma***[,]" and "negative cells." EX1005, [0006]; *see also id.*, [0020] ("classify cell nuclei as positively-stained nuclei or negatively-stained nuclei" and "disregard other tissue (e.g., ***stromata,*** lymphocytes, etc.)"). Chukka thus anticipates claim 4. EX1002, ¶¶87-89.

3. Claim 5

> The method of claim 1, wherein the structural tissue features comprises at least one of glands, ducts, vessels, and immune clusters.

As discussed above for claim 1, Chukka discloses using an "analyze cells component" to distinguish between negative tumor nuclei and lymphocytes, based on features identified in the tiles and contextual information in the region surrounding each tile. EX1005, [0044]. Chukka specifically discloses identifying "cell density" and "***lymphocyte clusters***". EX1005, [0044]-[0045]; EX1002, ¶¶90-91. A POSA would have understood that a lymphocyte cluster is an "immune cluster." EX1002, ¶92; *see also* EX1001, 5:47-48, 6:32-42, 22:24-26 (identifying "clusters of lymphocytes").

Chukka thus anticipates claim 5. EX1002, ¶93.

4. Claim 6

i. Preamble

> A method for tissue classification of a digital image of a slide, the method comprising:

As discussed above for claim 1, Chukka teaches systems and methods of "providing a learning-based image analysis approach for the automated detection, classification, and counting of objects (e.g., cell nuclei) within digitized pathology tissue slides." EX1005, Abstract; *see also id.*, [0020] (same); EX1002, ¶94.

ii. [6.A] Receiving

Element [6.A] is identical to element [1.A] and is disclosed by Chukka for the same reasons discussed for element [1.A]. EX1002, ¶95.

iii. [6.B] Tiling

Element [6.B] is substantially identical to element [1.B] and is disclosed by Chukka for the same reasons discussed for element [1.B]. EX1002, ¶96.

iv. [6.C] Identify Tile Features

Element [6.C] is identical to element [1.C] and is disclosed by Chukka for the same reasons discussed for element [1.C]. EX1002, ¶97.

v. [6.D] Identify Structural Tissue Features

Element [6.D] is identical to element [1.D] and is disclosed by Chukka for the same reasons discussed for element [1.D]. EX1002, ¶98.

vi. [6.E] Determine Predicted Class for Tiles

Element [6.E] is substantially identical to element [1.E] and is disclosed by Chukka for the same reasons discussed for element [1.E]. EX1002, ¶99.

vii. [6.F] Identify Cell Objects

> identifying a plurality of cell objects in the digital image;

Chukka discloses element [6.F]. EX1002, ¶¶100-104. As discussed above, Chukka discusses multi-step analysis of tissue slide image including grid separation. Chukka, for example, discloses identifying "cellular structures (e.g., nuclear objects, nuclei seed) and cells in a region of a slide (e.g., a particular tissue region of the slide) or the whole slide, based at least in part on information pertaining to data associated with tissue containing regions of the slide." EX1005, [0004]. Chukka also discloses to "automatically count and classify cells," to "accurately count nuclear objects to determine information about the tissue," and to use "positively-stained nuclear objects and/or negatively stained nuclear objects to score, for example, a biological specimen (e.g., tumor tissue)." *Id.* Chukka additionally discloses to "identify positive and negative nuclei" and distinguishing positive nuclei from negative nuclei, lymphocytes, and stroma. EX1005, [0006]; *see also id.*, [0045]-[0046] ("classify each of the extracted objects as a positively-stained nuclear objects, negatively-stained nuclear objects, stromata, and lymphocytes"), [0026] ("identify objects or seed points, for example, nuclear objects or nuclear seed points" as a "starting point for localizing objects."); EX1002, ¶¶103.

viii. [6.G] Determine Predicted Class of Cell Objects

> determining a predicted class for each of the plurality of cell objects; and

Chukka discloses element [6.G]. EX1002, ¶¶105-108. Chukka discloses using "classification and nuclei counting algorithms" for "each tile that contains tissue." EX1005, [0010], Fig. 3. The analyze slide component "loops through" the tiles to (1) "identify seeds within the [tile]" using a "detect seed points component," (2) identify objects within the tile using an "extract objects component," and (3) "classify each of the extracted objects as a positively-stained nuclear objects, negatively-stained nuclear objects, stromata, and lymphocytes." EX1005, [0044], [0046]; *see also* EX1005, [0026] (using object foreground mask and seed locations to identify cellular "blobs" and then classifying each "blob…using a classifier (e.g., a previously-trained classifier) to identify one or more of positively-stained nuclear objects, negatively-stained nuclear objects, stromata, and lymphocytes.").

ix. [6.H] Assign Predicted Class of Cell Objects

> for each of the plurality of tiles that corresponds to one of the plurality of cell objects, assigning the tile the predicted class of the corresponding cell object in place of the predicted class of the tile.

Chukka discloses element [6.H]. EX1002, ¶¶109-113. Chukka discloses classifying the image on a tile basis which is "initially considered at a coarse resolution (e.g., 2×) to identify, for example 'dense lymphocyte clusters' and 'stromal features.'" EX1005, [0045]. Chukka then "loops through each…tile" and performs a subsequent, finer analysis by (1) "identify[ing] seeds within the [tile]" using a "detect seed points component[,]" (2) identifying objects within the tile using an "extract objects component[,]" and (3) "us[ing] a classifier…to classify each of the extracted objects as a positively-stained nuclear objects, negatively-stained nuclear objects, stromata, and lymphocytes." *Id*., [0046]. Chukka thus discloses a first "coarse resolution tile-analysis" to predict the class of each tile, and then subsequently performs a finer analysis to classify cellular objects individually. *Id.*; *see also id.*, [0047] ("the facility may pre-process a slide by tiling the slide and then detecting and classifying objects within the slide…. Moreover, the facility may perform the tiling and analysis at varying levels of granularity to increase accuracy.”).

By virtue of Chukka’s description of the first stage as an initial “coarse-resolution” analysis, EX1005, [0045], to be followed by further “analysis at varying levels of granularity to increase accuracy,” EX1005, [0047], a POSA would have understood that further finer levels of analysis (such as identifying cells) involved replacing the initial, coarser texture-based classification with the subsequent, cell classification. EX1002, ¶112.

Accordingly, Chukka anticipates claim 6. EX1002, ¶113.

5. Claim 9

> The method of claim 6, further comprising: generating a digital overlay drawing for the digital image, where the digital overlay drawing is a histology mask displaying the plurality of tiles and the predict class for each tile.

Chukka teaches the limitations of claim 9. EX1002, ¶¶114-118. Chukka teaches generating “an overlay image” to “label features of interest” in the tissue slide image. EX1005, [0004]; *see also* EX1005, [0026] (applying “adaptive thresholding technique” to the tissue data “to distinguish between darker objects (e.g., cell nuclei) and other objects, (e.g., stroma and slide background) and generate an object foreground mask.”), [0051] (“extract objects component 114” used “to identify boundaries around seed points that correspond to an object[,]” “generate[] an object foreground mask…,” and “characterizes each of the identified objects based at least in part on location and any number of characteristics….”).

Chukka’s overlay image satisfies the claim with respect to the recited “histology mask.” EX1002, ¶115; EX1001, 12:40-44 (a mask “may be a copy of an image, where the colors, RGB values, or other values in the pixels are adjusted to show the presence or absence of an object of a certain type to show the location of all objects of that type”). As Dr. Papanikolopoulos explains, a POSA would understand that the term “histology mask” includes a mask where the colors, RGB values, or other values in the pixels are adjusted to show the presence or absence of histological objects or features (e.g., tissues, cell objects).

Chukka also teaches displaying the plurality of tiles and the predicted class for each tile. As discussed above, Chukka discloses generating digital overlay drawings to label features of interest, and Chukka discloses identifying features of interest in tiles, such as identifying portions of the image that correspond to predicted classes (e.g., lymphocyte, stromata). Chukka thus teaches displaying the plurality of tiles and the predict class for each tile.

Chukka thus anticipates claim 9. EX1002, ¶118.

6. Claim 10

The method of claim 6, further comprising:

generating a digital overlay drawing for the digital image; and

> displaying, in the digital overlay drawing, the plurality of tiles and the predicted class for each tile that does not correspond to a cell object, and displaying the plurality of cell objects and the predicted class of each cell object.

Chukka teaches the limitation of claim 10. EX1002, ¶¶119-121. As discussed above with respect to claim 9, Chukka discloses generating a digital overlay drawing for the digital image. EX1005, [0004], [0024], [0026]. Chukka further teaches that the overlay drawing displays the plurality of tiles and the predicted class of each tile that does not correspond to a cell object (e.g., stroma or cell background) and displaying the plurality of cell objects and the predicted class of each cell object (e.g., tumor positive, tumor negative, or lymphocytes). EX1005, [0026] (applying "adaptive thresholding techniques" to identify cell objects (e.g., cell nuclei) and other objects, (e.g., stroma and slide background)" to generate a "object foreground mask" and delineate cell "blobs" that are classified to "identify one or more of positively-stained nuclear objects, negatively-stained nuclear objects, stromata, and lymphocytes").

Chukka also teaches displaying the plurality of tiles, the predict class for each tile that does not correspond to a cell object, and the cell objects and predict class of each cell object. Chukka discloses generating digital overlay drawings to label features of interest, and Chukka discloses identifying features of interest in tiles, such as identifying portions of the image that correspond to predicted classes (e.g., lymphocyte, stromata). Chukka thus teaches displaying the plurality of tiles, the predict class for each tile that does not correspond to a cell object, and the cell objects and predict class of each cell object.

Chukka thus anticipates claim 10. EX1002, ¶121.

7. Claim 11

> The method of claim 6, further comprising:
>
> generating a digital overlay drawing for the digital image, wherein the digital overlay drawing includes the digital image; and
>
> displaying the digital overlay drawing.

Chukka teaches the limitation of claim 11. EX1002, ¶¶122-123. As discussed above with respect to claim 9, Chukka discloses generating a digital overlay drawing for the digital image. EX1005, [0004], [0024], [0026]. Chukka teaches that the system "displaying the images to the user" and "can assist a user … by detecting and classifying objects and scoring the whole slide and/or regions…of the slide." *Id.*, [0027]. Chukka thus anticipates claim 11.

8. Claim 12

> The method of claim 6, further comprising:
>
> generating a digital overlay drawing for the digital image, wherein the digital overlay drawing includes a generated version of the digital image; and
>
> displaying the digital overlay drawing.

Chukka teaches the additional limitation of claim 12. EX1002, ¶¶124-125.

As discussed above with respect to claim 9, Chukka discloses generating a digital overlay drawing for the digital image. EX1005, [0004], [0024], [0026]. Chukka further teaches that the facility "can generate a grayscale representation of the digitized slide data[.]" *Id.*, [0026]. Chukka teaches that the system "displaying the images to the user" and "can assist a user … by detecting and classifying objects and scoring the whole slide and/or regions…of the slide." *Id.*, [0027]. Chukka thus anticipates claim 12.

9. Claim 14

> The method of claim 6, further comprising:
>
> generating a digital overlay drawing for the digital image, where the digital overlay drawing comprises percentages of predict classes corresponding to the digital image.

Chukka teaches the additional limitation of claim 14. EX1002, ¶¶126-128. As discussed above with respect to claim 9, Chukka discloses generating a digital overlay drawing for the digital image. EX1005, [0004], [0024], [0026]. Chukka also teaches that "pathologists often report a score for the slide by visually reviewing and estimating the percentage of positively-stained (e.g., brown-colored) nuclear objects to the total number of positively-stained and negatively-stained (e.g., blue-colored) nuclear objects." EX1005, [0003] Chukka further teaches classifying cells in the tissue image as positive or negative for cancer and "to determine a score based on … percent positive/negative[.]" *Id.*, [0020]. Chukka thus discloses reporting a score that comprises a percentage of predicted classes in the slide (e.g., percentages of positively-stained cells). Chukka thus anticipates claim 14.

10. Claim 15

> The method of claim 6, further comprising:
>
> generating a digital overlay drawing for the digital image, where the digital overlay drawing comprises total counts of predict classes corresponding to the digital image.

Chukka teaches the limitation of claim 15. EX1002, ¶¶129-131. As discussed above with respect to claim 9, Chukka discloses generating a digital overlay drawing for the digital image. EX1005, [0004], [0024], [0026].

Chukka further teaches to "count and classify cells" such as counting "positively-stained nuclear objects and/or negatively-stained nuclear objects to score, for example, a biological specimen (e.g., tumor tissue)." EX1005, [0004]. Chukka then teaches to score the slide "[b]ased at least in part on the number of positive/negative nuclei." *Id.*, [0006]; *see also id.*, [0010] ("The tissue region is then segmented into tiles and classification and nuclei counting algorithms are performed with respect to each tile that contains tissue."); EX1002, ¶130.

By disclosing generating digital overlay drawings to label features of interest and identifying counting and classifying cells features of interest, Chukka anticipates claim 15. EX1002, ¶131.

11. Claim 17

> The method of claim 6, wherein the cell objects include lymphocyte cells and not lymphocyte cells.

Chukka teaches the limitation of claim 17. EX1002, ¶¶132-135. Chukka teaches using the classifier to distinguish "positive and negative nuclei" and to distinguish positive nuclei "from the negative nuclei, ***lymphocytes***, and stroma." EX1005, [0006] (distinguishing lymphocytes from negative nuclei and to "classify cell nuclei as positively-stained nuclei or negatively-stained nuclei" and "disregard other tissue (e.g., stromata, ***lymphocytes***, etc.)."); *see also id.*, [0044] (use analyze cell component 112 to distinguish between negative tumor nuclei and lymphocytes using contextual information in the region surrounding each tile "to discriminate between lymphocytes (generally densely packed) and negative tumor cells"). Chukka thus anticipates claim 17.

12. Claim 18

> The method of claim 6, wherein the structural tissue features comprises at least one of glands, ducts, vessels, and immune clusters.

Chukka teaches the limitation of claim 18. EX1002, ¶¶136-137. Chukka teaches to use an "analyze cells component" to distinguish between negative tumor nuclei and lymphocytes, based on features identified in the tiles and contextual information in the region surrounding each tile. EX1005, [0044]; EX1002, ¶91. Chukka specifically discloses identifying "cell density" and "***lymphocyte clusters***".

EX1005, [0044]-[0045]; EX1002, ¶91. As discussed above for claim 5, A POSA would understand that a lymphocyte cluster is an "immune cluster." EX1002, ¶92; *see also* EX1001, 22:24-27 ("As shown, an exemplary model overlay may include red tiles for identifying ***clusters of lymphocytes***, green tiles for identifying epithelium cells, and dark blue tiles for identifying tumor cells."). Chukka thus anticipates claim 18.

B. [Ground 2] Claims 2, 3, 7, and 8 Are Obvious over Chukka and Jones

Chukka teaches generating an object foreground mask and identifying seed points corresponding to nuclei. EX1005, [0051], Fig. 5 (reproduced herein). Chukka teaches using the foreground mask and nuclei to generate a Voronoi tessellation of the foreground image to identify portions or "blobs" that define the boundaries of the detected objects. *Id.*; EX1002, ¶140.

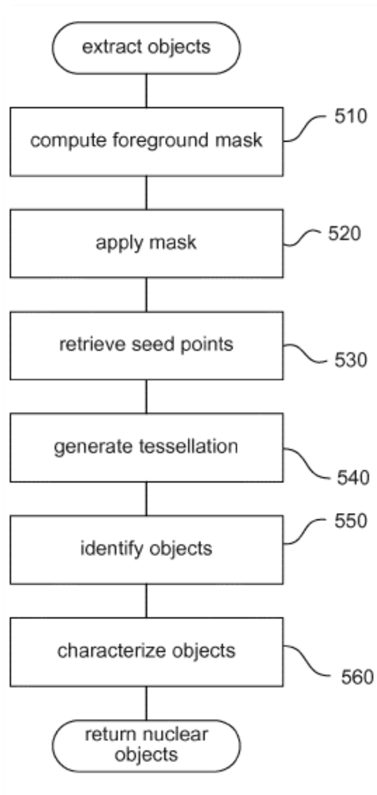


FIG. 5

To the extent that Chukka does not expressly explain how to use a Voronoi tessellation to identify blobs that define the boundaries of cells, it would have been obvious to a POSA how to do so, as evidenced by Jones. Accordingly, claims 2, 3, 7, and 8 would have been obvious over Chukka and Jones. EX1002, ¶¶138-147

Jones discloses and teaches the details of a specific method of defining cell-to-cell boundaries. Jones teaches "a method for finding the boundaries between adjacent regions in an image, where 'seed' areas have already been identified in the individual regions to be segmented." EX1006, Abstract; EX1002, ¶¶141-145. Jones specifically teaches that this method "operates by computing a discretized approximation of the Voronoi regions of each seed on a manifold with a metric controlled by local image features." *Id.*, 537. Jones teaches that its method is able to generate an outline of the cell from pre-determined seed regions (e.g., cell nuclei) and that its method performs well at determining cell-to-cell boundaries. *Id.*, 542, Fig. 1, Fig. 3:

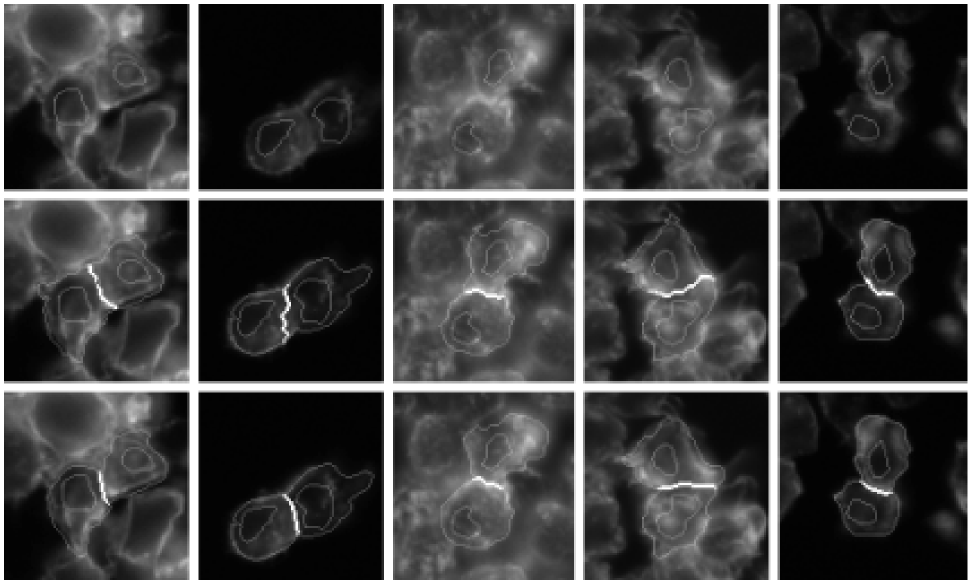


Fig. 1. Typical results from our algorithm. Internal shapes are seed regions, taken from manual segmentation of nuclei, and are the same in both rows. Bold lines show cell/cell boundaries that are compared. Top row: Cell images, with nuclei outlined. Middle row: Automatic segmentation with our method. Bottom row: Manual segmentation.

As Dr. Papanikolopoulos explains, a POSA would have had a good reason to combine the teachings of Chukka and Jones. EX1002, ¶146. Chukka suggests using Voronoi tessellations to identify portions or "blobs" that define the boundaries of detected cellular objects, and Jones teaches a specific method of doing so. *See* EX1005, [0026], [0051]; EX1006, 535-37. A POSA looking to implement Chukka's facility, and specifically its "extract objects component" to identify portions of the image corresponding to boundaries around detected cellular objects would have had a good reason to look at teachings of Jones to do so.

Moreover, a POSA would have had a reasonable expectation of success. EX1002, ¶147. Jones teaches that its method solves the "problem of segmenting cells as one of identifying boundaries between regions given 'seeds' in individual regions from which to start the segmentation." EX1006, 535. Jones further teaches that its method "does not compute a foreground/background separation, but instead relies on a such a label for each pixel to be given as input." *Id.*, 4. Chukka therefore provides precisely the information Jones' method requires, i.e., a seed point and an object foreground mask, to effectively outline the boundaries of cells.

1. Claim 2

> The method of claim 1, further comprising: generating a digital overlay drawing of an outer edge of each cell in the image.

Jones teaches the additional limitations of claim 2. EX1002, ¶¶148-153. Jones teaches generating a digital overlay drawing of an outer edge of each cell in the image. Jones teaches an algorithm to calculate cell-to-cell boundaries by "computing a discretized approximation of the Voronoi regions of each seed on a manifold with a metric controlled by local image features." EX1006, 537. Jones teaches that its algorithm performs well at identifying cell boundaries. EX1006, 8. For example, Jones teaches that its algorithm has been successfully implemented in several experiments "with a variety of cell types and morphologies." *Id.* As illustrated in Jones's Fig. 1, Jones teaches that its algorithm can generate a digital overlay drawing of an outer edge of each cell in the image. *Id.*, 5, Fig. 1.

Jones thus teaches the additional limitation of claim 2. Chukka and Jones thus render obvious claim 2 as a whole. EX1002, ¶153.

2. Claim 3

> 3. The method of claim 2, wherein the digital overlay drawing is prepared at the resolution level of an individual pixel.

Chukka and Jones both teach or suggest the additional limitations of claim 3. EX1002, ¶¶154-157. Chukka teaches generating an object foreground mask on a pixel resolution basis. EX1005, [0051] ("identifying those pixels that are darker than their local neighborhood intensity distribution and that exceed a global threshold" and assigning "a value of 1 for all pixels whose intensity value exceeds a mean intensity value for a local portion of the tissue…."). Jones specifically teaches that the digital overlay drawing may be at the resolution level of an individual pixel. *E.g.*, EX1006, 537 ("Pixels are then assigned to cells according to their distance from the corresponding nucleus under that metric."), ("distance between boundary pixels"). Accordingly, Chukka and Jones thus render claim 3 obvious.

3. Claims 7 and 8

> 7. The method of claim 6, further comprising:
>
> storing, in a first file, for each tile, a tile position and the predicted class of the tile; and
>
> storing, in a second file, for each cell object, a polygon outlining the cell object and the predicted class of the cell object.
>
> 8. The method of claim 6, further comprising: generating a digital overlay drawing for the digital image, where the digital

> overlay drawing is a cell mask displaying a polygon around each cell object.

Chukka and Jones teach the limitations of claims 7 and 8. EX1002, ¶¶158-165.

Chukka teaches storing in a first file, for each tile, a tile position and predicted class of the tile. Chukka teaches that the facility may comprise a "computer-readable storage medium that can store data[.]" EX1005, [0007], *see also* [0029], [0030], [0031]; EX1002, ¶161. Chukka teaches scoring the score of "one or more regions within in a slide…." EX1006, [0046]. Chukka then teaches storing, in a second file, for each cell object, a polygon outlining the cell object and the predicted class of the cell object. EX1002, ¶162; EX1005, [0051] (identifying portions of image that correspond to detected cells which are "returned for storage and classification by a trained classifier…."). Chukka teaches generating "an overlay image" to "label features of interest" in the tissue slide image. EX1005, [0004].

Jones teaches generating a polygon around each cell object and/or outlining each cell object. EX1002, ¶164; EX1006, 535-37. The '097 patent does not purport to have invented a new or novel cell outlining technology. Instead, the patent merely describes using a tissue detector to "outline[] a shape with a closed polygon." EX1001, 14:12-13; EX1002, ¶¶139, 160. As discussed above, Jones teaches using Voronoi tessellations of seed regions to determine cellular boundaries. Jones teaches that its algorithm has been successfully implemented in several experiments "with a variety of cell types and morphologies." *Id.*, 8. Jones teaches that its algorithm can generate a digital overlay drawing of an outer edge of each cell in the image. *Id.*, 5, Fig. 1.

Jones thus teaches or suggests the additional limitation of claims 7 and 8. Chukka and Jones render claims 7 and 8 obvious. EX1002, ¶165.

C. [Ground 3] Claims 12, 13, and 16 Are Obvious over Chukka and Sebastiao

Chukka teaches every element of claims 12, 13, and 16, with the possible exceptions of explicitly detailing the digital overlay drawing "includes a generated version of the digital image" (claim 12), "generating a plurality of digital overlay drawings" each corresponding to a "different predicted class" and "selectively displaying one" of those overlay drawings (claim 13), and the cell objects comprise "CD3, CD8, CD20, pancytokeratin, and smooth muscle actin (claim 16). EX1002, ¶¶166-167. Sebastiao teaches the additional elements of each of claims 12, 13, and 16. EX1002, ¶¶168-169.

As Dr. Papanikolopoulos explains, a POSA would have had a good reason to have considered the teachings of Chukka and Sebastiao together. EX1002, ¶¶170-172. Chukka and Sebastiao disclose similar and compatible systems developed by overlapping inventors on behalf of the same applicant. Both Chukka and Sebastiao teach examining of IHC slides to identify biomarkers associated with cancers (e.g., breast cancer). *See* EX1005, [0002]; EX1007, [0005]. In addition, both Chukka and Sebastiao teach identifying and classifying lymphocytes. *See* EX1005, [0044]; EX1007, [0030]. A POSA thus would have been motivated to look to both Chukka and Sebastiao when pursuing cancer diagnosis/prognosis by examination of IHC slides.

1. Claim 12

> The method of claim 6, further comprising:
>
> generating a digital overlay drawing for the digital image, wherein the digital overlay drawing includes a generated version of the digital image; and
>
> displaying the digital overlay drawing.

Claim 12 is anticipated by Chukka as discussed above. To the extent Patent Owner argues that "generated version of the digital image" requires more than providing a copy of the digital image, then claim 12 is obvious over Chukka and Sebastiao. EX1002, ¶¶173-177.

Sebastiao teaches that the image analysis algorithm receives a set of images of multiplex IHC slides and unmix the images into "separate image channels for each marker of the multiplex assay." EX1007, [0014]. Sebastiao also teaches that these separate channels may be combined into a surrogated image, wherein "the surrogated image is a combination of the image channel information of all the lymphocyte markers." *Id.* Sebastiao further teaches that the image may be transformed into a "grayscale or absorbance image." *Id.* Indeed, Sebastiao teaches generating a surrogated image of the slide for each region of interest. *Id.*, [0056]. Sebastiao then applies the "cell detection algorithm" to the surrogated image "to detect the lymphocytes." *Id.*, [0057]. "In an exemplary embodiment of the present invention, the score for each marker may be reported, along with the tissue context information, as output." *Id.*, [0051]. Therefore, Sebastiao teaches generating a version of the digital image that is more than a copy of the digital image. EX1002, ¶¶175-176.

Sebastiao explains the benefits of generating a surrogated image, which combines information from multiple image channels that have been filtered and transformed to better highlight features of interest and remove noise. EX1007, [0056]. A POSA would have had a good reason to generate an overlay image as taught in Chukka, wherein the overlay image comprises a generated (e.g., surrogated) version of the digital image as taught in Sebastiao. Accordingly, claim 12 is obvious over Chukka and Sebastiao. EX1002, ¶¶176-177.

2. Claim 13

The method of claim 6, further comprising:

> generating a plurality of digital overlay drawings for the digital image, where each digital overlay drawing corresponds to a different predicted class; and
>
> selectively displaying one of the plurality of digital overlay drawings.

Sebastiao teaches or suggests the limitations of claim 13. EX1002, ¶¶178-180. Sebastiao teaches generating "separate image channels for each marker of the multiplex assay" to identify "regions of interest in each image channel based on intensity information in each channel." EX1007, [0014]. Sebastiao then teaches a "cell detection algorithm" to each image channel or a combination of the image channels to identify and classify the detected cells, count the number of each type of cell, and generate a score of the tissue. *Id.* "In an exemplary embodiment of the present invention, the score for each marker may be reported, along with the tissue context information, as output." *Id.*, [0051].

Chukka teaches generating digital overlay drawings for the digital image and Sebastiao teaches that each of the plurality of digital overlay drawings may correspond to a different predicted class (e.g., separate image channels that correspond to different lymphocyte markers). EX1005, [0004]. Accordingly, Chukka and Sebastiao render claim 13 obvious. EX1002, ¶¶179-180.

3. Claim 16

> The method of claim 6, wherein the cell objects comprise CD3, CD8, CD20, pancytokeratin, and smooth muscle actin.

Sebastiao teaches the limitation of claim 16. EX1002, ¶¶182-185. For example, Sebastiao teaches computing an immune score from "a set images of multiplex IHC slides," including testing specifically for "lymphocyte markers CD3, CD8, CD20, FoxP3, and tumor detection markers." EX1007, [0014]. Indeed, Sebastiao teaches to "classify the detected cells as at least one of false positive cells, CD3 only T-cells, CD3 and CD8 T-cells, FP3 T-cells; and CD20 B-cells." EX1007, claim 15. Sebastiao further teaches detecting cytokeratin to identify epithelial tumor cells. *Id.*, [0048] ("Additionally, a tumor marker, for example a cytokeratin marker (e.g., Oscar), may also be included in the assay to identify the tumor…."), [0037] (identifying epithelial carcinomas using cytokeratin staining). A POSA would have understood that the cytokeratin marker disclosed by Sebastiao—i.e., Oscar—is a pancytokeratin marker. EX1030, 1.

As Dr. Papanikolopoulos explains, both Chukka and Sebastiao further suggest detecting smooth muscle actin (α-SMA) in breast and adenoid cystic carcinoma tumors. EX1002, ¶184. For example, Chukka teaches classifying tissue associated from breast biopsy, including differentiating connective (e.g., stroma) and immune tissues. EX1007, [0020]. A POSA would have known that prior art described stroma in breast cancers as being "characterized by high α-smooth muscle actin (α-SMA) expression." EX1024, 4862.

In addition, Sebastiao broadly describes detecting "tumor detection markers" along with lymphocyte markers. EX1007, [0014]; *see also id*., [0012] ("Our assay includes a tumor marker…"). A POSA would have understood from the prior art that "tumor detection markers" varied by tumor type. *See, e.g.*, EX1007, [0037] (describing markers useful for "epithelial" and "neuroectodermal" tumors). A POSA would have known that the prior art describes α-SMA as a marker of adenoid cystic carcinoma tumors. EX1025, 484 ("We found α-SMA to be an efficient immunohistochemical marker for ME ["myoepithelial cells"] and endorse that its differential expression in the epithelial and stromal compartments of the selected salivary gland lesions influences their morphological patterning, especially in ACC ["adenoid cystic carcinoma.]."); EX1002, ¶184.

Accordingly, Chukka and Sebastiao teach or suggest cell objects comprising CD3, CD8, CD20, pancytokeratin, and smooth muscle actin. Chukka and Sebastiao render claim 16 obvious. EX1002, ¶185.

D. [Ground 4] Claims 1, 4-6, 9-12, 14, 15, 17, and 18 Are Obvious Over Gallas and Chukka.

Analysis of tissue slides conventionally used overlays. These overlays, sometimes referred to as "reticles," were routinely included within the eyepiece of a microscope or applied as a digital overlay when viewing whole slide images ("WSI") on a computer screen. *See* §II; EX1002, ¶186. Regardless of form, such conventional overlays allowed visual inspection of an individual evaluation region (e.g., tile) along with the tissue surrounding the evaluation region. As discussed above, Chukka discloses separating tissue in a digital slide using a tiled overlay and considering tissue features in a tile in the context of surrounding tissue, and anticipates at least claims 1, 4-6, 9-12, 14, 15, 17, and 18. *See, e.g.*, §VII.A (Ground 1). Such a set-up for evaluating tissue slides is also illustrated in Gallas which itself arguably anticipates claims 1, 4, and 5 of the '097 patent. *E.g.*, EX1010, Fig. 6; *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) ("anticipation is the epitome of obviousness").

To the extent Patent Owner contests anticipation by Gallas arguing the claims require some level of automation, this is illustrated in and rendered obvious by Chukka. Chukka describes an automated method for dividing a digital image of a tissue slide into tiles and evaluating a tile along with the tissue surrounding an evaluation tile. *E.g.*, EX1005, [0039], [0044], [0044]-[0045]; *see also* §VII.A (Ground 1). Indeed, both Gallas and Chukka teach and corroborate that separating tissue in a slide using a tiled overlay and considering tissue features in a tile in the context of surrounding tissue was conventional in histological analysis and found in the prior art. There is nothing inventive about conducting a conventional prior art process using a computer. *W. Union Co. v. MoneyGram Payment Sys.*, 626 F.3d 1361, 1370 (Fed. Cir. 2010) ("Based on the Supreme Court's reasoning in *KSR*, we have subsequently held that applying computer and internet technology to replace older electronics has been commonplace in recent years."); *Leapfrog Enters. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1161 (Fed. Cir. 2007) ("Applying modern electronics to older mechanical devices has been commonplace in recent years."); see also *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 405 (2007) (invention likely obvious when it is "mere application of a known technique to a piece of prior art ready for the improvement"). As discussed further below, both references discuss the benefits of computer-implemented tissue analysis and Chukka's description of an automated approach confirms and corroborates the obviousness and reasonable expectation of successfully reaching the subject matter of the challenged claims.

Gallas (EX1010) teaches separating tissue in a digital slide using a tiled overlay and considering tissue features in an evaluation tile in the context of surrounding tissue. EX1010, 7; *see also* EX1002, ¶187. This is illustrated in Fig. 6(a) of Gallas, which shows digital overlay (a reticle)

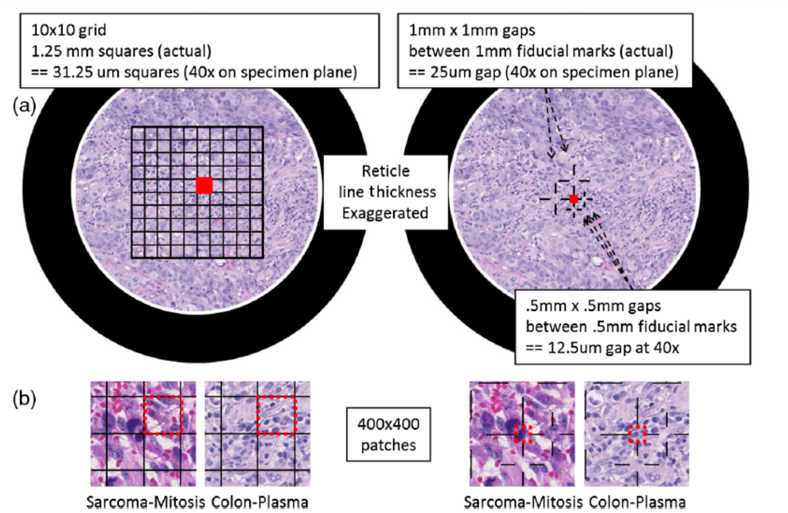
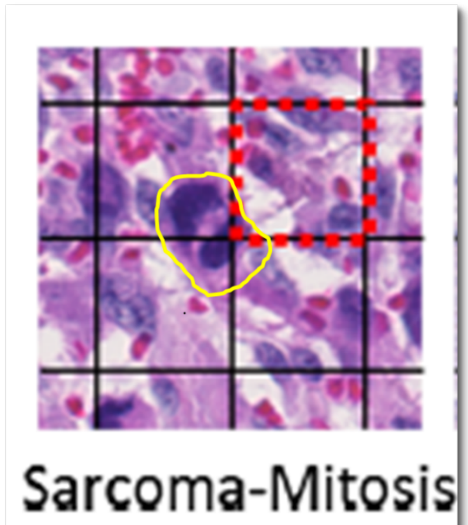


Fig. 6 Reticles (line thicknesses exaggerated) as seen through simulated microscope FOV (a) and 400 × 400 patches as they appear in eeDAP (b). The red squares in the simulated microscope FOVs and the red-dash boundary squares in the 400 × 400 patches indicate the "evaluation" areas. In the 400 × 400 sarcoma patch on the left, a majority of the obvious mitotic figure falls in the grid square to the left of the evaluation square. In the 400 × 400 sarcoma patch on the right, the central cross hairs point to the obvious mitotic figure. In the 400 × 400 colon patch on the left, there are several plasma-cell candidates in the "evaluation" square. In the 400 × 400 colon patch on the right, the cross hairs point to a single plasma-cell candidate to be evaluated.

overlaying an image of a tissue slide obtained from a digital camera mounted on a microscope. Fig. 6(b) illustrates a "patch" obtained from a WSI derived from the same slide as shown in (a) which also includes a reticle overlaying the image. The reticle overlays shown in Fig. 6, separate the tissue image into grid squares which facilitate evaluation of biopsied tissue such as sarcoma tissue for mitotic figures or colon tissue for the presence of plasma-cells.

EX1010, Fig. 6.



With respect to the sarcoma tissue slide, for example, Gallas describes evaluation of features such as a mitotic figure (e.g., tissue feature) that spans multiple squares. EX1002, ¶188. As Gallas explains, the evaluation square (red-dashed outline) includes a portion of the mitotic figure but the majority "falls in the grid square to the left." EX1010, Fig. 6 (reproduced in part herein with mitotic figure outlined in yellow); *see also id.*, Fig. 1 (showing screenshots of GUI used for identifying features). That is, Gallas teaches scoring mitotic figures involves analysis of the evaluation square along with and in the context of considering adjacent grid squares.

While Gallas describes visual identification of slide features by a user, it would have been obvious to conduct a known approach to tissue analysis using a computer-implemented approach. Such an approach is described by Chukka which further corroborates the obviousness of the challenged claims, including claims 1, 4-6, 9-12, 14, 15, 17, and 18. EX1002, ¶189.

As discussed in detail above, Chukka describes methods for automated tissue slide analysis. *See* §VII.A (Ground 1); *see also* EX1005, [0005], [0010], [0022], [0035]-[0046], Figs 2 & 3; EX1002, ¶189. Chukka teaches using the disclosed technology to identify, count, and classify cells in the digitized image of the tissue slide, including classifying cells as positively-stained nuclear objects, negatively-stained nuclear objects, stromata, or lymphocytes. EX1005, [0006], [0026]. Like Gallas, Chukka specifically teaches producing an "overlay image" to "label features of interest in the image of a specimen from a subject." *Id.*, [0004].

In addition to automated tissue analysis, Chukka describes that its classifier may be trained with user annotated digital slides. EX1005, [0035]-[0038], Fig. 2. Such annotated slides are described in Gallas. This further corroborates the compatability and related nature of both references' disclosure.

A POSA would also have been motivated to look to the teachings of both Gallas and Chukka with expectation of reaching what is claimed at least because both references discuss similar and related subject matter, and both references discuss benefits of using automation to improve evaluation of digital pathology slides. *E.g.*, EX1010, 8; EX1005, [0003] ("this 'representative' analysis can lead to sampling bias.”), [0047] (“augment the user’s own assessment”); EX1002, ¶190. For example, Gallas discusses mitigation of evaluation bias through application of algorithms for automated identification of cells and features:

> Future work may include the incorporation of algorithms for the automated identification of candidate cells to be classified or histopathological features to be evaluated. Such algorithms may be less biased and more objective in creating the study sets.

EX1010, 8; *KSR*, 550 U.S. 398 (explaining that an express suggestion in the literature, while not required to demonstrate obviousness, strongly supports a conclusion of obviousness). Chukka echoes the benefits of computer-implemented analysis, and further discusses use of automation to augment analysis performed by human analysts.:

> The user may use this displayed information to compare his or her own assessment of a slide or FOV to the automated assessment to gauge the accuracy of both the automated process and his or her own assessment. The disclosed techniques offer reliable and reproducible systems and methods for slide interpretation that can be used to augment the user's own assessment.

EX1005, [0047]; *see also id.*, [0003].

For these reasons, and further discussion herein, a POSA would have found the challenged claims obvious in view of prior art such as Gallas and Chukka.

EX1002, ¶191. An element-by-element discussion of the challenged claims is provided below.

1. Claim 1

i. Preamble

> A method for creating an overlay map on a digital image of a slide, the method comprising:

Methods for creating overlay maps on digital images were known well before the earliest claimed priority date of the ’097 patent. *See* §II. Indeed, such methods are illustrated by Gallas and Chukka. EX1002, ¶¶192-194.

Gallas describes overlaying reticles on digital images of slides to facilitate analysis. EX1002, ¶193. Gallas explains that use of reticles is important for “narrowing the evaluation area to a small ROI or an individual cell.” EX1010, 2. For example, Fig. 6(a) shows such a reticle mask overlayed on a digital camera image obtained from a slide. The reticle mask allows a portion of the digital image (e.g., red-filled square of Fig. 6(a)) to be mapped to the corresponding portion of the digital representation of the WSI (e.g., red-dash boundary of Fig. 6(b)). EX1010, Fig. 6 (“Reticles … as seen through simulated microscope FOV (a) and 400 × 400 patches as they appear in eeDAP (b)”). The red squares in the simulated microscope FOVs and the red-dash boundary squares in the 400 × 400 patches indicate the ‘evaluation’ areas.”).

As discussed above, Chukka teaches the preamble. *See* §VII.A.1.i.; EX1002, ¶192.

ii. 1.[A] Receiving

receiving the digital image;

Commercial platforms for digitizing histopathology slides have been in wide use since the late-1990s—20 years prior to the ’097 patent. EX1031, Abstract. Gallas and Chukka both teach receiving such digital images. EX1002, ¶¶195-197.

Gallas describes receiving digital histopathology images. EX1002, ¶196. Gallas describes a platform—referred to as eeDAP—for evaluating digital images. EX1010, 1 (“we present an evaluation environment for digital and analog pathology that we refer to as eeDAP”), Fig. 2. For example, Gallas describes receiving digital images including whole slide images (“WSI”) and real-time images from a microscope-mounted digital camera. EX1010, 1 (“The quantitative assessment of a pathologist’s ability to evaluate histopathology features in WSI compared to the microscope”), 1-2 (“where the digital image is registered to the real-time view”), 2 (“a tight comparison between WSI and optical microscopy”), 3 (“eeDAP hardware consists of an upright brightfield microscope, a digital camera”), Figs. 2 & 6. Gallas further describes displaying the digital images on a computer screen. EX1010, Figs. 1, 2, 4-6.

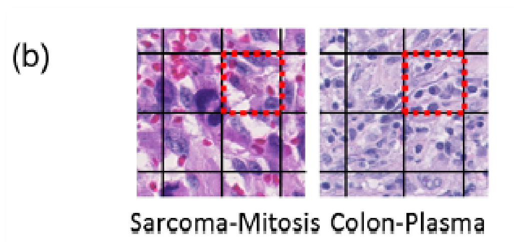
As discussed above, Chukka teaches element [1.A]. *See* §VII.A.1.ii; EX1002, ¶195. For example, Chukka describes an FOV approach in which "slide data" is received as part of workflow for training a classifier. EX1005, Fig. 2, [0035] ("In block 210, the component receives slide data."). Chukka further teaches that the slide data is digital. EX1005, [0008]-[0010] ("digitized images").

iii. 1.[B] Tiling

> separating the digital image into a plurality of tiles, each tile of the plurality of tiles contains a respective portion of the digital image of the slide;

Separating slide images into a plurality of tiles was conventional and described in the prior art. Reticles have long been used for such purposes and allow slide images to be divided into grid squares (e.g., tiles) for systematic analysis of individual tiles without obscuring the field of view. *See* §II. Both Gallas and Chukka teach tiling as recited in element [1.B]. EX1002, ¶¶198-200.

Gallas teaches separating slide images into a plurality of tiles. EX1002, ¶199. For example, Gallas describes use of a reticle overlay to separate digital images into a plurality of grid squares. *E.g.*, EX1010, 7 ("2.5 Reticles"). According to Gallas, a portion of the digital image (e.g., a 400 × 400 patch) is divided into a plurality of "grid square[s]." EX1010, Fig. 6b (reproduced in part herein). Each of Gallas's grid squares



corresponds to a portion of the digital image of the slide. EX1010, Fig. 6 ("a majority of the obvious mitotic figure falls in the grid square to the left of the evaluation square").

As discussed above, Chukka teaches element [1.B]. *See* §VII.A.1.iii. EX1002, ¶198.

iv. 1.[C] Identify Tile Features

> [1.C] for each tile of the plurality of tiles: identifying features of the tile;

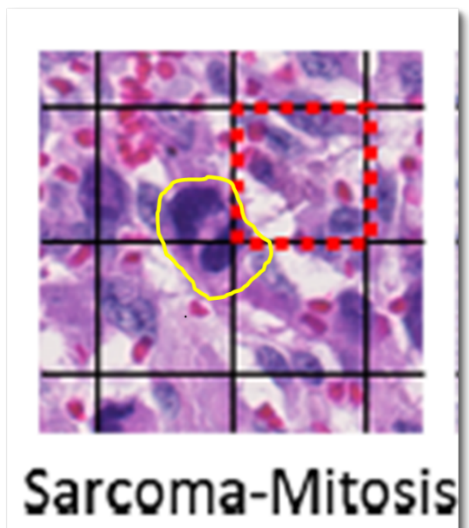
Gallas and Chukka teach identifying features in each tile of the plurality of tiles as recited in element [1.C]. EX1002, ¶¶201-203. As discussed, Gallas discusses a grid overlay with identified features of the separated tiles. In one example, Gallas describes "a 10 x 10 grid with squares that are 1.25 mm on a side." EX1010, 7. Gallas also describes identifying cells and nuclei in tiles such as those shown in Fig. 6. EX1010, 7 ("…, considering cells with at least half their nuclei in the square"). Gallas further describes identifying mitotic figures, plasma cells and clusters of plasma cells. EX1010, Fig. 6 ("obvious mitotic figure…several plasma-cell candidates"). Gallas further describes annotating identified features as part of the eeDAP platform. EX1010, 7 ("the instructions to score a square were to score the cell that was most likely the target (mitotic figure or plasma cell as shown in Fig. 1)"), Fig. 1.

As discussed above, Chukka teaches element [1.C]. *See* §VII.A.1.iv. EX1002, ¶201.

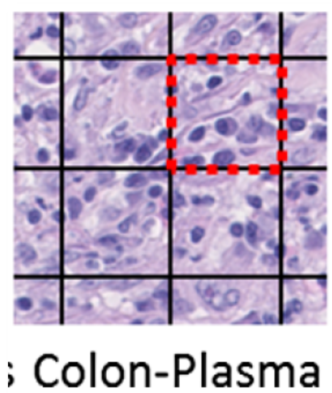
v. [1.D] Identify Structural Tissue Features

> identifying structural tissue features of a second portion of the digital image of the slide including at least a part of one or more tiles of the plurality of tile, wherein the second portion is larger than the respective portion of the digital image contained in the tile; and

Gallas and Chukka teach or suggest identifying structural features as recited in element [1.D]. EX1002, ¶¶204-207. Gallas broadly instructs evaluating surrounding tiles when identifying tissue features of any given tile. Specifically, Gallas instructs users to "consider[] cells with at least half their nuclei in the [evaluation] square." EX1010, 7. Thus, each time a tile is evaluated, a user must consider whether the majority of the nucleus is in the evaluation tile or a neighboring tile.



Gallas further describes identifying structural tissue features including mitotic figures and immune clusters (e.g., groupings of plasma cells) among the tiles. EX1002, ¶205. Gallas describes identifying structural tissue features that span multiple tiles. Referring to Fig. 6(b) (reproduced in part herein with mitotic figure circles in yellow), Gallas explains that "the red-dash boundary squares in the 400 × 400 patches indicate the 'evaluation' areas." Gallas further explains that "a majority of the obvious mitotic figure falls in the grid square to the left of the evaluation square." The mitotic figure described by Gallas spans four grid squares and is outlined in yellow. Thus, identifying the mitotic figure requires evaluating an area that includes the evaluation tile (red-dash boundary) and the additional surrounding tiles occupied by the mitotic figure. The portion of the digital image occupied by the mitotic figure (i.e., 4 tiles) is larger than the respective portion (i.e., the evaluation tile) of the image. Gallas further discloses identifying "several plasma-cell candidates" in the patch displayed in Fig. 6(b).



With respect to the colon tissue slide, Gallas describes evaluation of features such as a cluster of plasma cells in evaluation square. EX1010, Fig. 6 (reproduced in part herein). As with the mitotic figures, Gallas illustrates a larger portion including tiles surrounding the evaluation tile (red) where a POSA would have obviously evaluated plasma cells that span multiple grid squares. EX1002, ¶206.

As discussed above, Chukka teaches element [1.D]. *See* §VII.A.1.v. EX1002, ¶204.

vi. [1.E] Identify Majority Tissue Class

> identifying the majority class of tissue visible within the tile based at least in part on the features of the tile and the structural tissue features of the second portion of the digital image of the slide.

Gallas and Chukka teach or suggest identifying the majority class of tissue as recited in element [1.E]. EX1002, ¶¶208-210. As discussed herein, Gallas teaches separating tissue in a digital slide using a tiled overlay and considering tissue features in an evaluation tile in the context of surrounding tissue tiles. Gallas describes identifying the majority class of tissue (e.g., sarcoma and immune) in a tile based on structural features such as those identified according to element 1.D. For example, the majority class of tissue in the

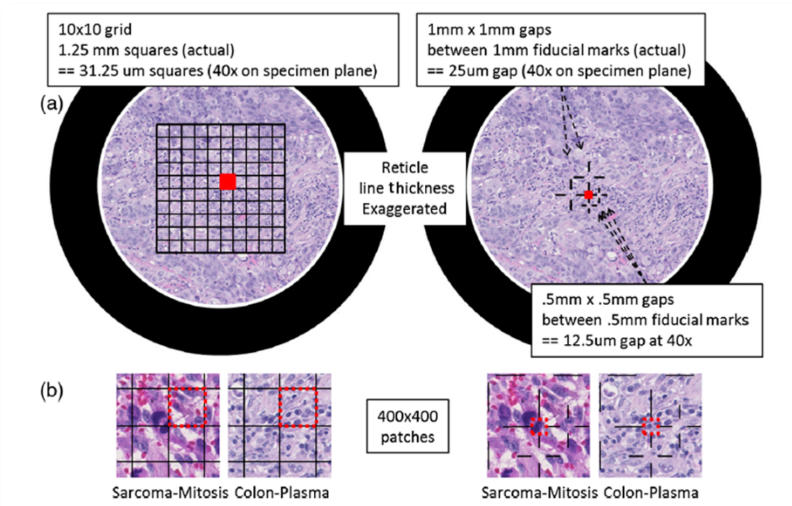


Fig. 6 Reticles (line thicknesses exaggerated) as seen through simulated microscope FOV (a) and 400 × 400 patches as they appear in eeDAP (b). The red squares in the simulated microscope FOVs and the red-dash boundary squares in the 400 × 400 patches indicate the "evaluation" areas. In the 400 × 400 sarcoma patch on the left, a majority of the obvious mitotic figure falls in the grid square to the left of the evaluation square. In the 400 × 400 sarcoma patch on the right, the central cross hairs point to the obvious mitotic figure. In the 400 × 400 colon patch on the left, there are several plasma-cell candidates in the "evaluation" square. In the 400 × 400 colon patch on the right, the cross hairs point to a single plasma-cell candidate to be evaluated.

evaluation tile (red-dash boundary tile) of the sarcoma patch in Fig. 6(b) is sarcoma tissue that is not undergoing mitosis. Gallas expressly confirms its identification included analysis of both the evaluation of tile features and tissue features of tiles in a surrounding second portion (e.g., including surrounding tiles), stating that "a majority of the obvious mitotic figure falls in the grid square to the left of the evaluation square." EX1010, Fig. 6 (marked up herein). Gallas further describes identifying immune tissue as the majority class of tissue in the evaluation tile. EX1010, Fig. 6 ("there are several plasma-cell candidates in the 'evaluation' square").

As discussed above, Chukka also teaches element [1.E]. *See* §VII.A.1.vi. EX1002, ¶208. Accordingly, Gallas and render claim 1 obvious.

2. Claim 4

> The method of claim 1, wherein the majority class of tissue is selected from the group consisting of epithelium, normal epithelium, immune, stroma, necrosis, blood, and fat.

Gallas and Chukka teach or suggest claim 4. EX1002, ¶211. Gallas teaches identifying immune cells as the majority class of tissue. EX1010, Fig. 6; *see also* EX1032, 13, 15. As discussed above, Chukka teaches the limitation of claim 4. *See* §VII.A.2. Accordingly, claim 4 is obvious in view of Gallas and Chukka.

3. Claim 5

> The method of claim 1, wherein the structural tissue features comprises at least one of glands, ducts, vessels, and immune clusters.

Gallas and Chukka teach or suggest claim 5. EX1002, ¶212. Gallas teaches identifying clusters of immune cells. EX1010, Fig. 6; *see also* §VII.D.1.v. As discussed above, Chukka teaches the limitation of claim 5. *See* §VII.A.3. Accordingly, claim 5 is obvious in view of Gallas and Chukka.

4. Claim 6

i. Preamble

> A method for tissue classification of a digital image of a slide, the method comprising:

Gallas and Chukka teach or suggest a method for tissue classification of a digital slide. EX1002, ¶213. As explained above, Gallas describes a platform (eeDAP) for "interpreting histopathology of whole slide images." EX1010, Abstract. Gallas further describes using the disclosed platform for classifying tissue. EX1010, Fig. 6 (discussing classifying sarcoma and colon tissue). As discussed above, Chukka teaches the preamble of claim 6. *See* §VII.A.4.i.

ii. [6.A] Receiving

Element [6.A] is identical to element [1.A] and is taught by Gallas and Chukka for the same reasons discussed for element [1.A]. EX1002, ¶214.

iii. [6.B] Tiling

Element [6.B] is substantially identical to element [1.B] and is taught by Gallas and Chukka for the same reasons discussed for element [1.B]. EX1002, ¶215.

iv. [6.C] Identify Tile Features

Element [6.C] is identical to element [1.C] and is taught by Gallas and Chukka for the same reasons discussed for element [1.C]. EX1002, ¶216.

v. [6.D] Identify Structural Tissue Features

Element [6.D] is identical to element [1.D] and is taught by Gallas and Chukka for the same reasons discussed for element [1.D]. EX1002, ¶217.

vi. [6.E] Determine Predicted Class for Tiles

As discussed above, Chukka teaches element [6.E]. *See* §VII.A.4.vi; EX1002, ¶218.

vii. [6.F] Identify Cell Objects

> identifying a plurality of cell objects in the digital image;

Gallas and Chukka teach or suggest element [6.F]. EX1002, ¶219. Gallas teaches identifying cell objects such as cells and nuclei. For example, Gallas explains that users may "consider[] cells with at least half their nuclei in the square." EX1010, 7; EX1002, ¶219. Gallas further describes identifying mitotic figures and plasma cells. EX1010, Fig. 6.

As discussed above, Chukka teaches element [6.F]. *See* §VII.A.4.vii; EX1002, ¶219.

viii. [6.G] Determine Predicted Class of Cell Objects

As discussed above, Chukka teaches element [6.G]. *See* §VII.A.4.viii; EX1002, ¶220.

ix. [6.H] Assign Predicted Class of Cell Objects

> for each of the plurality of tiles that corresponds to one of the plurality of cell objects, assigning the tile the predicted class of the corresponding cell object in place of the predicted class of the tile.

As discussed above, Chukka teaches element [6.H]. *See* §VII.A.4.ix. To the extent Patent Owner argues that Chukka does not expressly disclose 6[H] "assigning each tile to the predicted class of a cell…***in place*** of the predicted class of the tile," a POSA would have understood that Chukka's discussion of multi-stage tile analysis at a minimum renders obvious this element. EX1002, ¶221. As discussed above, Chukka also explains that "a pathologist" can replace "the automated score …with a manual score (e.g., a score based at least in part on visual inspection)." EX1005, [0005]. Chukka also teaches first performing a "coarse" texture-based classification of the tiled image, and then subsequently performing a second, finer classification by looping through each tile and identifying and classifying the cells within each tile. EX1005, [0045]-[0046]. By virtue of Chukka's description of the first stage as an initial "coarse-resolution" analysis, EX1005, [0045], to be followed by further "analysis at varying levels of granularity to increase accuracy," EX1005, [0047], a POSA would have understood that further finer levels of analysis (such as identifying cells) would involve replacing the initial, coarser texture-based classification with the subsequent, cell classification. EX1002, ¶221; *see also* EX1011, 1081-82; EX1012, 159-160; EX1015, 11.

Accordingly, Gallas and Chukka render claim 6 obvious. EX1002, ¶222.

5. Claim 9

> The method of claim 6, further comprising: generating a digital overlay drawing for the digital image, where the digital overlay drawing is a histology mask displaying the plurality of tiles and the predict class for each tile.

As discussed above, Chukka teaches claim 9. *See* §VII.A.5. To the extent that Patent Owner argues Chukka does not expressly teach the "a histology mask ***displaying*** the plurality of tiles and the predict class for each tile," it would have been obvious for a POSA to do so. As discussed above, Chukka discloses generating digital overlay drawings to label features of interest and identifying features of interest in tiles, such as identifying portions of the image that correspond to predicted classes (e.g., lymphocyte, stromata). It would have been readily apparent to that Chukka's digital overlay drawing would be used to display the plurality of tiles, and label features of interest such as the predicted class of each tile. EX1002, ¶223.

Accordingly, Gallas and Chukka render claim 9 obvious. EX1002, ¶224.

6. Claim 10

> The method of claim 6, further comprising:
>
> generating a digital overlay drawing for the digital image; and
>
> displaying, in the digital overlay drawing, the plurality of tiles and the predicted class for each tile that does not correspond to a cell object, and displaying the plurality of cell objects and the predicted class of each cell object.

As discussed above, Chukka teaches claim 10. *See* §VII.A.6. To the extent that Patent Owner argues Chukka does not expressly teach "***displaying***, in the digital overlay drawing, the plurality of tiles and the predicted class for each tile that does not correspond to a cell object, and ***displaying*** the plurality of cell objects and the predicted class of each cell object," it would have been obvious for a POSA to do so. As discussed above, Chukka discloses generating digital overlay drawings to label features of interest, and Chukka discloses identifying features of interest in tiles, such as identifying portions of the image that correspond to predicted classes (e.g., lymphocyte, stromata). It would have been readily apparent to that Chukka's digital overlay drawing would be used to display the plurality of tiles, and label features of interest including by displaying both the predicted class for each tile that does not correspond to a cell object, and the predicted class of each cell object. EX1002, ¶225.

Accordingly, Gallas and Chukka render claim 10 obvious. EX1002, ¶226.

7. Claim 11

> The method of claim 6, further comprising:
>
> generating a digital overlay drawing for the digital image, wherein the digital overlay drawing includes the digital image; and
>
> displaying the digital overlay drawing.

Gallas teaches generating a digital overlay drawing for a digital image as claimed. EX1002, ¶227. For example, Gallas describes overlaying a reticle on a digital image. EX1010, Fig. 6. Gallas further describes displaying the digital overlay drawings on a computer monitor. EX1010, 3 ("The eeDAP hardware consists of an upright brightfield microscope, a digital camera, …a computer monitor, and a computer (see Fig. 2)."), 6 ("The size of a patch seen by a pathologist depends on the computer monitor."), Fig. 5 ("as seen on a computer monitor"). As discussed above, Chukka teaches claim 11. *See* §VII.A.7. Accordingly, Gallas and Chukka render claim 11 obvious. EX1002, ¶228.

8. Claim 12

> The method of claim 6, further comprising:
>
> generating a digital overlay drawing for the digital image, wherein the digital overlay drawing includes a generated version of the digital image; and
>
> displaying the digital overlay drawing.

As discussed above, Chukka teaches claim 12. *See* §VII.A.8. Accordingly, Gallas and Chukka render claim 12 obvious. EX1002, ¶229.

9. Claim 14

> The method of claim 6, further comprising:
>
> generating a digital overlay drawing for the digital image, where the digital overlay drawing comprises percentages of predict classes corresponding to the digital image.

As discussed above, Chukka teaches claim 14. *See* §VII.A.9. To the extent that Patent Owner argues Chukka does not expressly teach that generating a digital overlay drawing that "comprises percentages of predict classes corresponding to the digital image," it would have been obvious for a POSA to do so. As discussed above, Chukka discloses generating digital overlay drawings to label features of interest, and Chukka discloses reporting a score that comprises percentages of predicted classes in the slide (e.g., percentages of positively-stained cells). It would have been readily apparent to that Chukka's digital overlay drawing would therefore comprise percentages of the predicted classes corresponding to the digital image. EX1002, ¶230.

Accordingly, Gallas and Chukka render claim 14 obvious. EX1002, ¶231.

10. Claim 15

> The method of claim 6, further comprising:
>
> generating a digital overlay drawing for the digital image, where the digital overlay drawing comprises total counts of predict classes corresponding to the digital image.

As discussed above, Chukka teaches claim 15. *See* §VII.A.10. To the extent that Patent Owner argues Chukka does not expressly teach that generating a digital overlay drawing that "comprises total counts of predict classes corresponding to the digital image," it would have been obvious for a POSA to do so. As discussed above, Chukka discloses generating digital overlay drawings to label features of interest, and Chukka discloses counting and classifying cells as, for example, positively-stained tumor cells. It would have been readily apparent to that Chukka's digital overlay drawing would therefore comprise total counts of predicted classes corresponding to the digital image. EX1002, ¶232.

Accordingly, Gallas and Chukka render claim 15 obvious. EX1002, ¶233.

11. Claim 17

> The method of claim 6, wherein the cell objects include lymphocyte cells and not lymphocyte cells.

Gallas renders obvious cell objects including lymphocyte cells and not lymphocyte cells. For example, Gallas describes a tissue slide comprising colon cells and plasma cells. EX1010, Fig. 6 ("In the 400 × 400 colon patch on the left, there are several plasma-cell candidates in the 'evaluation' square."); EX1032, 13, 15. As discussed above, Chukka teaches claim 17. *See* §VII.A.11. Accordingly, Gallas and Chukka render claim 17 obvious. EX1002, ¶234.

12. Claim 18

> The method of claim 6, wherein the structural tissue features comprises at least one of glands, ducts, vessels, and immune clusters.

Gallas teaches structural features including immune clusters. For example, Gallas describes a tissue slide comprising colon cells and a cluster of plasma cells. EX1010, Fig. 6 ("In the 400 × 400 colon patch on the left, there are several plasma-cell candidates in the 'evaluation' square."); EX1032, 13, 15. As discussed above, Chukka teaches claim 18. *See* §VII.A.12. Accordingly, Gallas and Chukka render claim 18 obvious. EX1002, ¶235.

E. [Ground 5] Claims 2, 3, 7, and 8 Are Obvious over Gallas, Chukka, and Jones

As discussed above, Gallas and Chukka render obvious independent claims 1 and 6. Additional disclosure in Jones renders obvious the limitations of dependent claims 2, 3, 7, and 8. As explained above, Chukka teaches using the foreground mask and nuclei to generate a Voronoi tessellation of the foreground image to identify portions or "blobs" that define the boundaries of the detected objects. EX1005, [0051], Fig. 5. Jones teaches the details of a specific method of defining cell-to-cell boundaries using Voronoi tessellations. EX1002, ¶236. As Dr. Papanikolopoulos explains, a POSA looking to implement Chukka's "extract objects component" to identify portions of the image corresponding to boundaries around detected cellular objects would have had a good reason to look at teachings of Jones to do so. Moreover, a POSA would have had a reasonable expectation of success at least because Chukka provides the information used by Jones' method (i.e., a seed point and an object foreground mask) to outline the boundaries of cells. EX1002, ¶¶146-147; *see also* § VII.B.

1. Claim 2

> The method of claim 1, further comprising: generating a digital overlay drawing of an outer edge of each cell in the image.

Jones teaches the additional limitations of claim 2 for the reasons discussed above in Ground 2. *See also* § VII.B.1; EX1002, ¶¶148-153. Accordingly, Gallas, Chukka and Jones render claim 2 obvious. EX1002, ¶237.

2. Claim 3

> 3. The method of claim 2, wherein the digital overlay drawing is prepared at the resolution level of an individual pixel.

Jones teaches the additional limitations of claim 3 for the reasons discussed above in Ground 2. *See also* § VII.B.2; EX1002, ¶¶154-157. Accordingly, Gallas, Chukka and Jones render claim 3 obvious. EX1002, ¶238.

3. Claims 7 and 8

> 7. The method of claim 6, further comprising:
>
> storing, in a first file, for each tile, a tile position and the predicted class of the tile; and
>
> storing, in a second file, for each cell object, a polygon outlining the cell object and the predicted class of the cell object.
>
> 8. The method of claim 6, further comprising: generating a digital overlay drawing for the digital image, where the digital overlay drawing is a cell mask displaying a polygon around each cell object.

Jones teaches the additional limitations of claims 7 and 8 for the reasons discussed above in Ground 2. *See also* § VII.B.3; EX1002, ¶¶158-165. Accordingly, Gallas, Chukka and Jones render claims 7 and 8 obvious. EX1002, ¶239.

F. [Ground 6] Claims 12, 13, and 16 Are Obvious over Gallas, Chukka and Sebastiao

As discussed above, Gallas and Chukka render obvious independent claim 6. Additional disclosure in Sebastiao renders obvious the limitations of dependent claims 12, 13, and 16. As explained above in Ground 3, a POSA would have had a good reason to have considered the teachings of Chukka and Sebastiao together because these references disclose similar and compatible systems developed by overlapping inventors on behalf of the same applicant. *See* § VII.C; EX1002, ¶¶170-172. The same reasoning applies to the combination of Gallas, Chukka and Sebastiao. EX1002, ¶240.

1. Claim 12

> The method of claim 6, further comprising:
>
> generating a digital overlay drawing for the digital image, wherein the digital overlay drawing includes a generated version of the digital image; and
>
> displaying the digital overlay drawing.

Sebastiao teaches the additional limitations of claim 12 for the reasons discussed above in Ground 3. *See also* § VII.C.1; EX1002, ¶¶173-177.

Accordingly, Gallas, Chukka and Sebastiao render claim 12 obvious. EX1002, ¶241.

2. Claim 13

> The method of claim 6, further comprising:
>
> generating a plurality of digital overlay drawings for the digital image, where each digital overlay drawing corresponds to a different predicted class; and
>
> selectively displaying one of the plurality of digital overlay drawings.

Sebastiao teaches the additional limitations of claim 13 for the reasons discussed above in Ground 3. *See also* § VII.C.2; EX1002, ¶¶178-180. Accordingly, Gallas, Chukka and Sebastiao render claim 13 obvious. EX1002, ¶242.

3. Claim 16

> The method of claim 6, wherein the cell objects comprise CD3, CD8, CD20, pancytokeratin, and smooth muscle actin.

Sebastiao teaches the additional limitations of claim 16 for the reasons discussed above in Ground 3. *See also* § VII.C.3; EX1002, ¶¶181-185. Accordingly, Gallas, Chukka and Sebastiao render claim 16 obvious. EX1002, ¶243.

VIII. CONCLUSION

For the reasons set forth above, claims 1-18 of the ’097 patent are unpatentable. Petitioner therefore requests that an inter partes review of these claims be instituted.

Respectfully submitted,

Dated: December 30, 2025

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
Reg. No. 52,182

IX. GROUNDS FOR STANDING

Petitioner certifies that, under 37 C.F.R. §42.104(a), the ’097 patent is available for inter partes review, and Petitioner is not barred or estopped from requesting *inter partes* review of the ’097 patent on the grounds identified.

X. MANDATORY NOTICES UNDER 37 C.F.R. §42.8

Real Party-in-Interest (37 C.F.R. §42.8(b)(1)): Guardant Health, Inc. is the real party-in-interest. The complaint in *Tempus AI, Inc. v. Guardant Health, Inc.*, 3:25-cv-00621 (S.D. Cal.) identifies Guardant as having a business relationship with Lunit Inc. *See* EX1034, 26.

Related Matters (37 C.F.R. §42.8(b)(2)): Tempus asserted the challenged patent (US 10,991,097), together with U.S. Patent Nos. 10,957,041; 11,640,859; and 12,112,839, in *Tempus AI, Inc. v. Guardant Health, Inc.*, 3:25-cv-00621 (S.D. Cal.) on March 14, 2025. Tempus returned a summons on March 26, 2025. By order of the court, that case was terminated on August 1, 2025, for transfer to the Northern District of California, resulting in the pending case *Tempus AI, Inc. v. Guardant Health, Inc.*, 3:25-cv-06622 (N.D. Cal.). Guardant has also asserted patent infringement against Tempus in *Guardant Health, Inc. v. Tempus AI, Inc.*, 1:24-cv-00687 (D. Del.) and *Guardant Health, Inc. v. Tempus AI, Inc.*, 1:25-cv-01013 (D. Del.), which were consolidated on October 16, 2025.

Lead and Back-Up Counsel (37 C.F.R. §42.8(b)(3))

Lead Counsel: Michael T. Rosato (Reg. No. 52,182)

Back-Up Counsel: Jad Mills (Reg. No. 63,344), Patrick Medley (Reg. No. 74,735), Sonja R. Gerrard (Reg. No. 72,802)

Service Information – 37 C.F.R. §42.8(b)(4). Petitioner hereby consents to electronic service.

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XI. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,963 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Dated: December 30, 2025

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
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XII. PAYMENT OF FEES UNDER 37 C.F.R. §§42.15(A) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 23-2415.

XIII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 10,991,097
1002	Papanikolopoulos Declaration
1003	Papanikolopoulos CV
1004	’097 Patent Prosecution History
1005	U.S. Patent Publication No. 2016/0042511 A1 to Chukka et al.
1006	Thouis R. Jones, et al., “Voronoi-based segmentation of cells on image manifolds.” *International Workshop on Computer Vision for Biomedical Image Applications*. Berlin, Heidelberg: Springer Berlin Heidelberg, 2005
1007	International Publication No. WO 2015/124737 A1 to Sebastiao, et al.
1008	Giuseppe Musumeci “Past, Present and Future: Overview on Histology and Histopathology.” *J. Histol. Histopathol.* 1.5: 1-3 (2014)
1009	Peter W. Hamilton et al. “Digital Pathology and Image Analysis in Tissue Biomarker Research.” *Methods* 70:59-73 (2014).
1010	Brandon D. Gallas et al. “eeDAP: an Evaluation Environment for Digital and Analog Pathology.” *Medical Imaging 2014: Image Perception, Observer Performance, and Technology Assessment*. Vol. 9037. SPIE (2014)
1011	Jun Kong, et al., “Computer-aided Evaluation of Neuroblastoma on Whole-slide Histology Images: Classifying Grade of Neuroblastic Differentiation.” *Pattern Recognition* 42.6: 1080-1092 (2009)
1012	Metin N. Gurcan et al., “Histopathological image analysis: A review.” *IEEE Reviews in Biomedical Engineering* 2: 147-171 (2009)

1013	Songfan Yang, et al., "Multi-scale Recognition with DAG-CNNs." *Proceedings of the IEEE International Conference on Computer Vision* (2015)
1014	Peter J. Burt, et al., "The Laplacian Pyramid as a Compact Image Code." *Readings in Computer Vision*. Morgan Kaufmann, 671-679 (1987)
1015	Jocelyn Barker, et al., "Automated Classification of Brain Tumor Type in Whole-Slide Digital Pathology Images Using Local Representative Tiles." *Medical Image Analysis* 30: 60-71 (2016)
1016	Xipeng Pan et al., "Cell Detection in Pathology and Microscopy Images with Multi-scale Fully Convolutional Neural Networks." *World Wide Web* 21.6:1721-1743 (2018)
1017	Sahirzeeshan Ali et al., "Segmenting Multiple Overlapping Objects Via a Hybrid Active Contour Model Incorporating Shape Priors: Applications to Digital Pathology." *Medical Imaging 2011: Image Processing*. Vol. 7962. SPIE (2011)
1018	Michael Barnes, et al., "Abstract P5-03-08: Development of a Histology-based Digital Pathology Image Analysis Algorithm for Assessment of Tumor Infiltrating Lymphocytes in HER2+ Breast Cancer." *Cancer Research* 78.4_Supplement: P5-03 (2018)
1019	Emilio Garcia, et al., "Automatic Lymphocyte Detection on Gastric Cancer IHC Images using Deep Learning." *2017 IEEE 30th International Symposium on Computer-Based Medical Systems (CBMS)*. IEEE, 2017
1020	Keith E. Steele, et al., "Measuring Multiple Parameters of CD8+ Tumor-infiltrating Lymphocytes in Human Cancers by Image Analysis." *Journal for Immunotherapy of Cancer* 6.1:20 (2018)
1021	Thomas Mentzel, et al., "Cutaneous Myoepithelial Neoplasms: Clinicopathologic and Immunohistochemical Study of 20 Cases Suggesting a Continuous Spectrum Ranging from Benign Mixed Tumor of the Skin to Cutaneous Myoepithelioma and Myoepithelial Carcinoma." *Journal of Cutaneous Pathology* 30.5 (2003): 294-302

1022	Michal Zamecnik, "Epithelioid Hemangioendothelioma with Actin+/Cytokeratin+ Myoblast-like Cells: Report of a Case." *Journal of Interdisciplinary Histopathology*, (2016)
1023	Nemanja Rajković, et al., "The Pan-cytokeratin Staining Intensity and Fractal Computational Analysis of Breast Tumor Malignant Growth Patterns Prognosticate the Occurrence of Distant Metastasis." *Frontiers in Oncology* 8:348 (2018)
1024	Mami Murakami, et al., "Docetaxel Conjugate Nanoparticles that Target α-smooth Muscle Actin–expressing Stromal Cells Suppress Breast Cancer Metastasis." *Cancer Research* 73.15: 4862-4871 (2013)
1025	Mahalakshmi Ravi, et al., "Expression of α-smooth Muscle Actin in Benign and Malignant Salivary Gland Tumors: An Immunohistochemical Study." *Indian Journal of Pathology and Microbiology* 61.4: 479-484 (2018)
1026	Michael J. Gerdes, et al. "Highly Multiplexed Single-Cell Analysis of Formalin-fixed, Paraffin-embedded Cancer Tissue." *Proceedings of the National Academy of Sciences* 110.29 (2013): 11982-11987
1027	Qiang Du, et al., "Centroidal Voronoi tessellations: Applications and algorithms." *SIAM Review* 41.4: 637-676 (1999)
1028	U.S. Patent Appl. Pub. No. 2016/0063724
1029	John D. Bancroft, ed. "Theory and Practice of Histological Techniques, Elsevier Health Sciences, 2008 (6th Ed.).
1030	Zeta Corp. Pancytokeratin brochure
1031	Liron Pantanowitz, et al., "Twenty Years of Digital Pathology: An Overview of the Road Travelled, What is on the Horizon, and the Emergence of Vendor-Neutral Archives." *Journal of Pathology Informatics* 9.1:40 (2018)
1032	Thomas J. Kindt, et al., Kuby Immunology, 2007 (6th Ed.)
1033	Defendant Guardant Health Inc.'s Memorandum of Points and Authorities in Support of Motion to Dismiss Pursuant to Fed. R. Civ. P.

	12(b)(6), *Tempus AI*, *Inc*. *v*. *Guardant Health*, *Inc*., Case No. 3:25-CV-00621-JO-MMP, Dkt. 11-1, (S.D. Cal. May 23, 2025).
1034	Plaintiff Tempus AI, Inc.'s Complaint for Patent Infringement, *Tempus AI, Inc*. *v*. *Guardant Health*, *Inc*., Case No. 3:25-CV-00621-JO-MMP, Dkt. 1, (S.D. Cal. Mar. 14, 2025).

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for Inter-Parties Review of U.S. Patent No. 10,991,097 (and accompanying Exhibits 1001-1034) by overnight courier (Federal Express or UPS), on this 30th day of December, on the Patent Owner at the correspondence address of the Patent Owner as follows:

4743 - MARSHALL, GERSTEIN & BORUN LLP

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Respectfully submitted,

Dated: December 30, 2025

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